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THESE

Présentée pour obtenir le titre de

DOCTEUR DE L'ECOLE POLYTECHNIQUE

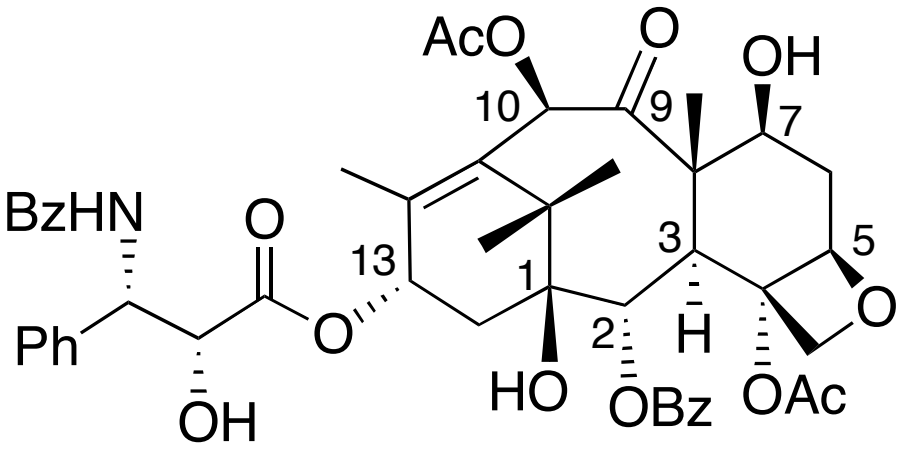
Spécialité

CHIMIE

Par

Cong Ma

VERS LA SYNTHESE DU TRICYCLE ABC DU TAXOL



Soutenue le 12 novembre 2008 devant le jury composé de:

M. Siméon Arseniyadis	Rapporteur
M. Cyrille Kouklovsky	Examinateur
M. Bastien Nay	Rapporteur
M. Ange Pancrazi	Président
Mme Joëlle Prunet	Directrice de thèse

Quelque mots…

Quand en été 2005, Joëlle m'a proposé la synthèse du taxol comme sujet de thèse au téléphone, elle avait l'air de s'inquiéter que peut-être je le refuse. En fait, j'était presque honoré de l'accepter puis que le taxol est tellement connu que j'en ai endentu parler tous les jours pendant toutes mes études de pharmacie et mon travail dans une compagnie pharmaceutique en Chine. Une thèse en synthèse totale du taxol, cela ne peut arriver qu'une fois dans la vie.

Tout ce que je n'ai jamais pensé, c'est qu'elle est beaucoup plus difficile que ce que j'ai pu estimer. Sans exagération, il n'y a même pas une étape facile à réaliser. Le temps que j'ai utilisé pour choisir une méthodologie et optimiser les rendements a pris une bonne place de ma thèse, je pense que c'est la raison pour laquelle je n'avance pas aussi vite que je le voulais.

Combien de temps devrait-on passer pour optimiser une belle réaction (si elle marche) ou arrêter puis réfléchir à une autre voie aussi délicate ? Si je n'avais pas passé toute la deuxième année à essayer de fabriquer le synthon 1 par 1,3-cyanation diastéréoséléctive, j'aurais pu avancer plus que maintenant ; mais si je n'avais pas testé plusieurs groupements protecteurs sur le carbon C7 du cycle C, je n'aurais pas pensé non plus à protéger sous la forme de cétal et réussi à faire le synthon 2.

Choisir, c'est toujours le plus difficile de tout.

C'est aussi difficile de rédiger une thèse au sujet du taxol, parce qu'il y a trop d'informations et de publications. Comme j'aime bien l'histoire et la littérature, j'essaie de rédiger cette thèse comme un roman pour les chimistes, afin que vous puissez tous lire jusqu'à la fin avec plaisir, sans sauter la partie bibliographique. ;)

A la fin, j'espère qu'à la lecture de ce "roman", vous y trouverez des choses intéressantes. Lao-Tzeu l'a dit: "il faut trouver la voie !" Avec la voie, pas forcément venue de ma thèse, la synthèse du taxol, ou de la brevetoxine, ou de la palau'amine, sera simple comme une saponification…

P.S. Si quelqu'un ne se rappelle pas la phrase de Lao-Tzeu, il faut qu'il révise <<Tintin: Le Lotus Bleu>>.

Avant-propos

Ce manuscrit présente les travaux effectués à l'Ecole Polytechnique (09/2005 – 09/2008) sous la direction du Dr. Joëlle Prunet dans le Laboratoire de Synthèse Organique dirigé par le Pr. Samir Zard.

Ce manuscrit est divisé en trois parties : le **chapitre I**, composé par des généralités sur le taxol et des différentes synthèses déjà publiées de cette molécule, ainsi que des généralités sur la métathèse qui représente l'outil de synthèse principal de notre approche du taxol ; le **chapitre II**, rassemble les travaux précédemment effectués au laboratoire (approche convergente par métathèse entre les carbones C9 et C10, approche semi-convergente entre C9 et C10, puis entre C10 et C11) et l'achèvement des études sur les bicycles BC modèles sans les fonctionnalités sur les carbones C13 et C7 du taxol ; le **chapitre III**, décrit la préparation de deux synthons du taxol et l'approche de synthèse du 7-désoxy taxol. Les protocoles expérimentaux ainsi que la description des produits synthétisés sont présentés dans la **partie experimentale**.

Les études sur les molécules bicycliques modèles dans le **chapitre II** ont fait l'objet de deux publications :

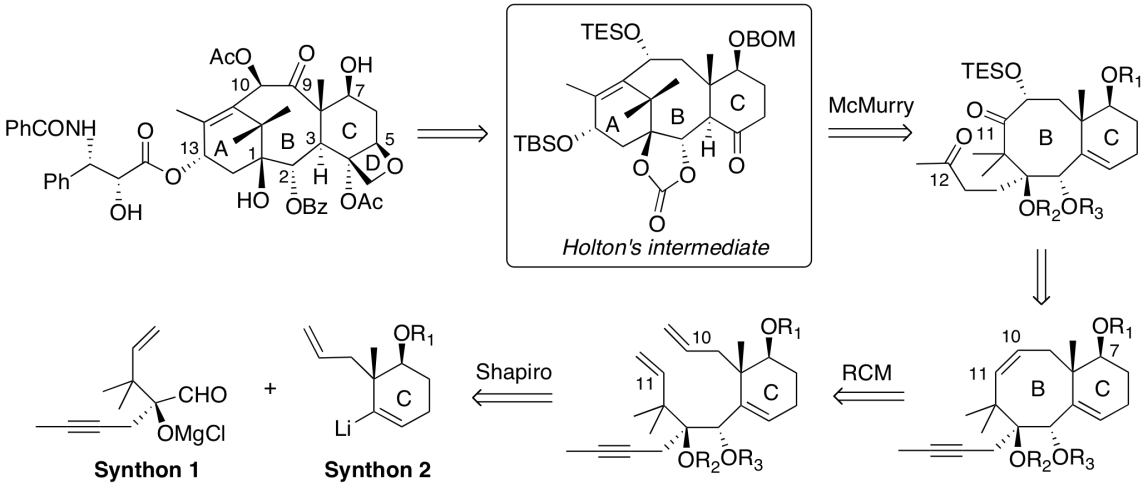
Ring-Closing Metathesis in the Synthesis of Model BC Bicycles of Taxol
Ma, C.; Schiltz, S.; Le Goff, X. F.; Prunet, J. *Chem. Eur. J.* **2008**, *14*, 7314-7323.

Synthesis of model BC bicycles of taxol using C10-C11 ring-closing metathesis strategy
Schiltz, S.; Ma, C.; Ricard, L.; Prunet, J. *J. Organomet. Chem.* **2006**, *691*, 5438-5443**.**

Note : Les composés décrits dans ce manuscrit sont désignés par des lettres et des chiffres gras. (ex : **RH-01** représente un composé synthétisé par Robert A. Holton ; **PW-23** est synthétisé par the Previous Workers.)

Résumé en français

Le Taxol™, extrait de l'écorce de l'if du Pacifique (*Taxus brevifolia* Nutt.), est l'anticancéreux aujourd'hui le plus vendu au monde. La synthèse totale semi-convergente envisagée au laboratoire est illustrée ci-dessous : le taxol pourrait être préparé à partir d'un intermédiaire déjà synthétisé par Holton, qui possède les trois cycles ABC principaux du taxol. La synthèse de cet intermédiaire pourrait être réalisée par la fermeture du cycle A par une condensation pinacolique entre deux cétones de la molécule. Cette dicétone serait synthétisée par une méthathèse cyclisante du diène pour fermer le cycle B suivie d'une dihydroxylation du cyclooctène obtenu. L'obtention de ce diène pourrait être effectuée par le couplage d'un aldéhyde (Synthon 1) et d'un vinyllithium (Synthon 2).



Nous avons commencé par effectuer une étude préliminaire de cette voie de synthèse en portant de modèle synthons **1** et **2** sans la fonction alkyne et le groupement $–OR_1$. Plusieurs bicycles BC avec divers groupements protecteurs $–OR_2$ et $–OR_3$ ont été ensuite synthétisés avec de bons rendements. Actuellement les synthons définitifs **1** et **2** ont été préparés et la synthèse formelle du taxol est en cours de réalisation.

Remerciements

Ce travail a été réalisé au laboratoire DCSO de l'Ecole Polytechnique, dirigé par Pr. Samir Zard, je tiens à le remercier pour m'avoir accueilli au sein du laboratoire.

Je voudrais adresser mes remerciements aux membres du jury : Dr. Siméon Arseniyadis, Pr. Cyrille Kouklovsky, Dr. Bastien Nay, et Pr. Ange Pancrazi pour avoir accepté de juger mon travail. Je vous remercie également pour la discussion très intéressante et vos conseils concernant mon manuscrit.

Je remercie la Direction des Relations Extérieures qui a financé ce travail pendant trois ans, surtout Mme Pascale Fuseau et Mlle Cécile Vigouroux pour les aides administratives.

Un grand merci au laboratoire LPSN à Orsay (Pr. Cyrille Kouklovsky, Dr. Nicolas Blanchard, Dr. Valérie Alezra, Dr. Yves Langlois, Dr. Robert Lett, Dr. Annie Pouilhes, Dr. Olivier Bedel, Dr. Géraldine Calvet, Dr. Cam Thuy Hoang, Dr. Mathieu Branca, Gilles Galvani, Dominique Callas) pour tout ce que vous m'avez offert, bien que je ne connaissais pas grand chose sur la chimie comme un papier blanc quand je suis arrivé en France après une formation de pharmacie et deux ans de travail dans le marketing, Six mois de stage chez vous m'ont donné les outils pour commencer une thèse.

Je remercie vivement le Dr. Joëlle Prunet qui m'a proposé un sujet extrêmement intéressant (je me suis bien amusé) et qui a dirigé ma thèse (il est difficile de me convaincre, hein?) pendant trois ans. Il faut savoir que j'avais un peu peur de toi au début de la thèse à cause des nombreuses questions que tu as posé à la soutenance du Dr. Olivier Bedel à l'époque où j'étais encore à Orsay. Mais avec le temps je t'ai trouvé finalement très sympathique, tu m'a laissé une grande liberté pour que je puisse tester mes idées qui viennent de ma tête têtue. J'ai vraiment apprécié ta disponibilité lorsque j'avais des problèmes. Désolé pour ne pas avoir terminé la synthèse même que tu me l'as demandé trois ans auparavant, après la soutenance de Stéphanie. C'est aussi grâce à toi que j'ai pu contacter Pr. Gregory C. Fu pour le post-doc dont j'ai rêvé depuis longtemps. Encore un grand merci car je suis le premier étudiant à qui tu as proposé de faire deux gâteaux chocolats pour le pot de thèse. J'aimerais bien en manger encore un quand je retournerais en France, et peut-être pourrions-nous faire aussi un match de tennis?

Je remercie aussi chaleureusement le Dr. Jean-Pierre Férézou. Bien que vous ne soyez pas mon encadrant de thèse, vous avez toujours été present pour répondre à mes questions avec

votre énorme expérience, sans parler des efforts pour lire mon manuscrit. J'ai bien apprécié également les discussions sur la culture française, bretonne, sur l'industrie pharmaceutique, et aussi sur l'histoire d'un étranger au Brésil. Bon courage avec les jeunes, je les sens bien.

Je remercie Jean-Pierre Pulcani, pour son aide en HPLC, je vous ai beaucoup embêté pour séparer mes produits souvent inséparables. Merci aussi pour les discussions très intéressantes sur l'électrochimie et la chromatographie.

Je remercie Dr. Issam Hanna, Dr. Béatrice Sire, Dr. Fabien Gagosz et Michel Levart. Tout ce que vous faite : la sécurité, la commande des produits et le HRMS sont indispensable pour le fonctionnement du labo.

Je remercie également Brigitte qui m'a soigneusement aidé pour les problèmes administratifs, sans vous je n'aurais pas pu me concentrer sur la paillasse.

Je remercie mes trois stagiaires, Jessica, Yann et Stefan, vous êtes venu avec un grand enthousiasme et malheureusement débuté avec une chimie qui marche difficilement. J'espère que vous continuez la chimie avec courage. Bonne chance à Oxford, Jessica (Ce n'est pas bien de travailler jusqu'à 4 heures du matin); Yann, tu vas découvrir tout les trésors de la chimie de l'or (il est déjà un trésor pourtant), et pour Stefan, bonne continuation à Harvard (C'est bon la Leffe, hein ?), on se reverra bientôt.

Je remercie aussi les personnes du laboratoire DCPH avec qui j'ai travaillé : Mr. François Mercier, pour la formation de l'hydrogénation de Noyori, je vous ai embêté chaque fois pour les même questions mais vous avez toujours été gentil avec moi ; Dr. Louis Ricard et Dr. Xavier Le Goff, pour les expériences de rayon-X.

Il reste à remercier tous les jeunes étudiants du labo : Labo 1, Michiel, Soizic, Inès, Zorana, Mathieu, Laurent, Can, Michal, German ; Labo 2, Thomas, Cathy, Célia, Aurélien, Guillaume, Rama ; Labo 2.5, Zhi, Chakib ; Labo 3, Jon, Emilie, Lisa, Myriem, Yann, Diego, Dan, Bernhard, Nicolas, Nahid, Alice, Labo 4, Lucie, Aurélie, Xavi, Shuji, Raphaël, Rémi, Mehdi, Marie-Gabrielle ; Labo 5, Sharan, Patrick, Julie, Stéphanie, Andréa, Florin, Igor, Yann, Rachel, Wioletta, Ryan. Ça a été un grand plaisir de travailler avec vous et participer aux activités avec vous. Désolé de ne pas pouvoir détailler mes remerciements pour chaque personne, sinon je n'aurais pas fini d'écrire cette année…Bon courage et bonne chance à vous tous. 万事如意，一路顺风。

STUDIES TOWARDS THE SYNTHESIS OF THE ABC TRICYCLE OF TAXOL

A Thesis

In Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy

By

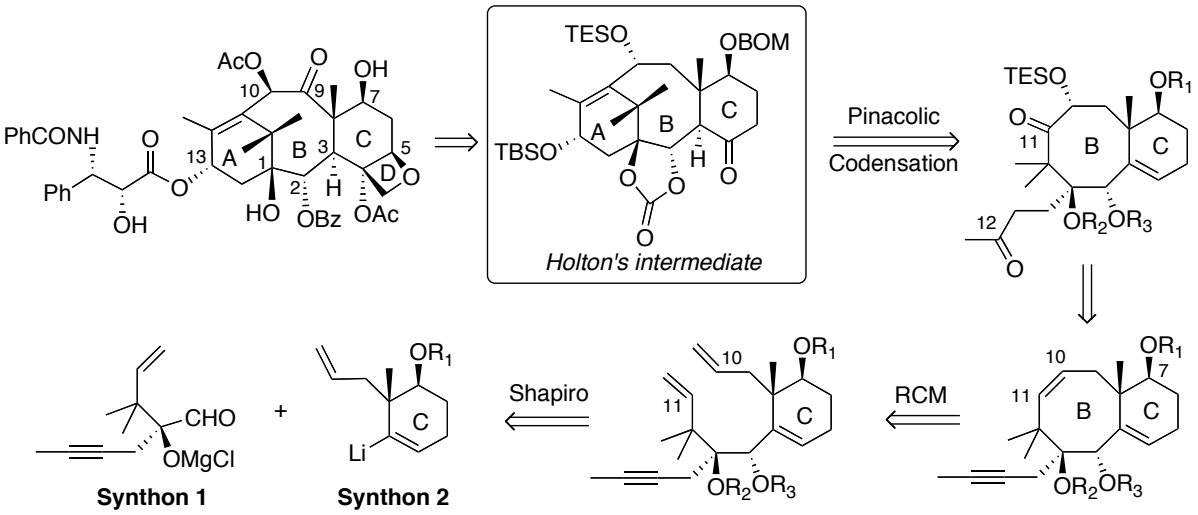
Cong Ma

Dr. Joëlle Prunet, Director

Ecole Polytechnique
Palaiseau, France
--11.12.2008--

Abstract in English

Taxol®, isolated from the bark of the Pacific yew tree (*Taxus brevifolia* Nutt.), is a very effective drug in the treatment of cancers worldwide. Six total syntheses and numerous synthetic works have been published since its discovery. We planned a semi-convergent total synthesis of taxol, which could be synthesized from an intermediate in Holton's synthesis. The **A** ring would be installed at a late stage by an intramolecular pinacolic condensation on a diketone. Bicycle **BC** would be formed by a ring-closing metathesis on a diene, which would be prepared by addition of a vinyllithium (**Synthon 2**) to an aldehyde (**Synthon 1**).



In the course of our studies, model BC ring-systems of taxol, which lack the oxygenated substituent at C7 and the alkyne moiety, have been efficiently synthesized. Comparison of ring-closing metatheses with similar substrates was thoroughly studied. We are currently preparing the synthesis of the ABC tricycle of taxol with all the required functionalities.

Keywords: Total synthesis; Taxol; Ring-Closing Metathesis; Diastereoselectivity

Abbreviations

Ac	Acetate
Aq.	Aqueous
Bn	Benzyl
BOM	Benzyloxymethyl
Bu	Butyl
Bz	Benzoyl
cat.	Catalytic
CDI	Carbonyl diimidazole
CM	Cross metathesis
conc.	Concentrated
CPTS	Collidinium *p*-toluenesulfonate
CSA	Camphorsulfonic acid
CSOA	Camphorsulfonyl oxaziridine
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undecene
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DIBALH	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	Dimethyl ether
DMF	*N,N*-Dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
equiv.	Equivalent
Et	Ethyl
h	Hours
Hex	Hexyl
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphorotriamide
IBX	*o*-Iodoxybenzoic acid
Im	Imidazole
i-Pr	Isopropyl
LAH	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
LHMDS	Lithium hexamethyldisilazide
LTMP	lithium tetramethylpiperidide
2,6-lut.	2,6-Lutidine
m-CPBA	*m*-Chloroperbenzoic acid
Me	Methyl
min	Minutes
MOM	Methoxymethyl
MEM	Metoxyethoxymethyl
MS	Molecular sieves
Ms	Methylsulfonyl
N	Normal
NBS	*N*-Bromosuccinimide
NMO	*N*-methylmorpholine oxyde
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
Piv	Pivalate
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid
Pyr	Pyridine
quant.	Quantitative
RCM	Ring-Closing Metathesis
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
ROM	Ring-opening metathesis
[RuIMes]	1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolylidene)(dichlorophenylmethylene)(tricyclohexylphosphine)ruthenium
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyledimethylsilyl
t-Bu	*tert*-Butyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetra-*n*-Propylammonium perruthenate
TPP	Triphenyl phosphite
TPS	2,4,6-triisopropylbenzenesulfonyl
Tris	Triisopropylbenzenesulfonyl
Ts	Tosyl

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CHAPTER I

INTRODUCTION

1. GENERALITES

In the last 30 years, no drug could gain as much public attention and scientific interest as taxol in the world (Figure-1.1). The interest primarily was due to taxol's delicate structure and excellent clinical utilization against ovarian,[1] breast cancers,[2] lately non-small cell lung cancer,[3] and several other cancers. Recently, the possible treatment for diseases such as Alzheimer's disease and tuberculosis has been explored. It is now the largest selling anticancer drug of all time, with sales of over 3 billions USD/yr for all the taxane market.[4]

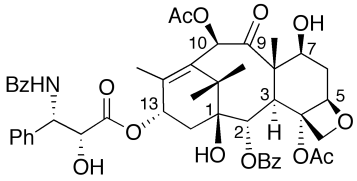


Figure-1.1: Taxol, the structure

1.1 DISCOVERY OF TAXOL

1) HISTORY OF TAXOL'S DEVELOPMENT AS AN ANTICANCER AGENT

Taxol was first discovered for its bioactivity in 1962 by Arthur Barclay, a botanist working for the US Department of Agriculture and the US National Cancer Institute (NCI) (Figure-1.2). He made a collection of the stem and bark of *Taxus brevifolia* Nutt. in Washington State. These plant samples, along with many others, were duly extracted and tested for bioactivity.

[1] McGuire, G. P.; Hoskins, K. J.; Brady, M. F. *Semin. Oncol*. **1996**, *23*, 40-47. McGuire, G. P.; Rowinsky, E. K.; Rosenshein, N. B. *Ann. Intern. Med*. **1989**, *111*, 273-279. Einzig, A. I.; Wiernik, P. H.; Saaloff, J.; Runowicz, C. D.; Goldberg, G. L. *J. Clin. Oncol*. **1992**, *10*, 1748-1753.
[2] Holmes, F. A.; Walters, R. S.; Theriault, R. L. *J. Natl. Cancer Inst*. **1991**, *83*, 1797-1805.
[3] Ettinger, D. S.; Finkelstein D. M.; Sarma, R. P.; Johnson, D. H. *J. Clin. Oncol*. **1995**, *13*, 1430-1435.
[4] Mitchell, S. *Health Business – Analysis,* **2007**, March 27.

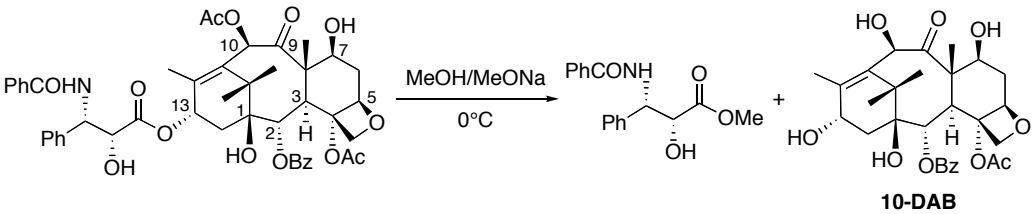
Botanist Arthur Barclay (in hat), records a plant collection in the field, early 1960s.

By Christmas of 1966 Wall was calling for 375 pounds of bark. For every 30 pounds he got, he was producing barely half a gram.

Figure-1.2: Natural collection of taxol

In 1963 the extract was confirmed to be cytotoxic against KB cells. A recollection of the bark was then made in 1965 and assigned to Dr Monroe Wall at Research Triangle Institute (RTI) in North Carolina. In 1966 the activity of the bark extract against mouse leukemia was confirmed in vivo and taxol was isolated in 1967 in 0.01% yield from the bark, since the wood and needles of the tree contained much less taxol.[5]

The structure was elucidated by a combination of X-ray studies on the degradation products methyl β-phenylisoserine ester and 10-deacetyl-baccatin III (Scheme-1.1), commonly known as 10-DAB, and then verified by 1H-NMR analysis of the intact molecule in 1971.[6]



Scheme-1.1: Cleavage of the side chain

The discovery of taxol was not very encouraging: it had only modest activity in vivo against various leukemia's and the Walker 256 carcinosarcoma; it was highly insoluble in water, and it was isolated in only very modest yield from the bark of the slow-growing yew tree.

Additional testing was still carried out in some new bioassays introduced by the NCI in the early 1970s, and these results proved to be crucial: the activity in a B16 mouse melanoma model was particularly important in this respect. Taxol was then selected as a development

[5] *Taxol: Science and Applications.* Suffness, M., Wall, M. E. ed. CRC Press, Inc., Boca Raton, FL, **1995**, p3.
[6] Wani, M. C., Taylor, M. E., Coggon, P., McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

candidate in 1977 following its good activity against the new MX-1 and NX-1 mammary and colon xenografts in nude mice. In 1979, when Susan Horwitz discovered taxol's mechanism of action, the interest in this compound increased significantly. The normal function of a cell requires microtubes and monomeric tubulin in dynamic equilibrium, and taxol was the first compound to promote tubulin assembly, and likely a cytotoxic agent, which could be possibly developed to be an anticancer drug.

Finally taxol completed preclinical formulation and toxicology studies in 1982 and entered Phase I clinical trials in 1984 and Phase II trials in 1985. The most serious side effect observed was hypersensitivity reactions, which were believed to be due to the Cremophor EL, a castor oil additive used to dissolve taxol. These reactions were unpredictable and led to two deaths. Fortunately a 24h infusion protocol was developed by Wiernik et al. in 1987 to avoid these hypersensitivity reactions before the clinical trials were halted.[7] These trials gave the first clear evidence of activity with responses in melanoma reported in 1987, in ovarian cancer in 1989[1] and in breast cancer[2] in 1991.

The large progress in clinic encouraged scientists to search for more efficient accesses to taxol. The first success came in France, where Pierre Potier looked at a semi-synthesis.

In the late 1960s, Pierre Potier, who worked as a CNRS (*Fr.* Centre National de la Recherche Scientifique, *Eng.* National Center for Scientific Research) director of research at the ICSN (*Fr.* Institut de Chimie des Substances Naturelles, *Eng.* Institute for Natural Product Chemistry) in the Paris suburb of Gif-sur-Yvette (Figure-1.3), also started looking for compounds that might have antitumor properties.

[7] Wiernik, P.H.; Schwartz, E. L.; Einzig, A. *J. Clin. Oncol.* **1987**, *8*, 1232-1239.

Pierre Potier (1934-2006), pharmacist and chemist, President of *Fondation internationale de la Maison de la chimie*, Fellow of *Académie des sciences*, *Académie des technologies* and *Académie de pharmacie*.[8]

Gif-sur-Yvette (Town view), where is situated ICSN laboratory, as well as other laboratories of CNRS, is a famous scientific site in France.

Figure-1.3: Pierre Potier and ICSN

One of Potier's colleagues, Dominique Pantaloni, a biologist in the CNRS Institute of Enzymology also on the Gif campus, was working on the biological structure of the protein tubulin, which is important in the structure of cells. He drew to Potier's attention that tubulin was affected by mescaline (alkaloid obtained from magic mushrooms), which is chemically close to the vinca alkaloids that Potier was looking at more closely at the time for anticancer drugs' research. By 1978, a test using tubulin was then developed in France, which can measure the inhibition of its polymerization by various chemicals, and gave a more direct detection of cell division and hence of tumor growth than conventional screens using animal cells.[9] As a result with the tubulin test, Navelbine™ (vinorelbine) was patented as a semi-synthesized vinca alkaloid by CNRS with Pierre Potier and his colleagues, and eventually marketed in 1989.

After Horwitz's publication, Potier and his group began to collect *Taxus baccata*, the European yew, that was growing everywhere in CNRS Gif campus, as raw material. They thought they might find something else in high concentration, which could be a starting material for the synthesis of taxol, and also to make other compounds with a similar structure to taxol with anticancer properties, as they did for Navelbine™ from vinca alkaloids.[10]

Extracts from the needles of the ubiquitous *T. baccata*, or European yew, had been found to have some activity in inhibiting depolymerization in the tubulin test. The tubulin test was then

[8] Chast, F. *Nature* **2006**, *440*, 291.
[9] Zavala, F.; Guénard, D.; Potier P. *Experientia* **1978**, *34*, 1497-1499.
[10] Walsh, V.; Le Roux, M. *Research Policy* **2004**, *33*, 1307-1327.

used to guide fractionation into constituent parts. The major constituent of the yew needles was 10-deacetylbaccatin III, which was easy to isolate.[11] The European yew is loaded with this compound, which contains the complex core of Taxol minus a simple side chain. Most importantly, 10-DAB comes from the needles, a renewable resource. After several years of trials, Potier and his colleagues succeeded in attaching to 10-DAB a synthetic side-chain to achieve a semi-synthesis of taxol. This accomplishment led to the development of the first semi-synthesis of taxol and also Taxotere™.[12]

With the clinical trials going well, the NCI began to look for a pharmaceutical company willing to take a chance on turning taxol into a marketable drug. In August 1989 the institute advertised that it had a Cooperative Research and Development Agreement (CRADA) to issue to the company with the best proposal. Later in the year, the grant went to Bristol-Myers (soon merged with Squibb). Bristol-Myers Squibb then worked out with Robert H. Holton to use his semi-synthetic process for the production of taxol. In December 1992, thirty years after USDA botanists first sampled *Taxus brevifolia* in a Washington State forest, and more than twenty years after Wall and Wani reported the isolation and structure of Taxol, the Food and Drug Administration granted approval for taxol's use against refractory ovarian cancer. It has since been approved for use in the treatment of breast cancer and AIDS-related Kaposi's sarcoma.

2) THE SOURCE OF TAXOL

As described above, *Taxus Brevifiolia* was first found in USA and is just only one of the several yew species that occur around the world, primarily in temperate climates. Other known yew species include *Taxus floridana* (USA), *T. baccata* (Europe), *T. Canadensis* (Canada), *T. media* (Canadian modified), *T. globosa* (Mexico), *T. wallichiana* (Himalaya region), *T. nucifera* (Japan), *T. cuspidate* (Russia, North China, Japan, Korea), *T. yunnanensis* (South China, Burma), *T. chinensis* (China), and *Austrotaxus spicata* (Australia).[13,14]

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[11] Chauviere, G.; Guenard, D.; Picot, G.; Senilh, V.; Potier. P. *C. R. Acad. Sc. Paris, Serie II* **1981**, *293*, 501–503.
[12] Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917-5919.
[13] Pandey, R. C. *Med. Res. Rev.* **1999**, *18*, 333-346.
[14] Parmar, V. S.; Jha, A.; Bisht, K. S.; Taneja, P.; Singh, S. K.; Kumar, A.; Poonam, no first name; Jain, R.; Olsen, C. E. *Phytochemistry* **1999**, *50*, 1267-1304.

In these species the taxol percentage is sometimes different. *T. yunnanensis* contains the most taxol in the bark of a matured tree of all the species but a accompanying analog cephalomannine makes the industrial separation difficult. The most practical is *T. media*, which was grafted by Canadian botanists; taxol can be obtained with a yield of 0.02-0.04% from branches and leaves of 3-5 year-old trees. It is now largely commercially planted worldwide.

Another interesting story is about the common yew *T. baccata* in Europe, which is quite toxic, and has been responsible for many stock poisonings and human poisonings, with records going back at least to the epoch of Julius Caesar. Now this toxicity was discovered and proved to due to the significant amounts of the toxic alkaloids taxines A and B contained in this yew (Figure-1.4).

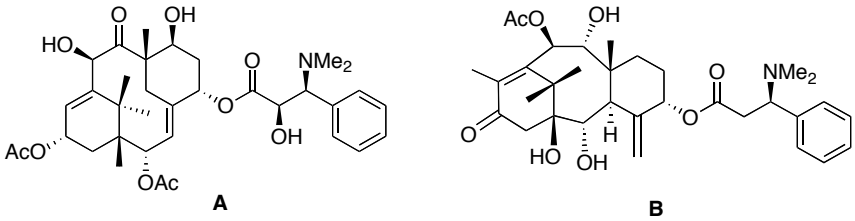


Figure-1.4: Taxines A, B

So Itokawa made a reasonable hypothesis:[15] if Wall and Wani used *T. baccata* in their investigations, it is likely that they would either have found the extract to be toxic and not pursued fractionation, or would have isolated the taxines rather than taxol, given the bioassays that they were using at that time. In either case they would not have good results. US Department of Agriculture had made a very lucky decision to collect *Taxus Brevifiolia* species for their screening program, which contains little amounts of the taxines, so that the work was successful and taxol was obtained.

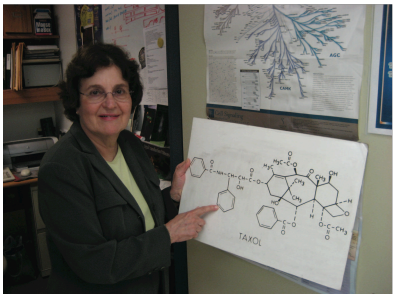
1.2 BIOACTIVITY

1) THE INTERACTION OF TAXOL WITH TUBULIN

In August 1978 Monroe Wall received a letter from John Douros, who worked for the CCNSC: "Dear Monroe: Can you help this poor girl?" …

[15] *Taxus: The Genus Taxus.* Itokawa, H., Lee, K-H. (Eds.) Taylor & Francis, London and New York, **2003**, 1-474.

That was a letter from Susan Horwitz for asking some radio labelled Taxol® for experiments on its mechanism of action. At that moment, Horwitz, a young molecular pharmacologist in the Albert Einstein College of Medicine (Figure-1.5), had been hearing reports about taxol. She had managed to obtain a few more milligrams of the substance, which she used to kill cancer cells growing in a culture.[16]



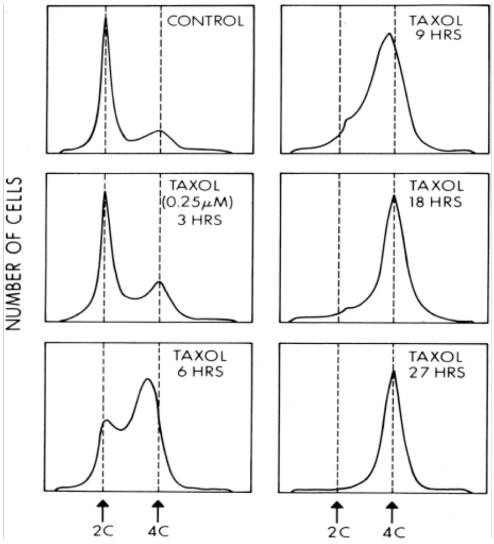
Pr. Susan B. Horwitz, Fellow of *National Academy of Sciences*, Albert Einstein College of Medicine.

Figure-1.5: Susan Horwitz and taxol

The decision of Horwitz to study the action of taxol was based on the unique chemical structure of the taxane ring system, and the biological properties of none of the isolated taxoid compounds had been studied. She had thought that taxol might have a unique cytotoxic mechanism of action, since it had a novel structure at the time.[17]

The first experiments performed in 1977 indicated that taxol was worth further exploration: low concentrations of taxol in the nanomolar range inhibited the replication of HeLa cells. On examination of the effect of taxol on the progression of HeLa cells through the cell cycle, it proved to be antimitotic by blocking cells in metaphase (Figure-1.6).[18] After 18 h in the presence of 250nM of taxol, all the cells had essentially replicated their DNA, had a tetraploid DNA content, and were blocked in metaphase.

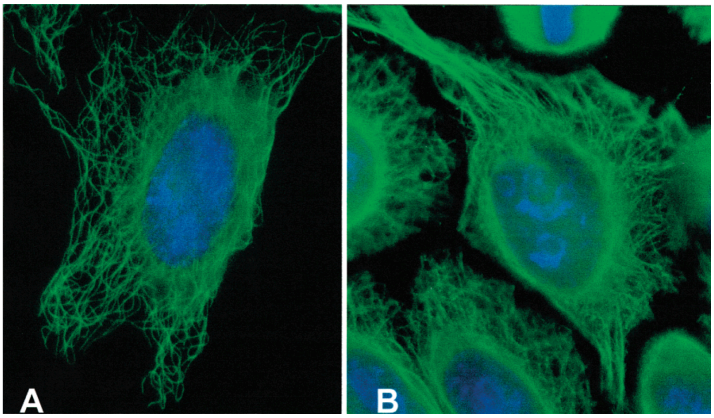
[16] *Taxol® becomes a drug.* National Historic Chemical Landmark, American Chemical Society, http://acswebcontent.acs.org/landmarks/landmarks/taxol/drug.html (accessed July 12 2008)
[17] Horwitz, S. B. *J. Nat. Prod*. **2004**, *67*, 136-138.
[18] Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A*. **1980**, *77*, 1561-1565.



Flow cytometry of the DNA content of HeLa cell after incubation with taxol. The arrows indicate the modal positions of cells having diploid (2C) and tetraploid (4C) DNA contents did not vary significantly during the time course of the experiment.

Figure-1.6: Taxol blocks cells in mitosis

Although a number of anticancer drugs such as colchicine and Vinca alkaloids blocked cells in the mitotic phase of the cell cycle, only cells treated with taxol reorganized their microtubules so that distinct bundles of microtubules could be seen in cells (Figure-1.7). The formation of microtubule bundles, which are highly stable, are diagnostic of taxol treatment and a hallmark of taxol binding to microtubules in cells.



Indirect immunofluorescence of HeLa cells, using a monoclonal antibody against R-tubulin (green) and DAPI staining (blue) for DNA in the nucleus. (A) Control. (B) 10 μM taxol for 30 min. Courtesy of Dr. Laura Klein, Albert Einstein College of Medicine.

Figure-1.7: Taxol caused formation of microtubule bundles in HeLa cells

As shown in Figure-1.8, tubulin is a heteodimer formed by a α-subunit and a β-subunit that share 40% sequence identity but almost identical three-dimensional structure.[19] Microtubules, which result from the head-to-tail longitudinal self-assembly of tubulin dimers to form protofilaments, interact laterally to constitute the wall of microtubules. The process is driven by GTP binding and hydrolysis and the exchangeable E-site of β-tubulin. GTP binds also to α-tubulin but at the no-exchangeable N-site. Microtubules exhibit a highly dynamic behavior

[19] Nogales, E.; Wolf, S. G.; Downing, K. H. *Nature* **1998**, *391*, 199 –203.

that is essential to carrying out their functions, and they undergo rapid and stochastic transitions from growing to shrinking phases resulting in a dynamic exchange of tubulin dimers at microtubules ends.[20]

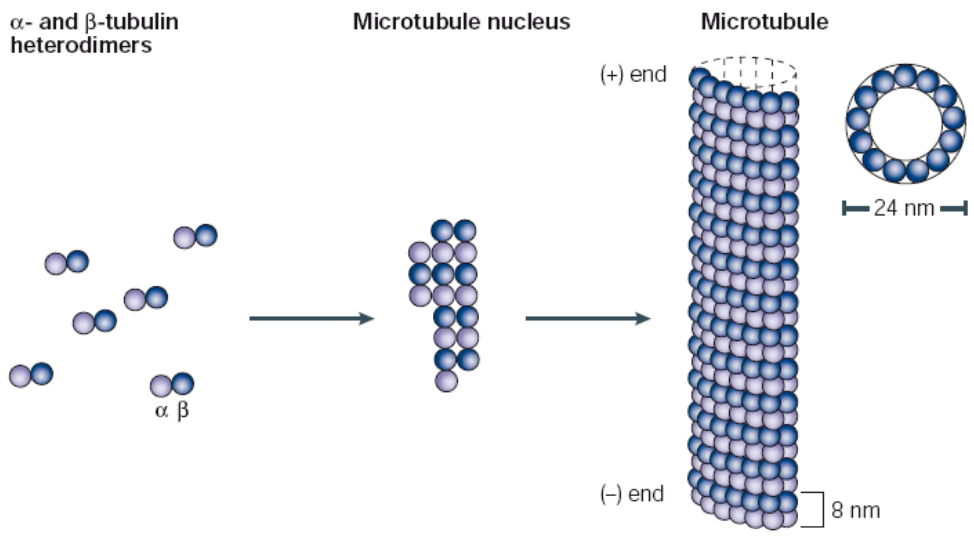
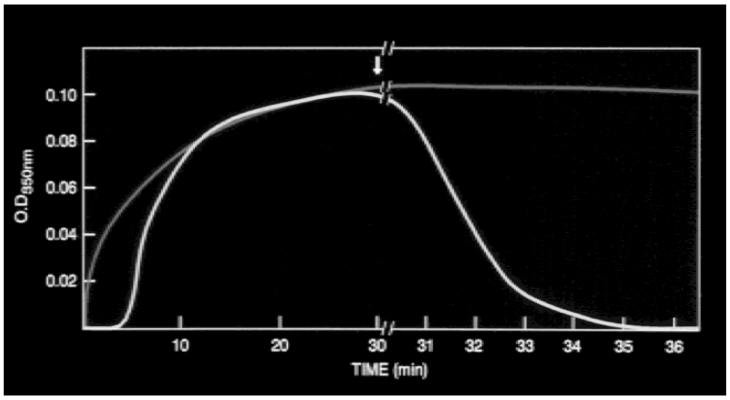


Figure-1.8: Formation of microtubule

Microtubules composed of α- and β-tubulin dimers were then studied in a cell-free system. Tubulin was purified from calf brain, a rich source of the protein, and its assembly into microtubules, which occurred at 37˚C in the presence of GTP, was monitored by an increase in absorption at 350 nm. When this experiment was performed in the presence of taxol, the 3-4 min lag period presented in the absence of drug was eliminated.[21] As shown in Figure-1.9, it's clear that taxol enhanced the initiation phase of microtubule polymerization. Moreover, taxol was able to polymerize tubulin in the absence of GTP and at cold temperatures.

Most important was that the microtubules formed in the presence of taxol were stable to depolymerisation at 4˚C and by treatment with Ca^{2+}, conditions that normally depolymerize microtubules (Figure-1.9). The maximum effect of taxol on tubulin stabilization was observed when the taxol concentration was stoichiometric to the tubulin dimer concentration.[22]

[20] Desai, A.; Mitchison, T. J. *Annu. Rev. Cell Dev. Biol.* **1997**, *13*, 83-117.
[21] Schiff, P. B.; Horwitz, S. B. *Nature* **1979**, *277*, 665-667.
[22] Parness, J.; Horwitz, S. B. *J. Cell Biol.* **1981**, *91*, 479-487.



Taxol enhances in vitro tubulin polymerization and microtubule stabilization. No additions (white line); 10 μM taxol (gray line). $CaCl_2$ is added at a concentration of 4 mM at 30 min (↓).

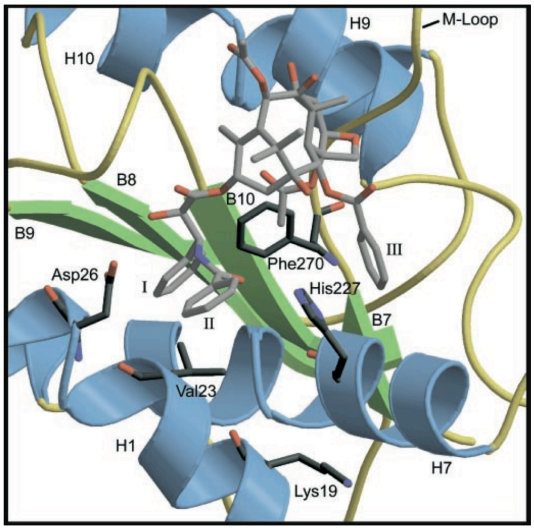
Figure-1.9: tubulin polymerization and microtubule stabilization by taxol

This was the first biological discovery about taxol; finally Horwitz had revealed taxol's function, which turned out to be a mechanism completely new to scientists, because before taxol, previous compounds killed cancer cells by interrupting their division by inhibiting the polymerization of tubulin to form microtubules. But taxol worked differently: instead of preventing the formation of microtubules, it stimulated their development. Cells treated with taxol begin churning out too many microtubules so that they are unable to coordinate cell division. As a result, cells die of continued attempts to replicate their DNA in the absence of the ability to divide.[23] Armed with this information, Horwitz was able to consider taxol as a candidate for further development because of its unique structure and mechanism of action. Then taxol's success in causing regression in the mammary tumor xenograft showed that taxol was a potential "miracle drug".

Today we know that taxol binds to β-tubulin in the microtubule and its mechanism of action in cells is dependent on the concentration. At low taxol concentrations (<10 nM), where only a fraction of the total taxol-binding sites are occupied, there is no obvious effect on polymer mass and the principal effect of taxol is suppression of microtubule dynamics.[24] At higher taxol concentrations, it alters the equilibrium between soluble tubulin dimers and microtubules, resulting in an increase in polymer mass. Recent studies stressed the importance of the dynamics for tubulin assembly. It is even proposed that taxol exerts its effect through affecting the dynamic of microtubules rather than its mass.[25]

[23] Xiao, H.; Verdier-Pinard, P.; Fernandez-Fuentes, N.; Burd, B.; Angeletti, R.; Fiser, A.; Horwitz, S. B.; Orr, G. A. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 10166-10173.
[24] Derry, W. B.; Wilson, L.; Jordan, M. A. *Biochemistry* **1995**, *34*, 2203-2211.
[25] Jordan, M. A.; Wilson, L. *Curr. Opin. Cell Biol.* **1998**, *10*, 123-130.

A successful mutagenesis was used to engineer taxol-binding activity in *Saccharomyces cerevisiae* tubulin (Figure-1.10).[26] Several structurally diverse antimitotic compounds including the epothilones, competed with taxol for binding to mammalian microtubules, suggesting that taxol and these compounds share an overlapping binding site. However, taxol has no effect on tubulin or microtubules from *S. cerevisiae*, whereas epothilone does. After considering data on taxol binding to mammalian tubulin and recent modeling studies, the researchers hypothesized that differences in five key amino acids are responsible for the lack of taxol binding to yeast tubulin. After changing these amino acids to those found in mammalian brain tubulin, taxol-related activity was observed in yeast tubulin comparable to that in mammalian tubulin.



Taxol binding site on mammalian Lys-19, Val-23, Asp-26, His-227, and Phe-270 are indicated and are shown in dark gray. Labels on Taxol (gray) denote the following: I, C3' phenyl ring; II, C3' benzamido phenyl ring; and III, C2 benzoyl phenyl ring. Specific regions of β-tubulin that form the binding pocket are labeled, including α-helices H1, H7, H9, and H10, the β-strands B7–B10, and the B7–H9 M-loop. The structure was drawn with the modeling programs MOLSCRIPT and RASTER3D by using the coordinates (PDB ID code 1JFF) determined by Snyder et al.[27] for T-Taxol bound to the refined model of bovine brain tubulin.

Figure-1.10: Taxol binding site

Taxol-binding site in β-tubulin was also studied in vivo:[28] multi-copy simultaneous search (MCSS) was used to analyze the maps of four kinds of functional groups (the hydrophobic, hydrophilic, positive charge and negative charge functionalities) in the taxol-binding site of β-tubulin. Based on the result, the hydrophobic groups were distributed above Phe-270, and then among Asp-26, Glu-27, Val-23 and Pro-358. The hydrophilic functionalities scatter around the hydroxyl of Glu-22, Asp-224 and Asp-26 and beneath the guanidyls of Arg-276 and Arg-282. The positive charge functionalities were around the carboxyl of Asp-224, Asp-26 and Glu-22, and the hydroxyl of Gln-278. The negative charge ones were beneath the

[26] Gupta Jr, M. L.; Bode, C. L.; Georg, G. I.; Himes, R. H. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 6394-6397.
[27] Snyder, J. P.; Nettles, J. H.; Cornett, B.; Downing, K. H.; Nogales, E. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5312–5316.
[28] Li, Y.; Zhou, Y.; Zhu, J.; Zheng, C.; Zhang, M.; Sheng, C.; Chen, J.; Lu, J. *Chem. J. Chin. Univ.* **2006**, *27*, 2084-2087.

guanidyl of Arg-276 and Arg-282, and between the side chains of His-22 and Leu-228 (Figure-1.10).

While many studies concentrated on β-tubulin, the role of α-tubulin in the binding process was barely known. In a recent report, the authors found that assembly of different α-tubulin isoforms differs greatly in the presence of taxol, and thus proposed at least partial involvement of α-tubulin in the binding process.[29]

2) TAXOL'S STRUCTURE-ACTIVITY RELATIONSHIP

The antitumor activity of taxol originates from its binding to tubulin, though taxol also interacts with Bcl-2 protein and induces hyperphosphorylation of the latter.[30] It was recently shown that this process is likely to result from complex formation between taxol and tubulin.[31] More directly than the research methods described in the previous chapter, the steric structure of the binding site was determined by electronic crystallography[32] and photoaffinity labeling:[33] a deep hydrophobic pocket near the protein surface. However, the four flexible rotating-free chains attaching to the taxane skeleton could eventually give numerous conformers. Knowledge of the binding conformations could help to find the pharmacophore of taxol and lead to the design of New Chemical Entities (NCE). The first crystallographic study of α,β-tubulin heterodimer indicated that taxol binds to the biotarget in the "hydrophobic collapse"[34] (polar) conformation (Figure-1.11).[19]

[29] Banerjee, A.; Kasmala, L. T. *Biochem. Biophys. Res. Commun*. **1998**, *245*, 349-351.
[30] Rodi, D. J.; Janes, R. W.; Sanganee, H. J.; Holton, R. A.; Wallace, B. A.; Makowski, L. *J. Mol. Biol*. **1999**, *285*, 197-203.
[31] Blagosklonny, M. V.; Giannakakou, P.; El-Deiry, W. S.; Kingston, D. G. I.; Higgs, P. I.; Neckers, L.; Fojo, T. *Cancer Res*. **1997**, *37*, 130-135.
[32] Lowe, J.; Li, H.; Downing, K. H.; Nogales, E. *J. Mol. Biol*. **2001**, *313*, 1045-1057.
[33] Rao, S.; He, L.; Chakravarty, S.; Ojima, I.; Orr, G. A.; Horwitz, S. B. *J. Biol. Chem*. **1999**, *274*, 37990-37994.
[34] Hydrophobic collapse is a hypothesized event that occurs during the folding process of globular proteins, suggested on the basis of the observation that proteins' native states often contain a hydrophobic core of non-polar amino acid side chains (interspersed with charged side chains that are neutralized by salt bridges) in the protein's interior, leaving most of the polar or charged residues on the solvent-exposed protein surface. The energetic stabilization conferred on the protein by the sequestration of the hydrophobic side chains from the surrounding water is thought to stabilize folding intermediates.

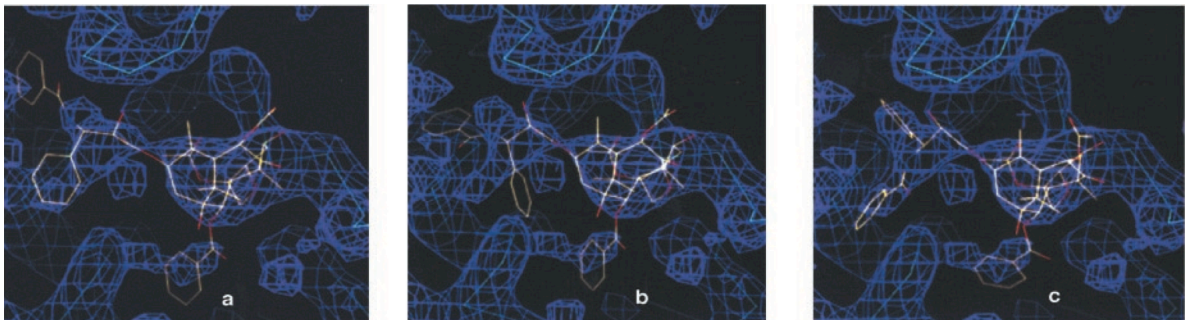


Figure-1.11: Three taxol conformers docked into the ligand electron crystallographic density of a and b, were derived from taxol analogs determined by single-crystal x-ray crystallography. The best-fit conformer, shown in c, was obtained by NMR deconvolution.[27]

Moreover, medicinal chemists used the ability of a taxol analog to promote polymerization of tubulin with formation of microtubules for the research of the pharmacophore of taxol. Sometimes the cytotoxicity also served as screening tool.[35] The first summary was concluded as shown in Figure-1.12: red highlighted parts are necessary for the biological activity, blue highlighted are changeable.[36] Similar structure-activity relationship was also detailed years later by Kingston.[37]

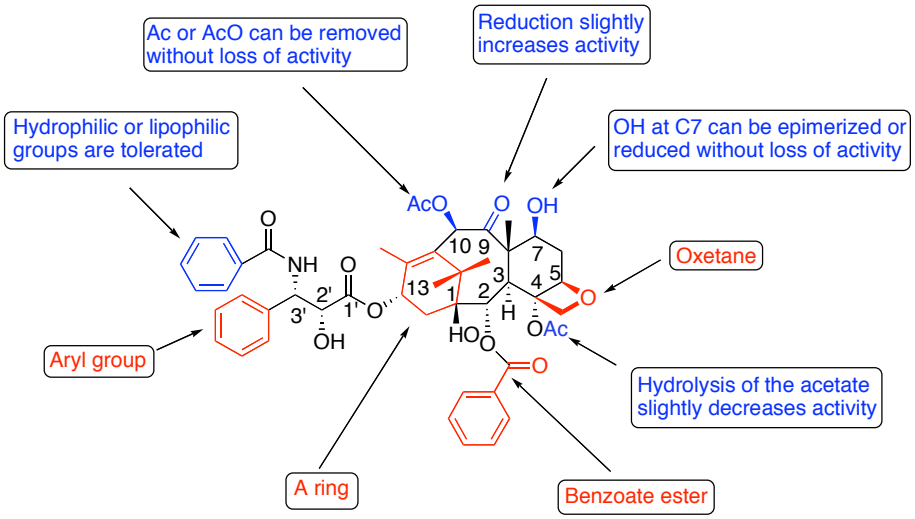


Figure-1.12: Taxol structure-activity relationship

1.3 DRUG DESIGN

[35] Cytotoxicity depends not only on the affinity for tubulin, but also on the ability to penetrate through cell membrane, resistance to metabolic enzymes, and some other factors.
[36] Guénard, D.; Guéritte-Vogelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160-167.
[37] Kingston, D. G. I. *Phytochemistry* **2007**, *68*, 1844-1854.

After Horwitz reported the encouraging news about taxol in 1979, then came a disastrous discovery: taxol is virtually insoluble in water. No matter how good taxol was shown to be, if it could not be added to a medium so that it could be administered intravenously, it was worthless. After a year of reseach, the NCI drug formulation team found that taxol dissolved in a special elixir made of castor oil and marketed as Cremophor EL. This paved the way for taxol to move into clinical trials on humans.[38]

1) TAXOL METABOLISM

Pharmacogenetics, including pharmacokinetics and pharmacodynamics, are very important part for drug utilization; research of ADME (Absorption, Distribution, Metabolism, Excretion) is also indispensable in drug discovery. Clinical observation shows taxol is primarily metabolized through oxidation processes and biliary excretion; only 5-10% of taxol is renally eliminated.[39] Hepatic metabolism was first studied in rats then in humans; all metabolites were hydroxylated though obvious significant differences exist in the site of hydroxylation and metabolite proportions found in bile. The predominant major human metabolite discovered was 6α-hydroxy taxol;[40] two other major metabolites are 3'-*p*-hydroxy taxol and 6α, 3'-*p*-dihydroxy taxol.

In fact, 6α-hydroxy taxol showed no activity against ovarian and colorectal cancer cell line, but is approximately 30 times less cytotoxic than taxol, thus, hydroxylation at C-6α position is likely a detoxification reaction.[40] However, activity of 3'-*p*-hydroxy taxol was reduced but not absent in ovarian cancer cell lines, and all three metabolites retained bone marrow toxicity when tested on human bone marrow cells.[41] Subsequently, cytochrome P450 2C8, 3A4, 3A5 and P-glycoprotein were proven to be responsible for all three metabolites.[42] Polymorphisms in the enzyme system responsible for taxol metabolism have also been found. More research results are expected to individualize clinical utilization of taxol and contribute to the discovery of taxol analogues as new drugs.

2) TAXOL'S ANALOGUES AS PRODRUG

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[38] *Biopharmaceutics of paclitaxel (taxol): formulation, activity, and pharmacokinetics.* Suffness, M. (Ed.), Taxol®: Science and Application. CRC press, NY, **1995.**
[39] Baker, S. D.; Verweij, J.; Rowinsky, E. K. *J. Natl. Cancer Inst*. **2002**, *94*, 1883-1888.
[40] Harris, J. W.; Katki, A.; Anderson, L. W.; Chmurny, G. N.; Paukstelis, J. V.; Collins, J. M. *J. Med. Chem*. **1994**, *37*, 706-709.
[41] Sparreboom, A.; Huizing, M. T.; Boesen, J. J.; Nooijen, W. J.; van Tellingen, O.; Beijen, J. H. *Cancer Chemother. Pharmacol*. **1995**, *36*, 299-304.
[42] Spratlin, J.; Sawyer, M. B. *Crit. Rev. Oncol. Hematol*. **2007**, *61*, 222-229.

As described in precedent paragraphs, Cremophor EL resolved the problem of solubility for inserted utilization, but this additive also caused a lot of side effects. Research of taxoid prodrugs were first envisioned to bypass the problem of systemic toxicity, low solubility and inacitivity against certain drug resistant tumors, and also to improve oral bioavailability, and tumor specific delivery.

A majority of the taxoid prodrugs to improve oral bioavailability and solubility were synthesized by linking hydrophilic groups to the C2'-OH position of taxol or taxotere (Figure-1.13); C10-OH (OAc) and C7-OH modification have also been reported. Recently, numerous drug delivery systems, such as polymeric micelles, colloidal nanoparticles, dendrimers, aerosols, and liposomes, have been sought to enhance the circulation time of the drug in plasma. These agents would protect the drug from plasma-induced transformations and also transport an adequate amout of drug to the appropriate site.[43] Moreover, estradiol as nuclear protein of estrogen receptor (ERs), antibody, enzyme, folic acid, peptide, gold nanoparticle, hyaluronic acid and fatty acid were grafted to taxol for better tumor specific delivery.[44]

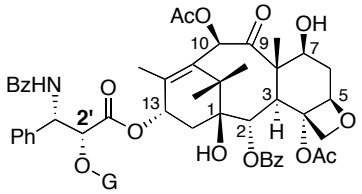


Figure-1.13: Newest semisynthetic taxoids at C2'-OH

A significant successful application was Abraxane® (taxol protein-bound particles) approved by FDA in 2005, which is a breast cancer treatment drug that does not contain chemical solvents, and could be administered in just 30 minutes. As taxol is bonded to albumin as a delivery vehicle in this formulation, Abraxane® could by used for 50% more quantities than taxol in chemotherapy in clinic. Moreover, the most adverse reactions caused by Cremophor EL as solvent were not observed, and the allergy test was not necessary.[45]

1.4 POLITICS AND ECONOMY

1) TAXOL'S NAME

[43] Medina, O. P.; Zhu, Y.; Kairemo, K. *Curr. Pharma. Design* **2004**, *10*, 2981-2989.
[44] Ganesh, T. *Bioorg. Med. Chem*. **2007**, *15*, 3597-3623.
[45] Kingston, D. G. I.; Newman, D. J. *Curr. Opin. Drug Discov. Devel*. **2007**, *10*, 130-144. For more information about Abraxane®, see: http://www.fda.gov/cder/foi/label/2005/021660lbl.pdf (accessed July 15 2008)

Because of the publicity surrounding the taxol supply crisis and its initial perception as a "miracle drug", the name taxol became well recognized by the general public, and thus became a valuable commercial property. It was generally assumed that Wall and Wani were the first to use this name, but they did not take out a patent on taxol, nor did they trademark its name. Indeed it is doubtful whether taxol could have been patented as a natural product in the late 1960s to early 1970s in USA, although the process for making it could have been. Changes since 1980s in intellectual property legislation, and in its interpretation (particularly concerning the distinction between the result of "nature" rather than "human labor and ingenuity") have been discussed earlier. It is impossible to say whether taxol might have been patented had it been discovered more recently, or had these changes evolved earlier, since such decision depend on the goals and equally strategies of inventors as well as on what is legally possible or culturally normal. It is impossible to know whether the taxol story might have evolved differently, had taxol been patented.

By September 1988, the taxol-working group learned that USD 2 millions was needed to complete the extraction and purification of taxol from collections of bark already made or scheduled, while only one tenth of this amount was available. The NCI had determined on getting rid of the problems associated with taxol by handing it over to a pharmaceutical company using a Co-operative Research and Development Agreement (CRADA). Introduced under the terms of the Federal Transfer of Technology Act (1986), the purpose of the CRADA is to encourage the transfer of commercially exploitable knowledge produced by federal agencies or government funded researchers to (US) industry. One of its explicit purposes is to discourage the exploitation by foreigners of research funded by US taxpayers (Eisenberg, 1996). On August 1, 1989, a CRADA partner to commercialize taxol was sought by advertisement (Federal Register, 1989). Only four companies applied: Bristol-Myers Squibb, Rhône-Poulenc (merged first with Hoechst AG to form Aventis in 1999 and then with Sanofi Synthélabo to compose Sanofi-Aventis in 2004), and two small biotech firms.

In 1991 the NCI, the USDA and the Department of the Interior signed CRADAs with Bristol-Myers Squibb. It turned out that the name "Taxol" had been trademarked by Continental Laboratories for a laxative product. In 1994 Bristol-Myers Squibb acquired the rights to this trademark, and then succeeded in applying it to their formulation of taxol, so the official chemical name for the compound previously known as taxol is now paclitaxel, and the name

Taxol™ applies to the BMS formulation of this chemical compound,[46] even though Monroe Wall had chosen the name back in 1967, and it was first published in 1969. The company pursued an aggressive policy of threatening legal action against anyone who used the name taxol thereafter to mean anything other than Bristol-Myers Squibb's branded product: from a firm making generic taxol for sale outside the USA[47] to the editor of *Nature* who criticized the company privatization of a name that had been used by the research community for over 20 years.[48] The firm was able to enlist the supports of state agencies to threaten US trade sanctions against any country that marketed the generic product in the home market.[49]

This appropriation of a common name as a trademark has been deplored but has not been reversed. Nonetheless, chemists persist in using the historical name for the compound.

2) TAXOL AND TAXOTÈRE

As Wall and Wani's work had already indicated both the ring and the side chain were necessary for anticancer activity, and this was verified with the tubulin test. Pierre Potier found Andrew Greene to participate in the project of making the side chain and attaching it to 10-DAB once he first isolated it. A US patent filed in 1987 (Colin et al., 1989a, 1989b) and the route was published in 1988.[12] At the same time they tested all the intermediate products on the way to taxol. Two steps before they reached taxol, they found taxotère, a product with twice the activity of taxol in the tubulin test (Figure-1.14). A US patent was filed for taxotère on the same day as the one for synthesis of taxol; clinical trials began in 1990 and Rhône-Poulenc Company received marketing approval in 1996. Finally taxol (paclitaxel, Taxol™) commercialized by Bristol-Myers Squibb using Holton's semi-synthesis and analog taxotère (docetaxel, Taxotere™, **4**) developed by Rhône-Poulenc, are now constantly used for the treatment of ovarian cancer,[1] breast cancer[2] and non-small cell lung cancer.[3]

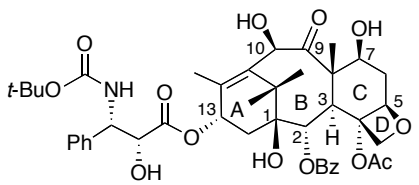


Figure-1.14: Taxotere™

[46] Anonymous, *Nature* **1995**, *373*, 370-371.
[47] Bristol-Myers Squibb (plaintiff) and Corporation Biolyse Pharmacopée International (defendant), Federal Court of Canada, Trial Division, T-946-94, June 29, 1995.
[48] Chesnoff, S. *Nature* **1995**, *374*, 208.
[49] Ralph Nader and James Love to President Bill Clinton, February 4, 1997. http://www.cptech.org/pharm/registration.html (accessed December 11, 2000)

Taxol™ had been the first anticancer drug to reach sales of over USD 1 billion, and the best-selling anticancer drug ever made with its sales peaked at USD 1.6 billion in late 2000. Taxotère™ sales reached USD 1.19 billion in 2002 and are still increasing; it is expected to reach USD 1.69 billion in 2010 with new indications.[4]

However, the ICSN team became convinced that several of the steps involved in the semi-synthesis by Bristol-Myers Squibb came from their own work and therefore infringed the patents Rhône-Poulenc (now Sanofi-Aventis) that had taken out in their names. A court case between BMS and SA ensured, as part of which many of the ICSN achievements have been taken into the possession of the American court.[10]

As also described at the beginning of this chapter, Pierre Potier and his group had played an important role in the development of taxol, but the assignment of credit for taxol research has not been short on controversy. Potier and colleagues wrote to *Chem. Eng. News* that a cover story[50] article on getting taxol to the market ostensibly forgot to give proper credit to the French group for their groundbreaking effort: "*Unfortunately, the impression given to the readers that all was achieved by americans is quite misleading*."[51]

Similarly, the chronology of the first total synthesis of taxol is often reported in a misleading manner. Robert A. Holton and Kyriacos C. Nicolaou[52] both declared they are the first one who accomplished the total synthesis of taxol. Eventually, Holton's paper was received by the *JACS* editorial office on December 12, 1993, and published in issue #4 of the journal on February 23, 1994; Nicolaou's paper was received in *Nature* on January 24, 1994, and published in the February 17, 1994 issue. The pursuit of recognition as well as the assignment of credit is often subject to behind-the-scenes events prevalent in today's science.[51]

3) CRISIS IN THE FOREST: TAXOL PRODUCTION

In July 1977 Matthew Suffness of the NCI placed an order with the USDA for 7,000 pounds of bark, which meant felling about 1,500 trees. Such a large order attracted the attention of environmentalists who began to wonder about the government's sudden interest in the Pacific yew, long considered a "trash tree." To environmentalists, the tree scattered in patches hidden within millions of acres, had a place in the virginal, old-growth forests of the Pacific

[50] Morrissey, S. R. *Chem. Eng. News* **2003**, *81*, 17–20.
[51] *The way of synthesis.* Hudliky, T.; Reed, J. W. (Eds.) WILEY-VCH Verlag GmbH&Co. KGaA, Weinheim, **2007**.
[52] The two syntheses are described in the next chapter.

Northwest. Environmentalists feared a massive attack on the Pacific yew would spell ecological disaster for the region. In the next decade this fear became enmeshed in the debate over the northern spotted owl, which lived in the forests of the Pacific Northwest and which the federal government eventually declared threatened.

Taxol progressed fairly smoothly through clinical Phase I and Phase II trials, once patients were premedicated to suppress severe allergic reactions to Cremophor EL. In fact, the results of Phase II trials against refractory ovarian cancer showed a previously unheard of response rate of thirty percent. The clamor about taxol intensified, forcing NCI to do the math. If taxol were made available to all victims of ovarian cancer, the institute would have to produce 240 pounds of the drug. That would mean killing 360,000 Pacific yews. It did not take a mathematical prodigy to understand that this was an equation without a future.

With the increasing utilization of taxol for the treatment of additional cancer types and other human diseases, for application much easier in the course of intervention, for combination therapies with other antineoplastic agents, and as the platform for the development of the next generation of more efficacious drugs and pro-drugs, the market for taxol and its congeners is expected to expand further. Drug sourcing and patient treatment costs will clearly remain important issues.

In the next chapter, taxol production as well as biological and chemical syntheses will be described.

2. TAXOL PRODUCTION METHODS

2.1 BIOLOGICAL METHODS AND BIOSYNTHESIS

1) CELL CULTURE

Taxus cell culture has been considered as a promising tool to produce taxol and avoid tissue collection. Studies to optimize the production rate show an enhanced content of taxol by differently treated *Taxus* cell cultures compared with control (Table-1.1). Taxol concentration in the plant cells was discovered to reach approximately 0.5% of dry weight by adding methyl jasmonate, because methyl jasmonate induces the upregulation of secondary metabolic genes specifically involved in stress, wounding and pathogen ingress.[53] The use of a mechanical stimulus, ultrasound, and a putative chemical elicitor, methyl jasmonate, combined with in situ solvent extraction (two-phase culture) was proven to enhance taxol production, and it was found that the enzyme activity of secondary metabolic pathways was stimulated, which was partially responsible for enhanced taxol production.[54]

Table-1.1 Extracellular taxol production rates by cell cultivation described in the literature[55]

Cell line	Production rate (mg l^{-1} day^{-1})	Reference
	In flasks	
T. baccata	1.02	Khosroushahi et al. 2006
T. canadensis(C93AD)	1.68	Kim et al. 2006
T. chinensis	2.24	Kim et al. 2001
T. chinensis	3.27	Choi et al. 2000
T. chinensis	3.64	Choi et al. 2000
T. mairei	4.76	Mulabagal and Tsay 2004
T. cuspidata	5.32	Nguyen et al. 2001
T. media	7.86	Yukimune et al. 1996
T. canadensis	9.75	Ketchum et al. 1999
	In bioreactors	
T. cuspidata	0.11	Son et al. 2000
T. x media var. Hicksii	0.31	Syklowska-Baranek and Furmanowa 2005

[53] Yukimune, Y.; Tabata, H.; Higashi, Y.; Hara, Y. *Nat. Biotechnol*. **1996**, *14*, 1129–1132.
[54] Wu, J.; Lin, L. *Appl. Microbiol. Biotechnol*. **2003**, *62*, 151-155.
[55] Zhong, J. J. *J. Biosci. Bioeng*. **2002**, *94*, 591–599.

T. media	0.53	Cusido et al. 2002
T. wallichiana	0.75	Navia-Osorio et al. 2002
T. cuspidata	1.10	Pestchanker et al. 1996
T. chinensis	1.50	Wang et al. 2001
T. chinensis var. *mairei*	1.52	Yuan et al. 2001
T. yunnanensis	1.90	Zhang et al. 2002
T. baccata	2.71	Bentebibel et al. 2005

The production has been scaled up, and presently, bioreactors are being employed by ESCAgenetic (CA, USA), Phyton (NY, USA), Samyang Genex (Taejon, Korea), and Phyton Biotech. However, taxus plant cell cultures are still limited for large-scale commercial use because of the low and unstable taxol yield, as well as high production cost, low natural yields, and selectivity over unwanted byproducts. Additionally, cell cultures display a large degree of heterogeneity in secondary metabolite production capabilities. There have been few reports on this variability in plant cell cultures, particularly the long-term stability of cell suspensions to maintain high levels of productivity.[56]

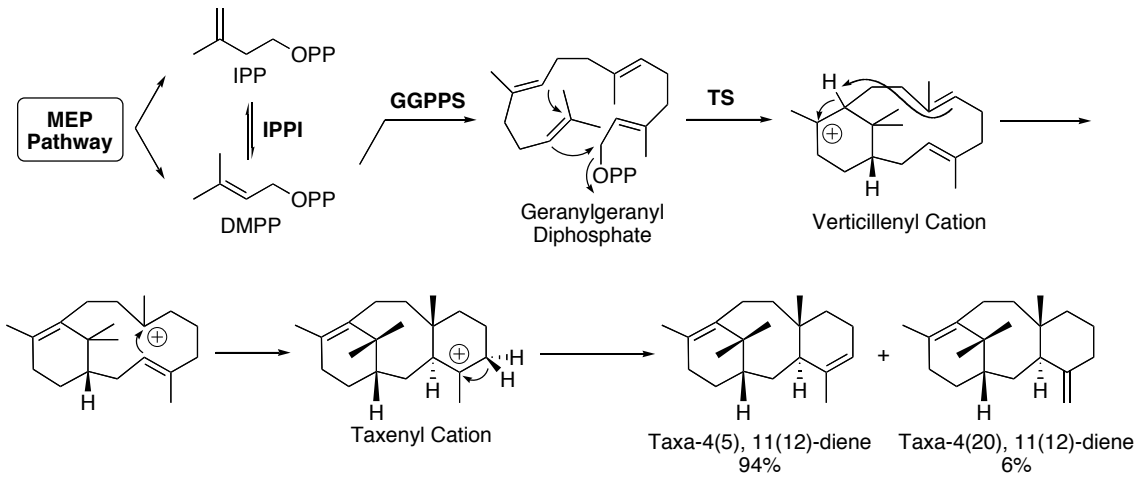
2) BIOSYNTHETIC PATHWAY

Taxus cell suspension cultures, especially those that are inducible with methyl jasmonate for increased taxoid production, are highly amenable to biochemical and molecular study. The knowledge of biosynthetic approach would offer a viable commercial production platform for the pharmaceutical industry that is more controllable and that is free of the environmental and political issues which may attend tissue collection, and that also has the potential for molecular genetic manipulation of taxoid composition and yield with relatively short development times.

The biogenesis of taxol can be conceptually divided into several processes, the first being the construction of the taxane skeleton that is followed by the addition of eight oxygen functional groups to the core. The diterpenoid taxane core is derived *via* the plastidial 2-C-methyl-D-erythritol phosphate (MEP) pathway, which supplies the C5 isoprenoid precursors isopentenyl

[56] Frense, D. *Appl. Microbiol. Biotechnol*. **2007**, *73*, 1233-1240.

disphosphate (IPP) and dimethylallyl diphosphate (DMAPP) (Scheme-1.2).[57] The parental taxane clearly arises in plastids, as almost certainly do all plant diterpenes, from acyclic precursor geranylgeranyl diphosphate (GGPP). The formation of the taxane skeleton was realized by cyclization of the geranylgeranyl skeleton to taxadiene by an enzymatic type of electrophilic mechanism in the presence of taxadiene synthase (TS).

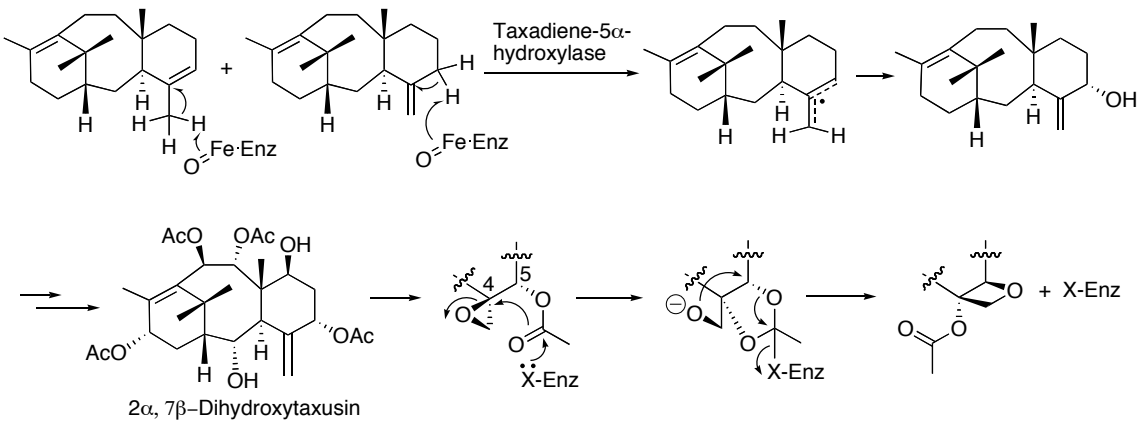


Scheme-1.2: Biosynthesis of the ABC tricycle of taxol. Cyclization of geranylgeranyl diphosphate by taxadiene synthase involving ionization of the diphosphate with closure of the first ring, intramolecular transfer of a proton in the resulting verticillenyl cation to promote the second closure, and deprotonation of the resulting taxenyl cation to yield taxa-4(5),11(12)-diene (major product) and taxa-4(20),11(12)-diene (minor product).[58]

Cytochrome p450 taxoid oxygenase localized in the endoplasmic reticulum then mediate hydratations of taxadiene, consequently with 5α-, 10β-, 13α-, 14β-, 7β- and 2α-, or 7β- and 2α-hydroxylases (Scheme-1.3). The obtained 2α,7β-dihydroxytaxusin is likely subjected to oxomutase reaction involving intramolecular exchange of the C5α-acetoxy group and the C4β-oxide group catalyzed by a transferase-type mechanism.

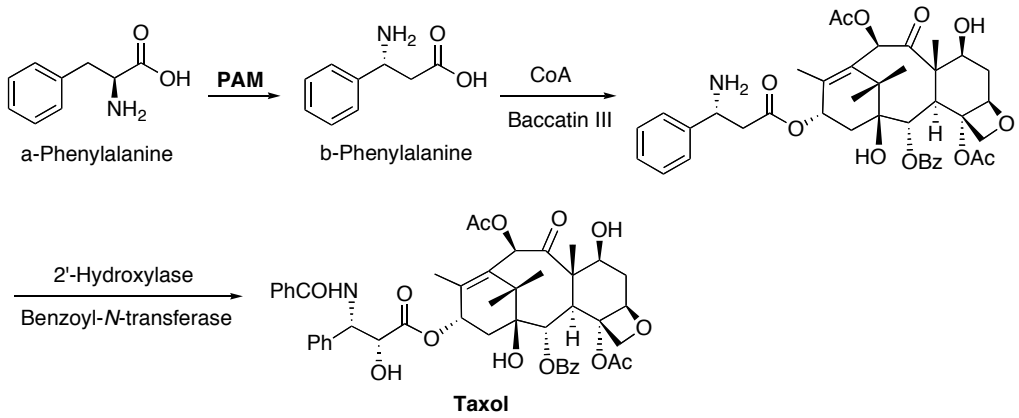
[57] Eisenreich, W.; Menhard, B.; Hylands, P. J.; Zenk, M. H.; Bacher, A. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 6431-6436.

[58] A homology-based cloning strategy was employed to acquire the TS cDNA from a *T. brevifolia* stem library, then the mechanistic and stereochemical details of the cyclization of the ABC tricycle of taxol were explored in vitro. For more details, see: Lin, X.; Hezari, M.; Koepp, A. E.; Floss, H. G.; Croteau, R. *Biochemistry* **1996**, *35*, 2968-3977. Williams, D. C.; Carroll, B. J.; Jin, Q.; Rithner, C.; Lenger, S. R.; Floss, H. G.; Coates, R. M.; Williams, R. M.; Croteau, R. *Chem. Biol*. **2000**, *7,* 969-977. Williams, D. C.; Wildung, M. R.; Jin, A.; Jin, Q.; Dalal, D.; Oliver, J. S.; Coates, R. M.; Croteau, R. *Arch. Biochem. Biophys*. **2000**, *379*, 137-146. Jin, Q.; Williams, D. C.; Hezari, M.; Croteau, R.; Coates, R. M. *J. Org. Chem*. **2005**, *70*, 4667-4675. Jin, Y.; Williams, D. C.; Croteau, R.; Coates, R. M. *J. Am. Chem. Soc*. **2005**, *127*, 7834-7842.



Scheme-1.3: Biosynthesis of the oxetane ring of taxol

The final steps involved the assembly of the C13 side chain: ligation of coenzyme A with β-phenylalanine produced from natural amino acid with Peptidylglycine Alpha-amidating Monooxygenase (PAM) (Scheme-1.4), followed by transformation to baccatin III, hydroxylation at C2' and benzoylation at C2 afford taxol.[59]



Scheme-1.4: Biosynthesis of the side chain of taxol

3) BACTERIA, FUNGI AND ENZYMATIC SEMISYNTHESIS

The first isolation of a taxol-producing fungus, Taxomyces andreanae, from *T. brevifolia* was reported by Strobel in 1993.[60] In the following years, three strains of fungi HQD33, HQD48, HQD54 were isolated. Protoplast mutagenesis was realized by using ultraviolet, radiation and combined treatment of UV and LiCl for improvement of taxol production by fungi.[61] These studies have important significance for the biotechnological production of taxol in the future.

[59] Croteau, R.; Ketchum, R. E. B.; Long, R. M.; Kaspera, R.; Wildung, M. R. *Phytochem. Rev*. **2006**, *5*, 75-97.
[60] Stierle, A.; Strobel, G. A.; Stierle, D. *Science* **1993**, *260*, 214-216.
[61] Zhao, K.; Zhou, D. P.; Ping, W. Y. *Chin. J. Biotechnol*. **2005**, *21*, 848-851.

The enzymes from bacteria were also isolated and cloned (Table-1.2). Expression of these enzymes in bacteria, yeasts, fungi, or plants and the development of bioreactors would alternatively resolve the supply problem of taxol.

Table-1.2: The cloned genes involved in Taxol biosynthesis pathway in Taxus[62]

Enzyme	Reference
Geranylgeranyl diphosphate synthase	Hefner et al. 1998
Taxadiene synthase	Wildung and Croteau 1996
Taxane 5α-hydroxylase	Jennewein et al. 2004b
Taxa-4(20), 11(12)-dien-5α-ol-O-acetyltransferase	Walker et al. 2000c
Taxane 10β-hydroxylase	Schoendorf et al. 2001
Taxane 13α-hydroxylase	Jennewein et al. 2001
Taxane 2α-O-benzoyltransferase	Walker and Croteau 2000b
10-Deacetylbaccatin III-10-O-acetyltransferase	Walker and Croteau 2000a
Phenylalanine aminomutase	Walker et al. 2004
Baccatin III:3-amino-3-phenylpropanoyltransferase	Walker et al. 2002a
3′-N-debenzoyl-2′-deoxytaxol N-benzoyltransferase	Walker et al. 2002b

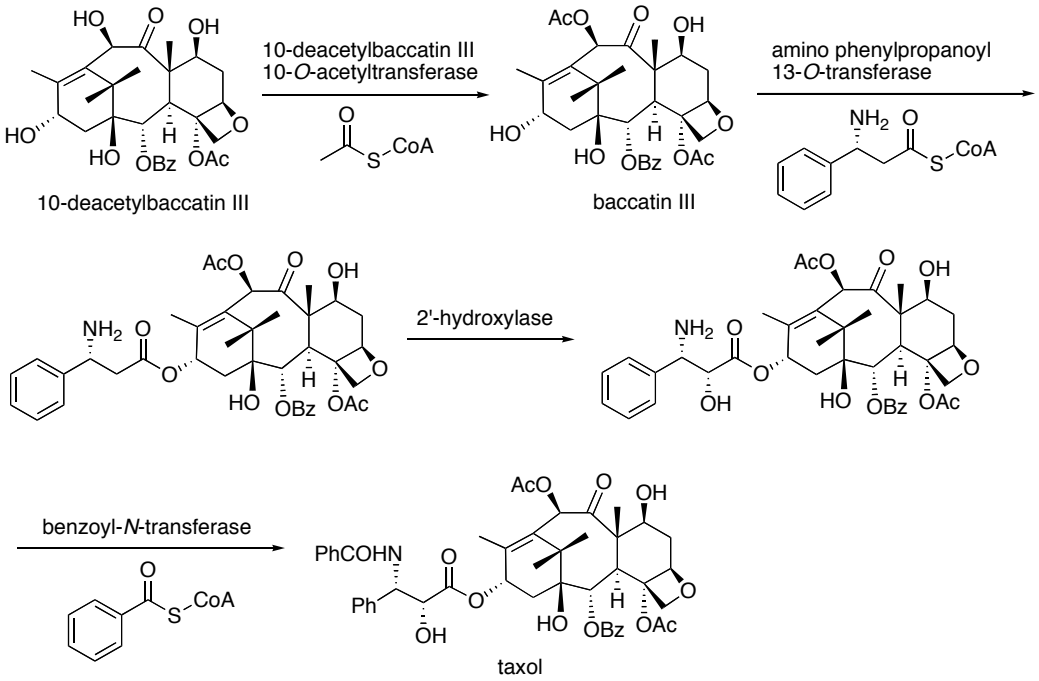
4) PRODUCTION IN REACTORS

Zocher reported the first cell-free acetylation of 10-deacetylbaccatin III in crude extracts from roots of *T. baccata* saplings using ^{14}C- or ^{3}H-labeled acetyl-CoA as the acetyl donor.[63] The expression of the cloned cDNA of 10-deacetylbaccatin III-10-*O*-acetyltransferase from *T. baccata* in *E. coli* was investigated and optimized using three kinds of isopropyl-β-*D*-thiogalactopyranoside (IPTG) inducible fusion expression systems.[64]

The enzyme 10-deacetylbaccatin III-10-*O*-acetyltransferase, which was expressed in *E. coli*, was used for the semisynthesis of baccatin III from 10-deacetylbaccatin III. A new enzyme membrane bioreactor on the basis of a hollow fiber membrane was developed (Scheme-1.5); the enzyme and substrate circulate in the inner side of the hollow fibers, the water-insoluble

[62] Nims, E.; Dubois, C. P.; Roberts, S. C.; Walker, E. L. *Metab. Eng*. **2006**, *8*, 385–394.
[63] Zocher, R.; Weckwerth, W.; Hacker, C.; Kammer, B.; Hornbogen, T. *Biochem. Biophys. Res. Commun*. **1996**, *229*, 16–20.
[64] Fang, J. J.; Ewald, D. *Protein Expr. Purif*. **2004**, *35*, 17–24.

organic solvent on the outer-side.



Scheme-1.5: Synthesis of taxol in reactors

Effort of biologists led to the development of several biosynthetic processes that would potentially replace tissue collection in taxol production. Unfortunately, the environmental problem always remains at the moment and stable, large-scale productions are still needed from natural harvest.

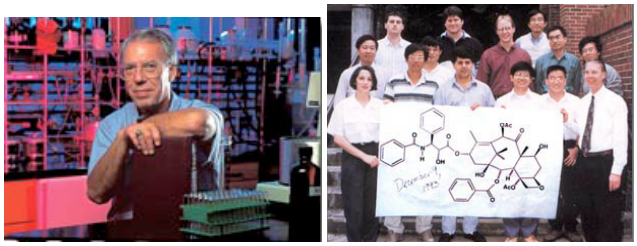
2.2 TOTAL SYNTHESES

In medicinal chemistry, one of the main roles of synthetic chemists is supplying medicinally important compounds by an artificial way to alleviate the crisis of natural harvest; another important point is that synthetic chemistry allows access to natural product analogues or simplified analogues not available from nature, which contain similar or better activities. However, the highly functionalized and high sterically hindered ABCD ring system of taxol is rarely encountered in chemical synthesis. Obviously, even an academic-type synthesis of taxol poses a major challenge with such a structure, unlikely to be solved by a preparation under 30 or 40 steps. Nevertheless, taxol generated the focused interest of organic chemists: at

one time more than 35 groups were actively pursuing its total synthesis,[65] and many more investigators reported syntheses of the side chain and its analogues.

To date six total syntheses of taxol *via* baccatin III have been reported by Holton, Nicolaou, Danishefsky, Wender, Kuwajima and Mukaiyama. Holton and Wender's syntheses are linear, employing natural products β-patchoulene (*ent*-taxol obtained) and pinene, respectively, as starting materials. Nicolaou's strategy is convergent connecting A and C, closing ring B, and finally incorporating the ring D oxetane. Similar strategy was also employed in the Kuwajima synthesis. Mukaiyama's preparation is unusual in that ring B was first constructed, followed by the sequence BC-ABC-ABCD. Danishefsky's synthesis is the only one in which the oxetane ring is carried through most of the synthetic sequence: CD-ACD-ABCD.

1) HOLTON'S SYNTHESIS



Professor Dr. Robert A. Holton, Department of Chemistry & Biology, Florida State University.

A happy team of FSU Taxol researchers led by Holton (bottom row, right) claimed victory in totally synthesizing the drug on Dec. 9, 1993.

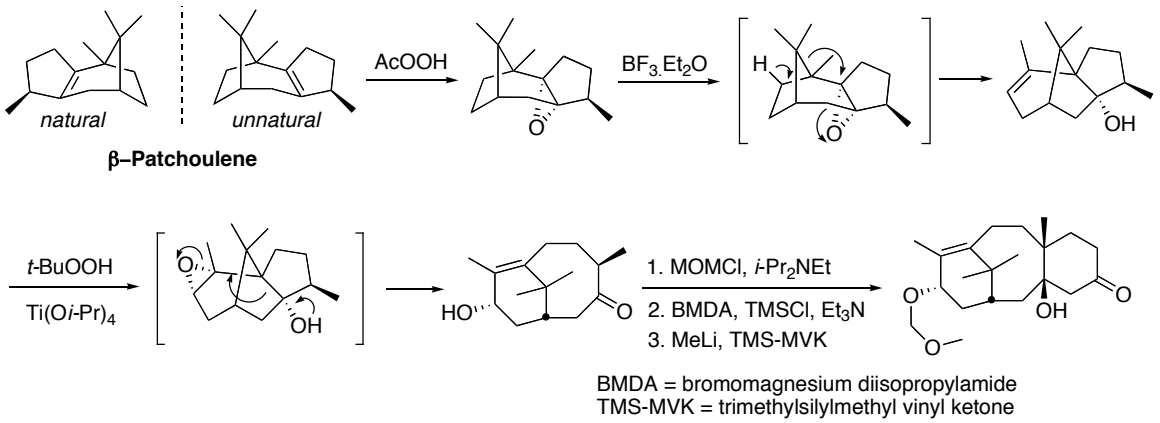
Figure-1.15: Holton and his group

The first synthesis of taxol was completed by Holton[66] late in 1993 and was based on the skeletal rearrangement of β-patchoulene oxide (Figure-1.15), which had been investigated early on by Büchi in connection with structural studies of patchouli alcohol.[67] The synthesis

[65] Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878-5879.
[66] Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc*. **1994**, *116*, 1597-1598; Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *ibid*. **1994**, *116*, 1599-1600.
[67] Büchi, G.; MacLeod, W. D. Jr.; Padilla, O. J. *J. Am. Chem. Soc*. **1964**, *86*, 4438-4444.

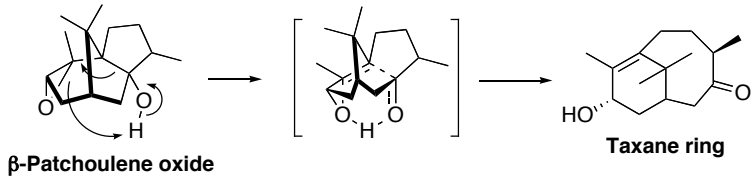
of patchouli alcohol started with (+)-camphor and was completed in 22 steps *via* a remarkable cationic rearrangement.

In 1984, Holton had published a short synthesis of the taxol ring system based on this rearrangement (Scheme-1.6).[68] Patchoulene oxide rearranged under Lewis acid treatment to the homoallylic alcohol, which was converted in one operation to the bicyclic ketone AB ring system of taxol, *via* an unstable epoxy alcohol. The C ring was then installed by a Robinson annulation in presence of MeLi and trimethylsilylmethyl vinyl ketone.



Scheme-1.6: Synthesis of taxane ring system

The creative rearrangement could be taken in the "system resonance"[69] or "family of isomeric ensembles of molecules (FIEM)"[70] concept (Scheme-1.7). Holton used then this elegant approach for the construction of the bridged bicyclic ring system in his synthesis of (-)-taxusin,[71] a model molecule of taxol.

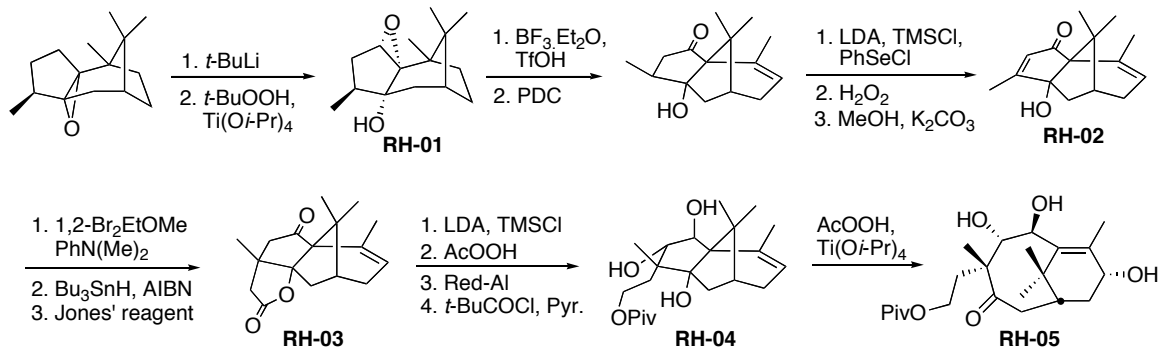


Scheme-1.7: System resonance

The synthesis of (-)-taxusin started with natural β-patchoulene oxide (Scheme-1.8). Treatment with *t*-BuLi gave a tertiary allylic alcohol, which was epoxidized to furnish compound **RH-01**. This epoxy alcohol rearranged to the diol, which was oxidized to form the corresponding α,β-

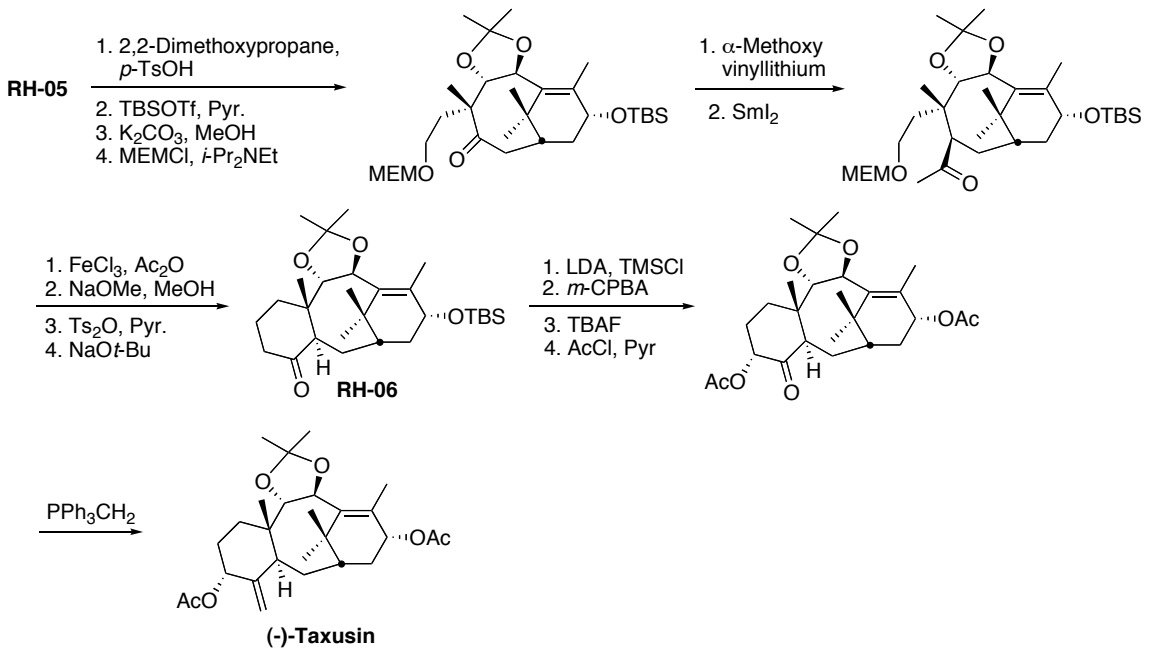
[68] Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731-5732.
[69] Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691-6707.
[70] Gasteiger, J.; Gillespie, P. D.; Marquarding, D.; Ugi, I. *Top. Curr. Chem.* **1974**, *48*, 1-37.
[71] Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558-6560.

unsaturated ketone **RH-02** after selenoxide elimination. Hydroxyl enone **RH-02** reacted with 1,2-dibromoethyl methyl ether to provide the corresponding bromoacetal, which upon radical cyclization, hydrolysis and oxidation led to keto-lactone **RH-03**. The silyl enol ether of **RH-03** reacted with peracetic acid to give the corresponding hydroxy ketone, which was reduced and converted to trihydroxy pivalate **RH-04**. Sharpless epoxidation was unsuccessful, but use of an excess of peracetic acid provided the epoxide, which rearranged by treatment with Ti(O*i*-Pr)$_4$ to furnish **RH-05**, containing the AB ring system of taxusin.



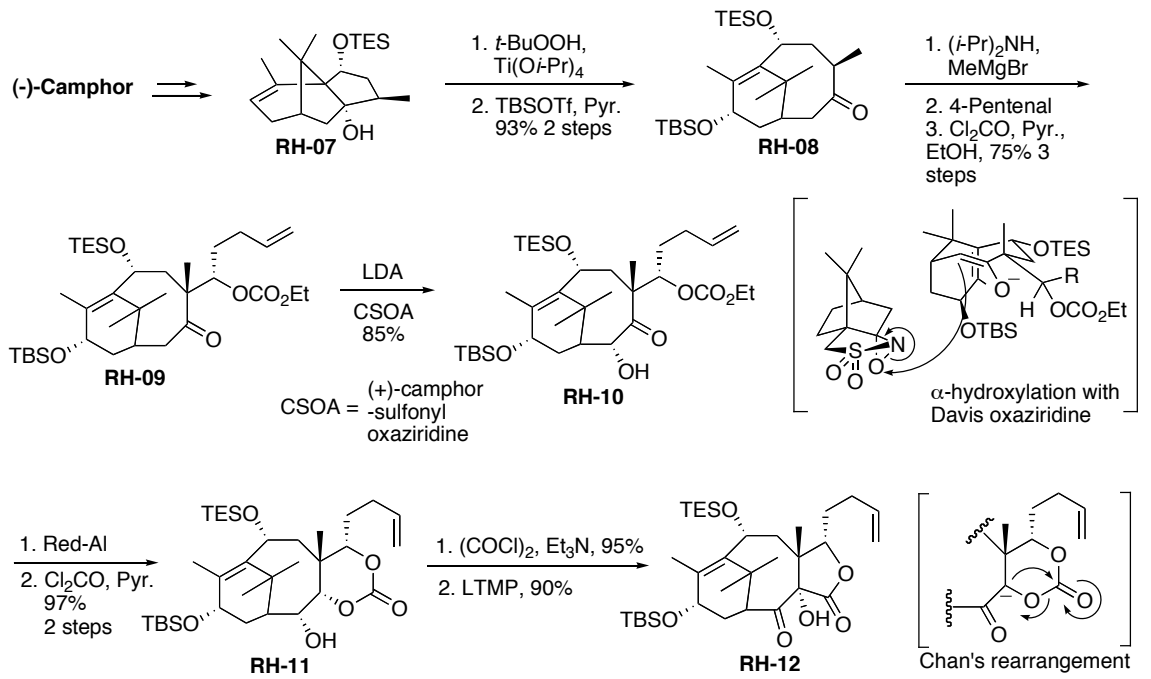
Scheme-1.8: Synthesis of AB ring system of taxusin

After several protections on **RH-05**, homologation of the ketone functionality was realized by addition of α-methoxyvinyl lithium, followed by in situ hydrolysis and radical reduction (Scheme-1.9). The observed stereospecificity is due to the directing effect exerted by the MEM protecting group. Removal of the MEM ether followed by cyclization gave **RH-06**, then stereospecific oxidation of the silyl enol ether of **RH-06** was followed by deprotection, acetylation and olefination to provide (-)-taxusin, which has identical NMR, IR spectra and opposite optical rotation regarding to natural (+)-taxusin.



Scheme-1.9: Synthesis of taxusin

The first synthesis of taxol proceeded from the experience acquired in the model studies as well as in the syntheses of the taxane ring system and taxusin (Scheme-1.10). One of the enantiomers of the intermediate **RH-01** from the taxusin synthesis was converted to **RH-07**, containing the additional siloxyl group. **RH-07** was obtained from (-)-camphor described in the synthesis of patchouli alcohol by Büchi. Rearrangement of β-patchoulene oxide and protection with TBSCl conducted to **RH-08** with taxol's AB ring system.

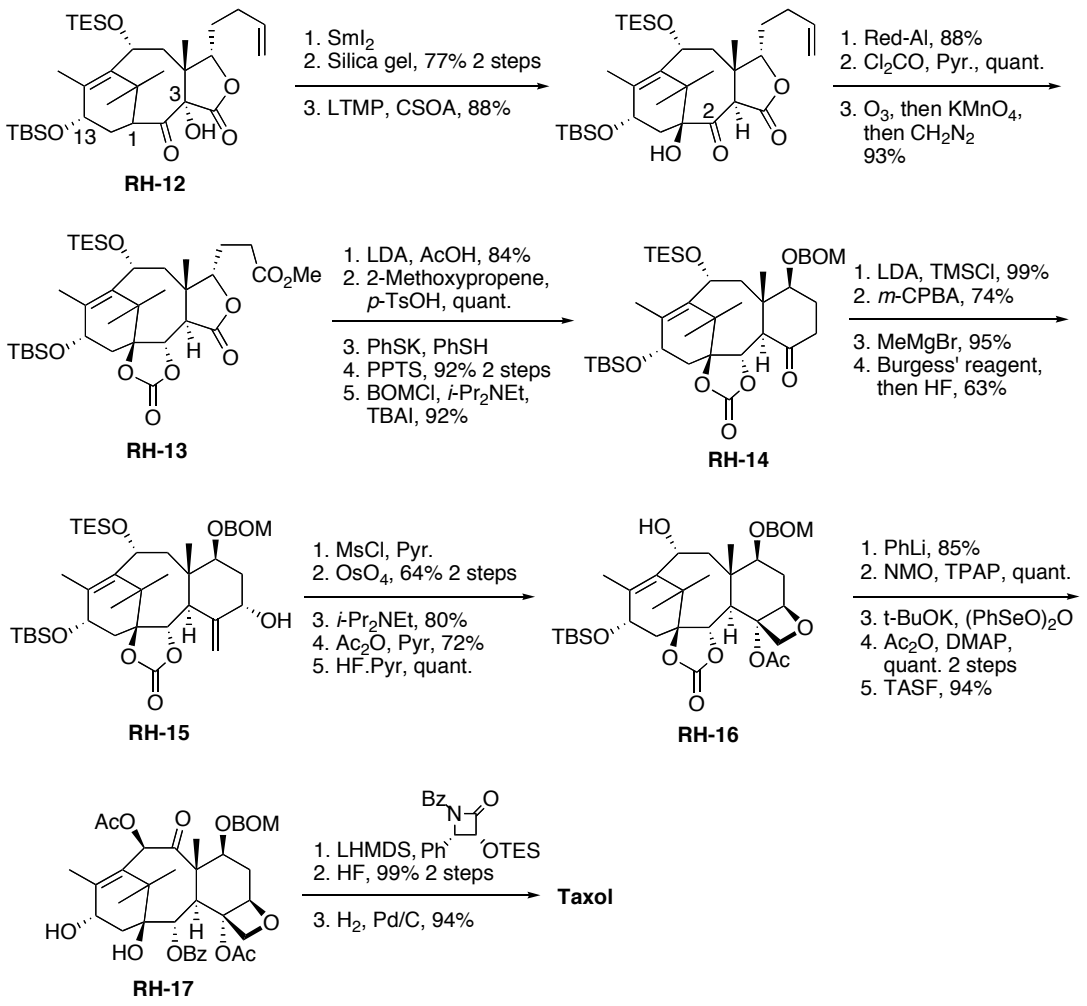


Scheme-1.10: Synthesis of AB ring system of taxol

The magnesium enolate of ketone **RH-08** underwent aldol condensation with 4-pentenal. The crude product was then protected to give carbonate **RH-09**. Davis' hydroxylation protocol provided **RH-10**, then reduction and protection of this intermediate conducted to cyclic carbonate **RH-11**. Swern oxidation[72] and Chan's rearrangement[73] provided the five-membered ring lactone **RH-12** in eight steps from alcohol **RH-07** (Scheme-1.10). Utilization of Chan's rearrangement is not often exploited in total synthesis, and was just applied twice more in White's syntheses of (+)-aplasmomycin[74] and a subunit of rapamycin.[75]

The hydroxyl group of **RH-12** was reduced with samarium iodide to a 6:1 mixture of *cis* and *trans*-fused lactones from which the major *cis* isomer was separated by crystallization and carried forward (Scheme-1.11). Holton noted that the deprotonation occurred first, and perhaps only at C-1. Reduction and cyclic carbonate generation of the obtained intermediate was followed by oxidation of the terminal olefin to provide methyl ester **RH-13**. During the reduction of the C-2 carbonyl and the basic work-up, the C-3 center epimerized to the correct *trans*-fused configurations. Dieckmann condensation and decarboxylation with PhSK led to construction of the C ring, which was converted to benzyloxyl methoxyl ether **RH-14**, containing the ABC tricycle of taxol with most of the required stereogenic centers.

[72] Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.
[73] Lee, S. D.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett*. **1984**, *25*, 3399-3402.
[74] White, J. D.; Vedananda, T. R.; Kang, M. C.; Choudhry, S. C. *J. Am. Chem. Soc*. **1986**, *108*, 8105-8107.
[75] White, J. D.; Jeffrey, S. C. *J. Org. Chem*. **1996**, *61*, 2600-2601.



Scheme-1.11: Synthesis of taxol

The TMS enol ether of **RH-14** underwent oxidation to the corresponding trimethylsilyloxy ketone, which was converted to the allylic alcohol **RH-15** by addition of methyl magnesium and elimination with Burgess' reagent. After formation of mesylate, osmylation and cyclization, oxetane **RH-16** was created. Addition of phenyllithium to **RH-16**, oxidation of the C-10 hydroxy group followed by α-hydroxylation rearrangement with benzeneseleninic anhydride provided cyclic carbonate cleavage and C-9, C-10 functionalities and stereochemistry were installed. Acetylation and removal of the TBS protecting group gave alcohol **RH-17**. Taxol was obtained by treatment of lithium alkoxide of **RH-17** with the appropriate β-lactam, then desilylation and hydrogenolysis (Scheme-1.11).

The synthesis provided (+)-taxol from (-)-patchino or the natural (-)-taxol from (-)-camphor or (-)-borneol. The overall yield from **RH-07** was 2.33% over 38 chemical steps, or 56 steps on counting the additional 18 operations for the conversion of camphor to **RH-07**.

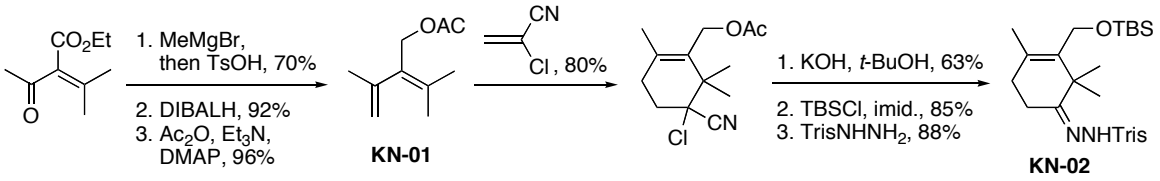
2) NICOLAOU'S SYNTHESIS

Dr. Kyriacos C. Nicolaou, Professor of Chemistry, University of California in San Diego; Professor of Chemical Biology, The Scripps Institute.

Figure-1.16: Kyriacos C. Nicolaou

The synthesis was described as a preliminary communication in *Nature*,[76] and the details of the entire synthetic work were published a year later in four papers (Figure-1.16).[77] A convergent strategy was adopted to construct the ABC ring system.

The preparation of A ring began with a α-carbonyl unsaturated ester (Scheme-1.12). The carbonyl group reacted with methyl magnesium bromide and the corresponding alcohol was eliminated to afford a double bond. Reduction of the ester followed by acetylation then gave acetate **KN-01**. Electronic induction in the Diels-Alder reaction conducted to a single regioisomer. Application of Shiner's protocol led to transformation of the obtained α-chloronitrile to α-ketone and elimination of acetyl group. Unsuccessful protection of the primary alcohol as benzyl ether was due to the ease of enolization in presence of KH, but after protection of the primary alcohol with TBSCl, the carbonyl group was transformed to trisyl hydrazone **KN-02**.



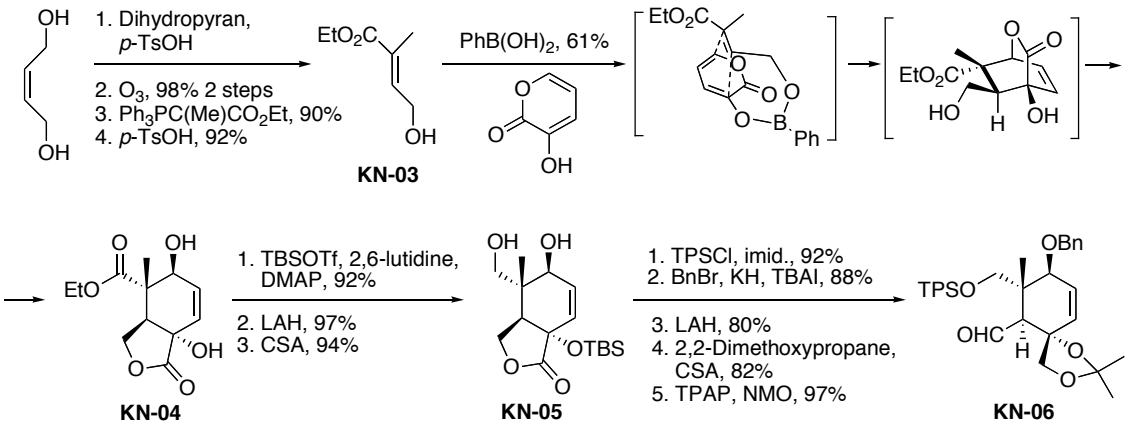
Scheme-1.12: Synthesis of the A ring of taxol

On the other hand dienophile **KN-03** was prepared from dihydroxybutene by oxidative cleavage and Wittig reaction (Scheme-1.13). The presence of phenylboronic acid favored

[76] Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630-634.

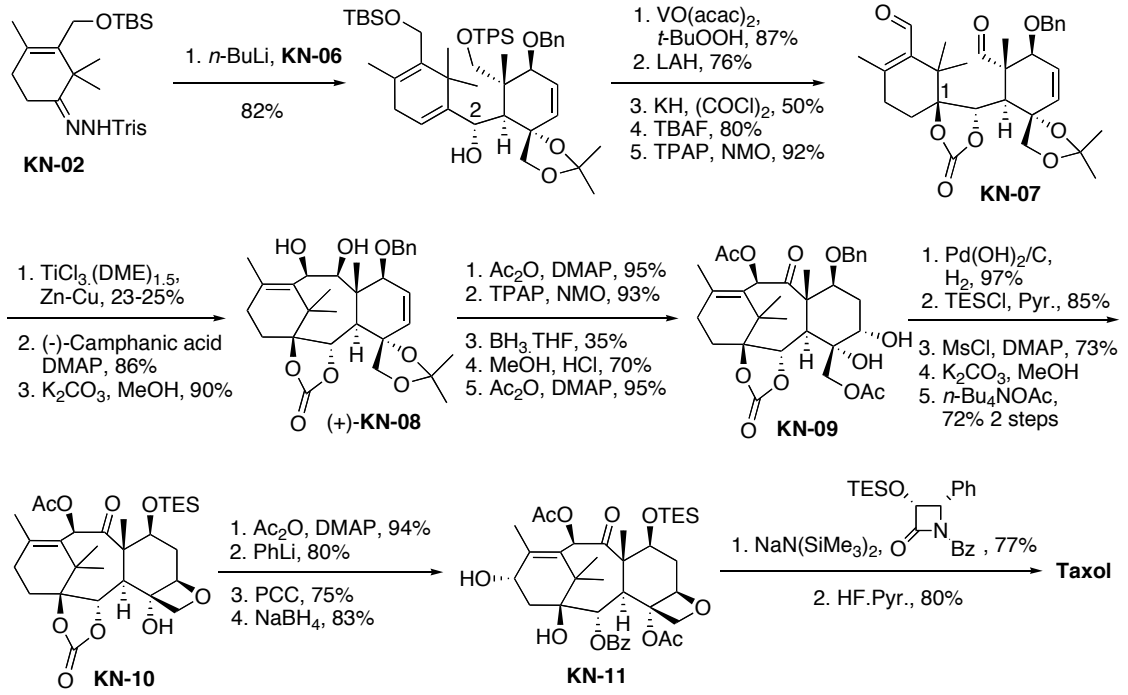
[77] Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624-633. Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *ibid.* **1995**, *117*, 634-644. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *ibid.* **1995**, *117*, 645-652. Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *ibid.* **1995**, *117*, 653-659.

complexation with the two hydroxy groups and led to a single Diels-Alder reaction product, followed by rearrangement *via* intramolecular acyl transfer to afford **KN-04**. Protection of the diol as a silyl ether, reduction of ester and selective deprotection of the secondary silyl ether gave **KN-05**, which was converted to aldehyde **KN-06** after several protection steps.



Scheme-1.13: Synthesis of the C ring of taxol

A Shapiro reaction was used for the coupling between **KN-02** and **KN-06** in the presence of *n*-BuLi to produce a single diastereoisomer (Scheme-1.14). The authors claimed that the complexation between lithium and two oxygen atoms from the aldehyde and the acetonide groups fixed the conformation of **KN-06**, leading to addition of the vinyl anion generated from **KN-02** from only one side, opposite to the quaternary methyl group.

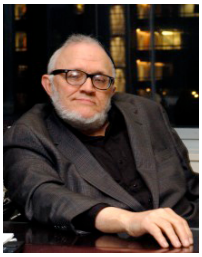


Scheme-1.14: Synthesis of taxol

Regioselective epoxidation and ring-opening of the epoxide to install the tertiary hydroxyl at C1, followed by subsequent desilylation and oxidation led to dialdehyde **KN-07**, which was subjected to a McMurry cyclization to afford the ABC ring system (Scheme-1.14). Resolution of the racemate through its diastereomeric camphanate ester at C9 gave **(+)-KN-08**, which was transformed to **KN-09** by acetylation, oxidation, hydroboration, deprotection of acetonide and acetylation. **KN-10** was then obtained by transformation of the benzyl ether to a silyl ether followed by formation of the oxetane ring through elimination of a mesylate group. Finally, creation of a hydroxy group by treatment with PCC and borohydride followed by esterification and desilylation afforded taxol.

The synthesis of Nicolaou provided natural taxol from small chemical molecules. The overall yield was 0.02% over 44 chemical steps. Despite numbers of protection-deprotection steps, Nicolaou's group proposed the first convergent total synthesis and the experience gained during this effort was then employed in the preparation of new taxoid derivatives with different biological properties.

3) DANISHEFSKY'S SYNTHESIS



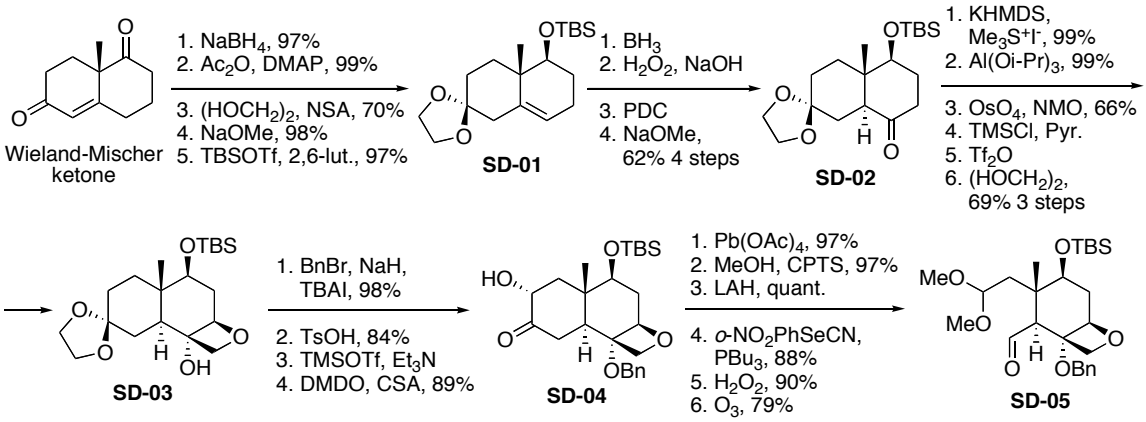
Professor Dr. Samuel J. Danishefsky, Department of Chemistry, Columbia University.

Figure-1.17: Samuel J. Danishefsky

Danishefsky's group proposed a convergent synthesis, in which the CD ring system is carried through the entire synthetic route (Figure-1.17). A metal-halide exchange mediated nucleophilic addition led to the coupling of the A ring and the C ring, followed by Heck reaction between a terminal double bond and a vinyl triflate functionalities to construct the ABCD skeleton of taxol. The synthesis was accomplished in 1995[78] and the full paper was published one year later.

[78] Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 1723-1726. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859.

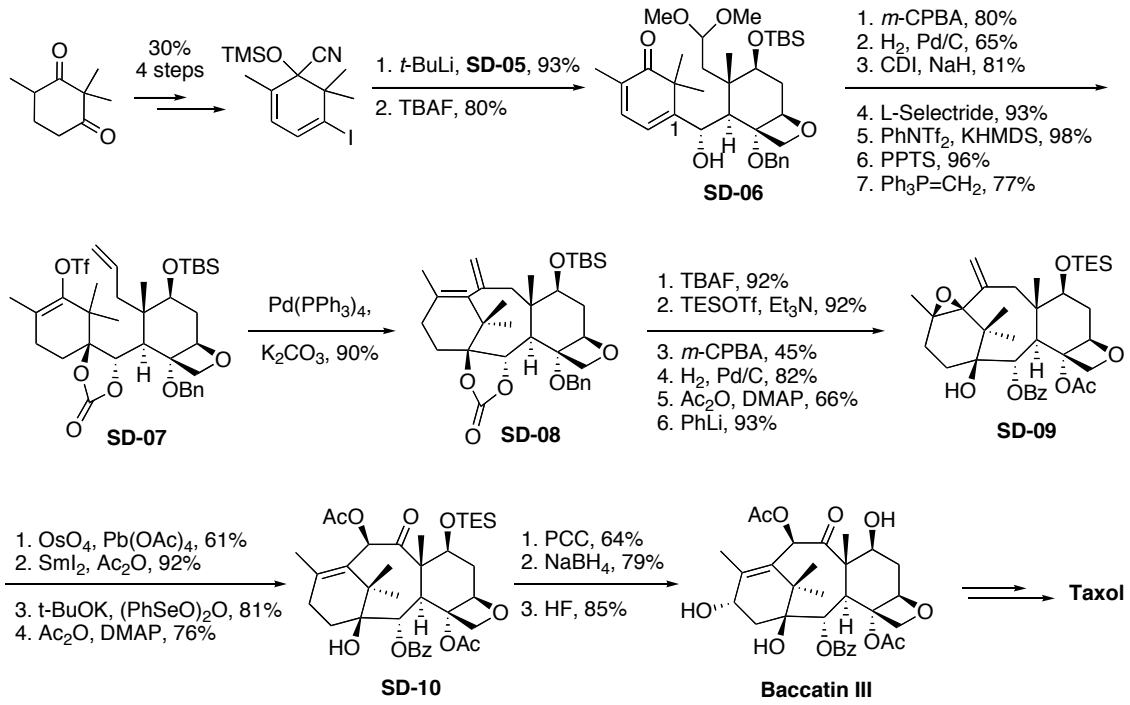
Wieland-Miescher ketone was selectively reduced to alcohol according to a known protocol;[79] **SD-01** was then obtained by transformation of the acetate to the silyl ether and deconjugation of the α,β-unsaturated ketone *via* ketal (Scheme-1.15). Hydroboration followed by oxidation of the alcohol afforded ketone **SD-02**, which was subjected to formation of the oxetane ring: epoxidation, allylic alcohol formation through epoxide opening with Lewis acid, dihydroxylation with osmium tetraoxide, substitution of the triflate by refluxing in ethylene glycol. Alcohol **SD-03** was then protected as its benzyl ether, and the ketal group was then converted to the silyl enol ether followed by oxidation with DMDO to give α-hydroxy ketone **SD-04**. Ring fragmentation was performed with lead tetraacetate in methanol. The obtained aldehyde was then transformed to the dimethyl acetal while the methyl ester was reduced then converted to the terminal olefin according to Grieco's protocol. Oxidative cleavage of the olefin gave aldehyde **SD-05**.



Scheme-1.15: Synthesis of the CD ring of taxol

A vinyllithium agent prepared from a simple diketone was subjected to nucleophilic addition with **SD-05** (Scheme-1.16). A single diastereoisomer **SD-06** was obtained as in Nicolaou's case. Moreover, several of the subsequent steps were also similar to the synthesis of Nicolaou: epoxidation, epoxide opening and carbonation. Hydrogenation of the product with *L*-Selectride, followed by vinyl triflate and terminal olefin formations gave precursor **SD-07**, ready for the closure of taxol B ring by Heck reaction. In the presence of palladium (0), the Heck product **SD-08** was successfully obtained and subjected to epoxidation, which protects the tetrasubstituted olefin, followed by transformation of the benzyl ether to the acetate, and carbonate ring-opening to afford **SD-09**. Treatment with osmium tetraoxide led to the formation of a putative osmate ester, which was converted to the ketone with lead tetraacetate.

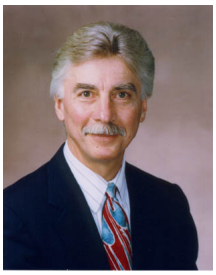
[79] Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746-1757.



Scheme-1.16: Synthesis of taxol

Holton's protocol was then applied to install the C10 functionality to provide **SD-10**, which is an intermediate in Nicolaou's synthesis (Scheme-1.16). Taxol was finally obtained by Danishefsky's group in 48 steps with an overall yield of 0.03%. The synthesis was very similar to the one of Nicolaou, but the stereochemistry was introduced using enantiopure Wieland-Miescher ketone, thus avoiding the use of non-natural starting material, as patchouli in Holton's synthesis.

4) WENDER'S SYNTHESIS



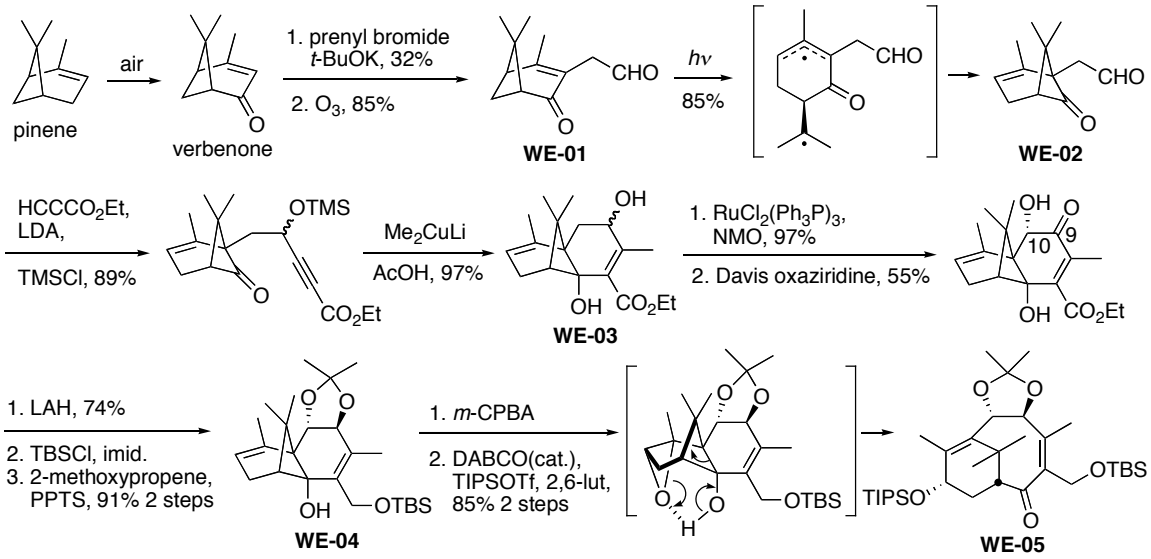
Professor Dr. Paul Wender, Department of Chemistry, Stanford University.

Figure-1.18: Paul Wender

The synthesis realized by Wender's group is based on research resulted from pinene, verbenone, and chrysanthenone (Figure-1.18). A ring fragmentation conceptually similar to

Holton's synthesis was first employed for the synthesis of AB bicycle and led to the preparation of several aromatic C ring precursors of taxol from pinene.[80] The ABC ring system was then prepared,[81] leading to the final synthesis of taxol.[82]

The synthesis began with the air oxidation of pinene to verbonene, which was converted to keto-aldehyde **WE-01** by addition of prenyl bromide in presence of *t*-BuOK, followed by selective ozonolysis of the more electron-rich double bond (Scheme-1.17). A photochemical rearrangement provided the chrysanthenone derivative **WE-02** according to a known process.[83]



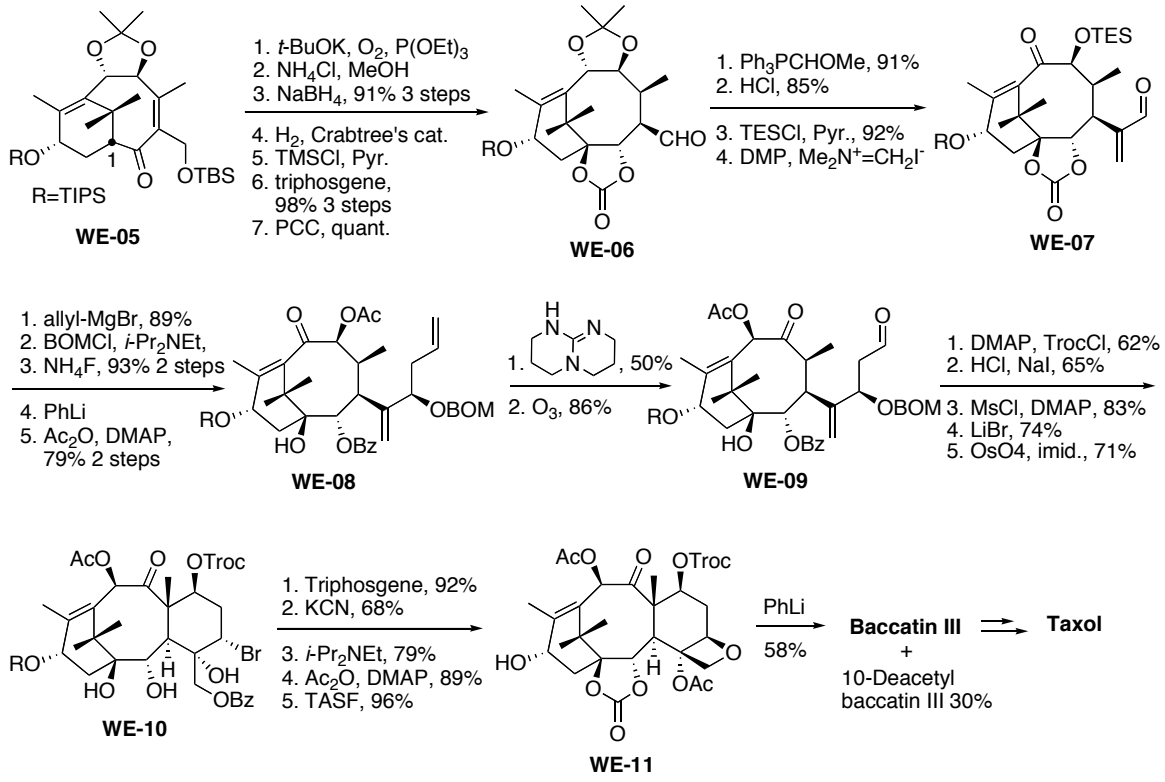
Scheme-1.17: Synthesis of the AB ring of taxol

Selective addition of lithium ethyl propiolate to the aldehyde and protection of the alkoxide in situ as its silyl ether yielded a mixture of diastereomers, Treatment with Me_2CuLi introduced a methyl group, generating a vinyl anion that reacts intramolecularly with the carbonyl group to give **WE-03** (Scheme-1.17). The obtained **WE-03** was then subjected to oxidation with a ruthenium catalyst and NMO followed by treatment with Davis' oxaziridine to give the α-hydroxy ketone, which was converted to **WE-04** by reduction of the ketoester, selective

[80] Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878-5879.
[81] Wender, P. A.; Glass, T. E.; Krauss, N. E.; Mühlebach, M.; Peschke, B.; Rawlins, D. B. *J. Org. Chem.* **1996**, *61*, 7662-7663.
[82] Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755-2756. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *ibid.* **1997**, *119*, 2757-2758.
[83] Hurst, J. J.; Whitham, G. H. *J. Chem. Soc.* **1960**, 2864-2869. Chrétien-Bessière, Y.; Retemar, J.-A. *Bull. Soc. Chim. Fr.* **1963**, 30, 884-886.

protection of the primary alcohol as its silyl ether and protection of the diol as the acetonide. After epoxidation of the more electron-rich double bond, DABCO induced fragmentation, similar to the rearrangement of patchoulene oxide in Holton's synthesis, followed by protection of the alcohol as its silyl ether in situ, provided taxol AB ring **WE-05**.

Generation of the alcohol at C1 with *t*-BuOK and $P(OEt)_3$ under an oxygen atmosphere, followed by removal of the TBS group and reduction of the carbonyl group, gave the triol product (Scheme-1.18). Hydrogenation of the double bond with Crabtree's catalyst[84] and protection of the primary alcohol as a silyl ether in situ provided a diol product, which was protected as the carbonate and subjected to oxidation to afford **WE-06**. Wittig reaction, hydrolysis, protection of C9-OH as its silyl ether, oxidation of C10-OH with Dess-Martin periodinane and introduction of terminal olefin with Eschenmoser's salt led to **WE-07**, which was converted to **WE-08** by allylation, protection of the secondary alcohol as its BOM ether, carbonate ring-opening and replacement of the silyl ether by an acetate ester.



Scheme-1.18: Synthesis of taxol

Aldehyde **WE-09**, obtained by treatment with guanidine base and ozonolysis, was subjected to intramolecular aldol reaction for the closure of the C ring (Scheme-1.18). Transformation

[84] Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655-2661.

of the BOM ether to the bromide, dihydroxylation with an unexpected migration of the benzoyl group, afforded **WE-10**, which was converted to the carbonate, followed by removal of the benzoyl group, oxetane ring formation, acetylation, removal of TIPS group to afford **WE-11**. After treatment with PhLi, known sequences were employed to provide taxol.

The total synthesis proposed by Wender's group required 37 steps from verbenone with a global yield of 0.09%. In spite of a linear synthetic route and a rearrangement similar to the one developed by Holton, the use of easily available natural product as starting material in Wender's synthesis and less protection steps comparable to the others brought compactness and elegance to the synthesis.

5) KUWAJIMA'S SYNTHESIS

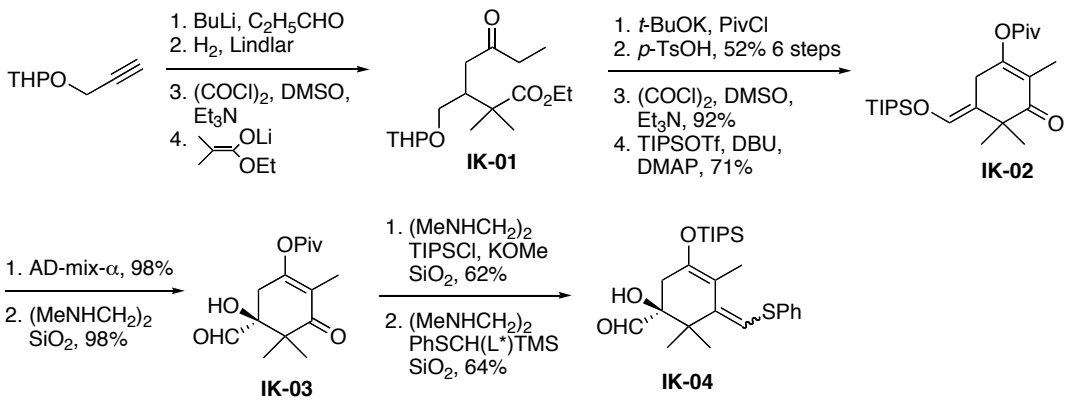
Professor Dr. Isao Kuwajima, Department of Chemistry, Tokyo Institute of technology.

Figure-1.19: Isao Kuwajima

Kuwajima's synthesis is convergent, connecting the A ring and the C ring between a lithiated diene and a hydroxy aldehyde, then a dienol ether aldol-type addition to an acetal was used for the closure of the eight-membered B ring (Figure-1.19). This Lewis acid-mediated reaction was previously exploited in his synthesis of taxusin,[85] then applied to the synthesis of taxol.[86]

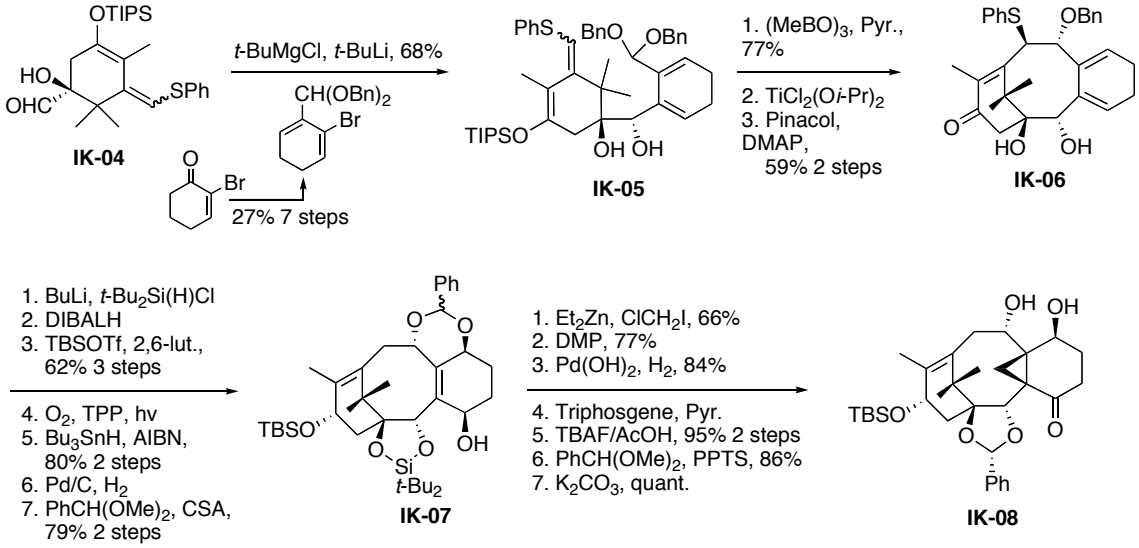
The synthesis of the A ring began with addition of lithiated propargyl ether to propionaldehyde, followed by Lindlar reduction, Swern oxidation and addition of isobutylic ester enolate to give keto ester **IK-01** (Scheme-1.19). Nucleophilic cyclization promoted by *t*-BuOK, transformation of the carbonyl group to the pivalate, removal of the THP protecting group and oxidation provided an aldehyde, which was converted to *E*-silyl enol ether **IK-02**, due to the *gem*-dimethyl group. Asymmetric dihydroxylation led to **IK-03**, but aminal formation and hydrolysis were necessary to gain good recovery of the product. Transformation of the pivalate to the silyl enol ether and asymmetric Peterson olefination afforded α-hydroxy aldehyde **IK-04** using aminal formation-removal procedure.

[85] Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc*. **1996**, *118*, 9186-9187.
[86] Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc*. **1998**, *120*, 12980-12981. Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *ibid*. **2000**, *122*, 3811-3820.



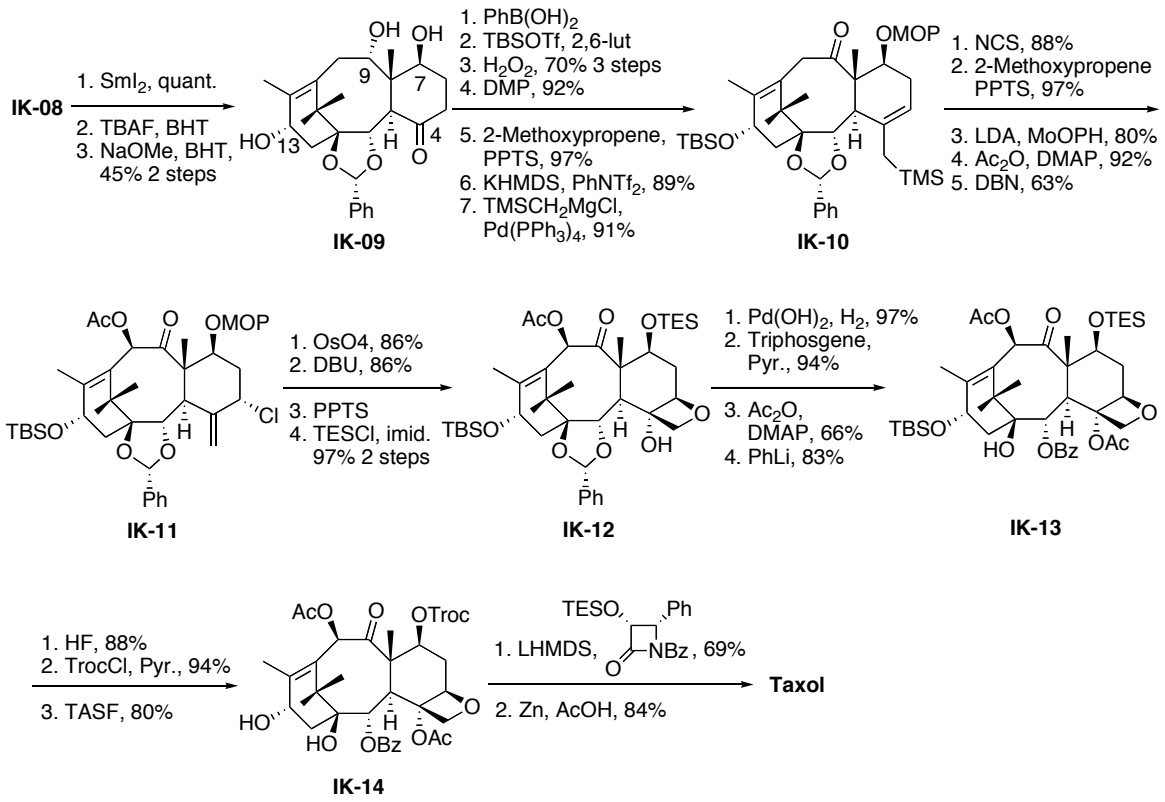
Scheme-1.19: Synthesis of the A ring of taxol

Chelation-controlled coupling of **IK-04** with the C ring fragment synthesized from 2-bromo cyclohexenone led to the diastereoselective formation of diol **IK-05**, which was converted to the corresponding 1,2-boronate (Scheme-1.20). Treatment with $TiCl_2(O\textit{i}\text{-}Pr)_2$ led to the formation of the B ring of the molecule and transformation of the silyl enol ether to the ketone, gave **IK-06** after removal of the boronate protecting group. Protection of the diol as dioxasilapentane, followed by reduction of the carbonyl group and protection provided the diene product, which was subjected to singlet oxygen oxygenation. Treatment with Bu_3SnH and AIBN resulted in both peroxide cleavage and removal of the phenylthio group. Removal of the benzyl group and protection of the diol afforded **IK-07** as a mixture of diastereomers. Cyclopropanation with zinc carbenoid and oxidation of the hydroxy group afforded **IK-08** with several transformations of protecting group of the diol moieties, due to reactivity and stability issues of the molecule.



Scheme-1.20: Synthesis of the ABC ring of taxol

A key cyclopropyl ring-opening through enol formation of the carbonyl group by treatment with SmI_2 led, after treatment under basic conditions, to **IK-09** (Scheme-1.21), which was converted to **IK-10** by protection of the hydroxy group at C13 as its silyl ether through protection-deprotection of the diol at C7 and C9, then selective oxidation of the hydroxy group at C9, protection of the hydroxy group at C7 and a Kumada cross-coupling process.



Scheme-1.21: Synthesis of taxol

Chlorination, olefination by elimination of the silyl group and enolate oxidation with MoO_5•pyr•HMPA, followed by acetylation and inversion of the stereochemistry of the acetate provided **IK-11**, which was subjected to dihydroxylation, oxetane ring formation and transformation of the MOP ether to the silyl ether to give **IK-12** (Scheme-1.21). Transformation of the benzylidene group to benzoyl group afforded **IK-13**, replacement of the TES group by a Troc group gave **IK-14**, which was attached to the side chain and the protecting groups was removed to afford taxol.

The synthesis required 62 steps with a global yield of 0.007%, which represents the longest synthesis of taxol. However, the diastereoselectivity in the coupling reaction of A and C rings, the formation of quaternary methyl group by cyclopropanation and ring opening created a new synthetic route to taxol-type skeletons.

6) MUKAIYAMA'S SYNTHESIS

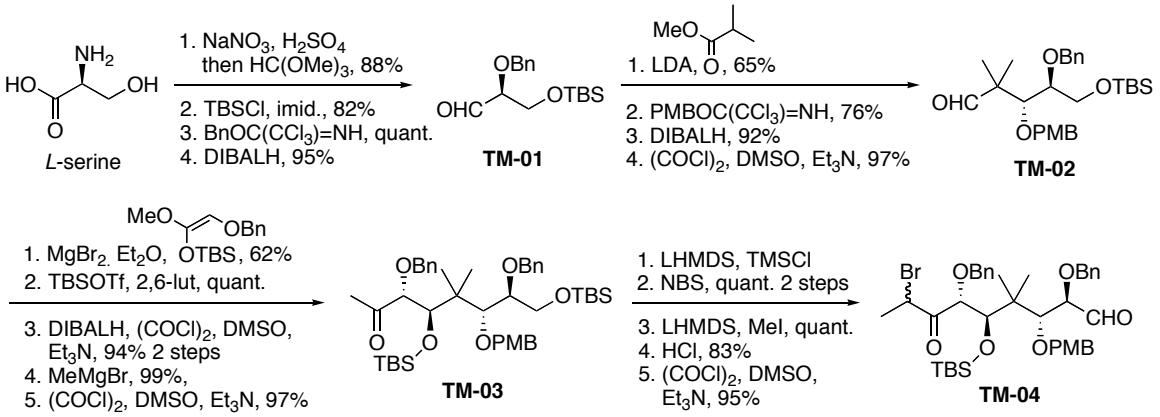
Professor Dr. Teruaki Mukaiyama, Department of Applied Chemistry, Tokyo University of Science.

Figure-1.20: Teruaki Mukaiyama

The synthesis was first outlined in *Proc. Jpn. Acad.* (Figure-1.20).[87] The preliminary reports of the constructions of intermediate skeleton for taxol have appeared in *Chem. Lett.*,[88] and the complete process was published in *Chem. Eur. J.* as a full paper in 1999.[89]

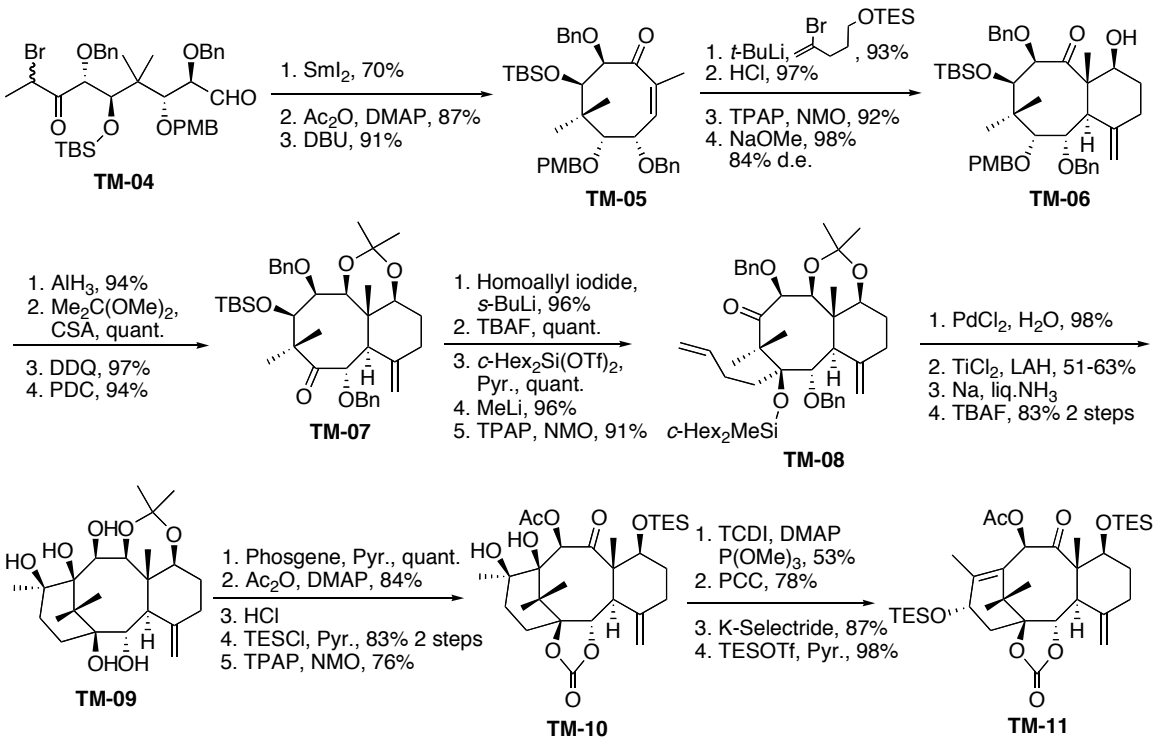
The synthesis began with formation of the eight-membered B ring, which was synthesized from *L*-serine (Scheme-1.22). Transformation of the amine to the hydroxy group, selective protections of the diol group and reduction of the ester to the aldehyde gave **TM-01**, which was subjected to aldol reaction, followed by reduction of the ester and oxidation of the resulting alcohol to provide aldehyde **TM-02**. $MgBr_2 \bullet Et_2O$-promoted Mukaiyama aldol reaction afforded a stereoselective addition, then protection of the hydroxy group as its silyl ether and formation of the carbonyl group produced **TM-03**, which was transformed to the corresponding silyl enol ether. Treatment with NBS and use of LHMDS and MeI, followed by removal of terminal silyl group and oxidation led to the formation of α-bromoketo aldehyde **TM-04**.

[87] Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Jpn. Acad*. **1997**, *73B*, 95-100.
[88] Shiina, I.; Saitoh, K.; Fréchard-Ortuno, I.; Mukaiyama, T.; *Chem. Lett*. **1998**, 3-4.
[89] Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, H.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J*. **1999**, *5*, 121-161.



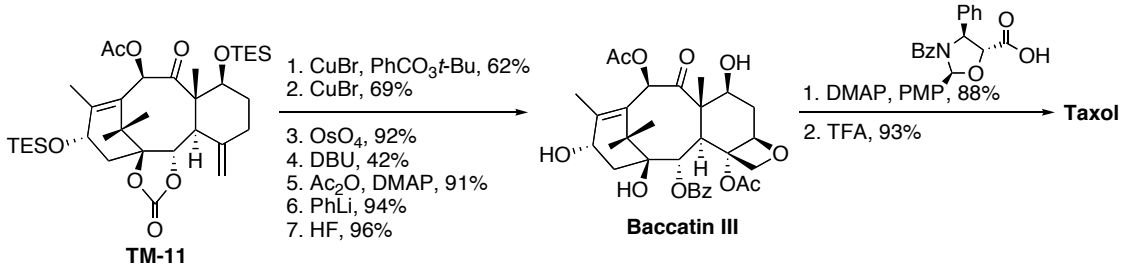
Scheme-1.22: Synthesis of the B fragment of taxol

SmI_2-promoted cyclization, formation of the acetate and elimination gave B ring **TM-05**, which was subjected to Michael addition (Scheme-1.23). Formation of the keto-aldehyde through removal of the silyl group and oxidation, followed by intramolecular aldol reaction gave BC bicycle **TM-06** with the correct configuration at C7 and C8. Diastereoselective reduction with AlH_3 and protection of the diol group provided the acetonide product, which was converted to the ketone **TM-07** by removal of the PMB group and oxidation of the resulting alcohol. Alkylation with homoallyllithium, followed by removal of the TBS group and protection of the diol group led to the silylene compound. This silylene was opened by methylation and the resulting hydroxyl group was oxidized to furnish **TM-08**. Wacker reaction of the terminal double bond and intramolecular pinacol coupling reaction in the presence of $TiCl_2$ and LAH gave the ABC tricyle, and the benzyl and silyl groups were removed to provide the pentol **TM-09**.



Scheme-1.23: Synthesis of the ABC ring of taxol

Several selective protections were realized to give α-keto acetate **TM-10**, which was converted to **TM-11** by reduction of the diol group at A ring through desulfurization of the intermediate thionocarbonate, followed by oxidation, reduction and protection as in the Nicolaou's synthesis (Scheme-1.23).



Scheme-1.24: Synthesis of taxol

The synthesis was completed by creation of the oxetane ring system from the terminal olefin (Scheme-1.24). A slightly different connection with the side chain provided a better yield of taxol from baccatin III. The synthesis required 52 steps with a global yield of 0.05%. The stereochemistry was efficiently introduced by *L*-serine, and the construction of the taxol skeleton around the central molecule was unique around all the syntheses of taxol.

7) FINAL CONSIDERATIONS

Among all the six successful (formal) total syntheses, the crucial preparation of highly functionalized ABC ring system takes the central place of the synthesis. More than 30 steps and numbers of protection-deprotection processes are necessary (Table-1.3). Moreover, the construction of highly sterically hindered eight-membered B ring is particularly important. Several methods were applied but often the yields were relatively moderate. Therefore, a new synthetic route to taxol and exploration of a suitable methodology for the closure of the taxol B ring are needed, and also useful for the preparation of taxol analogs.

Table-1.3: Six total syntheses of taxol

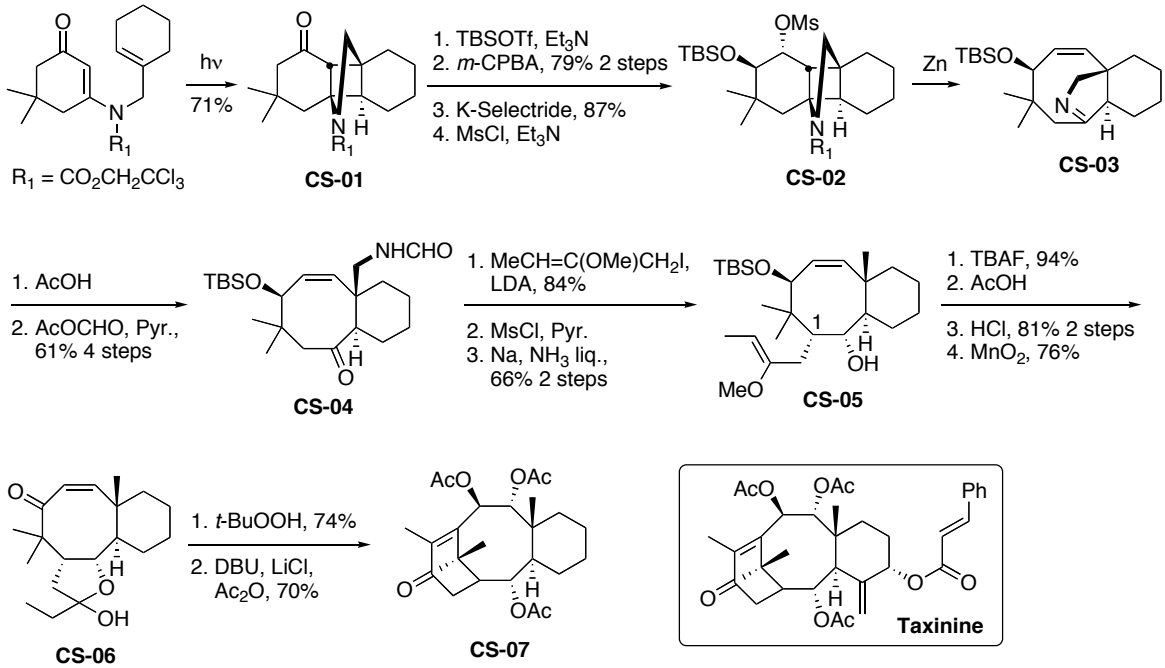
	Synthetic sequence	Steps	Global yield	Strategies
Holton	AB→ABC→ABCD	56	2.33%[a]	Cationic rearrangement Chan's rearrangment Dieckmann condensation Oxidation with seleninic anhydride
Nicolaou	A+C→AC→ABC→ABCD	44	0.02%	Asymmetric Diels-Alder reaction Chelated nucleophilic addition McMurry cyclization Allylic oxidation with PCC
Danishefsky	C→CD→ACD→ABCD	53	0.03%	Diastereoselective nucleophilic addition Heck coupling reaction Oxidation with seleninic anhydride Allylic oxidation with PCC
Wender	AB→ABC→ABCD	37	0.09%	Cationic rearrangement Utilization of Eschenmoser's salt Intramolecular aldol reaction
Kuwajima	A+C→AC→ABC→ABCD	62	0.007%	*Gem*-dimethyl induced conformation Diastereoselective Shapiro reaction Cationic cyclization Singlet oxygen oxygenation Cyclopropyl ring-opening
Mukaiyama	B→BC→ABC→ABCD	52	0.05%	SmI_2-promoted cyclization Michael addition Intramolecular aldol reaction Wacker reaction Pinacol coupling reaction Corey-Winter olefination

[a] calculated from a protected derivative of non-natural (+)-patchino, which needs to be synthesized in 18 steps from natural (-)-camphor.

2.3 SOME SYNTHETIC WORKS

1) TAXININE AB RING SYSTEM

The synthesis proposed by professor Charles S. Swindell began with an intramolecular [2+2] photoaddition of a vinyl amide to conduct to **CS-01** (Scheme-1.25). The ketone was converted to the silyl enol ether and then to the epoxide, which was reduced to the corresponding alcohol with transposition of the silyl group, giving **CS-02** after mesylation. In the presence of zinc metal, a fragmentation by elimination of the mesylate group gave imine **CS-03**, which was hydrolyzed and transformed to **CS-04**. Alkylation at C1 and dehydration of formamide then metal reduction of the corresponding isocyanide afforded **CS-05**. Desilylation, acid treatment of **CS-05** and oxidation of the allylic alcohol gave hemiketal **CS-06**, which was subjected to epoxidation and aldol-Payne rearrangement to furnish tricyclic **CS-07**, containing the taxinine AB ring system.



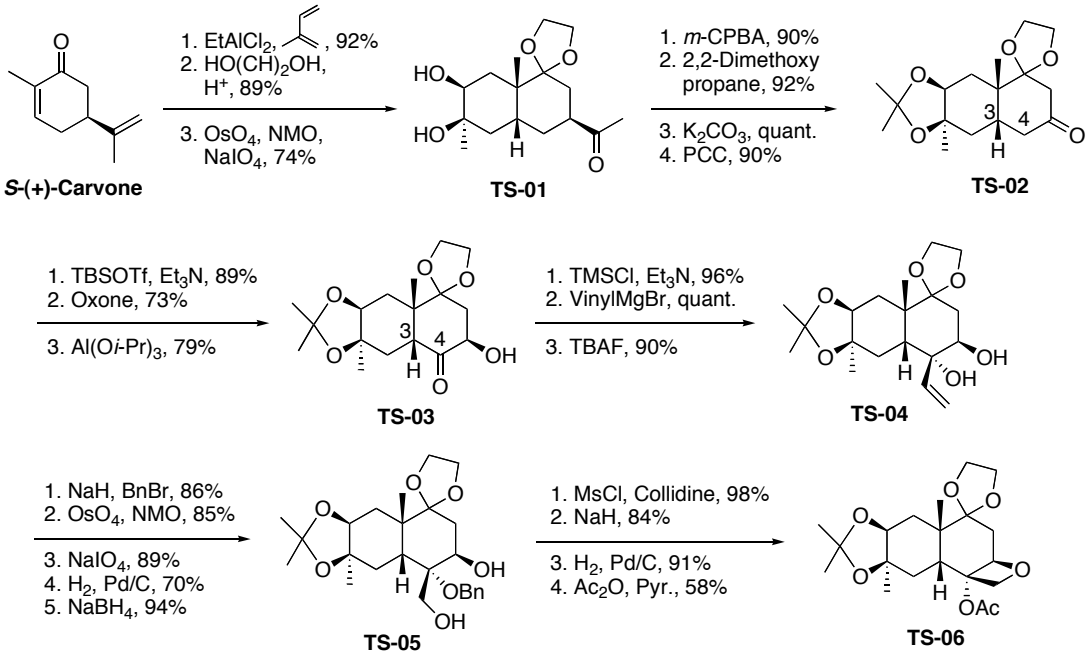
Scheme-1.25: Synthesis of taxinine AB ring system

The synthesis of taxinine AB system through an aldol-Payne rearrangement annulation was accomplished;[90] the molecular construction offers a potential synthetic route to the closure of A ring of taxol.

[90] Swindell, C. S.; Patel, B. P. *J. Org. Chem*. **1990**, *55*, 3-5.

2) TAXOL CD RING SYSTEM

Professor Tony K. M. Shing proposed a synthesis of taxol CD ring system from (*S*)-(+)-carvone through an asymmetric Diels-Alder reaction.[91] The enantiopure preparation may find an application in taxol synthesis.



Scheme-1.26: Synthesis of taxol CD ring system

An intermolecular Diels-Alder reaction between *S*-(+)-carvone and isoprene gave the adduct with the correct configuration of the quaternary methyl group of taxol. Protection of the ketone with ethylene glycol, then dihydroxylation and selective terminal glycol cleavage oxidation furnished **TS-01** (Scheme-1.26). Baeyer-Villiger oxidation of the ketone, protection of diol and oxidation of the secondary alcohol afforded **TS-02**. The obtained silyl enol ether was oxidized with oxone to give α-hydroxy ketone, which underwent an intramolecular Oppenaurer oxidation and Meerwein-Ponndorf-Verley reduction using Al(O*i*-Pr)$_3$ to afford **TS-03**. Diol **TS-04** was obtained by addition of vinylmagnesium bromide followed by removal of the TMS group. Conversion of both alcohols to the benzyl ethers and oxidative cleavage of the terminal olefin gave the aldehyde while the secondary benzyl ether was selectively transformed to alcohol. S_N2 reaction of the mesylate of **TS-05** gave the oxetane ring and transformation of the benzyl ether to the acetate afforded **TS-06**.

[91] Shing, T. K. M.; Lee, C. M.; Lo, H. Y. *Tetrahedron Lett*. **2001**, *42*, 8361-8363.

The product was constructed from *S*-(+)-carvone in 21 steps with an overall yield of 4%, containing the quaternary methyl group with the correct absolute conformation. However, the configuration of C3 needs to be inverted to taxol-like type, which might be realized around the C4 keto group, generating additional steps. Elimination of the redundant methyl on the acetonide group should also be seriously considered.

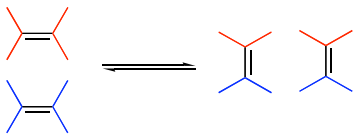
3. METATHESIS, CYCLOOCTENES

"The power of olefin metathesis is that it transforms the carbon-carbon double bond, a functional group that is unreactive toward many reagents that react with many other functional groups. With certain catalysts, new carbon-carbon double bonds are formed at or near room temperature even in aqueous media from starting materials that bear a variety of functional groups."[92]

Once the metathesis was discovered, it found rapidly numerous applications. Danishefsky and Nicolaou used it to synthesize epothilones;[93] Kiessling uses it to prepare carbohydrate-containing polymers with significant biological activities;[94] Seeberger uses it to cleave linkers in solid-phase oligosaccharide synthesis[95]… As such a versatile and powerful tool, we also thought of synthesizing taxol in an efficient way with metathesis.

3.1 GENERALITIES

In the 1950s Yves Chauvin of the French Oil Institute in Rueil-Malmaison observed some interesting reactions in the process of the petrochemicals industry, which transformed a certain class of carbon compounds in the presence of nickel metal. The process involves two molecules that each contains a double bond. The bond acts rather like a double handclasp between a pair of dancers (Scheme-1.27), and during the reaction, the molecules effectively exchange partners.

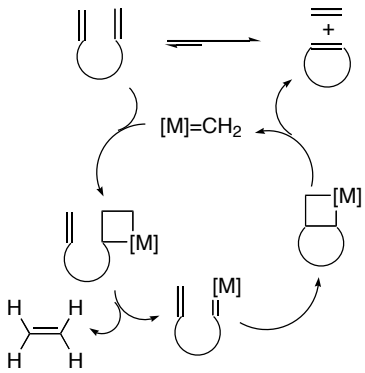


Scheme-1.27: Olefin metathesis as dancers

In 1971 Chauvin and his student Jean-Louis Hérisson showed how the metal-atom catalyst coordinates the rearrangement of carbon-carbon bonds (Scheme-1.28).[96] The catalytic cycle consists of a sequence of metathetical [2+2] cycloaddition-cycloreversion of metallic carbene

[92] Rouhi, A. M. *Chem. & Eng. News* **2002**, *80*, 29-33.
[93] Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073-10092. Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166–168.
[94] Pohl, N. L. ; Kiessling, L. L. *Synthesis* **1999**, 1515-1519.
[95] Kanemitsu, T.; Seeberger, P. H. *Org. Lett.* **2003**, *5*, 4541-4544.
[96] Hérisson, J.-L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161-176.

and metallacyclobutane. Although each step of the reaction is reversible, formation of ethylene entropically favors the catalytic process.



Scheme-1.28: Mechanism of olefin metathesis by Chauvin

Soon after, Richard Schrock began to look for more effective catalysts than those found fortuitously in industry. Between 1980 and 1990 he found that compounds containing molybdenum and tungsten were particularly efficient (Figure-1.21). But Schrock's catalysts still had drawbacks: they react with other functional moieties attached to the double bonds, and glove box manipulation is also inevitable. In 1992, Grubbs discovered that ruthenium compounds interfered less, and were more stable in air.

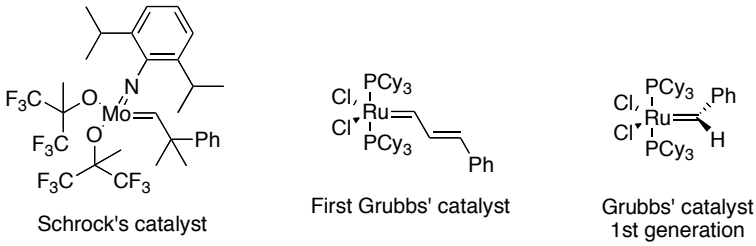
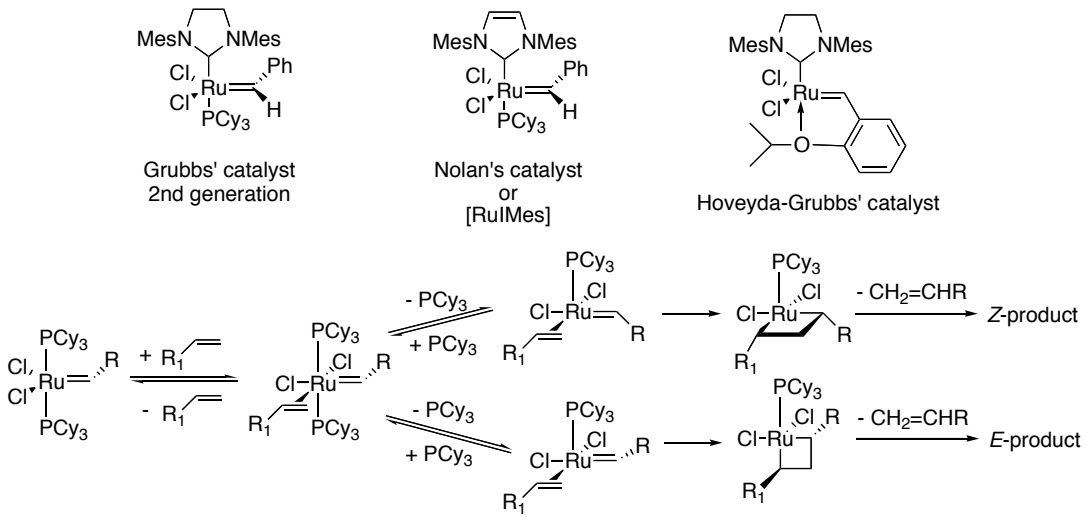


Figure-1.21: Metathesis catalysts

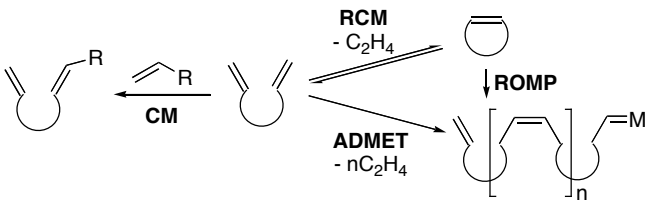
The second-generation catalysts were then developed. As shown in Scheme-1.29, the catalysts comport a neutral ruthenium in an oxidation state (II) with 16 electrons in external orbital and the HOMO is the 5p. Grubbs proposed a more detailed mechanism with the participation of an electron-rich atom (phosphine, or oxygen in the case of Hoveyda-Grubbs) by a dissociation-association pathway.[97]

[97] Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18-29.



Scheme-1.29: Metathesis mechanism by Grubbs

With the development of these highly efficient catalysts, several types of metathesis were conducted (Scheme-1.30): **ADMET** (**A**cyclic **D**iene **Met**athesis), and **ROMP** (**R**ing **O**pening **M**etathesis **P**olymerization), which was widely applied in polymer industry.

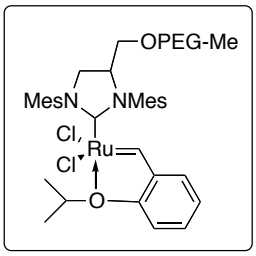


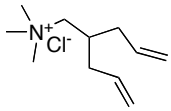
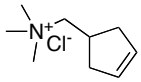
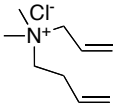
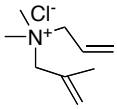
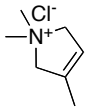
Scheme-1.30: Several types of metathesis

Effect of ligand modifications to enhance the catalytic cycle was proven useful. A homogeneous catalyst was also discovered to perform the metathesis under aqueous conditions (Table-1.4).[98]

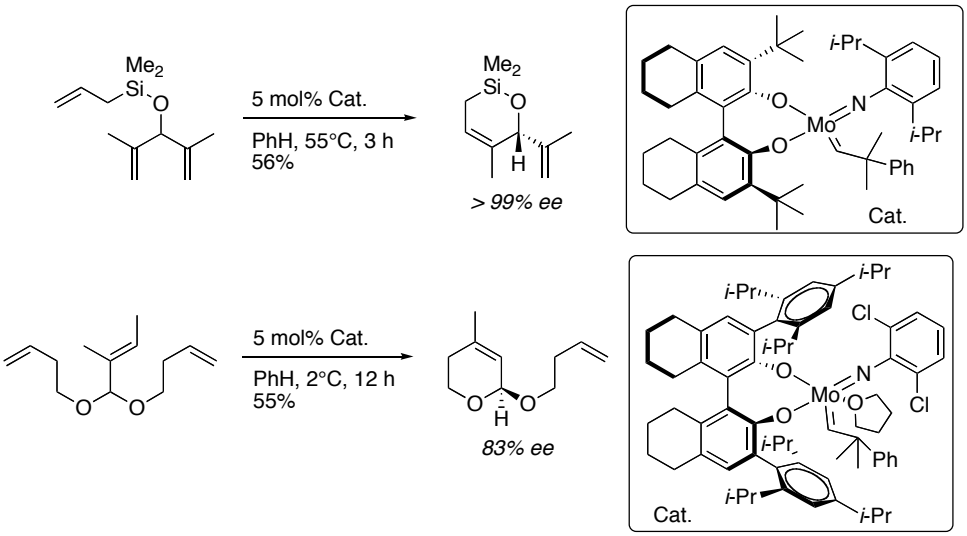
[98] Grubbs, R. H.; Hong, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508-3509.

Table-1.4: Metathesis under aqueous conditions



Substrate	Time	Product	Conversion
	12 h		> 95%
	24 h		> 95%
	24 h		42%

A remarkable innovation was the development of asymmetric metathesis through attachment of chiral ligands (Scheme-1.31). The chiral Mo-alkylidene complex introduces the stereochemistry by promoting metallabutane on one face of the triene compound, to afford the product with excellent enantioselective excess.[99]

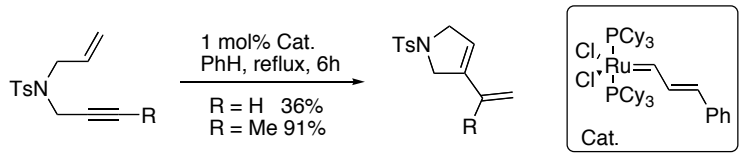


Scheme-1.31: Asymmetric metathesis

[99] Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945-950.

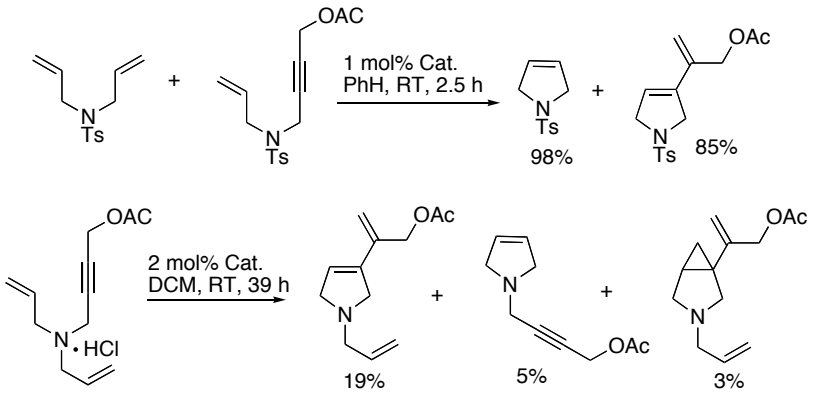
3.2 ENYNE METATHESIS

In 1994 Mori discovered the first enyne metathesis reaction in the presence of Grubbs catalyst 1st generation (Scheme-1.32).[100] With electron-donor substitution on the alkyne moiety, the metathesis reaction performed more efficiently.



Scheme-1.32: Enyne metathesis

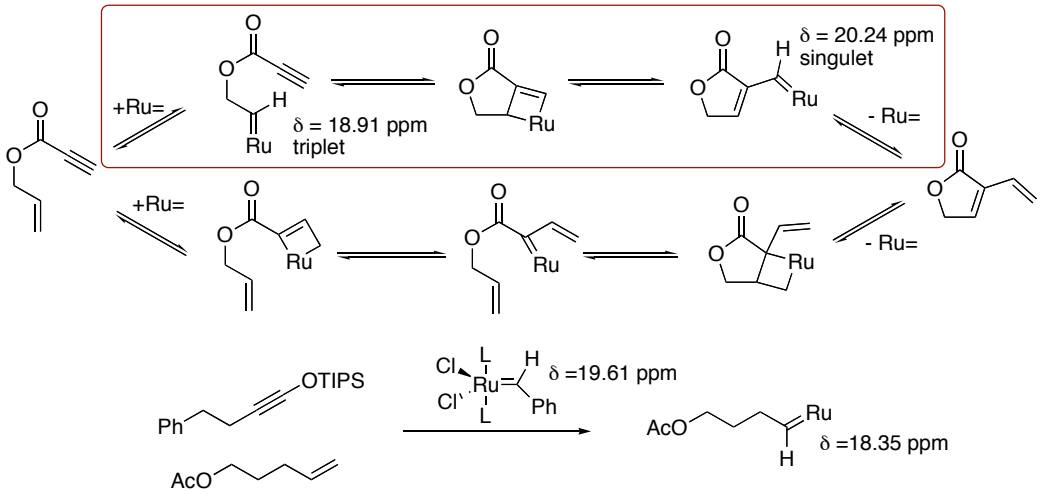
With the same catalyst, the reactivity of alkenes and alkynes in the metathesis reaction was then examined. A better yield was observed in ene-ene metathesis, which might be explained by a less tensional ruthenacyclobutane formation than ruthenacyclobutene in ene-yne metathesis (Scheme-1.33). However, a dominant ene-yne metathesis in the presence of ene-ene possibility for the closure of five-membered rings was probably due to lower kinetic activation energy in the former case.



Scheme-1.33: Enyne and ene-ene metathesis

Mechanistic studies about enyne metathesis were first performed with NMR analysis. Formation of the two vinyl carbene surveyed by ^{1}H NMR proved the initiation of propagating ruthenium species began with the terminal olefin (in the case of the electron-deficient alkynes) (Scheme-1.34).[101] A similar observation with substituted alkynes confirmed the former experiment.

[100] Kinoshita, M.; Mori, M. *Synlett* **1994**, *12*, 1020-1022.
[101] Hoge, T. R.; Donaldon, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277-279.



Scheme-1.34: Mechanism confirmed by NMR

A DFT study of enyne metathesis catalyzed by Grubbs catalyst was performed using the B3LYP/LACV3P**+//B3LYP/LACVP* level of theory as implemented in the Jaguar 4.1 quantum chemistry program package.[102] As shown in Figure-1.22, the acetylene insertion in enyne metathesis requires an overall Gibbs free activation energy of δG^{τ}=105.1 kJ mol^{-1}, which is more exergonic than ethylene (76.1 kJ mol^{-1}) in ene-ene metathesis. Thus, the slow insertion process with high barrier represents the rate-limiting step in the enyne catalytic cycle.

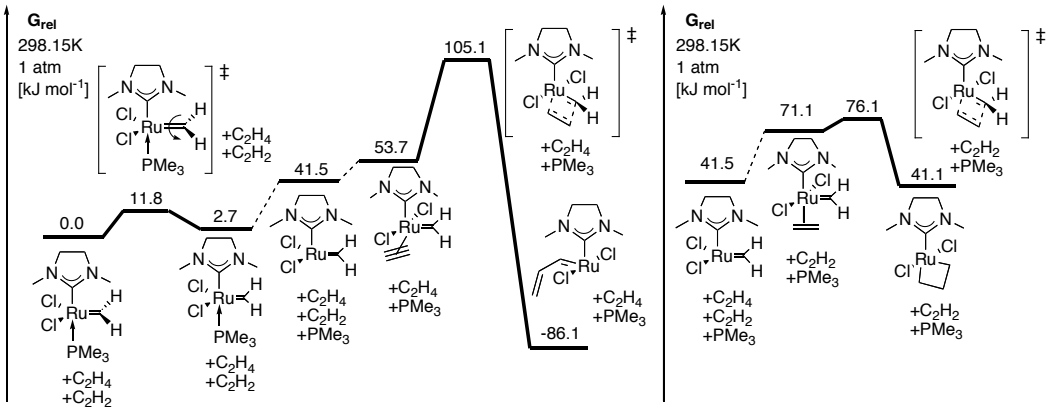


Figure-1.22: DFT study on acetylene insertion and ethylene insertion

In the more precise case of an intramolecular enyne metathesis, alkyne insertion was disfavored with an overall Gibbs free activation energy of 115.1 kJ mol^{-1} in comparison with a primary alkene insertion (95.3 kJ mol^{-1}) in the two hypothetical mechanism pathways (Figure-1.23, 1.24); moreover, higher exergonic enyne metathesis step (178.8 kJ mol^{-1}) was irreversible while ene-ene metathesis (28.7 kJ mol^{-1}) would be a reversible step.

[102] Lippstreu, J. L.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444-7457.

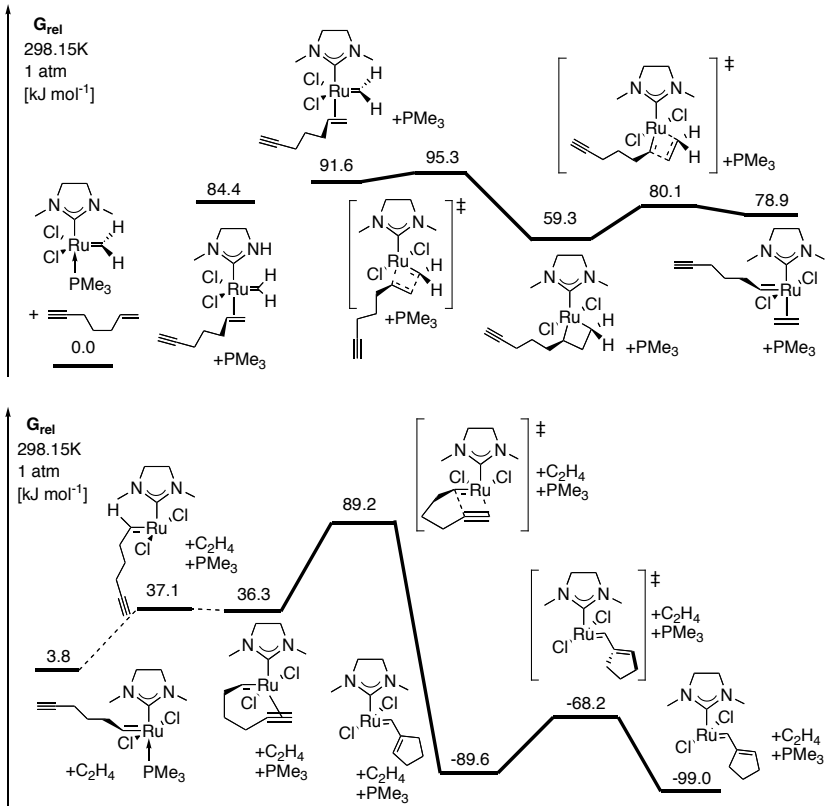


Figure-1.23: DFT study on alkene insertion sequence

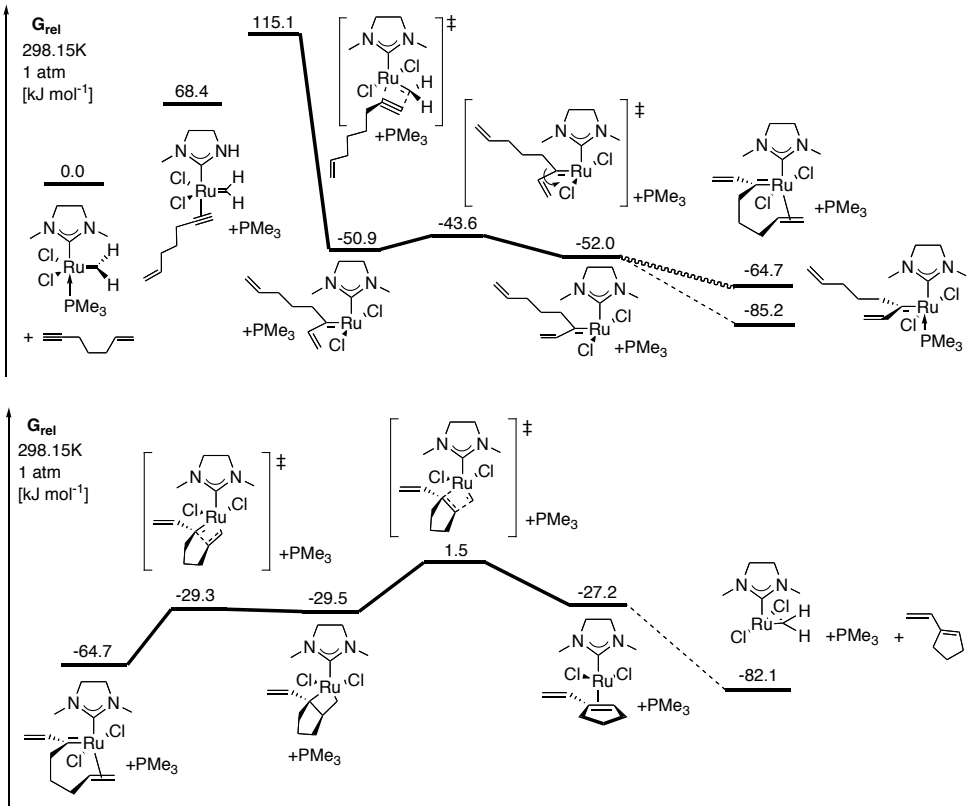
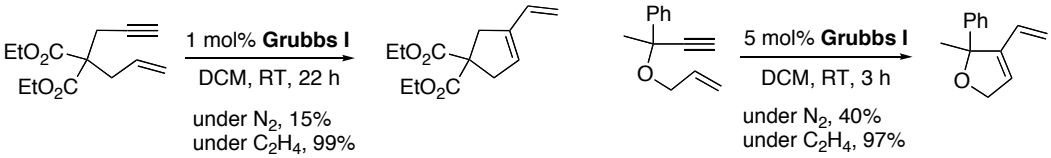


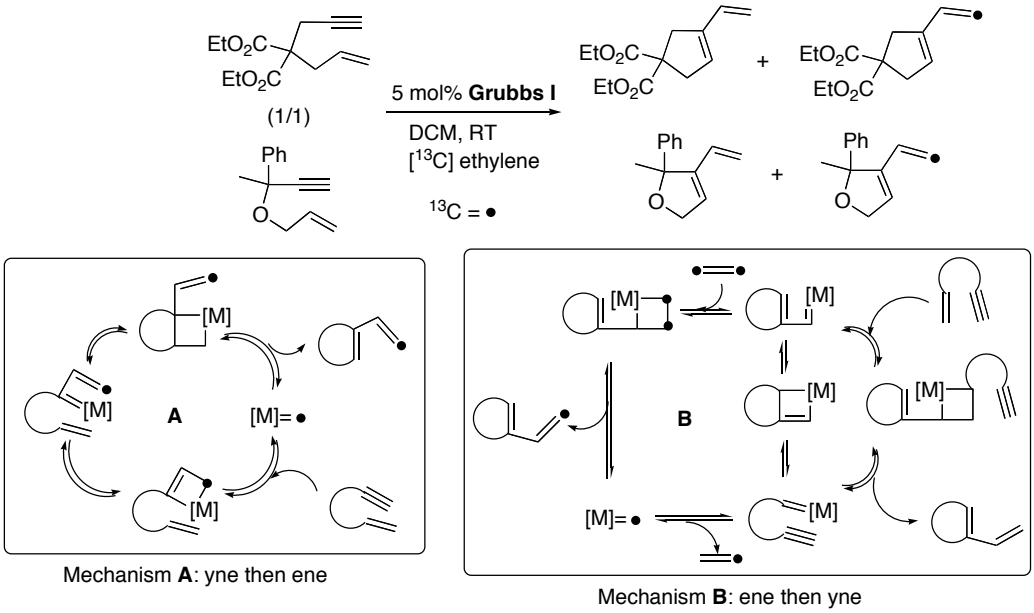
Figure-1.24: DFT study on alkyne insertion sequence

As shown in Scheme-1.35, ethylene was involved in the first pathway. Mori reported that ethylene has a dramatic effect on the yield of Ru-catalyzed enyne ring-closing metathesis;[103] so the experimental rate enhancement of metathesis in ethylene atmosphere condition would be more compatible with "ene then yne" mechanism.



Scheme-1.35: Enhancement of metathesis by ethylene

An experience of ^{13}C-labeled metathesis also proved that the enyne metathesis mechanism takes place by alkene insertion followed by enyne metathesis (Scheme-1.36).[104] The accelerating effect for the first reaction is increased 2.8 times over that of the second reaction in the presence of ethylene atmosphere, and the resulting reaction rates were similar ($8.3x10^{-4}$ and $9.7x10^{-4}$, respectively). So according to the mechanism A, the $^{13}C/^{12}C$ incorporation into two products should be equal under [^{13}C] ethylene conditions; conversely, a greater level of ^{13}C through two catalytic cycle of mechanism B should reflect the 2.8-fold difference.

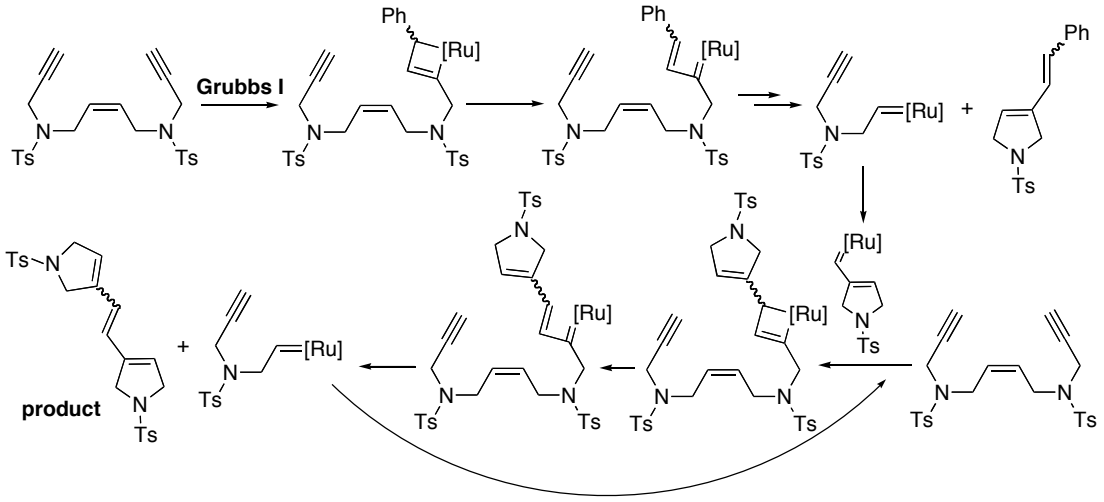


Scheme-1.36: ^{13}C-labeled metathesis

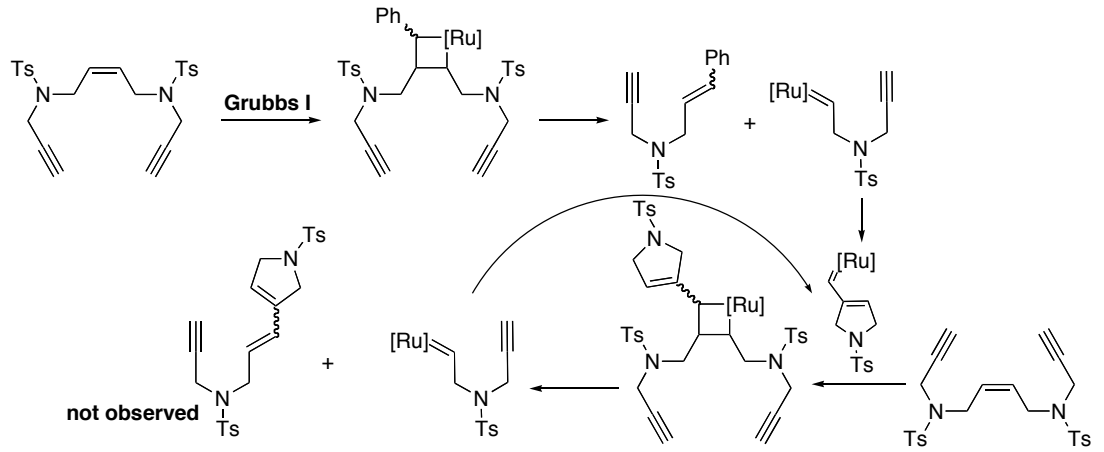
Effectively, the initial ratio of $^{13}C/^{12}C$ incorporation was 2.3±0.6:1, which is in good agreement with that predicted by mechanism B, "ene then yne".

[103] Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082-6083. Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678-693.
[104] Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 7442-7447.

However, "yne then ene" mechanism with initial alkyne insertion pathway was also proven to be possible in the presence of disubstituted alkenes, due to its lesser activity. As shown in Scheme-1.37, the bicyclic product was obtained following "yne then ene" pathway, while the product by "ene then yne" mechanism was not observed (Scheme-1.38).[105] These findings were very important to develop ene-yne-ene and ene-yne-yne cascade metatheses with controlled chemoselectivity.



Scheme-1.37: Alkyne insertion sequence



Scheme-1.38: Alkene insertion sequence

Furthermore, ene-yne-ene and ene-yne-yne cascade metathesis were also discovered.[106]

[105] Dieltiens, N.; Moonen, K.; Stevens, C. V. *Chem. Eur. J.* **2007**, *13*, 203-214.
[106] Banti, D.; North, M. *Tetrahedron Lett.* **2003**, *44*, 8157-8160.

3.3 CYCLOOCTENE BY RING-CLOSING METATHESIS

For a long time, formation of eight-membered rings had been a challenge for organic chemists due to the transannular interactions that caused unfavorable entropy and enthalpy.

The conformations of eight-membered ring were studied by several methods.[107] Three principal types of conformations are commonly observed: boat-chair (BC), crown (C) and boat-boat (BB) (Figure-1.25). The interconversion among these conformations depends on the molecular energy barrier of differently substituted eight-membered rings. In general, boat-chair represents the most stable conformation with minimized transannular interactions and weakened ring tension.

Figure-1.25: cyclooctene conformations

Numerous natural products possess eight-membered rings, as shown in Figure-1.26.

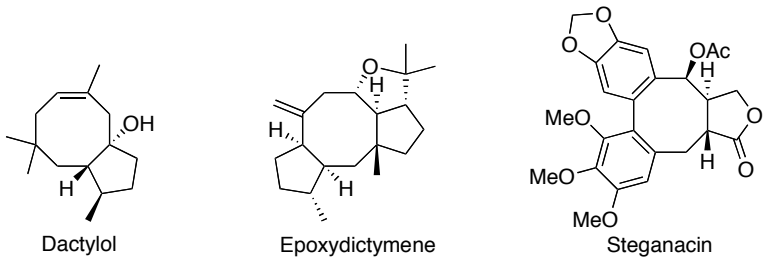


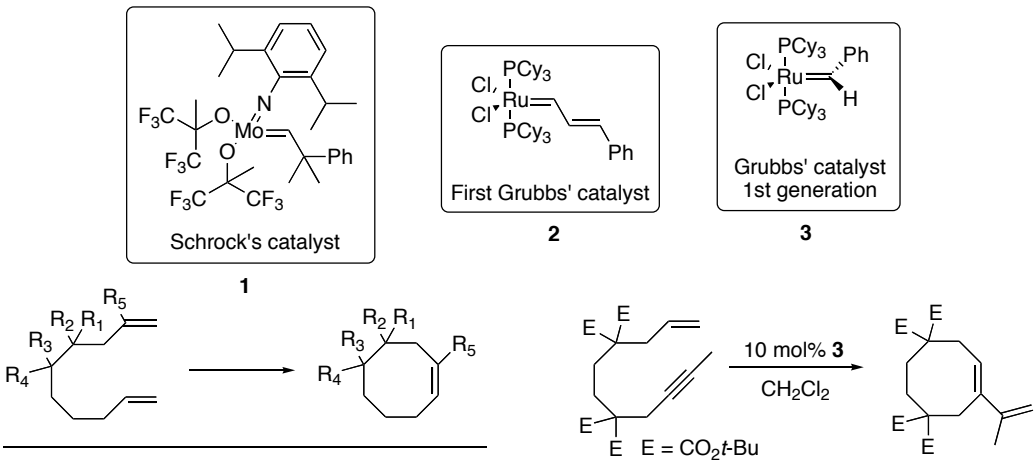
Figure-1.26: natural products containing eight-membered ring

For the formation of eight-membered rings, electrophilic cyclizations, aldol reactions, nucleophilic addition on carbonyl groups, radical cyclizations, cycloadditions (Diels-Alder, ring expansion or fragmentation) were frequently used. Generally, the C-C bond formation was favorized by reactional entropy and ring conformation.[108]

In the 1990s, ring-closing metathesis (RCM) has been explored and became a powerful and versatile tool for the formation of cyclic compounds. However, cyclooctene was not as facile to obtain as other cyclic compounds.[109] Grubbs published the first approach of ring-closing

[107] Anet, F. A. L.; Anet, R. *Top. Curr. Chem.* **1974**, *45*, 169-220. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981-3996.
[108] Yet, L. *Chem. Rev.* **2000**, *100*, 2963-3007.
[109] Michaut, A.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5740-5750.

metathesis of eight-membered ring in 1995 (Scheme-1.39);[110] an enyne ring-closing metathesis performed in the presence of *gem*-disubstituents by Mori also proved the difficulty of the reaction.[111]

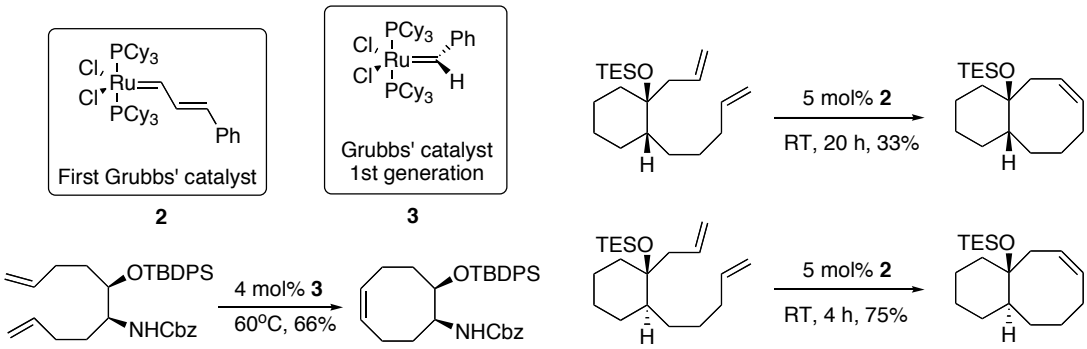


R_1	R_2	R_3	R_4	R_5	Cat.	Yield (%)
Me	TESO	H	H	H	**2**	0
H	H	CO_2Et	CO_2Et	H	**1**, **3**	0
H	H	CO_2Et	CO_2Et	Me	**1**, **3**	0

Conditions	Time (h)	Yield (%)
reflux	36	50
RT	22	0

Scheme-1.39: Cyclooctene formations by metathesis

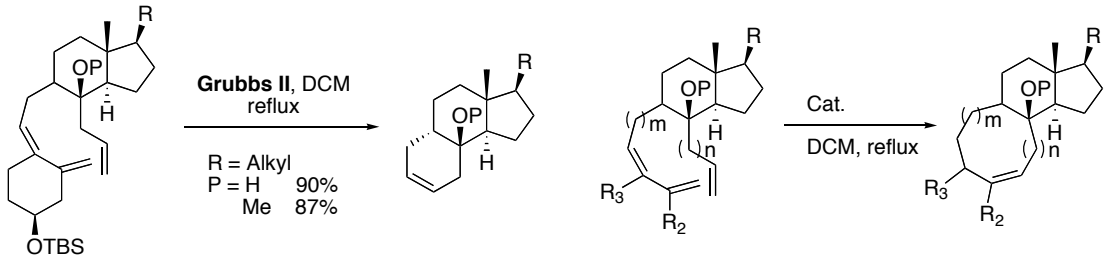
However, cyclooctene formation by metathesis could be realized in the presence of certain conformational constraints such as a preexisting ring or highly sterically hindered 1,2-disubstituents (Scheme-1.40).[14, 112] Curiously, the *cis* junction bicycle precursor is less reactive than its *trans* diastereomer, and a computed calculation showed a difference in free energy of 2 kJ mol^{-1} between the two resulting bicyclic diastereomers.[113]



Scheme-1.40: Influence of conformational constraints

[110] Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108-2109.
[111] Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654-664.
[112] Van den Nieuwendijk, A. M. C. H.; Ghisaidoobe, A. B. T.; Overkleeft, H. S.; Brussee, J.; van der Gen, A. *Tetrahedron* **2004**, *60*, 10385-10396.
[113] Morehead, A. Jr.; Grubbs, R. H. *Chem. Commun*. **1998**, 275-276.

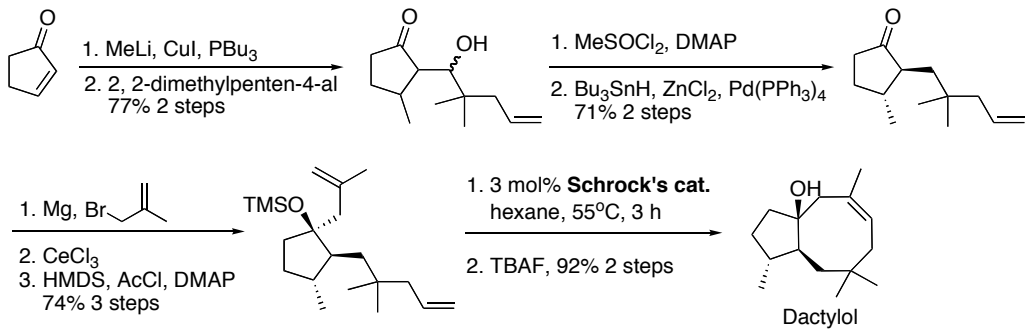
Also, it was shown that cyclooctene formation could be influenced by crucial constraints of substituents. In Granja's studies, the cyclohexene formation was favorized even though the cyclooctene formation should be less hindered (Scheme-1.41). Further trials were then performed with no cyclic constraints on the terminal olefin: only *O*-homoallyl olefin can form ruthenacyclobutane but *O*-allyl olefin not; only Grubbs II catalyst can catalyze metathesis reaction with a *gem*-disubstituted olefin (Scheme-1.41, entry 5).[114]



Entry	P	R_2	R_3	m	n	Cat.	Yield (%)
1	H	H	H	1	1	**Grubbs I**	86
2	H	H	H	2	0	**Grubbs I/II**	—
3	Me	H	H	2	0	**Grubbs I/II**	—
4	Me	Me	H	1	1	**Grubbs I**	—
5	Me	Me	H	1	1	**Grubbs II**	92
6	H	Me	H	1	1	**Grubbs II**	89
7	Me	$(CH)_4$		1	1	**Grubbs II**	—

Scheme-1.41: Influence of substituents

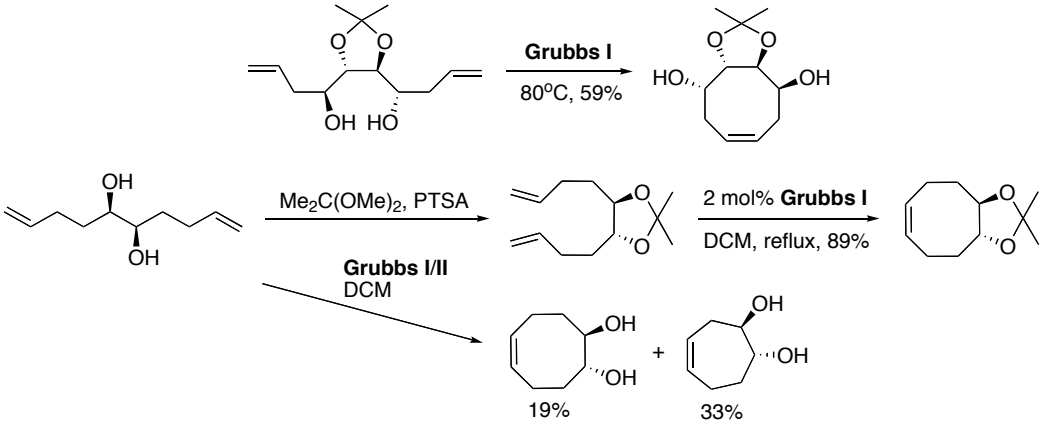
In the synthesis of dactylol proposed by Fürstner, the closure of the eight-membered ring was realized with excellent yield in the presence of a fused five-membered ring and a *gem*-dimethyl group (Scheme-1.42). Protection of the hydroxy group as a silyl ether was necessary for the metathesis to proceed.



Scheme-1.42: Synthesis of dactylol by metathesis

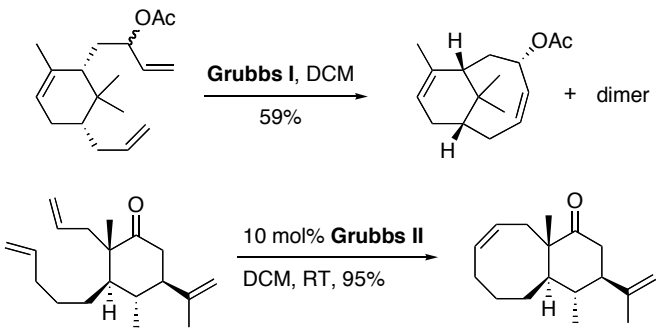
[114] Codesido, E. M.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 1483-1486.

The metathesis is compatible with many functional groups, including hydroxy, carbonyl, phosphonate, and metal complex.[115] Even in the presence of dihydroxy groups, the ring-closing metathesis afforded the desired cyclooctene (Scheme-1.43).[116] However, 1,2-dihydroxy groups can complex ruthenium species, and low reactivity and occasionally loss of methylene were observed.[117]



Scheme-1.43: Metathesis in the presence of the dihydroxy group

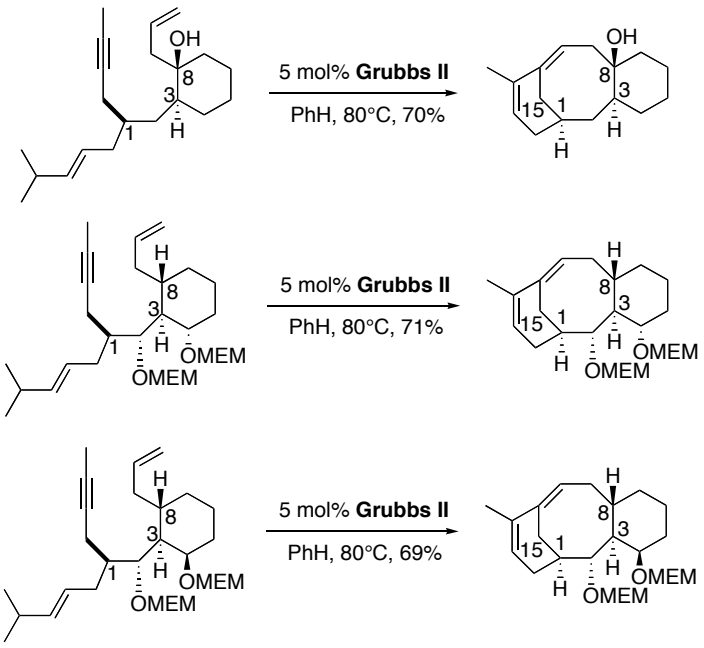
Finally, a taxol AB bicycle ring system without a dihydroxy group on the B ring was constructed by ring-closing metathesis. One isomer cyclized to afford the bicyclic product, but the other dimerized, probably due to steric effect (Scheme-1.44).[118] Another example of BC bicyle without the *gem*-dimethyl group and the dihydroxy group on the B ring was also reported.[119]



Scheme-1.44: Synthesis of taxol AB and BC ring system by metathesis

[115] Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012-3043.
[116] McNulty, J.; Grunner, V.; Mao, J. *Tetrahedron Lett.* **2001**, *42*, 5609-5612.
[117] Braddock, D. C.; Cansell, G.; Hermitage, S. A.; White, A. J. P. *Tetrahedron: Asymmetry* **2004**, *15*, 3123-3129.
[118] Wenz, M.; Großbach, D.; Beitzel, M.; Blechert, S. *Synthesis* **1999**, 607-614.
[119] Srikrishna, A.; Dattatraya, H. D.; Kumar, P. R. *Tetrahedron Lett.* **2004**, *45*, 2939-2942.

Very recently, a model taxane skeleton was synthesized by Granja using ene-yne-ene metathesis (Scheme-1.45).[120] In the presence of Grubbs II catalyst, the ABC tricycles without the *gem*-dimethyl group at C15 and the quaternary methyl group at C8 were obtained in satisfying yields. However, these model compounds possess the wrong configuration at C1. The author has also shown that diene-ynes epimeric at C1 do not lead to the desired tricycles. Thus, apparently the natural taxane skeleton cannot be obtained with this cascade ring-closing metathesis.



Scheme-1.45: Synthesis of model taxane ABC ring system by ene-yne-ene metathesis

Metathesis has taken a route, not unusual in chemistry, from industry to the academic laboratory and then back to industry. Along the way, it was transformed from a curious observation to a systematic and useful methodology. It is now widely used in the synthesis of all kinds of organic compounds, from plastics to pharmaceuticals and herbicides.[121] Grubbs' catalyst was even applied in the aerospace industry: small microcracks produced in spaceship's hull would be sealed by contacting with capsules of dicyclopentadiene and Grubbs' catalyst in the hull forms, which could undergo ring opening metathesis polymerization (ROMP) to solidify the spaceship.[122]

[120] Aldegunde, M. J.; Castedo, L.; Granja, J. R. *Org. Lett.* **2008**, *10*, 3789-3792.
[121] *Handbook of Metathesis* Grubbs, R. H. ed. Wiley-VCH Verlag GmbH, Weinheim, Germany, **2003**.
[122] White, S. R.; Sottos, N. R.; Geubelle, P. H.; Moore, J. S.; Kessler, M. R.; Sriram, S. R.; Brown, E. N.; Viswanathan, S. *Nature* **2001**, *409*, 794-797.

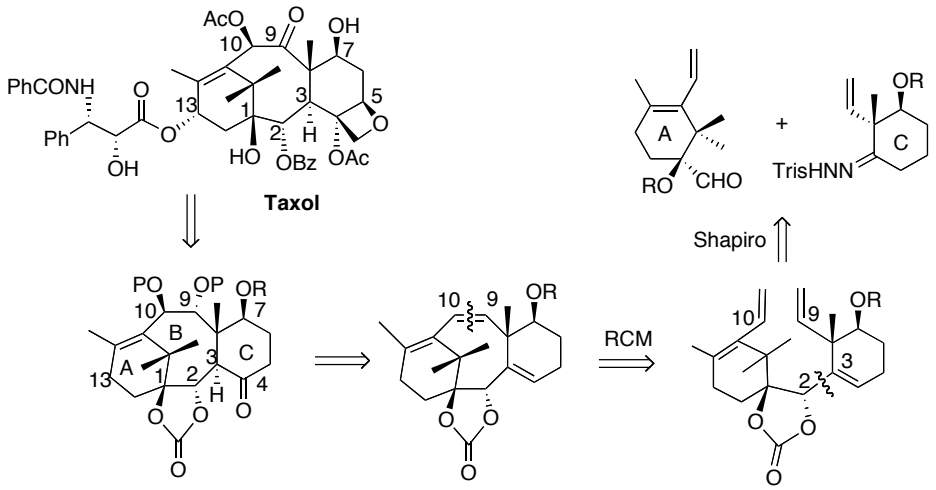
Chapter II

SYNTHESIS OF BC RING SYSTEMS
OF TAXOL

1. PREVIOUS WORK IN THE LABORATORY[123]

1.1 CONVERGENT APPROACH

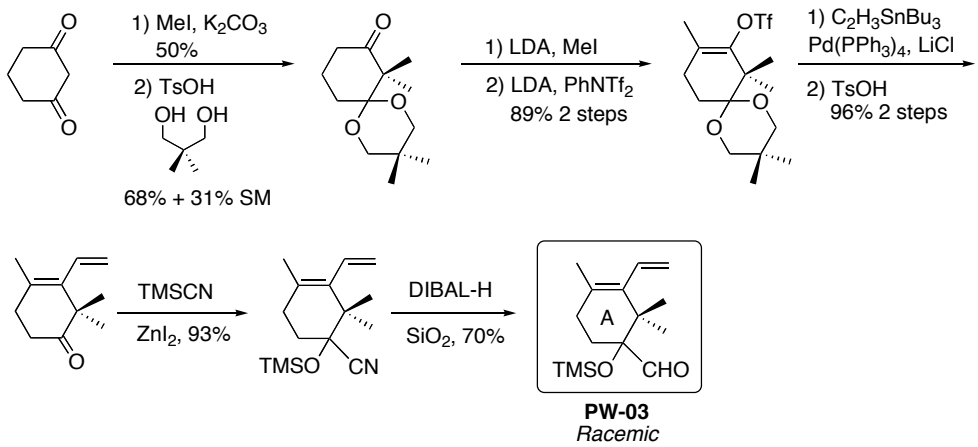
At the moment when the project was initiated, neither were there publications about total synthesis of taxol, nor the formation of cyclooctenes by ring-closing metathesis. As shown in Scheme-2.1, a convergent retrosynthesis was envisioned. Taxol would be synthesized from a tricyclic compound; the lateral chain could be attached after functionalization at C13 with PCC; the oxetane D ring could be created using Holton's strategy (cf. p. 32). The B ring would be formed by ring-closing metathesis between C9 and C10, and the metathesis precursor would be obtained by coupling the A ring and the C ring by a key Shapiro reaction.



Scheme-2.1: Retrosynthesis for a convergent approach

In the first approach to taxol, the A ring was prepared as a racemic mixture (Scheme-2.2): 1,3-cyclohexadione was subjected to alkylation to provide the dimethyl adduct then one carbonyl group was protected to give ketal **PW-01**. Methylation and vinyl triflate formation led to a suitable substrate to realize a Stille coupling reaction, which was followed by removal of the ketal protecting group under acidic conditions to afford **PW-02**. At the end, ZnI_2-catalyzed cyanation, partial reduction then hydrolysis conducted to racemic **PW-03**.[124]

[123] Dr. Benoît Muller (Ph.D. Thesis, Ecole Polytechnique, 1996); Dr. Damien Bourgeois (Ph.D. Thesis, Ecole Polytechnique, 2000); Dr. Stéphanie Schiltz (Ph.D. Thesis, Ecole Polytechnique, 2005).
[124] Muller, B.; Delaloge, F.; den Hartog, M.; Férézou, J.-P.; Pancrazi, A.; Prunet, J.; Lallemand, J.-Y.; Neuman, A.; Prangé, T. *Tetrahedron Lett*. **1996**, *37*, 3313-3316.



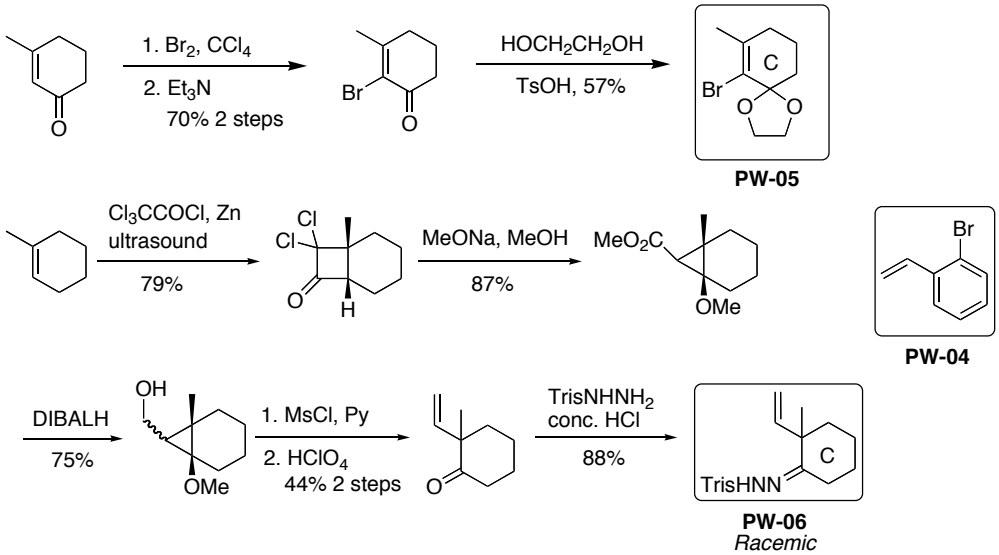
Scheme-2.2: Synthesis of A ring PW-03

Three types of model C rings were then prepared to test the Shapiro reaction (Scheme-2.3):

1. Commercial 2-bromostyrene **PW-04** with an aromatic C ring.[125]

2. Vinyl bromide **PW-05** was synthesized from α,β-unsaturated 3-methylcyclohexenone by dibromation, followed by elimination of HBr and protection of the ketone as a ketal.

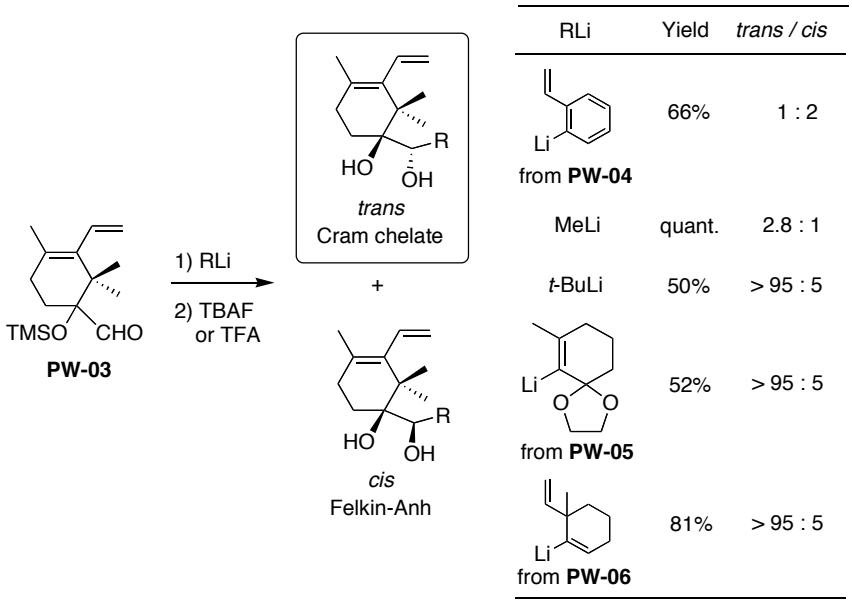
3. Vinyl hydrazone **PW-06** was prepared from methyl cyclohexene by [2+2] cycloaddition and ring rearrangement, followed by reduction giving the [3,6]-bicyclic alcohol, which was subjected to elimination, oxidation and transformation of the ketone to the hydrazone.



Scheme-2.3: PW-04 and synthesis of model C ring PW-05 and 7-deoxy C ring PW-06

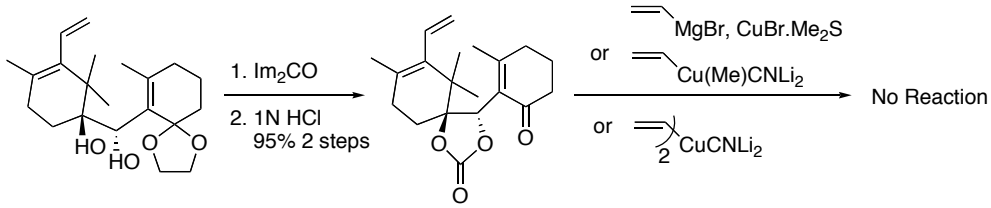
[125] Fletcher, V. R.; Hassner, A. *Tetrahedron Lett.* **1970**, *13*, 1071-1074. Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* **1999**, *121*, 4074-4075.

Shapiro coupling reactions were then realized to form diverse *seco*-taxanes (Scheme-2.4).[126] Experiments with **PW-04** and MeLi resulted in low diastereoselectivity. However, addition of *t*-BuLi or hindered C ring nucleophiles proved very diastereoselective showing that a certain steric hindrance was necessary to afford a single product. The Cram-chelate product was obtained[127] and this unusual selectivity will be discussed later.



Scheme-2.4: Coupling reaction of PW-03 with nucleophiles

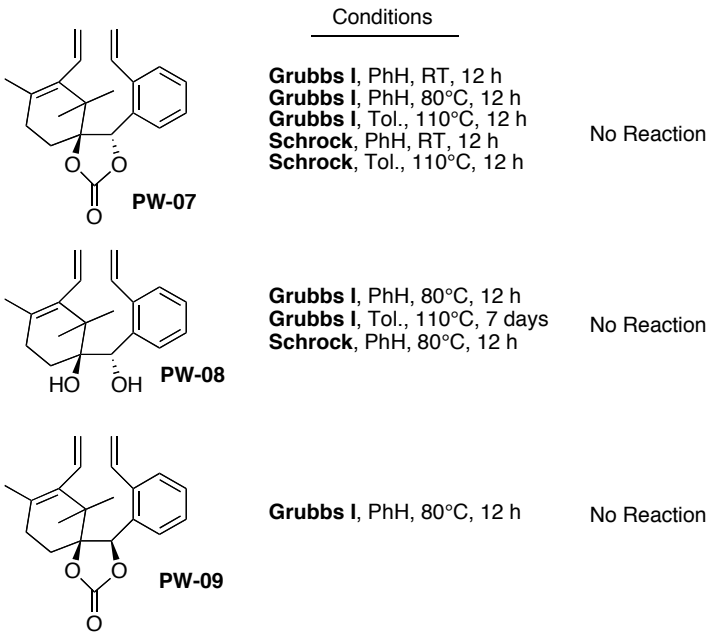
Michael addition of a vinyl group to the Shapiro adduct prepared from **PW-05** was unsuccessful, which showed that the substrate was probably too hindered (Scheme-2.5).



Scheme-2.5: Trials of Michael addition

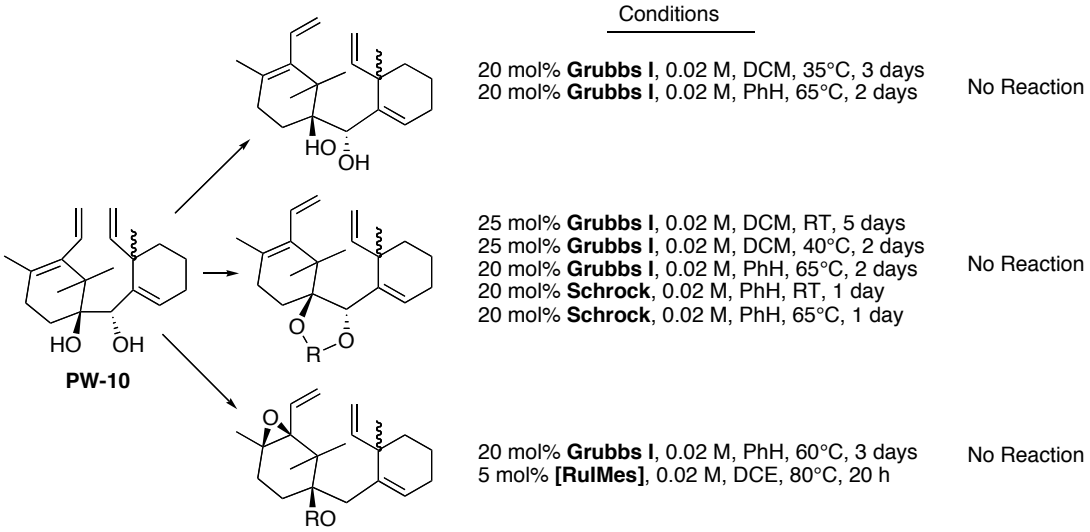
Ring-closing metathesis was first carried out with trienic carbonate **PW-07** and *anti*-dihydroxyl triene **PW-08**. No reaction occurred either in the presence of Grubbs I catalyst, or with Schrock's catalyst (Scheme-2.6). Another diastereomeric triene **PW-09** with the *syn*-dihydroxy group protected as a carbonate was also subjected to metathesis but no progress was observed in the reaction.

[126] Bourgeois, D.; Lallemand, J.-Y,; Pancrazi, A.; Prunet, J. *Synlett* **1999**, 1555-1558.
[127] The diol would be *trans* if the B ring were closed.



Scheme-2.6: Metathesis attempts of PW-07, PW-08, PW-09 bearing aromatic C ring

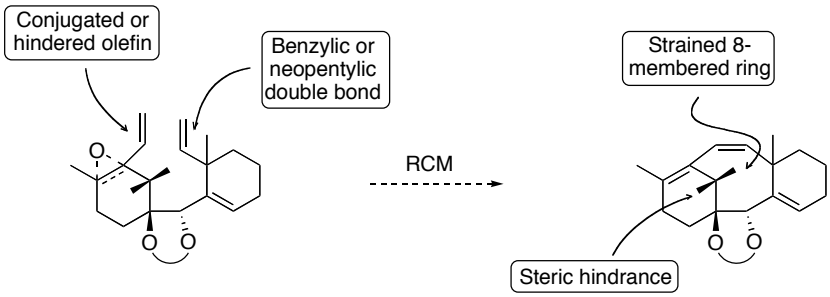
A series of metathesis precursors were prepared from **PW-10**, which contains an aliphatic C ring. Unfortunately, no reaction occurred in the metathesis of these substrates (Scheme-2.7).



Scheme-2.7: Metathesis attempts of PW-10 and its derivatives

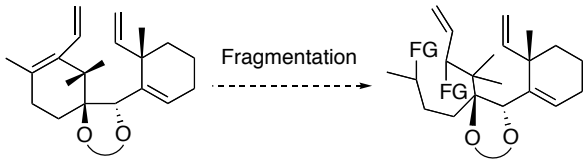
Several reasons could be claimed to explain the lack of success of this metathesis (Scheme-2.8): on the A ring, the terminal double bond is deactivated by either electronic effect of the conjugated olefin or steric hindrance in the case of epoxide; on the C ring, the benzylic or neopentylic double bond also disfavors the metathesis reaction; moreover, the desired product comporting a strained eight-membered ring, a conjugated double bond and a *gem*-dimethyl

group is disfavored by thermodynamic control ($\Delta G^{\ddagger} = 20$kcal).[128] In fact, formation of metallabutane has never been observed in our experiments.



Scheme-2.8: Main steric and electronic constraints

So one solution would be fragmenting the A ring in the metathesis precursor to release the steric hindrance and activate the terminal double bond (Scheme-2.9).

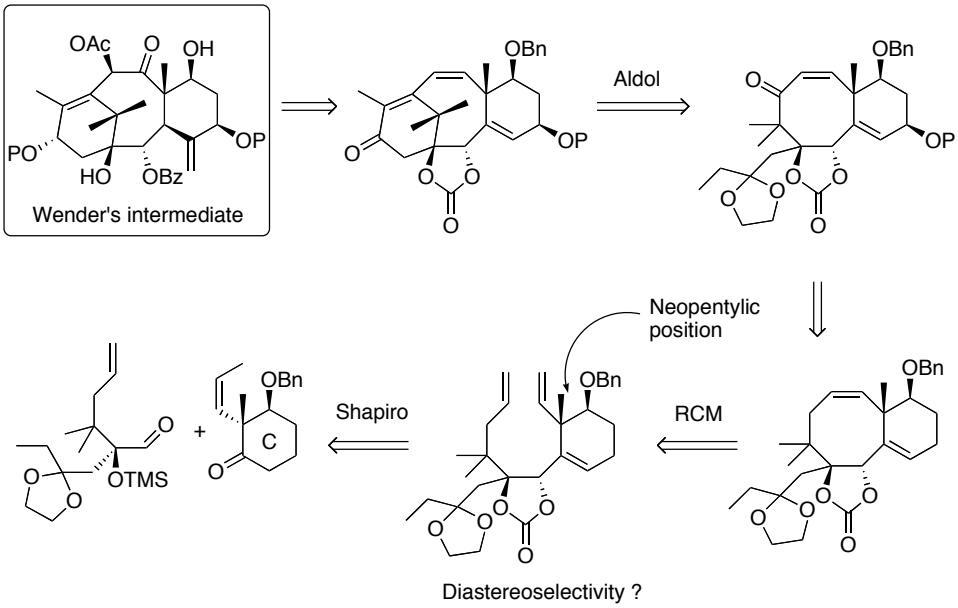


Scheme-2.9: Releasing the steric hindrance by fragmentation

[128] The energy calculation was performed on Chem3D (CambrigeSoft Corporation).

1.2 SEMI-CONVERGENT APPROACH (C9 - C10)

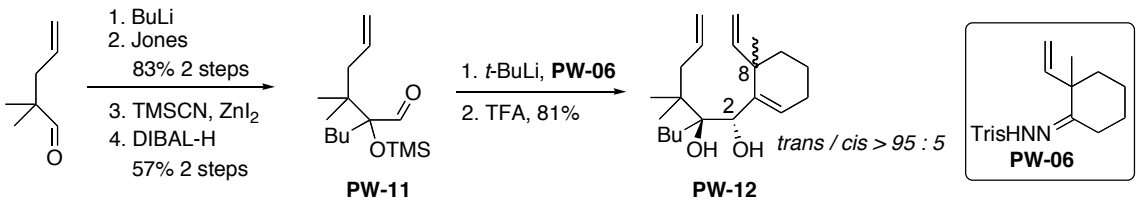
A semi-convergent synthesis was therefore adopted (Scheme-2.10): taxol would be prepared from a highly advanced intermediate described in Wender's synthesis, which would be formed by closure of the A ring by intramolecular aldol reaction. The two oxygenated functions at C5 and C11 on the BC bicycle would be generated by double allylic oxidation and the B ring would be formed by ring-closing metathesis of the diene, which would be prepared by Shapiro coupling reaction of the A fragment and the C ring.



Scheme-2.10: Semi-convergent retrosynthesis

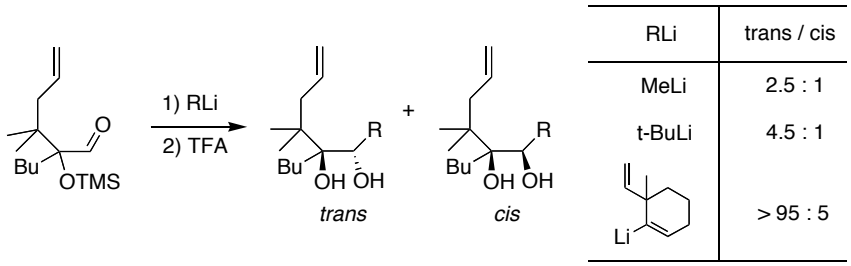
It was still envisioned to realize a ring-closing metathesis with a neopentylic olefin borne by the C ring, because the alkene insertion step of metathesis could be first realized on the terminal double bond of the A fragment, which is sterically much less hindered. Whether the Shapiro reaction would still be diastereoselective with an acyclic A fragment was also a question.

The model A fragment **PW-11** without the ketal functionality was first prepared so that the Shapiro reaction would be investigated. As shown in Scheme-2.11, reaction of **PW-06** with the model A fragment **PW-11**, which was prepared from commercially available 2,2-dimethylpent-4-enal by addition of *t*-BuLi, oxidation, cyanation and reduction, is very diastereoselective for the formation of the C2 stereocenter (two epimers were obtained at C8, because the coupling partners were racemic).



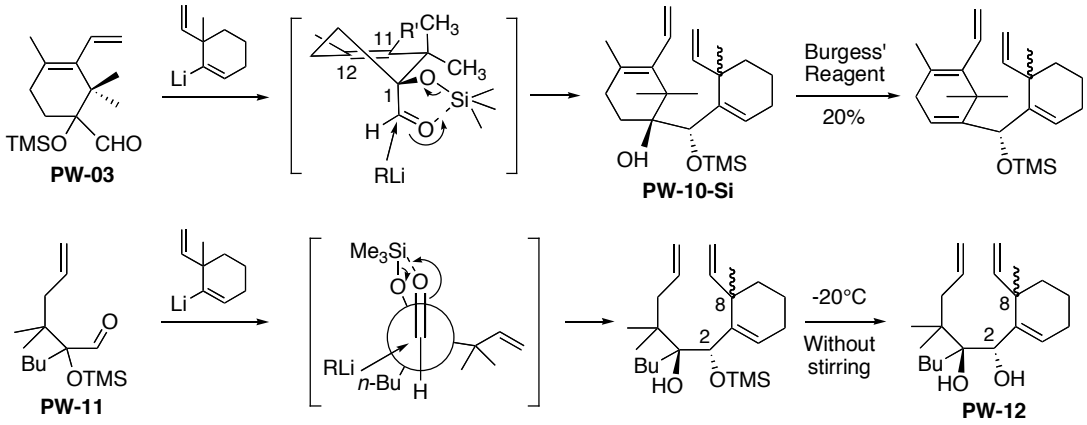
Scheme-2.11: Synthesis of trienic diol PW-12

Further condensation reactions were then performed between **PW-11** and diverse lithiated reagents. The results described in Scheme-2.12 showed that the selectivity in favor of the *trans*-product increased with the size of the nucleophile.



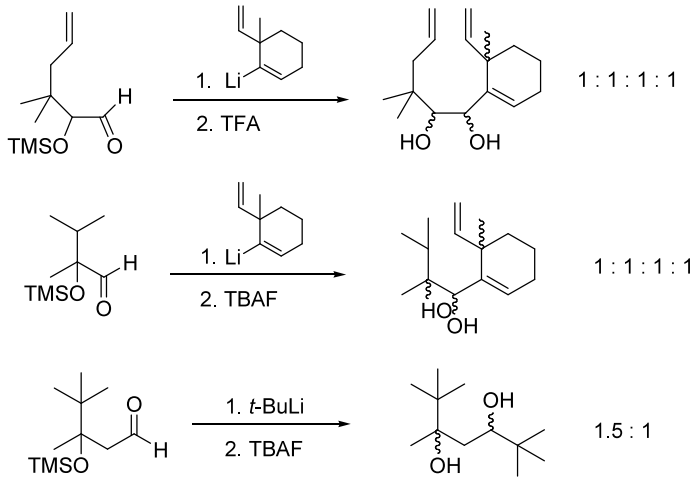
Scheme-2.12: Selectivity increased with the size of nucleophiles

Treatment with Burgess' reagent to eliminate the hydroxy group of **PW-10-Si** gave the alkene product with the TMS group on the secondary alcohol, which proved that the silyl group is transferring during the addition reaction, and that this addition proceeds *via* a chelate-like transition state (Scheme-2.13). **PW-12** could be obtained by keeping the crude product at -20°C overnight without stirring. It seems that the migration of the silyl group also occurred in the case of the non cyclic A fragment, which was followed by hydrolysis of the secondary siloxy group to give the diol product.



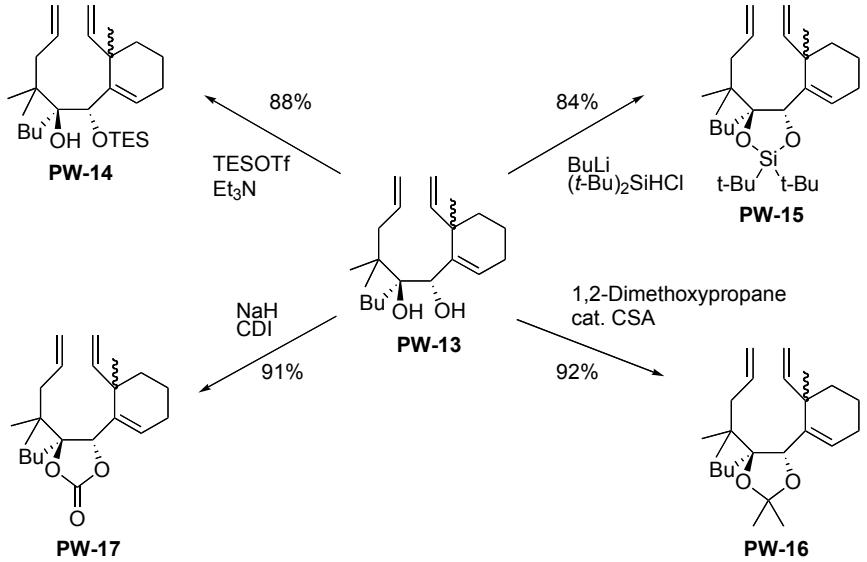
Scheme-2.13: Position of the siloxy group determined by elimination of the hydroxy group

Further experiments showed that the diastereoselectivity of the Shapiro reaction controlled by silyl group transfer necessitates the presence of two contiguous quaternary centers adjacent to the aldehyde (Scheme-2.14).[129]



Scheme-2.14: Diastereoselectivity influenced by electrophiles

To test the viability of ring-closing metathesis, several metathesis precursors were prepared from the mixture of the two diastereomers of **PW-13** by protecting the dihydroxy group, which was transformed to mono-silyl ether **PW-14**, cyclic silyl ether **PW-15**, acetonide **PW-16** and carbonate **PW-17** (Scheme-2.15).

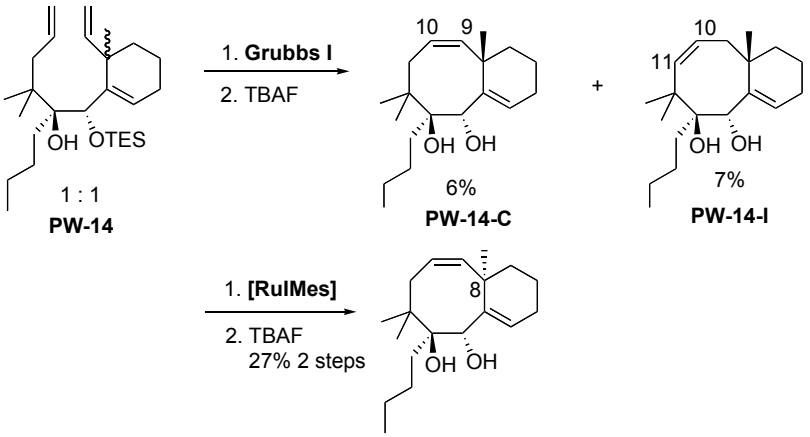


Scheme-2.15: Syntheses of different metathesis precursors

Mono-silyl ether **PW-14** was first subjected to metathesis reaction. The taxol-like model compound cyclized in the presence of Grubbs' catalyst 1st generation to furnish the expected

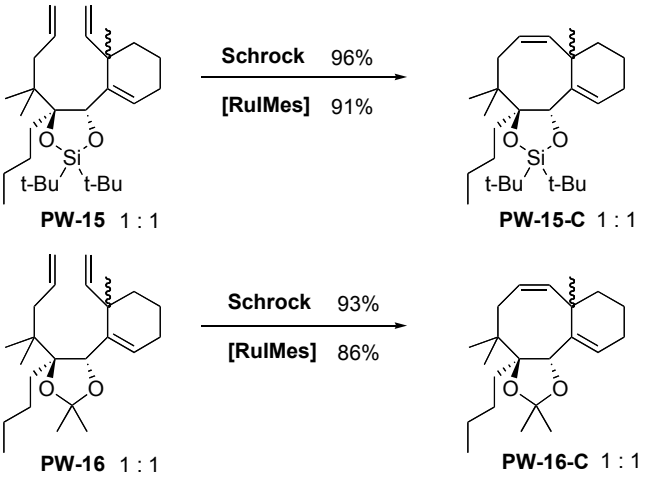
[129] Bourgeois, D.; Maiti, G.; Pancrazi, A.; Prunet, J. *Synlett* **2000**, 323-326.

bicyclic product **PW-14-C** and its isomer **PW-14-I** with the double bond at C10-C11, in moderate yields (Scheme-2.16). The latter is thermodynamically more stable (ΔG = 3kcal) in computational calculation. The diastereomer containing the wrong stereochemistry at C8 was formed exclusively when **[RuIMes]** catalyst was used to form the BC bicyclic product.[130]



Scheme-2.16: Metathesis in the presence of the diol group mono-substituted by the triethylsiloxy group

Ring-closing metathesis with both cyclic silylene **PW-15** and acetonide **PW-16** led to two diastereomeric products **PW-15-C** and **PW-16-C** in the presence of Schrock's or **[RuIMes]** catalyst (Scheme-2.17), but no reaction occurred with Grubbs' catalyst 1st generation.

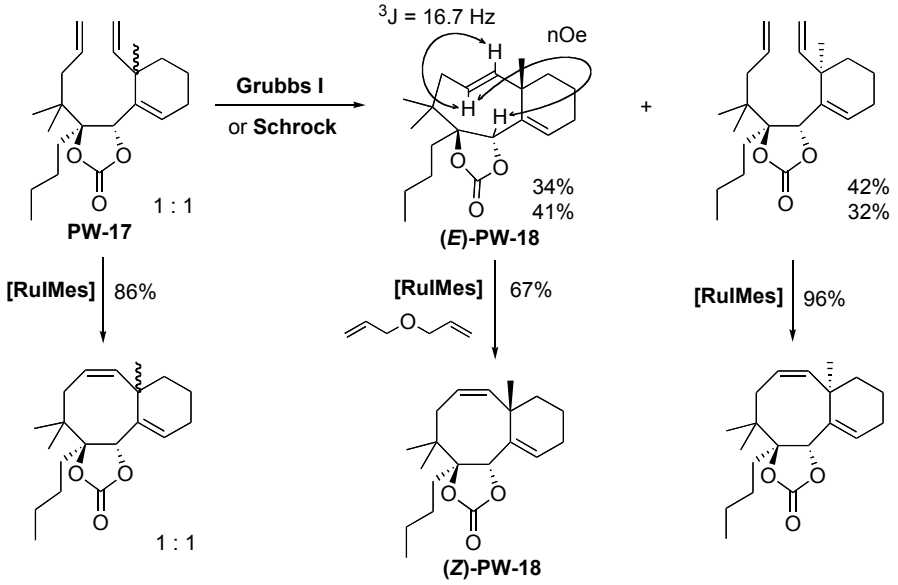


Scheme-2.17: Metathesis in the presence of the diol group protected by the silylene and acetonide groups

In the presence of Grubbs's catalyst 1st generation or Schrock's catalyst, ring-closing metathesis was achieved with the taxol-like substrate **PW-17** but not with its epimer at C8 (Scheme-2.18). Curiously, the formed cyclooctene B ring product contains a *trans* double bond, which was the first case of *trans* cyclooctene formation by ring-closing metathesis.

[130] Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869-882.

However, metathesis reaction of both diastereomers with **[RuIMes]** catalyst furnished the *cis* cyclooctene in good yields. Moreover, in the presence of allyl ether, the *trans* cyclooctene could be transformed to the *cis* diastereomer by reaction with **[RuIMes]** catalyst, which showed the reaction was performed under thermodynamical control in this case, and that the **[RuIMes]** catalyst is more active for ring cyclization.[131]

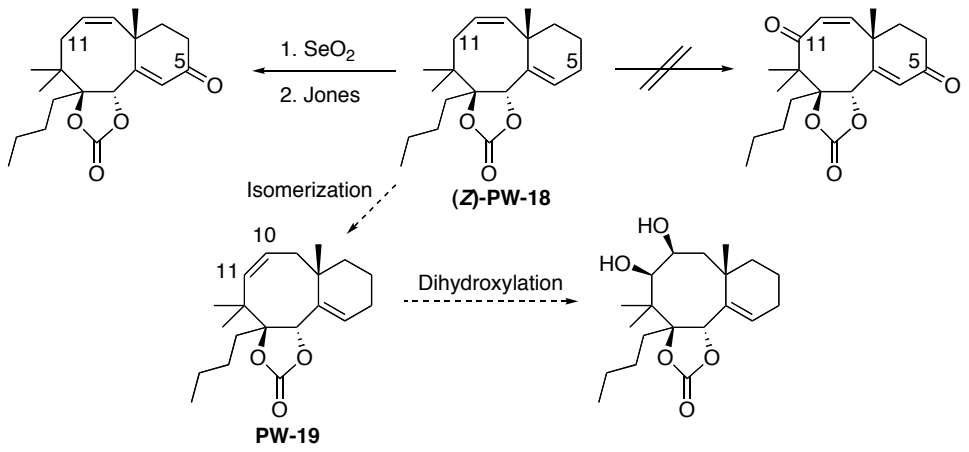


Scheme-2.18: Metathesis in the presence of the diol group disubstituted by the carbonate group

The BC bicycle (*Z*)-**PW-18** was then subjected to oxidation with SeO_2 then Jones' reagent in an attempt to generate the two α,β-unsaturated carbonyl groups. The reaction at the C11 position failed, probably due to the bulky *gem*-dimethyl group (Scheme-2.19).

However, since computational calculation showed the BC bicycle with a double bond at C10-C11 was more stable than that of C9-C10, **PW-18** could be isomerized to **PW-19** (Scheme-2.19). The functionality on the B ring would then be created by dihydroxylation of the C10-C11 double bond, and if the AD-mix-β would be used in the reaction, the dihydroxylation would be chemoselective because the approach of the C3-C4 double bond by the osmium complex would be disfavored by a mismatch effect between the chiral ligand and the C8 stereocenter.

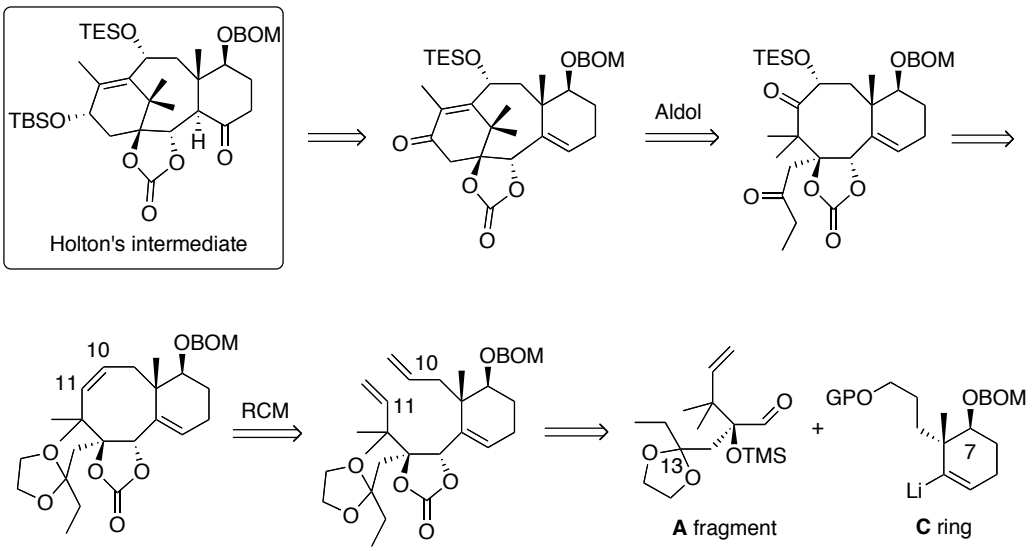
[131] Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem.* **2000**, *112*, 742-744; *Angew. Chem. Int. Ed.* **2000**, *39*, 725-728.



Scheme-2.19: Mono-oxidation at C5

Another option would be to obtain **PW-19** by RCM between two double bonds at C10 and C11. We chose this alternative, because we were interested in studying the formation of highly substituted cyclooctenes by metathesis.

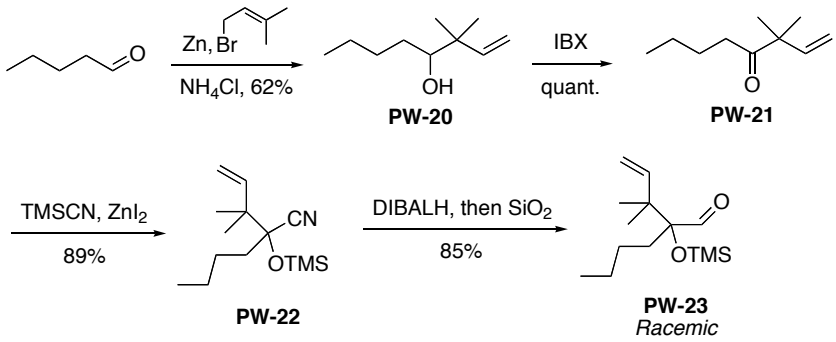
So a modified semi-convergent synthesis was designed (Scheme-2.20): the final steps of taxol synthesis would be achieved from a highly advanced intermediate described in Holton's synthesis, which contains the ABC tricyclic scafford with all the required functionalities. The A ring would be closed by intramolecular aldol reaction at a later stage, as in the previous retrosynthesis. The BC bicycle would be formed by ring-closing metathesis on a diene, which would be prepared by stereocontrolled addition of a vinyllithium (C ring) to an aldehyde (A fragment).



Scheme-2.20: Semi-convergent retrosynthesis (C10-C11)

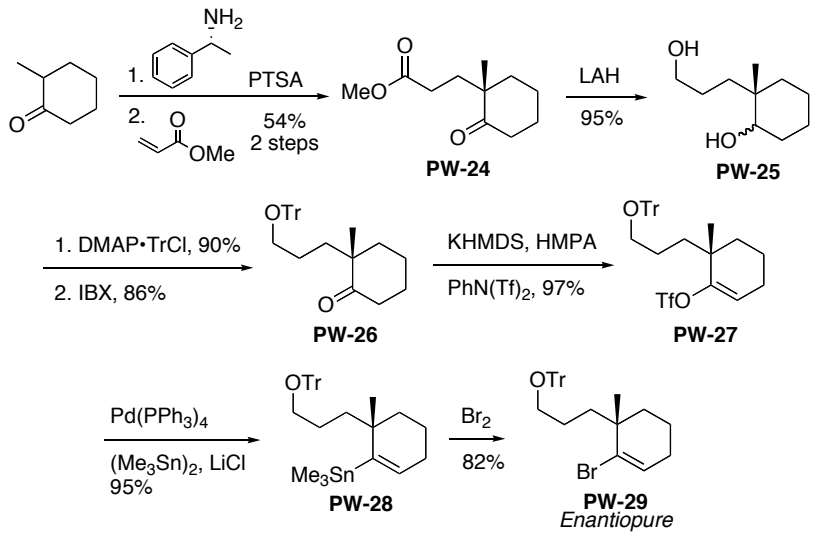
1.3 SEMI-CONVERGENT APPROACH (C10 - C11)

Regarding this proposal, a racemic model A fragment without functionality at C13 and a 7-deoxy C ring were synthesized in a first time. The synthesis of the model A fragment began with valeraldehyde. Barbier reaction conducted to alcohol **PW-20**, which was oxidized to form ketone **PW-21** (Scheme-2.21). ZnI_2-catalyzed cyanation of **PW-21** led to cyanohydrin **PW-22**, which was subjected to reduction and hydrolysis of the resulting imine to give α-siloxy aldehyde **PW-23**, as a model A fragment.



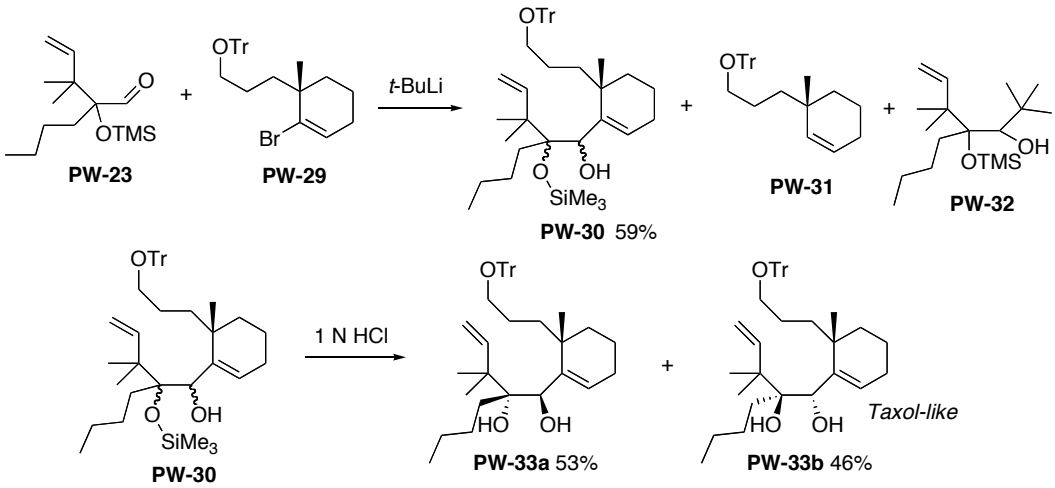
Scheme-2.21: Synthesis of racemic model A fragment PW-23

For access to 7-deoxy C ring, the known diol **PW-25** was synthesized by d'Angelo's method, an enantioselective Michael addition *via* enantiopure enamine formation to define the stereochemistry of the quaternary methyl group of **PW-24** (Scheme-2.22). Regioselective protection of the primary alcohol as a trityl ether, followed by oxidation of the secondary one afforded ketone **PW-26**. In the previous work from the laboratory, the Shapiro reaction was difficult to realize, and the yield was also irreproducible. It was thus decided to attempt another method, halogen-metal exchange, to obtain the coupling product of the model A fragment and the C ring. Thus ketone **PW-26** was subjected to vinyl triflate formation, Stille coupling and bromation to furnish vinyl bromide **PW-29**.



Scheme-2.22: Synthesis of 7-deoxy C ring PW-29

Coupling between aldehyde **PW-23** and vinyl bromide **PW-29** in the presence of *t*-BuLi led to the formation of two inseparable epimeric adducts **PW-30**,[132] with the *trans* 1,2-diol moiety for both,[133] along with byproduct **PW-31**, and **PW-32** if a large excess of *t*-BuLi was used (Scheme-2.23). Acidic treatment of the **PW-30** mixture conducted to the two diols **PW-33a** and **PW-33b**, which could be separated by flash chromatography.

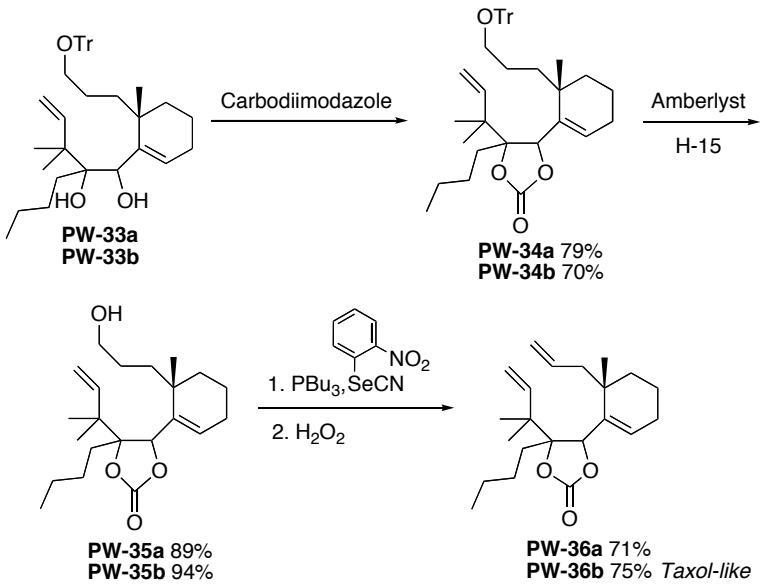


Scheme-2.23: Reaction of aldehyde PW-23 and vinyl bromide PW-29

Both **PW-33a** and taxol-like **PW-33b** diastereomers were separately subjected to the preparation of metathesis precursors. Reflux of **PW-33a** and **PW-33b** with carbodiimidazole led to the protection of the diol moiety to give carbonates **PW-34a** and **PW-34b**, which were

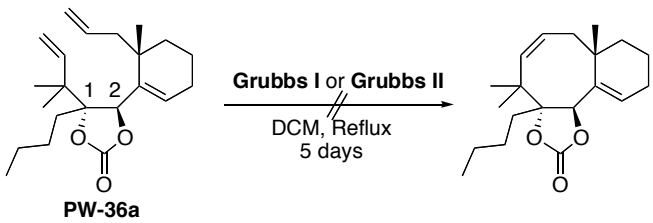
[132] Coupling reactions with different protecting groups for the primary alcohol of **PW-29** proved that the trityl group furnished the best yield in comparing with the PMB group, the TES group and the TIPS group.
[133] The stereochemistry of the two diastereomers was proven by X-ray analysis of **PW-33b** and of the triol derived from **PW-33a**.

then hydrolyzed with amberlyst H-15 to afford alcohols **PW-35a** and **PW-35b** (Scheme-2.24). The primary alcohol was transformed into the imidazolyl carbamate byproduct if the hydrolysis step with amberlyst H-15 was performed before the protection of the diol as the carbonate. Finally, Grieco's reaction was performed to transform alcohols **PW-35a** and **PW-35b** to trienic carbonates **PW-36a** and **PW-36b**.



Scheme-2.24: Synthesis of metathesis precursors, trienic carbonates PW-36a and PW-36b

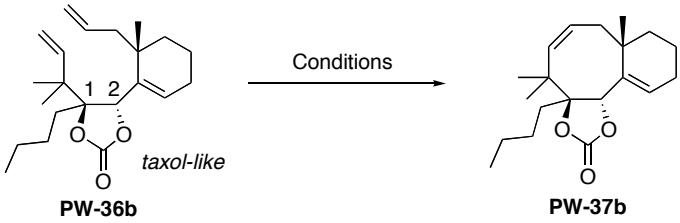
Trienic carbonates **PW-36a** and **PW-36b** were then subjected to ring-closing metathesis. The experiments were first tested with carbonate **PW-36a**, which possesses the wrong-*trans* stereochemistry at C1 and C2 for taxol. No cyclized product was observed with Grubbs' catalysts 1st or 2nd generation in 1,2-dichloroethane at reflux (Scheme-2.25), and prolonged reaction time (several days) with the latter complex only resulted in decomposition.



Scheme-2.25: Metathesis attempt of trienic carbonate PW-36a

In contrast, when treated with a catalytic quantity (12 mol%) of Grubbs I catalyst, taxol-like **PW-36b** led to a mixture of starting material **PW-36b** and the thermodynamic product (*Z*)-**PW-37b** (Scheme-2.26). Moreover, when diastereomer **PW-36b** was submitted to 30 mol% of Grubbs I, after several days at ambient temperature, the corresponding cyclooctene **PW-37b** was obtained in 65% yield. No *trans* cyclooctene was observed, contrary to our previous

study where the metathesis occurred between C9 and C10. Use of Grubbs 2nd generation or **[RuIMes]** catalysts was more efficient, furnishing **PW-37b** in comparable yield (69% and 72%, respectively) after only one hour.



PW-36b **PW-37b**

Cat.	Quantity	Solv.	Temp.	Time	Product
Grubbs I	12 mol%	PhH	reflux	7 days	Z/SM = 1:1
Grubbs I	30 mol%	DCE	RT	5 days	Z only, 65%
Grubbs II	10 mol%	DCE	reflux	1 h	Z only, 69%
[RuIMes]	5 mol%	DCE	reflux	1 h	Z only, 72%

Scheme-2.26: Metathesis of trienic carbonate PW-36b

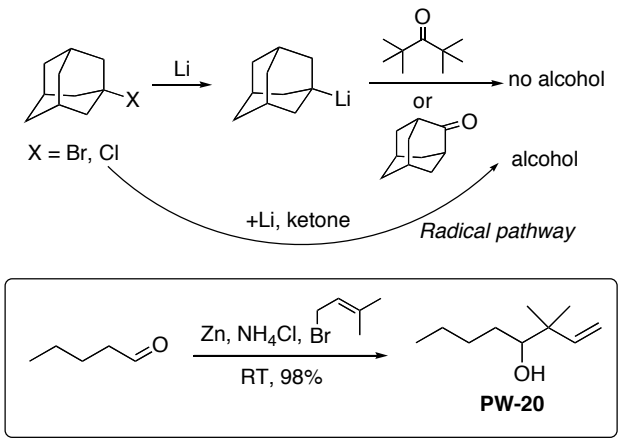
With the success of this C10-C11 route, we then planned to optimize the syntheses of the model A fragment and the 7-deoxy C ring.

2. COMPLETION OF THE SYNTHESIS OF MODEL BC RING SYSTEMS

2.1 SYNTHESES OF THE MODEL A FRAGMENT

As described in the previous chapter, the model A fragment without functionality at C13 was first prepared.

Valeraldehyde was subjected to Barbier reaction with prenyl bromide to produce the secondary alcohol **PW-20**. Barbier reaction is a classic reaction to generate secondary or tertiary alcohols discovered by French chemist P. Barbier,[134] which generally was performed between an alkyl halide and a carbonyl group as an electrophilic substrate in the presence of aluminium, zinc, sometimes indium, tin or its salts.[135] As a one-pot organometallic nucleophilic addition, for a long time, Barbier reaction was considered as an alternative choice for the reactions with Grignard reagents, named after his student P. Grignard. But the discovery that lithium metal efficiently enhanced the nucleophilic addition with organolithium (Scheme-2.27), revealed that the Barbier reaction could possibly proceed through a radical pathway.[136] Several years later, this supposition was proven by experiments of Barbier reactions in aqueous conditions reported by Luche.[137]



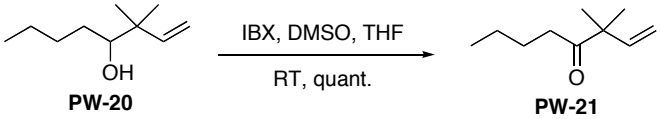
Scheme-2.27: Synthesis of PW-20 by Barbier reaction

Luche's conditions were used in our case and the reaction was regioselective, probably due to the zinc metal as coordinating agent. The temperature of addition of zinc metal should be

[134] Barbier, P. *Compt. Rend*. **1898**, *128*, 110.
[135] *The Barbier reaction and related one-step processes reactivity and structure: Concepts in organic chemistry, vol. 31,* Massey, A. G. Cornelius Blomberg Springer-Verlag, **1993**.
[136] Molle, G.; Bauer, P. *J. Am. Chem. Soc*. **1982**, *104*, 3481-3487.
[137] Petrier, C.; Luche, J. L. *J. Org. Chem*. **1985**, *50*, 910–912. Petrier, C.; Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 1445–1448. Einhorn, C.; Luche, J. L. *J. Organomet. Chem*. **1987**, *322*, 177–183.

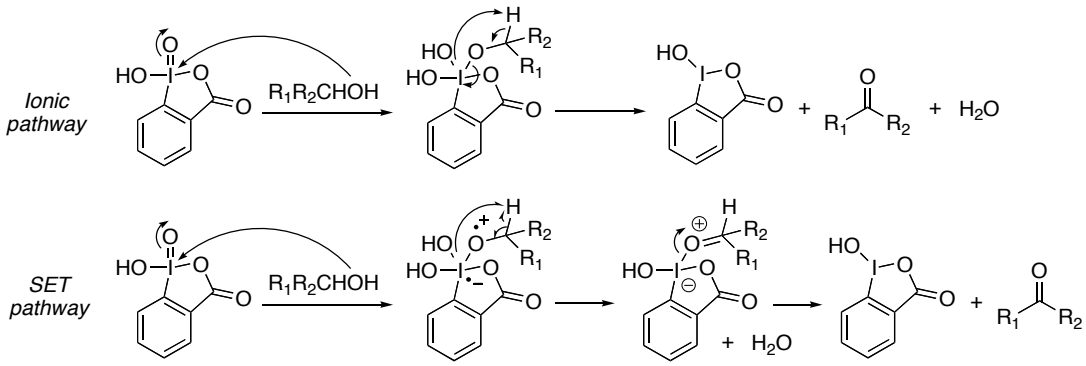
controlled at 0°C to minimize side reactions, then after stirring overnight, the racemic product was obtained in excellent yield (98% versus 62% reported by Dr. Stéphanie Schiltz).

Several oxidizing agents were used for oxidation of the alcohol **PW-20**. Iodoxybenzoic acid gave the best yield, because of the steric hindrance of the bulky *gem*-dimethyl group (Scheme-2.28).



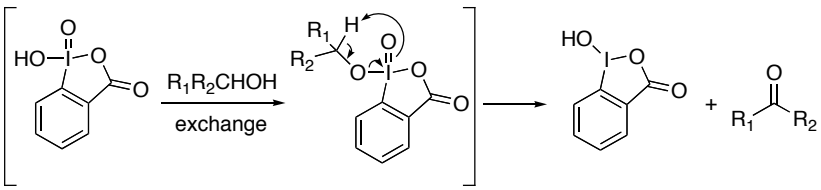
Scheme-2.28: Oxidation of PW-20 in the presence of IBX

The mechanism of oxidation by IBX is generally represented as an ionic and a radical pathway, as shown in Scheme-2.29.



Scheme-2.29: Ionic and SET mechanisms of IBX oxidation

Recently, the "hypervalent twist (HT) mechanism" was explored,[138] which involves ligand exchange reaction replacing the hydroxy group by the alcohol, followed by twist and elimination reaction (Scheme-2.30).



Scheme-2.30: Hypervalent twist (HT) mechanism of IBX oxidation

Computational calculation showed that the twist is required for the concerted elimination because the iodine oxygen double bond is oriented out of plane with the alkoxy group. The rearrangement in which the oxygen atom is moved into a proper plane for a 5-membered

[138] Su, J. T.; Goddard III, W. A. *J. Am. Chem. Soc.* **2005**, *127*, 14146-14147.

cyclic transition state in the elimination reaction was demonstrated to be the rate-determinating step in the oxidation (Figure-2.1).

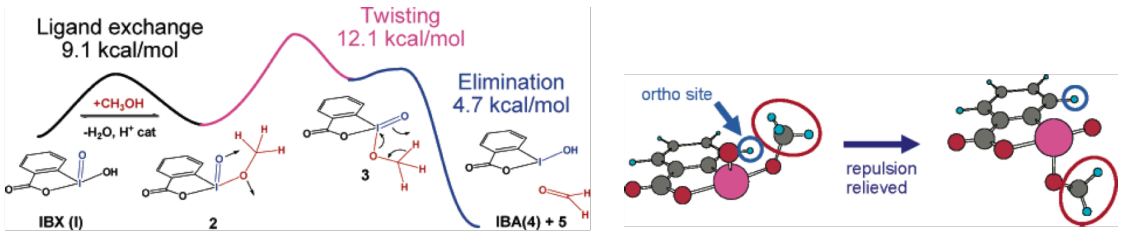
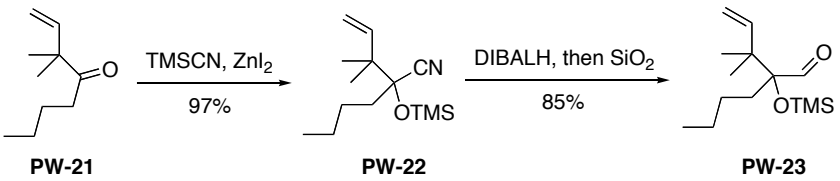


Figure-2.1: a. The coordinated motion that converts intermediate 2 to 3 is the rate-limiting step of the reaction. b. Large alcohols twist IBX more easily, which makes them oxidize more quickly.

With this mechanism, the reason that oxidation is faster for larger alcohols than smaller ones could be explained: the twist is driven forward by the steric repulsion that exists between the *ortho*-H atom and the protons from the alkoxy group; larger alkoxy groups create larger steric repulsion. To prove this hypothesis, the authors reported that a more hindered IBX derivative with the *ortho*-H atom replaced by a methyl group facilitated the twist with 100 fold reaction rate until the elimination reaction takes prevalence as the rate determining step.

The cyanation of **PW-21** was performed in the presence of ZnI_2 as Lewis acid, which could also be replaced by an amine such as triethylamine or DABCO to mediate the base-catalyzed cyanation.[139] The reaction was accomplished in dichloromethane at reflux, and the cyanohydrin product **PW-22** was then subjected to reduction with DIBALH and hydrolysis of the resulting imine with silica gel at -20°C, to afford aldehyde **PW-23**, the model A fragment (Scheme-2.31). The quality of the DIBALH reagent and dichloromethane as solvent are important factors for an efficient reduction of the nitrile to the aldehyde. The overall yield of the synthesis of the model A fragment was 81% (versus 47% reported by Dr. Stéphanie Schiltz) for 4 steps.

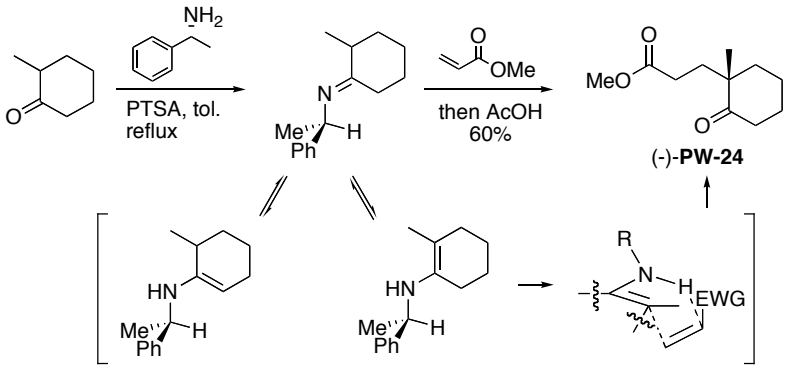


Scheme-2.31: Synthesis of model A fragment PW-23

[139] Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537-540.

2.2 SYNTHESIS OF THE 7-DEOXY C RING

The 7-deoxy C ring was prepared in an enantiopure form according to Stéphanie Schiltz's work, as the enantioselective synthesis was not longer than the racemic route. D'Angelo reported an enantioselective Michael addition through a chiral imine intermediate, which was synthesized from 2-methylcyclohexanone and (*R*)-phenylethylamine by refluxing in toluene (Scheme-2.32).[140]



Scheme-2.32: Enantioselectivity controlled by chiral imine formation

The tautomeric equilibrium of imine to enamine to minimize the main steric interactions was confirmed by a deuteration experiment. In the more substituted enamine, the *syn* N-H bond and double bond favored internal concerted proton transfer, which was also stabilized by hyperconjugation of the methyl group. So the approach was specific from one face of the double bond and was favored by electron orbitals overlap between the nitrogen atom and the electron-withdrawing group, to furnish the product **PW-24** in enantiopure form (Figure-2.2).

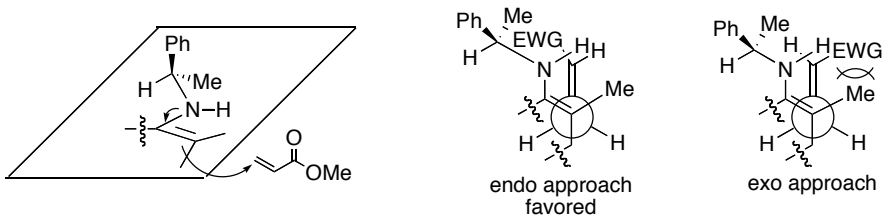
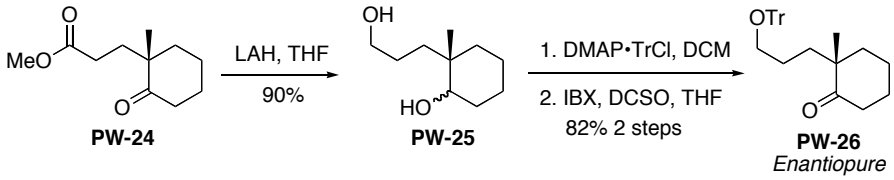


Figure-2.2: Specific approach only from one face

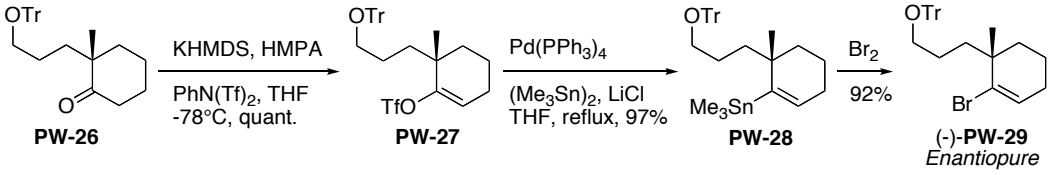
[140] Cavé, C.; Desmaële, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 4361-4368.

Reduction with LAH as described in the literature[141] and selective protection of the primary alcohol as a trityl ether gave the corresponding alcohol, which was oxidized with IBX to provide ketone **PW-26** (Scheme-2.33).



Scheme-2.33: Synthesis of ketone PW-26

As described in the previous work, ketone **PW-26** was first transformed to the corresponding vinyl triflate, which was subjected to Stille coupling to provide the corresponding vinyl stannane **PW-28**, followed by bromation to give (-)-**PW-29** (Scheme-2.34). This route was efficient, but good yield necessitated toxic $(Me_3Sn)_2$ for the Stille reaction.



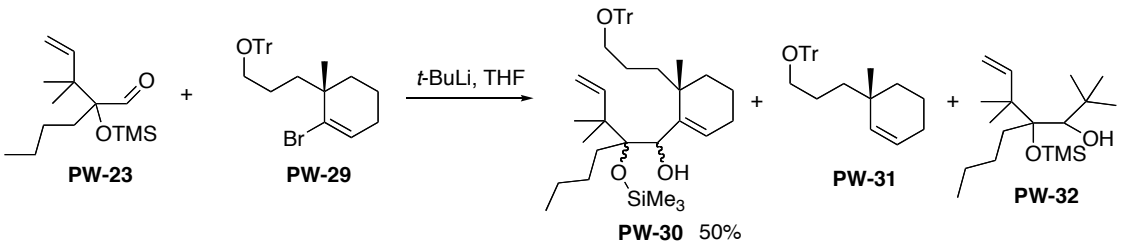
Scheme-2.34: Synthesis of vinyl bromide (-)-PW-29

The overall yield of the synthesis of the 7-deoxy C ring was 40% (versus 30% reported by Stéphanie Schiltz) for 8 steps.

2.3 SYNTHESES OF THE METATHESIS PRECURSORS

We then tried to optimize the coupling of aldehyde **PW-23** with vinyl bromide **PW-29**. Halogen-metal exchange proceeded in the presence of *t*-BuLi, which was stirred with **PW-29** in THF at -78°C for ca. 30 min until the color of the reaction mixture turned pure red. The aldehyde was then added. **PW-30** was obtained in 50% yield, along with **PW-31** and **PW-32** (Scheme-2.35), such as observed by Dr. Stéphanie Schiltz.

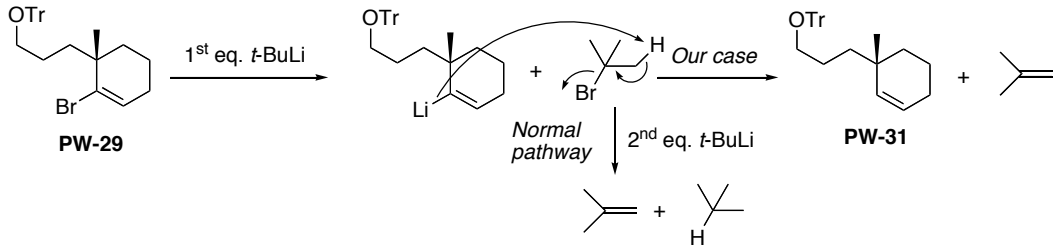
[141] Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228-229.



Scheme-2.35: First trial of addition by metal-halogen exchange

Theoretically halogen-metal exchange should be complete with two equivalents of *t*-BuLi, but the production of the olefin **PW-31** was inevitable even in the presence of excess *t*-BuLi, and addition of a large excess of *t*-BuLi led to apparition of the *t*-butyl adduct **PW-32**.

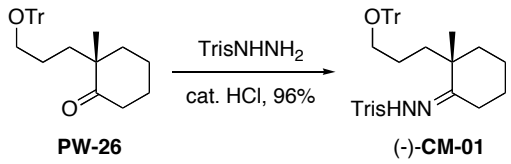
Co-presence of **PW-31** and **PW-32** in the products showed that protonation of the vinyl anion occurred while *t*-BuLi had not been completely consumed. The halogen-metal exchange proceeded with the first equivalent of *t*-BuLi and conducted to the formation of vinyllithium and *t*-butyl bromide. Normally, the second equivalent of *t*-BuLi should function as a base to eliminate HBr in *t*-butyl bromide to produce isobutane and isobutene. In our reaction, the nucleophilic vinyllithium formed with the first equivalent of *t*-BuLi must be basic enough to compete with *t*-BuLi to participate in the elimination of HBr, and olefin **PW-31** was therefore obtained (Scheme-2.36).



Scheme-2.36: Formation of alkene PW-31

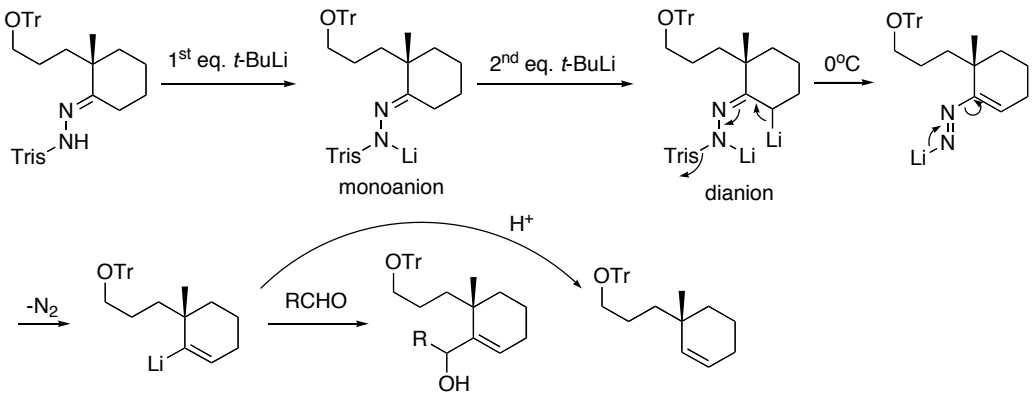
When *t*-BuLi was added rapidly to vinyl bromide **PW-24**, the best yield obtained was 59%. However, when two equivalents of *t*-BuLi were premixed with THF at -78°C, and **PW-29** was then added dropwise, we could optimize the yield to 71%, but the formation of olefin **PW-31** could not always be avoided.

So we turned back to the Shapiro reaction, to avoid the formation of **PW-31**. Transformation of ketone **PW-26** to hydrazone **CM-01** was performed in the presence of several drops of concentrated hydrochloric acid as catalyst (Scheme-2.37). The chemical equilibration of the carbonyl group to the hydrazone group was achieved in 3 hours, and too much HCl could cause hydrolysis of the trityl group.



Scheme-2.37: Formation of CM-01

The Shapiro reaction was difficult to operate. Rearrangement of the hydrazone dianion formed in the reaction by treatment with two equivalents of *t*-BuLi, which was first discovered by Shapiro for the transformation of ketones to alkenes,[142] then utilization of different electrophiles to trap the vinyllithium was developed to perform nucleophilic additions from ketones (Scheme-2.38).[143] Triisopropylbenzenesulfonyl hydrazine was chosen in our reaction to avoid deprotonation on the aromatic ring.

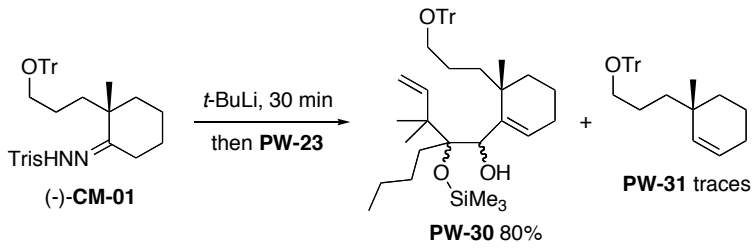


Scheme-2.38: Mechanism of Shapiro coupling reaction

The difficulty in the reaction is the formation of the second anion, which could be easily detected by color change from red (monoanion) to dark-red (dianion). *n*-BuLi with or without additive such as TMEDA is a common choice for the Shapiro reaction. However, our case necessitated *t*-BuLi to achieve the dianion formation, whereas an unsuccessful trial with MeLi proved that the basicity predominates over the steric hindrance.

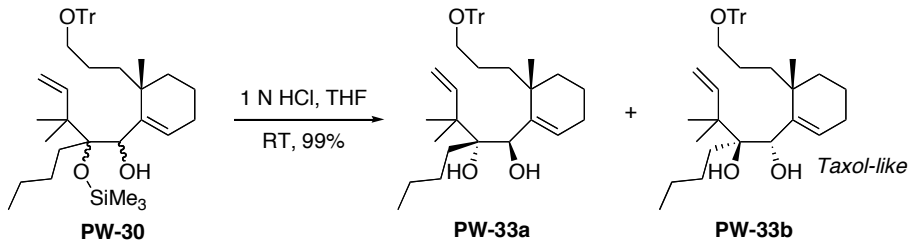
The first trial with hydrazone **CM-01** gave the desired product **PW-30**, along with olefin **PW-31** as byproduct, despite no proton source was theoretically present in the reaction. So a slight excess of *t*-BuLi was added to the reaction and an overall yield of 80% was obtained (Scheme-2.39).

[142] Shapiro, R. H.; Hornamoan, E. J. *J. Org. Chem.* **1974**, *39*, 2302-2303.
[143] Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147-154. Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55-59. Chamberlin, A. R. Bloom, S. H. *Org. React.* **1990**, *39*, 1-83.



Scheme-2.39: Formation of PW-30 by Shapiro reaction to avoid by-product PW-31

The inseparable mixture of the two diastereomers of **PW-30** was subjected to acidic hydrolysis to remove the TMS group as before. Diols **PW-33a** and **PW-33b** were then separated by flash chromatography in a ratio of ca. 1:1 (Scheme-2.40).[123]



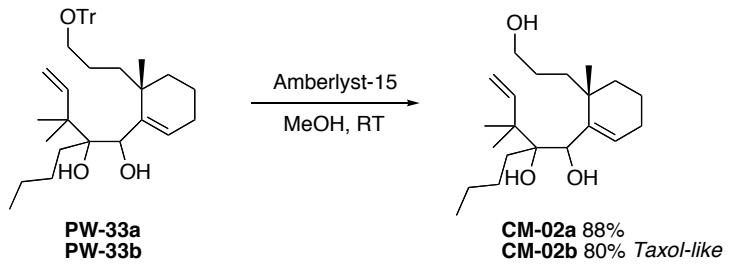
Scheme-2.40: Removal of the silyl group

Since the 1,2-diol configuration was *trans* as in the C9-C10 semi-convergent approach, Shapiro reaction with the α-siloxy aldehyde A fragment was diastereoselective.

However, in this C10-C11 route, migration of the TMS group was not observed, and its hydrolysis always necessitated a strong acid. Discussion about the diastereoselectivity of the Shapiro reaction will be carried out in **Chapter III**.

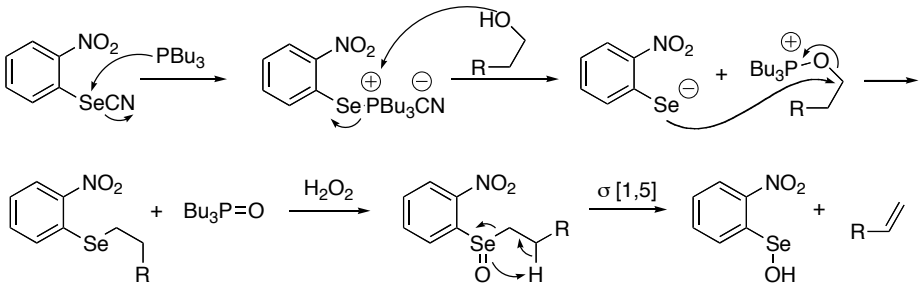
Preparation of the metathesis precursors was performed separately from the two diastereomers obtained from the Shapiro coupling reaction, to test the viability of ring-closing metathesis, in comparing with the previous route involving cyclooctene formation at C9-C10.

Removal of the trityl group under acidic conditions with Amberlyst H-15 gave triols **CM-10a** and **CM-10b** in satisfying yields (Scheme-2.41), which served as starting material to synthesize a variety of metathesis precursors by differently protecting the 1,2-diol moiety, since the previous results showed different behaviors with varied protecting groups in the ring-closing metathesis reaction.



Scheme-2.41: Removal of the trityl group

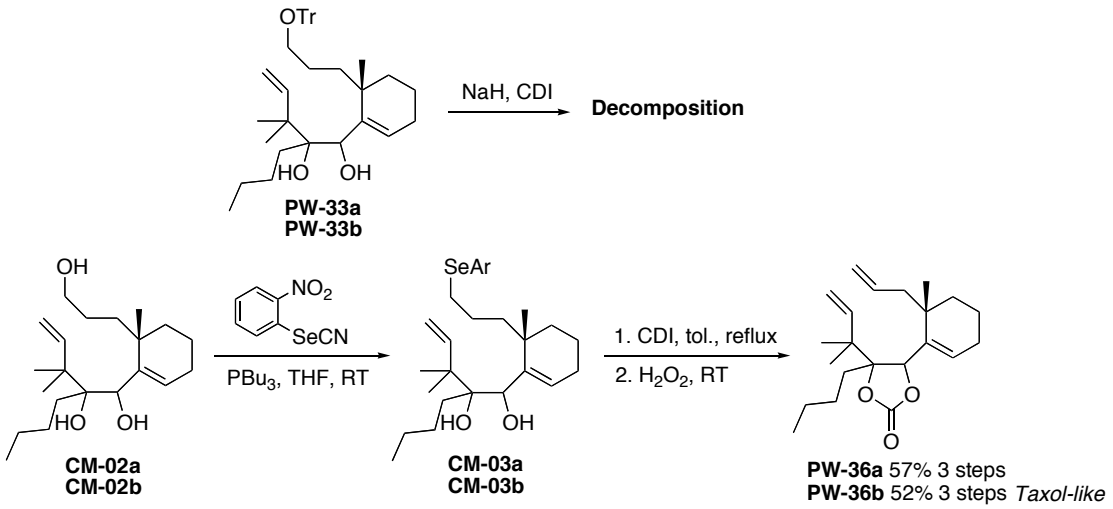
As the primary hydroxy group should be transformed to the terminal olefin, we chose Grieco's method[144] to perform the dehydration step. The first nucleophilic attack by the hydroxy group to the selenophosphonium formed by the presence of the selenocyanate and tributylphosphine leads to the formation of an oxaphosphonium and a selenyl anion (Scheme-2.42). Addition of the selenyl anion to the former provide the selenyl ether product, which is then subjected to oxidative elimination by [1,5] sigmatropic rearrangement to furnish the terminal olefin. The *o*-nitrophenylselenyl group intermediate formed in the first step could herein serve as protecting group for the primary alcohol while manipulating the 1,2-diol moiety.



Scheme-2.42: Mechanism of olefination by Grieco's method

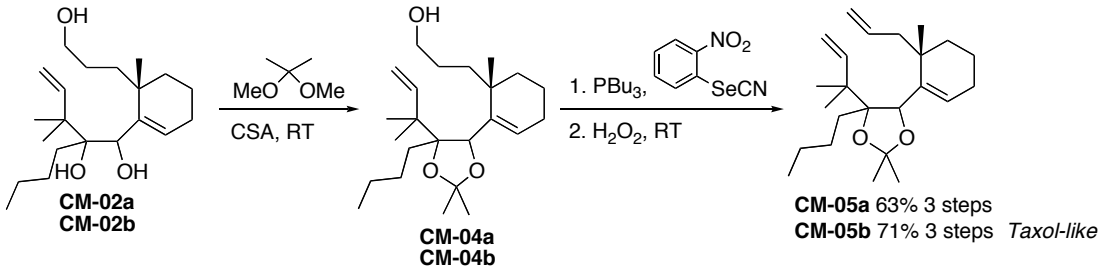
Dr. Stéphanie Schiltz proved that reflux in toluene with carbodiimidazole in the presence of a base such as NaH caused degradation of **PW-34** (cf. p. 77), but reaction under the same conditions without base led to the 1,2-diol protected as a carbonate. The same procedure was applied to **CM-03a** and **CM-03b**; the corresponding carbonates were obtained by refluxing for 3 days (Scheme-2.43). These carbonates were then subjected to reaction with hydrogen peroxide overnight to provide trienic carbonates **PW-36a** and **PW-36b**. The whole process could be performed without purification of the intermediates in good overall yields.

[144] Grieco, P. A.; Gilman, S. Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486.



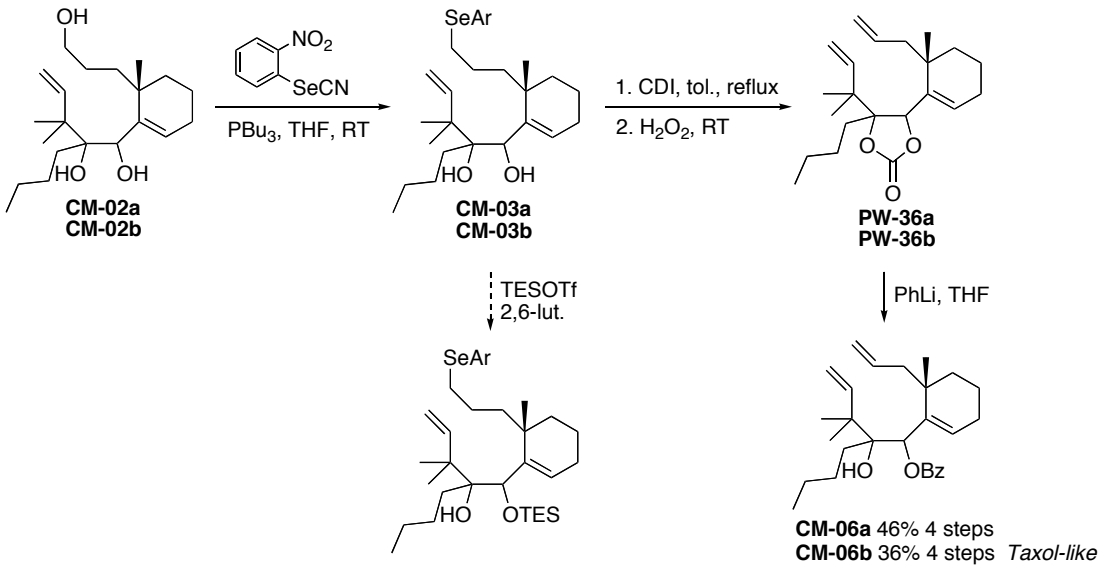
Scheme-2.43: Syntheses of metathesis precursors, trienic carbonates PW-36a and PW-36b

Protection of the 1,2-diol moiety of the triol as the acetonide was achieved with 2,2-dimethoxypropane in the presence of camphorsulfonic acid as catalyst to give **CM-04a** and **CM-04b** (Scheme-2.44). The selenyl ether formation to protect the terminal hydroxy group was not necessary, since the ketal formed on the primary alcohol was instable contrary to the former case of the carbonate. Grieco's method was then applied to provide trienic acetonides **CM-05a** and **CM-05b**.



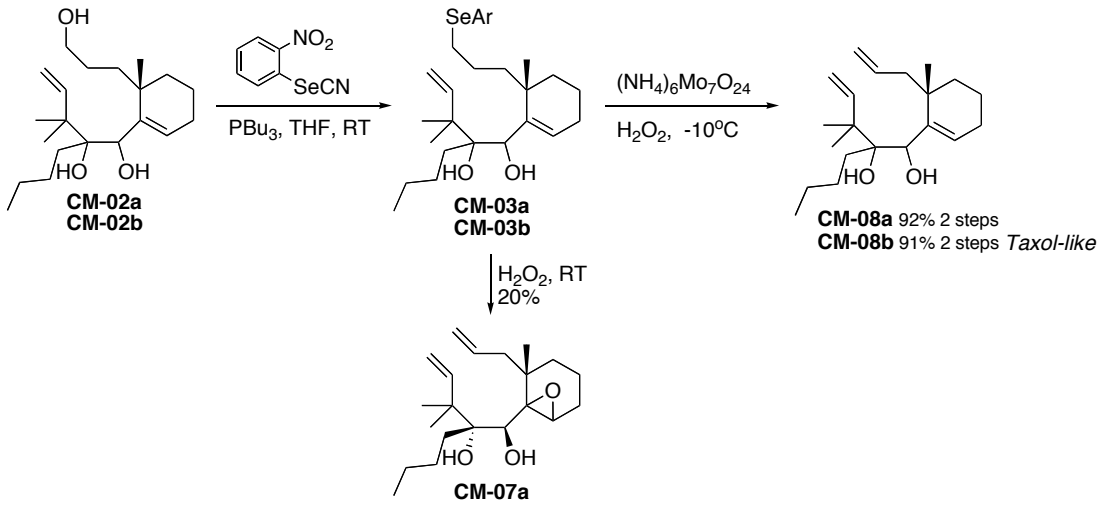
Scheme-2.44: Syntheses of metathesis precursors, trienic acetonides CM-05a and CM-05b

Direct transformation of the 1,2-diol in **CM-03a** or **CM-03b** to the mono-protected silyl ether was unsuccessful, probably due to steric hindrance. However, nucleophilic addition of PhLi to carbonates **PW-36a** and **PW-36b** conducted to ring-opening to furnish trienic benzoates **CM-06a** and **CM-06b** (Scheme-2.45). Fresh preparation of PhLi was necessary to obtain a good yield.



Scheme-2.45: Syntheses of metathesis precursors, trienic benzoates CM-06a and CM-06b

Treatment of compound **CM-03a** with H_2O_2 only gave epoxide **CM-07a** in a moderate yield (Scheme-2.46). The hydroxy group at the allylic position may function as electron-donor to activate the double bond. However, the oxidative elimination could be accomplished in 5 minutes by treatment with ammonium molybdate premixed with hydrogen peroxide at -10°C. Trienic diols **CM-08a** and **CM-08b** were obtained in good yields.

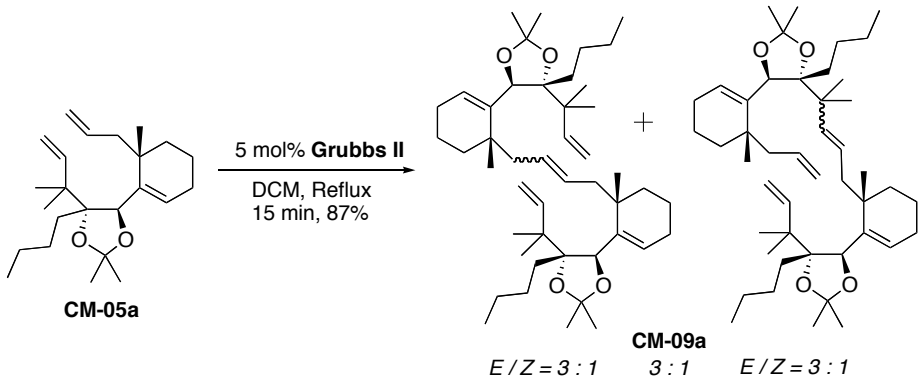


Scheme-2.46: Syntheses of metathesis precursors, trienic diols CM-08a and CM-08b

2.4 RCM TO MODEL BC BICYCLES

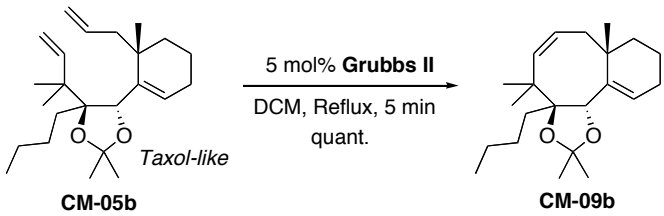
With all the metathesis precursors in hand, we then turned to the study of the ring-closing metathesis reaction. Treatment of carbonates **PW-36a** and **PW-36b** with Grubbs II catalyst led to results very similar to the ones reported by Dr. Stéphanie Schiltz: decomposition of **PW-36a**, and obtention of the desired cyclooctene **PW-37b** in ca. 70% yield (cf. p. 82).

The acetonide derivatives were then subjected to Grubbs II catalyst. After 30 min in CH_2Cl_2 at reflux, diastereomer **CM-05a** only led to the mixture of dimeric products **CM-09a** in a 3:1 ratio, favoring the head-to-head dimer (Scheme-2.47). This result confirmed that the less hindered C10 olefin is the site of initial carbene formation. Prolonged reaction time did not show significant effect.



Scheme-2.47: Metathesis of CM-05a

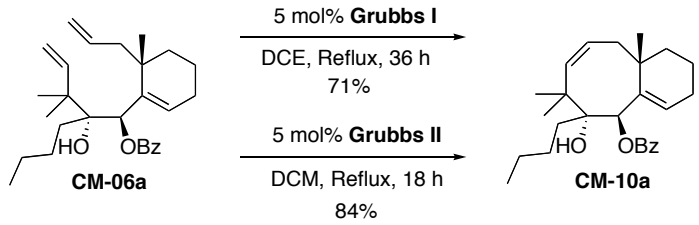
In contrast, cyclization of the other diastereomer **CM-03b** was exceptionally rapid, and bicycle **CM-07b** was obtained in quantitative yield after only 5 min in 1,2-dichloroethane at reflux (Scheme-2.48).



Scheme-2.48: Metathesis of CM-05b

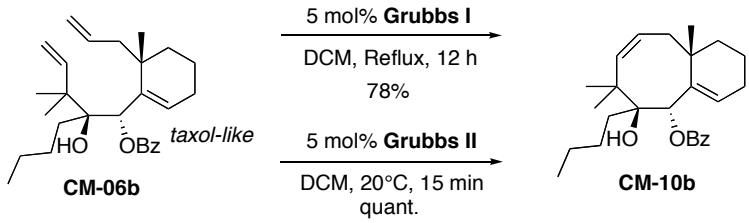
Our attempt at ring-closing reaction with dienes **CM-06a** and **CM-06b** showed interesting conformation-reactivity relationship. Treatment of benzoate **CM-06a** (wrong diastereomer) with both Grubbs I and Grubbs II catalysts provided the desired cyclized product (Scheme-2.49). These results tend to prove that the cyclic protecting groups lock the metathesis

precursors in an unfavorable conformation for cyclization. Heating **CM-06a** with Grubbs I in 1,2-dichloroethane at reflux for 36 h or with Grubbs II in dichloromethane at reflux for 18 h furnished the same cyclooctene **CM-10a** in 71% and 84% yield, respectively. No product was observed at lower temperature.



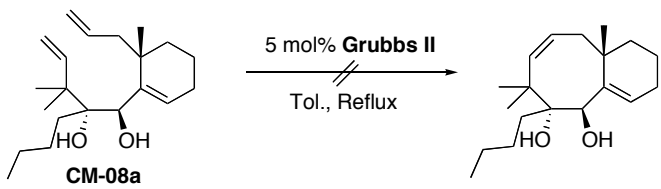
Scheme-2.49: Metathesis of CM-06a

Diastereomer **CM-06b**, when reacted with Grubbs I and Grubbs II, also afforded the corresponding cyclooctene **CM-10b**, but the reaction conditions were relatively milder. Bicycle **CM-10b** was obtained by treatment with Grubbs I at 40°C in 78% yield and with Grubbs II catalyst at ambient temperature in quantitative yield (Scheme 2.50).



Scheme-2.50: Metathesis of CM-06b

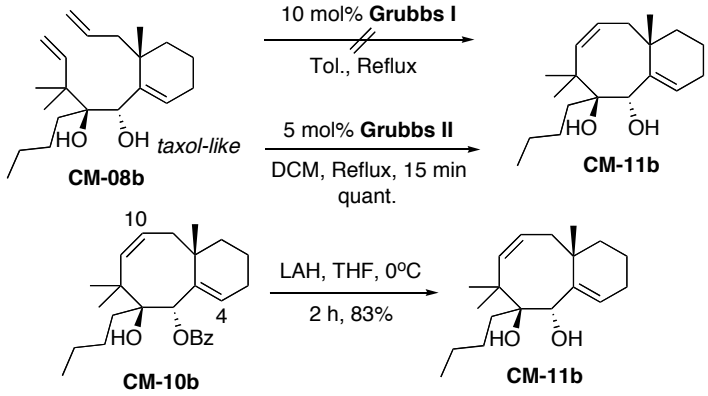
Diols **CM-08a** and **CM-08b** were then submitted to the different Grubbs catalysts. Unfortunately, diol **CM-08a** only led to decomposition (Scheme-2.51).



Scheme-2.51: Metathesis of CM-08a

However, diastereomer **CM-08b** was successfully converted to the corresponding cyclooctene **CM-11b** as colorless needle crystals in quantitative yield after 1 h in dichloromethane at reflux (Scheme-2.52). The structure of this cyclooctene was confirmed by X-ray analysis. The

decomposition or low reactivity[145] or occasional loss of methylene[146] in ring-closing metathesis reactions in the presence of a diol were not observed in our case.



Scheme-2.52: Metathesis of CM-08b to afford CM-11b and correlation by reduction of CM-10b

The ^{1}H NMR spectrum of cyclooctene **CM-10b** exhibits enlarged signals for the protons at C4 and C10, probably due to the presence of rotamers induced by the benzoate group. The expected NMR spectrum could be observed by heating **CM-10b** at 65°C in deuterated DMSO (Figure-2.3). This compound was also correlated to cyclic diol **CM-11b** by reduction of the benzoate ester with $LiAlH_4$ (Scheme-2.52).

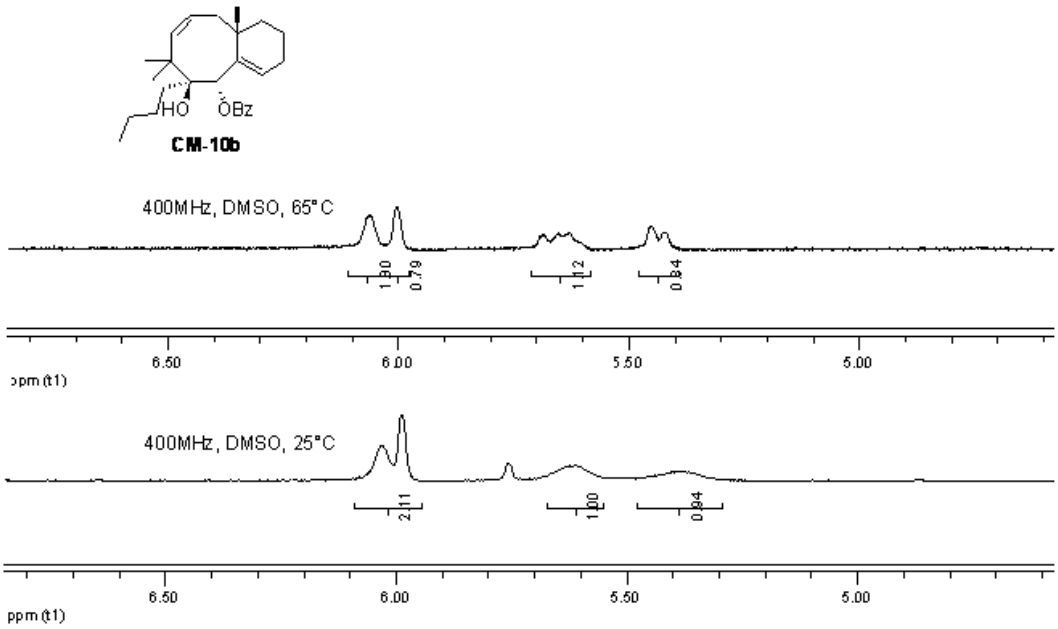
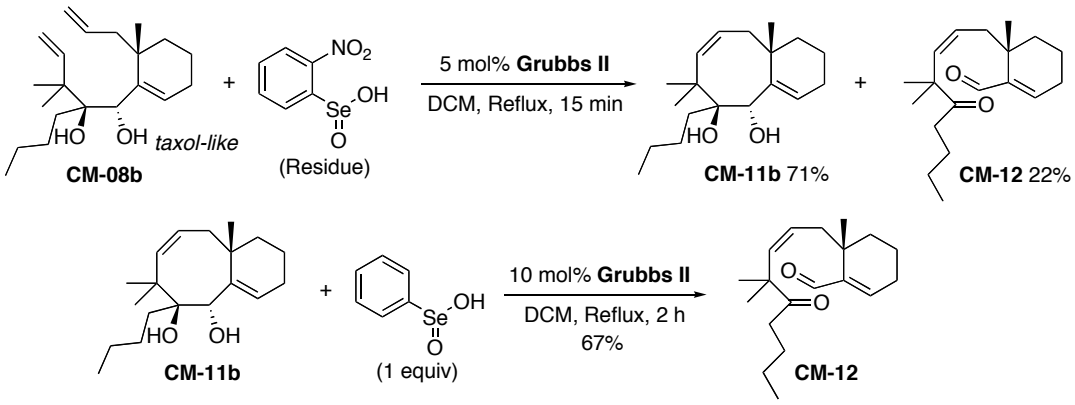


Figure-2.3: ^{1}H NMR spectrum influenced by the presence of the benzoyl group

An unusual oxidative fragmentation of the 1,2-diol moiety was observed in our attempt to form bicycle **CM-11b** from unpurified diol **CM-08b**. As shown in Scheme-2.53, the

[145] Neimert-Andersson, K.; Somfai, P. *Eur. J. Org. Chem*. **2006**, *4*, 978-985.
[146] Braddock, D. C.; Cansell, G.; Hermitage, S. A.; White, A. J. P. *Tetrahedron: Asymmetry* **2004**, *15*, 3123-3129.

metathesis reaction on unpurified diol **CM-08b** led to the desired cyclic product **CM-11b** in 71% yield, along with keto-aldehyde **CM-12** in 22% yield (Scheme-2.53). We assumed that this oxidative cleavage was mediated by a high oxidation state ruthenium complex derived from the Grubbs II catalyst and the residual *o*-nitrophenyl seleninic acid from the Grieco reaction, which is the only oxidant present in the reaction. To check this hypothesis, reaction of diol **CM-11b** with Grubbs II catalyst was then carried out in the presence of a stoichiometric amount of phenyl seleninic acid, and the oxidized product **CM-12** was obtained in 67% yield.



Scheme-2.53: Oxidative cleavage catalyzed by Grubbs II catalyst in the presence of high-valence selenium

Molecular modeling has been performed to try to explain the difference in behavior between the two diastereomers of the metathesis precursors bearing a cyclic protecting group for the diol moiety. Systematic energy minimization experiments led to the preferred conformations of carbonates **PW-36a** and **PW-36b** (Figure-2.4). Comparison between the C10-C11 distances in both diastereomers clearly shows that cyclization should be favored in the case of **PW-36b**, which comports the taxol-like 1,2-diol configuration. We supposed that the chemoselectivity of ring-closing metathesis for trienic diols **CM-08a** and **CM-08b** could also be explained by similar molecular conformations due to chelation of the ruthenium atom by the 1,2-diol moiety.

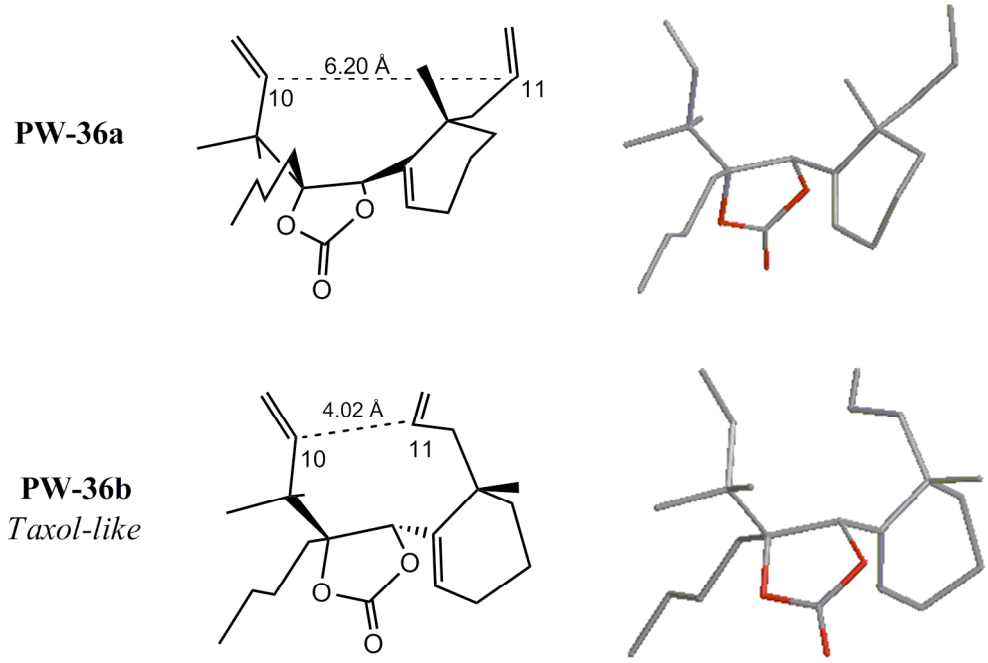


Figure-2.4: Molecular modeling of PW-36a and PW-36b

With the results of the synthesis of BC bicycles of taxol by ring-closing metathesis at C10-C11 in hand, we can directly compare them with the former synthetic route that involves metathesis at the C9-C10 position (Figure-2.5 and 2.6).

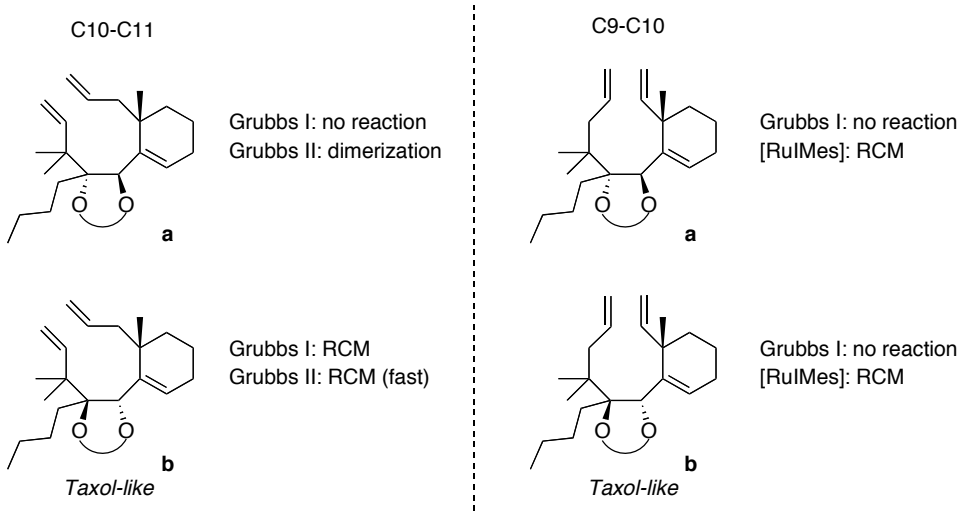


Figure-2.5: Comparison of the metatheses at C10-C11 and C9-C10 in the presence of cyclic protecting groups for the diol moiety

When the 1,2-diol moiety was diprotected in a cyclic form, the metathesis between C10-C11 terminal olefins of the precursors comporting taxol-like stereochemistry proceeded more easily than that of C9-C10 position. Neither of the products with the wrong configuration for

taxol led to cyclized products in the C10-C11 route, contrary to the wrong diastereomers in the C9-C10 route, which led to cyclic products with the 2nd generation catalysts.

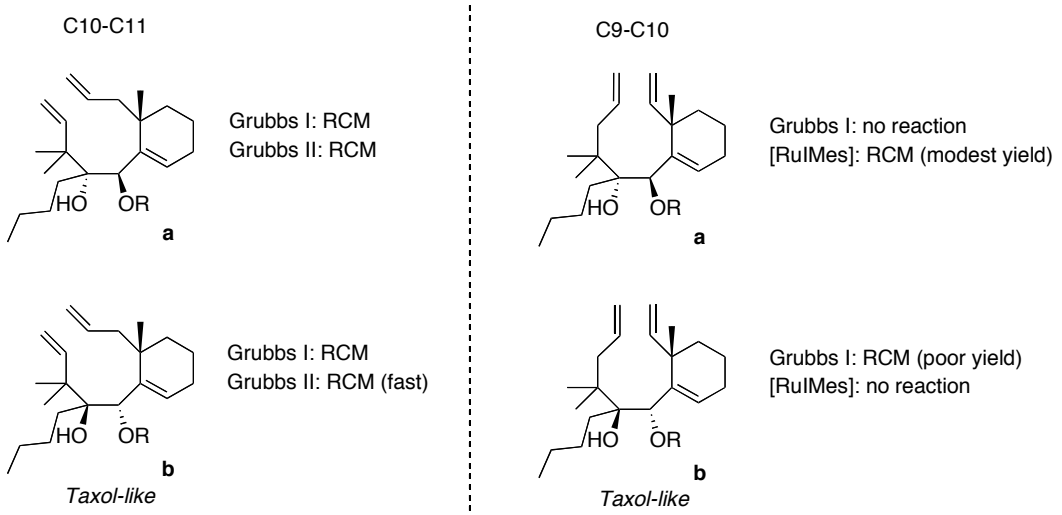


Figure-2.6: Comparison of the metatheses at C10-C11 and C9-C10 in the presence of the mono-protected diol

In the case the 1,2-diol moiety was mono-protected, both diastereomers can undergo the metathesis to furnish the cyclic products. But the reactions at C10-C11 position were much easier to realize than C9-C10 position.

In summary, the strategy of ring-closing metathesis at C10-C11 to construct the B ring of taxol was promising and the overall yields for the synthesis of the 7-deoxy BC bicycles with different protecting groups were satisfying. We then planned to realize the syntheses of the two metathesis precursors with all the functionalities required for taxol.

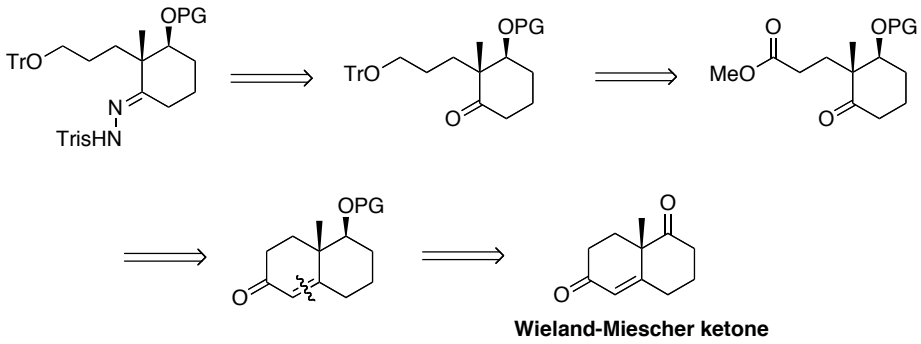
CHAPTER III

TOWARD TAXOL AND 7-DEOXY TAXOL

1. SYNTHESIS OF THE C RING

With the 7-deoxy BC bicycle ring-systems in hand, we then focused on synthesizing the C ring with all the functionalities required for taxol.

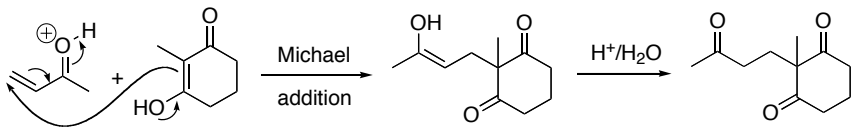
We planned an enantioselective synthetic route of the C ring inspired by the synthesis of the 7-deoxy C ring described in **Chapter II**. The target hydrazone would be formed from the corresponding hydroxy-protected ketone, which would be obtained by reduction and protection of the primary hydroxy group. The keto ester compound would be formed by oxidative cleavage of a derivative of the Wieland-Miescher ketone (Scheme-3.1).[147]



Scheme-3.1: Retrosynthesis of the C ring

Enantiopure Wieland-Miescher ketone was chosen as our starting material, which could be synthesized under Hajos-Parrish reaction conditions. By this organocatalyzed annelation, the stereochemistry on the quaternary methyl group required for taxol will be defined.[148]

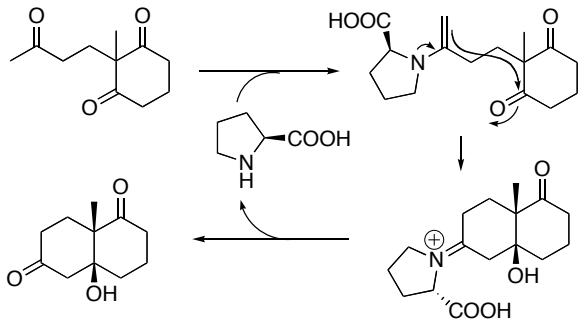
The first step is a Michael addition of 2-methyl-1,3-cyclohexanedione to methyl vinyl ketone. The enol formation proceeded thermodynamically under acidic aqueous conditions, then addition to α,β-unsaturated ketone and hydrolysis of the enol adduct were performed to furnish the *meso* trione compound (Scheme-3.2).



Scheme-3.2: Michael addition to furnish the trione intermediate

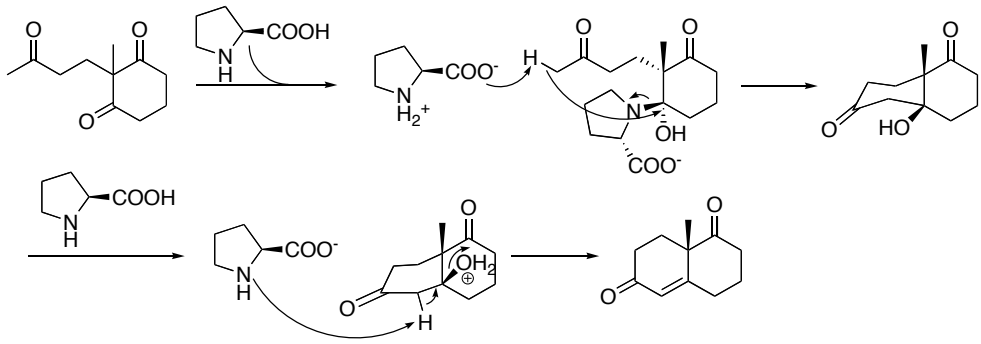
[147] Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215-2228.
[148] Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis* **1977**, 167-168. Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth.* **1985**, *63*, 37-43.

Two types of mechanism for (*L*)-proline catalyzed Robinson annelation were first proposed by Hajos and Parrish.[149] The first one is enamine formation followed by intramolecular nucleophilic addition, in which the stereochemistry is dictated by facial attack of the enamine bearing a chiral amino acid moiety (Scheme-3.3).



Scheme-3.3: Mechanism proposed for enantioselective annelation through enamine formation

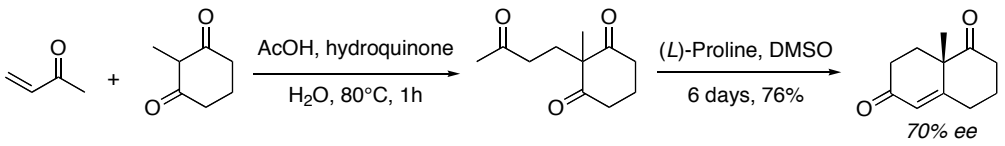
Another one is carbinolamine formation[150] followed by annelation involving a second (*L*)-proline molecule, which participates in deprotonation to afford the product. The latter was favored by theoretical calculation of transition state energies (Scheme-3.4).[151]



Scheme-3.4: Mechanism proposed for enantioselective annelation through carbinolamine formation

However, classic synthesis of Wieland-Miescher ketone led to the product in an enantiomeric excess of only 70%. After recrystallization, 99% ee may be obtained but the process needs to be performed on large scale and is not always reproducible; in addition, the yield often fell to ca. 40% (Scheme-3.5).

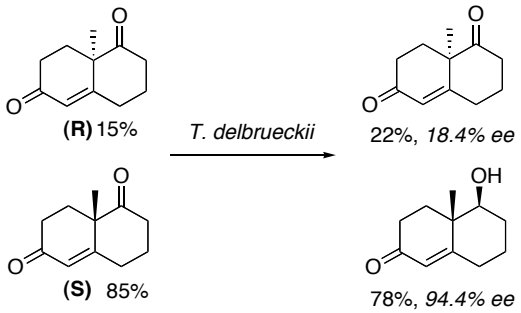
[149] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615-1621.
[150] Agami, C.; Meynier, F.; Puchot, C.; Guilhem, J.; Pascard, C. *Tetrahedron* **1984**, *40*, 1031-1038. Agami, C.; Levisalles, J.; Puchot, C. *J. Chem. Soc., Chem. Commun*. **1985**, *8*, 441-442.
[151] Clemente, F. R.; Houk, K. N. *Angew. Chem. Int. Ed*. **2004**, *43*, 5766-5768.



Scheme-3.5: Formation of Wieland-Miescher ketone

As enantiopure Wieland-Miescher ketone is no more commercially available since 2006, we decided to explore an enantioselective synthesis of Wieland-Miescher ketone or its derivatives. Several enantioselective syntheses of Wieland-Miescher ketone derivatives were described in the literature.

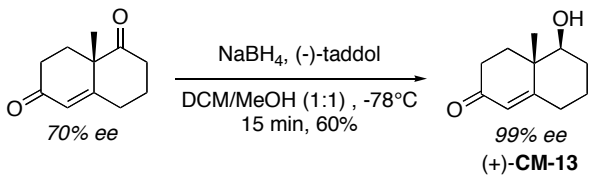
Sugai's group realized a yeast-mediated reduction of 70% ee (+)-Wieland-Miescher ketone through kinetic resolution with *T. delbrueckii,* which afforded the reduced alcohol in 78% yield with an enantiomeric excess of 94.4%. No reduction occurred with the (-)-enantiomer, so that the separation of the resulting mixture could be realized by simple flash chromatography (Scheme-3.6).[152] However, after contact with the author, we were told that our project was interesting but his group could not furnish us enough yeast.



Scheme-3.6: Enantioselective reduction of (+)-Wieland-Miescher ketone by *T. delbrueckii*

Another example was the reduction of enantiomerically impure Wieland-Miescher ketone with $NaBH_4$ in the solid state in the presence of (-)-taddol, using a test-tube shaker to give exclusively (+)-Wieland-Miescher hydroxy ketone derivative, while the wrong enantiomer decomposed during the reaction.[153] In our case, reduction of Wieland-Miescher ketone (70% ee) in 1:1 dichloromethane/MeOH at -78°C in the presence of one equivalent of (-)-taddol conducted to enantiopure alcohol **CM-13**, with an optical rotation matching the value described in the literature (Scheme-3.7), and the wrong enantiomer decomposed during the reaction.

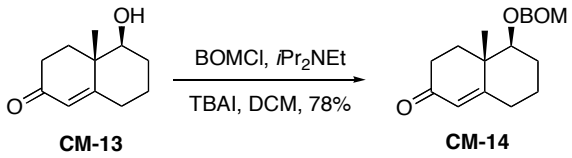
[152] Fuhshuku, K.-I.; Funa, N.; Akeboshi, T.; Ohta, H.; Hosomi, H.; Ohba, S.; Sugai, T. *J. Org. Chem.* **2000**, *65*, 129-135.
[153] Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 320-321.



Scheme-3.7: enantioselective reduction of (-)-Wieland-Miescher ketone

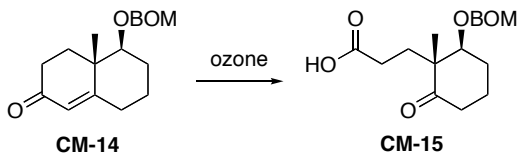
In summary, synthesis of **CM-13** was performed from 2-methyl-1,3-cyclohexanedione in a satisfying yield over 3 steps. The reduction with sodium borohydride in the presence of (-)-taddol was enantioselective by realizing the attack of hydride on the less bulky face, and also chemoselective on the carbonyl group in the presence of the α,β-unsaturated carbonyl group because of the former having a lower LUMO.

Since our target is one advanced intermediate of Holton's synthesis, transformation of the hydroxyl group to the BOM ether was chosen at first (Scheme-3.8).



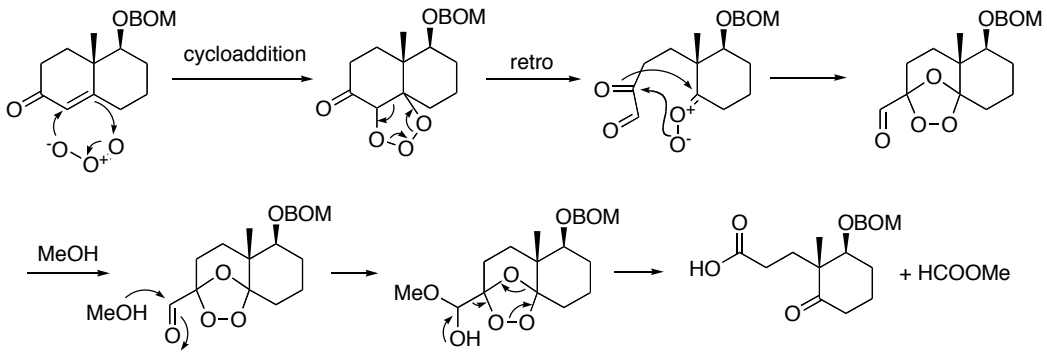
Scheme-3.8: Protection of the alcohol as the BOM ether

The formed **CM-14** was then subjected to ozonolysis in methanol, which proceeds in a classical fashion to realize the oxidative cleavage of the double bond to give keto acid **CM-15** (Scheme-3.9).



Scheme-3.9: Ozonolysis of CM-14

The following mechanism can be proposed to explain the event (Scheme-3.10): when the carbonyl and the carbonyl oxide are generated from the molozonide formed in the reaction, the non-terminal carbonyl groups of the molecule should participate in the following cycloaddition, then the addition of MeOH followed by rearrangement provides the corresponding carboxylic acid and methyl formate.



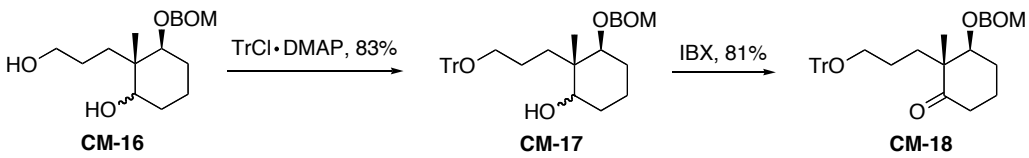
Scheme-3.10: Proposed Mechanism of ozonolysis to give the carboxylic acid

In this reaction, some decomposition was always observed, probably due to interaction of ozone with the BOM ether moiety. **CM-15** was then carried on to the next step without purification.

A trial of chemoselective reduction of the carboxyl group to the hydroxy group in the presence of the carbonyl group with borane dimethylsulfide and trimethyl borate[154] conducted to diol **CM-16** as a mixture of two diastereomers, so the same reduction was realized with the cheaper LAH (Scheme-3.11).

Scheme-3.11: Reduction of keto acid CM-15

Protection of the primary hydroxy group as its trityl ether furnished **CM-17**, which was subjected to oxidation with IBX to afford ketone **CM-18** (Scheme-3.12).

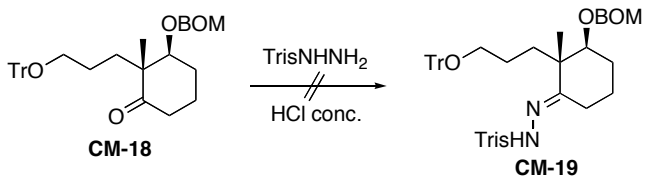


Scheme-3.12: Protection and oxidation of diol CM-16

Unfortunately, transformation of the carbonyl group of **CM-18** to the hydrazone performed with concentrated HCl led to removal of the trityl group (Scheme-3.13). This side reaction was not observed in our previous studies on 7-deoxy C ring. No reaction occurred under the

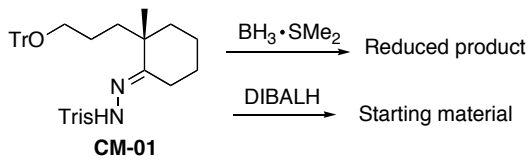
[154] Jung, J.-C.; Kache, R.; Vines, K. K.; Zheng, Y.-S.; Bijoy, P.; Valluri, M.; Avery, M. A. *J. Org. Chem.* **2004**, *69*, 9269-9284.

conditions Smith III used in his approach to spongistatin 1, which transformed the ketone to the hydrazone without HCl in excellent yield.[155]



Scheme-3.13: Attempt of hydrazone preparation

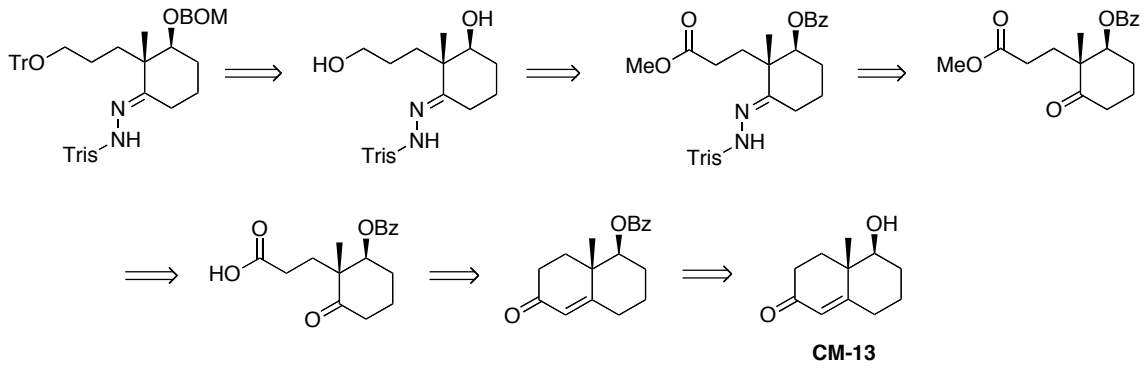
Since HCl was necessary for the formation of the hydrazone, we thought of realizing this step before protection of the diol group of the target molecule. In other words, the hydrazone moiety must tolerate reduction conditions under which the diol function would be obtained. Reduction assays of **CM-01** with DIBALH and dimethylsulfide borane that are normally unreactive with imines were performed. Only the former did not reduce the hydrazone group (Scheme-3.14).



Scheme-3.14: Reduction trials with the hydrazone group

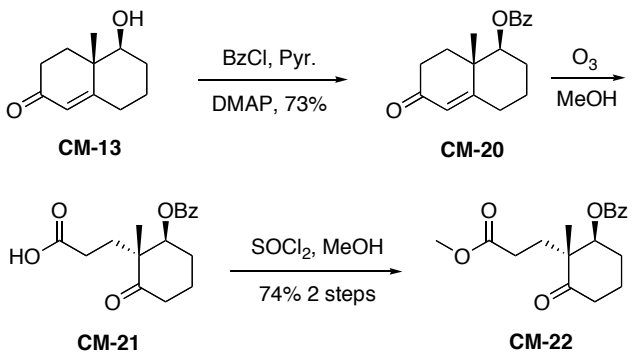
So the retrosynthesis of the C ring was slightly modified according to Scheme-3.15: reduction and protection of the diol group would be carried out at a later stage, hydrazone formation would be realized after ozonolysis and esterification of the corresponding product, and protection of **CM-13** as a benzoate ester would be performed so this protecting group would be removed during the reduction of the ester.

[155] Smith III, A. B.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783-786.



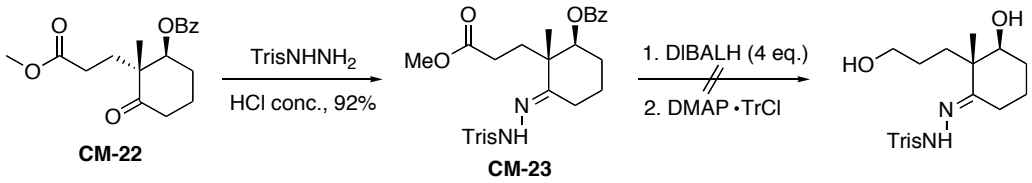
Scheme-3.15: Modified retrosynthesis involving the 7-benzoyl group

Protection of the hydroxy group of **CM-13** furnished benzoate **CM-20** (Scheme-3.16). Similar to what was observed with BOM ether **CM-14**, ozonolysis of **CM-20** also gave carboxylic acid **CM-21**, which was directly submitted to $SOCl_2$ in MeOH to afford methyl ester **CM-22**.



Scheme-3.16: Transformation of CM-13 to keto ester CM-22

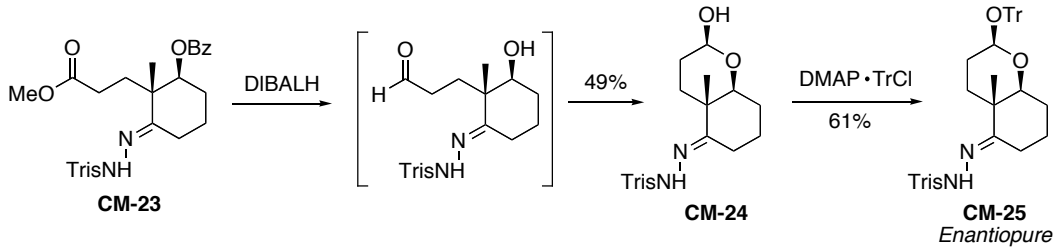
Transformation of the carbonyl group of **CM-22** to the hydrazone led to **CM-23**. However, reduction of **CM-23** with four equivalents of DIBALH followed by protection with 4-dimethylamino-*N*-triphenylmethyl pyridinium chloride did not furnish the desired dihydroxy hydrazone (Scheme-3.17).



Scheme-3.17: Trial of reduction of CM-23

In fact, hemiacetal **CM-24** was obtained, probably through hydroxy aldehyde formation pathway. When only three equivalents of DIBALH were added to the reaction, the aldehyde

peak was observed in ^{1}H NMR spectrum, and four equivalents of DIBALH led to formation of **CM-24** in 49% yield. Protection of the resulting hemiacetal afforded the corresponding trityl acetal **CM-25** (Scheme-3.18).

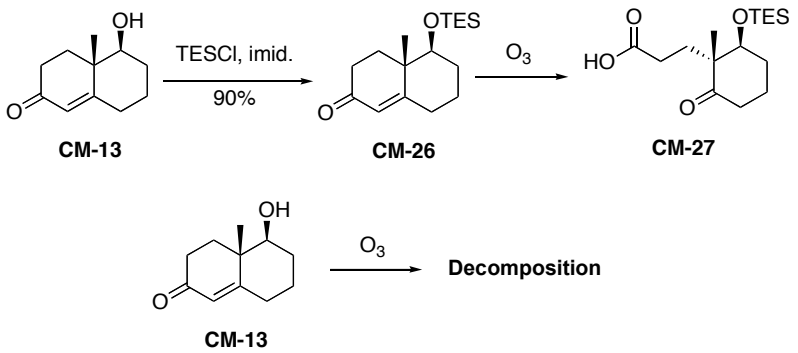


Scheme-3.18: Formation of hemiacetal CM-24 and trityl acetal CM-25

In summary, we synthesized a suitable precursor for the Shapiro reaction in 6 steps in a yield of 15% from Wieland-Miescher alcohol **CM-13**. However, the step of reduction of diester **CM-23** to hemiacetal **CM-24** was not satisfying because of the cost of 4 equivalents of DIBALH used in the reaction and the modest yield obtained; moreover, the bulky trityl acetal **CM-25** may cause some problems in the Shapiro coupling reaction with the sterically hindered aldehyde, corresponding to the future A fragment of taxol.

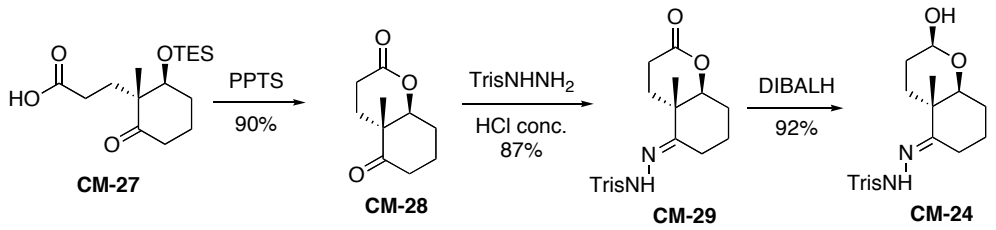
So the retrosynthesis was modified again: the C ring would be synthesized by transformation of the ketone to the hydrazone at a later stage, and the two hydroxy groups at C7 and C10 would be masked as the methyl acetal.

This time **CM-13** was transformed to silyl ether **CM-26**, which was subjected to ozonolysis to afford **CM-27** (Scheme-3.19). Direct ozonolysis of **CM-13** conducted to decomposition, although some ozonolysis reactions realized in the presence of hydroxy groups were described in the literature.



Scheme-3.19: Formation of keto acid CM-27

Lactonization of keto acid **CM-27** to **CM-28**, followed by transformation of the resulting ketone to the hydrazone conducted to **CM-29**, which was subjected to reduction with DIBALH to afford the corresponding lactol (Scheme-3.20), which was identical to the previously obtained hemiacetal **CM-24**.

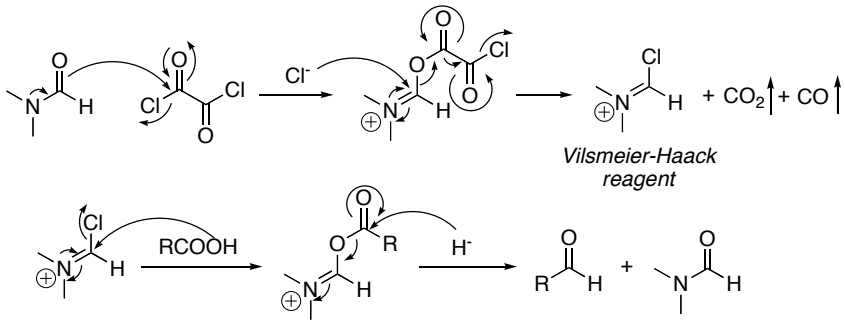


Scheme-3.20: Second synthesis of hemiacetal CM-24

Protection of the hemiacetal group as the methyl acetal was attempted using several methods. However, PPTS with methyl orthoformate conducted to removal of the hydrazone group because of acidic conditions; MeI in the presence of NaH or Ag_2O only led to decomposition.

We then thought of realizing this synthesis following another sequence: transformation of the hydroxy carboxylic acid to the hemiacetal, followed by protection of the hemiacetal as methyl acetal before the formation of hydrazone. For the reduction of the carboxylic acid to the aldehyde, we turned to the Vilsmeier-Haack reagent.

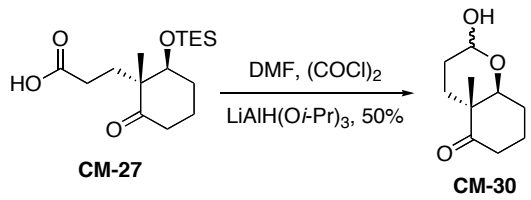
Vilsmeier-Haack reaction[156] is a classical reaction to produce the aryl aldehydes and ketones by reaction of activated arenes and substituted chloroiminium salts, which can be synthesized by reaction between a substituted amide and phosphorus oxychloride. In our case, the Vilsmeier-Haack reagent was produced to activate the carboxyl group and allowed its reduction to the aldehyde in the presence of the ketone (Scheme-3.21).



Scheme-3.21: Reduction of carboxylic acids to aldehydes using Vilsmeier-Haack reagent

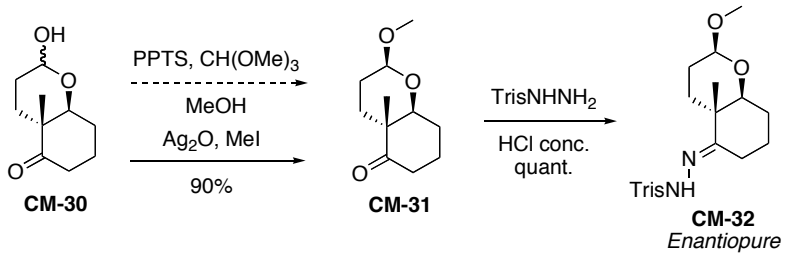
[156] Vilsmeier, A.; Haack, A. *Berichte* **1927**, *60*, 119-122.

This reaction was realized under Lebreton's conditions.[157] Vilsmeier-Haack reagent was formed by mixing a large excess of DMF and oxalyl chloride at -20ºC, then crude carboxylic acid **CM-27** was added followed by the reductive reagent; finally, acidic treatment *in situ* removed the TES group and conducted to a mixture of epimeric hemiacetals **CM-30** (Scheme-3.22).



Scheme-3.22: Formation of hemiacetal CM-30

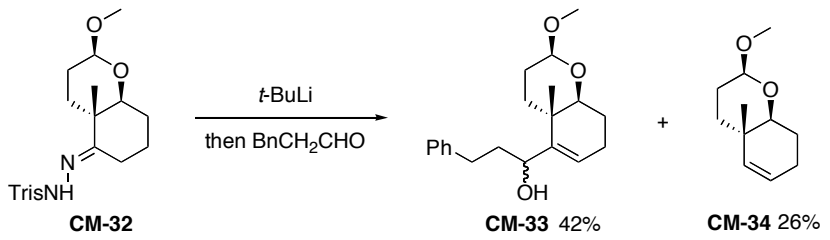
We then attempted to form the corresponding methyl acetal **CM-31**. Curiously, no reaction occurred in the presence of PPTS and methyl orthoformate, but silver (I) oxide promoted methylation of **CM-30** to afford methyl acetal **CM-31** in excellent yield, according to Paquette's conditions (Scheme-3.23).[158] Finally, transformation of **CM-31** to hydrazone **CM-32** proceeded in one hour in quantitative yield.



Scheme-3.23: Formation of enantiopure methyl acetal CM-32

With hydrazone **CM-32** in hand, we then tested the Shapiro reaction on a simple aldehyde. Hydrocinnamaldehyde was added to the reaction mixture containing the vinyl anion that was formed by treatment of **CM-32** with two equivalents of *t*-BuLi. Nucleophilic adduct **CM-33**, and alkene **CM-34** formed by protonation of the vinyl anion, were obtained in 42% and 26% respective yields (Scheme-3.24).

[157] Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* **2002**, *58*, 7381-7389.
[158] Paquette, L. A.; Sturino, C. F.; Wang, X.; Prodger, J. C.; Koh, D. *J. Am. Chem. Soc.* **1996**, *118*, 5620-5633.



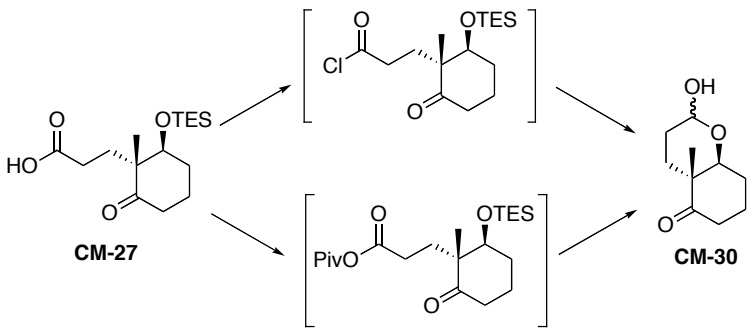
Scheme-3.24: Shapiro reaction of CM-32 with hydrocinnamaldehyde

The enantiopure C ring was synthesized in 8 step from 2-methyl-1,3-cyclohexanedione in 24% yield *via* enantiopure **CM-13**; a trial of the Shapiro reaction with hydrocinnamaldehyde was also successful.

However, the yield of the reduction of carboxylic acid **CM-27** to the aldehyde using Vilsmeier-Haack reagent was not very satisfying, probably due to the harsh basic and then acidic treatments. Several direct reductions of the carboxylic acid to the aldehyde could be tried instead:

a) An acyl halide could be formed *in situ*, which then would be reduced using metal borohydride[159] or H_2 in the presence of the palladium catalyst[160] to the aldehyde (Scheme-3.25), according to Rosenmund reaction conditions.

b) Yamamoto discovered that in the presence of pivalic anhydride, the carboxylic acid could be reduced to the aldehyde in excellent yield under 30 atm of H_2 by transforming the carboxylic acid to the carboxylic anhydrides followed by reduction catalyzed by $Pd(PPh_3)_4$ (Scheme-3.25).[161]



Scheme-3.25: Reduction of the carboxylic acids to the aldehydes

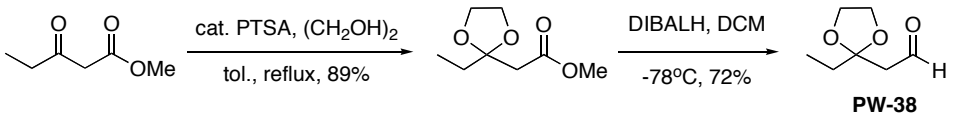
[159] Entwistle, I. D.; Boehm, P.; Johnstone R. A. W.; Telford, R. P. *J. Chem. Soc., Perkin Trans.* **1980**, *1*, 27-30.
[160] Rachlin, A. I. ; Gurien, H. ; Wagner, D. P. *Org. Synth.* **1971**, *51*, 8-10.
[161] Nagayama, K.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1803-1815.

With the enantiopure C ring in hand, we then focused on the synthesis of the A fragment of taxol.

2. SYNTHESIS OF THE A FRAGMENT

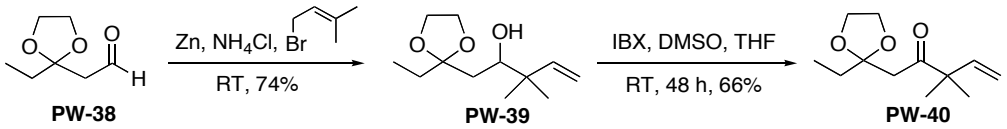
2.1 PREVIOUS WORK IN THE LABORATORY

The synthesis of the A fragment with all the functionalities required for taxol was first performed by Dr. Stéphanie Schiltz. Methyl 3-oxovalerate was chosen as the starting material. Transformation of the carbonyl to the ketal group in the presence of *p*-toluenesulfonic acid, followed by reduction of the resulting ketal ester afforded aldehyde **PW-38** (Scheme-3.26).



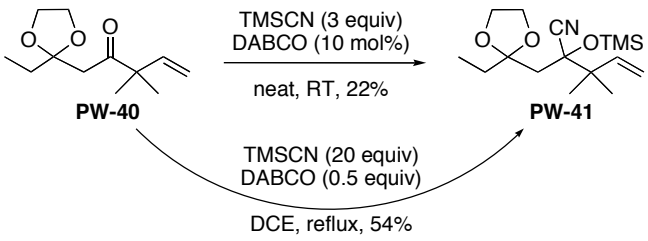
Scheme-3.26: Formation of ketal aldehyde PW-38

Barbier reaction was then applied to provide *gem*-dimethyl alcohol **PW-39**, which was subjected to oxidation with IBX to furnish ketone **PW-40** (Scheme-3.27). The oxidation necessitated a remarkably long time, probably due to steric hindrance of the bulky ketal group.



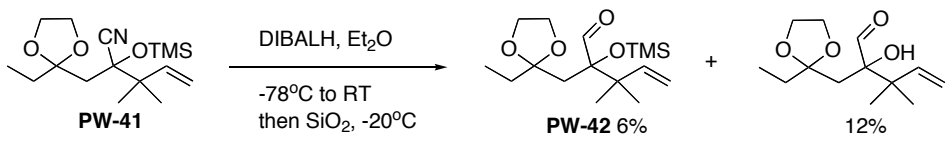
Scheme-3.27: Formation of ketal ketone PW-40

The first trial of cyanation of **PW-40** catalyzed by ZnI_2 did not conduct to the desired product. A trial in the presence of a Lewis base such as DABCO led to ketal cyanohydrin **PW-41** in 22% yield. Finally, this reaction was optimized to afford **PW-41** in 54% yield by refluxing in 1,2-dichloroethane for 5 days (Scheme-3.28).



Scheme-3.28: Formation of cyanohydrin PW-41

A first attempt of reduction of cyanohydrins **PW-41** with DIBALH conducted in low yields to aldehyde **PW-42** and its derivative resulting from removal of the TMS group in the reaction (Scheme-3.29).

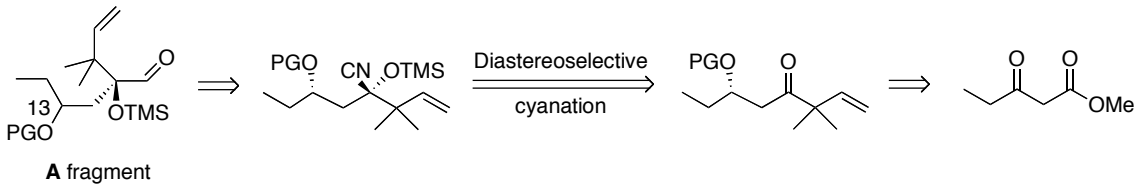


Scheme-3.29: Formation of α-siloxy aldehyde PW-42 (first attempt)

In summary, the A fragment was synthesized in 6 steps, but the overall yield was modest, for which the highly sterically hindered ketal group was probably responsible. A less bulky protecting group for the 3-oxo position should be chosen for the synthesis of the A fragment.

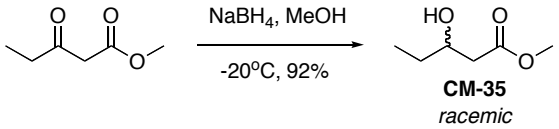
2.2 SYNTHESIS OF THE A FRAGMENT

So the semi-convergent retrosynthesis of taxol was slightly modified: the A fragment would still be synthesized from the same starting material methyl 3-oxovalerate; the carbonyl group should be would be masked as a secondary protected alcohol and the chosen protecting group should be less hindered than the ketal group in the former strategy. In this synthetic route, a diastereoselective cyanation under 1,3-chelate control to afford the *syn*-cyanohydrin would be investigated (Scheme-3.30).



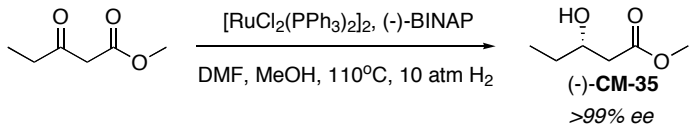
Scheme-3.30: Modified retrosynthesis of the A fragment

Reduction of methyl 3-oxovalerate to 3-hydroxy valerate was performed with sodium borohydride at -20°C (Scheme-3.31). The temperature was very important for reduction of such a substrate. A quite important amount of diol could be obtained as byproduct when the reaction was performed at 0°C as normally described in the literature.



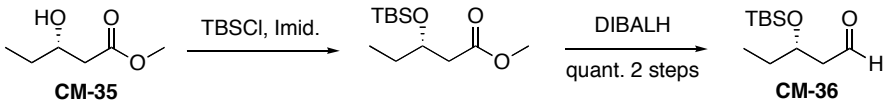
Scheme-3.31: Racemic reduction to CM-35

Enantioselective reduction was also realized under high-pressure hydrogen atomosphere (10 atm) in the presence of $[RuCl_2(PPh_3)_2]_2$ and (-)-BINAP, according to Noyori's method.[162] Freshly distilled DMF and degassed MeOH are necessary to achieve the asymmetric hydrogenation with an excellent enantiomeric excess (Scheme-3.32).



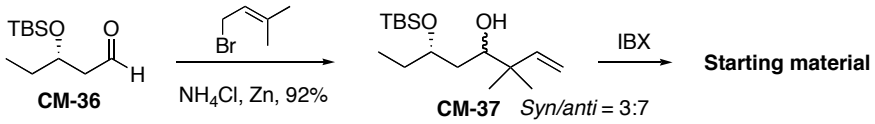
Scheme-3.32: Enantioselective reduction to CM-35

3-Hydroxy valerate **CM-35** was protected to the corresponding *tert*-butyldimethylsiloxy ether in good yield (Scheme-3.33). Reduction of the ester to aldehyde **CM-36** was done with DIBALH at -78°C in 15 minutes, to avoid the formation of the alcohol as a side reaction.



Scheme-3.33: Protection and reduction of CM-35 to aldehyde CM-36

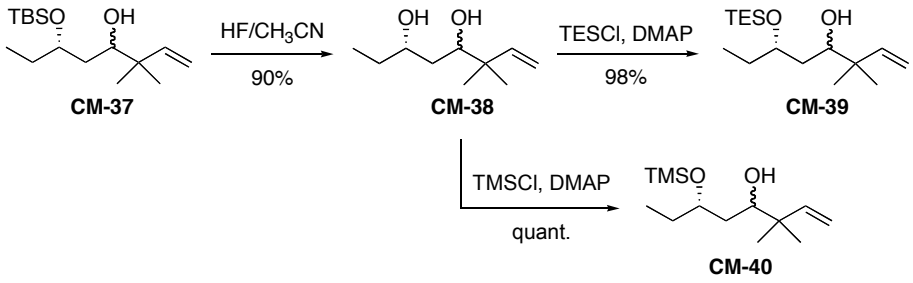
Barbier reaction was then performed to give alcohol **CM-37**, as a 3:7 mixture of *syn/anti* diastereomers (Scheme-3.34). However, oxidation of **CM-37** with IBX was unsuccessful, probably due to steric hindrance of the TBS group.



Scheme-3.34: Unsuccessful oxidation of β-siloxy alcohol CM-37 with IBX

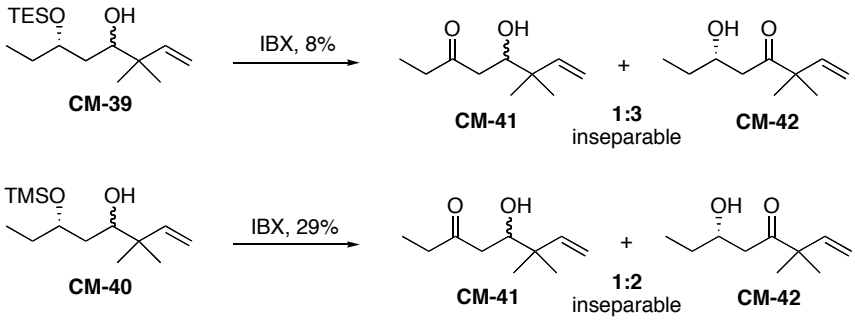
To minimize the steric hindrance present in **CM-37**, removal of the TBS group gave **CM-38**, then the dihydroxy group was mono-protected regioselectively to furnish TES ether **CM-39** and TMS ether **CM-40** (Scheme-3.35).

[162] Hoppen, S.; Bäurle, S.; Koert, U. *Chem. Eur. J.* **2000**, *6*, 2382-2396.



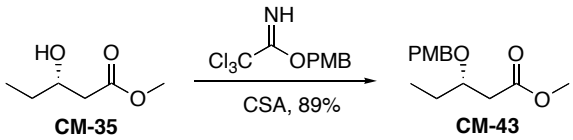
Scheme-3.35: Formation of ketones CM-39 and CM-40

However, IBX-mediated oxidation of **CM-39** and **CM-40** conducted to partial migration of the siloxy groups, and an inseparable mixture of the oxidized products **CM-41** and **CM-42** were obtained in 1:3 and 1:2 ratios in the two cases, respectively, after hydrolysis of the siloxy groups (Scheme-3.36).



Scheme-3.36: Migration and removal of the siloxy groups

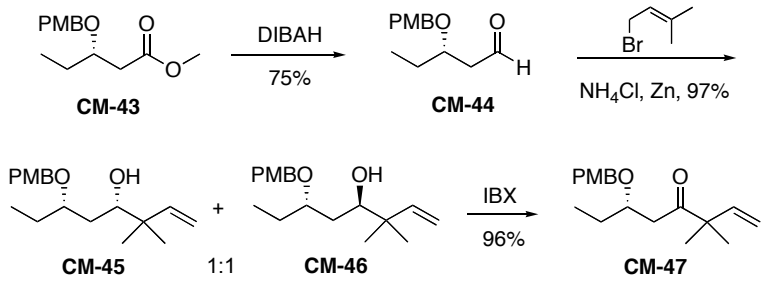
The PMB ether was then used to protect the hydroxy group of **CM-35** for its lesser group size and migration ability. **CM-35** was protected using *p*-methoxybenzyloxy acetimidate, to avoid retro aldol reaction under basic conditions. After several trials for the selection of acid catalysts, Kobayashi's conditions[163] using camphor sulfonic acid were chosen to realize the protection with the acetimidate at room temperature. 3-*p*-Methoxybenzyloxy valerate **CM-36** was obtained in good yield (Scheme-3.37).



Scheme-3.37: Protection of CM-35 as the PMB ether

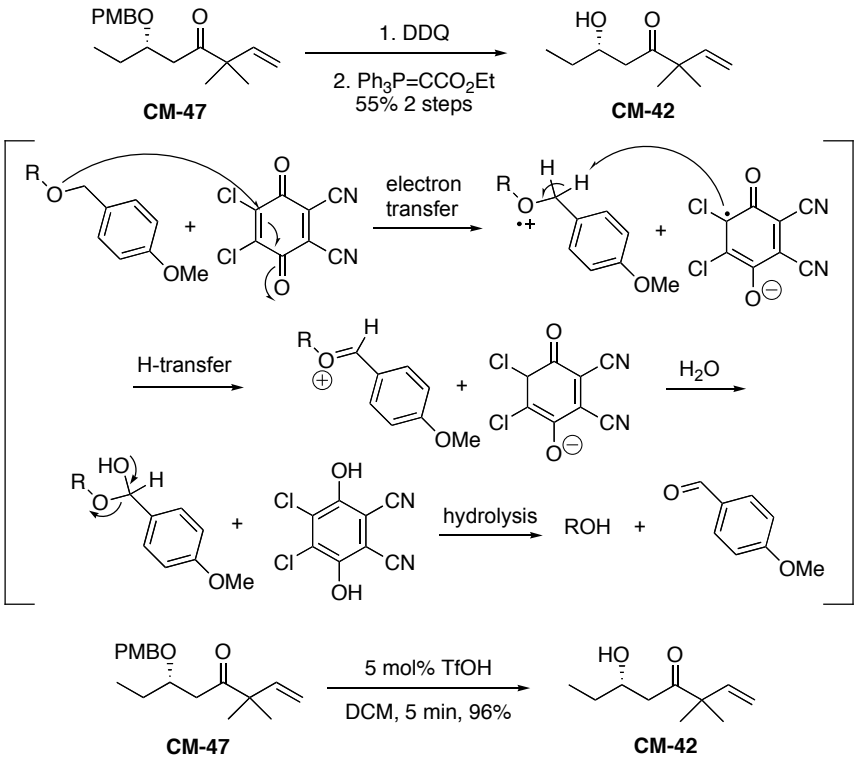
[163] Wang, Y.-G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615-4618.

Reduction of **CM-43** with DIBALH gave aldehyde **CM-44**, which was subjected to Barbier reaction to provide two diastereomeric alcohols **CM-45** and **CM-46** in a 1:1 ratio (Scheme-3.38). Oxidation of **CM-45** and **CM-46** with IBX gave ketone **CM-47** in good yield.



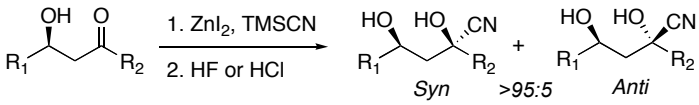
Scheme-3.38: Formation of ketone CM-47 from ester CM-43

Removal of the PMB group of **CM-47** was then carried out with DDQ to realize an oxidative cleavage. However, the resulting *p*-methoxybenzaldehyde (anisaldehyde) by-product was inseparable from β-hydroxy ketone **CM-42**, either by flash chromatography or by distillation (Scheme-3.39). Moreover, treatment with sodium hydrogensulfite to eliminate anisaldehyde unfortunately just worked one time, and additional step such as a Wittig reaction to transform anisaldehyde into a less polar compound caused low yield. Finally, removal of the PMB group was accomplished under acidic conditions with 5% TfOH in dichloromethane at room temperature for 5 minutes in excellent yield (Scheme-3.39). The product spectrally correlated to **CM-42** obtained in the oxidation reactions of **CM-39** and **CM-40**.



Scheme-3.39: Removal of the PMB group

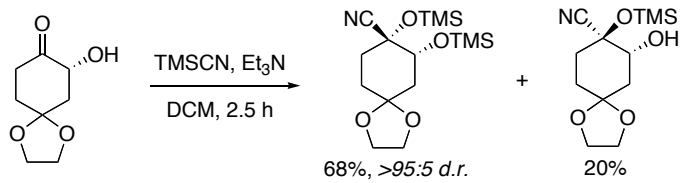
With β-hydroxy ketone **CM-42** in hand, we attempted to synthesize a single diastereomeric cyanohydrin product. Brunet and coll. reported a diastereoselective cyanation in the presence of ZnI_2. When R_1 = Et and R_2 = *t*-Bu, the cyanohydrin was obtained with a diastereomeric ratio of more than 95:5 (Scheme-3.40). However, bulkier R_1 or less hindered R_2 cannot offer good diastereoselectivities.[164]



Scheme-3.40: Diastereoselective cyanation with zinc iodide

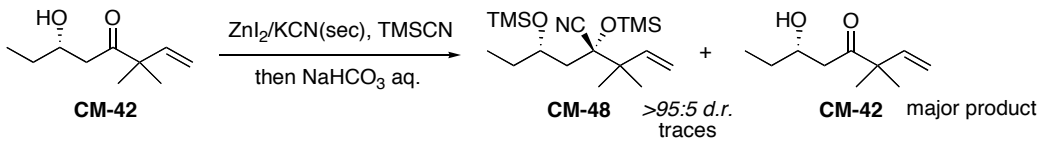
Another diastereoselective cyanation was also reported in the presence of triethylamine:[165] after stirring for 2.5 hours, the bis-trimethylsilyl cyclocyclohexane was obtained in 68% yield with a diastereomeric ratio of more than 95:5, along with the diastereomeric mono-trimethylsilyl cyclocyclohexane in 20% yield (Scheme-3.41). Steric hindrance promoted kinetic discrimination between the diastereomers during the formation of the second ether and resulted in the formation of the bis-trimethylsilyl ether in an excellent diastereomeric ratio.

[164] Batra, M. S.; Aguilar, F. J.; Brunet, E. *Tetrahedron* **1994**, *50*, 8169-8184.
[165] Yamaguchi, J.; Toyoshima, M.; Shoji, M.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 789-793.



Scheme-3.41: Diastereoselective cyanation by kinetic discrimination

With these encouraging reports, our cyanation was first tested with ketone **CM-42** and TMSCN in the presence of one equivalent of activated ZnI_2 and dried KCN, according to Brunet's method. The reaction was nearly complete by stirring at room temperature for one hour, as indicated by TLC, and then quenched with a saturated aqueous sodium hydrogencarbonate solution. However, the NMR spectrum of the crude product showed that the major compound present was the starting material with only trace of the expected cyanohydrin product obtained in a diastereomeric ratio of more than 95:5 (Scheme-3.42). So a retro-cyanation reaction must take place during the aqueous work-up.



Scheme-3.42: First trial of cyanation

To understand this reaction, we first examined all the reagents present in the reaction. The reaction results are summarized in Table-3.1.

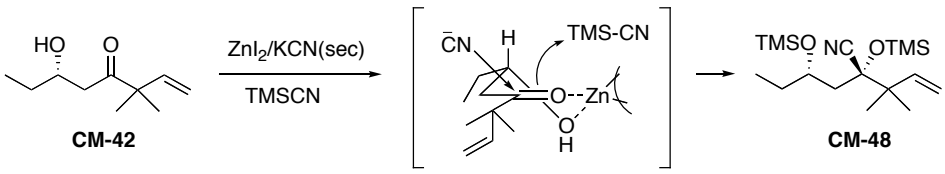
Table-3.1: Diastereoselective cyanation trials

Entry	Conditions	Treatment	Result	Diastereoselectivity syn/anti
1	ZnI_2, TMSCN	H_2O	Starting Material	----
2	ZnI_2, KCN	H_2O	Starting Material	----
3	ZnI_2, TMSCN, KCN	H_2O	**CM-48** (traces)	>95:5[b]
4	$AlCl_3$, TMSCN, KCN	----[a]	Starting Material	----
5	$MgBr_2$, TMSCN, KCN	----	Starting Material	----
6	$MgBr_2$, TMSCl, KCN	----	**CM-48** (traces)	1:1
7	$AlMeCl_2$, TMSCN, KCN	----	Starting Material	----
8	ZnI_2, TMSCN, KCN	----	**CM-48** (traces)	>95:5

[a] Direct evaporation by rotaratory evaporator with a trap of KOH/NaClO. [b] Analysis by ^{1}H NMR spectra

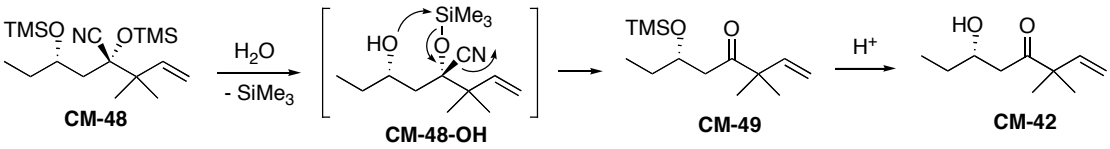
Without KCN, the reaction progressed difficultly, and without TMSCN, no reaction occurred. So this nucleophilic addition was probably KCN promoted but realized by attack of TMSCN

with the silyl group as counter ion (Scheme-3.43). Several chelating Lewis acids were also tested to verify the different diastereoselectivities. Only ZnI_2 present in the reaction with **CM-42** led to a good diastereomeric excess, despite the problem of retro-cyanation. Direct evaporation of the reaction mixture gave siloxy ketone **CM-49** (Scheme-3.44) as the major product and a little more of the desired **CM-48** than that with an aqueous treatment.



Scheme-3.43: Diastereoselective cyanation of CM-42

Retrocyanation in the quench process could be caused by removal of the TMS group on the secondary alcohol during aqueous treatment, and then migration of the TMS group from the tertiary alcohol to the secondary one conducts to elimination of the cyanide group. We tried to remove the two TMS groups by treatment with HCl to form the dihydroxy cyanohydrin to avoid the migration of the TMS group, but only hydroxy ketone **CM-42** was obtained (Scheme-3.44).



Scheme-3.44: Retrocyanation of CM-48

Subsequently, different work-up procedures were examined (Table-3.2). Reprotection of **CM-48-OH** with the PMB acetimidate or bromide conducted to retrocyanation; methylation in the presence of NaH caused decomposition; protection in the presence of HMDS and TMSCl led to obtention of **CM-48** and **CM-49** in variable proportions; reaction *in situ* with TMSOTf and 2,6-lutidine provided **CM-48** and **CM-49** in a 2:1 ratio; addition of pyridine resulted in retrocyanation; addition of triethylamine afforded **CM-48** and **CM-49** in a 2:1 ratio. The retrocyanation seems inevitable.

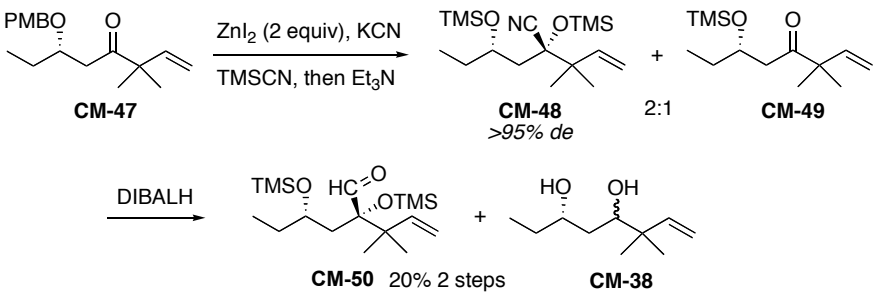
Table-3.2: Different treatments to obtain CM-48

Entry	Treatments	Temperature	Treatment	Result
1	$CCl_3(C{=}NH)OPMB$, CSA	rt	----	**CM-42**
2	PMBBr, NaH	rt	----	Decomposition

3	PMBBr, NaH	0°C	$NaHCO_3$ aq.	**CM-49**
4	NaH, MeI	0°C	$NaHCO_3$ aq.	Decomposition
5	HMDS, TMSCl, Pyr., pentane	reflux	----	Precipitation
6	HMDS, TMSCl, Pyr.	rt	----	**CM-48/CM-49** (variable)
7	TMSOTf, 2,6-lutidine	-78°C	MeOH	**CM-48/CM-49** (2:1)
8	Pyr.	rt	----	**CM-49**
9	Et_3N, TMSCl	0°C	----	**CM-48/CM-49** (6:4)
10	Et_3N	0°C	----	**CM-48/CM-49** (6:4)
11	Et_3N	-78°C-0°C	----	**CM-49**
12	Et_3N	-10°C	----	**CM-48/CM-49** (2:1)

We also observed that if **CM-47** was directly subjected to cyanation in the presence of one equivalent of ZnI_2, only a diastereomeric ratio of 8:2 was obtained. However, with two equivalents of ZnI_2 present in the reaction, the diastereomeric ratio increased to more than 95:5. In fact, TLC check showed that removal of the PMB group proceeded *in situ* to afford **CM-42** ready to participate in the cyanation reaction (Scheme-3.45).

Addition of DIBALH to the reaction mixture obtained after cyanation, to reduce directly the mixture of cyanohydrin **CM-48** and ketone **CM-49**, barely conducted to aldehyde **CM-50**. We often observed severe decomposition by TLC. Nevertheless, we successed to isolate **CM-50** in 20% overall yield once and carry on characterization, even though this reaction was irreproducible (Scheme-3.45). Other methods such as transformations of the nitrile to carboxylic acid or amide then to the aldehyde were also tested but without success, probably due to harsh acidic or basic conditions.



Scheme-3.45: Cyanation of CM-47 and reduction of CM-48

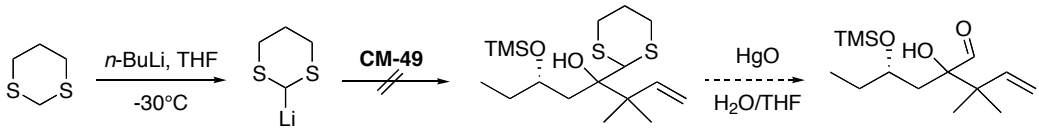
Reduction of **CM-48** was also attempted with $LiAlH(OEt)_3$ and $LiAlH_2(OEt)_2$ generated by LAH and EtOH or AcOEt *in situ*, which normally could reduce the nitriles to the aldehydes.[166] Unfortunately, no reaction occurred.

Reduction of nitriles to aldehydes with Raney-Ni was reported in the presence of NaH_2PO_2,[167] but no reaction occurred in our case.

In summary, the A fragment was synthesized in 7 steps in an overall yield of 12%. We performed a diastereoselective cyanation with a highly sterically hindered molecule as substrate, but migration of the labile TMS group caused retrocyanation resulting in modest yield, and the reduction of the nitrile to the aldehyde was difficult to realize.

As the synthetic route to ketone **CM-47** was efficient (62% yield over 6 steps), we thought of other methods that may conduct to aldehyde **CM-50**. Several methods were investigated.

Corey-Seebach reaction was performed at first.[168] **CM-49** was added to lithiated 1,3-dithiane prepared with *n*-BuLi at -30°C, which can generally realize the nucleophilic addition to ketones to afford the α-hydroxy dithiane, and after oxidative hydrolysis, the α-hydroxy aldehyde (Scheme-3.46).[169] Unfortunately, no addition of dithiane to ketone **CM-49** was observed.

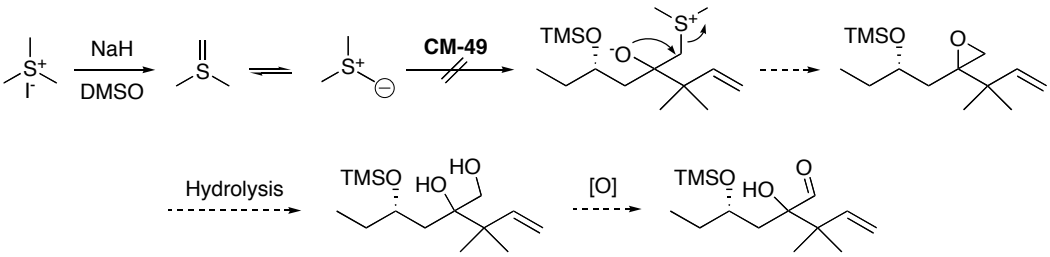


Scheme-3.46: Trial of Corey-Seebach reaction to obtain the aldehyde

Corey-Chaykovsky reaction was also examined:[170] the ylide was generated *in situ* by deprotonation of sulfonium halide with NaH, which initially acted as a nucleophile toward the carbonyl group of **CM-49**. The resulting oxygen anion then should react as an intramolecular nucleophile toward the now electrophilic ylide carbon, which bears a sulfonium cation as a good leaving group to furnish the epoxide product. Conversion to the diol and oxidation of

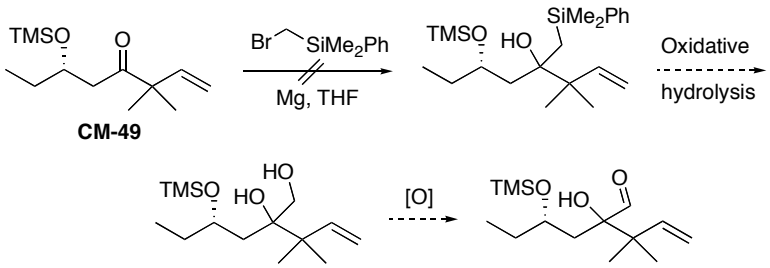
[166] Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc*. **1964**, *86*, 1085-1089. Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc*. **1964**, *86*, 1089-1095.
[167] Heffner, R. J.; Jiang, J.; Joullié, M. *J. Am. Chem. Soc*. **1992**, *114*, 10181-10189. Amat, M.; Bassas, O.; Canto, M.; Llor, N.; Santos, M. M. M.; Bosch, J.; *Tetrahedron* **2005**, *61*, 7693-7702.
[168] Chamchaang, W.; Prankprakma, V.; Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Synthesis* **1982**, 579-580.
[169] Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357-402.
[170] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc*. **1965**, *87*, 1353-1364.

the resulting primary alcohol would afford the α-hydroxy aldehyde (Scheme-3.47). But no reaction occurred in our case.



Scheme-3.47: Trial of Corey-Chaykovsky reaction to obtain the aldehyde

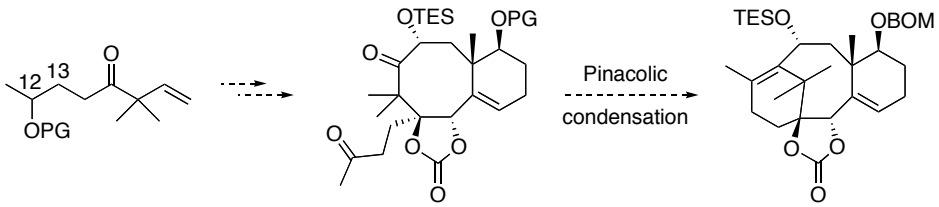
Finally, nucleophilic addition of $BrMgCH_2SiMe_2Ph$ was tested. Hydrolysis of the phenyldimethylsilyl group of the resulting adduct of **CM-49** to the corresponding 1,2-diol, followed by oxidation of the primary alcohol would form the α-hydroxy aldehyde product (Scheme-3.48).[171] But no reaction occurred one more time.



Scheme-3.48: Trial of addition of Grignard reagent

As described above, the substitution at the β-position of *gem*-dimethyl ketone **CM-47** is always too bulky to perform the desired manipulation on the carbonyl group. To minimize the steric hindrance, different modifications of the functional group could be envisaged as follows:

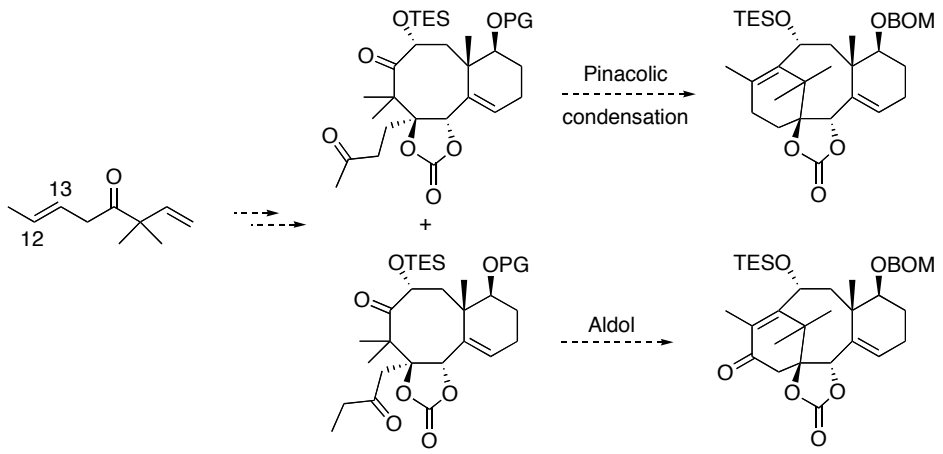
1. Substitution at C12 instead of C13, then closure of the A ring by pinacolic condensation (Scheme-3.49);



Scheme-3.49: Proposal of substitution at C12

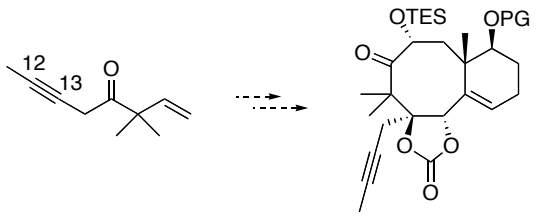
[171] Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem*. **1983**, *48*, 2120-2122. Kim, M.; Grzeszczyk, B.; Zamojski, A. *Tetrahedron* **2000**, *56*, 9319-9337.

2. Double bond at C12-C13, then Wacker oxidation followed by pinacolic condensation or intramolecular aldol reaction because of the poor regioselectivity of the Wacker oxidation of the internal olefin (Scheme-3.50);[172]



Scheme-3.50: Proposal of double bond at C12-C13

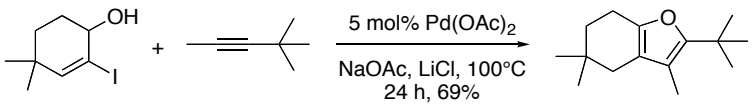
3. Triple bond at C12-C13 to synthesize a BC ring-system at first, according to Scheme-3.51;



Scheme-3.51: Proposal of triple bond at C12-C13

Several subsequent transformations would then allow formation of the A ring:

a) Larock reported palladium-catalyzed annulations of internal alkynes using substituted vinyl halide or vinyl triflate (Scheme-3.52).[173]

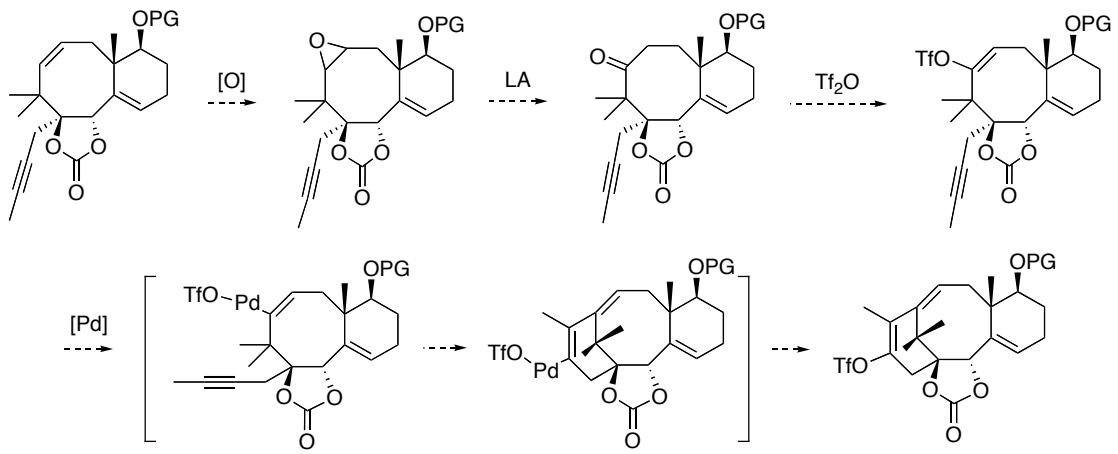


Scheme-3.52: Larock's precedent

By analogy to Larock's precedent, direct cyclization of a convenient C ring organopalladate onto the triple bond can be envisioned: epoxidation of the double bond at C10-C11 followed by ring-opening at the electron-rich site should give the corresponding ketone; formation of

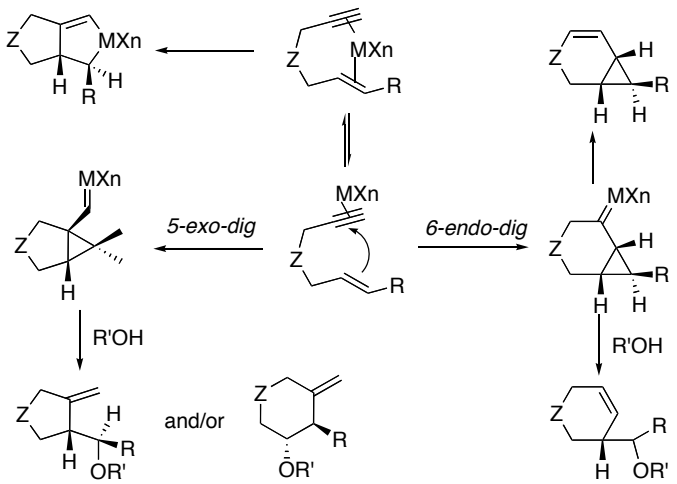
[172] Takikawa, H.; Tobe, M.; Isono, K.; Sasaki, M. *Tetrahedron* **2005**, *61*, 8830-8835.
[173] Larock, R. C.; Doty, M. J.; Han, X. *Tetrahedron Lett*. **1998**, *39*, 5143-5146.

the vinyl triflate would afford a suitable substrate for palladium-catalyzed annelation; then the closure of A ring would proceed because of the reduced energy of the final product (Scheme-3.53).



Scheme-3.53: Possible route of the closure of the A ring by palladium catalysis

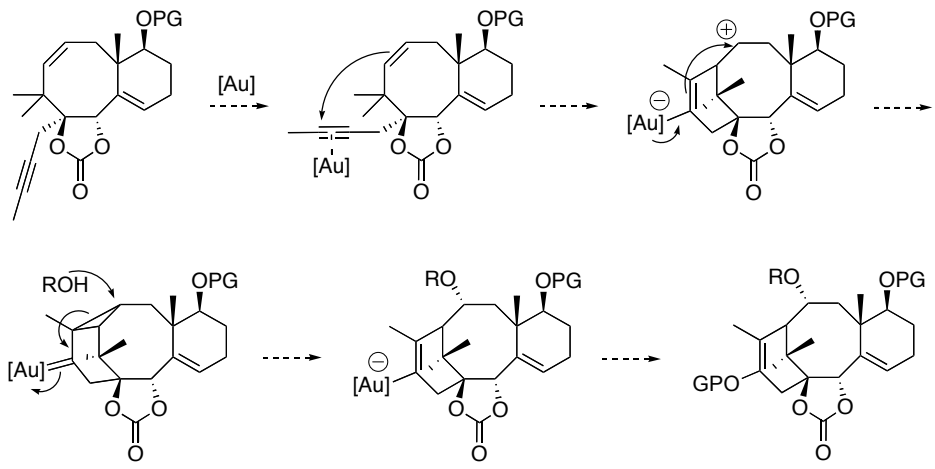
b) Metal-catalyzed cyclization of 1,6-enynes was developed with Hg,[174] Fe,[175] Pd salts, but also with Pt and Au salts.[176] The cyclization could proceed by *5-exo-dig* or *6-endo-dig* pathway (Scheme-3.54).[177]



Scheme-3.54: Mechanism of enyne cyclization by metal catalysis

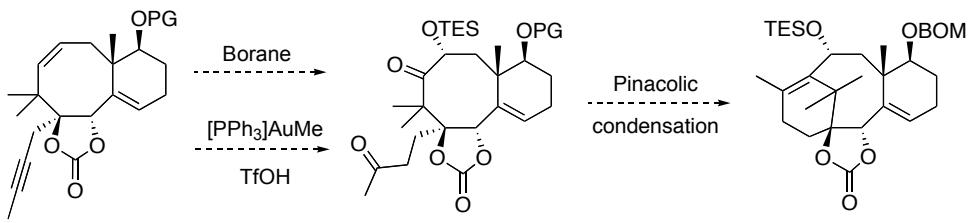
[174] Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609-1611.
[175] Pearson, A. J.; Dubbert, R. A. *Organometallics* **1994**, *13*, 1656-1661.
[176] Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.
[177] Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785-6786. Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.

With an Au catalyst, for example Echavarren's catalyst [PPh$_3$]Au(NCMe), this type of cyclization was recently realized in the presence of water, MeOH, or BnOH as nucleophiles. We would use this method to close the A ring (Scheme-3.55).



Scheme-3.55: Possible route for the closure of the A ring by gold catalysis

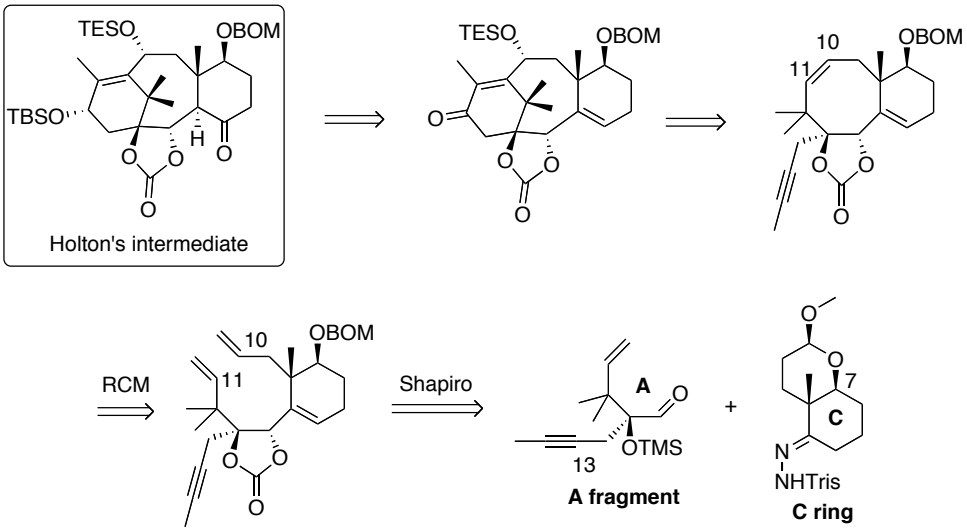
c) A classical method would be generating the carbonyl group by hydroboration or gold-catalyzed hydration[178] of the triple bond, which should be regioselective by steric control. The pinacolic condensation would then be carried out to afford the ABC tricycle (Scheme-3.56).



Scheme-3.56: Possible route of the closure of the A ring by hydroxylation of the triple bond

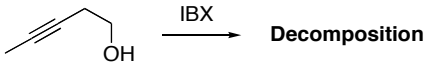
Among the three possible functional modifications envisioned for the construction of the A fragment, we thought that the third one with a triple bond at C12-C13 seemed to be the most promising and original route, comparing to all the total syntheses of taxol. So the retrosynthesis was modified as shown in Scheme-3.57: the final steps of taxol synthesis would be achieved from an intermediate in Holton's synthesis. The A ring would be installed at a late stage; BC bicycle would be formed by ring-closing metathesis on a diene, which would be prepared by addition of a vinyllithium to an aldehyde. The aldehyde would be synthesized in a similar way as before, but an enantioselective cyanation would be necessary in this case.

[178] Mizushima, E.; Sato, K.; Hayashi, T.; Tanak, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563-4565.



Scheme-3.57: Retrosynthesis with the butynyl A fragment

To achieve the synthesis of the new A fragment, 3-pentyn-1-ol was chosen as starting material. In the literature 3-pentynol can be converted to the corresponding aldehyde with TEMPO/PhI(OAc)$_2$ in 41% yield; Dess-Martin periodinane (DMP) was also used but no yield furnished.[179] So experiments of oxidation were first investigated: IBX conducted to decomposition of the substrate (Scheme-3.58).

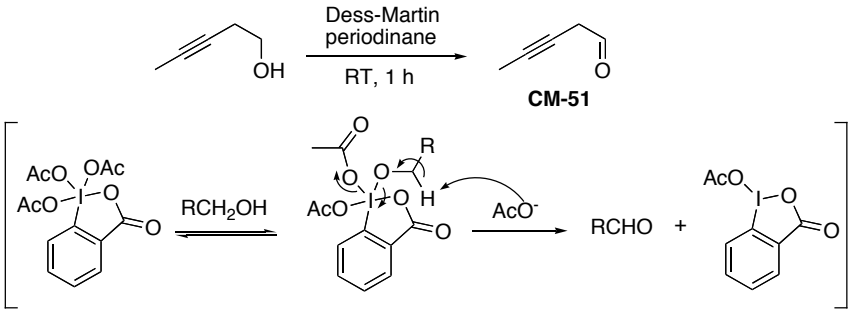


Scheme-3.58: Oxidation with IBX

Thinking the product was not stable under acidic conditions, we then performed Swern oxidation,[180] which can oxidize the hydroxyl group under basic conditions, but no reaction occurred. PCC oxidation[181] also led to decomposition; no progress was observed with TEMPO/oxone,[182] either with TEMPO/trichloroisocyanuric acid;[183] no reaction occurred with *p*-nitrobenzaldehyde in the presence of AlMe$_3$ according to Oppenauer oxidation conditions; in the end, bleach oxidation[184] conducted to decomposition.

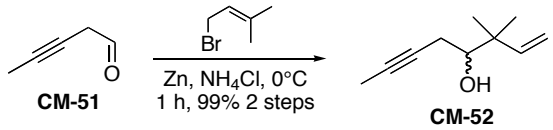
[179] Vugts, D. J.; Veum, L.; al-Mafraji, K.; Lemmens, R.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Hanefeld, U.; Orru, R. V. A. *Eur. J. Org. Chem*. **2006**, 1672-1677.
[180] Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.
[181] Corey, E. J.; Suggs, J. M. *Tetrahedron Lett.* **1975**, *16*, 2647-2650.
[182] Bolm, C.; Magnus, A. S.; Hildebrand, J. P. *Org. Lett*. **2000**, *2*, 1173-1175.
[183] De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett*. **2001**, *3*, 3041-3043.
[184] Mirafzal, G. A.; Lozeva, A. M. *Tetrahedron Lett.* **1998**, *39*, 7263-7266.

Fortunately, oxidation with Dess-Martin periodinane produced the desired aldehyde **CM-51** (Scheme-3.59). After precipitation of the iodoxy salt in pentane at -78°C,[185] the crude product was recovered by filtration through silica gel and concentration without further purification, because of its instability and low boiling point.



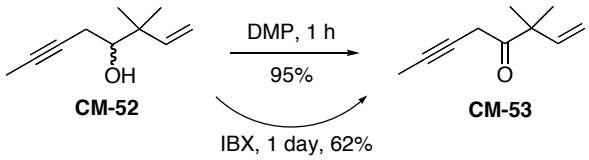
Scheme-3.59: Oxidation with DMP

Barbier reaction performed under the same conditions as before (room temperature, overnight) only led to decomposition. However, stirring for one hour at 0°C sufficed to obtain racemic alcohol **CM-52** in excellent yield over two steps (Scheme-3.60). Prolonged reaction time at this temperature conducted to slight decomposition.



Scheme-3.60: Barbier reaction of CM-51 under milder conditions

Oxidation of **CM-52** was performed with DMP to furnish ketone **CM-53** in excellent yield (Scheme-3.61). This reaction could also be realized with IBX, which necessitated a longer reaction time and resulted in a lower yield.

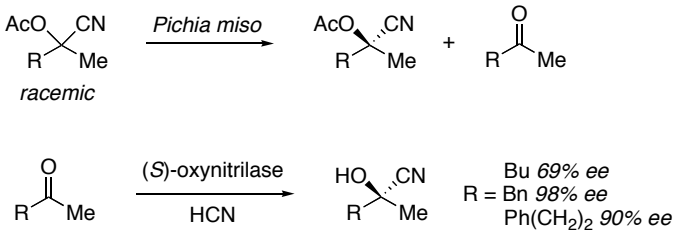


Scheme-3.61: Oxidation of CM-52

Several methods are reported in the literature to realize an enantioselective cyanation of ketones. The first one was discovered by Sugai's group and consists of an enzymatic hydrolysis of a racemic α-acetoxy nitrile using a microorganism, *Pichia miso* IAM 4682, to

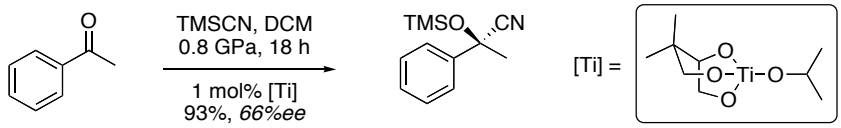
[185] Schneider, R.; Charrier, F.; Razungles, A.; Baumes, R.; *Anal. Chim. Acta* **2006**, *563*, 58-64.

isolate the non-hydrolyzed enantiomer in enantioenriched form.[186] (*R*)- and (*S*)-oxynitrilases isolated from almonds and the rubber tree could directly catalyze the enantioselective cyanation of aldehydes and ketones, despites the scale limit and the poor conversion (Scheme-3.62).[187]



Scheme-3.62: Enzymatic enantioselective cyanation

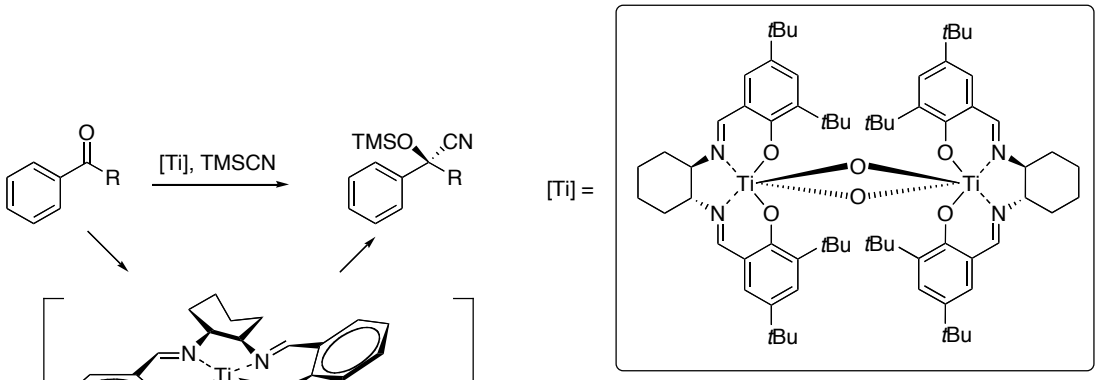
Choi then described the first example of enantioselective cyanation of ketones at high pressure using a chiral titanium catalyst (Scheme-3.63),[188] which had been developed to catalyze the cyanation of aldehydes at atmospheric pressure.[189]



Scheme-3.63: First enantioselective cyanation using chiral titanium catalyst

Another titanium catalyst containing a tetradentate ligand, salen, was also developed (Scheme-3.64).[190] In the presence of this catalyst, aromatic ketones could be transformed to siloxy cyanohydrin in ca. 70% ee at atmospheric pressure. However, increase of the catalyst quantity or of the aliphatic group size led to decrease of the enantiomeric excess.

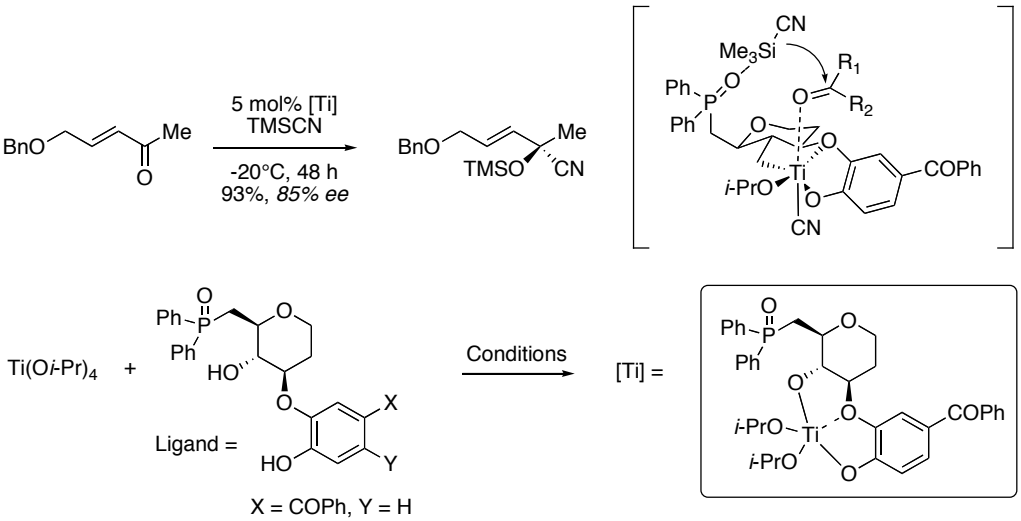
[186] Ohta, H.; Kimura, Y.; Sugano, Y.; Sugai, T. *Tetrahedron* **1989**, *45*, 5469-5476.
[187] North, M. *Synlett* **1993**, 807-820. Effenberger, F. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555-1564. North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147-176.
[188] Choi, M. C. K.; Chan, S. S.; Matsumoto, K. *Tetrahedron Lett.* **1997**, *38*, 6669-6672.
[189] Callant, D.; Stanssens, D.; de Vries, J. G. *Tetrahedron: Asymmetry* **1993**, *4*, 185-188.
[190] Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; Larichev, V. S.; Lokshin, B. V.; Moscalenko, M. A.; North, M.; Orizu, C.; Peregudov, A. S.; Timofeeva, G. I. *Eur. J. Org. Chem.* **2000**, 2655-2661.



R	[Ti] (mol%)	Time (day)	Yield (%)	ee (%)
Me	0.1	1	38	70
Me	0.5	1	100	66
Et	0.5	4	64	32
i-Pr	0.5	no reaction		

Scheme-3.64: Enantioselective cyanation with titanium (salen) catalysis

With titanium, Shibasaki's group developed a tridentate ligand to form the (*R*)-cyanohydrin in the presence of TMSCN (Scheme-3.65).[191] This titanium complex can catalyze the cyanation of both aromatic and aliphatic ketones, which were obtained in good enantiomeric excesses.

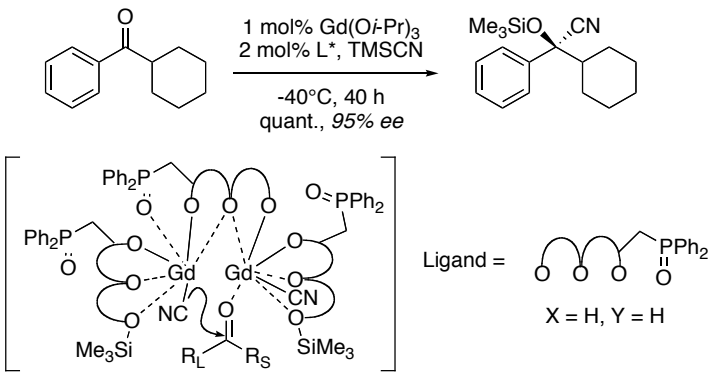


Scheme-3.65: Enantioselective cyanation by titanium catalysis

Also with the same ligand, (*S*)-cyanohydrin could be obtained in good enantiomeric excess if gadolinium or samarium salts were used (Scheme-3.66).[192] However, the preparation of

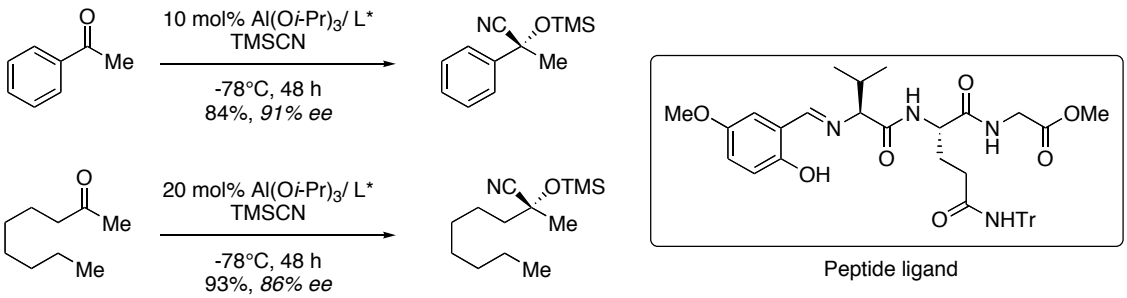
[191] Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412-7413. Fuji, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733-736.
[192] Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647-8651.

Shibasaki's catalyst complexes necessitates complex manipulations, and the conditions to generate these complexes have to be optimized for every substrate.



Scheme-3.66: Enantioselective cyanation by gadolinium catalysis

Another Schiff base as ligand in the enantioselective cyanation was reported by Hoveyda's and Snapper's groups. In the presence of a catalytic quantity of aluminum isopropoxide and the ligand, aromatic and aliphatic ketones were converted to siloxy cyanohydrins in excellent yields and good enantiomeric excesses (Scheme-3.67). The synthesis of the oligopeptide ligand required 6 steps and was effected in 75% overall yield.[193]

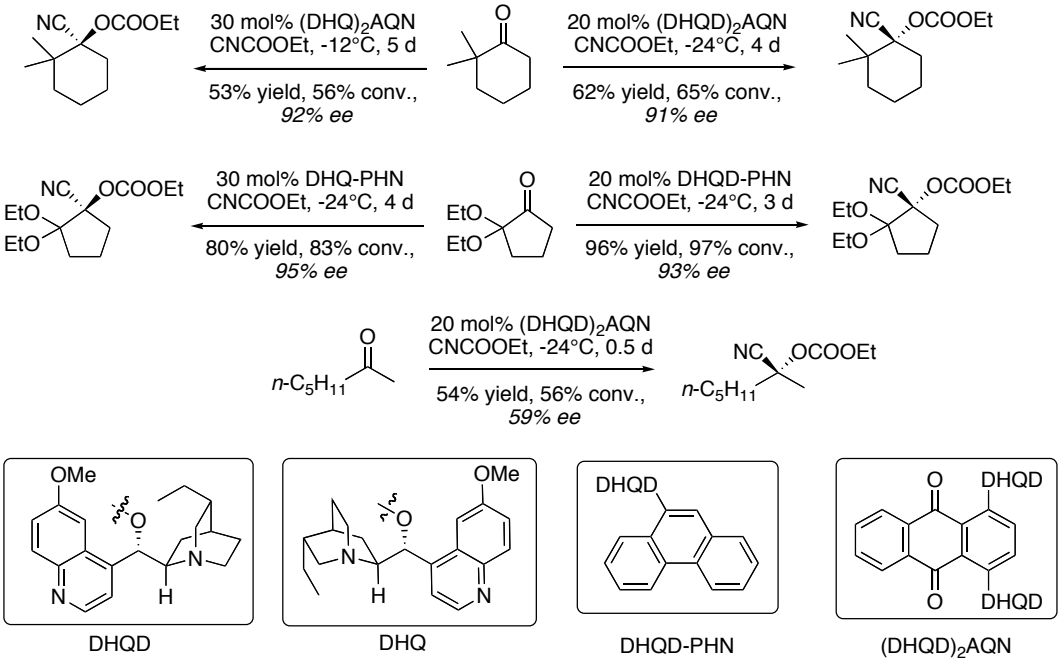


Scheme-3.67: Enantioselective cyanation by aluminum catalysis

A Lewis base was also used to catalyze the cyanation reaction. Deng's group performed an enantioselective cyanation with tertiary chiral amines, cinchona alkaloids, developed by Sharpless in his asymmetric aminohydroxylation.[194] Using DHQD or DHQ, (*R*)- or (*S*)-cyanohydrins were obtained in excellent enantiomeric excesses (Scheme-3.68).[195] Cyanation of α-dialkoxy ketones could also be performed with TMSCN in place of ethyl

[193] Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1009-1012.
[194] Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813-2817.
[195] Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195-6196.

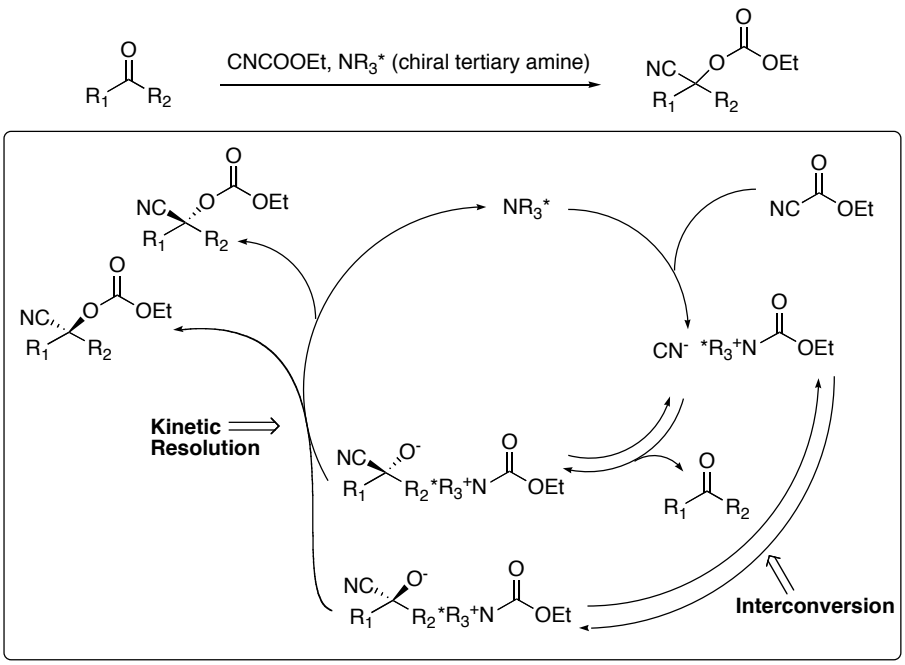
cyanoformate.[196] A surprising finding in this reaction is that the sterically more hindered ketones conducted to better results.



Scheme-3.68: Enantioselective cyanation by chiral amines catalysis

The authors proposed a mechanism involving a kinetic resolution to explain the enantioselectivity found for the different substrates (Scheme-3.69). When the rate of interconversion is not significantly faster than that of the kinetic resolution step, the enantiomeric excess decreases. As α-dialkoxy ketones are more easily attacked by nucleophiles because of the effect of the electron-withdrawing group, the rate of interconversion increased, and high enantiomeric excesses were obtained for the enantioselective cyanation of α-dialkoxy ketones. The authors also showed that addition of MeOH to the cyanation reaction medium of pinacolone resulted in the formation of the α-hydroxy cyanohydrin in a low enantionmeric excess (21% versus 83% ee for the carbonate cyanohydrin).[197]

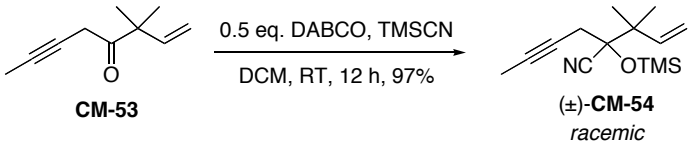
[196] Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900-9901.
[197] The author assumed that the protonation was much faster than the interconversion. For more details, see: Tian, S.-K.; Deng, L. *Tetrahedron* **2006**, *62*, 11320-11330.



Scheme-3.69: Proposed mechanism of the enantioselective cyanation by chiral amines

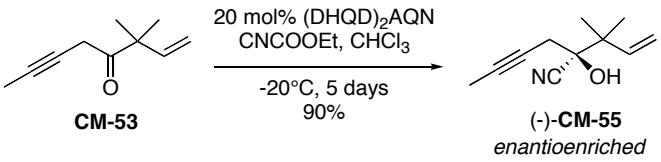
As described above, Deng's method seems efficient for the cyanation of highly sterically hindered ketones, and the catalyst used in the reaction such as $(DHQD)_2AQN$ could be directly purchased from chemical suppliers.

We first decided to test the racemic cyanation of **CM-53** with TMSCN in the presence of a Lewis base, a substoichiometric quantity of DABCO, according to Deng's first trial. Siloxy cyanohydrin **CM-54** was obtained in 97% yield after stirring overnight at room temperature (Scheme-3.70). Chiral-amine catalyzed enantioselective cyanation was then experimented.



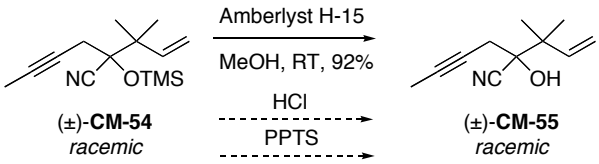
Scheme-3.70: Cyanation in the presence of DABCO

20 mol% $(DHQD)_2AQN$ was then engaged in the reaction of **CM-53** with ethyl cyanoformate. After 5 days at -20°C without stirring, surprisingly, cyanohydrin **CM-55** without the ester group was obtained with an optical rotation of -74.1 (*c* 1.7, CH_2Cl_2) (Scheme-3.71).



Scheme-3.71: Enantioselective cyanation in the presence of $(DHQD)_2AQN$

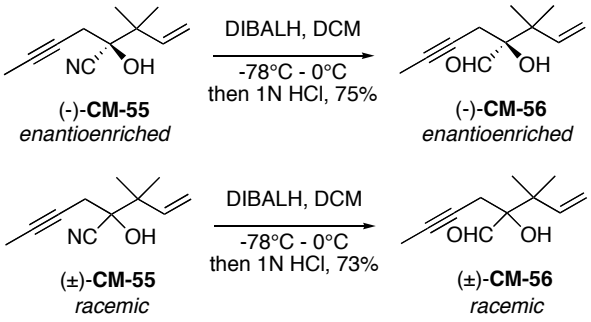
Removal of the TMS group of racemic nitrile **CM-54** for proposes of comparaison with (-)-**CM-55** with amberlyst H-15 furnished racemic α-hydroxy cyanohydrin **CM-55** (Scheme-3.72). No reaction occurred with a one molar aqueous HCl solution or pyridinium *p*-toluenesulfonate (PPTS), probably due to steric hindrance.



Scheme-3.72: Removal of the TMS group with amberlyst H-15

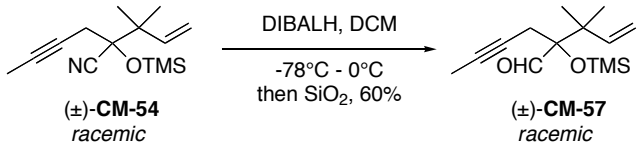
However, **CM-55** cannot be detected in high-performance liquid chromatography because of its UV-inactive character.

Reduction of both racemic and enantioenriched **CM-55** then produced aldehyde **CM-56** (Scheme-3.73), which is UV-active and was determinated in a 99% enantiomeric excess by HPLC analysis of racemic and (-)-**CM-56**. The decrease of enantioselectivity Deng obtained for the formation of α-hydroxy cyanohydrin was not observed in our case. Hydrolysis of the carbonate group must proceed during the treatment of the reaction, after the kinetic resolution step in the proposed reaction mechanism.



Scheme-3.73: Reduction of enantioenriched CM-55

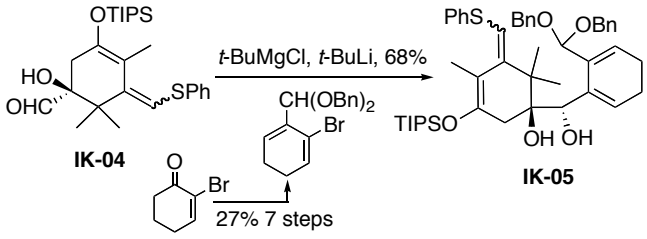
(±)-**CM-54** was also subjected to reduction with DIBALH to afford racemic α-siloxy aldehyde **CM-57** (Scheme-3.74), as another Shapiro reaction precursor. The yield was lower than in the case of the reduction of the α-hydroxy nitrile.



Scheme-3.74: Reduction of racemic CM-54

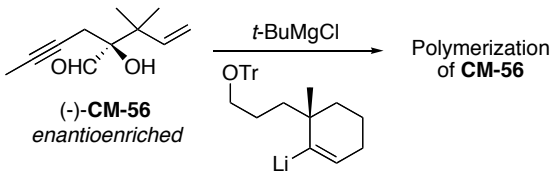
With (-)-**CM-56** in hand, we attempted to realize the Shapiro coupling reaction with the 7-deoxy C ring to examine the feasibility of this approach toward taxol, and to find a reliable way toward 7-deoxy taxol, which has similar bioactivity to taxol.

Kuwajima realized the nucleophilic addition of a vinyl bromide to the α-hydroxy aldehyde **IK-04** in a specific way: three equivalents of *t*-BuLi were added to two equivalents of the vinyl bromide at -94°C. After 15 minutes, one equivalent of **IK-04** pretreated with one equivalent of *t*-BuMgCl was then added to afford the adduct **IK-05** in 68% yield (Scheme-3.75).



Scheme-3.75: Nucleophilic addition by Kuwajima

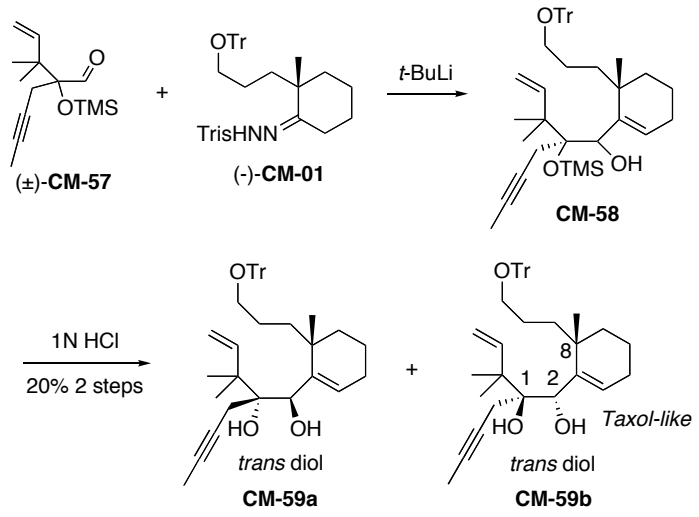
According to Kuwajima's method, one equivalent of *t*-BuMgCl was added to (-)-**CM-56** to deprotonate the hydroxy group to form the chelate with the aldehyde group, then the reaction mixture was added to the vinyllithium derived from hydrazone **CM-01**. However, only an unidentified product resulting from polymerization of (-)-**CM-56** was obtained (Scheme-3.76).



Scheme-3.76: Trial of Shapiro reaction with CM-56

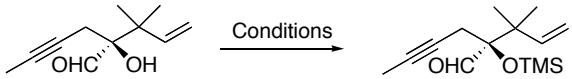
When the mixture of *t*-BuMgCl and (-)-**CM-56** was directly quenched with an aqueous $NaHCO_3$ solution, only polymerized (-)-**CM-56** was obtained. The same result was obtained with the mixture of one equivalent of *t*-BuLi or LiHMDS and (-)-**CM-56**.

However, Shapiro reaction between racemic α-siloxy aldehyde **CM-57** and **CM-01** led to 1:1 mixture of adducts **CM-58** in 20% yield (Scheme-3.77). Removal of the TMS group with a one molar aqueous HCl solution at room temperature gave **CM-59a** and **CM-59b**, which could be easily separated by flash chromatography.



Scheme-3.77: Trial of Shapiro reaction with racemic CM-57

So protection of the tertiary hydroxyl group of (-)-**CM-56** was carried out to bypass the problem of polymerization. After several trials, only a large excess of premixed triethylamine and TMSCl in the presence of LHMDS conducted to enantiopure α-siloxy aldehyde **CM-57**. This compound was obtained in quantitative yield (Scheme-3.78).



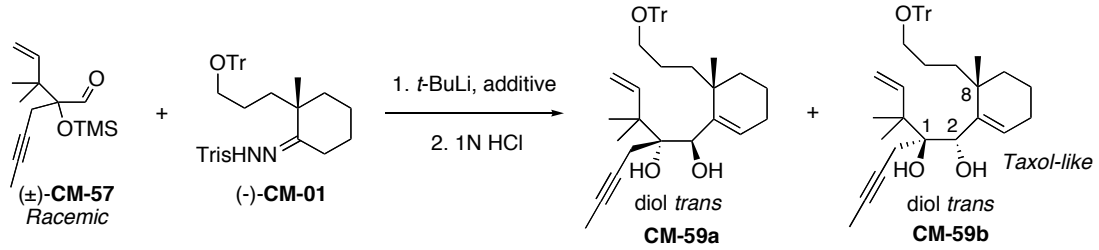
(-)-**CM-56** (-)-**CM-57**

Conditions	Result
TMSOTf, 2,6-lut., -78°C	SM
TMSOTf, *t*-BuLi, -78°C	Decomposition
TMSOTf, Et_3N, -78°C	SM
TMSCl, LiHMDS, -78°C	Decomposition
TMSCl, Et_3N, LiHMDS, -78°C	**CM-57** quant.

Scheme-3.78: Protection of the tertiary alcohol as the TMS ether

3. APPROACH TOWARD 7-DEOXY TAXOL

As the Shapiro reaction of aldehyde **CM-57** and hydrazone **CM-01** conducted to adduct **CM-58** in only 20% yield, we attempted to increase the nucleophilicity of the vinyl anion derived from **CM-01** by transmetallation of the lithium ion (Scheme-3.79).



Additive	Time after addition	Yield (2 steps)	Selectivity (*trans/cis*)
none	—	20%	>95:5
$MgBr_2$	30 min	—	—
$ZnCl_2$	30 min	trace	—
$CeCl_3$	20 min	60%	15:1
$CeCl_3$	30 min	85%	>95:5

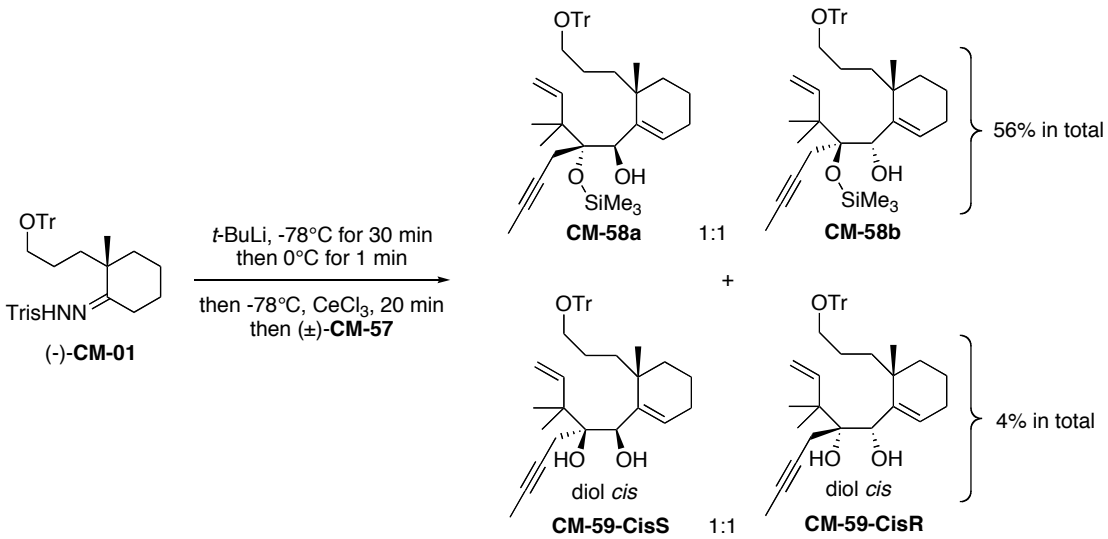
Scheme-3.79: Shapiro reaction with different metallated anions

As shown in Scheme-3.79, the best result was obtained with $CeCl_3$, which was titrated with *t*-BuLi,[198] and added to a mixture of 2 equivalents of *t*-BuLi and **CM-01**. After stirring for 30 minutes, racemic aldehyde (±)-**CM-57** was then added to provide the desired product **CM-58**. After stirring for 2 h at room temperature with a 1N aqueous HCl solution, **CM-58** was converted to **CM-59a** and **CM-59b**, which were easily separated by flash chromatography.

The stereochemistry of the diol group in **CM-59a** and **CM-59b** was not determined directly because no crystal could be isolated (as it was the case for **PW-33b** and the triol derived from **PW-33a** in the model studies, cf. p. 77) to perform the X-ray analysis (cf. below for stereochemical assignment).

Curiously, when $CeCl_3$ was stirred for only 20 min with the vinyl anion, siloxy adducts **CM-58** were obtained along with two diastereomeric diols **CM-59-CisR** and **CM-59-CisS** in a 15:1 ratio (Scheme-3.80).

[198] Paquette, L. A.; Huber, S. K.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 6874-9882.



Scheme-3.80: Shapiro reaction with $CeCl_3$ stirring for 20 min

In comparing the ^{1}H NMR spectra of **PW-33a**, **CM-59a** and **CM-59-CisR**, or **PW-33b**, **CM-59b** and **CM-59-CisS**, the similarities between **PW-33a** and **CM-59a**, **PW-33b** and **CM-59b** showed that **CM-59a** and **CM-59b** obtained from Shapiro reaction followed by hydrolysis of the siloxy group of **CM-58a** and **CM-58b** contained the *trans* diol moiety as in the model studies (Figure-3.1, 3.2).

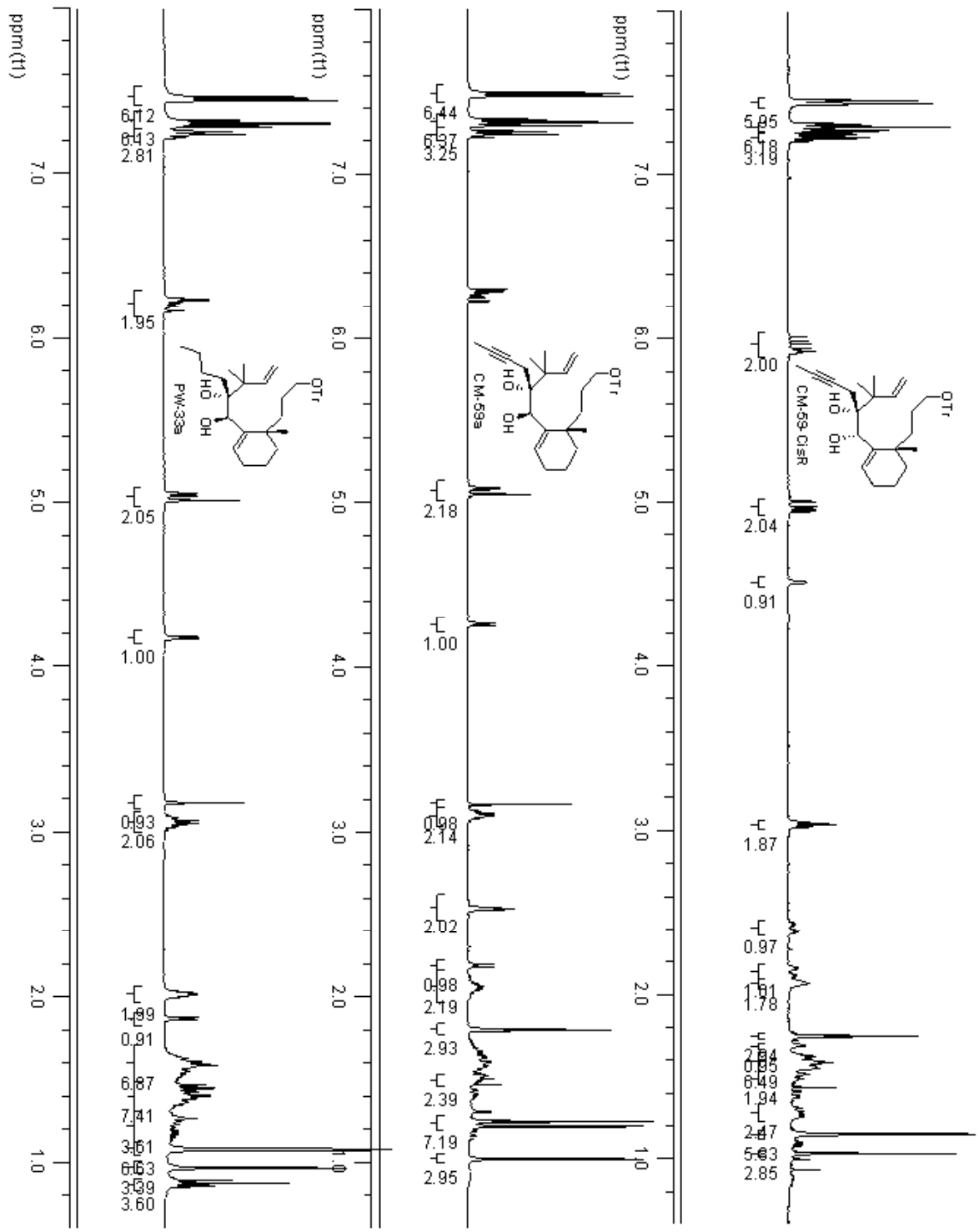


Figure-3.1: ^{1}H NMR spectra of PW-33a, CM-59a and CM-59-CisR

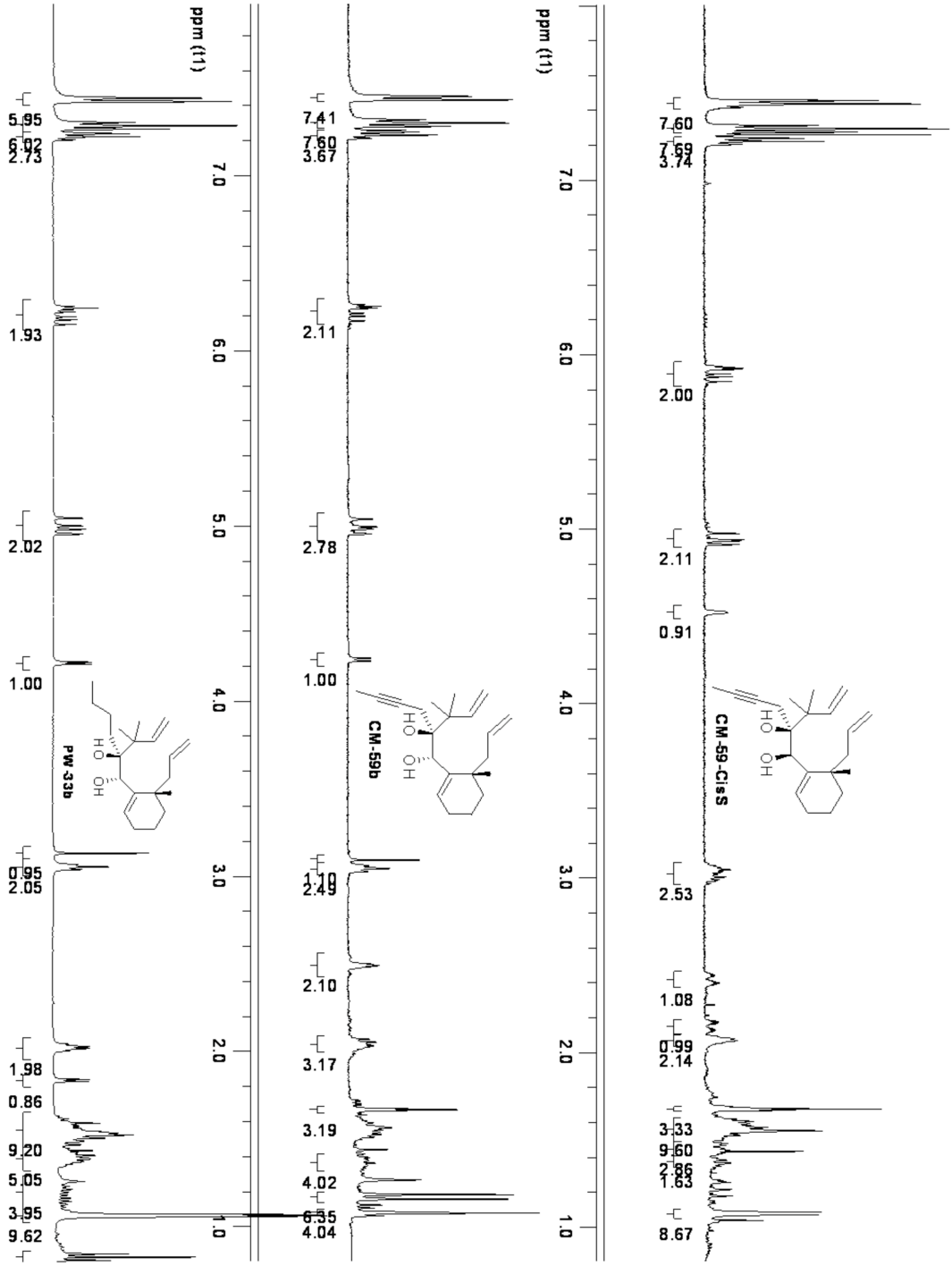
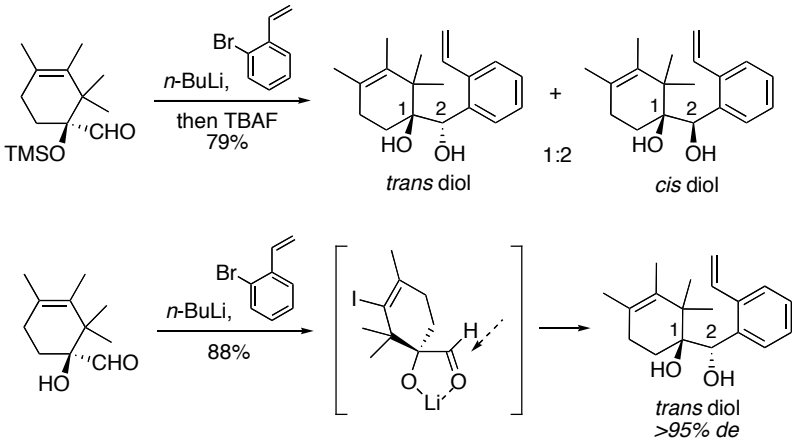


Figure-3.2: 1H NMR spectra of PW-33b, CM-59b and CM-59-CisS

The diastereoselectivity of the addition of nucleophiles to an aldehyde at the C2 position to form the C1-C2 diol system of taxol was first studied by Danishefsky.[199] When a cyclic α-siloxy aldehyde was added to lithiated styrene, the *trans*-dihydroxy adduct was obtained along with the *cis* adduct in a 1:2 ratio; however, α-hydroxy aldehyde underwent a

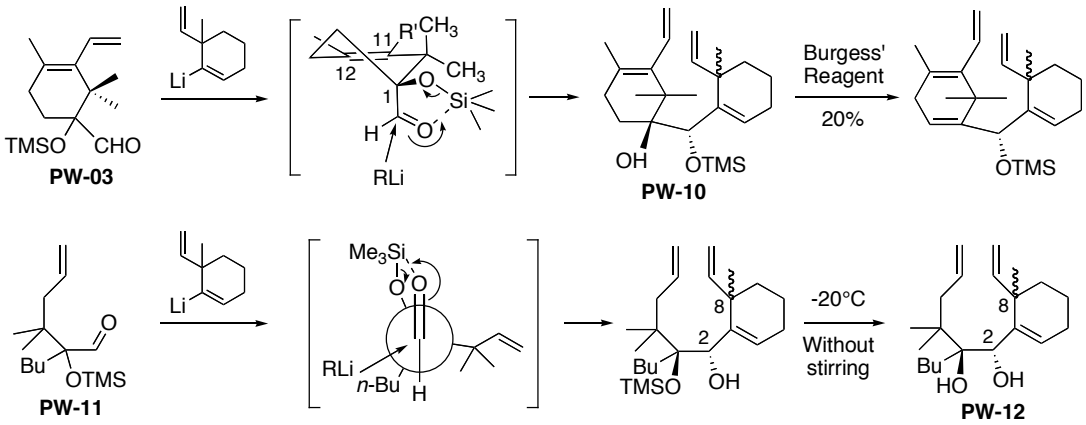
[199] Young, W. B.; Masters. J. J.; Danishefsky, S. *J. Am. Chem. Soc*. **1995**, *117*, 5228-5234.

diastereoselective addition to afford exclusively the *trans*-dihydroxy adduct because of the chelate between lithium and the two oxygens of the alkoxide and the aldehyde (Scheme-3.81).



Scheme-3.81: ***trans*** **diol obtained by chelation with lithium**

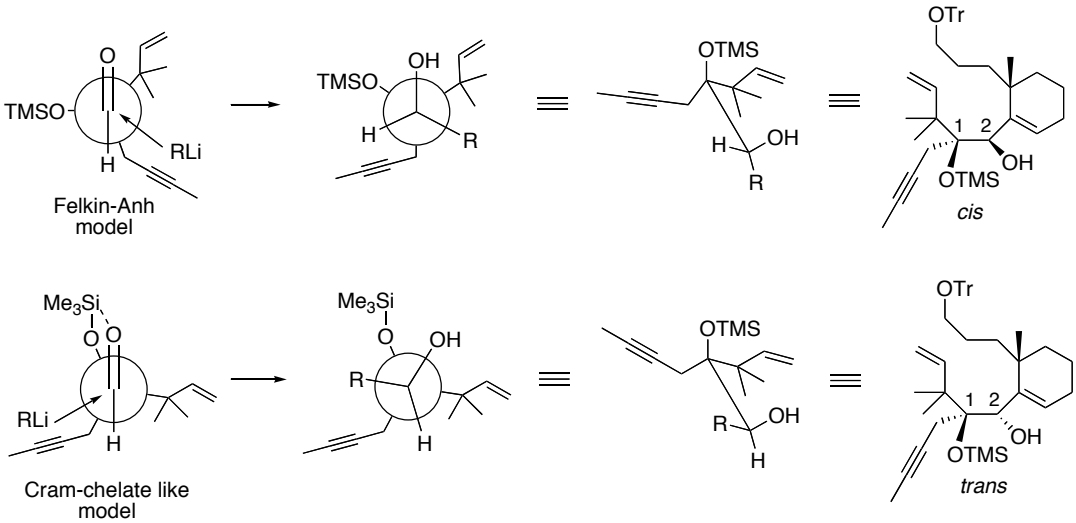
In the previous approaches in these laboratories, Dr. Damien Bourgeois observed the migration of the silyl group from the tertiary oxygen site to the secondary hydroxy group (cf. p. 71), and the *trans* product was equally obtained in a 95:5 ratio (Scheme-3.82). It was claimed that the steric hindrance of the *gem*-dimethyl group oriented the silicon atom toward the aldehyde, and the reaction proceeded *via* a chelate-like transition state with concomitant transfer of the silyl group.



Scheme-3.82: ***trans*** **diol obtained by chelation with silicon**

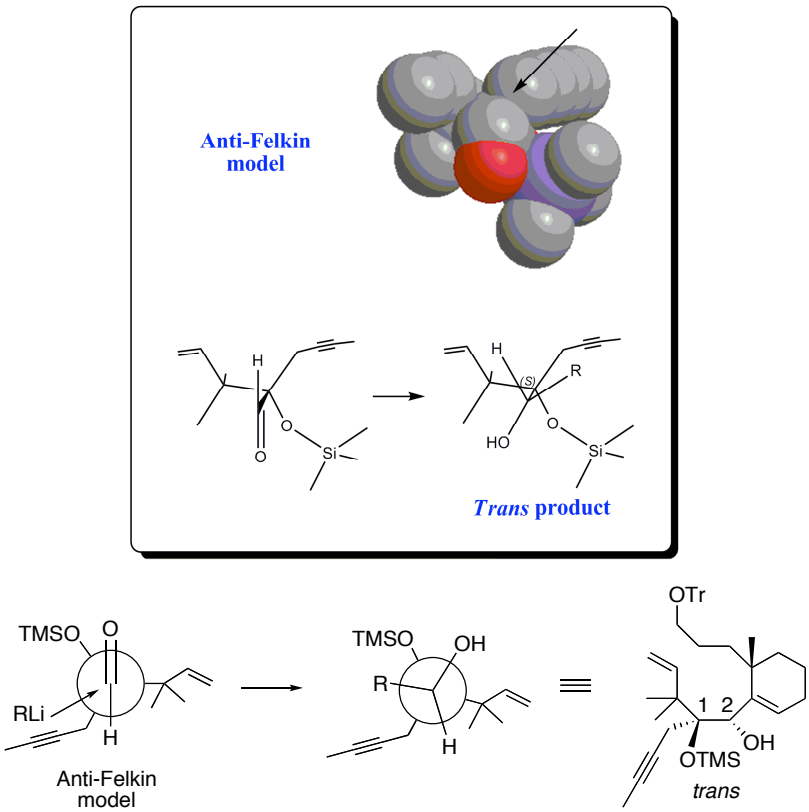
However, in the case of the model semi-convergent approach (cf. p. 87) and of our current experiments, transfer of the silyl group was not observed, and removal of the silyl group necessitated a strong acid.

As shown in Scheme-3.83, the transition state *via* a Felkin-Anh model conducts to the *cis* 1,2-dihydroxy product. The siloxy group is orthogonal to the carbonyl group, because the overlap between the σ* C-OSi and the π* C=O, which lowers the energy of the HOMO of the π system and thus renders it more reactive, is maximum in this conformation. The Cram-chelate like model leads to the *trans* 1,2-dihydroxy product because of the complexation between the siloxy group and the carbonyl moiety. In our experiments, the silyl group may temporarily complex to the oxygen of the aldehyde to furnish the *trans* products but the silyl group transfer did not occur.



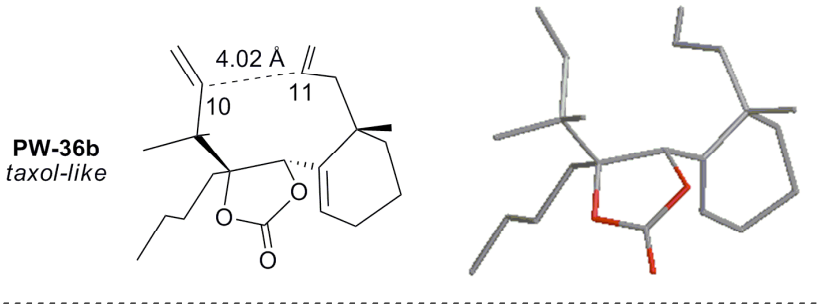
Scheme-3.83: Felkin-Anh model and Cram-chelate model

Another possibility to give the *trans* products is *via* an anti-Felkin transition state. If steric effects predominate over electronic effects, the most hindered chain which comports the *gem*-dimethyl and vinyl group should be considered the largest group and be positioned perpendicularly to the aldehyde, such a conformation corresponds to the more stable conformer accessible to the nucleophile, thus the attack of the nucleophiles would occur as shown in Scheme-3.84 to provide the *trans* product.



Scheme-3.84: Anti-Felkin model to give the *trans* product

With taxol-like *trans* diol **CM-59b** in hand, we attempted to synthesize the corresponding metathesis precursor. Transformation of taxol-unlike **CM-59a** to the corresponding metathesis precursor was also carried out, because when the molecular modeling of taxol-unlike trienic carbonates **PW-36a** was performed in the model studies, we found the two conformations of **PW-36a** at the lowest molecular energy level, of which one showed that the butyl group approaches the terminal double bond borne by the 7-deoxy C ring (Figure-3.3).



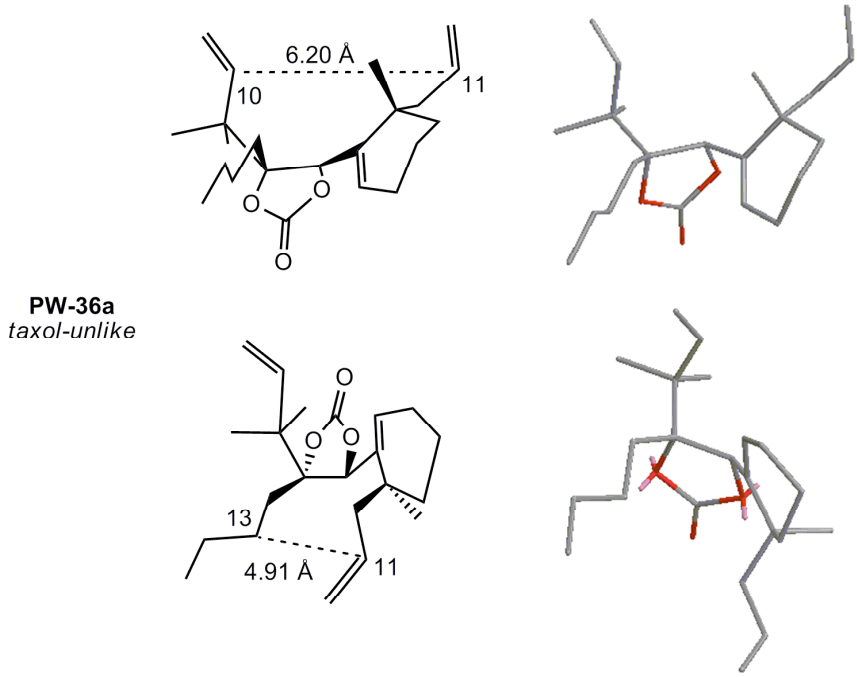
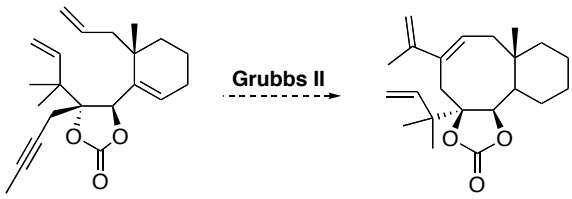


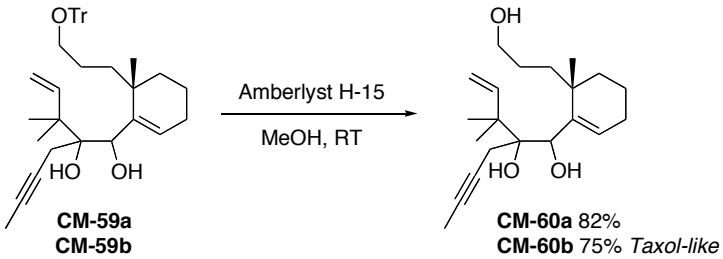
Figure-3.3: Stable conformations of PW-36b and PW-36a

So in our current case, an enyne metathesis may occur between the triple bond and the terminal double bond of the 7-deoxy C ring of the other *trans* diastereomer containing the wrong stereochemistry of the diol group for taxol, to afford a new cyclooctene (Scheme-3.85).



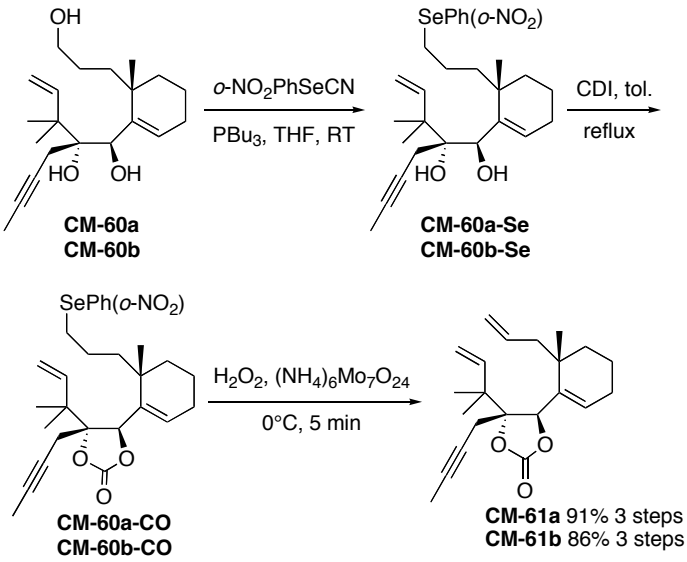
Scheme-3.85: Hypothesis for the formation of a new cyclooctene by enyne metathesis

To test this hypothesis, both diols **CM-59a** and **CM-59b** were then subjected separately to removal of the trityl group as before, and triols **CM-60a** and **CM-60b** were obtained in good yields (Scheme-3.86).



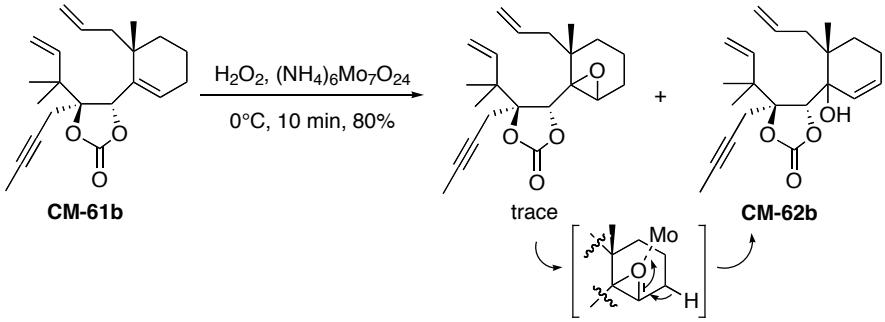
Scheme-3.86: Removal of the trityl group

Grieco's olefin dehydration and carbonate formation was applied to **CM-60a** and **CM-60b** to afford **CM-61a** and **CM-61b**, respectively (Scheme-3.87). This time, protection of the 1,2-diol moiety of selenyl ether **CM-60a-Se** to the corresponding carbonate **CM-60a-CO** was complete in only 24 hours, while the same reaction with **CM-60b-Se** required 3 days for completion.



Scheme-3.87: Formation of trienic carbonates CM-61a and CM-61b

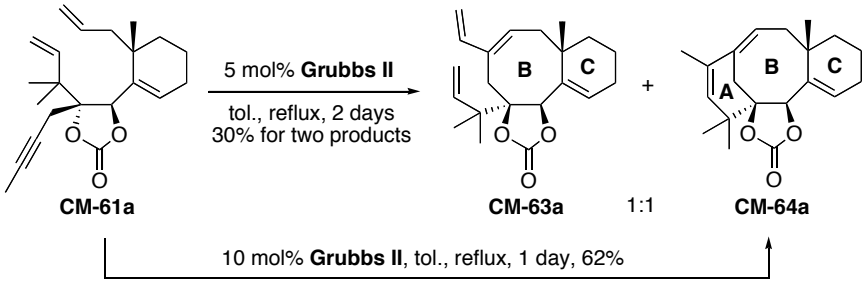
In the last step of Grieco's process, we observed that treatment of **CM-61b** with an excess of H_2O_2 led to epoxidation of the C ring olefin followed by ring-opening of the epoxide to furnish allylic alcohol **CM-62b**. The mechanism possibly proceeded as shown in Scheme-3.88. Curiously, in the presence of ammonium molybdate, which was used to avoid the epoxidation of the double bond during the treatment with H_2O_2, all the epoxide intermediate was converted to allylic alcohol **CM-62b**.



Scheme-3.88: Formation of allylic alcohol CM-62b

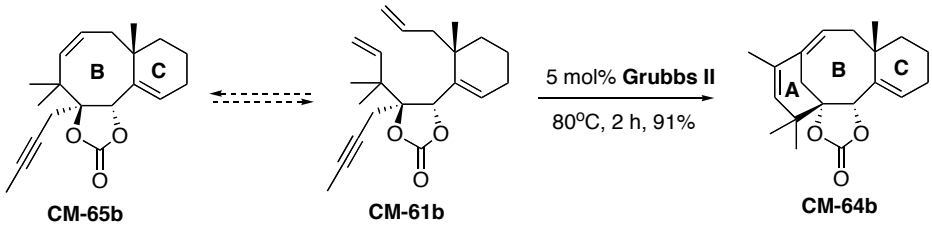
CM-61a was then subjected to ring-closing metathesis in the presence of 5 mol% Grubbs II catalyst. After stirring for 2 days in toluene at reflux, an inseparable mixture of two products

in a 1:1 ratio was obtained, which corresponds to BC bicycle **CM-63a** and ABC tricycle **CM-64a** (Scheme-3.89). We then set up the same reaction with 10 mol% Grubbs II catalyst, which conducted to a single isotaxane **CM-64a** after one day.



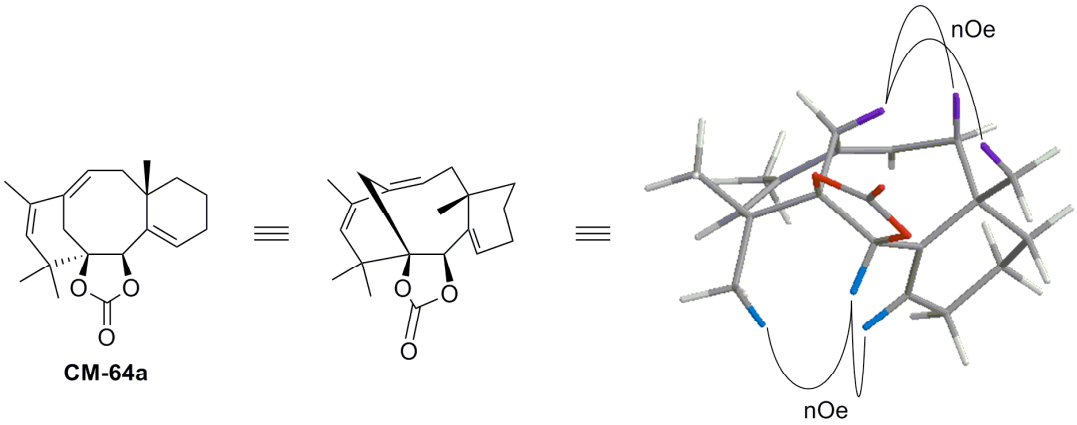
Scheme-3.89: Formation of isotaxane CM-64a from CM-61a

CM-61b was also subjected to the metathesis reaction (Scheme-3.90). Contrary to our expectation, in the presence of 5 mol% Grubbs II catalyst, ABC tricycle **CM-64b** was obtained by stirring at 80°C for only 2 hours in excellent yield. No trace of BC bicycle **CM-65b** resulting from ene-ene metathesis was observed.



Scheme-3.90: Formation of isotaxane CM-64b from CM-61b

NOESY experiments showed that **CM-64a** and **CM-64b** contained the *cis* 1,2-carbonate group (Figure-3.4), which proved that the Shapiro reaction furnished the *trans* product as expected.



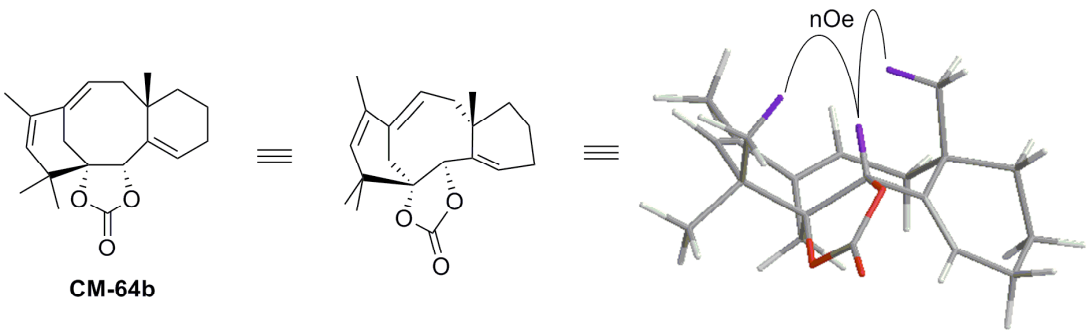


Figure-3.4: NOESY of CM-64a and CM-64b

Molecular modeling of **CM-61b** showed that the butynyl group can approach the terminal olefin borne by the 7-deoxy C ring to realize an enyne metathesis reaction (Figure-3.5). Although ene-ene metathesis normally occurs more easily than ene-yne metathesis (cf. p. 55), the fact that only **CM-64b** was obtained proved that the tricyclic compound was more stable than bicyclic **CM-65b**. Molecular modeling also showed that the ruthenated intermediate **CM-63b** obtained from ene-yne metathesis could approach the terminal olefin borne by the A fragment to conduct to the tricyclic product.

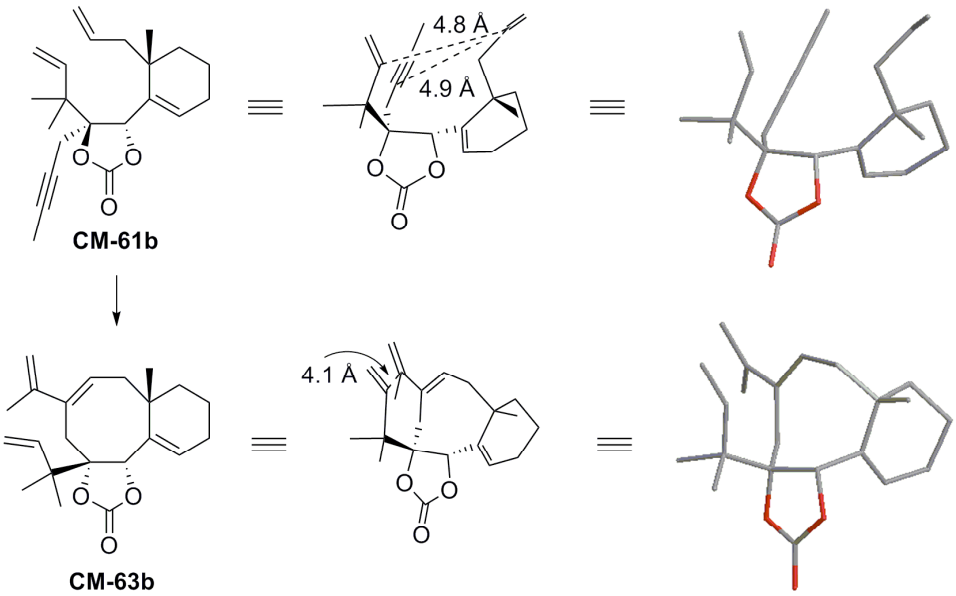


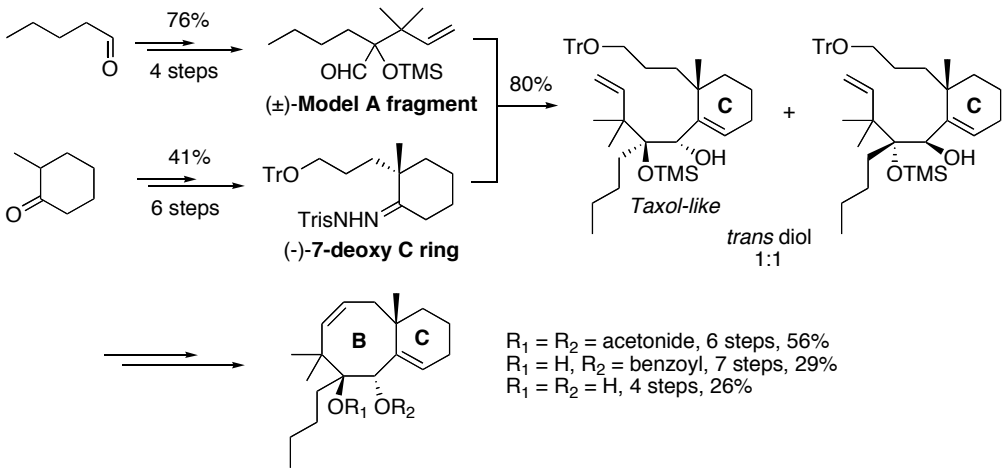
Figure-3.5: Energy minimization on CM-61b and its intermediate CM-63b

This is the first synthesis of this type of isotaxane skeleton with the *gem*-dimethyl group on the A ring. The synthesis described here offers a general method involving enyne metathesis to prepare these new analogues of taxol, which may exhibit some interesting bioactivities.

4. CONCLUSION AND PERSPECTIVES

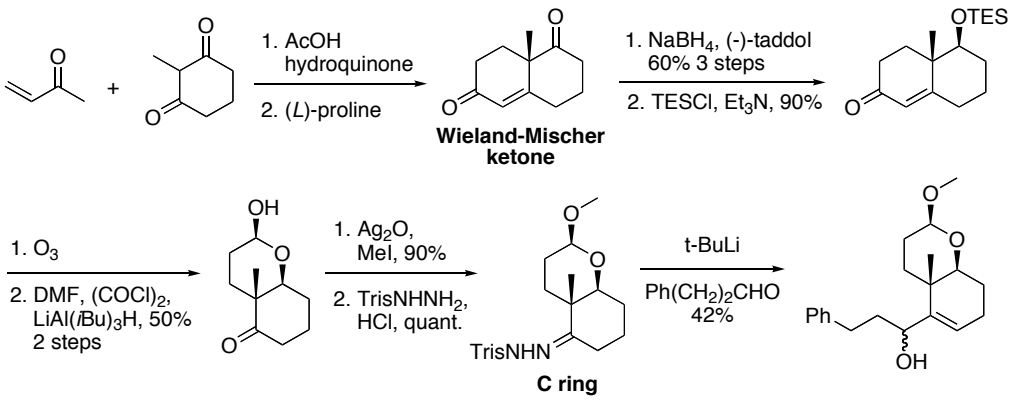
4.1 CONCLUSION

We have optimized the synthesis of the model A fragment and the 7-deoxy C ring of taxol and realized several syntheses of model 7-deoxy BC ring-systems in good yields (Scheme-3.91). These results showed the feasibility and viability of the elected synthetic route.



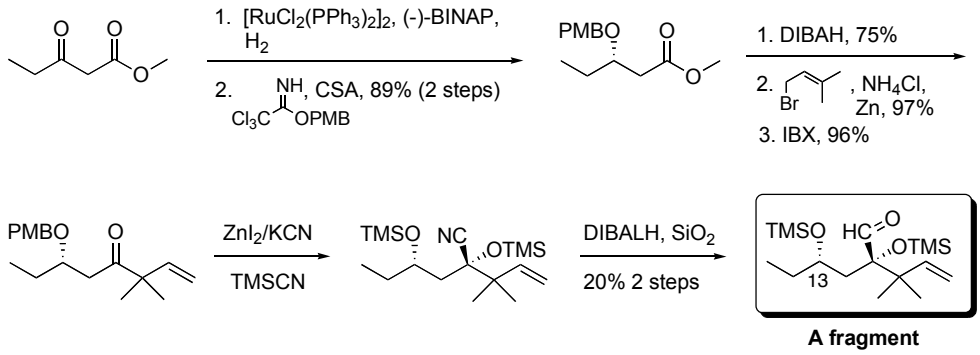
Scheme-3.91: Syntheses of BC ring-systems of taxol

We then synthesized the C ring as a bicyclic ketalic hydrazone in enantiopure form with all the functionalities required for taxol in good yield. A first trial of Shapiro coupling reaction with hydrocinnamaldehyde was also successful (Scheme-3.92).



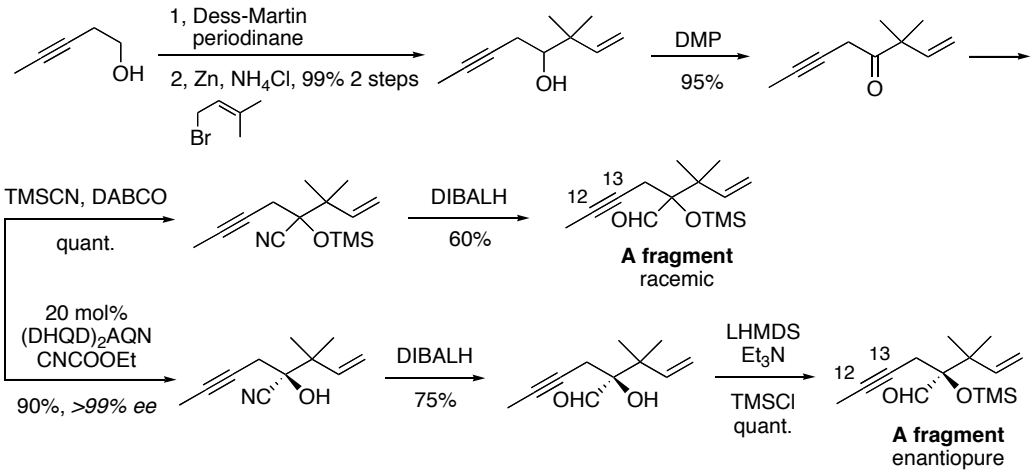
Scheme-3.92: Syntheses of BC ring-systems of taxol

The synthesis of the A fragment with a protected hydroxy group at C13 was performed, but the yield of the last two steps remains moderate and shows reproducibility problems (Scheme-3.93).



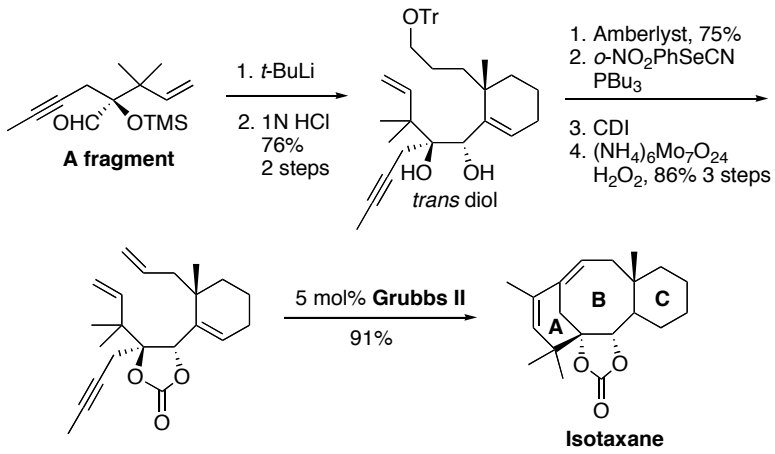
Scheme-3.93: Syntheses of A fragment of taxol with OH at C13

We then turned to an A fragment possessing a triple bond at C12-C13. These A fragment precursors were synthesized in both racemic and enantiopure forms, in good yields (Scheme-3.94).



Scheme-3.94: Synthesis of the A fragment possessing a triple bond at C12-C13

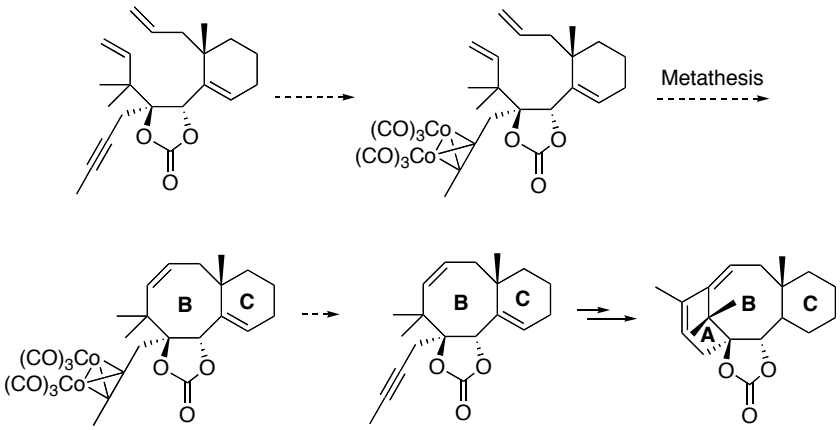
Shapiro reaction of this A fragment with 7-deoxy C ring was successful, giving the expected *trans* 1,2-diol with a good stereoselectivity. Ring-closing metathesis experiments led to an isotaxane skeleton instead of the desired BC ring of taxol (Scheme-3.95).



Scheme-3.95: Synthesis of the isotaxane framework

4.2 PERSPECTIVES

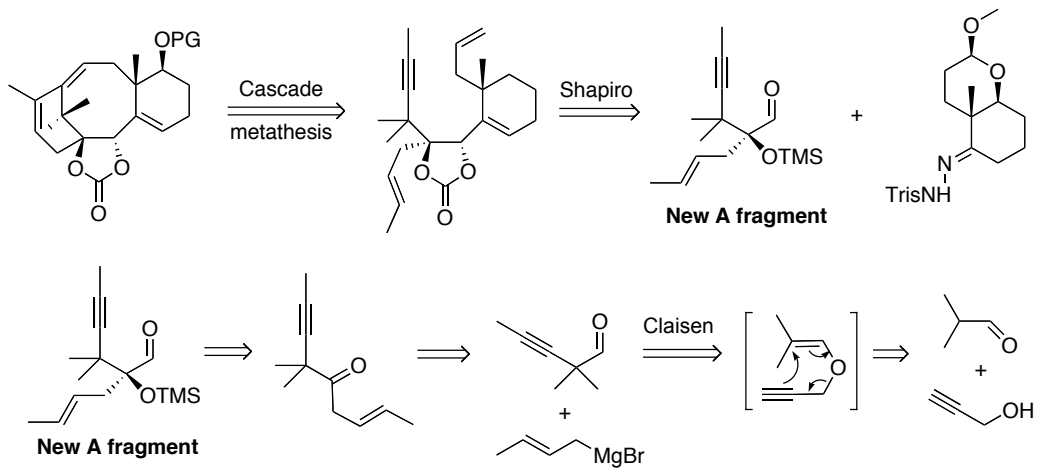
1. In order to avoid preferential enyne metathesis, BC bicycle of taxol could be obtained by protection of the triple bond as the hexacarbonyl dicobalt complex,[200] followed by ene-ene metathesis and decomplexation (Scheme-3.96). The ABC tricycle would then be synthesized through the operations envisaged before.



Scheme-3.96: Protection of the triple bond

2. We also want to exploit the ene-yne-ene metathesis, which was successful for the formation of the isotaxane skeleton, to realize the synthesis of the ABC tricycle of taxol and 7-deoxy taxol with the *gem*-dimethyl group at the correct position. For that purpose, we need to exchange the position of the alkyne and the alkene on the A fragment (Scheme-3.97). The synthesis of the new A fragment would be performed by Claisen rearrangement for the formation of the required pentynal and nucleophilic addition of a Grignard reagent to this aldehyde, followed by a similar synthetic route as described in this thesis.

[200] Young, D. G.; Burlison, J. A.; Peters, U. *J. Org. Chem*. **2003**, *68*, 3494-3497.



Scheme-3.97: New retrosynthesis with "inverted" double and triple bonds

EXPERIMENTAL SECTION

General

Melting points (M.p.) were determined on a REICHERT apparatus and are uncorrected.

Infrared spectra (IR) were obtained on a PERKIN-ELMER FT 1600 instrument and are reported in terms of frequency of absorption (ν, cm-1).

^{1}H NMR spectra were recorded on a BRUKER AM 400 (400 MHz) or on a BRUKER Avance 400 (400 MHz) instrument. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform (7.27 ppm). Data are reported as follows: δ, chemical shift; multiplicity (recorded as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; hex, hexuplet; hept, heptuplet; oct, octuplet and m, multiplet), integration and coupling constants (*J* in Hertz, Hz).

^{13}C NMR spectra were recorded on the same instruments at 100.6 MHz. The chemical shifts are expressed in parts per million (ppm), reported from the central peak of deuterochloroform (77.00 ppm). Assignments were obtained using J-mod or DEPT experiments, and when necessary, COSY, NOESY, HSQC and HMBC experiments.

Mass spectra (MS) were obtained on a HEWLETT-PACKARD HP 5989B spectrometer *via* either direct injection or GC/MS coupling with a HEWLETT-PACKARD HP 5890 chromatograph. Ionization was obtained either by electron impact (EI) or chemical ionization with ammonia (CI, NH_3) or methane (CI, CH_4). Mass spectrum data are reported as m/z.

High Resolution Mass Spectra (HRMS) were performed with a Jeol GC Mate II apparatus, by direct introduction of the compound, in magnet mode.

Flash chromatography was performed using silica gel 60, 230-400 mesh.

Thin Layer Chromatography (TLC) was performed on precoated plates of silica gel 60F.

Visualization was performed with a UV light then 7-10% ethanolic phosphomolybdic acid solution, anisaldehyde solution, ceric ammonium molybdate solution or vanillin/sulphuric acid as developing agents.

♦ Anisaldehyde solution was prepared in ethanol (338 mL) with anisaldehyde (9.2 mL), acetic acid (3.8 mL), concentrated sulphuric acid (12.5 mL) and stored at 4°C.

♦ Ceric ammonium molybdate was prepared in water (900 mL) with $Ce(SO_4).4H_2O$ (4.0 g), $MoNH_4$ (100 g) and concentrated sulphuric acid (100 mL).

♦ Vanillin / sulphuric acid was prepared as follows: vanillin (5.0 g) was dissolved in ethanol (100 mL) followed by careful addition of sulphuric acid (1.5 mL).

♦ $KMnO_4$ solution was prepared in water (300 mL) with $KMnO_4$ (3.0 g), K_2CO_3 (20 g) and acetic acid (0.25 mL).

♦ Phosphomolybdic acid solution was prepared using phosphomolybdic acid hydrate (50 g) in absolute ethanol (1 L).

Optical rotations were determined on a Perkin-Elmer 241-instrument operating at the D-line of Na and are reported as follows: $\mathbf{[\alpha]^{20}_{D}}$**:** (g/10 mL, solvent).

X-Ray structures were solved at the DCPH, Ecole Polytechnique, using a Nonius KappaCCD diffractometer, φ and ω scans, Moκα radiation (λ = 0.71069 Å), graphite monochromator, T = 150 K, structure solution with SIR97 and refined in SHELXL-97 by full matrix least-squares using anisotropic thermal displacement parameters for all-non hydrogen atoms.

Titration of organometallic bases:

To a solution of di-*tert*-butyl-*para*-cresol (375 mg, 1.70 mmol) and a catalytic pinch of

fluorene in THF (6.8 mL) at 0°C was added the solution to be titrated with a syringe (1 mL = 1.7 M). The addition was stopped after the colorless mixture turned to orange.

Solvent distillation:

♦ Tetrahydrofuran (THF) and diethyl ether were distilled from sodium-benzophenone.

♦ Dichloromethane (DCM), dimethyl sulfoxide (DMSO), dimethyl formamide (DMF) were distilled from calcium hydride, and amines (triethylamine, pyridine, di*iso*propylethylamine) were distilled from potassium hydroxide.

♦ Toluene was kept on pre-activated 4 Å molecular sieves.

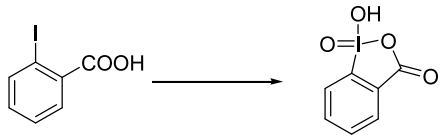
Usual procedures:

♦ All air and/or water sensitive reactions were carried out under an argon atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. All corresponding glassware was carefully dried under vacuum with a flameless heat gun.

♦ Bulb-to-bulb distillations were performed on a Büchi GKR 51 Kugelrohr apparatus.

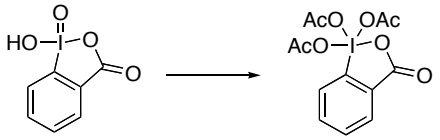
♦ Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated.

Preparation of IBX[201]



Potassium bromate (88.9 g, 0.53 mol, 1.32 equiv) was added over 30 min to a vigorously stirred mixture of 2-iodobenzoic acid (100 g, 0.40 mol) and sulphuric acid (0.73 M, 860 mL, 39 mL of concentrated sulfuric acid diluted to 1 L). During the addition the temperature was kept below 55°C. The mixture was then warmed to 65°C and stirred for 3-4 h. It was then cooled to 0°C, filtered and the white solid was washed with water (1 L) and twice with absolute ethanol (50 mL). It was then dried under vacuum overnight.

Preparation of DMP[202]



IBX (100 g) was added to Ac_2O (400 mL) and TsOH•H_2O (0.5 g). The mixture was stirred at ca. 80°C for 2 h and then cooled in an ice-water bath. The cold mixture was filtered followed by rinsing with anhydrous ether (5 x 50 mL). The resulting white crystalline solid (138 g, 91%) was quickly transferred to an argon flushed amber-glass bottle and stored in a freezer.

Preparation of $[Pd(PPh_3)_4]$[203]

$$2\ PdCl_2 + 8\ PPh_3 + 5\ NH_2NH_2.H_2O \rightarrow 2\ [Pd(PPh_3)_4] + 4\ NH_2NH_2.HCl + N_2 + 5\ H_2O$$

$PdCl_2$ (0.5 g, 2.8 mmol) and PPh_3 (3.7 g, 14.0 mmol, 5.0 equiv) were placed in a 50 mL threenecked flask under argon and dissolved in freshly distilled DMSO (33 mL). The mixture was then heated for 30 min at 150-160°C, and turned from yellow to dark red. The oil bath was then removed, and 3 min later $NH_2NH_2.H_2O$ (0.6 mL, 11.0 mmol, 4.0 equiv) was rapidly added. The solution became bright yellow, and was allowed to cool to room temperature. The yellow solid was filtered under argon, washed with absolute ethanol (50 mL) and distilled diethyl ether (50 mL). It was then dried under vacuum for 2 h.

Preparation of PMBBr[204]

A solution of PMB-OH (2.5 g) in diethyl ether (10 mL) was shaken with hydrobromic acid (48% sol in water, 5 mL) in a separatory funnel. The organic phase was then washed with aqueous sodium bromide (sat., 20 mL), dried over K_2CO_3, filtered and concentrated *in vacuo*.

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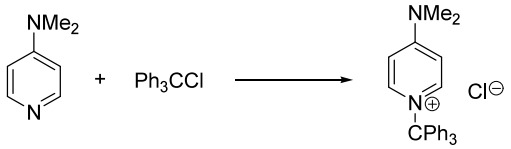
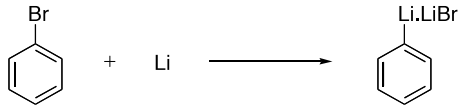
[201] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.
[202] Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899-2899.
[203] Coulson, D, *Inorg. Synth.* **1972**, *13*, 121-123.
[204] Ruder, S. M.; Ronald, R. C. *Tetrahedron Lett.* **1987**, *28*, 135-138.

Preparation of 4-dimethylamino-*N*-triphenylmethyl pyridinium chloride[205]



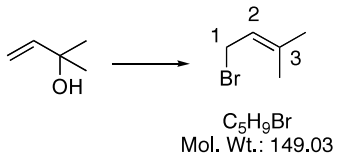
Freshly recrystallized trityl chloride (3.07 g, 11.0 mmol, 1.10 equiv) and DMAP (1.22 g, 10.0 mmol) in dichloromethane0 (20 mL) were stirred for 30 min at room temperature. Addition of diethyl ether (100 mL) precipitated the product which was filtered, washed with diethyl ether and dried under vacuum for 2 h.

Preparation of a *ca.* 1.0 M solution of phenyl lithium in diethyl ether[206]



To an over-dried schlenk tube, under a flow of argon, was added at room temperature bromobenzene (2.63 mL, 25.0 mmol) followed by dry diethyl ether (25 mL). To the stirred colorless solution thus obtained was added excess lithium wire freshly cut into small pieces. The high exothermic reaction led quickly to a dark brown solution that was stirred overnight at room temperature without flow of argon. The solution was used within 3 days after it was prepared.

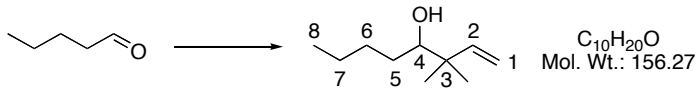
Preparation of 1-Bromo-3-methylbut-2-ene[207]



2-Methyl-3-buten-2-ol (20.0 g, 232 mmol) was cooled to 0°C in a round-bottom flask. Then hydrobromic acid (93 mL, 48% aq.) was slowly introduced into the reaction flask and the resulting mixture was stirred at 0°C for 30 min. The two layers were then separated and the aqueous layer was extracted with dichloromethane (3*50 mL). The combined organic fractions were washed with water (50 mL) then brine (50 mL), dried over magnesium sulfate, filtered and concentrated at reduced pressure. Distillation of the crude product afforded the desired 1-bromo-3-methylbut-2-ene **(1)** (29.0 g, 83%) as a colorless oil.

[205] Hernandez, O.; Chaudhary, S. K.; Cox, R. H.; Porter, J. *Tetrahedron Lett.* **1981**, *22*, 1491-1494.
[206] Stent, M. *SyntheticPage* **2002**, 195-195.
[207] De Mattos, M. C. S.; Sanseverino, A. M. *Synth. Commun.* **2003**, *33*, 2181-2186.

3,3-Dimethyloct-1-en-4-ol (PW-20)



PW-20

Freshly prepared 1-bromo-3-methylbut-2-ene (6.35 g, 42.61 mmol, 1.20 equiv) was added to a solution of valeraldehyde (3.78 mL, 35.5 mmol) in THF (20 mL). This was followed by the addition of aqueous ammonium chloride (sat., 100 mL). The resulting mixture was cooled to 0°C, and activated zinc dust (6.96 g, 106 mmol, 3.00 equiv) was added slowly. The mixture was then stirred vigorously at room temperature for 1 h (no inert atmosphere is necessary). After completion of the reaction, the mixture was filtered through a pad of celite, the two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired 3,3-dimethyloct-1-en-4-ol **PW-20** (5.43 g, 98%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.82 (dd, 1H, *J* = 17.5 Hz, 10.8 Hz, H-2), 5.11-5.00 (m, 2H, H-1), 3.30-3.26 (m, 1H, H-4), 1.57-1.51 (m, 3H, H-5 and OH), 1.42-1.23 (m, 4H, H-7 and H-6), 1.01 (s, 6H, Me), 0.90 (t, 3H, *J* = 7.3 Hz, H-8).

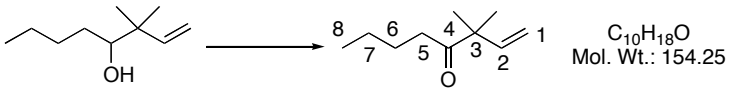
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 145.5 (C-4), 113.2 (C-1), 78.2 (C-2), 42.6 (C-3), 31.1 (C-5), 29.4 (C-6), 23.1 (Me), 22.7 (C-7), 21.9 (Me), 14.1 (C-8).

IR (film): 3388, 3082, 2958, 2872, 1637, 1467, 1415, 1379, 1362, 1314 cm^{-1}.

MS (CI, NH_3): *m/z* 174 ($M+NH_4^+$), 157 ($M+H^+$), 139.

***R*$_f$** 0.5 (E/PE 10/90).

3,3-Dimethyloct-1-en-4-one (PW-21)



PW-20 **PW-21**

A solution of IBX (22 g, 100 mmol, 1.2 equiv) in DMSO (150 mL) was added slowly at room temperature to a stirred solution of 3,3-dimethyloct-1-en-4-ol **PW-20** (13 g, 83 mmol) in THF (150 mL). The resulting mixture was stirred in the dark at room temperature overnight. When the reaction was complete, water (100 mL) was added then the organic phase was diluted with diethyl ether (100 mL). The biphasic system was stirred for at least 3 h. The white salts were then filtered through a pad of celite. The aqueous phase was extracted with diethyl ether (3*80 mL) then the combined organic fractions were washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95 then 10/90) afforded the desired 3,3-dimethyloct-1-en-4-one **PW-21** (12.6 g, quantitative yield) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.90 (dd, 1H, *J* = 17.5, 10.5 Hz, H-2), 5.15-5.11 (d, m, 2H, H-1), 2.44 (t, 2H, *J* = 7.2 Hz, H-5), 1.53-1.46 (m, 2H, H-6), 1.29-1.21 (m, 2H, *J* = 7.6 Hz, H-7), 1.21 (s, 6H, Me), 0.88 (t, 3H, *J* = 7.2 Hz, H-8).

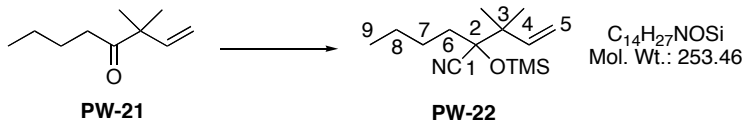
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm)213.2 (C-4), 142.7 (C-2), 114.1 (C-1), 65.8 (C-5), 50.8 (C-3), 37.1 (CH_2), 26.1 (CH_2), 23.5 (Me), 15.2 (Me), 13.9 (C-8).

IR (film): 3087, 2961, 2933, 2873, 1711, 1636, 1466, 1413, 1379, 1364, 1260 cm^{-1}.

MS (CI, NH_3): *m/z* 172 ($M+NH_4^+$), 155 ($M+H^+$), 105.

***R*$_f$** 0.67 (E/PE 2/98).

2-(1,1-Dimethylallyl)-2-trimethylsiloxyhexanenitrile (PW-22)



A catalytic amount of zinc iodide was added to a solution of 3,3-dimethyloct-1-en-4-one **PW-21** (3.33 g, 21.6 mmol) in freshly distilled dichloromethane (70 mL) and TMSCN (4.32 mL, 32.4 mmol, 1.50 equiv) was added dropwise. The resulting mixture was refluxed for 2 h. The solvents and excess TMSCN were then evaporated at reduced pressure (with a NaOCl/NaOH trap). Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 2/100 then 5/100) afforded the desired 2-(1,1-dimethylallyl)-2-trimethyl siloxyhexanenitrile **PW-22** (5.33 g, 97 %) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.96 (dd, 1H, *J* = 17.3 Hz, 11.0 Hz, H-4), 5.14-5.09 (m, 2H, H-5), 1.67-1.61 (m, 2H, H-6), 1.52-1.46 (m, 2H, H-7), 1.38-1.30 (m, 2H, H-8), 1.16 (s, 3H, Me), 1.13 (s, 3H, Me), 0.92 (t, 3H, *J* = 7.3 Hz, H-9), 0.25 (s, 9H, TMS).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 142.4 (C-4), 120.4 (C-1), 114.4 (C-5), 79.7 (C-2), 45.2 (C-3), 36.5 (C-6), 27.5 (C-7), 22.7 (C-8), 22.6, 22.4 (Me), 14.0 (C-9), 1.73 (TMS).

IR (film): 3087, 2961, 2875, 2361, 2342, 1639, 1468, 1417, 1381, 1365, 1254, 1127, 1112, 1066, 1005 cm^{-1}.

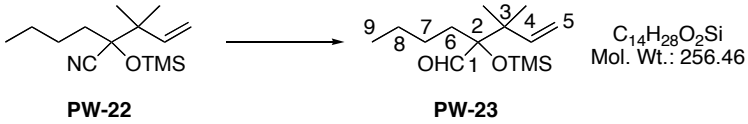
MS (CI, NH_3): *m/z* 271 ($M+NH_4^+$), 227, 172, 91.

***R*$_f$** 0.87 (E/PE 5/95).

Anal. Calcd for $C_{14}H_{27}NOSi$: C, 66.34; H, 10.74.

Found: C, 66.31; H, 10.87.

2-(1,1-Dimethylallyl)-2-trimethylsiloxyhexanal (PW-23)



Nitrile **PW-22** (2.28 g, 8.99 mmol) was dissolved in diethyl ether (40 mL) and cooled to -78°C. DIBAL-H (22.1 mL, 1 M in hexanes, 22.1 mmol, 2.50 equiv) was then added dropwise. The reaction mixture was warmed to 0°C and stirred for 2 h. The reaction was quenched by addition of ethyl acetate (4 mL), diluted with diethyl ether (150 mL) and allowed to warm to room temperature. Silica (40 g) was added to the solution, which was then placed at -20°C overnight. After completion of the reaction, the mixture was warmed to room temperature and the silica was filtered off. Solvents were evaporated at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 1/99) afforded the desired 2-(1,1-dimethylallyl)-2- trimethylsilyloxyhexanal **PW-23** (1.96 g, 85%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.58 (s, 1H, H-1), 6.01 (dd, 1H, *J* = 17.5 Hz, 10.9 Hz, H-4), 5.07-4.99 (m, 2H, H-5), 1.83-1.76 (m, 1H, H-6), 1.65-1.57 (m, 1H, H-6), 1.29-1.23 (m, 4H, H-7 and H-8), 1.04 (s, 3H, Me), 1.03 (s, 3H, Me), 0.87 (t, 3H, *J* = 7.2 Hz, H-9), 0.16 (s, 9H, TMS).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 204.8 (C-1), 144.0 (C-4), 113.2 (C-5), 87.7 (C-2), 44.3 (C-3), 31.9 (C-6), 26.3, 23.2 (C-7, C-8), 22.8 (Me), 22.4 (Me), 14.0 (C-9), 2.9 (TMS).

IR (film): 3086, 2960, 2874, 1735, 1638, 1468, 1416, 1380, 1364, 1254 cm^{-1}.

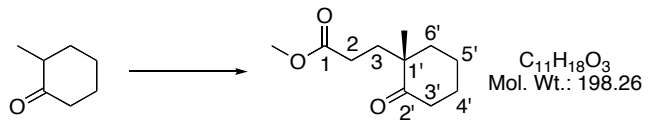
MS (CI, NH_3): *m/z* 274 ($M+NH_4^+$), 257 ($M+H^+$), 91.

***R*$_f$** 0.76 (E/PE 2/100).

Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.27; H, 11.00.

Found: C, 65.38; H, 10.99.

(1'*S*)-3-(1-Methyl-2-oxocyclohexyl)methyl propionate (PW-24)



PW-24

2-Methylcyclohexanone (18.4 mL, 152 mmol), (*R*)-(+)-α-methylbenzylamine (20.0 mL, 155 mmol, 1.02 equiv) and *p*-TsOH (61 mg, 0.2 mol%) were dissolved in dry toluene (100 mL) and heated to reflux with a Dean-Stark trap attached. After 3 h, the Dean-Stark trap was replaced by a distillation head and most of the toluene was distilled off. Then the residue was distilled (120-145 °C/1 mm Hg) to obtain a clear oil. Methyl acrylate (9.03 mL, 155 mmol, 1.02 equiv) was then added and the mixture was stirred at room temperature for 10 days. The reaction was quenched by addition of aqueous acetic acid (10%, 10 mL) and stirred for 2 h. The phases were then separated and the aqueous phase was extracted with diethyl ether (3*50 mL). The combined organic fractions were washed with brine (2*50 mL), dried over magnesium sulfate, filtered before removal of the solvent at reduced pressure. Purification of the crude product by distillation (85-95°C/1 mm Hg) afforded the desired (*S*)-methyl-3-(1-methyl-2-oxocyclohexyl) propionate **PW-24** (16.0 g, 54% yield over two steps) as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.66 (s, 3H, OMe), 2.42-2.36 (m, 2H, H-2), 2.15 (ddd, 1H, *J* = 16.7 Hz, 11.3 Hz, 5.1 Hz, H-3'), 2.04 (ddd, 1H, *J* = 16.7 Hz, 11.3 Hz, 5.1 Hz, H-3'), 1.75 (m, 8H, H-4', H-5', H-6' and H-3), 1.06 (s, 3H, Me).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 215.1 (C-2'), 174.0 (C-1), 51.5 (OMe), 47.8 (C-1'), 39.2 (C-2), 38.6 (C-3'), 32.4, 28.9, 27.3 (C-4', C-5' and C-6'), 22.3 (Me), 20.9 (C-3).

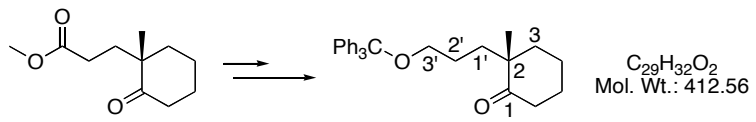
IR (film): 2936, 2865, 1741, 1702, 1438, 1378, 1305, 1172 cm^{-1}.

MS (CI, NH_3): *m/z* 216 ($M+NH_4^+$), 199 ($M+H^+$), 168.

$[\alpha]^{20}_D$: -31.9 (*c* 12.6, EtOH).

R_f 0.6 (E/PE 50/50).

(2*S*)-2-Methyl-2-(3-trityloxypropyl)cyclohexanone (PW-26)



PW-24 **PW-26**

A solution of keto ester **PW-24** (8.00 g, 40.4 mmol) in THF (85 mL) was added dropwise at 0°C to a suspension of $LiAlH_4$ (3.80 g, 101 mmol, 2.50 equiv) in THF (100 mL). The resulting mixture was then allowed to warm slowly to room temperature, and stirred for 7 h. After cooling to 0°C, water (4 mL), aqueous NaOH (6N, 4 mL) and water (12 mL) were added, then the mixture was stirred for 45 min. The aluminum salts were filtered at reduced pressure through a pad of celite then the organic phase was dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure to afford the desired (1*RS*,2*S*)-2-(3-hydroxypropyl)-2-methylcyclohexanol (6.60 g, 95%) as a white solid as a 1/1 mixture of diastereomers. The crude diol was used in the next step without any purification. 4-Dimethylamino-N-triphenylmethyl pyridinium chloride (11.3 g, 27.9 mmol, 1.20 equiv) was added at room temperature to a solution of diol (4.0 g, 23 mmol) in dichloromethane (60 mL). The resulting mixture was refluxed overnight. After cooling, diethyl ether (30 mL) was added, and the white salts were filtered off. The solution was dried over magnesium sulfate, filtered and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography (diethyl ether/petroleum ether: 30/70 then 40/60) to give the desired (1*RS*,2*S*)-2-methyl-2-(3-trityloxypropyl) cyclohexanol (8.63 g, 90% yield) as a white solid as a 1/1 mixture of diastereomers. A solution of IBX (1.92 g, 6.80 mmol, 1.20 equiv) in DMSO (15 mL) was added slowly at room temperature to a stirred solution of alcohol (2.35 g, 5.67 mmol) in THF (15 mL). The resulting mixture was stirred at room temperature overnight. When the reaction had gone to completion, water (40 mL) was added then the organic phase was diluted with diethyl ether (30 mL). The biphasic system was stirred for 3 h. The white salts were then filtered on a pad of celite. The phases were separated and the aqueous phase was extracted with diethyl ether (3*20 mL). The combined organic fractions were washed with water (20 mL) then brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 50/50) afforded the desired (2*S*)-2-methyl-2-(3-trityloxypropyl)cyclohexanone **PW-26** (2.01 g, 86% yield) as a white solid.

M.p. 117-118°C.

$[\alpha]^{20}_{D}$: -32.0 (*c* 2.76, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45-7.42 (m, 6H, H-Ar(*o*)), 7.33-7.28 (m, 6H, H-Ar(*m*)), 7.25-7.21 (m, 3H, H-Ar(*p*)), 3.07-3.03 (m, 2H, H-3'), 2.44-2.28 (m, 2H, H-6), 1.92-1.86 (m, 1H, CH_2), 1.80-1.73 (m, 4H, CH_2), 1.71-1.53 (m, 3H, CH_2), 1.46-1.31 (m, 2H, CH_2), 1.05 (s, 3H, Me).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 216.1 (C-1), 144.4 (C-q), 128.7, 127.7, 126.8 (C-*o*, C-*m*, C-*p*), 86.4 (C-Ar), 64.0 (C-3'), 48.4 (C-2), 39.3 (C-6), 38.8 (CH_2), 33.9 (CH_2), 27.5 (CH_2), 24.4 (CH_2), 22.6 (Me), 21.1 (CH_2).

IR (CaF_2, CCl_4, 1 mg/mL): 3087, 3061, 3034, 2935, 2867, 2360, 1708, 1491, 1449, 1378, 1314 cm^{-1}.

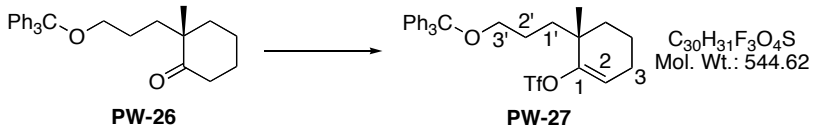
MS (CI, NH_3): *m/z* 243 (Ph_3C^+).

***R*$_f$** 0.6 (E/PE 20/80).

Anal. Calcd for $C_{29}H_{32}O_2$: C, 84.43; H, 7.82.

Found: C, 84.21; H, 8.08.

(6*S*)-6-Methyl-6-(3-trityloxypropyl)cyclohex-1-enyl trifluoromethanesulfonate (PW-27)



KHMDS (2.16 mL, 0.97 mmol, 2.00 equiv, 0.45 M in toluene) was added dropwise at -78°C to a solution of ketone **PW-26** (200 mg, 0.49 mmol) and HMPA (84 µL, 0.49 mmol, 1.0 equiv) in THF (5.0 mL). The reaction mixture was then warmed to -10°C for 30 min then cooled again to -78°C. *N*-Phenyltriflimide (294 mg, 0.824 mmol, 1.70 equiv) in THF (4.0 mL) was added *via* cannula to the cooled solution. The resulting mixture was allowed to warm to room temperature slowly and stirred for 2 h at this temperature. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (pure petroleum ether then diethyl ether/petroleum ether: 1/100 then 2/100) afforded the desired **PW-27** (265 mg, quantitative yield) as a pale yellow solid.

M.p. 56°C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.48-7.44 (m, 6H, H-Ar(*o*)), 7.34-7.29 (m, 6H, H-Ar(*m*)), 7.28-7.22 (m, 3H, H-Ar(*p*)), 5.74 (t, 1H, *J* = 4.0 Hz, H-2), 3.10-3.04 (m, 2H, H-3'), 2.21-2.15 (m, 2H, H-3), 1.79-1.71 (m, 1H, CH_2), 1.72-1.42 (m, 7H, CH_2), 1.15 (s, 3H, Me).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.3 (C-1), 144.3 (C-q), 128.6, 127.7, 126.9 (C-*o*, C-*m*, C-*p*), 118.3 (q, *J* = 314.0 Hz, CF_3), 117.0 (C-2), 86.4 (C-Ar), 63.9 (C-3'), 38.0 (C-6), 35.2 (CH_2), 35.0 (CH_2), 24.8 (C-3), 24.6 (Me), 18.4 (CH_2).

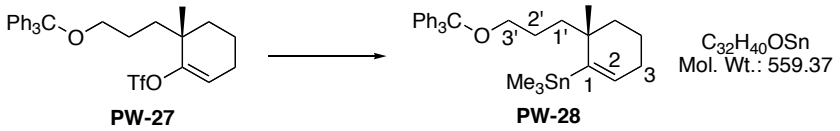
IR (CaF_2, CCl_4, 1 mg/mL): 3062, 2939, 2869, 1675, 1597, 1491, 1446, 1414, 1247, 1216 cm^{-1}.

MS (CI, NH_3): *m/z* 243 (Ph_3C^+).

[α]$^{20}_{D}$: +5.85 (*c* 2.49, CH_2Cl_2).

***R*$_f$** 0.9 (E/PE 20/80).

(6*S*)-Trimethyl[6-methyl-6-(3-trityloxypropyl)cyclohex-1-enyl]stannane (PW-28)



LiCl (308 mg, 7.27 mmol, 6.00 equiv), [$Pd(PPh_3)_4$] (151 mg, 0.12 mmol, 0.10 equiv) and $(Me_3Sn)_2$ (276 µL, 1.33 mmol, 1.10 equiv) were added to a solution of vinyl triflate **PW-27** in THF (20 mL). The resulting mixture was degassed three times then placed under an argon atmosphere and refluxed gently for 3 h. After cooling, petroleum ether (20 mL) was added, followed by aqueous sodium hydrogencarbonate (sat., 10 mL). The phases were separated then the aqueous layer was extracted three times with petroleum ether (3*20 mL). The combined organic fractions were washed with sodium hydrogencarbonate (sat., 15 mL) and brine (15 mL), dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. The product was taken up in petroleum ether and filtered through silica gel (pretreated with 20% triethylamine in petroleum ether, elution with 1% triethylamine in petroleum ether) to give the desired (6*S*)-trimethyl[6-methyl-6-(3-trityloxypropyl)cyclohex-1-enyl]stannane **PW-28** (660 mg, 97% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45-7.50 (m, 6H, H-Ar(*o*)), 7.45-7.37 (m, 6H, H-Ar(*m*)), 7.35-7.26 (m, 3H, H-Ar(*p*)), 5.78 (t, 1H, J = 3.6 Hz, $J_{1H\text{-}117Sn} = J_{1H\text{-}119Sn}$ = 40.0 Hz, H-2), 3.15-3.03 (m, 2H, H-3'), 2.10-2.02 (m, 2H, H-3), 1.72-1.57 (m, 4H, CH_2), 1.60-1.52 (m, 1H, CH_2), 1.48-1.33 (m, 3H, CH_2), 1.02 (s, 3H, Me), 0.16 (s, 9H, Me_3Sn).

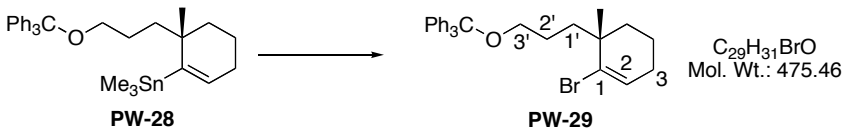
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 152.0 (C-1), 144.4 (C-*q*), 136.2 (C-2), 128.7, 127.6, 126.7 (C-*o*, C-*m*, C-*p*), 86.2 (C-Ar), 64.2 (C-3'), 39.7 (CH_2), 38.9 (C-6), 34.5 (CH_2), 28.5 (Me), 27.5 (C-3), 24.8 (CH_2), 19.0 (CH_2), -7.40 (Me_3Sn).

IR (film): 3059, 2925, 2359, 2343, 1957, 1598, 1490, 1448, 1374, 1222, 1073 cm^{-1}.

MS (CI, NH_3): *m/z* 243 (Ph_3C^+).

***R*$_f$** 0.8 (E/PE 5/100).

(6*S*)-[6-Methyl-6-(3-trityloxypropyl)cyclohex-1-enyl]bromide (PW-29)



vinyl stannane **PW-28** (8.70 g, 15.3 mmol) was dissolved in dichloromethane (80 mL) and the resulting mixture was cooled to –78°C. A freshly prepared solution of bromine (16.8 mL, 16.8 mmol, 1.10 equiv, 1 M in dichloromethane) was added dropwise. The solution turned

slightly yellow and was stirred for 15 min. The mixture was then poured into a cold aqueous solution of aqueous sodium thiosulfate (sat., 50 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (50 mL). The combined organic fractions were washed successively with sodium thiosulfate (sat., 30 mL), brine (50 mL), dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 1/100) afforded the desired (6*S*)-[6-methyl-6-(3-trityloxypropyl) cyclohex-1-enyl] bromide **PW-29** (4.87 g, 82% yield) as a white solid.

M.p. 84-86°C.

$[\alpha]^{20}_{D}$: -7.87 (*c* 2.71, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.48-7.44 (m, 6H, H-Ar(*o*)), 7.33-7.28 (m, 6H, H-Ar(*m*)), 7.28-7.21 (m, 3H, H-Ar(*p*)), 6.07 (t, 1H, *J* = 4.1 Hz, H-2), 3.11-3.00 (m, 2H, H-3'), 2.05-2.01 (m, 2H, H-3), 1.85-1.77 (m, 1H, CH_2), 1.68-1.61 (m, 3H, CH_2), 1.61-1.50 (m, 4H, H-1' and H-2'), 1.10 (s, 3H, Me).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 144.5 (C-q), 134.7 (C-1), 130.4 (C-2), 128.7, 127.9, 126.8 (C-*o*, C-*m*, C-*p*), 86.4 (C-Ar), 64.2 (C-3'), 40.6 (C-6), 37.2 (CH_2), 35.0 (CH_2), 28.1 (C-3), 27.0 (Me), 24.8 (CH_2), 18.9 (CH_2).

IR (CaF_2, CCl_4, 1 mg/mL): 2937, 2289, 1549, 1252, 1217 cm^{-1}.

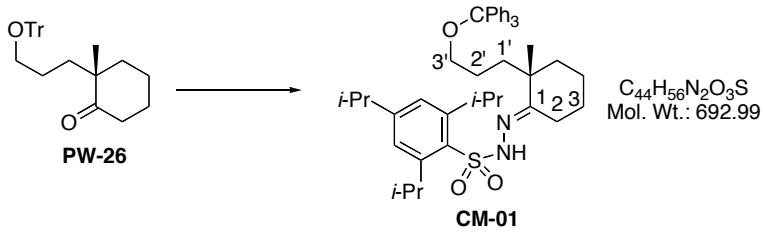
MS (CI, NH_3): *m/z* 243 (Ph_3C^+).

***R*$_f$** 0.8 (E/PE 2/98).

Anal. Calcd for $C_{29}H_{31}OBr$: C, 73.26; H, 6.57.

Found: C, 73.11; H, 6.55.

N-[(*S*)-2-Methyl-2-(3-trityloxypropyl)cyclohex-1-ylidene]-*N'*-(2,4,6-triisopropyl benzenesulfono)hydrazone (CM-01)



Two drops of concentrated hydrochloric acid were added to a solution of ketone **PW-26** (1.00 g, 2.42 mmol) and triisopropylbenzenesulfonohydrazine (723 mg, 2.42 mmol, 1.00 equiv) in THF (5.0 mL). The resulting solution was stirred at room temperature for 1 h, and then the reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 mL). The phases were separated then the aqueous phase was extracted with diethyl ether (3*10 mL). The combined organic fractions were washed with brine (15 mL) and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80) yielded the desired pure hydrazone **CM-01** as white crystals (1.62 g, 96% yield).

M.p. 75-77°C

$[\alpha]^{20}_{D}$: -59.6 (c 1.67, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.42-7.39 (m, 7H, NH and H-Ar), 7.31-7.22 (m, 9H, H-Ar), 7.11 (s, 2H, H-Ar'), 4.19 (septet, 2H, *J* = 6.7 Hz, Ar-CH), 2.88 (dt, 2H, *J* = 6.2, 1.2 Hz, H-3'), 2.81 (septet, 1H, *J* = 6.9 Hz, Ar-CH), 2.38 (dt, 1H, J = 14.6 Hz, 4.6 Hz, H-2), 1.93 (ddd, 1H, J = 14.6 Hz, 11.2 Hz, 5.1 Hz, H-2), 1.78-1.69 (m, 1H, CH_2), 1.68-1.49 (m, 4H, CH_2), 1.48-1.36 (m, 2H, CH_2), 1.24 (dd, 12H, *J* = 10.4 Hz, 6.7 Hz, Me(Ar')), 1.17 (dd, 6H, *J* = 6.9 Hz, 2.8 Hz, Me(Ar')), 0.90 (s, 3H, Me).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 163.0 (C-1), 152.9, 151.0 (C-Ar), 146.8 (C-*q*), 144.3 (C-1'), 131.3, 127.9, 127.6, 127.2, 126.8 (Ar, Ar'), 123.3 (C-2'), 86.2 (Ar-CH_2), 63.9 (C-3), 41.7 (C-2), 39.3 ($(CH_3)_2$-CH-Ar'), 34.3, 34.0 ($(CH_3)_2$-CH-Ar'), 29.8, 25.8, 24.8, 24.2, 24.0, 23.5, 23.5, 22.8 (C-4, C-5, C-6), 20.8 (Me(C-2')), 14.0 (Me(C-2)).

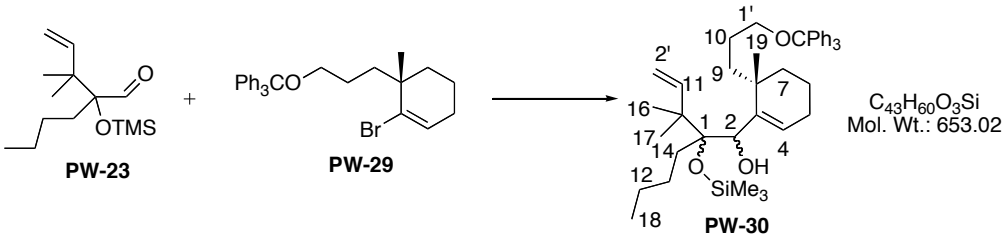
IR (film): 3243, 2957, 2869, 1600, 1563, 1496, 1454, 1384, 1323, 1152, 1108, 911, 733 cm^{-1}.

MS (CI, NH_3): *m/z* 539 ($M+H^+$), 449, 300, 276, 259, 151, 108, 91.

***R*$_f$** 0.2 (E/PE 20/80).

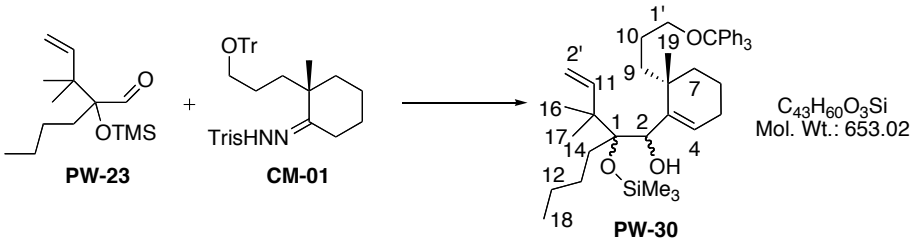
2-(1,1-Dimethylallyl)-1-[6-methyl-6-(3-trityloxypropyl)cyclohex-1-enyl]-2-trimethyl siloxyhexan-1-ol (PW-30)

Method A :



A solution of vinyl bromide **PW-29** (600 mg, 1.26 mmol) in THF (2.0 mL) was added dropwise to *tert*-butyllithium (2.60 mL, 2.78 mmol, 2.20 equiv, titrated 1.05 M) in THF (5 mL) at -78°C. The solution turned red and was stirred at -78°C for 30 min. When the halogen-metal exchange was complete (checked by TLC, diethyl ether/petroleum ether 1/100), a cooled solution of aldehyde **PW-23** (421mg, 1.64 mmol, 1.30 equiv) in THF (2.0 mL) was added dropwise *via* cannula. The resulting mixture became light yellow and was allowed to stir at -78°C for 30 min then allowed to warm to room temperature over 1 h. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 mL). The phases were separated then the aqueous phase was extracted with diethyl ether (3*10 mL). The combined organic fractions were washed with brine (15 mL) and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (100% petroleum ether then diethyl ether/petroleum ether: 1/100) yielded two fractions: a mixture of the alkene by-product and excess of aldehyde, and 587 mg of the desired compound (71% yield) as a pale yellow oil as a 1/1 mixture of diasteromers **PW-30**.

Method B:

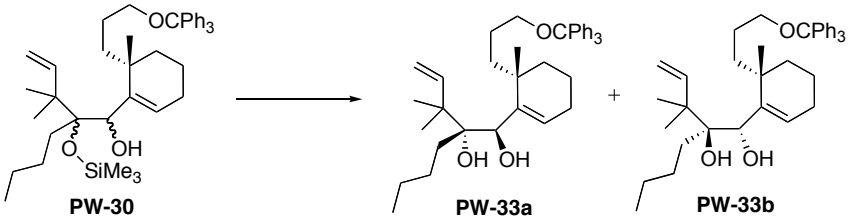


tert-Butyllithium (2.48 mL, 4.51 mmol, 2.20 equiv, titrated 1.82 M) was added dropwise to a solution of hydrazone **CM-01** (1.42 g, 2.05 mmol, 1.00 equiv) in THF (10 mL) at -78°C. The solution turned red and was stirred at -78°C for 30 min until the color turned dark red, then the temperature was allowed to warm to 0°C. When nitrogen evolution was finished and the color had turned to red, the solution was cooled again to -78°C. A cooled solution of aldehyde **PW-23** (526 mg, 2.05 mmol) in THF (5.0 mL) was added dropwise *via* cannula. The resulting mixture became light yellow and was stirred at -78 °C for 30 min. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 10 mL). The phases were separated then the aqueous phase was extracted with diethyl ether (3*15 mL). The combined organic fractions were washed with brine (20 mL) and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (100% petroleum ether then diethyl ether/petroleum ether: 1/100) yielded two fractions: a mixture of the alkene by-product and excess of aldehyde, and 1.07 g of the desired compound (80% yield) as a pale yellow oil as a 1/1 mixture of diasteromers **PW-30**.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.52-7.46 (m, 6H, H-Ar(*o*)), 7.37-7.30 (m, 6H, H-Ar(*m*)), 7.30-7.26 (m, 3H, H-Ar(*p*)), 6.14 (dd, 0.5H, *J* = 17.2, 10.8 Hz, H-11), 6.08 (dd, 0.5H, *J* = 17.6, 10.8 Hz, H-11), 5.93 (t, 0.5H, *J* = 4.0 Hz, H-4), 5.87 (t, 0.5H, *J* = 4.0 Hz, H-4), 5.04-4.86 (m, 2H, H-2'), 4.37 (d, 1H, *J* = 7.2 Hz, H-2), 3.95 (d, 1H, *J* = 7.0 Hz, OH), 3.17-3.05 (m, 2H, H-1'), 2.10-2.03 (m, 2H, H-5), 1.65-1.49 (m, 10H, CH_2), 1.49-1.36 (m, 4H, CH_2), 1.15-1.08 (m, 9H, Me(C-15) and Me(C-8)), 0.90 (t, 1.5H, *J* = 7.2 Hz, Me(C-12)), 0.84 (t, 1.5H, *J* = 7.2 Hz, Me(C-12)), 0.16 (s, 4.5H, TMS), 0.08 (s, 4.5H, TMS).

***R*$_f$** 0.4 (E/PE 2/100).

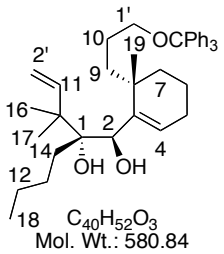
(1*R*,2*R*)-2-(1,1-Dimethylallyl)-1-[(6*S*)-6-methyl-6-(3-trityloxypropyl)cyclohex-1-enyl]hexane-1,2-diol (PW-33a) and **(1*S*,2*S*)-2-(1,1-Dimethylallyl)-1-[(6*S*)-6-methyl-6-(3-trityloxypropyl)cyclohex-1-enyl]hexane-1,2-diol (PW-33b)**



Aqueous HCl 1N (0.88 mL, 0.88 mmol, 1.50 equiv) was added at 0°C to a solution of addition product **PW-30** (385 mg, 0.59 mmol) in THF (5.0 mL). The resulting mixture was allowed to warm to room temperature over 1 h and stirred overnight. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 3 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (5 mL), dried over magnesium sulfate, filtered and

the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) allowed separation of the two diastereomers to afford the desired diols: diasteromer **PW-33a** (181 mg, 53% yield) as a pale yellow oil, and diasteromer **PW-33b** (159 mg, 46% yield) as a white solid (99% global yield).

(PW-33a)



[α]$^{20}_{D}$: +9.48 (*c* 1.12, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.47-7.43 (m, 6H, H-Ar(*o*)), 7.33-7.23 (m, 6H, H-Ar(*m*)), 7.23-7.15 (m, 3H, H-Ar(*p*)), 6.24-6.16 (m, 2H, H-4 and H-11), 5.06-5.00 (m, 2H, H-2'), 4.17 (d, 1H, *J* = 4.4 Hz, H-2), 3.18 (s, 1H, OH(C-1)), 3.11-3.00 (m, 2H, H-1'), 2.05-1.99 (m, 2H, H-5), 1.86 (d, 1H, *J* = 4.4 Hz, OH(C-2)), 1.69-1.47 (m, 6H, CH_2), 1.47-1.31 (m, 6H, CH_2), 1.31-1.11 (m, 2H, CH_2), 1.07, 1.06 (2s, 6H, H-16, H-17), 0.97 (s, 3H, H-19), 0.87 (t, 3H, *J* = 7.2 Hz, H-18).

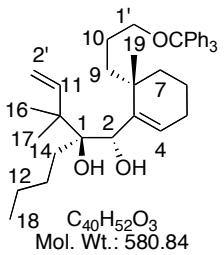
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 147.1 (C-11), 146.9 (C-3), 144.4 (C-*q*), 128.7 (C-*o*), 128.2 (C-4), 127.7, 126.8 (C-m, C-p), 112.1 (C-2'), 86.4 (C-Ar), 78.1 (C-1), 69.5 (C-2), 64.4 (C-1'), 47.0 (C-15), 37.1 (C-8), 36.4 (C-5), 35.1, 33.3, 27.0 (CH_2), 25.9 (C-19), 25.7, 24.5, 23.7 (CH_2), 22.9 (C-16 or C-17), 22.8 (C-17 or C-16), 18.8 (CH_2), 14.1 (C-18).

IR (CaF_2, CCl_4, 1 mg/mL): 3610, 3534, 2959, 2931, 2871, 2289, 2002, 1854, 1549, 1449, 1380, 1252, 1217, 1067 cm^{-1}.

MS (CI, NH_3): *m/z* 243 (Ph_3C^+).

***R*$_f$** 0.5 (E/PE 20/80).

(PW-33b)



M.p. 102-105°C.

[α]$^{20}_{D}$: +9.42 (*c* 1.00, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.53-7.48 (m, 6H, H-Ar(*o*)), 7.38-7.32 (m, 6H, H-Ar(*m*)), 7.32-7.26 (m, 3H, H-Ar(*p*)), 6.31 (t, 1H, *J* = 4.0 Hz, H-4), 6.25 (dd, 1H, *J* = 17.6, 10.8 Hz, H-11), 5.08 (d, 1H, *J* = 17.6 Hz, H-2'(*trans*)), 5.03 (d, 1H, *J* = 10.8 Hz, H-2'(*cis*)), 4.28 (d, 1H, *J* = 4.4 Hz, H-2), 3.19 (s, 1H, OH(C-1)), 3.14-3.09 (m, 2H, H-1'), 2.12-2.05 (m, 2H, H-5), 1.89 (d, 1H, J = 4.4 Hz, OH(C-2)), 1.70-1.52 (m, 8H, CH_2), 1.52-1.40 (m, 3H, CH_2), 1.35-1.14 (m, 3H, CH_2), 1.15-1.10 (m, 9H, H-16, H-17, H-19), 0.89 (t, 3H, *J* = 7.6 Hz, H-18).

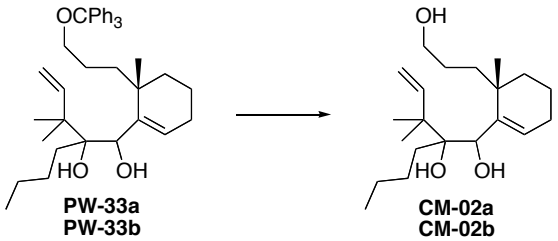
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 147.9 (C-3), 147.1 (C-11), 144.4 (C-Ar(*q*)), 128.6 (C-Ar(*o*)), 127.7 (C-4), 127.0, 126.8 (C-Ar(*m*), C-Ar(*p*)), 112.1 (C-2'), 86.2 (C-Ar), 78.1 (C-1), 70.0 (C-2), 64.0 (C-1'), 46.9 (C-15), 36.7 (C-8), 36.2 (C-5), 35.0, 33.4, 27.0 (CH_2), 25.7 (C-19), 25.1, 24.4, 23.6 (CH_2), 22.9 (C-16 or C-17), 22.8 (C-17 or C-16), 18.6 (CH_2), 14.1 (C-18).

IR (CaF_2, CCl_4, 1 mg/mL): 3610, 3537, 3061, 2959, 2930, 2871, 2291, 2004, 1856, 1550, 1449, 1379, 1252, 1217, 1067 cm^{-1}.

MS (CI, NH_3): *m/z* 243 (Ph_3C^+).

***R*$_f$** 0.3 (E/PE 20/80).

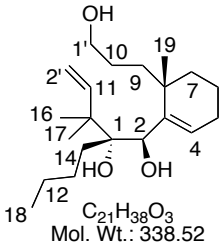
(1*R*,2*R*)-2-(1,1-Dimethyl-allyl)-1-[(*S*)-6-(3-hydroxy-propyl)-6-methyl-cyclohex-1-enyl]hexane-1,2-diol (CM-02a) and (1*S*,2*S*)-2-(1,1-Dimethyl-allyl)-1-[(*S*)-6-(3-hydroxy-propyl)-6-methyl-cyclohex-1-enyl]hexane-1,2-diol (CM-02b).



Diol **PW-33a** (251 mg, 0.43 mmol) was dissolved in MeOH (5 mL) at 20°C. Amberlyst H-15 (40 mg) was then added, and the mixture was stirred overnight at 20°C. The resin was then filtered off and the solvents were removed in *vacuo*. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80 then 50/50 then 80/20) afforded the desired alcohol **CM-02a** (128 mg, 88% yield) as a white solid.

The same procedure repeated with 223 mg of diol **PW-33b** afforded the desired alcohol **CM-02b** (104 mg, 80% yield) as a yellow oil.

CM-02a



M.p. 47-49°C.

$[\alpha]^{20}_{D}$: +1.03 (*c* 1.56, CH_2Cl_2).

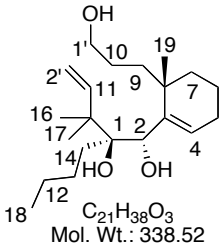
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.27 (t, 1H, *J* = 4.0 Hz, H-4), 6.18 (dd, 1H, *J* = 17.6 Hz, 10.9 Hz, H-11), 5.06 (m, 2H, H-2'), 4.18 (s, 1H, H-2), 3.70-3.65 (m, 1H, H-1'), 3.58-3.53 (m, 1H, H-1), 3.01 (sl, 1H, OH), 2.50 (sl, 1H, OH), 2.12 (sl, 1H, OH), 2.02-1.98 (m, 2H, H-5), 1.66-1.48 (m, 6H, CH_2), 1.46-1.40 (m, 2H, CH_2), 1.38-1.31 (m, 4H, CH_2), 1.27-1.12 (m, 2H, CH_2), 1.08 (s, 3H, H-16 or H-17), 1.07 (s, 3H, H-17 or H-16), 0.98 (s, 3H, H-19), 0.85 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 146.9 (C-11), 145.9 (C-3), 128.0 (C-4), 112.2 (C-2'), 78.2 (C-1), 69.3 (C-2), 63.1 (C-1'), 47.0 (C-15), 37.4 (C-8), 35.9 (C-5), 35.2 (C-7), 33.3 (C-9), 27.1 (C-14), 27.0 (C-10), 26.7 (C-19), 25.8 (C-6), 23.6 (C-13), 23.1 (C-16 or C-17), 22.8 (C-17 or C-16), 18.9 (C-12), 14.1 (C-18).

IR (CaF_2, CCl_4, 1 mg/mL): 3380, 2955, 2870, 1460, 1377, 785, 705, 603 cm^{-1}.

HRMS Calcd for $C_{21}H_{38}O_3$: 338.2821 **Found**: 338.2832.

CM-02b



$[\alpha]^{20}_{D}$: +0.35 (*c* 1.15, CH_2Cl_2).

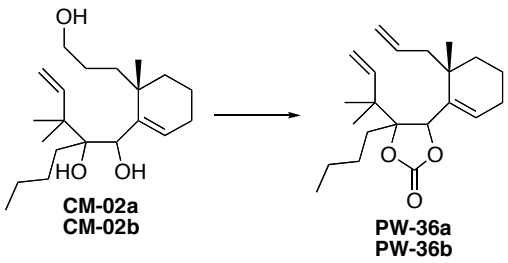
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.24-6.17 (m, 2H, H-14, H-11), 5.08-5.03 (m, 2H, H-2'), 4.20 (s, 1H, *J* = 4.5 Hz, H-2), 3.60 (t, 2H, *J* = 6.7 Hz, H-1'), 3.11 (s, 1H, OH), 2.03-1.99 (m, 2H, H-5), 1.85 (d, 1H, *J* = 4.7 Hz, OH), 1.63-1.49 (m, 6H, CH_2), 1.47-1.30 (m, 6H, CH_2), 1.28-1.12 (m, 2H, CH_2), 1.08-1.07 (m, 9H, H-16, H-17, H-19), 0.85 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 147.6 (C-11), 147.1 (C-3), 127.2 (C-4), 112.1 (C-2'), 78.2 (C-1), 70.2 (C-2), 63.7 (C-1'), 46.9 (C-15), 36.6 (C-8), 35.3 (C-5), 35.1 (C-7), 33.5 (C-9), 27.2 (C-14), 27.0 (C-10), 25.7 (C-6), 25.2 (C-19), 23.6 (C-13), 22.9 (C-16 or C-17), 22.8 (C-17 or C-16), 18.6 (C-12), 14.1 (C-18).

IR (film): 3412, 2954, 2867, 1461, 1377, 1055, 1011, 842, 737, 686, 625 cm^{-1}.

HRMS Calcd for $C_{21}H_{38}O_3$: 338.2821 **Found**: 338.2834.

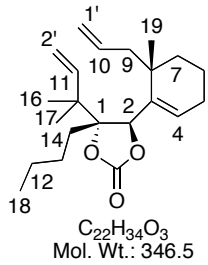
(4*R*,5*R*)-5-((6*S*)-6-Allyl-6-methylcyclohex-1-enyl)-4-butyl-4-(1,1-dimethylallyl)-[1,3]dioxolan-2-one (PW-36a) and (4*S*,5*S*)-5-((6*S*)-6-Allyl-6-methylcyclohex-1-enyl)-4-butyl-4-(1,1-dimethylallyl)-[1,3]dioxolan-2-one (PW-36b).



o-Nitrophenylselenocyanate (55 mg, 0.24 mmol, 2.4 equiv) was added in one portion at 20°C to a solution of alcohol **CM-02a** (34 mg, 0.10 mmol) in THF (1.0 mL). Tributylphosphine (60 μL, 0.24 mmol, 2.4 equiv) was then added dropwise. The resulting mixture was stirred at 20°C for 20 min. The completion of the reaction was checked by TLC. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. The crude product was used for the next step without purification. Carbonyl diimidazole (81 mg, 0.50 mmol, 5.0 equiv) was added at 20°C to a solution of the crude product in toluene (5 mL). The resulting mixture was refluxed for three days. After cooling, the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate. The phases were separated then the aqueous phase was extracted with. The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. The crude product was then dissolved in THF (1.0 mL). Aqueous hydrogen peroxide (1.5 mL, 10% wt solution in water) was added dropwise at 0°C. The mixture was then stirred overnight. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired diene **PW-36a** (32 mg, 57% yield over three steps) as a pale yellow oil.

The same procedure repeated with 30 mg of alcohol **CM-02b** afforded the desired diene **PW-36b** (16 mg, 52% yield over three steps) as a pale yellow oil.

PW-36a



$[\alpha]^{20}_{D}$: + 23.5 (*c* 0.92, CH_2Cl_2).

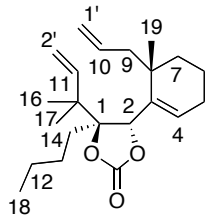
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.95 (dd, 1H, *J* = 17.6, 10.6 Hz, H-11), 5.85 (t, 1H, *J* = 4.1 Hz, H-4), 5.75 (ddt, 1H, *J* = 17.6, 10.6, 7.6 Hz, H-10), 5.22 (d, 1H, *J* = 10.5 Hz, H-2'(*cis*)), 5.21 (d, 1H, *J* = 17.4 Hz, H-2'(*trans*)), 5.10 (d, 1H, *J* = 7.6 Hz, H-1'(*cis*)), 5.06 (d, 1H, *J* = 17.6 Hz, H-1'(*trans*)), 4.98 (s, 1H, H-2), 2.32-2.26 (m, 1H, CH_2), 2.19-2.02 (m, 3H, CH_2), 1.85-1.50 (m, 4H. CH_2), 1.50-1.19 (m, 6H, CH_2), 1.15 (s, 3H, H-16 or H-17), 1.14 (s, 3H, H-17 or H-16), 0.98 (s, 3H, H-19), 0.87 (t, 3H, *J* = 7.6 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.7 (C=O), 141.9 (C-11), 139.3 (C-3), 133.9 (C-10), 131.2 (C-4), 118.1 (C-1'), 115.7 (C-2'), 90.7 (C-1), 79.0 (C-2), 46.6 (C-15), 44.9 (C-9), 36.9 (C-8), 35.7 (CH_2), 31.0 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 25.6 (C-19), 23.2 (CH_2), 22.3 (C-16 or C-17), 20.8 (C-17 or C-16), 18.2 (C-19), 13.8 (C-18).

IR (film): 3575, 3076, 2960, 2368, 1984, 1790, 1638, 1538, 1456, 1417, 1380, 1326, 1198, 1042 cm^{-1}. **MS** (CI, NH_3): *m/z* 364 ($M+NH_4^+$), 347 ($M+H^+$), 303, 285.

HRMS Calcd for $C_{22}H_{34}O_3$: 346.2508 **Found**: 346.2524.

PW-36b



$C_{22}H_{34}O_3$
Mol. Wt.: 346.5

$[\alpha]^{20}_D$: -19.3 (*c* 1.01, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.95 (dd, 1H, *J* = 17.6, 11.2 Hz, H-11), 5.79 (t, 1H, *J* = 4.1 Hz, H-4), 5.73 (ddt, 1H, *J* = 17.2, 10.4, 7.1 Hz, H-10), 5.23 (d, 1H, *J* = 11.2 Hz, H-2'(*cis*)), 5.21 (d, 1H, *J* = 17.6 Hz, H-2'(*trans*)), 5.06 (dd, 2H, *J* = 17.0, 10.6 Hz, H-1'), 5.02 (s, 1H, H-2), 2.14-2.00 (m, 4H, CH_2), 1.89-1.80 (m, 1H, CH_2), 1.74-1.55 (m, 4H, CH_2), 1.50-1.18 (m, 5H, CH_2), 1.16 (s, 3H, H-16 or H-17), 1.14 (s, 3H, H-16 or H-17), 1.07 (s, 3H, H-19), 0.88 (t, 3H, *J* = 7.6 Hz, H-18).

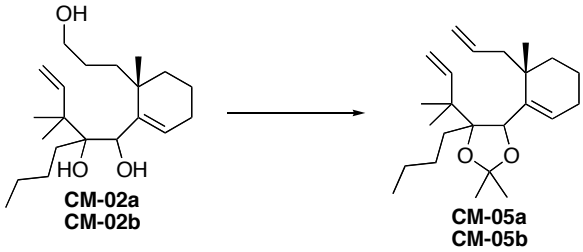
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 155.5 (C=O), 141.9 (C-11), 140.6 (C-3), 133.8 (C-10), 130.5 (C-4), 118.1 (C-1'), 115.8 (C-2'), 90.6 (C-1), 79.7 (C-2), 46.5 (C-15), 43.6 (C-9), 36.9 (C-8), 35.0 (CH_2), 31.1 (CH_2), 27.0 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 23.2 (CH_2), 22.4 (C-16 or C-17), 20.8 (C-17 or C-16), 18.0 (C-19), 13.8 (C-18).

IR (film): 3568, 3077, 2956, 2254, 1790, 1638, 1539, 1456, 1417, 1379, 1326, 1200, 1117, 1044 cm^{-1}.

MS (CI, NH_3): *m/z* 364 ($M+NH_4^+$), 347 ($M+H^+$), 285.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. **Found**: C, 76.01; H, 9.98.

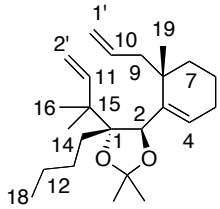
(4*R*,5*R*)-5-((*S*)-6-Allyl-6-methylcyclohex-1-enyl)-4-butyl-4-(1,1-dimethylallyl)-2,2-dimethyl-[1,3]dioxolane (CM-05a) and (4*S*,5*S*)-5-((*S*)-6-Allyl-6-methylcyclohex-1-enyl)-4-butyl-4-(1,1-dimethylallyl)-2,2-dimethyl-[1,3]dioxolane (CM-05b).



To triol **CM-02a** (38 mg, 0.111 mmol) was added 2,2-dimethoxypropane (5 mL) then a catalytic amount of CSA at 20°C, then the resulting mixture was stirred overnight. The reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate, the phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. The crude product was used for the next step without purification. *o*-Nitrophenylselenocyanate (58 mg, 0.254 mmol, 2.4 equiv) was added in one portion at 20°C to a solution of the crude product (40 mg, 0.106 mmol) in THF (1.0 mL). Tributylphosphine (64 μL, 0.254 mmol, 2.4 equiv) was then added dropwise. The resulting mixture was stirred at 20°C for 20 min. The completion of the reaction was checked by TLC. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. The crude product thus obtained was then dissolved in THF (1.0 mL), aqueous hydrogen peroxide (0.5 mL, 35% wt solution in water) was added dropwise at 0°C. The mixture was then stirred overnight. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired diene **CM-05a** (25 mg, 63% yield over three steps) as a colorless oil.

The same procedure was repeated with 30 mg of alcohol **CM-02b** to afford the desired diene **CM-05b** (23 mg, 71% yield over three steps) as a colorless oil.

CM-05a



$C_{24}H_{40}O_2$
Mol. Wt.: 360.57

$[\alpha]^{20}_{D}$: - 21.4 (*c* 1.5, CH_2Cl_2).

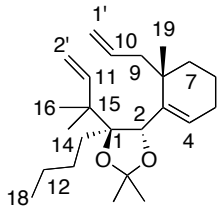
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.20 (dd, 1H, *J* = 17.6 Hz, 10.9 Hz, H-11), 6.03-5.98 (m, 1H, H-4), 5.89-5.77 (m, 1H, H-10), 5.01-4.91 (m, 4H, H-1', H-2'), 4.44 (s, 1H, H-2), 2.27 (d, 2H, *J* = 7.0 Hz, H-9), 2.14-1.99 (m, 2H, H-5), 1.82-1.79 (m, 2H, CH_2), 1.62-1.58 (m, 4H, CH_2), 1.46 (s, 3H, Me-C-O), 1.36 (s, 3H, Me-C-O), 1.33-1.16 (m, 4H, CH_2), 1.12-1.05 (m, H-9H, H-16. H-17, H-19), 0.90 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 146.9 (C-11), 139.2 (C-3), 136.2 (C-10), 129.1 (C-4), 116.5 (C-1'), 110.6 (C-2'), 104.3 (O-C-O), 88.3 (C-1), 77.1 (C-2), 44.8 (C-9), 43.3 (C-15), 37.9 (C-8), 35.9 (C-5), 33.5 (C-7), 28.0 (C-14), 27.9 (C-19), 26.3 (Me-C-O), 26.2 (Me-C-O), 26.1 (C-6), 25.4 (C-16 or C-17), 24.0 (C-13), 23.4 (C-17 or C-16), 17.9 (C-12), 14.3 (C-18).

IR (film): 3076, 2959, 2933, 2872, 1636, 1461, 1372, 1247, 1212, 1016, 910, 862, 793, 764, 626, 486 cm^{-1}.

HRMS Calcd for $C_{24}H_{40}O_2$: 360.3028 **Found**: 360.3028.

CM-05b



$C_{24}H_{40}O_2$
Mol. Wt.: 360.57

$[\alpha]^{20}_{D}$: - 1.23 (*c* 1.3, CH_2Cl_2).

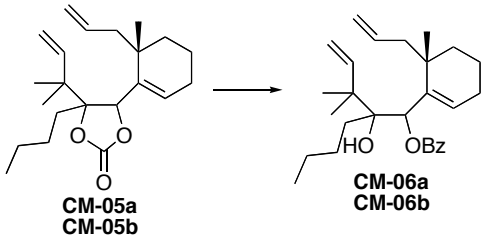
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.19 (dd, 1H, *J* = 17.7 Hz, 10.9 Hz, H-11), 5.92 (t, 1H, *J* = 3.8 Hz, H-4), 5.82-5.72 (m, 1H, H-10), 5.05-4.92 (m, 4H, H-1', H-2'), 4.44 (s, 1H, H-2), 2.32 (dd, 1H, *J* = 13.9 Hz, 7.2 Hz, H-9), 2.19 (dd, 1H, *J* = 13.9 Hz, 7.2 Hz, H-9), 2.10-2.05 (m, 2H, H-5), 1.82-1.76 (m, 2H, CH_2), 1.65-1.53 (m, 4H, CH_2), 1.46 (s, 3H, Me-C-O), 1.37 (s, 3H, Me-C-O), 1.32-1.22 (m, 4H, CH_2), 1.09-1.08 (m, 9H, H-16, H-17, H-19), 0.89 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 146.9 (C-11), 139.2 (C-3), 135.5 (C-10), 128.4 (C-4), 116.9 (C-1'), 110.7 (C-2'), 104.3 (O-C-O), 88.3 (C-1), 77.7 (C-2), 44.0 (C-9), 43.4 (C-15), 37.8 (C-8), 35.6 (C-5), 33.5 (C-7), 27.9 (C-14), 27.8 (C-19), 26.5 (Me-C-O), 26.3 (Me-C-O), 26.0 (C-6), 25.5 (C-16 or C-17), 23.9 (C-13), 23.5 (C-17 or C-16), 17.8 (C-12), 14.3 (C-18).

IR (film): 2959, 2931, 2869, 1636, 1459, 1373, 1253, 1017, 857, 802, 713, 695, 648, 632, 524, 462 cm^{-1}.

HRMS Calcd for $C_{24}H_{40}O_2$: 360.3028 **Found**: 360.3032.

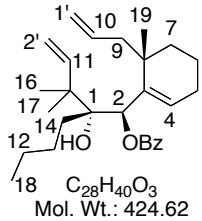
(1*R*,2*R*)-1-((*S*)-6-allyl-6-methylcyclohex-1-enyl)-2-(1,1-dimethylallyl)-2-hydroxyhexylbenzoate (CM-06a) and (1*S*,2*S*)-1-((*S*)-6-allyl-6-methylcyclohex-1-enyl)-2-(1,1-dimethylallyl)-2-hydroxyhexylbenzoate (CM-06b).



To a solution of crude diene **CM-05a** synthesized from 49 mg CM-**02a** in THF (5 mL) at -78°C was added dropwise a solution of phenyllithium in ether (0.3 M, 1.5 mL, 2.1 eq.). After 10 min the solution was poured into a saturated aqueous solution of sodium hydrogen carbonate, the phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95) afforded the diene **CM-06a** (30 mg, 46% yield over four steps from diol **CM-02a**) as a colorless oil.

The same procedure was repeated with 41 mg of triol **CM-02b** to afford the diene **CM-06b** (19.5 mg, 36% yield over four steps from **CM-02b**) as a colorless oil.

CM-06a



$[\alpha]^{20}_{D}$: + 1.6 (*c* 1.30, CH_2Cl_2).

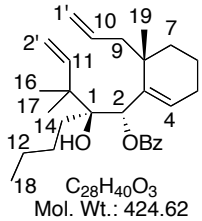
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.97-7.95 (m, 2H, H-Ar), 7.57-7.53 (m, 1H, H-Ar), 7.45-7.42 (m, 2H, H-Ar), 6.43 (t, 1H, *J* = 4.0 Hz, H-4), 5.96 (dd, 1H, *J* = 17.6 Hz, 10.9 Hz, H-11), 5.77 (s, 1H, H-2), 5.71-5.61 (m, 1H, H-10), 4.98-4.92 (m, 3H, H-1', H-2'), 4.77 (dd, 1H, *J* = 10.9 Hz, 1.2 Hz, H-1'), 2.59 (s, 1H, OH), 2.40 (dd, 1H, *J* = 14.0 Hz, 7.5 Hz, H-9), 2.12-2.07 (m, 3H, H-5, H-9), 1.68-1.58 (m, 3H, H-6, H-7), 1.55-1.39 (m, 2H, H-14), 1.33-1.18 (m, 5H, H-13, H-4, H-7), 1.11 (s, 3H, H-16 or H-17), 1.09 (s, 3H, H-17 or H-16), 1.06 (s, 3H, H-19), 0.90 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 164.7 (C=O), 145.1 (C-11), 142.9 (C-3), 135.1 (C-10), 132.8 (C-Ar), 131.0 (C-Ar), 130.5 (C-Ar), 129.6 (C-4), 128.4 (C-Ar), 117.1 (C-2'), 112.3 (C-1'), 79.3 (C-1), 72.5 (C-2), 46.6 (C-15), 44.0 (C-9), 36.9 (C-8), 34.9 (C-7), 33.3 (C-6), 26.9 (C-14), 25.7 (C-5), 25.5 (C-19), 23.6 (C-13), 23.2 (C-16 or C-17), 22.9 (C-17 or C-16), 18.0 (C-12), 14.2 (C-18).

IR (film): 3965, 3807, 3711, 2928, 2280, 1793, 1710, 1576, 1484, 1427, 1316, 1262, 1078, 976, 944, 919, 857, 835, 817, 765, 685, 602, 571, 509 cm^{-1}.

HRMS Calcd for $C_{28}H_{40}O_3$: 424.2978 **Found**: 424.2985.

CM-06b



$[\alpha]^{20}_{D}$: + 5.5 (*c* 1.30, CH_2Cl_2).

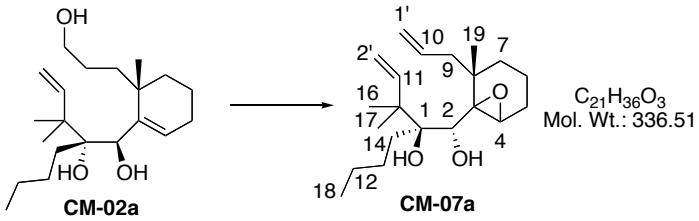
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.98-7.96 (m, 2H, H-Ar), 7.57-7.54 (m, 1H, H-Ar), 7.46-7.42 (m, 2H, H-Ar), 6.41 (t, 1H, *J* = 3.9 Hz, H-4), 5.99 (dd, 1H, *J* = 17.6 Hz, 10.9 Hz, H-11), 5.87-5.78 (m, 1H, H-10), 5.76 (s, 1H, H-2), 5.06-4.93 (m, 3H, H-1', H-2'), 4.79 (dd, 1H, *J* = 10.9 Hz, 1.2 Hz, H-2'), 2.61 (s, 1H, OH), 2.34 (dd, 1H, *J* = 13.1 Hz, 7.0 Hz, H-9), 2.17-2.07 (m, 3H, H-5, H-9), 1.67-1.63 (m, 2H, H-6), 1.58-1.36 (m, 6H, H-7, H-14, H-12), 1.33-1.18 (m, 2H, H-13), 1.13 (s, 3H, H-19), 1.08 (s, 3H, H-16 or H-17), 1.05 (s, 3H, H-17 or H-16), 0.90 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 165.0 (C=O), 145.3 (C-11), 142.8 (C-3), 134.9 (C-10), 132.8 (C-Ar), 131.0 (C-Ar), 130.7 (C-4), 129.6 (C-Ar), 128.4 (C-Ar), 117.5 (C-1'), 112.3 (C-2'), 79.4 (C-1), 73.9 (C-2), 46.5 (C-15), 44.5 (C-9), 36.8 (C-8), 35.8 (C-7), 33.7 (C-6), 26.8 (C-14), 25.8 (C-5), 25.7 (C-19), 23.6 (C-13), 23.4 (C-16 or C-17), 23.0 (C-17 or C-16), 18.0 (C-12), 14.1 (C-18).

IR (film): 3681, 2931, 2275, 1714, 1636, 1454, 1316, 1265, 1108, 964, 937, 902, 864, 844, 725, 694, 524 cm^{-1}.

HRMS Calcd for $C_{28}H_{40}O_3$: 424.2978 **Found**: 424.2964.

(1*S*,2*R*)-1-((*S*)-2-Allyl-2-methyl-7-oxabicyclo[4.1.0]hept-1-yl)-2-(1,1-dimethylallyl)hexane-1,2-diol (CM-07a).



o-Nitrophenylselenocyanate (145 mg, 0.66 mmol, 2.40 equiv) was added in one portion at 20°C to a solution of alcohol **CM-02a** (90 mg, 0.28 mmol) in THF (5.0 mL). Tributylphosphine (159 μL, 0.66 mmol, 2.39 equiv) was then added dropwise. The resulting mixture was stirred at 20°C for 20 min. The completion of the reaction was checked by TLC. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. The crude product thus obtained was then dissolved in THF (1.0 mL), and aqueous hydrogen peroxide (0.5 mL, 35% wt solution in water) was added dropwise at 0°C. The mixture was then stirred overnight. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the epoxide diene **CM-07a** (20 mg, 20% yield) as pale yellow oil.

$[\alpha]^{20}_{D}$: -17.2 (*c* 1.40, CH_2Cl_2).

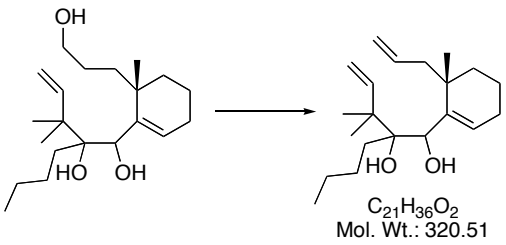
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.12 (dd, 1H, *J* = 17.4 Hz, 11.0 Hz, H-11), 5.88-5.78 (m, 1H, H-10), 5.09-5.01 (m, 4H, H-2'), 4.05 (d, 1H, *J* = 5.3 Hz, H-2), 3.93 (t, 1H, *J* = 2.4 Hz, H-4), 3.30 (d, 1H, *J* = 5.3 Hz, OH(C-2)), 2.86 (s, 1H, OH(C-1)), 2.30 (dd, 1H, *J* = 13.6 Hz, 7.5 Hz, H-9), 2.12 (dd, 1H, *J* = 13.6 Hz, 7.5 Hz, H-9), 1.87-1.83 (m, 2H, H-5), 1.60-1.48 (m, 2H, CH_2), 1.47-1.37 (m, 4H, CH_2), 1.36-1.17 (m, 4H, CH_2), 1.09-1.05 (m, 6H, H-16 or H-17, H-19), 1.03 (s, 3H, H-17 or H-16), 0.92 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 146.2 (C-11), 134.2 (C-10), 117.9 (C-2'), 112.6 (C-1'), 76.6 (C-1), 67.7 (C-2), 66.7 (C-3), 60.7 (C-4), 47.1 (C-15), 43.2 (C-9), 36.6 (C-8), 32.7 (C-5), 32.0 (C-7), 27.6 (C-14), 23.9 (C-6), 23.9 (C-19), 23.2 (C-13), 22.3 (C-16 or C-17), 21.9 (C-17 or C-16), 16.1 (C-12), 14.1 (C-18).

IR (film): 3494, 2958, 2874, 1636, 1460, 1381, 1077, 1000, 907, 878, 826, 804, 771, 708, 632, 591 cm^{-1}.

HRMS Calcd for $C_{21}H_{36}O_3$: 336.2665 **Found**: 336.2665.

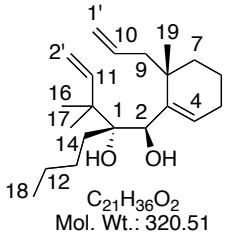
(1*R*,2*R*)-1-((*S*)-6-Allyl-6-methylcyclohex-1-enyl)-2-(1,1-dimethylallyl)-hexane-1,2-diol (CM-08a) and (1*S*,2*S*)-1-((*S*)-6-Allyl-6-methylcyclohex-1-enyl)-2-(1,1-dimethylallyl)-hexane-1,2-diol (CM-08b).



o-Nitrophenylselenocyanate (282 mg, 1.24 mmol, 2.40 equiv) was added in one portion at 20°C to a solution of alcohol **CM-02a** (175 mg, 0.52 mmol) in THF (1.0 mL). Tributylphosphine (49 μL, 0.2 mmol, 2.4 equiv) was then added dropwise. The resulting mixture was stirred at 20°C for 20 min. The completion of the reaction was checked by TLC. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. The crude product thus obtained was then dissolved in THF (1.0 mL), and aqueous ammonium molybdate in solution (6 M) of hydrogen peroxide (1.5 mL, 10% wt solution in water) was added dropwise at -10°C. The mixture was then stirred for 5 min. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80) afforded the desired diene **CM-08a** (152 mg, 92% yield) as a pale yellow oil.

The same procedure was repeated with 115 mg of alcohol **CM-02b** to afford the desired diene **CM-08b** (99 mg, 91% yield) as a pale yellow oil.

CM-08a



$[\alpha]^{20}_{D}$: + 3.3 (*c* 1.0, CH_2Cl_2).

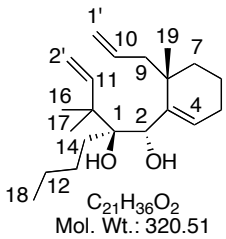
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.26-6.17 (m, 2H, H-4, H-11), 5.91-5.80 (m, 1H, H-10), 5.08-5.04 (m, 4H, H-1', H-2'), 4.20 (d, 1H, *J* = 3.4 Hz, H-2), 3.16 (s, 1H, OH(C-1)), 2.23 (dq, 2H, *J* = 14.0 Hz, 7.4 Hz, H-9), 2.04-2.00 (m, 2H, H-5), 1.90 (d, 1H, *J* = 3.8 Hz, OH(C-2)), 1.66-1.48 (m, 4H, H-6, H-7, H-12), 1.43-1.32 (m, 4H, H-6, H-7, H-14), 1.28-1.22 (m, 2H, H-13), 1.09 (s, 3H, H-16 or H-17), 1.08 (s, 3H, H-17 or H-16), 0.99 (s, 3H, H-19), 0.86 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 147.1 (C-11), 146.2 (C-3), 135.4 (C-10), 128.1 (C-4), 117.3 (C-2'), 112.1 (C-1'), 78.1 (C-2), 69.5 (C-1), 47.0 (C-15), 45.1 (C-9), 37.4 (C-8), 35.6 (C-7), 33.3 (C-6), 27.0 (C-14), 26.1 (C-19), 25.7 (C-5), 23.7 (C-13), 22.9 (C-16 or C-17), 22.8 (C-17 or C-16), 18.6 (C-12), 14.1 (C-18).

IR (film): 2929, 2278, 1587, 1511, 1450, 1328, 1304, 1096, 1030, 924, 890, 850, 810, 772, 648, 587, 532 cm^{-1}.

HRMS Calcd for $C_{21}H_{36}O_2$: 320.2715 **Found**: 320.2716.

CM-08b



$[\alpha]^{20}_{D}$: + 4.6 (*c* 1.20, CH_2Cl_2).

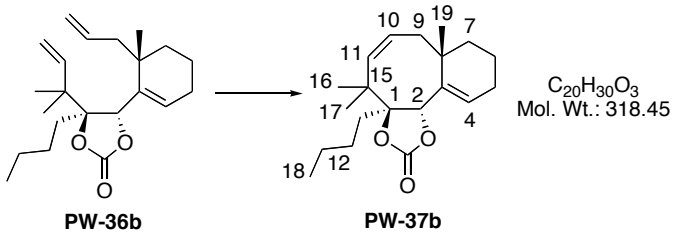
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.28-6.19 (m, 2H, H-4, H-11), 5.85-5.74 (m, 1H, H-10), 5.10-5.01 (m, 4H, H-1', H-2'), 4.22 (d, 1H, *J* = 4.3 Hz, H-2), 3.09 (s, 1H, OH(C-1)), 2.09 (d, 2H, *J* = 7.4 Hz, H-9), 2.02 (dt, 2H, *J* = 6.2 Hz, 4.2 Hz, H-5), 1.83 (d, 1H, *J* = 4.5 Hz, OH(C-2)), 1.66-1.60 (m, 1H, H-7), 1.57-1.49 (m, 3H, H-6, H-12), 1.45-1.33 (m, 4H, H-6, H-14, H-7), 1.33-1.12 (m, 2H, H-13), 1.10 (s, 3H, H-16 or H-17), 1.09 (s, 3H, H-17 or H-16), 1.07 (s, 3H, H-19), 0.86 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 147.1 (C-11), 134.7 (C-10), 127.5 (C-4), 117.6 (C-1'), 112.2 (C-2'), 78.2 (C-1), 70.1 (C-2), 47.0 (C-15), 44.0 (C-9), 37.0 (C-8), 35.2 (C-7), 33.5 (C-6), 27.0 (C-14), 25.7 (C-5), 25.2 (C-19), 23.6 (C-13), 22.9 (C-16 or C-17), 22.8 (C-17 or C-16), 18.4 (C-12), 14.1 (C-18).

IR (film): 2956, 2867, 1716, 1638, 1587, 1508, 1328, 1300, 1095, 1026, 910, 859, 828, 782, 694, 642, 603, 517, 478 cm^{-1}.

HRMS Calcd for $C_{21}H_{36}O_2$: 320.2715 **Found**: 320.2728.

(*Z*)-(2*R*,6*S*,11*S*)-6-Butyl-7,7,11-trimethyl-3,5-dioxatricyclo [9.4.0.0^{2,6}] pentadeca-1(15),8-dien-4-one (PW-37b).



Diene **PW-36b** (10 mg, 30 μmol) was dissolved in 1,2-dichloroethane (2.0 mL). The mixture was thoroughly degassed three times while stirring. Second-generation Grubbs' catalyst (2.6 mg, 3.0 μmol, 10 mol%) was added and the mixture was refluxed for 1 h. After cooling, the solvent was evaporated at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired (*Z*)-(2*R*,6*S*,11*S*)-6-butyl-7,7,11-trimethyl-3,5-dioxatricyclo[9.4.0.0^{2,6}]pentadeca-1(15),8-dien-4-one **PW-37b** (6.4 mg, 69% yield) as a pale yellow oil. The same procedure repeated with **[RuIMes]** catalyst (1.3 mg, 1.5 μmol, 5 mol%) afforded the compound **PW-37b** (6.6 mg, 72% yield).

$[\alpha]^{20}_{D}$: + 112.5 (*c* 1.17, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.06 (t, 1H, *J* = 4.4 Hz, H-4), 5.66 (ddd, 1H, *J* = 11.8, 10.6, 8.1 Hz, H-10), 5.39 (s, 1H, H-2), 5.36 (d, 1H, *J* = 11.8 Hz, H-11), 2.58 (dd, 1H, *J* = 14.2,

10.6 Hz, H-9), 2.26 (dt, 1H, *J* = 18.7, 5.8 Hz, H-5), 2.12-1.70 (m, 8H, CH_2), 1.46 (s, 3H, H-19), 1.33 (s, 3H, H-16 or H-17), 1.32-1.25 (m, 4H, CH_2), 1.18 (s, 3H, H-17 or H-16), 0.93 (t, 3H, *J* = 7.2 Hz, H-18).

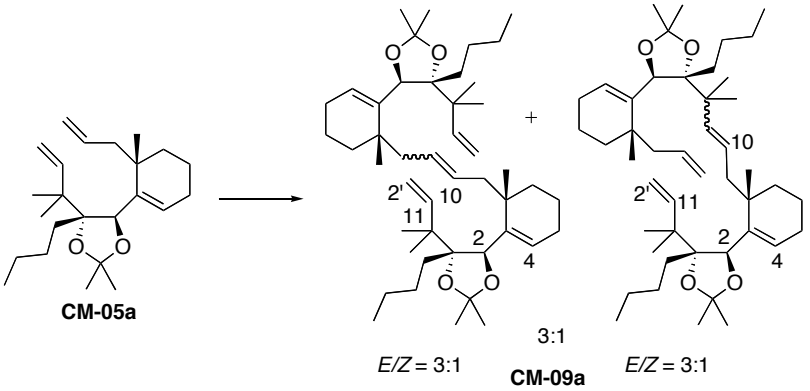
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.7 (C=O), 138.3 (C-11), 134.9 (C-3), 129.7 (C-10), 128.5 (C-4), 93.5 (C-1), 80.1 (C-2), 40.4 (C-15), 39.0 (C-8), 38.8 (C-9), 34.1 (C-7), 31.1 (CH_2), 28.8 (C-16 or C-17), 28.5 (C-17 or C-16), 27.7 (CH_2), 24.5 (CH_2), 23.3 (CH_2), 21.8 (C-19), 18.0 (CH_2), 13.9 (C-18).

IR (film): 3588, 2961, 2870, 2345, 1803, 1654, 1560, 1458, 1380, 1248 cm^{-1}.

MS (CI, NH_3): *m/z* 336 ($M+NH_4^+$), 319 ($M+H^+$), 258, 257.

HRMS Calcd for $C_{20}H_{30}O_3$: 318.2195. **Found**: 318.2206.

(CM-09a)

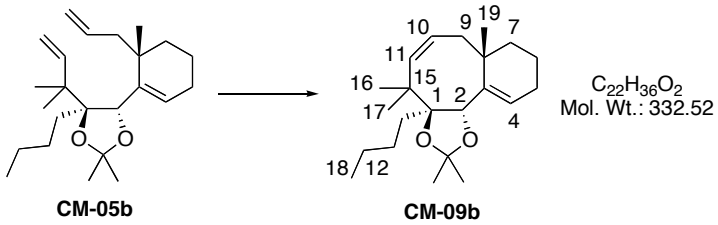


Diene **CM-05a** (24 mg, 0.067 mmol) was dissolved in dichloromethane (7.0 mL). The mixture was thoroughly degassed three times while stirring. Second-generation Grubbs' catalyst (2.8 mg, 3.3 μmol, 5 mol%) was added and the mixture was refluxed for 15 min. After cooling, the solvent was evaporated at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the mixture of **head-head** (15 mg, *E/Z*=3/1) and **head-tail** product **CM-09a** (5 mg, *E/Z*=3/1) (87% global yield) with a ratio of 3/1 as a pale yellow oil.

Fractions head-head product: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.37-6.12 (m, 2H, H-10, H-11), 6.04-6.01 (m, 2H, H-4), 5.55-5.46 (m, 3H, H-2', H-11), 5.02-4.91 (m, 3H, H-1', H-10), 4.49 (s, 0.75H, H-2), 4.21 (s, 0.25H, H-2), 2.54-2.42 (m, 2H, H-9), 2.26-2.20 (m, 2H, H-9).

Fractions head-tail product: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.24-6.16 (m, 2H, H-4), 6.01-5.96 (m, 2H, H-11), 5.50-5.48 (m, 0.5H, H-10), 5.40-5.38 (m, 1.5H, H-10), 4.98-4.90 (m, 4H, H-2'), 4.43 (s, 2H, H-2), 2.34-2.26 (m, 2H, H-9), 2.21-2.13 (m, 2H, H-9).

(*Z*)-(2*S*,6*S*,11*S*)-6-Butyl-4,4,7,7,11-pentamethyl-3,5-dioxatricyclo[9.4.0.0^{2,6}]pentadeca-1(15),8-diene (CM-09b).



Diene **CM-05b** (20 mg, 56 μmol) was dissolved in 1,2-dichloroethane (5.0 mL). The mixture was thoroughly degassed three times while stirring. Second-generation Grubbs' catalyst (2.4 mg, 2.8 μmol, 5 mol%) was added and the mixture was refluxed for 5 min. After cooling, the solvent was evaporated at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired bicycle **CM-09b** (19 mg, quantitative yield) as a pale yellow oil.

$[\alpha]^{20}_{D}$: + 124.0 (*c* 1.3, CH_2Cl_2).

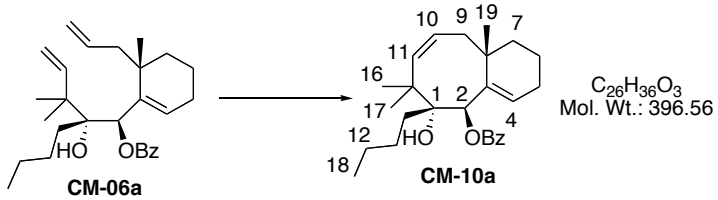
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.04 (m, 1H), 5.55-5.47 (m, 1H, H-4), 5.34 (d, 1H, *J* = 12.0 Hz, H-11), 4.69 (s, 1H, H-2), 2.65 (dd, 1H, *J* = 13.7 Hz, 10.7 Hz, H-9), 2.15 (dt, 1H, *J* = 18.3 Hz, 5.0 Hz, H-5), 1.98-1.90 (m, 1H, H-5), 1.87-1.62 (m, 5H, H-9, H-6, H-12), 1.59-1.51 (m, 2H, H-7), 1.47 (s, 3H, Me-C-O), 1.38 (s, 3H, H-16 or H-17), 1.35 (s, 3H, H-17 or H-16), 1.30-1.22 (m, 4H, H-14. H-13), 1.17 (s, 3H, H-19), 1.12 (s, 3H, Me-C-O), 0.86 (t, 3H, *J* = 7.2 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 141.2 (C-11), 137.6 (C-3), 127.7 (C-10), 125.8 (C-4), 104.5 (O-C-O), 89.1 (C-1), 75.5 (C-2), 40.5 (C-9), 38.9 (C-8), 38.8 (C-15), 34.4 (C-5), 34.4 (C-7), 29.7 (C-19), 29.6 (C-14), 28.8 (Me-C-O), 28.3 (Me-C-O), 26.5 (C-16 or C-17), 24.9 (C-6), 24.0 (C-13), 22.5 (C-17 or C16), 18.4 (C-12), 14.2 (C-18).

IR (film): 2929, 2866, 2360, 1701, 1666, 1594, 1458, 1372, 1247, 1041, 897, 833, 738, 539 cm^{-1}.

HRMS Calcd for $C_{22}H_{36}O_2$: 332.2715 **Found**: 332.2714.

(*Z*)-(5*R*,6*R*,10a*S*)-6-butyl-6-hydroxy-7,7,10a-trimethyl-1,2,3,5,6,7,10,10a-octahydro-benzocycloocten-5-ylbenzoate (CM-10a).



Diene **CM-06a** (15 mg, 35 μmol) was dissolved in dichloromethane (2.0 mL). The mixture was thoroughly degassed three times while stirring. Second-generation Grubbs' catalyst (1.5 mg, 1.8 μmol, 5 mol%) was added and the mixture was refluxed for 18 h. After cooling, the solvent was evaporated at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95) afforded the desired bicycle **CM-10a** (13 mg, 84% yield) as a pale yellow oil. The same procedure repeated with first-generation Grubbs' catalyst (1.5 mg, 1.8 μmol, 5 mol%) in 1,2-dichloroethane (2.0 mL) refluxed for 36 h afforded the compound **CM-10a** (9.0 mg, 71% yield).

$[\alpha]^{20}_{D}$: + 0.5 (*c* 1.10, CH_2Cl_2).

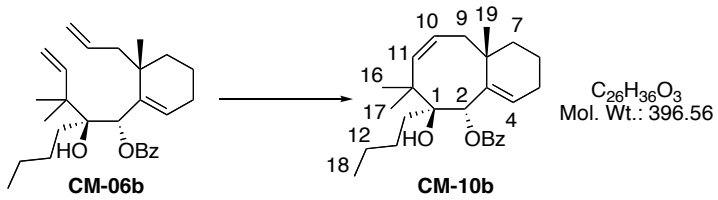
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.10-8.08 (m, 2H, H-Ar), 7.62-7.58 (m, 1H, H-Ar), 7.51-7.47 (m, 2H, H-Ar), 5.95-5.91 (m, 1H, H-4), 5.83 (s, 1H, H-2), 5.80-5.72 (m, 1H, H-10), 5.42 (d, 1H, *J* = 11.7 Hz, H-11), 3.26 (t, 1H, *J* = 11.9 Hz, H-9), 2.20-2.12 (m, 1H, H-5), 2.05-1.94 (m, 1H, H-5), 1.86-1.78 (m, 2H, H-6), 1.72-1.67 (m, 2H, H-14), 1.61 (s, 3H, H-16 or H-17), 1.54 (s, 3H, H-17 or H-16), 1.29-1.20 (m, 7H, H-13, H-12, H-7, H-9), 0.99 (s, 3H, H-19), 0.84 (t, 3H, *J* = 7.1 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 166.0 (C=O), 139.8 (C-11), 138.0 (C-3), 133.0 (C-4), 132.8 (C-Ar), 131.5 (C-10), 130.4 (C-Ar), 129.8 (C-Ar), 128.6 (C-Ar), 83.5 (C-2), 80.2 (C-1), 43.3 (C-15), 41.3 (C-8), 37.6 (C-9), 36.7 (C-7), 31.9 (C-6), 30.9 (C-19), 29.4 (C-13), 29.4 (C-14), 25.5 (C-5), 23.8 (C-16 or C-17), 23.4 (C-17 or C-16), 18.3 (C-12), 14.1 (C-18).

IR (film): 3544, 3435, 2926, 2866, 2360, 1722, 1453, 1264, 1099, 913, 861, 842, 778, 655, 563, 532 cm^{-1}.

HRMS Calcd for $C_{26}H_{36}O_3$: 396.2665 **Found**: 396.2656.

(*Z*)-(5*S*,6*S*,10a*S*)-6-butyl-6-hydroxy-7,7,10a-trimethyl-1,2,3,5,6,7,10,10a-octahydro-benzocycloocten-5-ylbenzoate (CM-10b).



Diene **CM-06b** (9.0 mg, 21 μmol) was dissolved in dichloromethane (2.0 mL). The mixture was thoroughly degassed three times while stirring. Second-generation Grubbs' catalyst (0.9 mg, 1.1 μmol, 5 mol%) was added and the mixture was stirred for 15 min at 20°C. The solvent was evaporated at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95) afforded the desired bicycle **CM-10b** (9.0 mg, quantitative yield) as a pale yellow oil. The same procedure repeated with first-generation Grubbs' catalyst (0.9 mg, 1.1 μmol, 5 mol%) in dichloromethane (2.0 mL) refluxed for 12 h afforded the compound **CM-10b** (7.2 mg, 78% yield).

$[\alpha]^{20}_D$: + 42.3 (*c* 1.30, CH_2Cl_2).

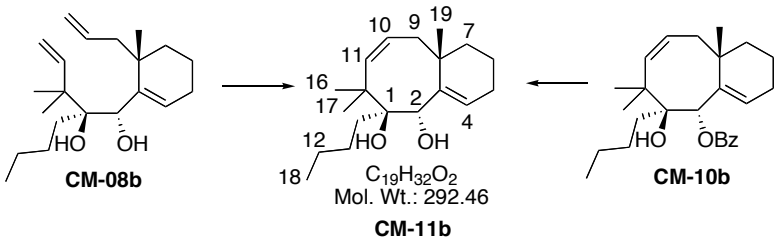
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.04-8.02 (m, 2H, H-Ar), 7.58-7.54 (m, 1H, H-Ar), 7.47-7.43 (m, 2H, H-Ar), 6.13 (s, 1H, H-2), 6.11-6.05 (m, 1H, H-4), 5.74-5.60 (m, 1H, H-10), 5.48-5.36 (m, 1H, H-11), 2.80-2.60 (sl, 1H, OH), 2.12-2.02 (m, 3H, H-5, H-9), 1.94 (t, 1H, *J* = 12.5 Hz, H-9), 1.76-1.66 (m, 2H, H-7), 1.62-1.58 (m, 2H, H-13), 1.54 (s, 3H, H-19), 1.36-1.31 (m, 2H, H-12), 1.36-1.26 (m, 4H, H-14, H-15), 1.23 (s, 3H, H-16 or H-17), 1.18 (s, 3H, H-17 or H-16), 0.95 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 166.1 (C=O), 142.4 (C-11), 139.7 (C-3), 132.8 (C-Ar), 130.6 (C-4), 129.7 (C-10), 129.1 (C-Ar), 128.4 (C-Ar), 81.3 (C-2), 77.2 (C-1), 38.4 (C-15), 31.9 (C-19), 30.3 (C-8), 28.1 (C-13), 28.1 (C-14), 27.6 (C-9), 25.9 (C-16 or C-17), 25.8 (C-17 or C-16), 23.9 (C-7), 22.7 (C-6), 18.5 (C-12), 14.2 (C-18).

IR (film): 3920, 3704, 3548, 2926, 2867, 2360, 1723, 1656, 1599, 1454, 1273, 1110, 1025, 873, 857, 840, 697, 518 cm^{-1}.

HRMS Calcd for $C_{26}H_{36}O_3$: 396.2665 **Found**: 396.2678.

(*Z*)-(5*S*,6*S*,10a*S*)-6-Butyl-7,7,10a-trimethyl-1,2,3,5,6,7,10,10a-octahydrobenzocyclooctene-5,6-diol (CM-11b).



Diene **CM-08b** (6 mg, 19 μmol) was dissolved in dichloromethane (2.0 mL). The mixture was thoroughly degassed three times while stirring. Second-generation Grubbs' catalyst (0.8 mg, 1.0 μmol, 5 mol%) was added and the mixture was refluxed for 1 h. The solvent was evaporated at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80) afforded the desired bicycle **CM-11b** (6 mg, quantitative yield) as pale yellow needles. Bicycle **CM-10b** (9.0 mg, 21 μmol) in THF (1.0 mL) was added dropwise to a suspension of $LiAlH_4$ (2.0 mg, 53 μmol, 2.3 equiv) in THF (5 mL) at 0°C, and the resulting mixture was stirred for 15 min at 0°C. Ethyl acetate was then added, and the reaction was quenched by addition of aqueous sodium and potassium tartrate solution (10%, 10 mL), and the mixture was stirred for 3 h. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80) afforded the same bicycle **CM-11b** (5.5 mg, 83% yield) as pale yellow needles.

M.p. 105-107°C.

$[\alpha]^{20}_{D}$: + 28.5 (*c* 1. 0, CH_2Cl_2).

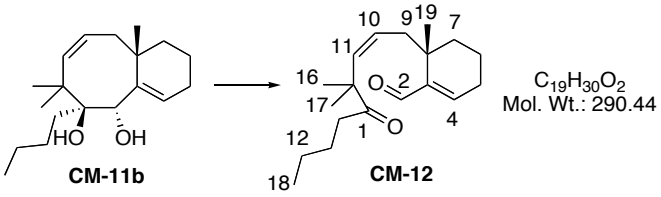
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.96 (dd, 1H, *J* = 4.8 Hz, 2.8 Hz, H-4), 5.62-5.55 (m, 1H, H-10), 5.35 (d, 1H, *J* = 11.7 Hz, H-11), 4.51 (s, 1H, H-2), 2.66-2.38 (sl, 1H, OH), 2.36-1.92 (m, 4H, H-9, H-5), 1.842-1.48 (m, 4H, H-6, H-14), 1.34 (s, 3H, H-19), 1.29-1.24 (m, 6H, H-7, H-13, H-12), 1.18 (s, 3H, H-16 or H-17), 1.15 (s, 3H, H-17 or H-16), 0.91 (t, 3H, *J* = 7.3 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 145.8 (C-3), 140.1 (C-11), 128.8 (C-10), 126.5 (C-4), 81.4 (C-1), 73.0 (C-2), 42.3 (C-8), 38.4 (C-15), 31.4 (C-9), 30.3 (C-19), 29.7 (C-16 or C-17), 28.2 (C-17 or C-16), 27.7 (C-6), 25.6 (C-7), 23.9 (C-5), 22.7 (C-14), 22.3 (C-13), 18.6 (C-12), 14.2 (C-18).

IR (film): 3791, 3477, 2927, 2866, 1718, 1588, 1514, 1452, 1330, 1265, 914, 885, 810, 788, 718, 685, 572 cm^{-1}.

HRMS Calcd for $C_{19}H_{32}O_2$: 292.2402 **Found**: 292.2405.

(*S*)-6-((*Z*)-4,4-Dimethyl-5-oxonon-2-enyl)-6-methylcyclohex-1-enecarbaldehyde (CM-12).



Benzeneseleninic acid (12 mg, 66 μmol, 2.0 equiv) was added to a solution of bicycle **CM-11b** (9.6 mg, 33 μmol) in dichloromethane (5 mL) then second-generation Grubbs' catalyst (2.8 mg, 3.3 μmol, 10 mol%) at 20°C, the mixture was refluxed for 6 h. The solvent was evaporated at reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded keto aldehyde **CM-12** (6.4 mg, 67% yield) as a colorless oil.

$[\alpha]^{20}_{D}$: -7.5 (*c* 0.4, CH_2Cl_2).

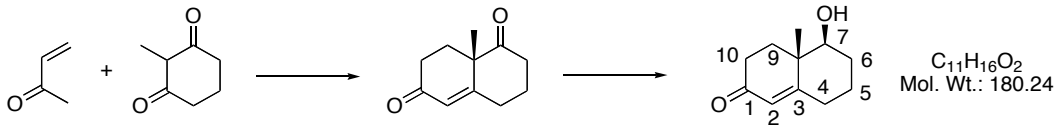
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.32 (s, 1H, H-2), 6.81 (t, 1H, *J* = 3.9 Hz, H-4), 5.45 (dt, 1H, *J* = 11.5 Hz, 2.1 Hz, H-11), 5.19-5.13 (m, 1H, H-10), 2.52 (ddd, 1H, *J* = 15.7 Hz, 5.2 Hz, 2.4 Hz, H-9), 2.46 (t, 2H, *J* = 7.5 Hz, H-14), 2.37-2.27 (m, 2H, H-5), 2.09 (ddd, 1H, *J* = 15.7 Hz, 8.8 Hz, 1.3 Hz, H-9), 1.67-1.58 (m, 4H, H-6, H-13), 1.34-1.25 (m, 4H, H-7, H-12), 1.23 (s, 3H, H-16 or H-17), 1.22 (s, 3H, H-17 or H-16), 1.17 (s, 3H, H-19), 0.90 (t, 3H, *J* = 7.4 Hz, H-18).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 214.3 (C-1), 194.6 (C-2), 155.1 (C-4), 146.8 (C-3), 135.8 (C-11), 129.4 (C-10), 128.0 (C-15), 49.1 (C-8), 37.6 (C-7), 36.7 (C-9), 35.8 (C-6), 27.2 (C-5), 26.5 (C-14), 26.3 (C-16 or C-17), 25.9 (C-17 or C-16), 25.6 (C-19), 22.5 (C-13), 18.0 (C-12), 14.1 (C-18).

IR (film): 3532, 2930, 2869, 2360, 1688, 1516, 1368, 1333, 998, 954, 908, 829, 802, 788, 755, 664, 624, 542, 493 cm^{-1}.

HRMS Calcd for $C_{19}H_{30}O_2$: 290.2246 **Found**: 290.2244.

(4a*S*,5*S*)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (CM-13)



CM-13

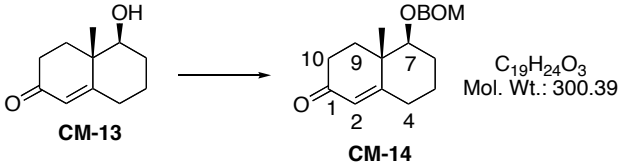
Acetic acid (50 μL), hydroquinone (1.8 mg, 0.16 mmol, 0.02 equiv) and freshly distilled methyl vinyl ketone (2.2 g, 32 mmol, 2.0 equiv) were added to a solution of 2-methyl-1,3-cyclohexanedione (2.0 g, 16 mmol) in distilled water (5 mL) at room temperature. The reaction mixture was stirred for 1 h at 80°C, then cooled to room temperature, treated with NaCl (1.6 g) and diluted with AcOEt (6 mL). The layers were separated, and the aqueous phase was extracted with AcOEt. The combined organic layers were washed twice with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude trione was dissolved in dried DMSO (20 mL) and recrystallized (*L*)-proline (92 mg, 0.8 mmol, 0.05 equiv) was added. The mixture was stirred at room temperature for 6 days. The solvent was then evaporated and the residue was filtered through a pad of silica gel to give the crude Wieland-Miescher ketone. To a solution of crude Wieland-Miescher ketone and (-)-taddol (7.5 g, 16 mmol, 1.0 equiv) in $MeOH/CH_2Cl_2$ (100 mL, 1:1) was added $NaBH_4$ (0.61 g, 32 mmol, 2.0 equiv) at -78°C. The reaction was stirred for 15 min at that temperature, then quenched with acetone, and the resulting mixture was allowed to warm up to room temperature. Water (10 mL) was added and the phases were separated, then the aqueous phase was extracted with dichloromethane. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed under reduced

pressure. Purification of the crude product by flash chromatography (ethyl acetate/petroleum ether: 80/20) afforded **CM-13** (1.7 g, 60% yield over three steps, in 99% enantiomeric excess according to the literature) as a yellow oil; the (-)-taddol was also recovered in quantitative yield.

$[\alpha]^{20}_{D}$: +122.0 (*c* 1.50, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.74 (s, 1H, H-2), 3.38 (dd, 1H, *J* = 11.5, 3.2 Hz, H-7), 2.74-2.58 (br s, 1H, OH), 2.40-2.26 (m, 2H, H-4), 2.19-2.12 (m, 2H, H-10), 1.86-1.76 (m, 3H, CH_2), 1.73-1.65 (m, 2H, CH_2), 1.43-1.34 (m, 1H, CH_2), 1.16 (s, 3H, Me-8).

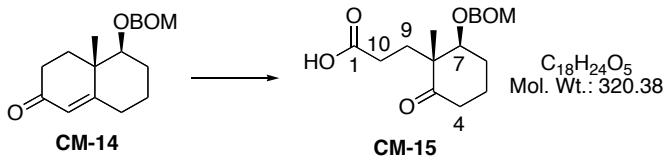
(4a*S*,5*S*)-5-Benzyloxymethoxy-4a-methyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (CM-14)



A solution of **CM-13** (200 mg, 1.12 mmol) in dichloromethane was treated with BOMCl (1.55 mL, 11.2 mmol, 10.0 equiv), TBAI (413 mg, 1.00 equiv), i-Pr_2NEt (2.92 mL, 15.0 equiv) at room temperature and the resulting mixture was stirred for 2 days, then diluted with water and extracted with dichloromethane. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (ethyl acetate/petroleum ether: 50/50) afforded **CM-14** (262 mg, 78% yield) as a pale yellow oil,

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37-7.35 (m, 5H, H-Ar), 5.78 (d, 1H, *J* = 1.8 Hz, H-2), 4.88 (d, 1H, *J* = 7.1 Hz, $BnOCH_2$), 4.76 (d, 1H, *J* = 7.1 Hz, $BnOCH_2$), 4.63 (s, 2H, $PhCH_2$), 3.38 (dd, 1H, *J* = 11.7, 4.3 Hz, H-7), 2.45-2.30 (m, 2H, H-4), 2.25-2.20 (m, 2H, H-10), 2.05-2.01 (m, 2H, CH_2), 1.92-1.84 (m, 2H, CH_2), 1.73-1.63 (m, 1H, CH_2), 1.424-1.32 (m, 1H, CH_2), 1.24 (s, 3H, Me-8).

3-((1*R*,2*S*)-2-Benzyloxymethoxy-1-methyl-6-oxocyclohexyl)propionic acid (CM-15)

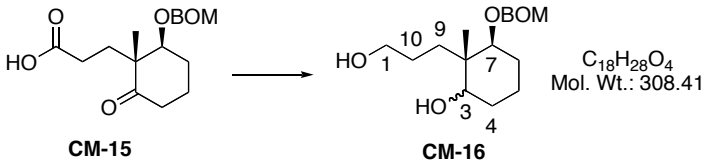


A stream of ozone was passed for 2 h through a solution of **CM-14** (2.00 g, 6.06 mmol) in methanol/dichloromethane (20 mL, 4:1) at -78°C. The reaction was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure to give crude **CM-15** as a colorless oil. The crude product was used for the following step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38-7.29 (m, 5H, H-Ar), 4.84 (d, 1H, *J* = 7.2 Hz, $BnOCH_2$), 4.72 (d, 1H, *J* = 7.2 Hz, $BnOCH_2$), 4.62 (d, 2H, *J* = 2.6 Hz, $PhCH_2$), 3.76 (dd, *J* = 6.9, 3.0 Hz, H-7), 2.40 (t, 2H, *J* = 6.8 Hz, H-4), 2.35 (dd, 1H, *J* = 11.0, 5.3 Hz, H-10), 2.29

(dd, 1H, J = 11.0, 5.3 Hz, H-10), 2.19-2.06 (m, 2H, CH_2), 2.05-2.00 (m, 2H, CH_2), 1.71-1.60 (m, 2H, CH_2), 1.15 (s, 3H, Me-8).

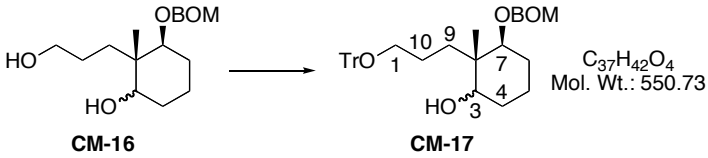
(2*S*,3*S*)-3-Benzyloxymethoxy-2-(3-hydroxypropyl)-2-methylcyclohexanol (CM-16)



A solution of the ketocarboxylic acid **CM-15** in THF (10 mL) was added dropwise at 0°C to a suspension of $LiAlH_4$ (0.58 g, 15.2 mmol, 2.50 equiv) in THF (50 mL). The resulting mixture was then allowed to warm slowly to room temperature, and stirred for 7 h. After cooling to 0°C, water (2 mL), aqueous NaOH (6 N, 2 mL) and water (6 mL) were added, then the mixture was stirred for 45 min. The aluminum salts were filtered off under reduced pressure through a pad of celite then the organic phase was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to afford **CM-16** (1.62 g, 79% over two steps) as a colorless oil as a 1/1 mixture of diastereomers.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.36-7.32 (m, 5H, H-Ar), 4.84 (d, 1H, J = 7.1 Hz, $BnOCH_2$), 4.73 (d, 1H, J = 7.1 Hz, $BnOCH_2$), 4.64 (d, 2H, J = 3.0 Hz, $PhCH_2$), 3.61-3.57 (m, 2H, H-7, H-3), 3.51-3.47 (m, 2H, H-1), 1.84-1.68 (m, 3H, CH_2), 1.61-1.53 (m, 5H, CH_2), 1.30-1.24 (m, 2H, CH_2), 1.01 (s, 3H, Me-8).

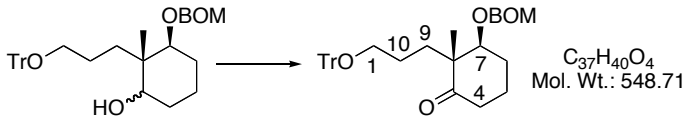
(2*S*,3*S*)-3-Benzyloxymethoxy-2-methyl-2-(3-trityloxypropyl)cyclohexanol (CM-17)



4-Dimethylamino-*N*-triphenylmethyl pyridinium chloride (2.07 g, 3.90 mmol, 1.20 equiv) was added at room temperature to a solution of diol **CM-16** (1.00 g, 3.25 mmol) in dichloromethane (10 mL). The resulting mixture was refluxed overnight. After cooling, diethyl ether (20 mL) was added, and the white salts were filtered off. The solution was dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (diethyl ether/petroleum ether: 30/70 then 40/60) to give **CM-17** (1.48 g, 83% yield) as a colorless oil as a 1/1 mixture of diastereomers.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.46-7.43 (m, 6H, H-Ar), 7.33-7.27 (m, 11H, H-Ar), 7.24-7.21 (m, 3H, H-Ar), 4.83 (d, 1H, J = 7.1 Hz, $BnOCH_2$), 4.73 (d, 1H, J = 7.1 Hz, $BnOCH_2$), 4.61 (s, 2H, $PhCH_2$), 3.55 (d, 1H, J = 4.9 Hz, H-3), 3.48 (dd, 1H, J = 7.3, 3.1 Hz, H-7), 3.06 (t, 2H, J = 6.4 Hz, H-1), 1.78-1.72 (m, 3H, CH_2), 1.64-1.59 (m, 3H, CH_2), 1.47-1.42 (m, 2H, CH_2), 1.31-1.25 (m, 2H, CH_2), 1.04 (s, 3H, Me-8).

(2*R*,3*S*)-3-Benzyloxymethoxy-2-methyl-2-(3-trityloxypropyl)-cyclohexanone (CM-18)

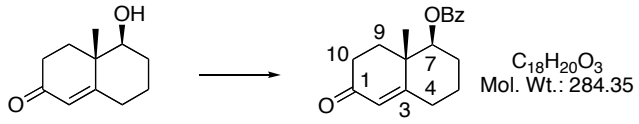


CM-17 **CM-18**

A solution of IBX (154 mg, 0.55 mmol, 1.20 equiv) in DMSO (15 mL) was added slowly at room temperature to a stirred solution of **CM-17** (200 mg, 0.36 mmol) in THF (15 mL). The resulting mixture was stirred at room temperature overnight. When the reaction had gone to completion, water (20 mL) was added then the organic phase was diluted with diethyl ether (10 mL). The biphasic system was stirred for 3 h. The white salts were then filtered off on a pad of celite. The phases were separated and the aqueous phase was extracted with diethyl ether (3*10 mL). The combined organic fractions were washed with water (20 mL) then brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80) afforded the desired **CM-18** (161 mg, 81% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.47-7.45 (m, 6H, H-Ar), 7.37-7.30 (m, 11H, H-Ar), 7.27-7.24 (m, 3H, H-Ar), 4.85 (d, 1H, *J* = 7.2 Hz, $BnOCH_2$), 4.74 (d, 1H, *J* = 7.2 Hz, $BnOCH_2$), 4.64 (d, 2H, *J* = 2.2 Hz, $PhCH_2$), 3.89 (d, 1H, *J* = 3.4 Hz, H-7), 3.12-3.05 (m, 2H, H-1), 2.31-2.51 (m, 2H, H-4), 2.16-1.92 (m, 3H, CH_2), 1.81-1.75 (m, 2H, CH_2), 1.70-1.54 (m, 2H, CH_2), 1.46-1.38 (m, 1H, CH_2), 1.18 (s, 3H, Me-8).

(1*S*,8a*S*)-8a-Methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-yl Benzoate (CM-20)

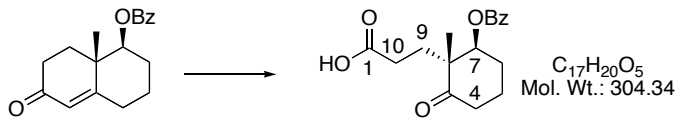


CM-13 **CM-20**

To a solution of **CM-13** (2.52 g, 14.0 mmol) in dichloromethane (20 mL) was added pyridine (2.28 mL, 28.0 mmol, 2.00 equiv) at 0°C, then BzCl (1.95 mL, 16.8 mmol, 1.2 equiv) and a catalytic quantity of DMAP were added. The resulting mixture was stirred for 12 h. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 10 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3*10 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 50/50) afforded **CM-20** (2.88 g, 73% yield) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.70-7.66 (m, 1H, H-Ar), 7.60-7.51 (m, 2H, H-Ar), 7.48-7.44 (m, 2H, H-Ar), 5.86 (d, 1H, *J* = 1.8 Hz, H-2), 4.91 (dd, 1H, *J* = 11.7, 4.5 Hz, H-7), 2.45-2.39 (m, 3H, H-10, H-4), 2.34-2.28 (m, 1H, H-10), 2.08-2.00 (m, 2H, CH_2), 1.94-1.80 (m, 2H, CH_2), 1.64-1.52 (m, 2H, CH_2), 1.43 (s, 3H, Me-8).

(1*S*,2*R*)-2-(2-Carboxyethyl)-2-methyl-3-oxocyclohexyl Benzoate (CM-21)

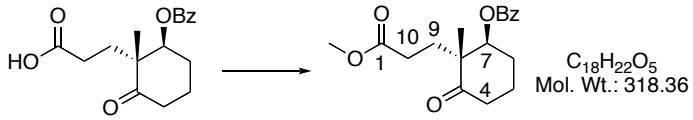


CM-20 CM-21

A stream of ozone was passed for 2 h through a solution of **CM-20** (1.00 g, 3.52 mmol) in methanol (70 mL) at -78°C. The reaction was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure to give crude **CM-21** as a colorless oil. The crude product was used for the following step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.64-7.61 (m, 1H, H-Ar), 7.54-7.46 (m, 2H, H-Ar), 7.41-7.37 (m, 2H, H-Ar), 5.28-5.26 (m, 1H, H-7), 2.56-2.49 (m, 1H, H-4), 2.44-2.32 (m, 3H, H-10, H-4, H-10), 2.22-2.14 (m, 2H, CH_2), 2.10-1.80 (m, 4H, CH_2), 1.11 (s, 3H, Me-8).

(1*S*,2*R*)-2-(2-Methoxycarbonylethyl)-2-methyl-3-oxocyclohexyl Benzoate (CM-22)



CM-21 CM-22

To a solution of **CM-21** and pyridine (0.83 g, 10.6 mmol, 3 equiv) in MeOH was added dropwise $SOCl_2$ (0.30 mL, 4.22 mmol, 1.20 equiv) at 0°C. The mixture was stirred for 1.5 h then concentrated *in vacuo* with a trap of aqueous NaOH solution. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80) yielded **CM-22** (0.83 g, 74% yield over two steps).

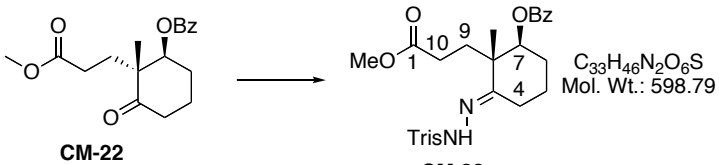
$[\alpha]^{20}_D$: +36.6 (*c* 1.35, CH_2Cl_2).

IR (film): 2954, 2874, 1715, 1600, 1449, 1270, 1173, 1107, 848, 795, 780, 661 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.99-7.97 (m, 2H, H-Ar), 7.58-7.55 (m, 1H, H-Ar), 7.45-7.42 (m, 2H, H-Ar), 5.30 (dd, 1H, *J* = 5.3, 2.8 Hz, H-7), 3.65 (s, 3H, COOMe), 2.60-2.52 (m, 1H, H-4), 2.49-2.34 (m, 2H, H-10, H-4), 2.28-2.16 (m, 2H, H-10, H-9), 2.12-1.84 (m, 5H, H-9, H-6, H-5), 1.15 (s, 3H, Me-8).

HRMS Calcd for $C_{18}H_{22}O_5$: 318.1467. **Found**: 318.1477.

(1*S*,2*R*)-2-(2-Methoxycarbonylethyl)-2-methyl-3-benzoylcyclohexyl-*N'*-(2,4,6-triisopropylbenzenesulfono)hydrazone (CM-23)



CM-22 CM-23

Two drops of concentrated hydrochloric acid were added to a solution of ketone **CM-22** (158 mg, 0.50 mmol) and triisopropylbenzenesulfonyl hydrazine (149 mg, 0.50 mmol, 1.00 equiv)

in THF (5.0 mL). The resulting solution was stirred at room temperature for 2.5 h, and the reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 mL). The phases were separated then the aqueous phase was extracted with diethyl ether (3*10 mL). The combined organic fractions were washed with brine (15 mL) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 50/50) yielded **CM-23** (274 g, 92% yield) as a colorless oil.

$[\alpha]^{20}_{D}$: +71.0 (*c* 1.35, CH_2Cl_2).

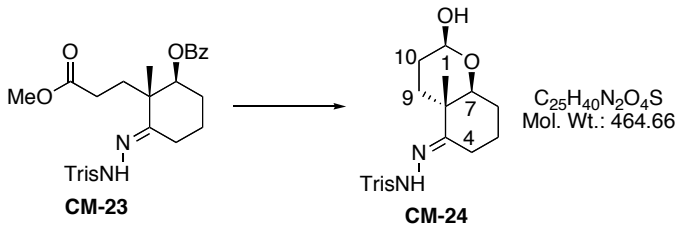
IR (film): 3243, 2958, 2871, 1720, 1600, 1596, 1453, 1319, 1270, 1163, 1110, 1026, 871, 794, 748, 632, 525 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.97 (s, 1H, NH), 7.89-7.86 (m, 2H, H-Ar), 7.53-7.50 (m, 1H, H-Ar), 7.36-7.33 (m, 2H, H-Ar), 7.17 (s, 2H, H-Ar), 5.06 (dd, 1H, *J* = 4.8, 2.7 Hz, H-7), 4.23 (septet, 2H, *J* = 6.7 Hz, Ar-CH), 3.58 (s, 3H, COOMe), 2.89 (septet, 1H, *J* = 6.9 Hz, Ar-CH), 2.53 (dt, 1H, *J* = 15.3, 5.0 Hz, H-4), 2.21-2.01 (m, 3H, H-4, H-10), 1.89-1.82 (m, 2H, H-6), 1.80-1.66 (m, 4H, H-5, H-9), 1.26-1.21 (m, 18H, H-*i*Pr), 0.99 (s, 3H, Me-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 173.7 (C-1), 165.5 (C-3), 158.4 (C-BzC=O), 153.2 (C-Ar), 151.2 (C-Ar), 132.9 (C-Ar), 131.0 (C-Ar), 130.0 (C-Ar), 129.5 (C-Ar), 128.3 (C-Ar), 123.5 (C-Ar), 77.4 (C-7), 51.5 (COOMe), 45.8 (C-8), 34.1 (C- *i*Pr), 31.0 (C-10), 29.8 (C-*i*Pr), 28.1 (C-6), 25.2 (C-9), 24.8 ($CH(CH_3)_2$), 24.7 ($CH(CH_3)_2$), 23.5 ($CH(CH_3)_2$), 23.4 ($CH(CH_3)_2$), 22.2 (C-4), 19.9 (C-5), 19.3 (Me-8).

HRMS Calcd for $C_{33}H_{46}N_2O_4S$: 598.3077. **Found**: 598.3081.

(2*S*,4a*R*,8a*S*)-2-Hydroxy-4a-methyloctahydrochromen-5-*N'*-(2,4,6-triisopropylbenzenesulfono)hydrazone (CM-24)



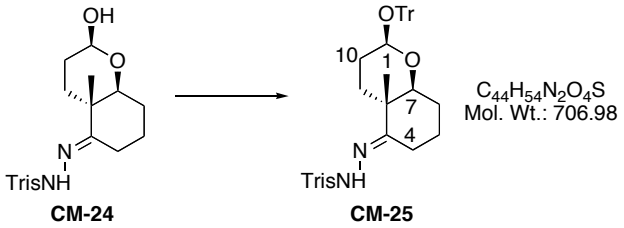
To a solution of **CM-23** (117 mg, 0.20 mmol) in dichloromethane (10 mL) was added dropwise DIBALH (0.80 mL, 1 M in hexanes, 0.80 mmol, 4.00 equiv) at -78°C, then the temperature was allowed to warm up to 0°C. The reaction was stirred at that temperature for 1 h and quenched with MeOH and a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*10 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded **CM-24** (45.0 mg, 49% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.16 (s, 2H, H-Ar), 4.19 (septet, 2H, *J* = 6.8 Hz, Ar-CH), 4.11 (d, 1H, *J* = 9.8 Hz, H-7), 3.22 (dd, 1H, *J* = 10.3, 5.8 Hz, H-1), 2.90 (septet, 1H, *J* = 6.9 Hz, Ar-CH), 2.62 (dt, 1H, *J* = 14.3, 7.1 Hz, H-4), 2.18 (ddd, 1H, *J* = 14.3, 5.3, 1.8 Hz, H-

4), 2.00-1.92 (m, 1H, H-10), 1.78-1.65 (m, 5H, H-10, H-6, H-9), 1.54-1.44 (m, 2H, H-5), 1.26-1.22 (m, 18H, H-*i*Pr), 1.14 (s, 3H, Me-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 213.3 (C-3), 153.2 (C-Ar), 151.5 (C-Ar), 131.1 (C-Ar), 123.7 (C-Ar), 89.1 (C-1), 80.0 (C-7), 77.2, 48.6 (C-8), 36.4 (C-4), 34.1 (C-*i*Pr), 29.8 (C-*i*Pr), 29.6 (C-6), 25.9 (C-10), 25.2 (C-9), 24.9 ($CH(CH_3)_2$), 24.8 ($CH(CH_3)_2$), 20.7 (C-5), 16.1 (Me-8).

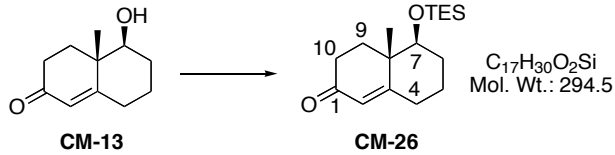
(2*R*,4a*R*,8a*S*)-4a-Methyl-2-trityloxyoctahydrochromen-5-*N'*-(2,4,6-triisopropylbenzenesulfono)hydrazone (CM-25)



4-Dimethylamino-*N*-triphenylmethyl pyridinium chloride (51.0 mg, 0.13 mmol, 1.30 equiv) was added at room temperature to a solution of **CM-24** (450.0 mg, 0.10 mmol) in dichloromethane (10 mL). The resulting mixture was refluxed overnight. After cooling, diethyl ether (20 mL) was added, and the white salts were filtered off. The solution was dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (diethyl ether/petroleum ether: 30/70 then 40/60) to give **CM-25** (42 mg, 61% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.98 (s, 1H, NH), 7.35-7.24 (m, 15H, H-Ar), 7.18 (s, 2H, H-Ar), 4.18 (septet, 2H, J = 6.7 Hz, Ar-CH), 4.01 (d, 1H, J = 12.0, 4.2 Hz, H-7), 3.22 (dd, 1H, J = 10.3, 5.8 Hz, H-1), 2.93 (septet, 1H, J = 6.9 Hz, Ar-CH), 2.62 (m, 2H, H-4), 2.05-1.91 (m, 4H, H-10, H-6), 1.82-1.68 (m, 4H, H-5, H-9), 1.28-1.24 (m, 18H, H-*i*Pr), 1.03 (s, 3H, Me-8).

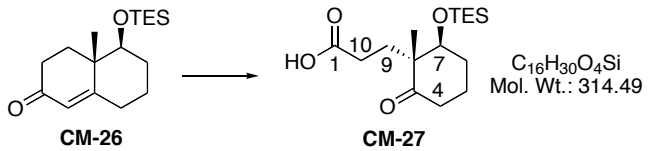
(4a*S*,5*S*)-4a-Methyl-5-triethylsiloxy-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (CM-26)



To a solution of **CM-13** (4.30 g, 30.7 mmol) in dichloromethane (10 mL) was added imidazole (5.23 g, 76.8 mmol, 2.50 equiv) and TESCl (6.90 g, 46.1 mmol, 1.50 equiv). The mixture was stirred for 12 h at room temperature, then quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded **CM-26** (6.32 g, 90%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.76 (s, 1H, H-1), 3.39 (dd, 1H, *J* = 10.6, 5.2 Hz, H-7), 2.42-2.36 (m, 2H, H-4), 2.33-2.27 (m, 1H, H-10), 2.21-2.08 (m, 2H, H-10, CH_2), 1.86-1.80 (m, 1H, CH_2), 1.76-1.70 (m, 2H, CH_2), 1.42-1.30 (m, 2H, CH_2), 1.16 (s, 3H, Me-8), 0.95 (t, 9H, *J* = 7.9 Hz, H-TES), 0.59 (q, 6H, *J* = 7.9 Hz, H-TES).

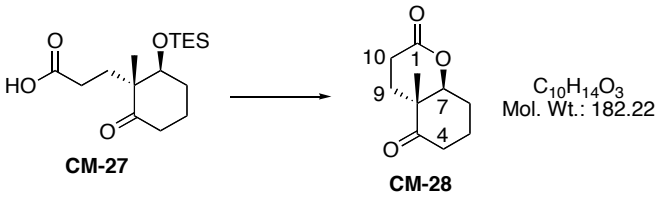
3-((1*R*,6*S*)-1-Methyl-2-oxo-6-triethylsiloxycyclohexyl)propionic Acid (CM-27)



A stream of ozone was passed for 2 h through a solution of **CM-26** (2.0 g, 6.37 mmol) in methanol (70 mL) at -78°C. The reaction was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure to give crude **CM-27** as a colorless oil. The crude product was used for the following step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.30-10.10 (br s, 1H, COOH), 3.82 (dd, 1H, *J* = 6.0, 2.0 Hz, H-7), 2.41-2.25 (m, 3H, H-4, H-10), 2.16-2.07 (m, 1H, H-10), 2.06-1.94 (m, 3H, CH_2), 1.78-1.65 (m, 3H, CH_2), 1.03 (s, 3H, Me-8), 0.90 (t, 9H, *J* = 7.9 Hz, H-TES), 0.54 (q, 6H, *J* = 7.9 Hz, H-TES).

(4a*R*,8a*S*)-4a-Methylhexahydrochromene-2,5-dione (CM-28)



To a solution of crude **CM-27** in dichloromethane (10 mL) was added a catalytic quantity of PPTS. The mixture was stirred for 1 h at room temperature, and then quenched with a saturated $NaHCO_3$ aqueous solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired **CM-28** (1.04 g, 90% over two steps) as a colorless oil.

$[\alpha]^{20}_D$: -41.3 (*c* 1.50, CH_2Cl_2).

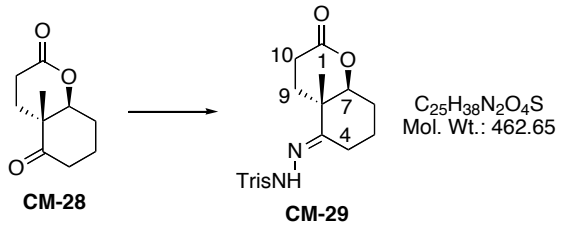
IR (film): 4197, 3465, 3059, 2963, 2883, 2306, 1743, 1454, 1425, 1380, 1216, 1184, 1053, 1015, 892, 821, 711, 659, 607 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.11 (dd, 1H, *J* = 11.6, 4.5 Hz, H-7), 2.61-2.45 (m, 3H, H-4, H-10), 2.20-2.10 (m, 2H, H-10, H-6), 2.00-1.85 (m, 3H, H-5, H-6), 1.68-1.63 (m, 1H, H-9), 1.54-1.40 (m, 1H, H-9), 1.11 (s, 3H, Me-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 210.1 (C-3), 170.5 (C-1), 81.0 (C-7), 47.9 (C-8), 36.1 (C-9), 26.6 (C-5), 26.2 (C-6), 25.5 (C-10), 19.7 (C-4), 16.3 (Me-8).

HRMS Calcd for $C_{10}H_{14}O_3$: 182.0943. **Found**: 182.0945.

(4a*R*,8a*S*)-4a-Methylhexahydrochromene-2-one-5-*N'*-(2,4,6-triisopropylbenzenesulfono)hydrazone (CM-29)

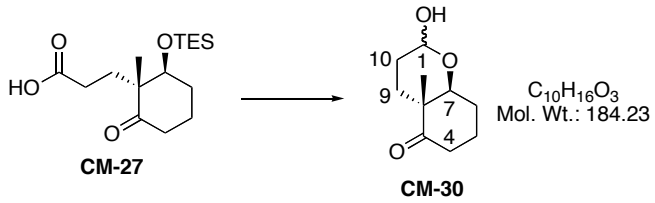


Two drops of concentrated hydrochloric acid were added to a solution of ketone **CM-28** (60 mg, 0.33 mmol) and triisopropylbenzenesulfonyl hydrazine (100 mg, 0.33 mmol, 1.00 equiv) in THF (5.0 mL). The resulting solution was stirred at room temperature for 1 h, and the reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 mL). The phases were separated then the aqueous phase was extracted with diethyl ether (3*10 mL). The combined organic fractions were washed with brine (15 mL) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80) yielded **CM-29** (132 mg, 87% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.33 (s, 1H, NH), 7.15 (s, 2H, H-Ar), 4.17 (septet, 2H, *J* = 6.7 Hz, Ar-CH), 3.99 (dd, 1H, *J* = 12.0, 4.2 Hz, H-7), 2.89 (septet, 1H, *J* = 6.9 Hz, Ar-CH), 2.68 (dt, 1H, *J* = 14.6, 5.0 Hz, H-4), 2.56-2.51 (m, 2H, H-10), 2.00-1.88 (m, 4H, H-4, H-9, H-6, H-7), 1.76-1.65 (m, 2H, H-6, H-7), 1.34-1.28 (m, 1H, H-9), 1.24-1.22 (m, 18H, H-*i*Pr), 1.01 (s, 3H, Me-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 171.1 (C-1), 158.4 (C-Ar), 153.2 (C-Ar), 151.0 (C-3), 130.8 (C-Ar), 123.4 (C-Ar), 82.3 (C-7), 41.4 (C-8), 33.9 (C-*i*Pr), 29.5 (C-*i*Pr), 28.6 (C-6), 26.9 (C-10), 26.0 (C-5), 24.7 ($C-CH(CH_3)_2$), 24.5 ($C-CH(CH_3)_2$), 23.4 ($C-CH(CH_3)_2$), 23.4 ($C-CH(CH_3)_2$), 21.7 (C-4), 20.7 (C-9), 16.8 (Me-8).

(4a*R*,8a*S*)-2-Hydroxy-4a-methyloctahydrochromen-5-one (CM-30)

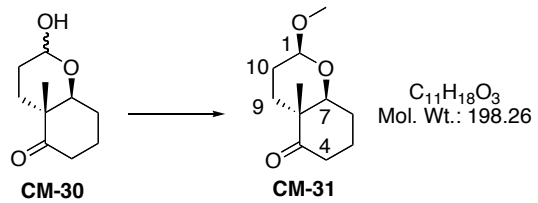


To a solution of DMF (5.88 mL, 76.5 mmol, 10.0 equiv) in anhydrous CH_2Cl_2 (20 mL) was added oxalyl chloride (2.00 mL, 23.0 mmol, 3.00 equiv) at -20°C. After 90 min, the mixture was concentrated under reduced pressure. Dry acetonitrile (10 mL) and THF (25 mL) were added at -30°C and a solution of **CM-27** (2.43 g, 7.65 mmol) in THF (10 mL) and pyridine (2 mL) was added dropwise. The resulting mixture was stirred for 90 min at -30°C, cooled to -

78°C and a solution of copper iodide (10 mol%) and tri-tert-butoxyaluminum hydride (3.89 g, 15.3 mmol, 2.00 equiv) in THF (15 mL) was added. After stirring for 15 min, the reaction was quenched with 7% aqueous HBr solution (15 mL). The resulting mixture was allowed to warm up to room temperature and basified with 30% aqueous NaOH solution (5 mL). The aqueous layer was extracted with diethyl ether. The combined extracts were washed with saturated aqueous sodium hydrogencarbonate solution, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (diethyl ether/petroleum ether 20/80) to give **CM-30** (704 mg, 50% yield) as a 1/1 mixture of diastereomers.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.24 (s, 0.5H, H-1), 4.72 (d, 0.5H, *J* = 10.3 Hz, H-1), 4.01 (dd, 0.5H, *J* = 12.0, 4.2 Hz, H-7), 3.58-3.54 (br s, 0.5H, OH), 3.37 (dd, 0.5H, *J* = 11.6, 4.2 Hz, H-7), 2.87-2.84 (br s, 0.5H, H-OH), 2.62 (dt, 1H, *J* = 14.4, 7.0 Hz, H-4), 2.23-2.16 (m, 1H, H-4), 2.02-1.92 (m, 1.5H, CH_2), 1.91-1.77 (m, 3H, CH_2), 1.74-1.68 (m, 1.5H, CH_2), 1.63-1.52 (m, 2H, CH_2), 1.25 (s, 1.5H, Me-8), 1.21 (s, 1.5H, Me-8).

(2*S*,4a*R*,8a*S*)-2-Methoxy-4a-methyloctahydrochromen-5-one (CM-31)



A solution of **CM-30** (515 mg, 2.8 mmol) in dichloromethane (10 mL) was treated with silver (I) oxide (650 mg, 2.8 mmol, 1.00 equiv) and excess methyl iodide (0.55 mL). The black suspension was stirred overnight at room temperature, then filtered through a cotton plug and concentrated *in vacuo*. The residue was purified by flash chromatography (diethyl ether/petroleum ether 10/90) to give **CM-31** (499 mg, 90% yield) as a colorless oil.

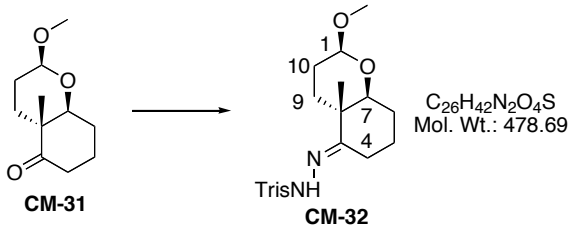
IR (film): 3682, 3510, 3403, 2854, 2747, 2641, 2251, 2140, 1915, 1736, 1431, 1337, 1264, 1247, 1080, 984, 953, 914, 856, 778, 730, 565 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.16 (dd, 1H, *J* = 9.6, 2.3 Hz, H-1), 3.36 (s, 3H, H-OMe), 3.20 (dd, 1H, *J* = 11.5, 4.3 Hz, H-7), 2.54 (dt, 1H, *J* = 14.5, 7.1 Hz, H-4), 2.23-2.16 (ddd, 1H, *J* = 14.7, 4.9, 1.5 Hz, H-4), 1.91-1.84 (m, 1H, C-10), 1.82-1.72 (m, 2H, C-6), 1.64-1.58 (m, 3H, C-9, C-5), 1.53-1.35 (m, 2H, C-5, C-10), 1.11 (s, 3H, Me-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 213.1 (C-3), 103.6 (C-1), 79.0 (C-7), 56.1 (C-OMe), 48.4 (C-8), 36.2 (C-4), 29.0 (C-9), 27.0 (C-5), 25.7 (C-6), 20.6 (C-10), 16.0 (Me-8).

HRMS Calcd for $C_{11}H_{18}O_3$: 198.1256. **Found**: 198.1255.

(2*S*,4a*R*,8a*S*)-2-Methoxy-4a-methyloctahydrochromen-5-*N'*-(2,4,6-triisopropylbenzenesulfono)hydrazone (CM-32)



Two drops of concentrated hydrochloric acid were added to a solution of ketone **CM-31** (499 mg, 2.55 mmol) and triisopropylbenzenesulfonyl hydrazine (912 mg, 3.06 mmol, 1.20 equiv) in THF (5.0 mL). The resulting solution was stirred at room temperature for 1 h, and the reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 5 mL). The phases were separated then the aqueous phase was extracted with diethyl ether (3*10 mL). The combined organic fractions were washed with brine (15 mL) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80) yielded **CM-32** (1.22 g, quantitative yield).

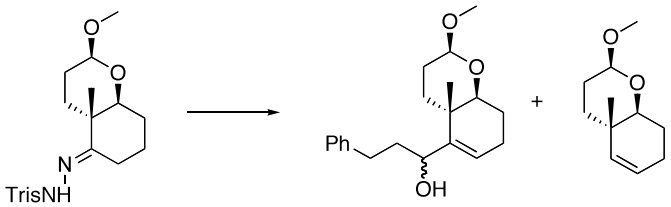
IR (film): 3240, 2954, 2872, 2836, 2752, 2635, 1712, 1629, 1596, 1550, 1453, 1384, 1326, 1252, 1203, 1160, 1067, 912, 730, 653, 584 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.67 (s, 1H, NH), 7.15 (s, 2H, H-Ar), 4.22-4.14 (m, 3H, Ar-CH, H-7), 3.45 (s, 3H, H-OMe), 3.11 (dd, 1H, *J* = 10.3, 5.6 Hz, H-1), 2.91 (septet, 1H, *J* = 6.9 Hz, Ar-CH), 2.56-2.50 (m, 1H, H-4), 2.01-1.96 (m, 1H, H-4), 1.92-1.87 (m, 2H, H-10), 1.72-1.66 (m, 2H, H-6), 1.64-1.51 (m, 4H, H-5, H-9), 1.26-1.22 (m, 18H, H-*i*Pr), 1.01 (s, 3H, Me-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 161.6 (C-Ar), 153.2 (C-Ar), 151.1 (C-3), 131.2 (C-Ar), 123.5 (C-Ar), 104.0 (C-1), 79.4 (C-7), 56.3 (C-OMe), 42.0 (C-8), 34.1 (C-*i*Pr), 31.3 (C-9), 29.8 (C-*i*Pr), 27.5 (C-5), 26.1 (C-6), 24.8 (C-$CH(CH_3)_2$), 24.7 (C-$CH(CH_3)_2$), 23.6 (C-$CH(CH_3)_2$), 23.5 (C-$CH(CH_3)_2$), 21.6 (C-10), 21.5 (C-4), 17.3 (Me-8).

HRMS Calcd for $C_{26}H_{42}N_2O_4$: 478.2865. **Found**: 478.2855.

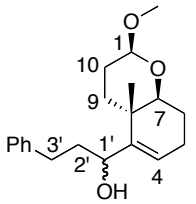
1-((2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromen-5-yl)-3-phenylpropan-1-ol (CM-33) and **(2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromene (CM-34)**



tert-Butyllithium (0.33 mL, 0.46 mmol, 2.20 equiv, titrated at 1.40 M) was added dropwise to a solution of hydrazone **CM-32** (100 mg, 0.21 mmol) in THF (10 mL) at -78°C. The solution turned red and was stirred at -78°C for 30 min until the color turned dark red, then the temperature was allowed to warm to 0°C. When nitrogen evolution was finished and the color had turned to red, the solution was cooled again to -78°C. A cooled solution of hydrocinnamaldehyde (30.5 μL, 0.23 mmol, 1.10 equiv) in THF (5.0 mL) was added

dropwise *via* cannula. The resulting mixture was stirred at -78 °C for 30 min. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 10 mL). The phases were separated then the aqueous phase was extracted with diethyl ether (3*15 mL). The combined organic fractions were washed with brine (20 mL) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/100) yielded **CM-33** (27 mg, 42% yield) and **CM-34** (9.8 mg, 26% yield) as pale yellow oils.

CM-33



$C_{20}H_{28}O_3$
Mol. Wt.: 316.43

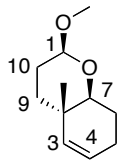
IR (film): 3041, 2957, 2863, 1451, 1434, 1281, 1266, 1250, 1065, 936, 787, 686, 664 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.30-7.26 (m, 2H, H-Ar), 7.21-7.18 (m, 3H, H-Ar), 5.70-5.68 (m, 1H, H-4), 4.37-4.32 (m, 1H, H-1'), 4.17-4.10 (m, 1H, H-1), 3.52 (s, 1.5 H, OMe), 3.51 (s, 1.5 H, OMe), 3.35-3.27 (m, 1H, H-7), 2.88-2.72 (m, 1H, H-3'), 2.68-2.58 (m, 1H, H-3'), 2.25-2.18 (m, 2H, H-5), 1.95-1.82 (m, 3H, H-6, H-2'), 1.78-1.65 (m, 3H, H-10, H-2'), 1.62-1.52 (m, 1H, H-9), 1.40-1.30 (m, 1H, H-9), 1.19 (s, 1.5H, Me-8), 1.10 (s, 1.5H, Me-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 148.2 (C-Ar), 146.8 (C-Ar), 142.0 (C-3), 141.9 (C-3), 128.4 (C-Ar), 128.4 (C-Ar), 125.8 (C-Ar), 121.4 (C-4), 121.2 (C-4), 103.9 (C-1'), 103.9 (C-1'), 78.9 (C-7), 78.7 (C-7), 69.4 (C-1), 69.0 (C-1), 56.3 (C-OMe), 56.3 (C-OMe), 39.6 (C-6), 39.3 (C-6), 36.5 (C-8), 36.2 (C-8), 32.7 (C-3), 32.5 (C-3), 32.4 (C-2'), 27.7 (C-9), 27.7 (C-9), 24.5 (C-5), 24.4 (C-5), 23.5 (C-10), 19.7 (Me-8), 19.6 (Me-8).

HRMS Calcd for $C_{20}H_{28}O_3$: 316.2039. **Found**: 316.2027.

CM-34



$C_{11}H_{18}O_2$
Mol. Wt.: 182.26

IR (film): 3041, 2985, 2956, 2844, 1449, 1388, 1250, 1159, 1109, 1062, 1010, 949, 686, 665 cm^{-1}.

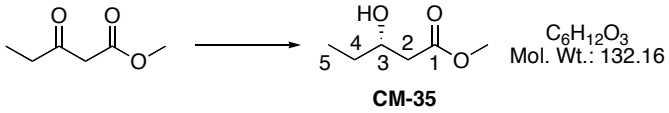
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.46-5.40 (m, 2H, H-3. H-4), 4.38 (dd, 1H, J = 8.4, 4.2 Hz, H-1), 3.52 (s, 3H, OMe), 3.28 (dd, 1H, J = 11.7, 4.4 Hz, H-7), 2.20-2.16 (m, 2H, H-5),

1.80-1.67 (m, 4H, H-6, H-10), 1.60-1.55 (m, 1H, H-9), 1.46-1.38 (m, 1H, H-9), 1.05 (s, 3H, Me-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 135.5 (C-4), 124.5 (C-3), 104.4 (C-1), 78.5 (C-7), 56.4 (C-OMe), 35.0 (C-9), 34.2 (C-8), 27.9 (C-10), 25.4 (C-5), 23.7 (C-6), 19.6 (Me-8).

HRMS Calcd for $C_{11}H_{18}O_2$: 182.1307. **Found**: 182.1316.

Methyl (*S*)-3-Hydroxypentanoate (CM-35)

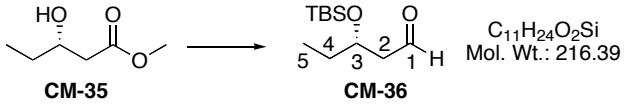


$[RuCl_2(PhH)_2]_2$ (48.1 mg, 0.074 mmol, 0.025 equiv) and (*S*)-(-)-BINAP (92.5 mg, 0.148 mmol, 0.05 equiv) were dissolved in dried DMF (3 mL) and stirred at 110°C for 20 min. A solution of methyl 3-oxovalerate (3.86 g, 29.6 mmol) in degassed methanol (12 mL) was added to the catalyst solution and the mixture was transferred to the hydrogenation reactor. The solution was treated at 110°C under 10 atm H_2 and vigorously stirred for 12 h. After cooling to room temperature, the dark red solution was concentrated *in vacuo* and purified by flash chromatography (diethyl ether/petroleum ether: 20/80) to afford **CM-35** (3.90 g, quantitative yield, in 99% enantiomeric excess according to the literature) as a colorless oil.

$[\alpha]^{20}_D$: -30.5 (*c* 1.60, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.98-3,90 (m, 1H, H-3), 3.71 (s, 3H, COOMe), 2.87 (d, 1H, *J* = 4.0 Hz, OH), 2.53 (dd, 1H, *J* = 16.4, 3.1 Hz, H-2), 2.41 (dd, 1H, *J* = 16.4, 8.9 Hz, H-2), 1.59-1.47 (m, 2H, H-4), 0.96 (t, 3H, *J* = 7.5 Hz, H-5).

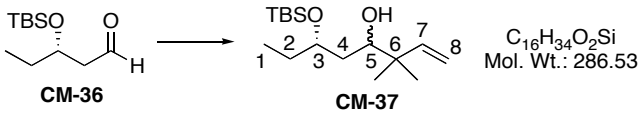
(*S*)-3-(*tert*-Butyldimethylsiloxy)pentanal (CM-36)



To a solution of **CM-35** (51.6 mg, 1.63 mmol) in DMF (5 mL) was added imidazole (276 mg, 4.06 mmol, 2.50 equiv) and TBSCl (366 mg, 2.44 mmol, 1.50 equiv). The mixture was stirred for 2 h at room temperature, then quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. To a solution of the crude product in dichloromethane (10 mL) was added dropwise DIBALH (2.3 mL, 1 M in hexanes, 2.27 mmol, 1.40 equiv) at -78°C. After stirring for 15 min at that temperature, the reaction was quenched with MeOH then with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired **CM-36** (351 mg, quantitative yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.81 (t, 1H, *J* = 2.5 Hz, H-1), 4.16-4.10 (m, 1H, H-3), 2.52-2.50 (m, 2H, H-2), 1.60-1.53 (m, 2H, H-4), 0.90 (t, 3H, *J* = 7.5 Hz, H-5), 0.87 (s, 9H, Si*t*-Bu), 0.07 (s, 3H, SiMe), 0.05 (s, 3H, SiMe).

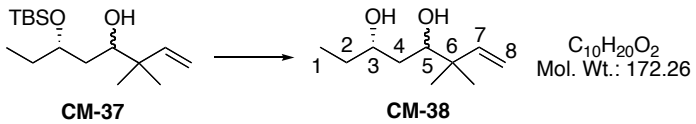
(*S*)-6-(*tert*-Butyldimethylsiloxy)-3,3-dimethyloct-1-en-4-ol (CM-37)



Freshly prepared 1-bromo-3-methylbut-2-ene (0.05 mL, 0.39 mmol, 1.20 equiv) was added to a solution of **CM-36** (71 mg, 0.33 mmol) in THF (5 mL). This was followed by the addition of aqueous ammonium chloride (sat., 10 mL). The resulting mixture was cooled to 0°C, and activated zinc dust (64.7 mg, 0.99 mmol, 3.00 equiv) was added slowly. The mixture was then stirred vigorously at room temperature for 1 h (no inert atmosphere is necessary). After completion of the reaction, the mixture was filtered through a pad of celite, the two phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95) afforded the desired **CM-37** (86.7 mg, 92%) as a colorless oil as a 7/3 mixture of *anti/syn* diastereomers.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.89-5.81 (m, 1H, H-7), 5.03-4.98 (m, 2H, H-8), 3.91-3.82 (m, 1H, H-3), 3.64 (dd, 0.7H, *J* = 10.6, 1.7 Hz, H-5 (*anti*-product)), 3.40 (d, 0.3H, *J* = 9.8 Hz, H-5 (*syn*-product)), 3.24 (s, 0.7H, OH (*anti*-product)), 3.00 (s, 0.3H, OH (*syn*-product)), 1.62-1.42 (m, 4H, H-4, H-2), 1.00-0.99 (m, 6H, Me-6), 0.89-0.88 (m, 9H, Si*t*-Bu), 0.87-0.82 (m, 3H, H-1), 0.10 (s, 0.9H, SiMe (*syn*-product)), 0.08 (s, 0.9H, SiMe (*syn*-product)), 0.07 (s, 2.1H, SiMe (*anti*-product)), 0.06 (s, 2.1H, SiMe (*anti*-product)).

(*S*)-6,6-Dimethyloct-7-ene-3,5-diol (CM-38)

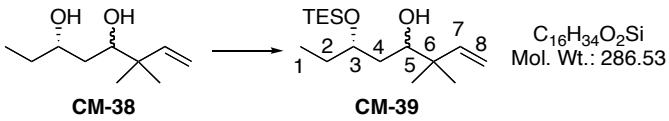


To a solution of **CM-37** (1.02 g, 3. 56 mmol) in ethyl acetate was added HF/MeCN (15 ml, 5/95) at room temperature. After stirring for 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired **CM-38** (552 mg, 90%) as a colorless oil as a 85/15 mixture of *anti/syn* diastereomers.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.83 (dd, 0.85H, *J* = 17.5, 10.8 Hz, H-7 *anti*-product), 5.83 (dd, 0.15H, *J* = 17.6, 10.8 Hz, H-7 *syn*-product), 5.12-5.04 (m, 2H, H-8), 3.81 (tt, 0.85H, *J* = 11.4, 6.2 Hz, H-3 *anti*-product), 3.75-3.71 (m, 0.15H, H-3 *syn*-product), 3.65 (dd, 0.85H,

J = 8.3, 4.5 Hz, H-5 *anti*-product), 3.55 (dd, 0.15H, *J* = 10.7, 1.7 Hz, H-5 *syn*-product), 2.08-2.05 (br s, 2H, OH), 1.59-1.48 (m, 4H, H-4, H-2), 1.02-1.01 (m, 6H, Me-6), 0.95 (t, 2.55H, *J* = 7.5 Hz, H-1 *anti*-product), 0.94 (t, 0.45H, *J* = 7.5 Hz, H-1 *syn*-product).

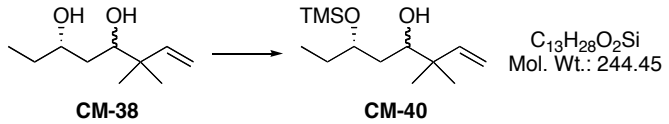
(*S*)-3,3-Dimethyl-6-triethylsiloxyoct-1-en-4-ol (CM-39)



To a solution of **CM-38** (51.6 mg, 0.30 mmol) in dichloromethane (5 mL) was added DMAP (40.3 mg, 0.33 mmol, 1.10 equiv) and TESCl (0.053 mL, 0.32 mmol, 1.05 equiv). The mixture was stirred for 2 h at room temperature, then quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded **CM-39** (84.0 mg, 98%) as a colorless oil as a 3/1 mixture of *anti/syn* diastereomers.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.86 (dd, 0.75H, *J* = 17.5, 10.9 Hz, H-7 *anti*-product), 5.86 (dd, 0.25H, *J* = 17.4, 11.0 Hz, H-7 *syn*-product), 5.05-4.99 (m, 2H, H-8), 3.92-3.83 (m, 1H, H-3), 3.65 (dt, 0.75H, *J* = 10.5, 1.9 Hz, H-5 *anti*-product), 3.43 (dt, 0.25H, *J* = 10.2, 1.7 Hz, H-5 *syn*-product), 3.36 (d, 0.75H, *J* = 1.9 Hz, OH *anti*-product), 3.32 (d, 0.25H, *J* = 1.7 Hz, OH *syn*-product), 1.62-1.43 (m, 4H, H-4, H-2), 1.01-1.00 (m, 6H, Me-6), 0.99-0.94 (m, 9H, H-TES), 0.86 (t, 0.75H, *J* = 7.5 Hz, H-1 *syn*-product), 0.85 (t, 2.25H, *J* = 7.5 Hz, H-1 *syn*-product), 0.65-0.58 (m, 6H, H-TES).

(*S*)-3,3-Dimethyl-6-trimethylsiloxyoct-1-en-4-ol (CM-40)



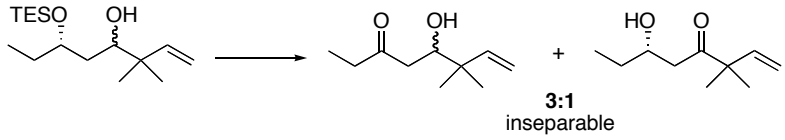
To a solution of **CM-38** (136 mg, 0.79 mmol) in dichloromethane (5 mL) was added DMAP (106 mg, 0.87 mmol, 1.10 equiv) and TMSCl (0.104 mL, 0.83 mmol, 1.05 equiv). The mixture was stirred for 1 h at room temperature, then quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired **CM-40** (192 mg, quantitative yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.86 (dd, 0.1H, *J* = 17.3, 11.1 Hz, H-7 *syn*-product), 5.85 (dd, 0.9H, *J* = 17.5, 10.9 Hz, H-7 *anti*-product), 5.06-5.00 (m, 2H, H-8), 3.90-3.85 (m, 1H, H-3), 3.60 (dd, 0.9H, *J* = 10.6, 1.5 Hz, H-5 *anti*-product), 3.42 (dt, 0.1H, *J* = 10.0, 0.6 Hz, H-5 *syn*-product), 3.01 (s, 0.1H, OH *syn*-product), 2.96 (s, 0.9H, OH *anti*-product), 1.62-1.42

(m, 4H, H-4, H-2), 1.01-1.00 (m, 6H, Me-6), 0.88-0.84 (m, 3H, H-1), 0.15 (m, 0.9H, H-TMS *syn*-product), 0.13 (m, 8.1H, H-TMS *anti*-product).

Oxidation product of CM-39

5-Hydroxy-6,6-dimethyloct-7-en-3-one (CM-41) and **(*S*)-6-Hydroxy-3,3-dimethyloct-1-en-4-one (CM-42)**

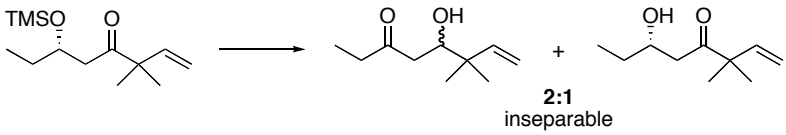


A solution of IBX (73 mg, 0.26 mmol, 1.20 equiv) in DMSO (10 mL) was added slowly at room temperature to a stirred solution of **CM-39** (62 mg, 0.22 mmol) in THF (10 mL). The resulting mixture was stirred in the dark at room temperature overnight. When the reaction was complete, water (10 mL) was added then the organic phase was diluted with diethyl ether (10 mL). The biphasic system was stirred for at least 3 h. The white salts were then filtered off through a pad of celite. The aqueous phase was extracted with diethyl ether (3*10 mL) then the combined organic fractions were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95 then 10/90) afforded an inseparable mixture **CM-41** and **CM-42** (4.9 mg, 8%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.89 (dd, 0.25H, *J* = 17.3, 10.8 Hz, H-7 **CM-42**), 5.83 (dd, 0.75H, *J* = 17.5, 10.9 Hz, H-7 **CM-41**), 5.19-5.10 (m, 0.5H, H-8 **CM-42**), 5.08-5.02 (m, 1.5H, H-8 **CM-41**), 3.92-3.86 (m, 0.25H, H-3 **CM-42**), 3.82 (dd, 0.75H, *J* = 10.2, 2.0 Hz, H-5 **CM-41**), 2.66-2.38 (br s, 1H, OH), 2.36-1.92 (m, 2H), 1.64-1.42 (m, 1H), 1.34-1.27 (m, 1H), 1.25-1.23 (m, 1.5H), 1.07-1.03 (m, 4.5H), 0.96-0.86 (m, 3H, H-1).

Oxidation product of CM-40

5-Hydroxy-6,6-dimethyloct-7-en-3-one (CM-41) and **(*S*)-6-Hydroxy-3,3-dimethyloct-1-en-4-one (CM-42)**

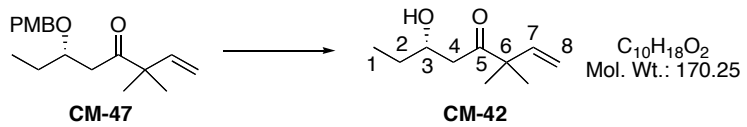


A solution of IBX (121 mg, 0.43 mmol, 1.4 equiv) in DMSO (10 mL) was added slowly at room temperature to a stirred solution of **CM-40** (75 mg, 0.31 mmol) in THF (10 mL). The resulting mixture was stirred in the dark at room temperature overnight. When the reaction was complete, water (10 mL) was added then the organic phase was diluted with diethyl ether (10 mL). The biphasic system was stirred for at least 3 h. The white salts were then filtered off through a pad of celite. The aqueous phase was extracted with diethyl ether (3*10 mL) then the combined organic fractions were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95 then 10/90) afforded an inseparable mixture **CM-41** and **CM-42** (15.0 mg, 29%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.89 (dd, 0.33H, *J* = 17.3, 10.8 Hz, H-7 **CM-42**), 5.83 (dd, 0.66H, *J* = 17.5, 10.9 Hz, H-7 **CM-41**), 5.18-5.14 (m, 0.66H, H-8 **CM-42**), 5.08-5.01 (m, 1.32H, H-8 **CM-41**), 3.91-3.85 (m, 0.33H, H-3 **CM-42**), 3.82 (dd, 0.66H, *J* = 10.2, 2.0 Hz, H-5 **CM-41**), 2.70-2.39 (m, 3.33H, H-4 **CM-42**, H-2, H-4, **CM-41**), 1.38-1.54 (m, 1H), 1.26-1.22 (m, 2.32H), 1.07-1.02 (m, 4.33H), 0.95-0.84 (m, 3H, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 214.8 (C-5, **CM-42**), 212.8 (C-3, **CM-41**), 144.7 (C-7, **CM-41**), 141.9 (C-7, **CM-42**), 114.7 (C-8, **CM-42**), 112.9 (C-8, **CM-41**), 73.8 (C-5, **CM-41**), 69.1 (C-3, **CM-42**), 50.9 (C-6, **CM-42**), 43.8 (C-4, **CM-41**), 43.4 (C-4, **CM-42**), 40.6 (C-6, **CM-41**), 36.8 (C-2, **CM-41**), 29.1 (C-2, **CM-42**), 23.3 (Me-6, **CM-42**), 23.2 (Me-6, **CM-42**), 23.0 (Me-6, **CM-41**), 22.1 (Me-6, **CM-41**), 9.8 (C-8, **CM-42**), 7.5 (C-8, **CM-41**).

(*S*)-6-Hydroxy-3,3-dimethyloct-1-en-4-one (CM-42)



To a solution of **CM-47** (1.00 g, 3.45 mmol) in dicholoromethane (25 mL) was added TfOH (5 mol%) at room temperature. After stirring for 5 min, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded **CM-42** (567 mg, 96%) as a colorless oil.

$[\alpha]^{20}_D$: +83.4 (*c* 1.35, CH_2Cl_2).

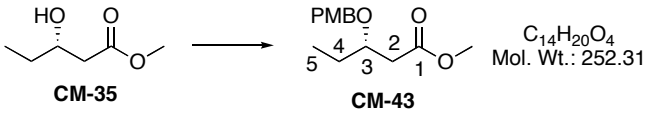
IR (film): 3450, 2969, 2932, 2878, 1704, 1463, 1371, 1060, 977, 919, 846, 750, 653, 586 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.66 (dd, 1H, *J* = 17.2, 10.9 Hz, H-7), 5.15-5.10 (m, 2H, H-8), 3.88-3.82 (m, 1H, H-3), 3.10 (br s, 1H, OH), 2.63 (dd, 1H, *J* = 17.8, 2.7 Hz, H-4), 2.48 (dd, 1H, *J* = 17.8, 9.0 Hz, H-4), 1.50-1.35 (m, 2H, H-2), 1.20 (s, 3H, Me-6), 1.19 (s, 3H, Me-6), 0.90 (t, 3H, *J* = 7.4 Hz, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 214.7 (C-5), 141.9 (C-7), 114.7 (C-8), 69.1 (C-3), 50.9 (C-6), 43.5 (C-4), 29.2 (C-2), 23.3 (Me-6), 23.2 (Me-6), 9.8 (C-1).

HRMS Calcd for $C_{10}H_{18}O_2$: 170.1307. **Found**: 170.1305.

Methyl (*S*)-3-(4-Methoxybenzyloxy)pentanoate (CM-43)



To a solution of **CM-35** (622 mg, 4.71 mmol) in dichloromethane (10 mL) was added freshly prepared *p*-methoxybenzyl trichloroacetimidate (2.60 g, 9.41 mmol, 2.00 equiv) and a catalytic quantity of camphorsulfonic acid (109 mg, 0.47 mmol, 0.10 equiv). The mixture was

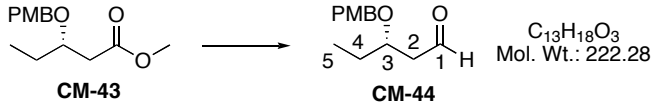
stirred for 12 h at room temperature, and then quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired **CM-43** (1.06 g, 89%) as a colorless oil.

IR (film): 2958, 2876, 1738, 1612, 1513, 1461, 1248, 1175, 1035, 880, 794, 734, 548 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.26-7.24 (m, 2H, H-Ar), 6.88-6.85 (m, 2H, H-Ar), 4.47 (s, 2H, $ArCH_2$), 3.82-3.80 (m, 1H, H-3), 3.79 (s, 3H, COOMe), 3.68 (s, 3H, ArOMe), 2.59 (dd, 1H, *J* = 15.1, 7.5 Hz, H-2), 2.47 (dd, 1H, *J* = 15.1, 5.4 Hz, H-2), 1.62-1.58 (m, 2H, H-4), 0.93 (t, 3H, *J* = 7.4 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 172.3 (C-1), 159.1 (C-Ar), 130.5 (C-Ar), 129.3 (C-Ar), 113.7 (C-Ar), 76.7 (ArOMe), 71.1 ($ArCH_2$), 55.2 (COOMe), 51.5 (C-3), 39.3 (C-2), 26.9 (C-4), 9.38 (C-5).

(*S*)-3-(4-Methoxybenzyloxy)pentanal (CM-44)



To a solution of **CM-43** (150 mg, 0.60 mmol) in dichloromethane (10 mL) was added dropwise DIBALH (0.71 mL, 1 M in hexanes, 0.71 mmol, 1.20 equiv) at -78°C. After stirring for 15 min at that temperature, the reaction was quenched with MeOH then a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired **CM-44** (103 mg, 75%) as a colorless oil.

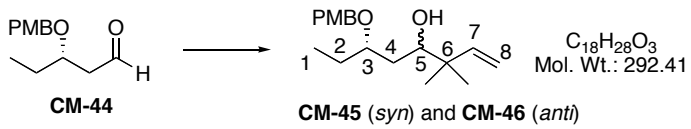
IR (film): 2963, 2873, 1723, 1513, 1247, 1059, 1033, 862, 779, 695, 674, 641, 548 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.78 (t, 1H, *J* = 2.2 Hz, H-1), 7.25-7.23 (m, 2H, H-Ar), 6.88-6.86 (m, 2H, H-Ar), 4.51 (d, 1H, *J* = 11.1 Hz, $ArCH_2$), 4.44 (d, 1H, *J* = 11.1 Hz, $ArCH_2$), 3.91-3.85 (m, 1H, H-3), 3.80 (s, 3H, ArOMe), 2.66 (ddd, 1H, *J* = 16.3, 7.5, 2.6 Hz, H-3), 2.66 (ddd, 1H, *J* = 16.3, 4.6, 1.9 Hz, H-3), 1.68-1.59 (m, 2H, H-4), 0.94 (t, 3H, *J* = 7.4 Hz, H-5).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 210.9 (C-1), 159.2 (C-Ar), 130.3 (C-Ar), 129.4 (C-Ar), 113.8 (C-Ar), 75.0 ($ArCH_2$), 70.8 (ArOMe), 55.3 (C-3), 47.8 (C-2), 26.8 (C-4), 9.3 (C-5).

HRMS Calcd for $C_{14}H_{20}O_4$: 222.1256. **Found**: 222.1260.

(*S*)-6-(4-Methoxybenzyloxy)-3,3-dimethyloct-1-en-4-ol (CM-45) and **(CM-46)**



Freshly prepared 1-bromo-3-methylbut-2-ene (37.9 mg, 0.25 mmol, 1.20 equiv) was added to a solution of **CM-44** (47.0 mg, 0.21 mmol) in THF (5 mL). This was followed by the addition of aqueous ammonium chloride (sat., 10 mL). The resulting mixture was cooled to 0°C, and activated zinc dust (41.5 mg, 0.64 mmol, 3.00 equiv) was added slowly. The mixture was then stirred vigorously at room temperature for 1 h (no inert atmosphere is necessary). After completion of the reaction, the mixture was filtered through a pad of celite, the two phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95) afforded the desired *syn*-product **CM-45** and *anti*-product **CM-46** (60 mg, 97% global yield) in a 1/1 ratio as colorless oils.

CM-45

IR (film): 3482, 2962, 2871, 1612, 1513, 1463, 1249, 1036, 882, 859, 780, 702, 656 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.27-7.25 (m, 2H, H-Ar), 6.88-6.85 (m, 2H, H-Ar), 5.86 (dd, 1H, *J* = 17.2, 11.1 Hz, H-7), 5.03-4.98 (m, 2H, H-8), 4.55 (d, 1H, *J* = 10.8 Hz, $ArCH_2$), 4.37 (d, 1H, *J* = 10.8 Hz, $ArCH_2$), 3.79 (s, 3H, ArOMe), 3.69 (d, 1H, *J* = 1.2 Hz, OH), 3.64-3.58 (m, 1H, H-3), 3.47 (dt, 1H, *J* = 10.2, 1.2 Hz, H-5), 1.67-1.43 (m, 4H, H-4, H-2), 1.01-1.00 (m, 6H, Me-6), 0.91 (t, 3H, *J* = 7.5 Hz, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 159.2 (C-Ar), 145.7 (C-Ar), 130.1 (C-Ar), 129.5 (C-Ar), 113.9 (C-7), 112.1 (C-8), 81.2 (ArOMe), 78.5 (C-3), 70.2 ($ArCH_2$), 55.3 (C-5), 41.3 (C-6), 34.8 (C-4), 25.8 (C-2), 23.2 (Me-6), 22.1(Me-6), 8.7 (C-1).

HRMS Calcd for $C_{18}H_{28}O_3$: 292.2039. **Found**: 292.2039.

CM-46

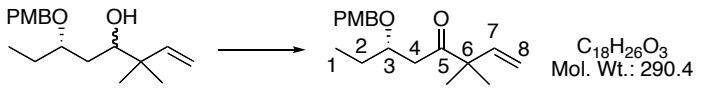
IR (film): 3484, 2961, 2871, 1612, 1513, 1247, 1036, 888, 834, 778, 740, 626 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.27-7.25 (m, 2H, H-Ar), 6.88-6.86 (m, 2H, H-Ar), 5.85 (dd, 1H, *J* = 17.5, 10.9 Hz, H-7), 5.07-5.00 (m, 2H, H-8), 4.55 (d, 1H, *J* = 10.8 Hz, $ArCH_2$), 4.37 (d, 1H, *J* = 10.8 Hz, $ArCH_2$), 3.80 (s, 3H, ArOMe), 3.63-3.58 (m, 2H, H-3, H-5), 2.57 (d, 1H, *J* = 2.9 Hz, OH), 1.77-1.50 (m, 4H, H-4, H-2), 1.01(s, 3H, Me-6), 1.00 (s, 3H, Me-6), 0.90 (t, 3H, *J* = 7.5 Hz, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 159.1 (C-Ar), 145.6 (C-Ar), 130.7 (C-Ar), 129.3 (C-Ar), 113.8 (C-7), 112.6 (C-8), 78.3 (ArOMe), 74.3 (C-3), 71 ($ArCH_2$), 55.3 (C-5), 41.2 (C-6), 34 (C-4), 26.2 (C-2), 22.8 (Me-6), 22.6 (Me-6), 10.0 (C-1).

HRMS Calcd for $C_{18}H_{28}O_3$: 292.2039. **Found**: 292.2037.

(*S*)-6-(4-Methoxybenzyloxy)-3,3-dimethyloct-1-en-4-one (CM-47)



CM-45 (*syn*) and **CM-46** (*anti*) **CM-47**

A solution of IBX (5.34 g, 19.0 mmol, 3.00 equiv) in DMSO (50 mL) was added slowly at room temperature to a stirred solution of **CM-45** and **CM-46** (1.84 g, 6.30 mmol) in THF (100 mL). The resulting mixture was stirred in the dark at room temperature overnight. When the reaction was complete, water (100 mL) was added then the organic phase was diluted with diethyl ether (100 mL). The biphasic system was stirred for at least 3 h. The white salts were then filtered off through a pad of celite. The aqueous phase was extracted with diethyl ether (3*80 mL) then the combined organic fractions were washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95 then 10/90) afforded the desired **CM-47** (1.75 g, 96%) as a pale yellow oil.

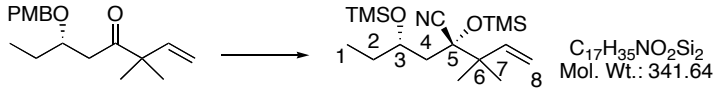
IR (film): 2967, 2932, 1708, 1513, 1248, 1035, 802, 633, 555, 479 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.23-7.21 (m, 2H, H-Ar), 6.86-6.84 (m, 2H, H-Ar), 5.89 (dd, 1H, *J* = 17.4, 10.4 Hz, H-7), 5.18-5.13 (m, 2H, H-8), 4.41 (s, 2H, $ArCH_2$), 3.90 (m, 1H, H-3), 3.79 (s, 3H, ArOMe), 2.83 (dd, 1H, *J* = 17.0, 7.0 Hz, H-4), 2.48 (dd, 1H, *J* = 17.0, 5.2 Hz, H-4), 1.57-1.49 (m, 2H, H-2), 1.22-1.21 (m, 6H, Me-6), 0.90 (t, 3H, *J* = 7.5 Hz, H-1).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 211.7 (C-5), 159 (C-Ar), 142.1 (C-Ar), 130.9 (C-Ar), 129.3 (C-Ar), 114.5 (C-7), 113.6 (C-8), 76.4 (ArOMe), 71.6 ($ArCH_2$), 55.3 (C-3), 51 (C-6), 42.3 (C-4), 27.1 (C-2), 23.3 (Me-6), 23.2 (Me-6), 9.6 (C-1).

HRMS Calcd for $C_{18}H_{26}O_3$: 290.1882. **Found**: 290.1881.

(2*S*,4*S*)-2-(1,1-Dimethylallyl)-2,4-bistrimethylsiloxyhexanenitrile (CM-48)



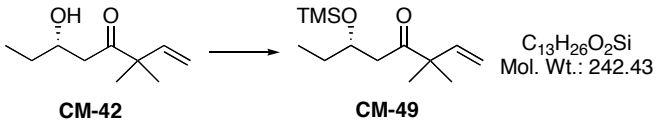
CM-47 **CM-48**

To a solution of **CM-47** (200 mg, 0.69 mmol) in CH_2Cl_2 (10 mL) was added dried KCN (45 mg, 0.69 mmol, 1.0 equiv) and activated ZnI_2 (440 mg, 1.38 mmol, 2.0 equiv). The mixture was stirred for 20 min, then TMSCN (0.230 mL, 1.72 mmol, 2.50 equiv) was injected and the resulting mixture was stirred for 1 hour. The reaction was quenched with triethylamine and the mixture was filtered through celite. The crude product was concentrated *in vacuo* with a trap (bleach/KOH) and purified by flash chromatography (diethyl ether/petroleum ether: 5/95) to afford an inseparable mixture of **CM-48** and **CM-49** (220 mg) in a 2:1 ratio.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.94 (dd, 1H, *J* = 17.4, 10.9 Hz, H-7), 5.17-5.09 (m, 2H, C-8), 3.91 (q, 1H, *J* = 5.1 Hz, C-3), 1.83 (d, 2H, *J* = 5.1 Hz, H-4), 1.64-1.56 (m, 2H, H-2), 1.16 (m, 3H, Me-6), 1.12 (m, 3H, Me-6), 0.88 (t, 3H, *J* = 7.4 Hz, H-1), 0.26 (s, 9H, H-TMS), 0.16 (s, 9H, H-TMS).

HRMS Calcd for $C_{17}H_{35}NO_2Si_2$: 341.2206. **Found**: 341.2216.

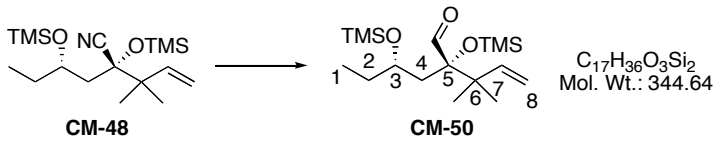
(*S*)-3,3-Dimethyl-6-trimethylsiloxyoct-1-en-4-one (CM-49)



To a solution of **CM-42** (136 mg, 0.79 mmol) in dichloromethane (5 mL) was added DMAP (106 mg, 0.87 mmol, 1.10 equiv) and TMSCl (0.104 mL, 0.83 mmol, 1.05 equiv). The mixture was stirred for 1 h at room temperature, then quenched with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (10 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired **CM-49** (192 mg, quantitative yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.87 (dd, 1H, *J* = 17.6, 10.5 Hz, H-7), 5.16-5.11 (m, 2H, H-8), 4.10 (tt, 1H, *J* = 7.0, 5.1 Hz, H-3), 2.71 (dd, 1H, *J* = 16.9, 7.3 Hz, H-4), 2.41 (dd, 1H, *J* = 16.9, 5.0 Hz, H-4), 1.48-1.35 (m, 2H, H-2), 1.19 (s, 3H, Me-6), 1.18 (s, 3H, Me-6), 0.86 (t, 3H, *J* = 7.4 Hz, H-1), 0.07 (s, 9H, H-TMS).

(2*S*,4*S*)-2-(1,1-Dimethylallyl)-2,4-bistrimethylsiloxyhexanal (CM-50)



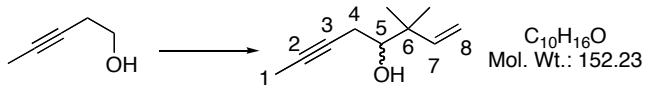
The crude nitrile **CM-48** (87.2 mg, 0.256 mmol) was dissolved in dichloromethane (10 mL) and cooled to -78°C. DIBAL-H (0.640 mL, 1 M in hexanes, 0.640 mmol, 2.50 equiv) was then added dropwise. The reaction mixture was warmed to 0°C and stirred for 2 h. The reaction was quenched by addition of ethyl acetate (4 mL), diluted with diethyl ether (150 mL) and allowed to warm to room temperature. Silica (40 g) was added to the solution, which was then placed at -20°C overnight. After completion of the reaction, the mixture was warmed to room temperature and the silica was filtered off. Solvents were evaporated under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 1/99) afforded **CM-50** (13.1 mg, 20% over two steps) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.59 (s, 1H, H-CHO), 5.99 (dd, 1H, *J* = 17.5, 10.8 Hz, H-7), 5.10-5.01 (m, 2H, C-8), 3.72-3.66 (m, 1H, C-3), 2.11 (dd, 1H, *J* = 14.4, 9.1 Hz, H-4), 1.94 (dd, 1H, *J* = 14.4, 3.0 Hz, H-4), 1.31-1.14 (m, 2H, H-2), 1.03-1.05 (m, 6H, Me-6), 0.83 (t, 3H, *J* = 7.3 Hz, H-1), 0.19 (s, 9H, H-TMS), 0.12 (s, 9H, H-TMS).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 204.2 (C-CHO), 113.8 (C-7), 113.7 (C-8), 86.3 (C-5), 69.5 (C-3), 44.7 (C-6), 41.4 (C-4), 30 (C-2), 23 (Me-6), 22.2 (Me-6), 9.8 (C-1), 3.0 (C-TMS), 0.3 (C-TMS).

HRMS Calcd for $C_{17}H_{36}O_3Si_2$: 344.2203. **Found**: 344.2204.

3,3-Dimethyl-oct-1-en-6-yn-4-ol (CM-52)



CM-52

To a solution of Dess-Martin periodinane (18.2 g, 0.043 mol, 1.10 equiv) in dichloromethane (100 ml) was added a solution of 3-pentynol (3.6 mL, 0.039 mol) in dichloromethane (20 mL) and a drop of water. After stirring for 1 h, the reaction was cooled to -78°C and pentane (50 mL) was added. The mixture was filtered through a pad of silica gel, and the crude product was concentrated *in vacuo* at room temperature. Freshly prepared 1-bromo-3-methylbut-2-ene (4.97 mL, 0.043 mmol, 1.10 equiv) was added to a solution of the crude product in THF (50 mL). This was followed by the addition of aqueous ammonium chloride (sat., 100 mL). The resulting mixture was cooled to 0°C, and activated zinc dust (7.60 g, 0.117 mmol, 3.00 equiv) was added slowly. The mixture was then stirred vigorously at room temperature for 1 h (no inert atmosphere is necessary). After completion of the reaction, the mixture was filtered through a pad of celite, the two phases were separated and the aqueous phase was extracted with diethyl ether (3*25 mL). The combined organic fractions were washed with brine (20 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded **CM-52** (5.92 g, 99%) as a colorless oil.

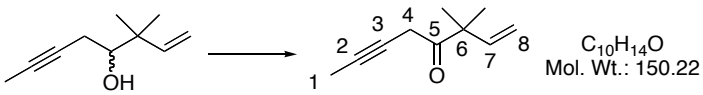
IR (film): 3583, 3083, 2967, 2922, 2869, 1639, 1466, 1420, 1387, 1272, 1192, 1072, 918, 688, 538 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.82 (dd, 1H, *J* = 17.5, 10.9 Hz, H-7), 5.03-4.97 (m, 2H, H-8), 3.41 (dt, 1H, *J* = 9.5, 2.9 Hz, H-5), 2.33 (dq, 1H, *J* = 16.3, 2.5 Hz, H-4), 2.16-2.07 (m, 2H, OH, H-4), 1.76 (t, 3H, *J* = 2.5 Hz, H-1), 1.00 (s, 3H, Me-6), 0.99 (s, 3H, Me-6).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 144.42 (C-7), 112.8 (C-8), 77.8 (C-3), 76.5 (C-5), 76.4 (C-2), 40.8 (C-6), 22.9 (C-4), 22.8 (Me-6), 22.4 (Me-6), 3.4 (C-1).

MS: 153 (MH+), 141, 135.

3,3-Dimethyloct-1-en-6-yn-4-one (CM-53)



CM-52 **CM-53**

To a solution of Dess-Martin periodinane (5.97 g, 14.1 mmol, 1.20 equiv) in dichloromethane (50 mL) was added a solution of **CM-52** (610 mg, 11.7 mmol) in dichloromethane (10 mL) and a drop of water. After stirring for 1 h, the reaction was cooled to -78°C and pentane (50 mL) was added. The mixture was filtered through a pad of silica gel, and the crude product was concentrated *in vacuo* and purified by flash chromatography (diethyl ether/petroleum ether: 5/95) to afford **CM-53** (570 mg, 95% yield) as a pale yellow oil.

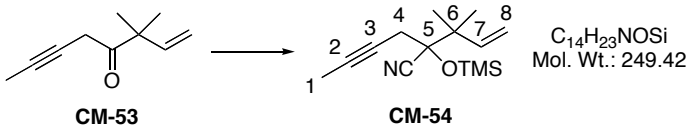
IR (film): 3086, 2959, 2250, 1719, 1635, 1452, 1322, 1240, 1171, 1078, 923, 673, 561 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.86 (dd, 1H, *J* = 17.7, 10.6 Hz, H-7), 5.14-5.10 (m, 2H, H-8), 3.30 (q, 2H, *J* = 2.5 Hz, H-4), 1.77 (t, 3H, *J* = 2.5 Hz, H-1), 1.20 (s, 3H, Me-6), 1.20 (s, 3H, Me-6).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 206.5 (C-5), 141.7 (C-7), 114.6 (C-8), 79.6 (C-3), 71.3 (C-2), 50.5 (C-6), 29.0 (C-4), 23.3 (Me-6), 3.3 (C-1).

HRMS Calcd for $C_{10}H_{14}O$: 150.1045 **Found**: 150.1048.

2-(1,1-Dimethylallyl)-2-trimethylsiloxyhex-4-ynenitrile (CM-54)



To a solution of **CM-53** (800 mg, 5.33 mmol) and DABCO (300 mg, 2.67 mmol, 0.50 equiv) in dichloromethane (10 mL) was added TMSCN (0.850 mL, 6.40 mmol, 1.20 equiv). The resulting mixture was refluxed for 2 h. The solvents and excess TMSCN were then evaporated under reduced pressure (with a NaOCl/NaOH trap). Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 2/100 then 5/100) afforded the desired **CM-54** (1.29 g, 97 %) as a pale yellow oil.

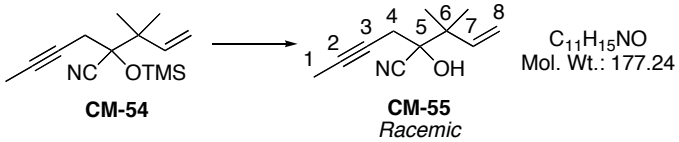
IR (film): 3087, 2969, 2926, 2249, 1640, 1465, 1379, 1255, 1139, 1004, 941, 902 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.92 (dd, 1H, J = 17.9, 10.9 Hz, H-7), 5.13-5.07 (m, 2H, H-8), 2.59 (dq, 1H, J = 16.8, 2.6 Hz, H-4), 2.41 (dq, 1H, J = 16.8, 2.6 Hz, H-4), 1.79 (t, 3H, J = 2.6 Hz, H-1), 1.15 (s, 3H, Me-6), 1.10 (s, 3H, Me-6), 0.26 (s, 9H, H-TMS).

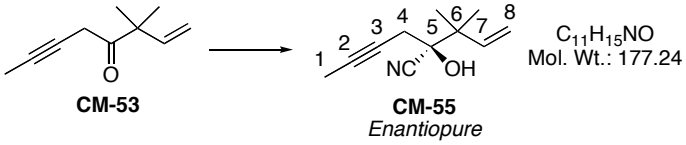
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 141.5 (C-7), 119.5 (C-CN), 114.9 (C-8), 80.2 (C-3), 78.9 (C-2), 74.2 (C-5), 45.1 (C-6), 28.4 (C-4), 22.5 (Me-6), 21.8 (Me-6), 3.5 (C-1), 1.3 (C-TMS).

HRMS Calcd for $C_{14}H_{23}NOSi$: 249.1549. **Found**: 249.1547.

(*S*)-2-(1,1-Dimethylallyl)-2-hydroxyhex-4-ynenitrile (CM-55)



To a solution of **CM-54** (250 mg, 1.00 mmol) in MeOH (5 mL) was added Amberlyst H-15 (40 mg) at room temperature, and the mixture was stirred overnight. The resin was then filtered off and the solvents were removed in *vacuo*. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired racemic alcohol **CM-55** (156 mg, 88% yield) as a colorless oil.



To a stirred solution of ketone **CM-53** (59 mg, 0.39 mmol) in chloroform (0.2 M) at -20°C was added $(DHQD)_2AQN$ (101 mg, 0.12 mmol, 30 mol%) and ethyl cyanoformate (78 μL,

0.79 mmol, 2 equiv). The resulting mixture was allowed to stand at that temperature in a freezer for 5 days without stirring. Aqueous HCl (1 N, 2.0 mL) was added to the reaction mixture. The mixture was extracted with ether, and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (diethyl ether/petroleum ether: 5/95) afforded enantiopure alcohol **CM-55** (62 mg, 90% yield, 99% enantiomeric excess by HPLC). To the aqueous layer was added K_2CO_3 to adjust the pH value of the solution to 9-11. The resulting mixture was extracted with EtOAc (10 mL), and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the recovered $(DHQD)_2AQN$.

$[\alpha]^{20}_D$: -74.1 (*c* 1.7, CH_2Cl_2).

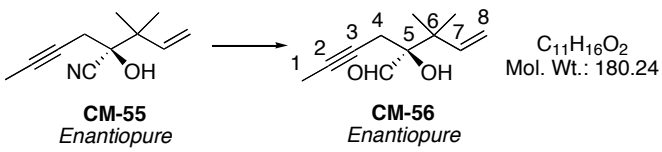
IR (film): 3391, 3087, 2926, 2732, 2240, 1960, 1851, 1719, 1678, 1639, 1416, 1291, 1181, 1115, 968, 871, 682, 557 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.97 (dd, 1H, *J* = 17.5, 10.9 Hz, H-7), 5.21-5.13 (m, 2H, H-8), 3.17 (s, 1H, OH), 2.64 (dq, 1H, *J* = 16.7, 2.5 Hz, H-4), 2.54 (dq, 1H, *J* = 16.7, 2.5 Hz, H-4), 1.86 (t, 3H, *J* = 2.5 Hz, H-1), 1.22 (s, 3H, Me-6), 1.20 (s, 3H, Me-6).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 203.2 (CHO), 140.8 (C-7), 115.7 (C-8), 82.3 (C-3), 76.3 (C-2), 71.8 (C-5), 43.1 (C-6), 27.9 (C-4), 22.2 (Me-6), 21.8 (Me-6), 3.6 (C-1).

HRMS Calcd for $C_{11}H_{15}NO$: 177.1154. **Found**: 177.1151.

(*S*)-2-(1,1-Dimethylallyl)-2-hydroxyhex-4-ynal (CM-56)



The enantiopure nitrile **CM-55** (150 mg, 0.85 mmol) was dissolved in dichloromethane (10 mL) and cooled to -78°C. DIBAL-H (2.54 mL, 1 M in hexanes, 2.54 mmol, 2.50 equiv) was then added dropwise. The reaction mixture was warmed to 0°C and stirred for 2 h. The reaction was quenched by addition of ethyl acetate (4 mL), diluted with diethyl ether (10 mL) and allowed to warm to room temperature. A saturated aqueous HCl solution (10 mL, 1 M) was added to the solution, which was then stirred for 1 h. After completion of the reaction, the mixture was warmed to room temperature and the silica was filtered off. Solvents were evaporated under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 5/95) afforded **CM-56** (114 mg, 75%) as a colorless oil.

$[\alpha]^{20}_D$: -8.0 (*c* 1.35, CH_2Cl_2).

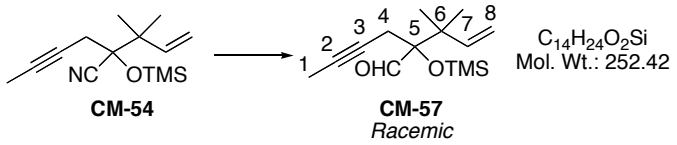
IR (film): 3510, 2978, 2927, 2859, 1725, 1465, 1336, 1254, 1123, 1033, 925, 910, 764, 533, 457 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.66 (s, 1H, CHO), 5.97 (dd, 1H, *J* = 17.4, 10.8 Hz, H-7), 5.14-5.05 (m, 2H, H-8), 3.51 (s, 1H, OH), 2.75 (dd, 1H, *J* = 16.7, 2.5 Hz, H-4), 2.52 (dd, 1H, *J* = 16.7, 2.5 Hz, H-4), 1.70 (t, 3H, *J* = 2.5 Hz, H-1), 1.08 (s, 3H, Me-6), 1.05 (s, 3H, Me-6).

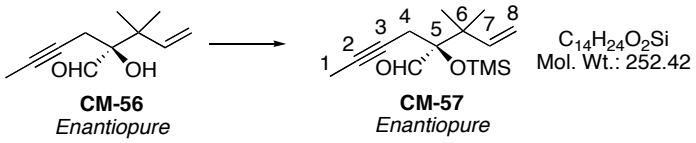
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 203.8 (CHO), 142.5 (C-7), 114.5 (C-8), 81.8 (C-3), 79.7 (C-2), 72.9 (C-5), 43.0 (C-6), 22.8 (C-4), 22.0 (Me-6), 21.7 (Me-6), 3.4 (C-1).

HRMS Calcd for $C_{16}H_{16}O_2$: 180.1150. **Found**: 180.1147.

(*S*)-2-(1,1-Dimethylallyl)-2-trimethylsilanyloxy-hex-4-ynal (CM-57)



The nitrile **CM-54** (220 mg, 0.88 mmol) was dissolved in dichloromethane (10 mL) and cooled to -78°C. DIBAL-H (2.21 mL, 1 M in hexanes, 2.21 mmol, 2.50 equiv) was then added dropwise. The reaction mixture was warmed to 0°C and stirred for 2 h. The reaction was quenched by addition of ethyl acetate (4 mL), diluted with diethyl ether (10 mL) and allowed to warm to room temperature. Silica (10 g) was added to the solution, which was then placed at -20°C overnight. After completion of the reaction, the mixture was warmed to room temperature and the silica was filtered off. Solvents were evaporated under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 1/99) afforded racemic **CM-57** (134 mg, 60%) as a colorless oil.



A solution of **CM-56** (550 mg, 3.1 mmol) in THF (10 mL) was cooled to -78°C and treated with a mixture of triethylamine (4.3 mL, 31 mmol, 10 equiv) and TMSCl (3.8 mL, 31 mmol, 10 equiv), stirred for 10 min. LiHMDS (6.1 mL, 1 M in THF, 6.1 mmol, 2.0 equiv) was added dropwise at that temperature, and the reaction mixture was stirred for 5 min, then quenched by a saturated aqueous $NaHCO_3$ solution, and warmed to room temperature. The two phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were concentrated and purified by flash chromathography to give enantiopure **CM-57** (770 mg, quantitative yield)

$[\alpha]^{20}_D$: -125.7 (*c* 0.7, CH_2Cl_2).

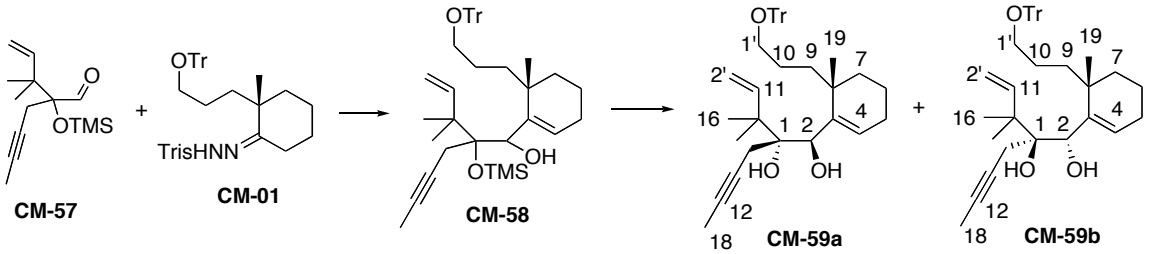
IR (film): 3055, 2964, 2928, 1735, 1463, 1422, 1253, 1153, 1009, 967, 926, 894, 857, 563, 502 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.64 (s, 1H, CHO), 5.96 (dd, 1H, *J* = 17.5, 10.9 Hz, H-7), 5.08-4.99 (m, 2H, H-8), 2.75 (dd, 1H, *J* = 16.8, 2.6 Hz, H-4), 2.38 (dd, 1H, *J* = 16.8, 2.6 Hz, H-4), 1.72 (t, 3H, *J* = 2.6 Hz, H-1), 1.03 (s, 3H, Me-6), 1.03 (s, 3H, Me-6), 0.21 (s, 9H, H-TMS).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 204.1 (CHO), 143.1 (C-7), 113.7 (C-8), 86.3 (C-3), 79.3 (C-2), 75.2 (C-5), 44.5 (C-6), 23.6 (C-4), 22.3 (Me-6), 22.0 (Me-6), 3.6 (C-1), 2.4 (C-TMS).

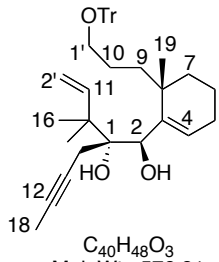
HRMS Calcd for $C_{14}H_{24}O_2Si$: 252.1546. **Found**: 252.1545.

(1*R*,2*R*)-2-(1,1-Dimethylallyl)-1-[(*S*)-6-methyl-6-(3-trityloxypropyl)cyclohex-1-enyl]hex-4-yne-1,2-diol (CM-59a) and **(1*S*,2*S*)-2-(1,1-Dimethylallyl)-1-[(*S*)-6-methyl-6-(3-trityloxypropyl)cyclohex-1-enyl]hex-4-yne-1,2-diol (CM-59b)**



tert-Butyllithium (2.65 mL, 3.98 mmol, 2.30 equiv, titrated 1.50 M) was added dropwise to a solution of hydrazone **CM-01** (1.20 g, 1.73 mmol) in THF (10 mL) at -78°C. The solution turned red and was stirred at -78°C for 30 min until the color turned dark red, then the temperature was allowed to warm to 0°C. When nitrogen evolution was finished and the color had turned to red, the solution was cooled again to -78°C. A solution of titrated $CeCl_3$ (426 mg, 1.73 mmol, 1.00 equiv) with *tert*-Butyllithium in THF (2 mL) was then added and stirred for 30 min. A cooled solution of aldehyde **CM-57** (480 mg, 1.90 mmol, 1.10 equiv) in THF (5.0 mL) was added dropwise *via* cannula. The resulting mixture was stirred at -78 °C for 30 min. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 10 mL). The phases were separated then the aqueous phase was extracted with diethyl ether (3*15 mL). The combined organic fractions were washed with brine (20 mL) and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 1/100) yielded **CM-58** as a pale yellow oil as a 1/1 mixture of diasteromers. Aqueous 1N HCl (3.46 mL, 3.46 mmol, 2.00 equiv) was added at 0°C to a solution of crude **CM-58** in THF (5.0 mL). The resulting mixture was allowed to warm to room temperature over 1 h and stirred overnight. The reaction was quenched by addition of aqueous sodium hydrogencarbonate (sat., 3 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3*5 mL). The combined organic fractions were washed with brine (5 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) allowed separation of the two diastereomers to afford the desired diols diasteromer **CM-59a** (438 mg, 44% yield over two steps) and diasteromer **CM-59b** (410 mg, 41% yield) as colorless oils (85% global yield).

CM-59a



$C_{40}H_{48}O_3$
Mol. Wt.: 576.81

$[\alpha]^{20}_{D}$: +100.7 (*c* 1.5, CH_2Cl_2).

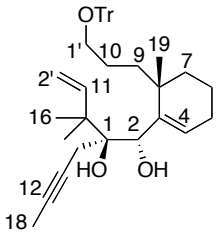
IR (film): 3602, 3533, 3062, 2933, 2868, 1956, 1632, 1597, 1487, 1150, 1383, 1221, 1115, 1080, 922, 900, 802, 719, 524 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.50-7.48 (m, 6H, H-Ar), 7.33-7.30 (m, 6H, H-Ar), 7.26-7.23 (m, 3H, H-Ar), 6.30-6.23 (m, 2H, H-4, H-11), 5.09-5.05 (m, 2H, H-2'), 4.26 (d, 1H, *J* = 6.1 Hz, H-2), 3.17 (s, 1H, OH (C-1)), 3.13-3.08 (m, 2H, H-1'), 2.59-2.49 (m, 2H, H-14), 2.19 (d, 1H, *J* = 6.1 Hz, OH (C-2)), 2.12-2.00 (m, 2H, H-5), 1.80 (t, 3H, *J* = 2.6 Hz, H-18), 1.71-1.56 (m, 6H, CH_2), 1.52-1.47 (m, 2H, CH_2), 1.24 (s, 3H, H-16 or H-17), 1.22 (s, 3H, H-17 or H-16), 1.02 (s, 3H, H-19).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 146.6 (C-3), 146.1 (C-Ar), 144.4 (C-11), 128.6 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 126.7 (C-4), 112.4 (C-2'), 86.4 (Ph_3C), 79.2 (C-13), 77.2 (C-1), 76.4 (C-12), 68.9 (C-2), 64.4 (C-1'), 46.4 (C-15), 37.1 (C-8), 36.6 (C-5), 35.2 (CH_2), 26.0 (CH_2), 26.0 (CH_2), 25.8 (C-19), 24.6 (C-14), 23.7 (C-16 or C-17), 23.2 (C-16 or C-17), 18.7 (CH_2), 3.6 (C-18).

HRMS Calcd for $C_{40}H_{48}O_3$: 576.3604. **Found**: 576.3599.

CM-59b



$C_{40}H_{48}O_3$
Mol. Wt.: 576.81

$[\alpha]^{20}_D$: +137.5 (*c* 1.6, CH_2Cl_2).

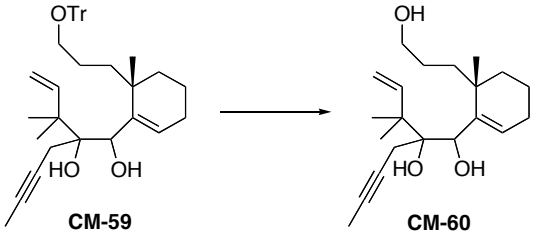
IR (film): 3604, 3535, 3062, 2930, 2866, 1490, 1450, 1380, 1222, 1073, 1029, 878.6, 802.2, 724, 626, 533 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.45-7.43 (m, 6H, H-Ar), 7.32-7.28 (m, 6H, H-Ar), 7.25-7.21 (m, 3H, H-Ar), 6.26-6.17 (m, 2H, H-4, H-11), 5.04-4.96 (m, 2H, H-2'), 4.24 (d, 1H, *J* = 6.1 Hz, H-2), 3.09 (s, 1H, OH (C-1)), 3.05 (t, 2H, *J* = 6.9 Hz, H-1'), 2.55-2.43 (m, 2H, H-14), 2.07-2.03 (m, 3H, H-5, OH (C-2)), 1.67 (t, 3H, *J* = 2.4 Hz, H-18), 1.61-1.51 (m, 4H, CH_2), 1.41-1.33 (m, 4H, CH_2), 1.18 (s, 3H, H-16 or H-17), 1.16 (s, 3H, H-17 or H-16), 1.08 (s, 3H, H-19).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 147.2 (C-3), 146.6 (C-Ar), 144.4 (C-11), 128.6 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 126.8 (C-4), 112.5 (C-2'), 86.3 (Ph_3C), 79.3 (C-13), 77.2 (C-1), 76.4 (C-12), 69.5 (C-2), 64.4 (C-1'), 46.4 (C-15), 36.6 (C-8), 35.7 (C-5), 34.9 (CH_2), 26.1 (CH_2), 25.8 (C-19), 25.0 (CH_2), 24.4 (C-14), 23.7 (C-16 or C-17), 23.3 (C-17 or C-16), 18.5 (CH_2), 3.7 (C-18).

HRMS Calcd for $C_{40}H_{48}O_3$: 576.3604. **Found**: 576.3605.

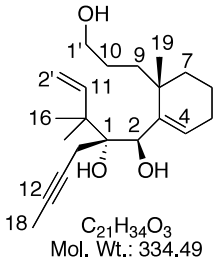
(1*R*,2*R*)-2-(1,1-Dimethylallyl)-1-[(*S*)-6-(3-hydroxypropyl)-6-methylcyclohex-1-enyl]hex-4-yne-1,2-diol (CM-60a) and **(1*S*,2*S*)-2-(1,1-Dimethylallyl)-1-[(*S*)-6-(3-hydroxypropyl)-6-methylcyclohex-1-enyl]hex-4-yne-1,2-diol (CM-60b)**



Diol **CM-59a** (120 mg, 0.21 mmol) was dissolved in MeOH (5 mL) at 20°C. Amberlyst H-15 (40 mg) was then added, and the mixture was stirred overnight at 20°C. The resin was then filtered off and the solvents were removed *in vacuo*. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 20/80 then 50/50) afforded the desired alcohol **CM-60a** (57 mg, 82% yield) as a colorless oil.

The same procedure repeated with 32 mg of diol **CM-59b** afforded the desired alcohol **CM-60b** (14 mg, 75% yield) as a yellow oil.

CM-60a



$[\alpha]^{20}_{D}$: +14.7 (*c* 1.5, CH_2Cl_2).

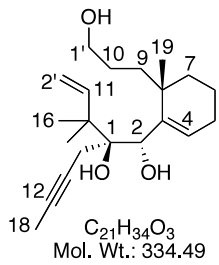
IR (film): 3636, 3456, 3082, 2924, 2868, 2735, 2669, 1723, 1633, 1460, 1416, 1383, 1236, 1063, 1004, 913, 681, 618, 508 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.27 (t, 1H, *J* = 4.0 Hz, H-4), 6.19 (dd, 1H, *J* = 17.9, 10.5 Hz, H-11), 5.06-5.02 (m, 2H, H-2'), 4.21 (s, 1H, H-2), 3.66 (dt, 1H, *J* = 10.4, 5.3 Hz, H-1'), 3.51 (dt, 1H, *J* = 10.4, 6.7 Hz, H-1'), 3.07 (s, 1H, OH (C-1)), 2.92-2.80 (br s, 1H, OH (C-2)), 2.53-2.41 (m, 2H, H-14), 2.06-1.92 (m, 2H, H-5), 1.76 (t, 3H, *J* = 2.6 Hz, H-18), 1.68-1.59 (m, 2H, CH_2), 1.58-1.51 (m, 4H, CH_2), 1.42-1.33 (m, 2H, CH_2), 1.18 (s, 3H, H-16 or H-17), 1.15 (s, 3H, H-17 or H-16), 0.97 (s, 3H, H-19).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 146.3 (C-3), 144.9 (C-11), 128.9 (C-4), 112.6 (C-2'), 79.6 (C-13), 77.1 (C-1), 76.2 (C-12), 68.7 (C-2), 62.9 (C-1'), 46.4 (C-15), 37.4 (C-8), 35.9 (C-5), 35.2 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 26.1 (C-19), 25.9 (C-14), 23.8 (C-16 or C-17), 23.2 (C-17 or C-16), 18.8 (CH_2), 3.7 (C-18).

HRMS Calcd for $C_{21}H_{34}O_3$: 334.2508. **Found**: 334.2507.

CM-60b



[α]$^{20}_{D}$: +50.8 (*c* 1.2, CH_2Cl_2).

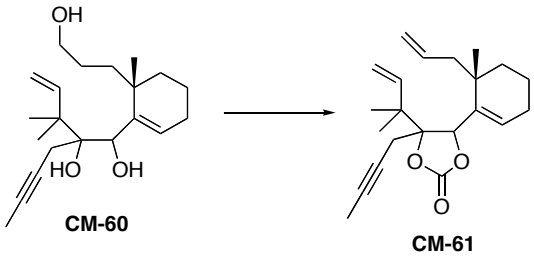
IR (film): 3636, 3533, 2932, 2867, 1460, 1380, 1117, 1048, 1008, 857, 829, 718, 618, 561, 470 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.30-6.23 (m, 2H, H-4, H-11), 5.09-5.06 (m, 2H, H-2'), 4.28 (d, 1H, *J* = 4.2 Hz, H-2), 3.61 (t, 2H, *J* = 6.6 Hz, H-1'), 3.05 (s, 1H, OH (C-1)), 2.51 (q, 2H, *J* = 2.7 Hz, H-14), 2.06-2.00 (m, 3H, H-5, OH (C-2)), 1.79 (t, 3H, *J* = 2.7 Hz, H-18), 1.66-1.59 (m, 2H, CH_2), 1.57-1.50 (m, 4H, CH_2), 1.40-1.32 (m, 2H, CH_2), 1.24 (s, 3H, H-16 or H-17), 1.20 (s, 3H, H-17 or H-16), 1.09 (s, 3H, H-19).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 147.1 (C-3), 146.8 (C-11), 127.7 (C-4), 112.6 (C-2'), 79.3 (C-13), 77.5 (C-1), 76.6 (C-12), 69.8 (C-2), 63.8 (C-1'), 46.4 (C-15), 36.6 (C-8), 35.3 (C-5), 35.0 (CH_2), 27.1 (CH_2), 26.2 (CH_2), 25.8 (C-19), 25.1 (C-14), 23.7 (C-16 or C-17), 23.3 (C-17 or C-16), 18.5 (CH_2), 3.7 (C-18).

HRMS Calcd for $C_{21}H_{34}O_3$: 334.2508. **Found**: 334.2495.

(4*R*,5*R*)-5-((*S*)-6-Allyl-6-methylcyclohex-1-enyl)-4-but-2-ynyl-4-(1,1-dimethylallyl)-[1,3]dioxolan-2-one (CM-61a) and **(4*S*,5*S*)-5-((*S*)-6-Allyl-6-methylcyclohex-1-enyl)-4-but-2-ynyl-4-(1,1-dimethylallyl)-[1,3]dioxolan-2-one (CM-61b)**



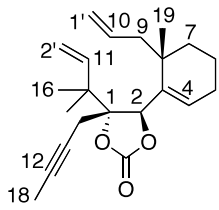
o-Nitrophenylselenocyanate (61.0 mg, 0.269 mmol, 2.40 equiv) was added in one portion at 20°C to a solution of alcohol **CM-60a** (60.0 mg, 0.180 mmol) in THF (1.0 mL). Tributylphosphine (0.067 mL, 0.269 mmol, 2.40 equiv) was then added dropwise. The resulting mixture was stirred at 20°C for 20 min. The completion of the reaction was checked by TLC. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was used for the next step without purification. Carbonyl diimidazole (291 mg, 1.80 mmol, 10.0 equiv) was added at 20°C to a solution of the crude product in toluene (5 mL). The resulting mixture was refluxed for three days. After cooling, the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate. The phases were separated then the aqueous phase was extracted with ether. The combined organic fractions were washed with brine, dried over magnesium

sulfate, filtered and the solvent was removed under reduced pressure. The crude product was then dissolved in THF (1.0 mL). Premixed aqueous hydrogen peroxide (1.5 mL, 10% wt solution in water) with ammonium molybdate (7 M) was added dropwise at -10°C. The mixture was then stirred for 5 min. Water was then added, and the solution was diluted with diethyl ether. The phases were separated then the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded the desired diene **CM-61a** (56 mg, 91% yield over three steps) as a pale yellow oil.

The same procedure repeated with 30 mg of alcohol **CM-60b** afforded the desired diene **CM-61b** (26 mg, 86% yield over three steps) as a pale yellow oil.

Treatment of **CM-61b** (10 mg, 0.029 mmol) with an excess of premixed aqueous hydrogen peroxide (2 equiv) with ammonium molybdate (7 M) at 0°C afforded **CM-62b** (8 mg, 80% yield) as a colorless oil.

CM-61a



$[\alpha]^{20}_{D}$: +19.0 (*c* 1.6, CH_2Cl_2).

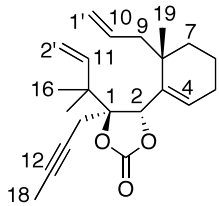
IR (film): 3078, 2930, 2870, 1807, 1640, 1520, 1459, 1424, 1334, 1176, 1043, 923, 815, 639, 464 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.03 (ddd, 1H, *J* = 17.8, 10.5, 1.5 Hz, H-4), 5.95 (dt, 1H, *J* = 3.9, 1.5 Hz, H-11), 5.82-5.72 (m, 1H, H-10), 5.25-5.20 (m, 2H, H-2'), 5.09-5.01 (m, 3H, H-1', H-2), 2.74 (dq, 2H, *J* = 17.3, 2.3 Hz, H-14), 2.27 (dd, 1H, *J* = 13.9, 6.7 Hz, H-9), 2.16-2.10 (m, 3H, H-5, H-9), 1.75-1.73 (m, 3H, H-18), 1.66-1.57 (m, 2H, C-6), 1.43-1.33 (m, 2H, C-7), 1.23 (d, 3H, *J* = 1.5 Hz, H-16 or H-17), 1.22 (s, 3H, H-17 or H-16), 1.01 (d, 3H, *J* = 1.5 Hz, H-19).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 141.9 (C-11), 138.5 (C-3), 134.0 (C-10), 133.3 (C-4), 118.0 (C-1'), 115.9 (C-2'), 89.0 (C-13), 79.1 (C-12), 77.7 (C-1), 74.0 (C-2), 46.2 (C-15), 45.0 (C-8), 36.9 (C-9), 35.6 (C-5), 26.0 (C-6), 25.6 (C-19), 23.4 (C-14), 22.9 (C-16 or C-17), 21.2 (C-17 or C-16), 18.0 (C-7), 3.7 (C-18).

HRMS Calcd for $C_{22}H_{30}O_3$: 342.2195. **Found**: 342.2209.

CM-61b



$[\alpha]^{20}_{D}$: -66.7 (*c* 1.0, CH_2Cl_2).

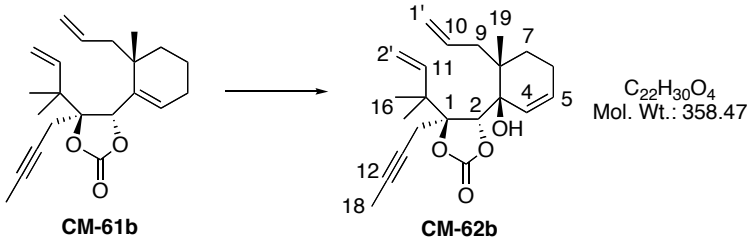
IR (film): 3078, 2966, 2933, 2867, 1809, 1639, 1459, 1425, 1175, 1042, 873, 678, 563 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.07 (dd, 1H, *J* = 17.2, 11.0 Hz, H-4), 5.91 (t, 1H, *J* = 4.0 Hz, H-11), 5.80-5.70 (m, 1H, H-10), 5.26-5.21 (m, 1H, H-2'), 5.08-5.00 (m, 3H, H-1', H-2), 2.76 (dq, 2H, *J* = 17.3, 2.5 Hz, H-14), 2.21 (dd, 1H, *J* = 13.5, 7.6 Hz, H-9), 2.15-2.10 (m, 2H, H-5), 2.07 (dd, 1H, *J* = 13.5, 7.0 Hz, H-9), 1.75 (t, 3H, *J* = 2.5 Hz, H-18), 1.69-1.57 (m, 3H, H-6, H-7), 1.38-1.32 (m, 1H, H-7), 1.43-1.33 (m, 1H, H-7), 1.25 (s, 3H, H-16 or H-17), 1.23 (s, 3H, H-17 or H-16), 1.08 (s, 3H, H-19).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 154.7 (C=O), 141.9 (C-11), 138.5 (C-3), 134.0 (C-10), 133.3 (C-4), 118.0 (C-1'), 115.9 (C-2'), 89.0 (C-13), 79.1 (C-12), 77.7 (C-1), 74.0 (C-2), 46.2 (C-15), 45.0 (C-8), 36.9 (C-9), 35.6 (C-5), 26.0 (C-6), 25.6 (C-19), 23.4 (C-14), 22.9 (C-16 or C-17), 21.2 (C-17 or C-16), 18.0 (C-7), 3.7 (C-18).

HRMS Calcd for $C_{22}H_{30}O_3$: 342.2195. **Found**: 342.2203.

(4*S*,5*S*)-5-((1*R*,6*S*)-6-Allyl-1-hydroxy-6-methylcyclohex-2-enyl)-4-but-2-ynyl-4-(1,1-dimethylallyl)-[1,3]dioxolan-2-one (CM-62b)



$[\alpha]^{20}_{D}$: -66.7 (*c* 1.0, CH_2Cl_2).

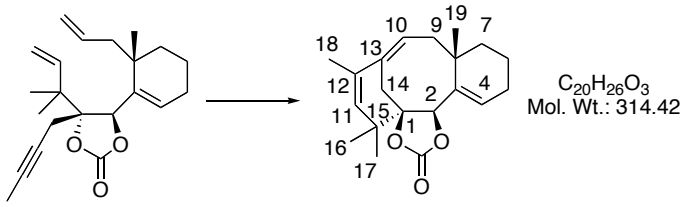
IR (film): 3078, 2966, 2933, 2867, 1809, 1639, 1459, 1425, 1175, 1042, 873, 678, 563 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.20 (d, 1H, *J* = 10.3 Hz, H-4), 6.03 (dd, 1H, *J* = 17.5, 10.9 Hz, H-11), 5.97-5.88 (m, 1H, H-10), 5.91 (t, 1H, *J* = 4.0 Hz, H-11), 5.78 (dt, 1H, *J* = 10.2, 3.2 Hz, H-5), 5.16 (s, 1H, H-2), 5.06-5.01 (m, 2H, H-2'), 5.01-4.96 (m, 2H, H-1'), 2.50-2.40 (m, 2H, H-14), 2.20-2.16 (m, 3H, H-6, H-9), 2.09 (dd, 1H, *J* = 18.9, 4.8 Hz, H-9), 1.76 (m, 3H, H-18), 1.62-1.41 (m, 2H, C-7), 1.08 (s, 3H, H-19), 1.05-1.02 (m, 6H, H-16, H-17).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 144.9 (C=O), 143.1 (C-11), 136.0 (C-10), 128.3 (C-4), 125.8 (C-5), 125.2 (C-3), 116.3 (C-1'), 112.9 (C-2'), 79.9 (C-13), 79.2 (C-12), 77.2 (C-1), 75.9 (C-2), 45.3 (C-15), 43.7 (C-8), 37.5 (C-9), 34.8 (C-6), 30.2 (C-19), 26.3 (C-14), 22.8 (C-16 or C-17), 22.7 (C-17 or C-16), 22.4 (C-7), 3.5 (C-18).

HRMS Calcd for $C_{22}H_{30}O_4$: 358.2144. **Found**: 358.2155.

(CM-64a)



CM-61a **CM-64a**

Diene **CM-61a** (30 mg, 95 μmol) was dissolved in toluene (5.0 mL). The mixture was thoroughly degassed three times while stirring. Second-generation Grubbs' catalyst (4.0 mg, 9.5 μmol, 10 mol%) was added and the mixture was refluxed for 12 h. After cooling, the solvent was evaporated under reduced pressure. Purification of the crude product by flash chromatography (diethyl ether/petroleum ether: 10/90) afforded **CM-64a** (17 mg, 62% yield) as a pale yellow oil.

$[\alpha]^{20}_{D}$: +104.8 (*c* 0.5, CH_2Cl_2).

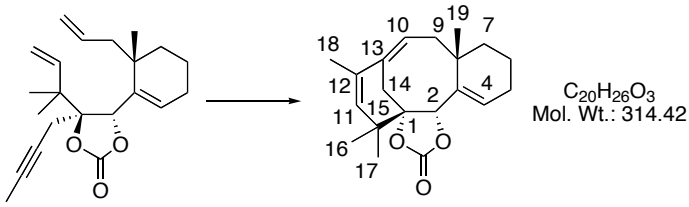
IR (film): 2929, 2858, 1809, 1462, 1261, 1191, 1052, 876, 826, 787, 749, 729, 679, 572 cm^{-1}.

^{1}**H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 5.71 (t, 1H, *J* = 3.8 Hz, H-4), 5.65 (t, 1H, *J* = 8.2 Hz, H-10), 5.13 (s, 1H, H-2), 4.98 (s, 1H, H-11), 3.11 (d, 1H, *J* = 12.5 Hz, H-14), 2.72 (dd, 1H, *J* = 14.4, 8.0 Hz, H-9), 2.66 (d, 1H, *J* = 12.5 Hz, H-14), 2.15 (dd, 1H, *J* = 14.4, 7.7 Hz, H-9), 2.12-2.00 (m, 2H, H-5), 1.72 (s, 3H, H-18), 1.68-1.55 (m, 4H, H-6, H-7), 1.27 (s, 3H, H-16 or H-17), 1.25 (s, 3H, H-19), 1.15 (s, 3H, H-17 or H-16).

^{13}**C NMR** ($CDCl_3$, 100.6 MHz): δ (ppm) 153.6 (C=O), 137.6 (C-3), 136.9 (C-4), 136.1 (C-12), 132.3 (C-13), 131.5 (C-11), 127.8 (C-10), 90.9 (C-2), 88.0 (C-1), 43.2 (C-6), 41.4 (C-9), 40.9 (C-15), 32.7 (C-14), 31.9 (C-8), 29.7 (C-16 or C-17), 27.5 (C-17 or C-16), 26.0 (C-5), 23.6 (C-19), 18.1 (C-7), 17.5 (C-18).

HRMS Calcd for $C_{20}H_{26}O_3$: 314.1882. **Found**: 314.1881.

(CM-64b)



CM-61b **CM-64b**

Diene **CM-61b** (20 mg, 58 μmol) was dissolved in toluene (5.0 mL). The mixture was thoroughly degassed three times while stirring. Second-generation Grubbs' catalyst (2.5 mg, 2.9 μmol, 5 mol%) was added and the mixture was stirred for 1 h at 80°C. After cooling, the solvent was evaporated under reduced pressure. Purification of the crude product by flash

chromatography (diethyl ether/petroleum ether: 10/90) afforded **CM-64b** (17 mg, 91% yield) as a pale yellow oil.

$[\alpha]^{20}_{D}$: +34.4 (*c* 1.7, CH_2Cl_2).

IR (film): 2973, 2931, 2864, 2253, 1804, 1732, 1461, 1379, 1261, 1153, 1119, 1044, 905, 856, 747, 639, 574 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.77 (t, 1H, *J* = 8.3 Hz, H-10), 5.73 (t, 1H, *J* = 3.8 Hz, H-4), 4.97 (d, 1H, *J* = 1.0 Hz, H-11), 4.92 (s, 1H, H-2), 2.84 (d, 1H, *J* = 11.3 Hz, H-14), 2.77 (dd, 1H, *J* = 13.0, 8.7 Hz, H-9), 2.50 (d, 1H, *J* = 11.3 Hz, H-14), 2.29-2.20 (m, 2H, H-5), 1.86-1.83 (m, 1H, H-7), 1.81 (d, 3H, *J* = 1.0 Hz, H-18), 1.78-1.75 (m, 1H, H-9), 1.70-1.58 (m, 2H, H-7, H-6), 1.48-1.43 (m, 1H, H-6), 1.20 (s, 3H, H-16 or H-17), 1.09 (s, 3H, H-19), 0.97 (s, 3H, H-17 or H-16).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 156.3 (C=O), 139.6 (C-13), 136.6 (C-3), 132.7 (C-12), 131.8 (C-11), 128.5 (C-4), 125.1 (C-10), 91.9 (C-1), 79.2 (C-2), 43.1 (C-15), 42.5 (C-8), 41.5 (C-6), 38.6 (C-9), 30.7 (C-14), 26.8 (C-19), 26.1 (C-5), 24.4 (C-17 or C-16), 24.2 (C-16 or C-17), 17.9 (C-18), 17.4 (C-7).

HRMS Calcd for $C_{20}H_{26}O_3$: 314.1882. **Found**: 314.1881.