universität wien

DISSERTATION

Titel der Dissertation

Studies Towards the Total Synthesis of Branimycin

angestrebter akademischer Grad

Doktor der Naturwissenschaften (Dr. rer. nat.)

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Wien, am 14 May. 2009

Acknowledgments

I would like to express my gratitude to many people for their support and help to make this work possible!

I would like to thank Prof. Dr. Mulzer for the great opportunity to work in his group, for the exciting research topics, for the freedom of creativity combined with a readiness to help with his tremendous knowledge. I thank for the lessons on strategy and tactics of chemical research and scientific public relations which I learned from him.

I thank my direct supervisor Univ.-Doz. Dr. Valentin Enev. His impact into this work, and most important, into my maturing as a scientist, cannot be overestimated. Without his mental and moral support many achievements would not be possible.

I would like to express my gratitude to Dr. Neil Sheddan and Dr. Uwe Rinner for their constant and invaluable help in preparation of this work as well as other publications.

For years of my stay in this research group, I was really happy to work with such friendly and bright individuals as:

Ass. Prof. Harry Martin, Dr. Konrad Tiefenbacher, Dipl. Ing. Harald Weinstabl, Dr. Wolfgang Felzmann, Dr. Roland Barth, Mag. Thomas Magauer, Dr. Daniela Rosenbeiger, Dr. Tanja Gaich, Dr. Andreas Gollner, Mag. Kathrin Prantz, Dr. Anna Innitzer, Dr. Marion Kögl, Dr. Peter Siengalewicz, Dr. Anna Galkina, Dr. Martin Green, Dr. Michael Gilbert, Dr. Maria Marques, Dr. Geraldine Garavel, Dipl. Chem. Lutz Kleemann, Dr. Edyta Kuliszewska, Dr. Dagmar Kapeller, Dipl. Ing. Jürgen Ramharter, Mag. Martin Himmelbauer, Dr. Katja Jantos, Mag. Christian Aichinger, Mag. Rita Fürst, Mag. Christoph Lentsch, Mag. Christina Nowikow and Mag. Anna Wieczorek.

My special thanks to Dr. Christian Pilger, Mag. Stefan Marchart and Ing. Martina Drescher and with whom I had a pleasure to “work shoulder to shoulder” every day.

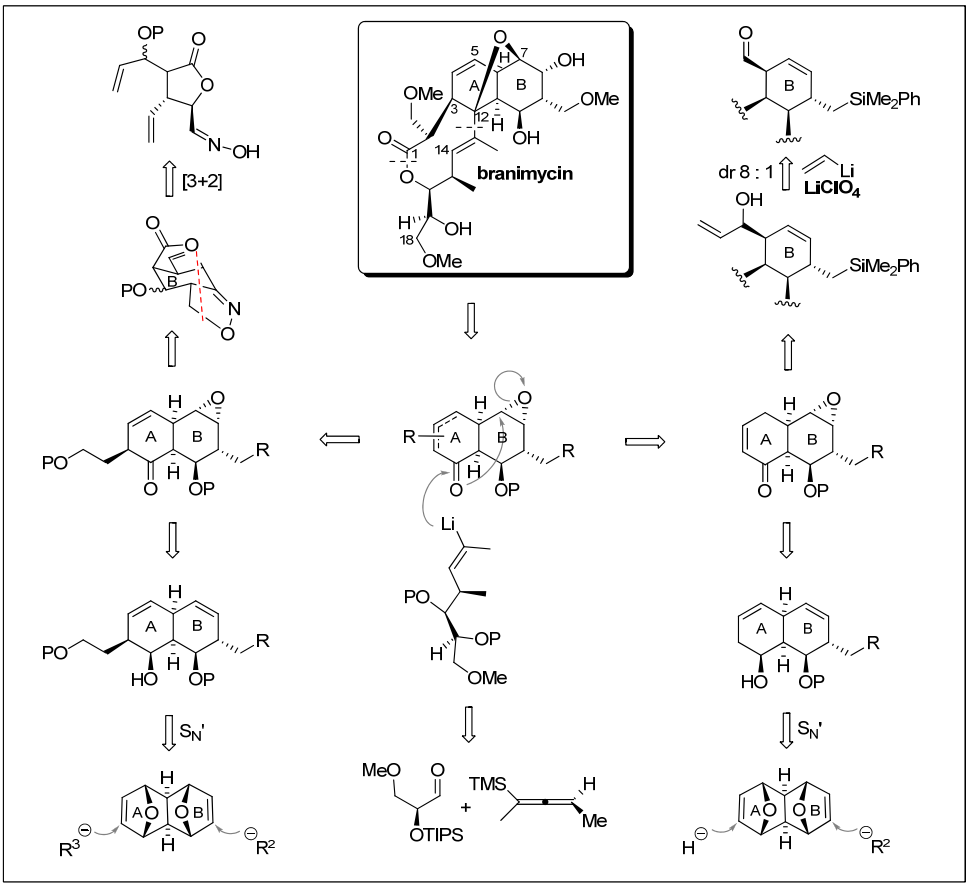
I am happy to thank Dr. Lothar Brecker and Dr. Hanspeter Kählig for their constant help in solving NMR challenges and Prof. Vladimir Arion for X-ray analysis.

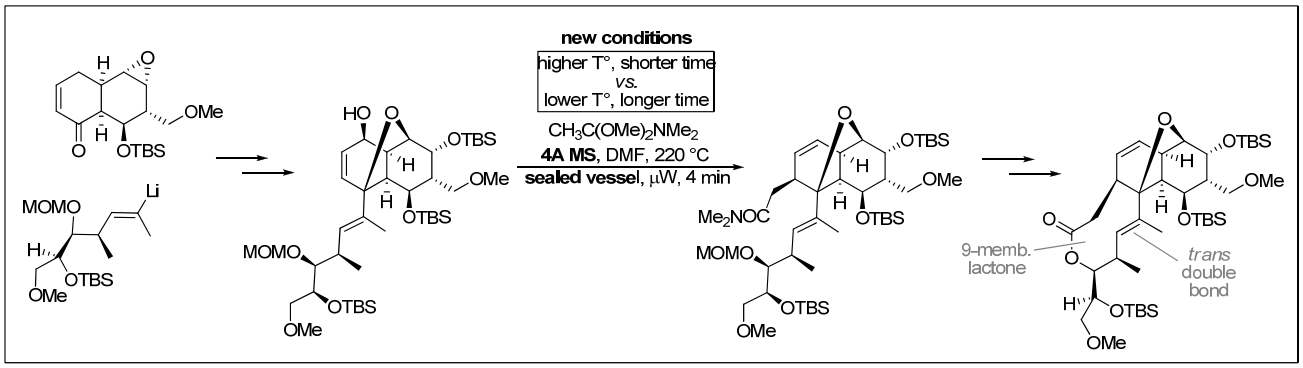
Equally, Ing. Susanne Felsinger, Sabine Schneider, Michael Zinke, Jale Özgür, Judith Humpelstetter, Walter Balba, Walter Dietrich, Martin Lux-Amon and Ing. Peter Unteregger are thanked for their reliable service jobs and friendly atmosphere.

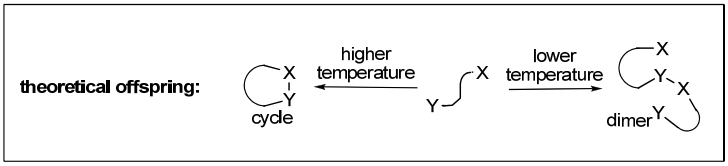
And of course, I thank my dear wife Dilbar and daughter Polina for their personal support and great patience at all times.

Many thanks to all of them!

Graphical Abstract







Abstract

Branimycin is a novel antibiotic, which belongs to a structurally new family of antibiotics: the nargenicins. It has demonstrated distinct antimicrobial activity, most notably against *Staphylococcus aureus*. Synthesis of branimycin would confirm the proposed structure and provide access to its derivatives.

Our retrosynthetic disconnection of branimycin gives two key synthetic intermediates: a *cis*-decalin core and a polyketide side-chain. This PhD thesis presents results of studies on the following topics:

- ✓ Improvement of the synthesis of the polyketide side-chain;
- ✓ Study of six approaches towards the *cis*-decalin core;
- ✓ Coupling of the *cis*-decalin core with the side-chain and subsequent elaboration to a highly advanced synthetic intermediate of branimycin

The studied approaches towards the *cis*-decalin core were based on the following key steps:

- an intramolecular [3+2] cyclization;
- a ketyl radical cyclization;
- desymmetrization of diepoxynaphthalene *via* a sequence of S_N'-openings of oxa-bridges with carbon or hydride nucleophiles.

In the course of studies of the intramolecular [3+2] cyclization of a nitrile oxide, for creation of the branimycin ring B, a beneficial effect of high temperatures in favor of cyclization *vs.* polymerization was observed. These results, coupled with a number of revealed literature precedents, allowed the generalization of this effect; and propose that an increase in reaction temperature will likely favor any kind of cyclization (characterized by strain and/or slow conformational changes) over dimerization and other intermolecular reactions with low activation enthalpy. A plausible explanation of this effect was also proposed.

The approaches to the *cis*-decalin core, *via* desymmetrization of diepoxynaphthalene, proved viable ways to access highly functionalized *cis*-decalins with different patterns of substituents. The best results were obtained *via* an S_N' opening of one of two oxa-bridges of diepoxynaphthalene, with $Me_2PhSiCH_2MgCl$ under copper catalysis, followed by S_N' opening of the second oxa-bridge, with formal hydride anion under chiral nickel catalysis. This sequence resulted in the synthesis of an enantioenriched *cis*-decalin fragment, which was successively coupled with the lithiated side-chain. After several synthetic manipulations, a key Eschenmoser-Claisen rearrangement was carried out, for which new conditions were developed: closed vessel, microwave irradiation, molecular sieves, DMF. Furthermore, it was shown that higher temperatures and shorter reaction times were important for obtaining a high yield. Additional synthetic transformations culminated in the synthesis of a seco-acid, which was cyclized to give a highly strained 9-membered lactone containing the internal *trans*-double bond. Summarizing, the combined synthetic efforts delivered a highly advanced intermediate which contained the entire carbon framework of branimycin including the 9-membered macrolactone.

Zusammenfassung

Branimycin ist ein neuartiges Antibiotikum sowie ein Vertreter einer strukturell neuen Familie von Antibiotika: den Nargenicinen. Es zeigt deutliche antimikrobielle Aktivität, insbesondere gegenüber *Staphylococcus aureus*. Die Synthese von Branimycin wäre der endgültige Strukturbeweis und würde einen Zugriff zu dessen Derivaten ermöglichen.

Die retrosynthetische Zerlegung von Branimycin ergibt zwei synthetische Intermediate: einen cis-Dekalin Kern sowie eine polyketidische Seitenkette. In dieser Dissertation werden folgende Ergebnisse präsentiert:

- ✓ Verbesserung der Synthese der polyketidischen Seitenkette
- ✓ Sechs verschiedene Zugänge zur Herstellung des cis-Dekalin Kerns
- ✓ Verknüpfung des cis-Dekalin Fragments mit der Seitenkette gefolgt von weiteren Syntheseschritten zu einer sehr fortgeschrittenen Vorstufe von Branimycin.

Die Zugänge zur Herstellung des Kernfragments basieren auf folgenden Schlüsselschritten:

- Einer intramolekularen [3+2]-Cyclisierung
- Einer Ketyl-Radikal Cyclisierung
- Desymmetrisierung eines Diepoxynaphthalins durch S_N' Öffnungen von Oxabrücken mittels Kohlenstoff- bzw. Hydrid-Nukleophilen.

Im Zuge der Studien der intramolekularen [3+2]-Cyclisierung eines Nitriloxids um den Ring B von Branimycin zu erhalten, stellte sich heraus, daß bei höheren Temperaturen eine Cyclisierung gegenüber Polymerisation begünstigt wird. Diese Resultate erlauben aufgrund zahlreicher Beispiele in der Fachliteratur eine Verallgemeinerung dieses Effekts: ein ansteigen der Reaktionstemperatur begünstigt wahrscheinlich jede Cyclisierung (welche durch Spannung und/oder langsame Konformationsänderungen geprägt ist) gegenüber Dimerisierung und anderen intermolekularen Reaktionen mit niedriger Aktivierungsenthalpie. Eine plausible Erklärung für diesen Effekt wurde ebenfalls ausgearbeitet.

Es gelang mittels Desymmetrisierung von Diepoxynaphthalin hochfunktionalisierte cis-Dekaline mit unterschiedlichem Substitutionsmuster zu generieren. Die besten Ergebnisse lieferte eine S_N' Öffnung der einen Oxa-Brücke des Diepoxynaphthalins mit $Me_2PhSiCH_2MgCl$ unter Kupfer Katalyse, gefolgt von einer S_N' Öffnung der zweiten Oxa-Brücke mit einem formalen Hydrid-Anion unter Verwendung eines chiralen Nickel Katalysators.

Diese Synthesesequenz führte zu einer Anreicherung des gewünschten cis-Dekalin Enantiomers, welches desweiteren erfolgreich mit der lithiierten Seitenkette verbunden werden konnte. Nach einigen darauffolgenden Syntheseschritten wurde eine Eschenmoser-Claisen Umlagerung durchgeführt wofür neue Reaktionsbedingungen entwickelt wurden: geschlossenes System, Mikrowelle, Molekularsiebe, DMF. Im Zuge dessen stellte sich heraus, daß höhere Temperaturen und kürzere Reaktionszeiten die Ausbeute erhöhen. Weitere Transformationen resultierten in einer Seco-Säure deren Cyclisierung ein sehr gespanntes, eine trans-Doppelbindung inkludierendes neungliedriges Lacton ergab.

Im Zuge dieser Doktorarbeit wurde ein sehr fortgeschrittenes Intermediat hergestellt, das bereits das gesamte Kohlenstoffgerüst von Branimycin enthält, inklusive des neungliedrigen Makrolactons

Publications and Conferences Resulting from this Thesis

Accepted publications:

"Improved synthesis of parent fused 7-oxanorbornenes"

Gromov,* A.; Enev,* V.; Mulzer,* J.

Synthetic Communications (accepted)

Publications in preparation:

"A desymmetrization approach towards highly oxygenated *cis*-decalins"

Gromov,* A.; Enev, V.; Mulzer*, J.

Organic Letters (under revision)

"Remarkable Temperature Effect in a Competition of Intramolecular [3+2] Cyclization Versus Oligomerization"

Gromov, A.; Enev, V.; Pilger, C.; Mulzer,* J.

Tetrahedron Letters (in preparation)

"Intramolecular cyclization *versus* oligomerization: effect of temperature"

Gromov,* A.; Enev,* V.; Mulzer,* J.

(in preparation)

A few other publications are in preparation.

Conferences:

"Towards the total synthesis of branimycin"

Gromov*, A.; Enev*, V.; Mulzer*, J.

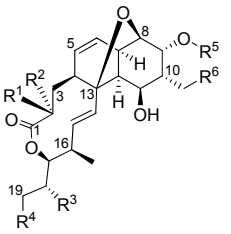
Poster presentation at the 11th Belgian Organic Synthesis Symposium, Ghent, Belgium, **2008**.

Table of Contents

1. Branimycin and Related Natural Products

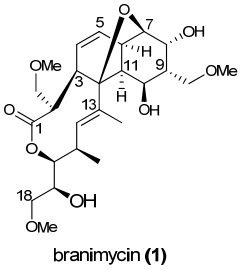
1.1. Isolation, Biological Activity and Structure Elucidation of the Nargenicin Family

The Nargenicin family could be described by the oxygen-bridged *cis*-decalin core annulated to a macrolactone, which so far is represented by ten members (Scheme 1).



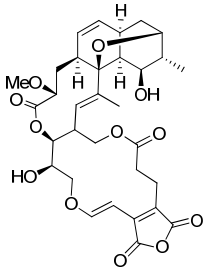
Name	R^1	R^2	R^3	R^4	R^5	R^6	Ref.
Nodusmicin **(2)**	OMe	H	OH	H	H	H	1
Nargenicin A_1 **(3)**	OMe	H	OH	H	PC	H	2
18-Deoxynargenicin **(4)**	OMe	H	H	H	PC	H	3
Nargenicin B_1 **(5)**	H	OH	OH	OMe	PC	OMe	4
Nargenicin B_2 **(6)**	H	OH	H	OH	PC	OMe	4
Nargenicin B_3 **(7)**	H	OH	OH	OMe	PC	H	4
Nargenicin C_1 **(8)**	OMe	H	OH	OMe	PC	OMe	4

PC =  2-pyrrole-carboxylate



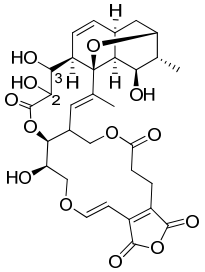
branimycin **(1)**

Ref. 5



luminamicin (coloradocin) **(9)**

Ref. 6



lustromycin **(10)**

Ref. 7

Scheme 1: Members of the Nargenicin family

The various nargenicins and nodusmicin exhibit antibacterial activity against several microorganism, among which *Staphylococcus aureus* is probably the most interesting. Luminamicin and lustromycin were shown to be active against pathogenic species of Clostridium. Branimycin proved to be active against *Staphylococcus aureus, E-coli, Bacillus subtilis and Streptomyces viridochromogenes.*

Determination of their structures proved not to be trivial. NMR studies of the initially isolated nargenicin A_1 allowed initial assignment of all stereocenters except positions 2, 16, 17 and 18 residing on the flexible macrolactone ring (Scheme 1). Degradation studies of nargenicin A_1 revealed that nodusmicin, another antibiotic, differs only at the C9 position in lacking 2-pyrrole-carboxylate functionality. Fortunately, nodusmicin proved crystalline and its structure was unambiguously determined by X-ray diffraction studies. Based on this information, the structure of nargenicin A_1 was also successfully elucidated.

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[1] Whaley, H. A.; C. G. Chidester, C. G.; Mizsak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659-3662.
[2] (a) Celmer, W. D.; Chmurny, G. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102,* 4203. (b) Celmer, W. D.; Cullen, W. P.; Moppett, C. E.; Jefferson, M. T.; Huang, L. H.; Shibakawa, R.; Tone, J. **U.S.** Patent 4,148,883, 1979.
[3] Magerlein, B. J.; Reid, R. J. *J. Antibiot.* **1982**, *35,* 254-255.
[4] Celmer, W. D.; Cullen, W. P.; Shibakawa, R.; Tone, J. **U.S.** Patent 4,435,747.
[5] (a) Speitling, M. Ph.D. Thesis, Universität Göttingen, **1998**. (b) Speitling, M.; Grün-Wollny, I.; Hannske, F. G.; Laatsch, H. *12. And 13. IRSEER Naturstofftage der DECHEMA e.V. Irsee* **2000**, **2001**, poster sessions.
[6] (a) Omura, S.; Iwata, R.; Iwai, Y.; Taga, S.; Tanaka, Y.; Tomoda, H. *J. Antibiot.* **1985**, *38*, 1322-1326. (b) Gouda, H.; Sunazuka, T.; Ui, H.; Handa, M.; Sakoh, Y.; Iwai, Y.; Hirono, S.; Omura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 18286-18291.
[7] (a) Omura, S.; Imamura, N.; Oiwa, R.; Kuga, H.; Iwata, R.; Masuma, R.; Iwai, Y. *J. Antibiot.* **1986**, *39*, 140. (b) Tomoda, T.; Iwata, R.; Takahashi, Y.; Iwai, Y.; Oiwa, R.; Omura, S. *J. Antibiot.* **1986**, *39*, 1205-1210.

The absolute configuration of nargenicin A_1 was determined[8] by non empirical CD exciton chirality method and independently confirmed by feeding experiments (*vide infra*). Basing on these results, absolute configurations of other members of the Nargenicin family were hypothesized.

The structure of 18-deoxynargenicin was confirmed by selective deoxygenation of nargenicin A_1 at the C18 position.[9]

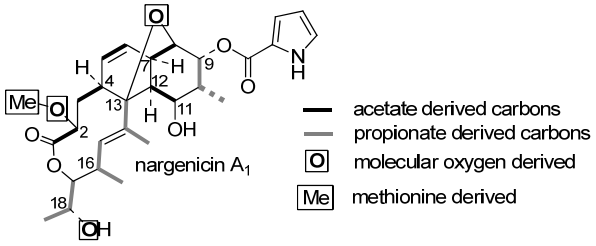
Although structures of luminamycin (coloradocin) and lustramycin differ from nargenicin A_1 quite substantially, they also could be ascribed to this family; they combine an oxa-bridge across a *cis*-decalin core and a condensed 10-membered lactone with a very similar substitution pattern. For determination of the structure of luminamicin, Mosher derivatization and molecular dynamic studies were carried out. To date, the structure of lustromycin is still not fully established, lacking assignment of the C2 and C3 stereocenters.

Elucidation of the branimycin structure[5] (Scheme 1) was only based on NMR studies and, similar to nargenicin A_1, only the stereocenters situated on the rigid *cis*-decalin frame could be reliably established (C3, C6-C12). Although assignment of the stereocenters at positions C2, C15-C17 was reported (based on NOE-experiments), we believe these results should be considered with great care due to a possible flexibility of the lactone ring (especially at the acyclic C17-position).

As a consequence, the total synthesis of branimycin would have not only a purely chemical interest, but would also confirm (or revise) the structure of branimycin.

1.2. Biosynthesis

Two independent studies of ^{13}C labeling revealed,[8,10] that the carbon skeletons of nargenicin A_1 and nodusmicin are assembled in nature from 4 propionate and 5 acetate units; and the Me group of the C2-OMe derived from methionine, thus demonstrating their polyketide origin (Scheme 2).



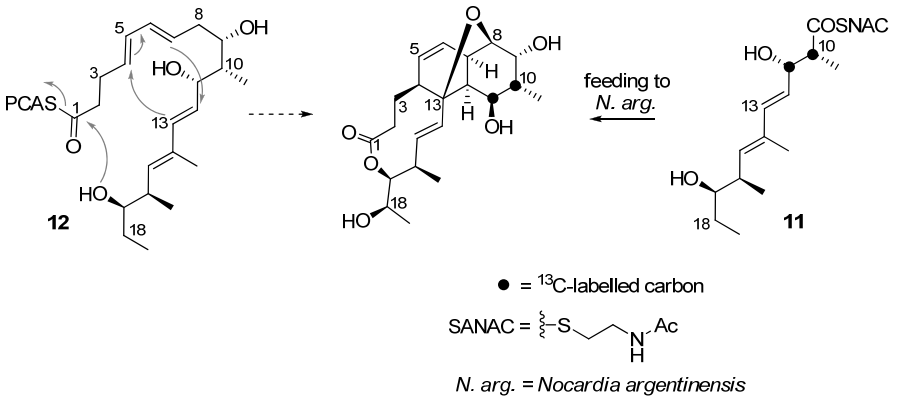
Scheme 2: Biosynthetic origin of nargenicin A

Experiments carried out in an $^{18}O_2$-atmosphere revealed[8] that the oxa-bridge, as well as the C2-O and C18-O are introduced into the structure at late stages of biosynthesis and are derived from molecular oxygen. Analyzing obtained results, the authors conclude that:

- The C4-C13 bond is not constructed *via* a simple aldol-type reaction, as the C13 oxygen is not derive from propionate.
- Epoxy-alcohol cyclization to form the oxa-bridge or epoxy-olefin cyclization to form C7-C12 can be excluded as neither the C9-O nor C11-O are derived from $^{18}O_2$.

Instead, the authors propose lactonization and intramolecular Diels-Alder cyclization reactions to be responsible for formation of the *cis*-decalin core (Scheme 3):

[8] (a) Cane, D. E.; Yang, C.-C. *J. Antibiot.* **1985**, *38,*423-426. (b) Cane, D. E.; Yang, C.-C. *J. Am. Chem. Soc.* **1984**, *106,* 6633-6634.
[9] Magerlein, B. J.; Reid, R. J. *J. Antibiot.* **1982**, *35,* 254-255.
[10] Snyder, W. C.; Rinehart, K. L. *J. Am. Chem. Soc.* **1984**, *106*, 787-789.



Scheme 3: Proposed biosynthesis of nargenicin A_1. Feeding experiment.

This hypothesis was to some extent supported by the incorporation of labeled polyketide chain elongation intermediate **11** into nargenicin A_1 in feeding experiments. Obtained results suggest that the diene moiety could indeed participate in formation of the *cis*-decalin core, and that stereocenters are set prior to the chain elongation.

Biosynthetic studies on luminamicin (coloradocin) showed[11] the same origin of carbons of the *cis*-decalin core and 10-membered lactone, as corresponding carbons of nargenicin A_1. Related studies with ^{18}O-labbelled molecular oxygen have not been reported so far, therefore it is not clear whether different positioning of oxa-bridges in these molecules results from different oxygen sources.

Unfortunately, no biosynthetic studies for branimycin have been reported so far. Even if to assume, that the general pathway to branimycin could be similar to the one leading to nargenicin A_1, two questions still cannot be answered: firstly, what is the origin of the 9-memberd lactone (in contrast to the 10-membered lactones of all other members of the Nargenicin family); and secondly, how the CH_2OMe group at the C2 position was introduced.

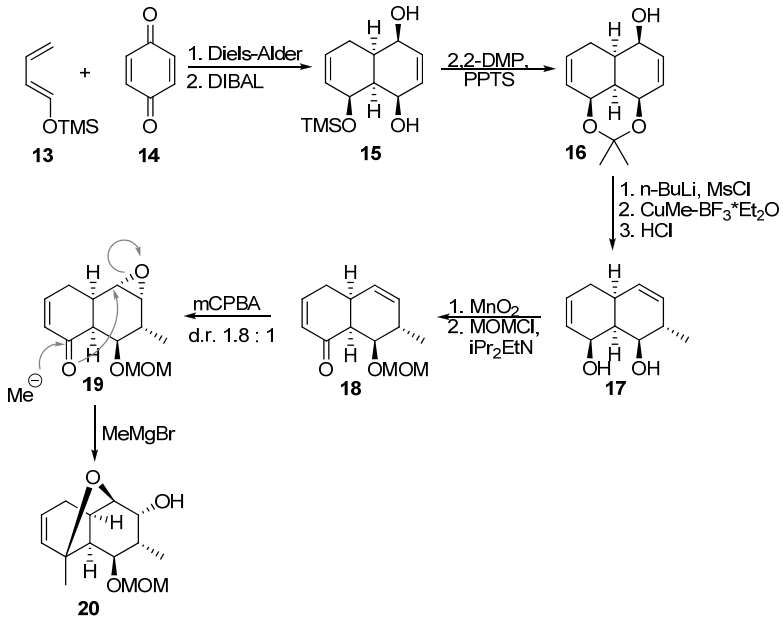
[11] McAlpine, J. B.; Mitscher, L. A.; Jackson, M.; Rasmussen, R. R.; Velde D.V.; Veliz, E. *Tetrahedron* **1996**, *52*, 10327-10334.

2. Synthetic Approaches Towards Members of the Nargenicin Family

This chapter presents literature describing various approaches towards syntheses of nargenicins and branimycin. Synthetic studies towards luminamicin[12] and lustromycin[12a] are not discussed, as to date efforts have focused solely on creation of the oxa-bridged *cis*-decalin core; which principally differs from branimycin in the position of the oxa-bridge.

2.1. Kallmerten's Synthesis of Oxa-Bridged *cis*-Decalin Nucleus of the Nargenicins.

The first synthetic effort towards the nargenicin family was reported by Kallmerten[13] on the development of a very elegant approach towards the oxa-bridged *cis*-decalin core of nargenicins (Scheme 4). The *cis*-decalin system was synthesized in a racemic manner *via* Diels-Alder cycloaddition between diene **13** and quinone **14**. Subsequent reduction of both carbonyl groups gave **15**, which was further acetalized to leave only one OH-group free. Introduction of the methyl substituent at C10 (nargenicin numbering) was accomplished *via* an S_N'-displacement of a mesylate derived from alcohol **16**.



Scheme 4: Kallmerten's model studies towards nargenicins core

The acetal was then cleaved and the allylic alcohol selectively oxidized to deliver ketone **18**. The remaining free OH-group was protected as a MOM-ether, followed by regioselective epoxidation at the more electron rich double bond to give epoxide **19** (dr 1.8 : 1). The key step of Kallmerten's approach comprises a 1,2-addition of a C-nucleophile (MeMgBr as a model nucleophile) to the carbonyl group, and the subsequent formation of the oxa-bridge *via* intramolecular opening of the epoxide with the resulted alkoxide.

2.2. Kallmerten's Synthesis of 18-Deoxynargenicin

A few years later, Kallmerten's group reported[14] the first total synthesis of 18-deoxynargenicin, basing on the earlier approach towards the oxa-bridged nargenicins core (Chapter 2.1). The C14-C19 side chain was synthesized based on opening of the chiral epoxide **21** and subsequent coupling of a sulfonate with a methylcuprate reagent (Scheme 5). Alkyne **22**

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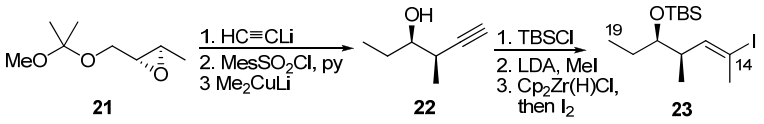
[12] (a) Sunazuka, T.; Handa, M.; Hirose, T.; Matsumaru, T.; Togashi, Y.; Nakamura, K.; Iwai, Y.; Omura, S Tetrahedron Lett., **2007**, *48*, 5297-5300. (b) Gossinger, E; Schwartz, A.; Sereinig, N. *Tetrahedron* **2000**, *56*, 2007-2014. (c) Evans, J. M.; Kallmerten, J. *Synlett* **1992**, *4*, 269-271.

[13] Kallmerten, J. *Tetrahedron Lett.* **1984**, *25*, 2843-2846.

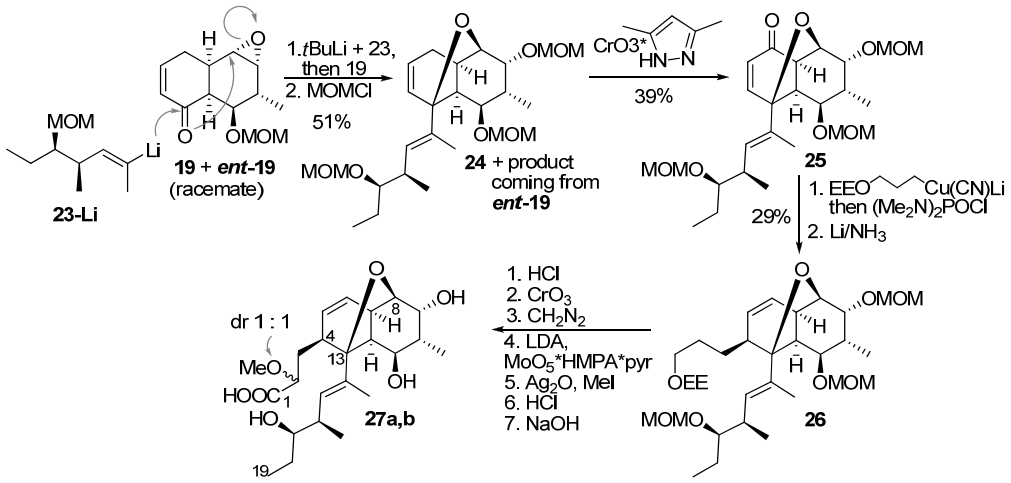
[14] Plata, D. J.; Kallmerten, J. *J. Am. Chem. Soc.* **1988**, *110*, 4041-4042.

was elaborated to give **23** in three steps: TBS-protection, terminal C-methylation and regioselective hydrozirconation-iodination.



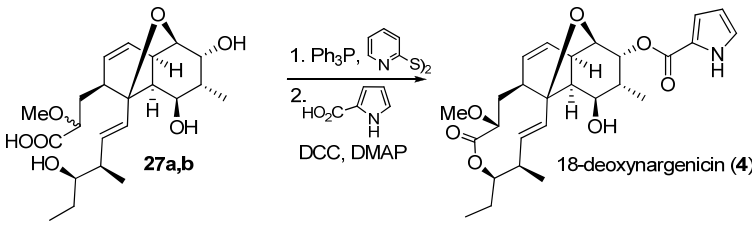
Scheme 5: Kallmerten′s synthesis of the C14-C19 side-chain

Connection of side chain **23** with *cis*-decalin core ***rac*-19** with concomitant formation of the oxa-bridge was achieved (Scheme 7) following their earlier strategy to give a mixture of diastereomeric products, as starting epoxy ketone **19** was



Scheme 6: Kallmerten′s synthesis of seco-acid **27a,b**

used in racemic form. Allylic oxidation gave α,β-unsaturated ketone **25**, which was subjected to stereoselective conjugate addition with C_3-nucleophile. The resulting enolate was then trapped as the phosphoimidate, which was reduced to the corresponding alkene **26** under Birch conditions. Conversion of the C4 side chain to the corresponding ester, α-oxygenation, methylation, saponification and global deprotection gave seco-acid **27a,b** as a mixture of diastereomers. Finally, macrolactonization and esterification at 9-OH completed the synthesis of 18-deoxynergenicin (Scheme 7). Interestingly, from two diastereomeric acids **27a,b**, only the desired diastereomer gave the product of macrolactonization.

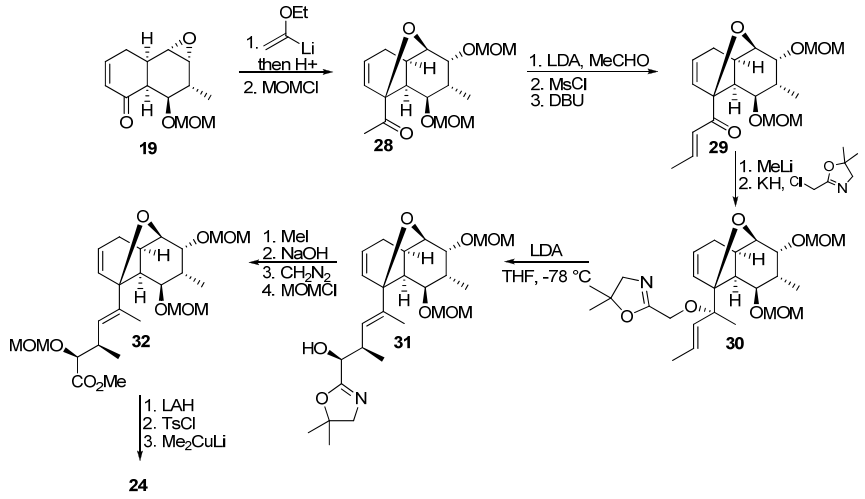


Scheme 7: Completion of the synthesis of 18-deoxynargenicin

Although the whole synthesis developed by Kallmerten is quite elegant, many steps unfortunately resulted in rather low yields (allylic oxidation, introduction of the C4 side chain) or stereoselectivity (epoxidation, ester α-oxygenation). Moreover, the *cis*-decalin core **19** was synthesized in racemic form. Nevertheless, so far it remains the only complete synthesis of a member of the nargenicin family.

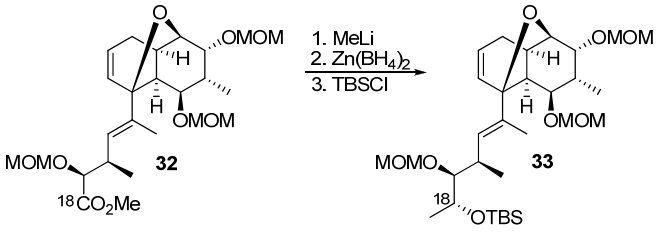
2.3. Kallmerten's synthesis of C14-C19 side-chains of nargenicins via [2,3] Wittig rearrangement

The same group also undertook studies[15] towards introduction of the C14-Cl9 side chain based on translation of stereo-information of core **19** (Scheme 8). The key steps include chelation-directed 1,2-stereoselective addition of MeLi to the carbonyl group of **29,** etherification and subsequent highly stereoselective [2,3] Wittig rearrangement to deliver **31.** To complete a formal synthesis of 18-deoxynargenicin, **31** was converted into synthetic intermediate **24** (*cf.* Scheme 6).



Scheme 8: Kallmerten's **s**ynthesis of the C14-C19 side-chain *via* [2,3] Wittig rearrangement

Installation of the oxygen functionality at C18 was achieved *via* diastereoselective reduction of a ketone, which in turn was derived from ester **32** (Scheme 9).



Scheme 9: Introduction of the C18 stereocenter

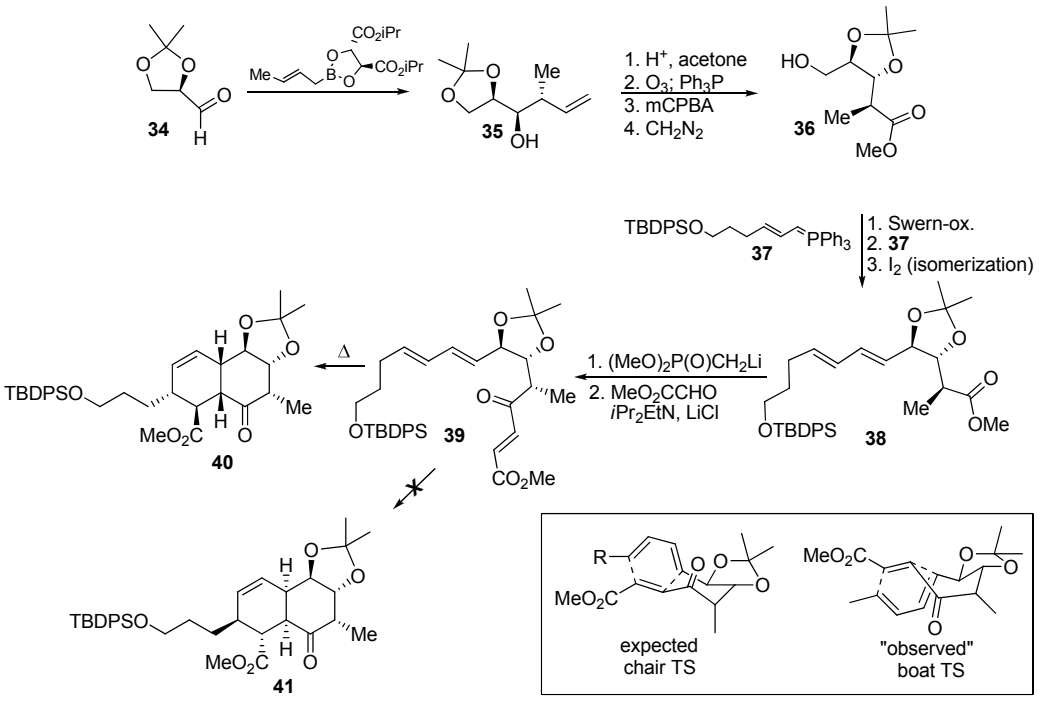
Although the sequences to **24** and **33** are highly diastereoselective, this approach suffers from lengthy linear sequences and relatively low overall yields.

2.4. Roush' IMDA Approach to the *cis*-Decalin Core of Nargenicins

Roush *at al*. carried out investigations of an intramolecular Diels-Alder reaction (IMDA) aimed at the synthesis of the *cis*-decalin core of nargenicin A_1.[16] Based on the expected for the key IMDA chair-like transition state (Scheme 10), a required substrate **39** was synthesized. Towards this end, aldehyde **34** underwent a crotylation reaction, to provide **35.** The acetonide protecting group was shifted; and the vinyl substituent converted to the corresponding aldehyde by ozonolysis. The

[15] Rossano, L. T.; Plata, D. J.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, 5189-5191.
[16] Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915-930.

latter underwent further oxidation to the carboxylic acid, which after esterification with CH_2N_2 gave **36**. The alcohol group was then oxidized to the aldehyde, which after a Wittig olefination reaction gave a mixture of diene isomers. Isomerization of the *Z*-diene with a catalytic amount of I_2 gave the desired *E*-diene **38** in configurationally pure form. Finally, **38** was elaborated to deliver **39** in two standard steps, thus setting the stage for the key IMDA.



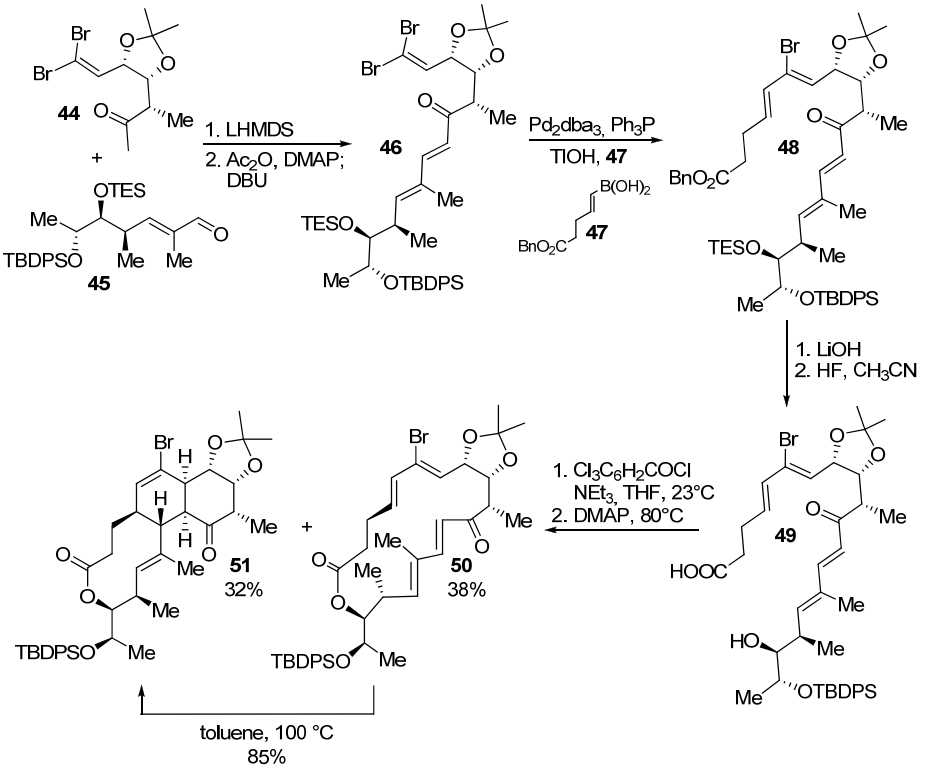
Scheme 10: Roush′ IMDA Approach to the *cis*-Decalin Core of Nargenicins

Surprisingly, the product **40** obtained from the IMDA reaction under thermal conditions, possessed a different configuration from that which was expected (**41**), what could be explained by the high preference for such a cyclization through boat-like transition state (Scheme 10). Investigations of various diastereomeric substrates revealed that the involvement of a boat-like transition state in decatrienone intramolecular Diels-Alder reactions appears to be general.

2.5. Roush′ Transannular Diels-Alder Cyclization to Nargenicin A_1 Framework

As studies of the IMDA reaction did not result in the synthesis of the nargenicin core, Roush *et al.* turned their attention to an alternative approach, to create complete carbon framework of nargenicin *via* a transannular Diels-Alder reaction.[17] Indeed, this approach seems to be very attractive, as all stereocenters would come from the requisite progenitor acyclic substrate, which in turn could be constructed employing well developed methods for synthesis of polyketide moieties. Moreover, the troublesome 10-membered lactone would be established by a ring contraction of the more easily synthesizable 18-membered lactone.

[17] Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J**.** *J. Am. Chem. Soc.* **1996**, *118,* 7502-7512.



Scheme 11: Roush′ Transannular Diels-Alder Cyclization to Nargenicin A_1 Framework.

Towards this end condensation between ketone **44** and aldehyde **45** gave dienone **46** possessing the required dienophile moiety for the forthcoming Diels-Alder cyclization. The diene moiety was then introduced *via* Suzuki coupling to give **48**, which in turn was subjected to saponification conditions and selective TES-deprotection. The key macrolactonization was performed employing Yamaguchi conditions, and yielded 18-membered lactone **50** together with the product of subsequent transannular Diels-Alder cyclization, **51**. Macrolactone **50** was converted to **51** under thermal conditions.

Although the carbon framework of nargenicin was established quite efficiently, all attempts to introduce the requisite oxa-bridge unfortunately failed, and so far this approach has not culminated in the completion of the synthesis.

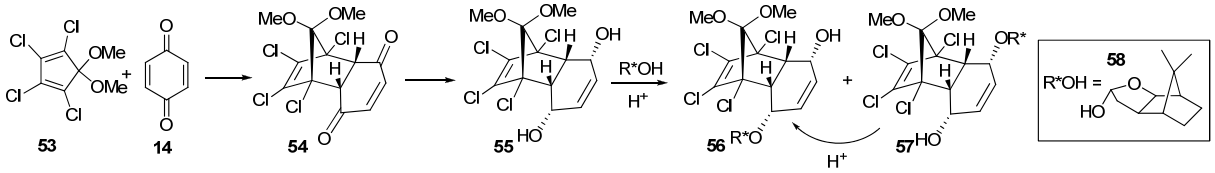
Interestingly, a sequence of a macrolactonization - transannular Diels-Alder cyclization is possibly used by nature for the biosynthesis of nargenicin A_1, as proposed by Cane *et al.* based on biosynthetic studies.[18]

2.6. Gössinger's Approach Towards Nodusomicin

Similar to the approach of Kallmerten to the nargenicin *cis*-decalin core, approach of Gössinger *et al.*[19] starts from Diels-Alder reaction of quinone **14** and cyclopentadiene **53** (Scheme 12). Subsequent reduction gave diol **55,** which was desymmetrized employing chiral derivatizing reagent, acetal **58**. In contrast to Kallmerten′s approach, this scheme gave access to a chiral *cis*-decalin core.

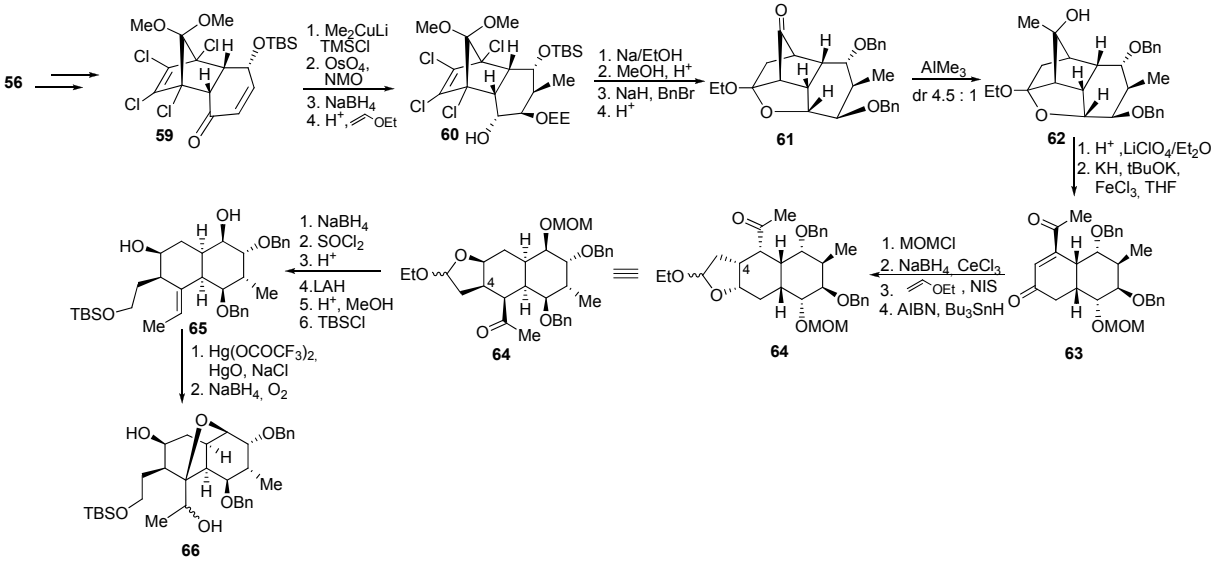
[18] Cane, D. E.; Guanglin, L. *J.* Am. Chem. Soc. **1995**,*117*, 6633-6634.

[19] (a) Gössinger, E.; Graupe, M.; Kratky, C.; Zimmermann, K. *Tetrahedron* **1997**, *53,* 3083-3100. (b) Gössinger, E.; Schwartz, A.; Sereinig, N. *Tetrahedron* **2000**, *56*, 2007-2014. (c) Gössinger, E.; Schwartz, A.; Sereinig, N. *Tetrahedron* **2001**, *57*, 3045-3061.



Scheme 12: Gössinger's approach towards enantiopure *cis*-decalin core **56**

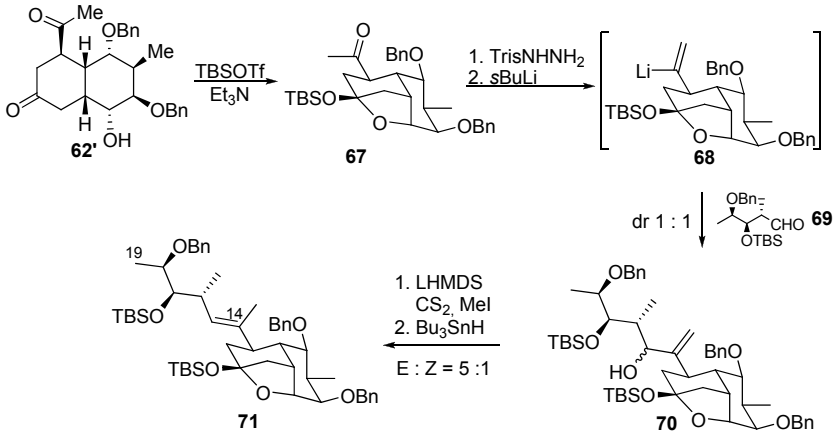
α,β-Unsaturated ketone **59** (Scheme 13), was prepared in a few steps from **56** and subjected to the stereoselective conjugate addition with dimethylcuprate, which was followed by stereoselective hydroxylation of the resulted silyl enolate. Carbonyl reduction and selective mono-protection delivered **60**. The double bond was then "desymmetrized" by formation of a THF-ring *via* intramolecular nucleophilic addition of sodium alcoholate and successive Cl-substitution and dechlorination in one step. The EE-protecting group was exchanged with benzyl, and the bridge situated acetal was hydrolized to give monoketone **61**.



Scheme 13: Gössinger's approach towards nodumicin

Crucial for the next step, the stereoselective addition of Me to the bridge residing carbonyl group was achieved by reaction with $AlMe_3$. Tertiary alcohol **62** was subjected to regioselective cleavage of the bridge *via* a pinacol-like rearrangement by treatment with an acid in a strong ionizing media. Subsequent introduction of the double bond gave endione **63**. The free OH-group was protected as its MOM-ether and a C4-side chain was introduced in three steps: regioselective reduction of the cyclic keto-group; formation of β-iodoacetal; and reductive radical cyclization to furnish **64**. Reduction of ketone **64**, followed by elimination of the resulted OH-group created the required *exo*-double bond. A sequence of standard transformations gave **65**, which was subjected to pivotal oxa-bridge formation *via* an oxymercuration reaction. Treatment of the resulted organomercury intermediate with $NaBH_4/O_2$ provided compound **66**. Compound **66** was the most advanced synthetic intermediate towards nargenicin A_1, reported by Gössinger group.

Studies towards the assembly of C14-C19 side chain resulted in development of the sequence are presented in Scheme 14. The cyclic ketone was selectively protected *via* formation of an acetal. The remaining carbonyl was converted into



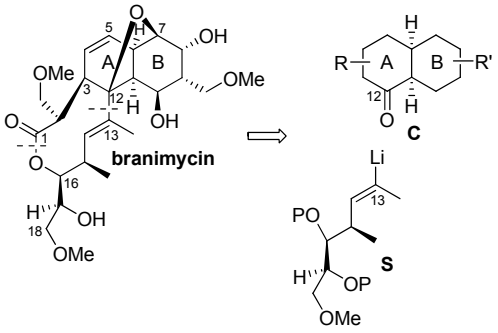
Scheme 14: Introduction of the C14-C19 side-chain

hydrozone and then into vinyllithium species **68**, which was reacted with aldehyde **69**. Reductive Barton-McCombie deoxygenation sequence accompanied with by a double bond shift led to **71** as a 5:1 mixture of E/Z geometric isomers.

The approach developed by Gössinger encompasses an impressive sequence of stereoselective reactions and creative ideas. Unfortunately, the relatively high number of steps and retirement of Prof. Gössinger precluded completion of the nargenicin synthesis.

2.7. Approaches Towards Branimycin in Mulzer Group

The general retrosynthetic analysis of branimycin in the Mulzer group features cleavage of macrolactone and disconnection at C12-C13 (Scheme 15). This provides the corresponding metallated side chain **S** and the *cis*-decalin core **C** possessing C12-keto group.



Scheme 15: General retrosynthetic analysis of branimycin in the Mulzer group

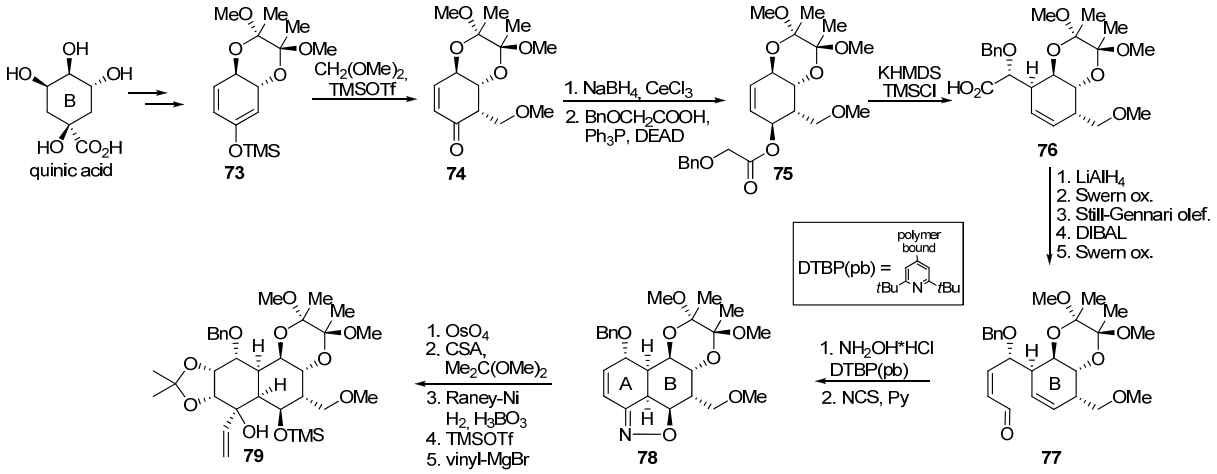
Besides aiming to accomplish the synthesis of branimycin, the focal point of the investigations in the Mulzer group lies on the development of various approaches towards the *cis*-decalin core **C**.

2.8. INOC Approach to the *cis*-Decalin Core of Branimycin (Mulzer Group)

This approach[20] (Scheme 16) was based on a possibility to construct the *cis*-decalin core of branimycin by intramolecular nitrile oxide cyclization (INOC). The synthesis commenced from literature known compound **73**, derived from naturally occurring (-)-quinic acid. Silyl enol ether **73** was alkylated at the α-position, to deliver ketone **74**. Luche reduction, followed by esterification under Mitsunobu conditions provided allylic ester **75**. In the next step, chelation-controlled glycolate enolate Ireland-Claisen rearrangement led to acid **76** as a single isomer. C_2-Elongation at the acid carbon

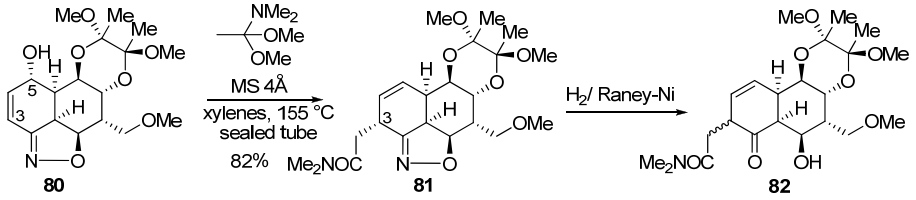
[20] Enev, V. S.; Drescher, M.; Mulzer, J. *Tetrahedron* **2007**, *63*, 5930-5939.

was performed in 5 standard steps to deliver *Z*-α,β-unsaturated aldehyde **77**. Challenging formation of the corresponding *Z*-α,β-unsaturated oxime without isomerization of the double bond to the *E*-isomer was performed employing polymer supported di-*tert*-butylpyridine, as a base, and thus the stage for the key INOC reaction was set. Treatment of the oxime with NCS/Py resulted in one step oxime chlorination; formation of a nitrile oxide and 1,3-diploal cycloaddition, giving the *cis*-decalin core **78** in high yield.



Scheme 16: INOC Approach to the *cis*-decalin core of branimycin

Stereoselective dihydroxylation, acetal formation, reductive cleavage of the isoxazoline moiety, followed by protection of the resulting alcohol as its TMS-ether gave a ketone, which was treated with vinylmagnesium bromide (as a model nucleophile), thus demonstrating, that such highly functinalized hindered substrate can undergo nucleophilic addition (**79**) to the carbonyl group (**79**) and not only enolization.



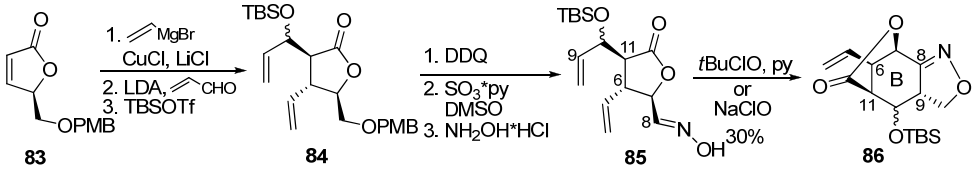
Scheme 17: Introduction of the C3 appendage *via* Eschenmoser-Claisen rearrangement

In the same work the authors tested introduction of the C3-appendage *via* Eschenmoser-Claisen rearrangement. Unfortunately, substantial epimerization occurred under conditions of the isoxazoline ring cleavage (Scheme 17).

2.9. INOC Approach Towards the Ring B of Branimycin (Mulzer Group)

An alternative approach towards the *cis*-decalin core of branimycin employed another INOC reaction for construction of the ring B.[21,22] The synthesis started with a copper catalyzed stereoselective Michael addition of vinyl Grignard reagent to **83**. Subsequent aldol reaction with acrolein and TBS-protection gave **84** as a mixture of diastereomers. PMB-cleavage, oxidation of the resulted alcohol to its aldehyde and reaction with hydroxylamine gave requisite oxime **85**. Treatment of **85** with *t*BuOCl or NaClO gave the desired products of INOC although in rather low yields.

[21] Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev V. S. *Chem. Eur. J.* **2006**, *12*, 5992 – 6001.
[22] Partly unpublished results are presented.

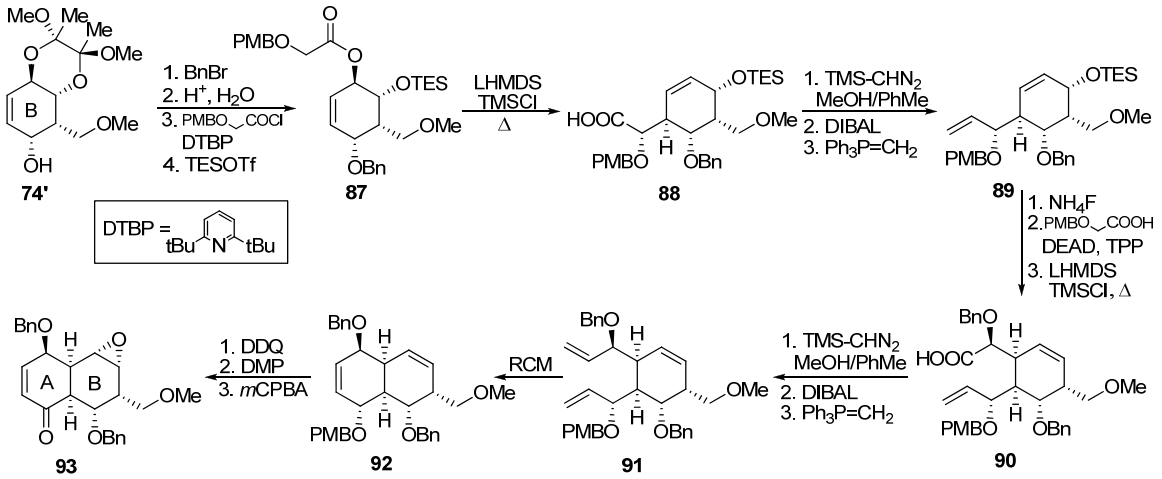


Scheme 18: INOC Approach towards the ring B of branimycin

Improvement of the key INOC reaction step was a part of this PhD thesis. Obtained results are discussed in Chapter4.

2.10. Double Claisen Rearrangement – RCM Approach Towards the *cis*-Decalin Core of Branimycin (Mulzer Group)

This approach was based on an idea to create the *cis*-decalin moiety by ring closing metathesis.[23] Departing from the appropriately functionalized ring B, vinylic substituents required for RCM were introduced in a stereoselective manner by two successive Ireland-Claisen rearrangements.



Scheme 19: Double Claisen rearrangement – RCM approach to the *cis*-decalin core of branimycin

The synthesis started from previously synthesized alcohol **74'**.[20] Protecting group manipulations followed by acylation gave allylic ester **87**, which was involved in a chelation-controlled glycolate enolate Ireland-Claisen rearrangement to give acid **88**. Esterification, reduction to its corresponding aldehyde followed by Wittig olefination provided **89**, containing the first of two vinylic substituent required for the forthcoming RCM. TES-cleavage and esterification, under Mitsunobu conditions, gave allylic ester, which was involved in the second Ireland-Claisen rearrangement to furnish acid **90**. Repetition of the established 3-step sequence introduced the second vinylic substituent in **91.** Ring closing metathesis successfully provided *cis*-decalin **92**, which was subjected to PMB-deprotection; Dess-Martin oxidation and epoxidation of the more electron rich double bond to accomplish the desired *cis*-decalin core **93**.

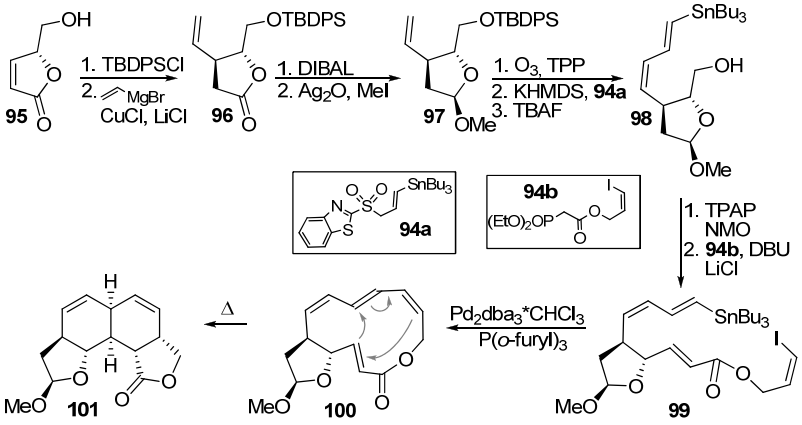
2.11. Trans-Annular Diels-Alder Approach to the *cis*-Decalin Core of Branimycin (Mulzer Group)

In this approach[24] from the Mulzer group, chiral information was transferred from lactone **95** (containing only one chiral center) to create 6 new chiral centers, 4 of which were set in just one step by a *trans*-annular Diels-Alder reaction.

Thus, protection of alcohol in **95** followed by diastereoselective Michael addition of vinyl Grignard reagent provided lactone **96**, which was partially reduced and protected as methyl the acetal. The double bond was then cleaved oxidatively

[23] Marchart, S.; Mulzer, J.; Enev, V. S. *Org. Lett.* **2007**, *9*, 813−816.
[24] Felzmann, W.; Arion, V. B.; Mieusset, J. L.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3849−3851.

and the resulting aldehyde used in a modified Julia olefination, after which TBDPS deprotection furnished stannylated diene **98**. A one-pot sequence of TPAP oxidation/Roush-Masamune olefination provided unsaturated ester bearing a vinyl iodide moiety **99**. The key intramolecular Stille-coupling reaction furnished the desired macrocycle **100**, which under thermal



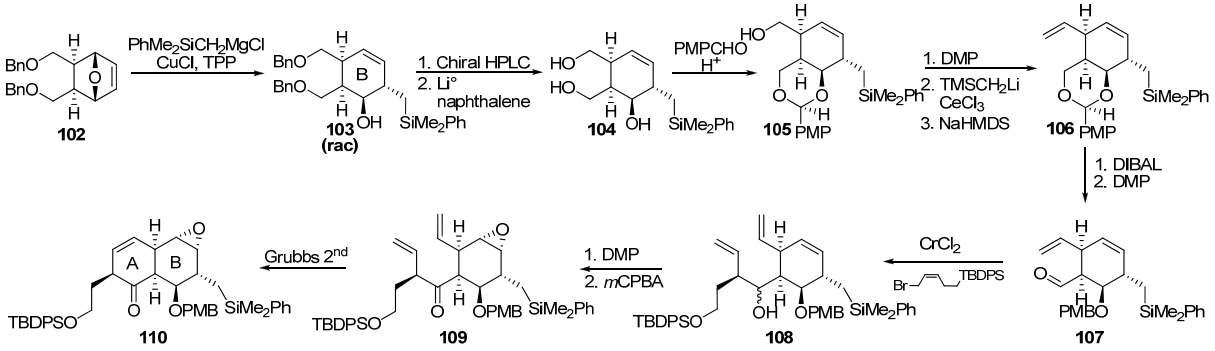
Scheme 20: *Trans*-annular Diels-Alder Approach to the *cis*-decalin core of branimycin

conditions was converted smoothly to **101**, containing the required *cis*-decalin core of branimycin, in highly diastereoselective manner (Scheme 20).

2.12. S_N' oxa-Bridge Opening – RCM Approach to the *cis*-Decalin Core of Branimycin (Mulzer Group)

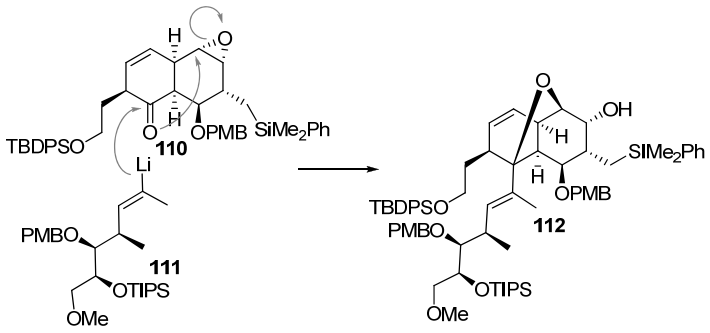
Similar to a previous approach from the Mulzer group (Chapter 2.10), this approach relied on the possibility to establish *cis*-decalin moiety *via* an RCM reaction.

The synthesis commenced with the opening of the oxa-bridge of **102** with a Grignard reagent under copper catalysis, to provide racemic **103**. Resolution of enantiomers by chiral HPLC and subsequent benzyl cleavage gave enantiomerically pure triol **104**. After regioselective formation of the PMB-acetal, with *p*-methoxybenzaldehyde, the remaining free primary alcohol was oxidized to its aldehyde by Dess-Martin periodinane. Olefin **106** was obtained, employing an especially devised modification of the Peterson protocol for enolizable substrates. Regioselective reductive opening of the PMB-acetal resulted in liberation of the primary alcohol to give **107**, which after oxidation resulted in aldehyde**107**. Further reaction of aldehyde



Scheme 21: S_N' oxa-Bridge opening – RCM approach to the *cis*-decalin core of branimycin

107 with an allyl-chromium reagent gave a mixture of diastereomeric alcohols, **108**. Oxidation to ketone, followed by epoxidation of the most electron rich double bond delivered epoxide **109** possessing both vinyl substituents for the RCM reaction. Ring closing metathesis resulted in clean formation of *cis*-decalin core **110** (Scheme 21).



Scheme 22: Coupling of the side-chain with the *cis*-decalin core and formation of the oxa-bridge

Connection of the *cis*-decalin core with the side chain and the subsequent oxa-bridge formation were performed by coupling epoxy ketone **110** with pre-metalated side chain **111** (derived from its corresponding vinyl iodide[25]) to give the expected oxa-bridged product **112** (Scheme 22). In contrast to Kallmerten's approach (Chapter 2.2), ketone **110** contains the α-proton highly acidified by the adjacent double bond. This makes addition (*vs.* enolization) of any nucleophiles to the carbonyl highly challenging!

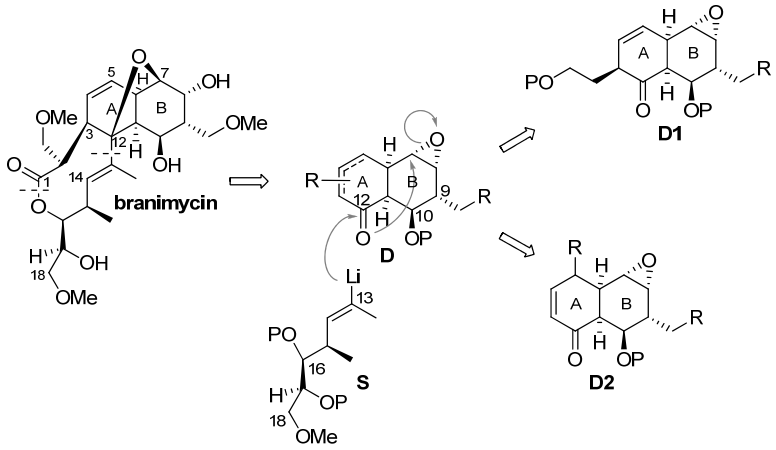
[25] Felzmann, W.; Castagnolo, D.; Rosenbeiger, D.; Mulzer, J. *J. Org. Chem.* **2007**, *72*, 2182-2186.

3. Structural Features of Branimycin and Outline of the Synthetic Plan

Besides its promising biological activity, branimycin (Scheme 15) attracted our attention by its very challenging structure. The key features of the branimycin structure are:

- a *cis*-decalin core
- an oxa-bridge across the *cis*-decalin core
- a 9-membered lactone with an internal *trans*-double bond
- a highly oxygenated structure
- 12 stereocenters

Our general retrosynthetic analysis of branimycin features cleavage of the macrolactone and disconnection of the C12-C13 bond (Scheme 15). This gives corresponding metallated side chain **S** and *cis*-decalin core **D.** For the latter, we imagined two candidates: core **D1**, containing C_2-appendage at C3; and core **D2**, where the C_2-appendage would be introduced at a later stage of the synthesis.



Scheme 23: Retrosynthesis of branimycin

Cis-Decalin Core

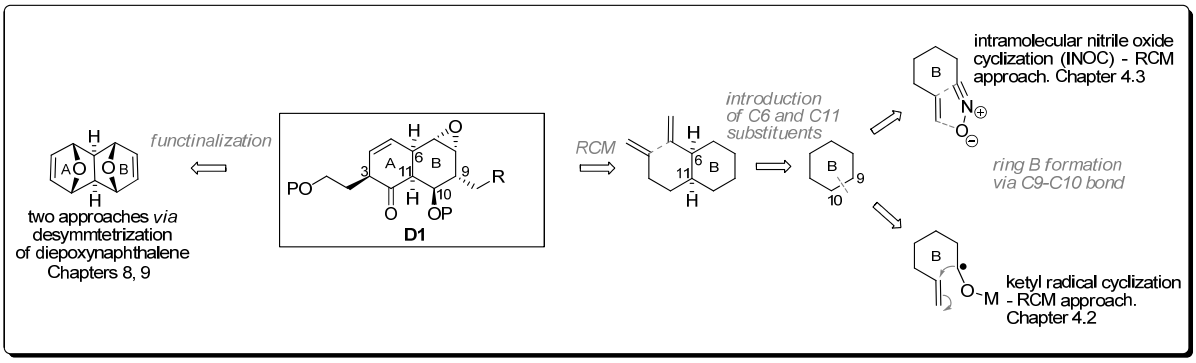
Four approaches towards **D1** and two approaches towards **D2** have been investigated in the course of our studies.

Approaches towards core **D1** are outlined in Scheme 24:

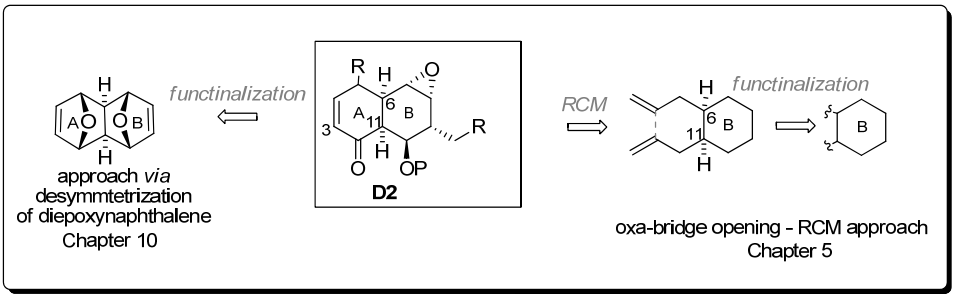
- two approaches based on creation of the carbocycle B *via* formation of the C9-C10 bond, introduction of alkene substituents at the C6 and C11 positions, and subsequent formation of the ring A *via* a ring closing metathesis. One of the approaches expected formation of the C9-C10 bond *via* an intramolecular [3+2] nitrile oxide cyclization (Chapter 4.3). In the other approach, this bond would be formed *via a* ketyl radical cyclization (Chapter 4.2).
- two approaches where the *cis*-decalin carbon framework was created right at the beginning, and all following transformations were focused on construction of the functional group pattern *via* desymmetrization of diepoxynaphthalene **141** (Chapters 8 and 9).

Approaches towards core **D2** can be seen in Scheme 25:

- an approach based on the functionalization of the initially presented ring B, followed by introduction of substituents at the C6 and C11 positions; and formation of ring A *via* ring closing metathesis (Chapter 5).
- an approach where the *cis*-decalin carbon framework was constructed right at the beginning, and all following transformations were focused on creation of the functional group pattern *via* desymmetrization of diepoxynaphthalene (Chapter 10).



Scheme 24: Approaches towards core **D1**



Scheme 25: Approaches towards core **D2**

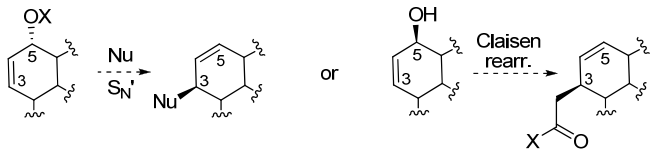
C13-C18 Side-Chain

The synthesis of side-chain **S** has been previously reported[25] in the Mulzer group. Substantial improvements have also, however, been achieved regarding its synthesis (Chapter 11).

End-Game

After connection of the *cis*-decalin core and the C13-C18 side-chain, the key points of the end game are as follows:

- In the approaches towards *cis*-decalin core of type **D2**, the C_2-appendage at the position C3 should be introduced at a late stage *via* an S_N' substitution or Claisen rearrangement (Scheme 26):



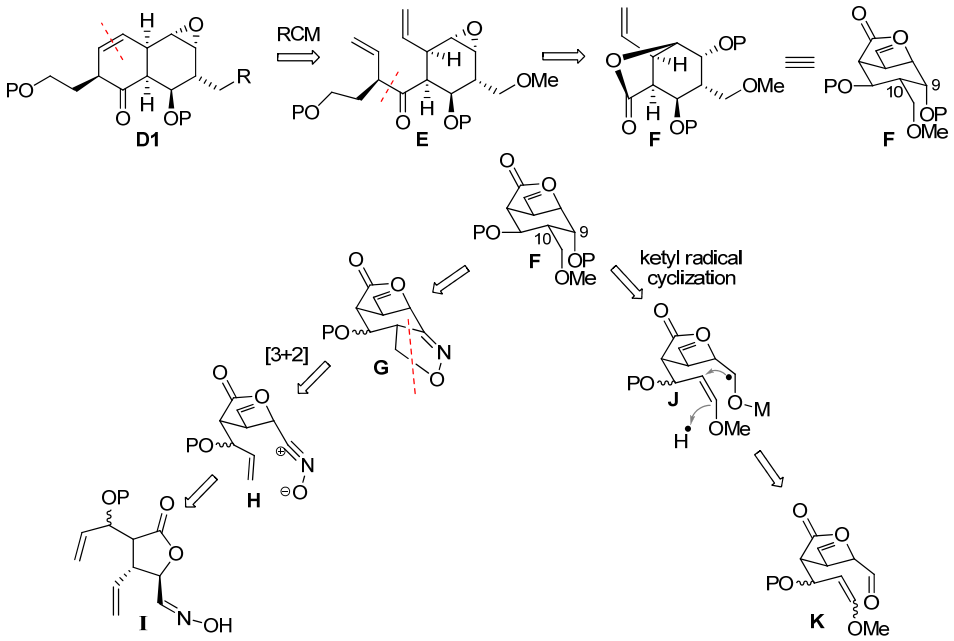
Scheme 26: Introduction of the C3 appendage

- Appendage CH_2OMe, at the C2-position, could be introduced either after macrolactonization by functionalization of the corresponding lactone; or alternatively, the order of these two steps could be reversed.
- Side-chain C13-C18 possesses two alcohol groups at C16 and C17. Although selective macrolactonization at 16-OH in the presence of free 17-OH cannot be excluded *a priori*, this route appears quite risky, as a10-membered lactone (i.e. cyclization on 17-OH) should be less strained than the 9-membered lactone (i.e. cyclization on 16-OH). Therefore, 16-OH and 17-OH should be protected by orthogonal protecting groups.

4. Lactone-Based RCM Approach Towards the *cis*-Decalin Core of Branimycin

4.1. Introduction and Synthetic Outline

The first option which we envisioned for a retrosynthetic disconnection of *cis*-decalin core **D1** is shown in Scheme 27. It was based on the possibility to create a *cis*-dicalin moiety *via* ring closing metathesis of corresponding diene **E**, which would be derived from lactone **F**.



Scheme 27: Lactone-based RCM approach towards core **D1**

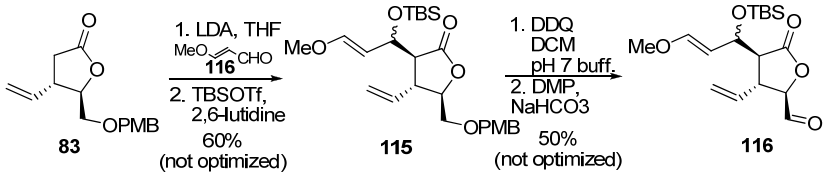
Earlier studies in the Mulzer group (Scheme 18) towards the synthesis of lactone **F** resulted[26] in development of synthesis of isoxazoline **86** (Scheme 18, **86** equals **G**, with P = TBS) *via* intramolecular 1,3-dipolar cyclization of nitrile oxide **85′** (**H**, P = TBS) derived from oxime **85** (**I**, P = TBS). Although the whole sequence the oxime **85** (**I**, P = TBS) was very efficient (Chapter 2.9)[26], the key [3+2] cycloaddition resulted in only 31% yield of isoxazoline **86** (**G**, P = TBS)**.**

Our initial goal consisted of optimization of this key [3+2] cycloaddition and parallel investigation of an alternative approach to lactone **F** *via* intramolecular cyclization of ketyl radical **J**, derived from aldehyde **K.**

4.2. Ketyl Radical Cyclization Approach Towards Key Lactone Intermediate

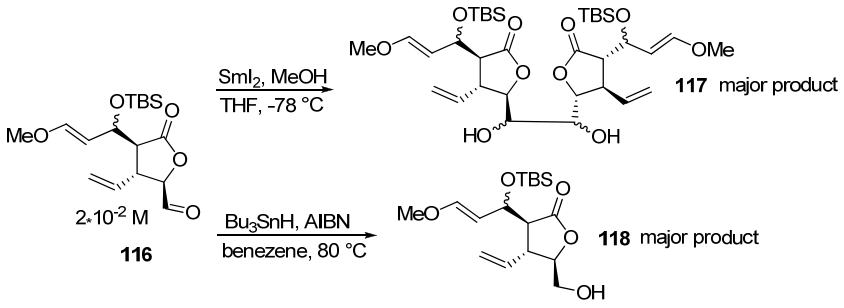
Requisite aldehyde **116** (**K**, P = TBS) for the cyclization was synthesized basing on the synthesis developed for **85** (Scheme 18). Lactone **83** was involved in an aldol reaction with literature known[27] aldehyde[28] *E*-methoxyacroleine (Scheme 28), giving a mixture 1 : 1 of diastereomeric alcohols. Subsequent TBS protection, cleavage of PMB and Dess-Martin oxidation of the resultant alcohol gave desired aldehyde **116.**

[26] Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev V. S. *Chem. Eur. J.* **2006**, *12*, 5992 – 6001.
[27] Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833-2838.
[28] We could not say *a priori* which configuration of the aldehyde double bond should give the desired configuration of new stereocenters. Therefore, the most easily accessible *E*-aldehyde **116** was chosen.



Scheme 28: Synthesis of aldehyde **116**

Unfortunately, all attempts to induce cyclization proved unsuccessful. Thus, treatment of aldehyde **116** with SmI_2 gave only a mixture of pinacol coupling products **117**; whereas reaction with Bu_3SnH and AIBN resulted in reduction to alcohol **118.**

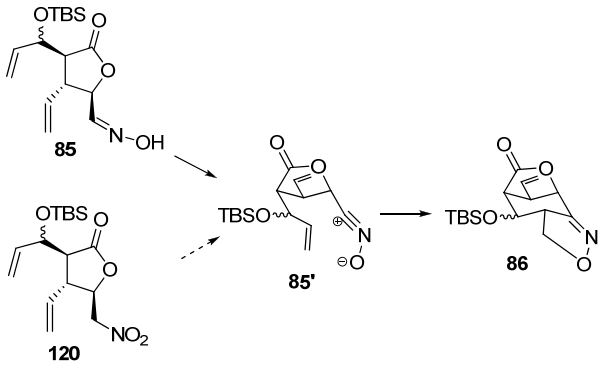


Scheme 29: Attempts towards the ketyl radical cyclizations

At this point we turned to the second approach, based on [3+2] cyclization, and further investigation of ketyl radical cyclizations were abounded.

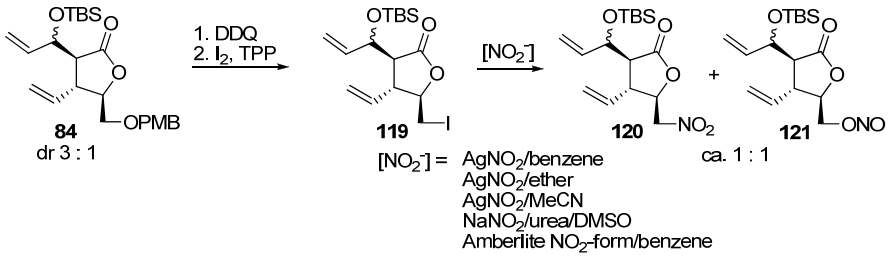
4.3. INOC Approach Towards Key Lactone Intermediate.

Parallel to the ketyl radical cyclization approach (Chapter 4.2), investigations were continued on intramolecular nitrile oxide cyclization (INOC) approach, which had been started earlier in our group (Chapter 4.1).



Scheme 30: Two approaches to nitrile oxide **85'**

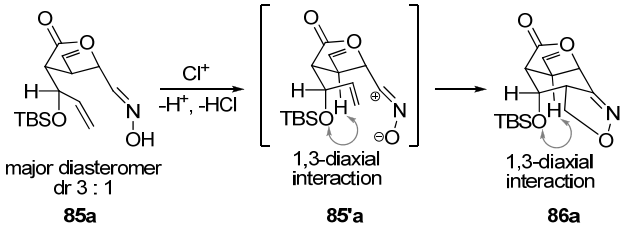
As oxime **85** gave a low yield (31%) in cyclization to **86**, we decided to generate nitrile oxide **85′** from its corresponding nitro compound **120,** instead of originally used oxime **85** (Scheme 30). Towards this end, iodide **119** was synthesized from a known[21] precursor **84** *via* PMB-deprotection, followed by an Appel reaction (Scheme 31).



Scheme 31: Synthesis of nitro compound **120**

Unfortunately, all attempts to convert iodide **119** into nitro compound **120** gave a mixture of **120** and nitrite **121** in moderate yields, and therefore this pathway was abandoned.

Coming back to generation of nitrile oxide from oximes, we analyzed possible reasons for the low yield of the cyclization of TBS-protected oxime **85.** We realized, that the major[29] diastereomer **85a** gives rise to product **86a** with OTBS-substituent in the axial position, which could lead to a 1,3-diaxial repulsion in transition state **85′a** (Scheme 32).



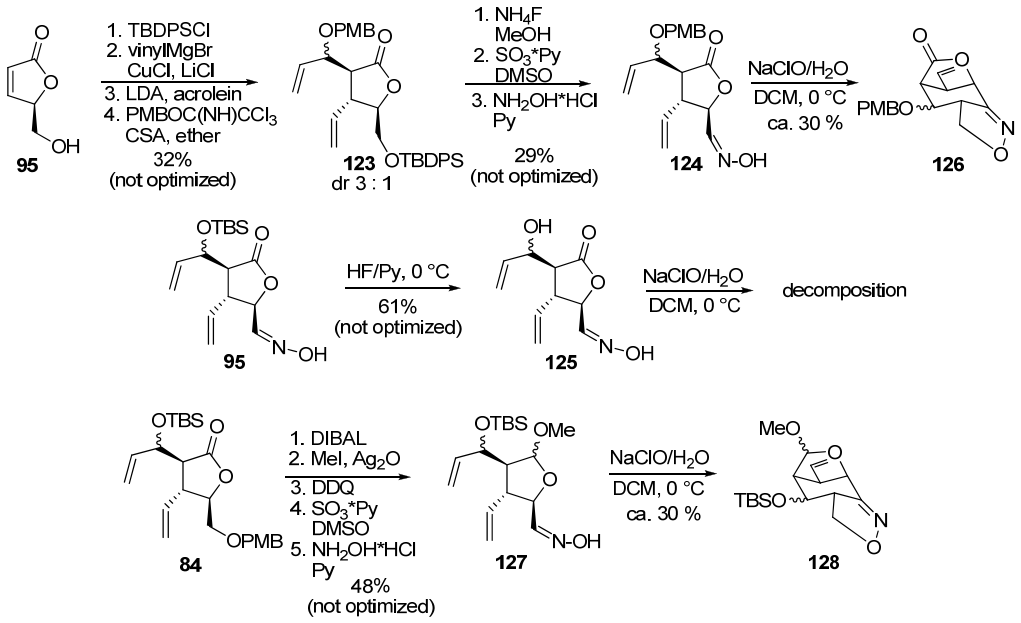
Scheme 32: Cyclization of the major diastereomer **85a**

We speculated that by changing to a smaller protecting group could diminish this unfavorable diaxial interaction. To this end, compound **124** with less bulky PMB-protecting group and compound **125** bearing no protecting group at the OH group were synthesized (Scheme 33). Thus, alcohol **95** was protected as its TBDPS-ether, followed by vinyl cuprate 1,4- addition; aldol reaction with acrolein and protection of the resulting alcohol with PMB-Bundle′s reagent, to give compound **123.** The silyl group was cleaved with NH_4F, the obtained alcohol oxidized to its corresponding aldehyde and converted to oxime **124.** Compound **125** was synthesized from oxime **85** by TBS-cleavage under mild conditions (Scheme 33).

Unfortunately, cyclization of oxime **125** under standard conditions resulted in decomposition, whereas oxime **124** gave the desired product in almost the same yield (30%) as was obtained from cyclization of oxime **85**.

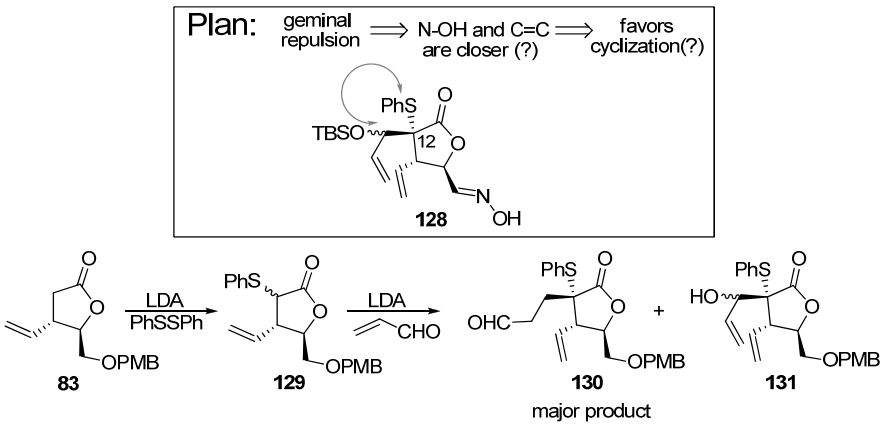
Continue variations in oximes structure, compound **127** with a methyl lactol moiety instead of the lactone group was synthesized from **84** in 5 steps (Scheme 33): reduction of lactone to lactol, methyl protection, PMB-deprotection, oxidation to aldehyde and conversion into oxime **127**. Disappointingly, cyclization of **127** gave the desired product **128** in the "already traditional" ca. 30% yield.

[29] Extensive studies by Dr. Pilger (Prof. Mulzer research group) did not result in desired inversion of stereoselectivity. A possibility to invert the configuration at C10 before cyclization did not seem promising (easy) due to lability of the vinyl aldol fragment in **84** (Scheme 18).



Scheme 33: Synthesis and [3+2] cyclizations of various substrates

As a "rescue plan", we decided to introduce a dummy SPh-group at C12 in **128**, which due to geminal steric repulsion had to bring the allylic alcohol substituent closer to the oxime group and possibly facilitate cyclization (Scheme 34). For this reason, lactone **83** was treated with LDA followed by PhSSPh to obtain **129.** Unfortunately, all attempts to perform the subsequent aldol reaction with acrolein gave mostly 1,4-addition product **130**, instead of the desired 1,2-addition product, **131**.[30] Alternative aldol reactions *via* Ti, Zn or Si-enolates resulted only in recovering starting lactone **129**.



Scheme 34: Effect of the dummy PhS-group

After all variations in the structures of oximes, we decided to come back to original oxime **85,** easily accessible, and study its cyclization more deep. After extensive experimentations, the yield of the desired [3+2] cyclization was dramatically improved. Results of undertaken investigations are to be submitted for publication in Tetrahedron Letters (for a copy of the manuscript see Chapter 4.4). Although the initial goal of our studies was achieved; an approach which had been investigated in parallel, appeared more promising. Therefore this INOC-based approach was fully abandoned.

[30] This could be explained *via* possibly reversible 1,2-addition due to the stabilization of enolate of **129** with the SPh-substituent and destabilization of the aldol product due to 1,2-steric repulsion of the SPh-group with the CH(OLi)vinyl-fragment.

Noteworthy, studies presented in Chapter 4.4 resulted in the development of a certain general conclusion, discussed in Chapter 13.

4.4. Publication:[31]

Remarkable Temperature Effect on the Yield of an Intramolecular [3+2] Cyclization

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Abstract: *Favoring of intramolecular cyclizations over oligomerization and other intermolecular processes can often be achieved by conducting the reaction at higher temperatures. Unfortunately, this effect seems to be relatively underrepresented in the synthetic organic literature. Herein we report one more example supporting this trend – an intramolecular nitrile oxide 1,3-dipolar cycloaddition. The yield of the desired product rose from 53% at 0 °C to 79% at 80 °C. A plausible kinetic background of this phenomenon is proposed in terms of activation enthalpy.*

Selectivity of a reaction (enantio-, diastereo-, regio-, chemoselectivity) carried out under kinetic control is often believed to increase at lower temperatures and decrease at higher temperatures. Although this phenomenon is observed quite often, this behavior should not be taken as a general rule. Indeed, a literature survey reveals a number of examples when at higher temperatures selectivity dramatically increased[32] and even the selectivity sense was inverted.[33] Moreover, temperature dependence can have a rather complex character, e.g. selectivity increases together with temperature, and after reaching a maximum starts decreasing, what is commonly attributed to a switch in a selectivity determining step.[34]

As a part of an ongoing study towards the total synthesis of branimycin[35] **1**, we explored an approach based on the construction of carbocycle B employing an intramolecular 1,3-dipolar cycloaddition of nitrile oxide **3**, derived from its corresponding oxime **4** (Scheme 2).[35] Although the whole sequence to **4** was quite efficient, the key [3+2] cyclization proved problematic.

Initial attempts to perform a sequence of *in situ* chlorination (with *t*-BuOCl/Py or $NaClO/H_2O/DCM$) - nitrile oxide formation - cyclization (Scheme 2) resulted in only 25-35% yield of the desired product **2a,b**. Therefore, we decided to carry out the chlorination as a separate reaction.

Thus, chloroxime **5a,b** was synthesized by reaction of **4a,b** with NCS[36] (Scheme 2), and then treated with a wide variety of different reagents: bases (Et_3N, 2,2′,6,6′-tetramethylpiperidine, $NaHCO_3$, MeMgCl); Lewis acids (Ag_2O, AgOTf + 2,6-ditertbutyl pyridine, $LiClO_4$+Py); combination of a weak base 2,6-ditertbutyl pyridine with a strong ionizing solvent CF_3CH_2OH; solid reagents-adsorbents (Al_2O_3, SiO_2, 4Å MS, 3Å MS). Surprisingly, in all cases the yield of product **2a,b** was

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[31] To be submitted for reviewing to Tetrahedron Letters. Compounds and Schemes numbering is kept as in the original manuscript. References and footnotes numbering continues numbering of this PhD thesis.

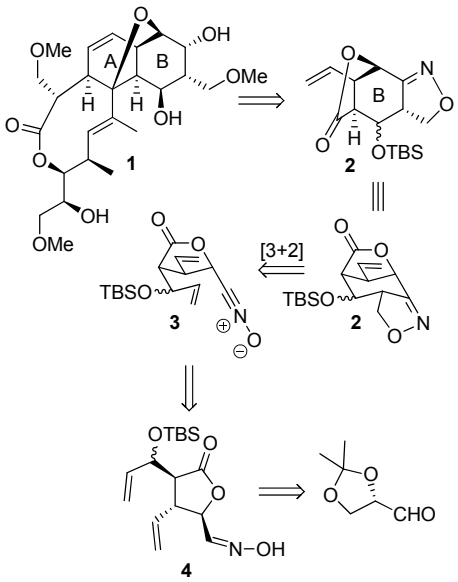
[32] For example see: (a) Ireland-Claisen rearrangement: Watanabe, T.; Hirai, G.; Kato, M.; Hashizume, D.; Miyagi, T.; Sodeoka, M. *Org. Lett.*, **2008**, *10*, 4167-4170. (b) Radical allylation: Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122,* 8873-8879. (c) Carbonyl reduction with CBS: Cho, T. R.; Chun, Y. S. *J. Chem. Soc*., *Perkin Trans. 1*, **1999**, 2095–2100.

[33] For example see: (a) Carbonyl reduction with CBS: Corey, E. J.; Yi, K. Y.; Matsuda, S. P. T. *Tetrahedron Lett.* **1992**, *33*, 2319 – 2322. (b) Michael addition: Sibi, M. P.; Gorikunti, U.; Liu, M. *Tetrahedron* **2002**, *58*, 8357–8363.

[34] For example see: (a) Addition of RLi to carbonyl: Cainelli, G.; Giacomini, D.; Galletti, P. *Chem. Commun.*, **1999**, 567–572. (b)[2+2]-Cycloaddition: Li, B.; Wang, Y.; Du, D.-M.; Xu, J. *J. Org. Chem*, **2007,** *72*, 990-997.

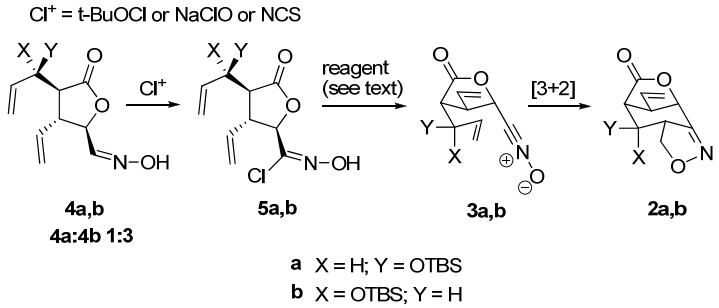
[35] Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev V. S. *Chem. Eur. J.* **2006**, *12*, 5992 – 6001.

[36] Davidson, N. E.; Rutherford**, T. J.;** Botting, N. P. *Carbohydr. Res.* **2001**, *330*, 295-307.



Scheme 1: Retrosynthesis of branimycin

in the same range of 25-35%. This fact suggested us, that constantly low yields under such different conditions could have a common origin. As there were no identifiable low molecular weight side products, we speculated that formation of nitrile oxide **3a**,**b** is not problematic, but that its *intramolecular* cyclization for some reasons is unfavorable and that **3a**,**b** could undergo *intermolecular* [3+2] cycloadditions instead leading to polymer formation.



Scheme 2: Intramolecular [3+2] cycloaddition

For further optimization studies we decided to employ the simplest option – treatment of **4a,b** with NaClO in DCM/H_2O. Slow addition of the substrate to the reagent did not substantially improve the yield possibly due to the presence of a double bond in the product **2a, b**, which could also react with nitrile oxides. In contrast, conducting the reaction simply under higher dilution ($1.5x10^{-3}$ M) resulted in distinct increase of yield (Table 1). Although encouraged by this result, it was still not satisfactory; as further dilution seemed impractical for synthesis of large amounts of **2a,b**, we turned our attention to the above mentioned temperature effect. To our delight, the yield of the cyclization product **2a,b** dramatically increased upon increase of the temperature (Table 1). Finally, when the reaction was carried out at 80 °C and at slightly higher dilution ($0.8x10^{-3}$ M), the desired product **2a,b** was isolated in 75% yield.[37]

The observed temperature effect could be rationalized by assuming that due to strain, activation enthalpy of intramolecular cyclization is higher than the activation enthalpy of intermolecular dimerization. Therefore, as follows on

[37] For the procedure and analytical data see Experimental Section for Chapter 4.4 (Publication).

from Eyring equation,[38] with increase in temperature, a reaction with a higher activation enthalpy will be accelerated more than a reaction with a lower activation enthalpy.

Table 1

Reaction of **4a,b*** with NaClO in H_2O/DCM to give **2a,b**

Conc., M	Temp.	Solvent	Yield**; dr **2b : 2a**
$1.5x10^{-2}$	0 °C	DCM	37%; 32 : 5 (31%; 28 : 3)
$1.5x10^{-3}$	0 °C	DCM	53%; 46 : 7
$1.5x10^{-3}$	22 °C	DCM or DCE	63%; 53 : 10
$1.5x10^{-3}$	40 °C	DCM or DCE	70%; 59 : 11
$1.5x10^{-3}$	60 °C	DCE	74%; 59 : 15
$1.5x10^{-3}$	80 °C	DCE	76%; 60 : 16
$0.8x10^{-3}$	80 °C	DCE	79%; 61 : 18 (75%; 60 : 15)

* 4b : 4a 75:25

** Yields were estimated39 from NMR using 4,4′-di-tert-butyl-biphenyl as an internal standard. Isolated yields and diastereoselectivity are given in parentheses. Yields are given for the mixture 2a+2b.

Favoring of cyclization over dimerization or over some other intermolecular processes due to an increase in temperature was reported for quite a number of different reactions,[40] but never observed for intramolecular 1,3-dipolar cyclization. Regarding the present work, this temperature effect was crucial for improving the intramolecular [3+2] cycloaddition leading to the key intermediate in our synthesis of branimycin.

Acknowledgment We thank Dr. Uwe Rinner (Universitiy of Vienna) and Dr. Neil Sheddan (LOBA Feinchemie GmbH) for help in the preparation of the manuscript.

[38] Eyring equation:

$$k = \frac{k_b}{h} T e^{(\frac{-\Delta H^{\neq}}{RT})} e^{(\frac{\Delta S^{\neq}}{R})} (c^{o})^{1-n} \qquad (eq.1)$$

Where k = reaction rate constant, k_B = Boltzmann′s constant [$1.381 \cdot 10^{-23}$ J K^{-1}]; T = absolute temperatures in degrees Kelvin (K); R = gas constant [8.314 J · K^{-1} · mol^{-1}]; h = Plank constant [$6.626 \cdot 10^{-34}$ J · s]; $\Delta H^{\neq}$ = activation enthalpy [J mol^{-1}]; $\Delta S^{\neq}$ = activation entropy [J · K^{-1} · mol^{-1}]; c^o = standard-state concentration [mol · L^{-1}], n = molecularity of the reaction.

[39] Although absolute values of yields determined from NMR are obviously affected by a certain measurement error, the tendency of yields changes is apparent.

[40] Yamaguchi Macrolactonization: (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115,* 4497-4513. (b) Evans, D. A.;Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671-8726. (c) Burke, S. D.; Heap, C. R.; Porter, W. J.; Song, Y. *Tetrahedron Lett.* **1996**, *37*, 343-346, 1996.

S_N2-Macrolactonization: (d) Karim, M. R.; Sampson, P.; *J.* Org. *Chem.* **1990**, *55*, 598-605. Compare dependence of rate constants at different temperatures demonstrate for cyclization and dimerization: (e) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.*, **1977**, *99*, 2591-2597.

Macrolactamization: (f) Hammond, P. J.; Beer, B. D.; Hall, C. D. *J. Chem. Soc*., *Chem. Commun*. **1983**, 1161–1163.

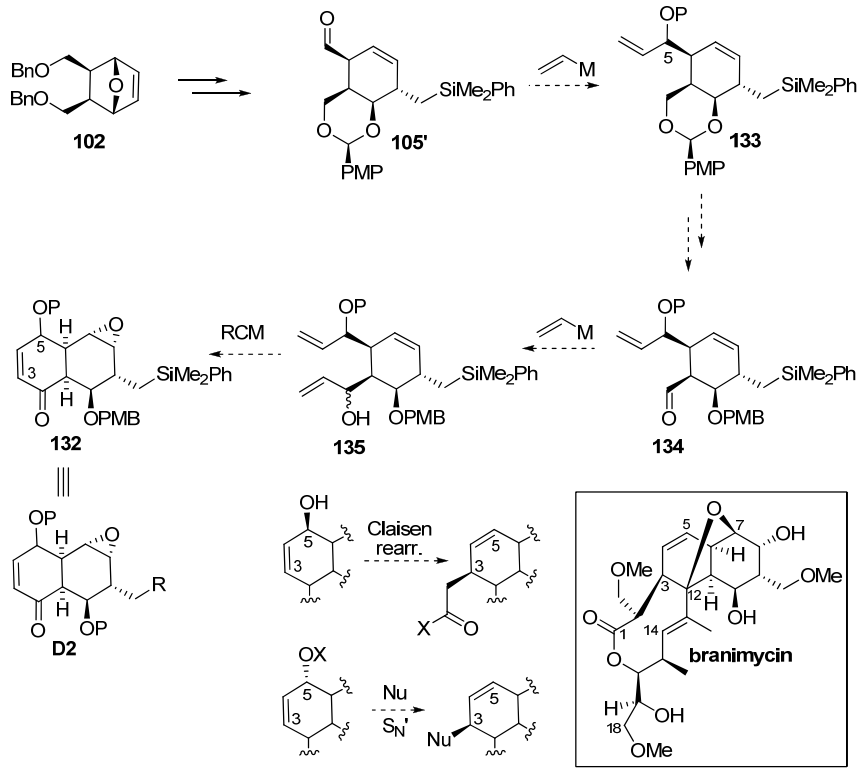
RCM: (g) Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett*. **2003**, *44*, 3297–3299.

Intramolecular oxidative coupling of acetylenes: (h) Höger, S.; Bonrad, K.; Karcher, L.; Meckenstock, A.-D. *J. Org. Chem.* **2000**, *65,* 1588-1589.

Radical cyclization: (i) Curran, D. P.; Tamine, J. *J. Org. Chem.*, **1991**, *56*, 2746-2750.

5. Oxa-Bridge Opening – RCM Approach Towards the *cis*-Decalin Core of Branimycin

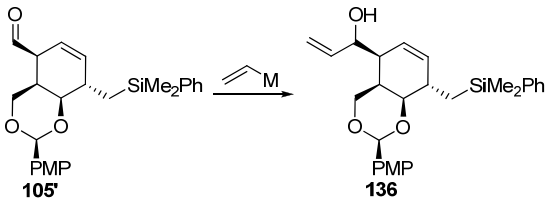
One of earlier developed in Mulzer group approaches towards the *cis*-decalin core of branimycin was based on S_N'-opening of the oxa-bridge in compound **102** (Scheme 21). Partly based on these results, a new synthetic plan to *cis*-decalin core **132** (corresponds to **D2**) was elaborated (Scheme 35). Oxygen functionality at C5 in **132** should allow introduction of the requisite C_2-appendage at the C3 position either *via* an S_N'-substitution or a Claisen rearrangement (depending on configuration).



Scheme 35: Oxa-bridge opening – RCM approach towards **D2**

We envisioned that the target *cis*-decalin compound could be created by ring closing metathesis of corresponding diene **135**. The latter could be derived from aldehyde **134**, derived *via* regioselective opening of PMB-acetal **133**. The vinyl substituent in **133** could be introduced by addition of vinyl-anion to aldehyde **105′**, which was synthesized previously in the Mulzer group (Chapter 2.12).

Table 1: Addition of vinyl organometallics to aldehyde **105'**



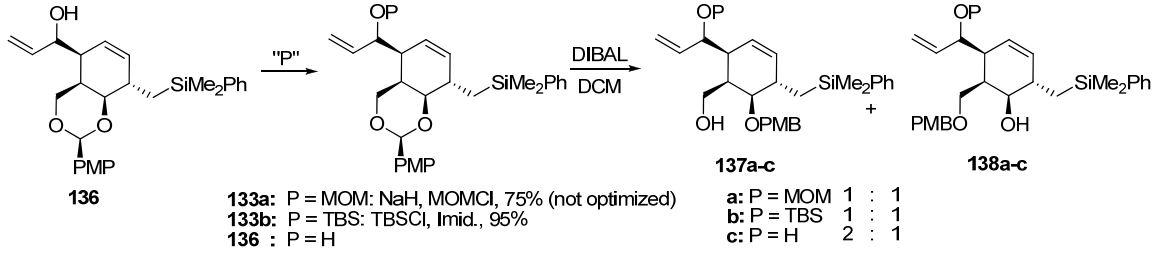
"M"	Conditions	dr (yield)
MgCl*CeCl3	THF, -78 to -20 °C	decomp.
Li*CeCl3	THF, -78 °C	decomp.
(Zn)2	THF, -78 °C to rt	decomp.
MgCl	THF, -100 to -78 °C	1 : 1
Li	Et_2O, -78 °C	1 : 1
Li	THF, -78 °C	2.5 : 1
Li + **$LiClO_4$**[a]	**THF, -78 °C**	**8 : 1 (89%)**

[a] Ratio vinylLi : $LiClO_4$: RCHO = 6 : 5 (0.4 M in THF) : 1.

Our approach started from the addition of various vinyl-nucleophiles to aldehyde **105′** (Table 1). Amongst the tested conditions, remarkable results were obtained with vinyl lithium and $LiClO_4$ as an additive, giving alcohol **136** in high yield and good stereoselectivity (dr 8 : 1). $LiClO_4$ was chosen as a potential Lewis acid[41] which does not form an ate-complex with vinyl lithium; but at the same time ccoul discriminate carbonyl sites *via* possible complexation: with substrate **105'** and vinyl lithium. Selection of $LiClO_4$ over LiCl was made due to its higher solubility in THF (which could become substantial at low temperatures) and presumably higher Lewis acidity.

Although the relative configuration of the OH-group in **136** was not known at this stage, both configurations were suitable (Scheme 35), and if necessary one could be interconverted to the other. We therefore continued our investigations and turned our attention to the regioselective opening of the PMB-acetal.

Towards this end, alcohol **136** was protected as a MOM-ether (**133a**) or as a TBS-ether (**133b**). Surprisingly, treatment of **133a** or **133b** with DIBAL resulted in formation of equal amounts of regioisomeric alcohols: desired **137** and undesired **138** (Scheme 36). Unprotected substrate **136** gave slightly better results (ratio 2 : 1).



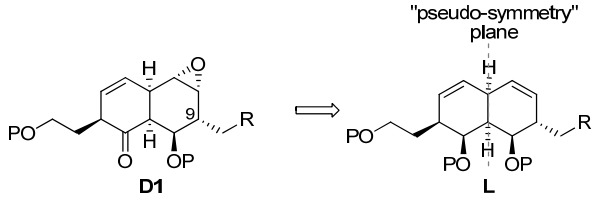
Scheme 36: Reductive opening of the PMB acetal moiety in **136**

[41] For a similar effect of $LiClO_4$ on MeLi addition to carbonyl group see: Ashby, E. C.; Nodling, S. A. *J. Org. Chem.* **1979**, *44*, 4371-4377.

Although there was room for optimization, further investigations were not carried out on this synthetic route, as at this time another approach became our main focus.

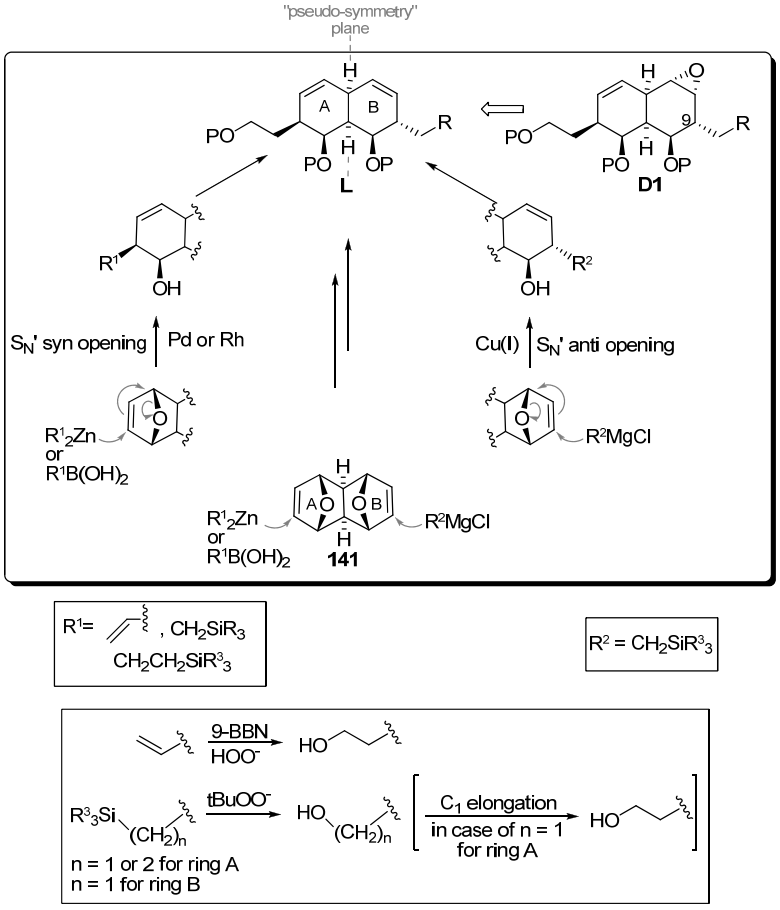
6. Desymmetrization of Diepoxynaphthalene. General Concept for Approaching the *cis*-Decalin Core of Branimycin

It was imagined that desired *cis*-decalin core **D1** could be derived from its corresponding dienic precursor **L** (Scheme 37) *via* a regioselective epoxidation, relying on coordination of an epoxidizing reagent (e.g. peroxy acids, V or Ti hydroperoxides) with the 9-CH_2OMe-group or 9-CH_2OH-group (i.e. **L** with R = OMe or OH resp.).
As can be seen from, the structure of **L** is pseudo-symmetrical.



Scheme 37: Pseudo-symmetry of diene **L**

As taking advantage of this symmetry element was both practical and potentially efficient, a new synthetic plan was designed to incorporate it (Scheme 38).

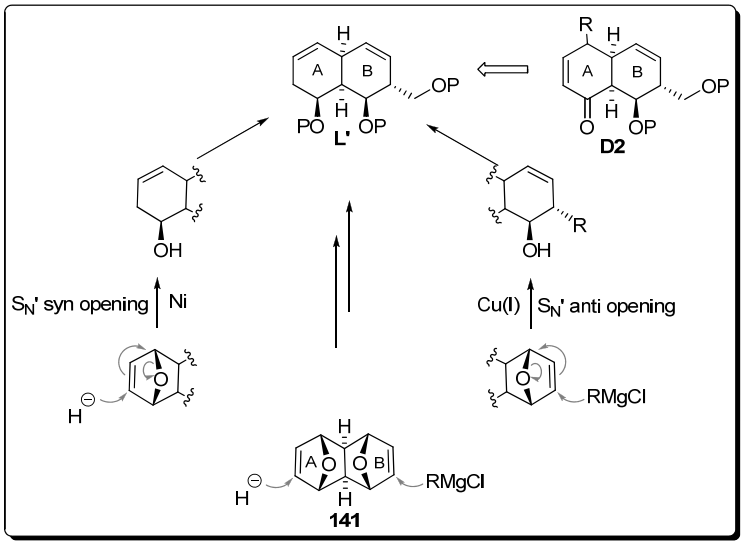


Scheme 38: Desymmetrization of diepoxynaphthalene **141** with carbon nucleophiles

The new plan was based on desymmetrization of diepoxynaphthalene **141** *via* sequential S_N' openings of two oxa-bridges. For creation of the pattern of ring A, an oxa-bridge would have to be opened in a *syn* fashion. On the other hand, for

functionalization of ring B, the other oxa-bridge would have to be opened *anti*. The symmetry of this new approach gave us a very important flexibility: we could desymmetrize **141** in two ways, starting either from ring A followed by ring B or *vice versa*. To our delight, literature study revealed that both types of oxa-bridge openings (*syn* and *anti*) were known, albeit for substrates containing only one oxa-bridge. Enantioselective *syn* opening has been described with diorganozinc nucleophiles under palladium catalysis[42]; or alternatively with organoboron nucleophiles under rhodium[43] catalysis. A*nti* S_N' opening is reported in a racemic mode with RMgX under copper catalysis[44] for not activated substrates; and enatioselectively (with R_2Zn[45] or RMgX[46] under copper catalysis) for more reactive substrates with benzylic[47] oxa-bridges.

It should be noted that nucleophiles in reactions of oxa-bridge opening cannot contain any type of functionalities. Taking these restrictions into consideration, we concluded that suitable for our purposes nucleophiles would either be of vinyl type or of silyl-bearing alkyl type (Scheme 38). For conversion of introduced side chains to the desired CH_2-CH_2-OR fragment, a vinyl substituent should be hydroborated, followed by oxidative cleavage. On the other hand, oxidative cleavage of an aliphatic silicon group (Tamao-Fleming oxidation) would give us access to an alcohol moiety (with one or two C-atoms) which could be further converted to a desired fragment (Scheme 38).



Scheme 39: Desymmetrization of diepoxynaphthalene **141** with carbon and hydride nucleophiles

Alternatively to the discussed scheme, employing a hydride anion for enantioselective opening of the oxa-bridge[48] in ring A in **141** (Scheme 39) would also provide a route to *cis*-decalin core of type **D2**, which was envisioned as an alternative option in our synthesis (Scheme 15).

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[42] (a) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437-1447. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834-6839. (c) Cabrera, S.; Arrayás, R. G.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938-17947.

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[44] Arrayás, R., G.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2003**, *5*, 1333-1336.

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[46] Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J.Org.Chem.* **2005**, *70*, 3734-3736.

[47] To date, enantioselective anti-opening with C-nucleophiles was reported only for substrates with benzylic oxa-bridges: 

[48] Lautens, M.; Rovis, T. *Tetrahedron* **1998**, *54*, 1107-1116.

7. Synthesis of Diepoxynaphthalene (141)

The new synthetic scheme discussed in Chapter 6 apparently required a reliable approach to the starting diepoxynapthalene **141.** Although this compound was literature known, the overall yield of **141** was < 2%, therefore a new synthesis had to be developed. Results of this work were submitted for publication in Synthetic Communications (for a copy of the manuscript see Chapter 7.1). Some further improvements in the synthesis of **141** were achieved additionally (see Chapter10.2).

7.1. Improved synthesis of parent fused 7-oxanorbornenes (Publication in Synthetic Communications)[49]

IMPROVED SYNTHESIS OF PARENT FUSED 7-OXANORBORNENES

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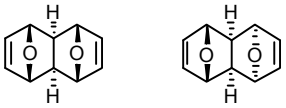
Abstract: The synthesis of parent fused 7-oxanorbornenes **1** and **2** based on double Diels-Alder reaction of methyl propiolate with furan, followed by saponification and reductive Barton decarboxylation is described.

Keywords: fused 7-oxanorbornenes, diepoxynaphthalenes, acyl tosylate, Barton decarboxylation, saponification.

Compounds bearing 7-oxanorbornene units have high potential in organic synthesis. Probably one of the most potential synthetic applications of this class of compounds is the opening of the oxa-bridge with different nucleophiles giving access to highly functionalized synthetic intermediates.[1] Moreover, such kind of oxa-bridged compounds are perspective copolymers[2] and building blocks for interesting molecules with extended π-systems.[3]

Herein we wish to report an improved synthesis[4] of fused 7-oxanorbornenes **1** and **2** (Figure 1), the parent systems of the corresponding classes of compounds.[1g-h] The approach is based on Diels-Alder formation of **2** and **3** (Scheme 1), followed by saponification and reductive Barton decarboxylation.



1 **2**

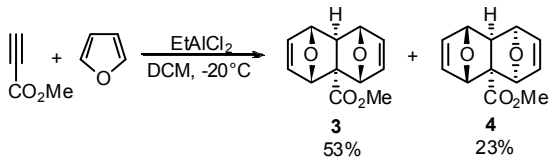
Figure 1

Our first goal was to improve a literature known[5] double Diels-Alder reaction of methyl propiolate with furan (Scheme 2). A number of different Lewis acids have been tested (Et_2AlCl, $EtAlCl_2$, $TiCl_4$, $Ti(OiPr)_4$, $Yb(OTf)_3$, $ZnCl_2$, $LiClO_4$) from which $EtAlCl_2$ proved to be far superior also in respect to $AlCl_3$ which has been employed in earlier studies.[5]

[49] Accepted for publication. Numbering of schemes, compounds and references is used as in the original publication.

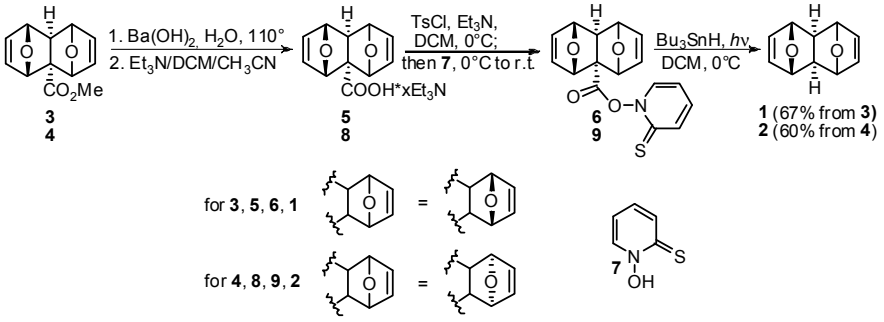
Under optimized conditions cycloaddition results in 79% yield of a 2.3:1 mixture of bis-adducts **3** and **4,** which were separated by column chromatography and used for subsequent transformations.

All further steps were optimized for the synthesis of **1** from **3**, whereas **2** was synthesized from **4** in full analogy. Initial attempts to isolate the corresponding acid after saponification of **3** were not successful because of low solubility of the acid in organic solvents suitable for extraction ($CHCl_3$, Et_2O, DCM, EtOAc). This problem was solved by saponification with



Scheme 1

$Ba(OH)_2$ followed by acidifying with H_2SO_4, removal of water, addition of Et_3N and dissolving the thriethylammonium salt **5** in DCM/CH_3CN. By following this procedure yields up to 99% were obtained. Interestingly, the use of KOH-HCl or NaOH-HCl instead of $Ba(OH)_2$-H_2SO_4 resulted in non reproducible yields of 75-95%.



Scheme 2

Direct preparation of **6** (with **7** and $Me_2N(CH_2)_3N{=}C{=}NEt{*}HCl$) as well as conversion of **5** into the corresponding acid chloride followed by reaction with **7** or its sodium salt proved problematic and low yielding. The best results were obtained by *in situ* conversion of **5** into the corresponding acyl tosylate followed by reaction with **7** in the presence of Et_3N. The resulting crude thiohydroxamic ester **6** was further subjected to reductive Barton decarboxylation[6] to give **1** in 67% yield starting from ester **3**. Interestingly, a corresponding product with inversion of configuration was not detected. By employing identical conditions, **2** was synthesized from **4** in 60% yield.

In conclusion, we have developed an efficient synthesis of fused 7-oxanorbornenes **1** and **2** starting from methyl propiolate and furan.

EXPERIMENTAL

See Experimental Section for Chapter 7.1.

ACKNOWLEDGMENT

We thank Dr. Uwe Rinner (University of Vienna) for help in preparation of this manuscript.

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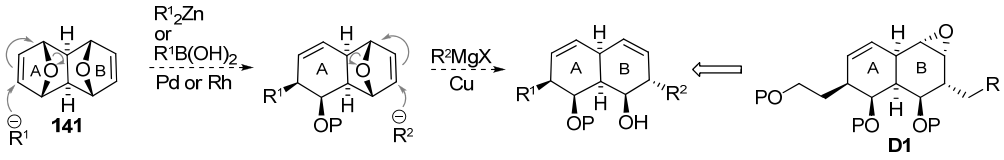
8. *cis*-Decalin Core of Branimycin *via* Desymmetrization of Diepoxynaphthalene: 1st Generation Approach

8.1. First Oxa-Bridge Opening

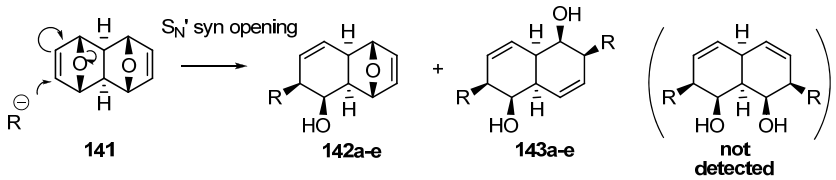
With a reliable synthesis of **141** in hand we could put our synthetic plans for the synthesis of the branimycin *cis*-decalin core into practice. From the three options discussed above (Scheme 38, Scheme 39) we chose first to approach ring A by opening of one of oxa-bridges with a carbon nucleophile in a *syn* fashion, followed by opening of the second oxa-bridge with a carbon nucleophile in an *anti* fashion to create the functional pattern required for ring B (Scheme 40).



Scheme 40: 1st Generation approach

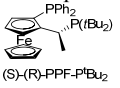
Boronic acids were chosen as the first type of nucleophiles to be investigated. Although, for the synthetic scheme, vinylboronic acid was required as the nucleophile, its instability[50] could complicate initial investigations. Therefore, we decided to test first a model nucleophile, *p*-tolylboronic acid. Unfortunately, selective opening of only one of oxa-bridges

Table 2: *Syn* opening of diepoxynaphthalene **141** oxa-bridges with nucleophiles



Entry #	" ⊖ " R	Convers.	Ratio **142#**/**143#**	Yield[d] brsm of **142#**, % (er)
a	pTolB(OH)$_2$[a]	ca. 60 %	1 : 1	**142a**, "good yield"
b	(vinyl)$_4$Sn	no rxn	-	**142b**, no rxn
c	(vinyl)$_2$Zn[e]	no rxn	-	**142c**, no rxn
d	Et$_2$Zn[b]	86 %	6.8 : 1	**142d**, 68 %
e	(TMSCH$_2$)$_2$Zn[b, f]	100 %	1 : 0	**142e**, 50% (> 95 : 5)[c]

[a] 5 mol % [Rh(COD)Cl]$_2$, Cs_2CO_3, 10 mol % (*S*)-(*R*)-PPF-PtBu$_2$, H_2O, THF, rt. [b] 7 mol % [(*R*)-Tol-BINAP]PdCl$_2$, Zn(OTf)$_2$, DCM; then EtMgBr.[51] [c] Determined from 1H NMR of corresponding Mosher esters.[d] Yields were not optimized. [e] Prepared from ethereal solutions of vinyllithium[52] and $ZnCl_2$ following the general[42a] procedure. [f] Prepared from $TMSCH_2Li$ and $ZnCl_2$ following the general[42a] procedure



was not possible following literature[43] conditions. Treatment of **141** with *p*-tolylboronic acid in the presence of a chiral rhodium catalyst and aqueous cesium carbonate delivered equal amounts of mono- and bis-opened products (**142a** and **143a**

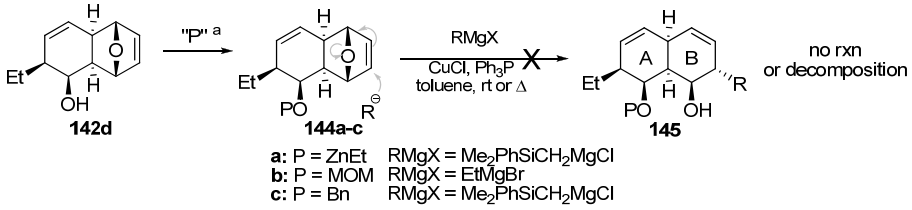
[50] Peyroux, E.;Berthiol, F.;Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2004**, 1075-1082.
[51] EtMgBr is necessary for this type of reaction and was used for any ZnR_2, as Et does not become incorporated into the product. For an explanation see ref. 42a.
[52] Solid vinyllithium was prepared according to Eyferat, D.; Weiner, M. *J. Am. Chem. Soc.* **1961**, *83*, 3583-3586.

resp.) even at ca. 60% conversion (Table 2, entry 1). Attempts to substitute boronic acids with tetravinyl tin under the same reaction conditions (with or without Cs_2CO_3) resulted in no reaction. At this point we decided to switch to another option: use of diorganozinc nucleophiles under chiral palladium catalysis.[42a]

Although attempts to react **141** with *in situ* prepared divinylzinc resulted in no reaction, employment of an aliphatic model nucleophile $ZnEt_2$ provided the desired mono-opened product[53] **142d** in good yield (Table 2). Moreover, prepared *in situ* $(Me_3SiCH_2)_2Zn$ also gave[53] very promising results: 50% yield of corresponding product **142e** was formed in enantiomeric ratio > 95 : 5. It should be noted, that the later nucleophile introduced an appendage potentially suitable for further transformation *via* oxidative silicon cleavage.

8.2. Attempts Towards Second Oxa-Bridge Opening

Next, we turned our attention to functionalization of ring B in **142d** (Scheme 41). To this end, three derivatives of alcohol **142d** were prepared, two of which (**144a:** P = ZnEt and **144b:** P = MOM) were planned to facilitate the opening of the oxa-bridge *via* possible complexation with a metal and the oxa-bridge. Unfortunately, all attempts to achieve the oxa-bridge opening either with EtMgBr or $Me_2PhSiCH_2MgCl$ resulted in no reaction at room temperature, and decomposition at higher temperatures.



[a] **144a**, P = ZnEt: $ZnEt_2$, toluene, 0°C (*in situ*); **144b**, P = MOM: MOMCl, iPr_2EtN, DCM, rt, 80% (not optimized); **144c**, P = Bn: BnBr, NaH, DMF, THF, rt, 82% (not optimized).

Scheme 41: Attempts towards second oxa-bridge opening

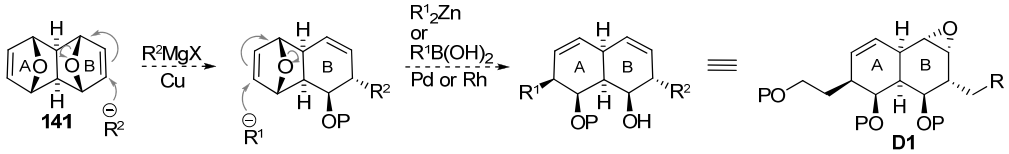
Parallel studies in another approach gave more promising results and therefore further investigations of this 1st generation approach were abandoned.

[53] Absolute configuration of corresponding products **142a-e** were assigned in analogy to literature precedents.

9. *cis*-Decalin Core of Branimycin *via* Desymmetrization of Diepoxynaphthalene: 2nd Generation Approach

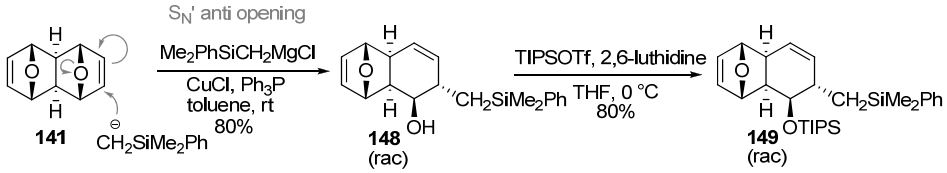
9.1. Opening of the First Oxa-Bridge

As was mentioned above (Chapter 6), another option consisted of reversing the order of oxa-bridge openings: first *anti* opening could lead to the functional pattern of ring B, followed by *syn* opening of the second oxa-bridge and thus functionalization of ring A (Scheme 42):



Scheme 42: 2nd Generation approach

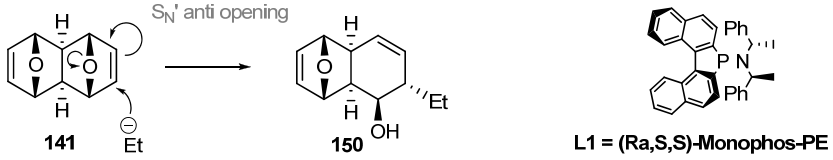
The main drawback of this approach was the absence of developed methodology which would allow enantioselective *anti* opening of non-activated oxa-bridges. Despite this disadvantage, investigations were started.



Scheme 43: Anti opening of the oxa-bridge in **141**

Gratifyingly, already the first attempts to make selective opening of only one of two oxa-bridges in **141** proved to be successful. Treatment of diepoxynaphthalene with a silyl bearing nucleophile, $Me_2PhSiCH_2MgCl$, under $CuCl/Ph_3P$ catalysis[44] resulted in formation of the desired product, **148**, in good yield (Scheme 43). Noteworthy, no products of a double opening were detected in the reaction mixture.

Table 3: Attempts towards enantioselective anti opening of the oxa-bridge in **141**



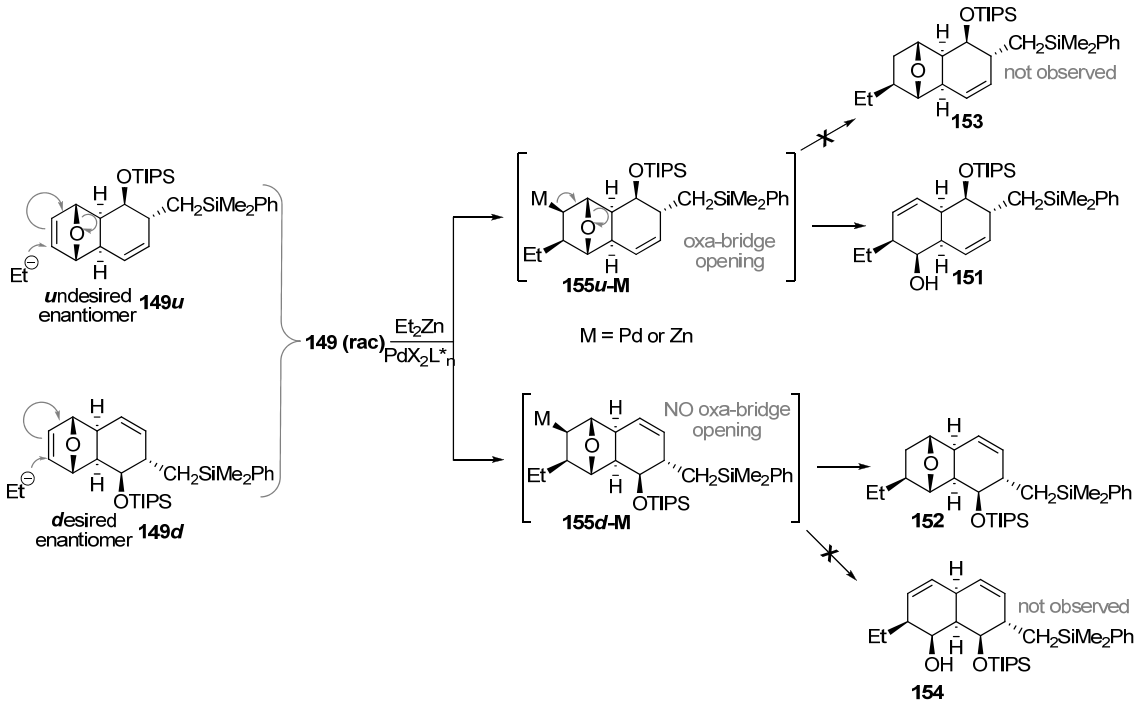
"$Et^{\ominus}$"	Conditions	er[a,b]
EtMgBr, 2 eq.	5 mol % $Cu(OTf)_2$, 13 mol % **L1**, toluene, 0 to +6 °C	55 : 45
EtMgBr, 2 eq.	10 mol % CuCl, 20 mol % **L1**, toluene, 0 to +6 °C	52 : 48
Et_2Zn, 1 eq.	5 mol % $Cu(OTf)_2$, 1 eq. Zn $(OTf)_2$, 13 mol % **L1**, toluene, 0 °C	*syn*-opening

[a] Determined from ^1H NMR of Mosher esters. [b] Absolute configuration was not established.

A few attempts towards enantioselective *anti* opening were done employing model[54] nucleophiles (Table 3), based on methodologies developed for enantioselective opening of activated oxa-bridges with Grignard[46] and diorganozinc[45] reagents. Unfortunately (although not surprisingly)[47] almost no enantioselection was observed, and for the sake of strategy it was decided to abandon investigations on enantioselective *anti* opening and to concentrate on further steps.

9.2. Second Oxa-Bridge Opening

Racemic alcohol **148** was further protected as its TIPS-ether to obtain **149** (Scheme 43), which could be tested in the opening of the second oxa-bridge. To our surprise, a reaction of **149** with model nucleophile $ZnEt_2$ under chiral palladium catalysis lead to a mixture of expected product **151** of the oxa-bridge opening and a product **152** of the simple addition to the double bond without opening of the oxa-bridge (Scheme 44).



Conditions: **149** + $ZnEt_2$ 1.5 eq. +7 mol % [(*R*)-Tol-BINAP]$PdCl_2$, $Zn(OTf)_2$, DCM, rt; then EtMgBr.[42a,51]

Scheme 44: Reaction of **149** with Et_2Zn

Although absolute configurations of products were not established, we speculated that **151** came from ***u***ndesired enantiomer **149*u*,** whereas **152** derived from ***d***esired enantiomer **149*d*** (***u*** = ***u***ndesired, ***d*** = **d**esired)**.** The following points supported our assumption:

1. Chiral ligand of Pd-catalyst should lead (in principle) to the same chiral sense of attack of Et on the double bond for **149*u*** and **149*d*.**
2. Two other possible regioisomeric products (**153** and **154,** Scheme 44) were not detected.

To explain formation of products **151** and **152**, we proposed the following hypothesis. In the first step $ZnEt_2$ adds under chiral palladium catalysis to the double bond of each enantiomer to give two corresponding organometallic intermediates

[54] $Me_2PhSiCH_2Mg$**Cl** was not tested as RMg**Cl** are known to give low enantiomeric ratio, and preparation of $Me_2PhSiCH_2Mg$**Br** was not developed at that time. $ZnEt_2$ was chosen as no reliable method for synthesis of $(Me_2PhSiCH_2)_2Zn$ was developed at that time.

155*u*-M and **155*d*-M** (**M** = metal).[55] For intermediate **155*u*-M**, a subsequent opening occurs smoothly giving the expected product **151**. In contrast, in the case of intermediate **155*d*-M** (which comes from desired enantiomer **149*d*),** opening of the oxa-bridge would lead to increase of the eclipsing of the developing "C-O$^-$" substituent and the bulky OTIPS-group. This unfavorable interaction presumably suppresses opening of the oxa-bridge (Figure 1).

We reasoned that if **155*d*-M** does correspond to the "not opened product" just before work up, then M is mostly Zn[56] and we should be able to react this organometallic intermediate with D_2O. This hypothesis was supported by literature precedent where authors observed sluggish oxa-bridge openings for certain substrates and corresponding organozinc intermediates(similar to intermediates **155*d*-M** and **155*u*-M,** M = ZnR, Scheme 44) had been trapped with some electrophiles.[42a]

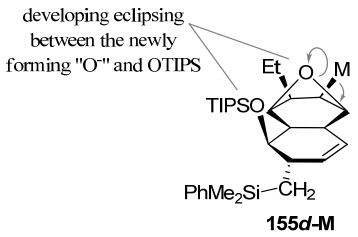


Figure 1: Proposed transition state for opening of the oxa-bridge in **155*d*-M**
(Geometry of **155*d*-M** is simplified for the sake of clarity)

In contrast, in our case quench of the reaction mixture with D_2O resulted in no incorporation of deuterium[57] into product **152** indicating that intermediate **155*d*-M** abstracts hydrogen from another source[58] before quench. From this results we concluded, that after the full conversion of **149*d*** (i.e. at the end of the reaction of addition of Et to the double bond of **149*d***), there is no organometallic intermediate **155*d*-M** (M = ZnR) in the reaction mixture. Consequently, applying forcing conditions (increase in temperature or reaction time, addition of Lewis acids etc.) at this stage would not lead to opening of the oxa-bridge.

Basing on the proposed eclipsing in the course of oxa-bridge opening (Figure 1), we decided to change TIPS with less sterically demanding protecting groups. To this end, alcohol **148** was protected with BnBr or PMBBr to obtain **156a** or **156b** respectively (Scheme 45). To our delight, opening of the oxa-bridges of these new substrates **156a,b** proceeded equally well for both enantiomers.[59]

According to our synthetic plan, the position C9 had to bear not CH_2SiMe_2Ph, but CH_2O-appendix, therefore **156b** was subjected to oxidative cleavage of silicon to obtain **159**, in good yield (Scheme 45). The newly formed alcohol was converted to two derivatives: protection as its TBS-ether to give **156c**, or methylation to give **156d**. Similar to **156a,b**, reactions of these "real" substrates with $ZnEt_2$ gave expected products without substantial complications.[60]

---

[55] Exact structure of intermediates **155*u*-M** and **155*d*-M** are not known. Although proposed mechanisms imply M = Pd (ref 42b,c), in certain cases intermediates with M = Zn were detected (ref. 42a,b).

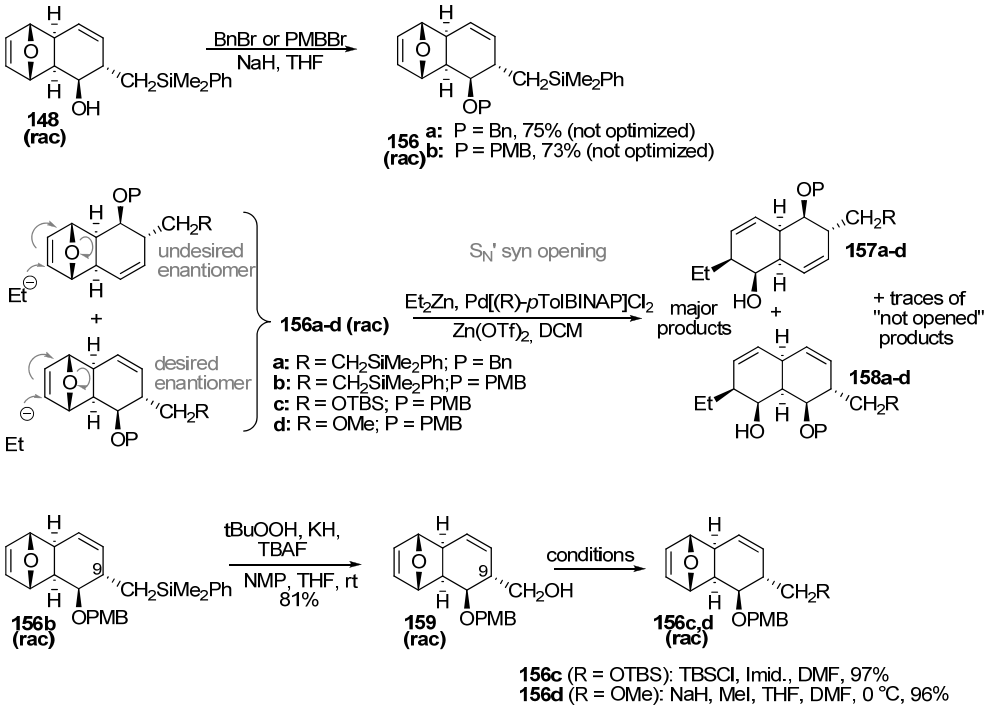
[56] Palldaium was used in catalytic amounts (7 mol %), therefore it cannot present in more than 7% of **155*d*-M**.

[57] No changes in 13C (JMODE) specatra were observed such as appearing of a new signal in CH/CH_3-hemiplane or a signal with a large (not suppresed) $^1J_{CH}$.

[58] E.g. *via* β-hydride elimination from a possible Pd-Et intermediate and subsequent reductive elimination.

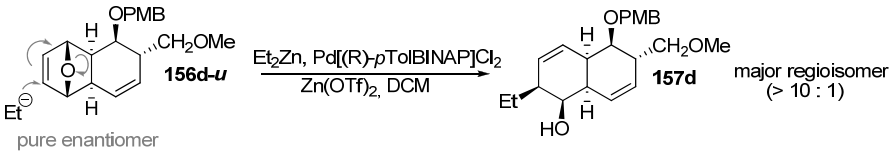
[59] A possible role of chelation between oxa-bridge and OBn or OPMB (what is less likely to occur in case of OTIPS) cannot be excluded, although it should be noted that for another enantiomer **155*u*-M** opening occurred smoothly even with the TIPS-group. Another reason could lie in possibly different geometry of corresponding intermediates **155*d*-M** in case of the bulky TIPS and the less bulky Bn (or PMB). This in turn could reflect on extent of overlap of CM-bond and breaking CO-bond of the oxa-bridge.

[60] Reactions with TBS group had to be carried out at 0 °C as partial TBS-deprotection took place.



Scheme 45: Preparation of new substrates and their reactions with Et_2Zn

Moreover, when pure enantiomer **156d-*u***[61] was submitted to a reaction with Et_2Zn under standard conditions, corresponding product **157d** was formed with good regioselectivity (>10 :1). This experiment shows that a reaction of racemic **156** likely leads to formation of a mixture of enantioenriched products **157** and **158**. Consequently, this approach could be suitable for synthesis of enantiopure *cis*-decalins starting from racemic precursors.

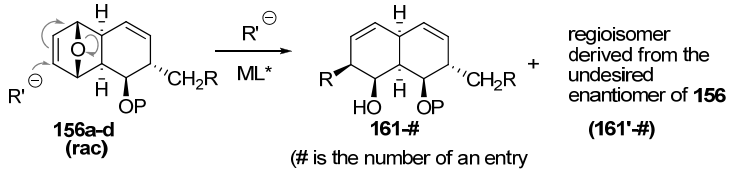


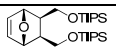
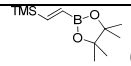
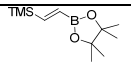
Scheme 46: Reaction of enantiopure **156d-*u*** with Et_2Zn

Encouraged by these promising preliminary results, we switched our attention from model nucleophile $ZnEt_2$ to nucleophiles bearing substituents suitable for further elaboration. Literature analysis showed that the presence of oxygen substituents in ZnR_2 inhibits the desired reaction,[42a] therefore divinylzinc or aliphatic silicon-containing diorganozinc reagents were chosen as potential nucleophiles.

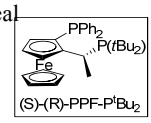
[61] **156d-*u*** and **156d-*d*** were obtained after separation of racemic **156d** by chiral HPLC. The experiment with Et_2Zn was carried out in order to determine the absolute configuration of enantiomers after separation. The corresponding reaction with enantiomer **156d-*d*** was not carried out as the results would not give an information on regioselectivity (i.e. enantioselectivity) of reaction with "real" (not model) nucleophiles.

Table 4: Reaction of **156a-d** with different nucleophiles



Entry #	" R' ⊖ "	Substarte	Conditions	Yield[a, b] of **161-#**
1	$(vinyl)_2Zn$[c]	**156a**	h, rt	n.r.
2	$(Me_2PhSiCH_2CH_2)_2Zn$[d]	**156c**	h, 0 °C	n.r.
3	$(Me_2PhSiCH_2CH_2)_2Zn$[e]	**156c**	h, 0 °C	n.r.
4	$(Me_2PhSiCH_2CH_2)_2Zn$[e]	**156b**	h, rt	n.r.
5	$(Me_2PhSiCH_2CH_2)_2Zn$[e]		h, rt	n.r.[62]
6	$(TMSCH_2)_2Zn$[f]	**156d**	h, rt	traces[65]
7	$(Me_2PhSiCH_2)_2Zn$[g]	**156b**	h, rt	n.r.
8		**156a**	i, rt or 0 °C	traces
9		**156d**	i, 40 °C	traces
10		**156a**	i or j, rt	n.r.
11		**156a**	i, rt	traces
12	$vinylB(OH)_2$, (Ref. 63)	**156a**	i, rt	traces
13	 (Ref.64)	**156b**	i, rt	very slow conversion
14	 (Ref.64)	**156b**	i, 40 °C	90%

[a] In some cases a yield of a reaction was estimated semi-quantitaevely from crude NMR and TLC. [b] n.r. = no reaction. [c] Prepared from ethereal solutions of vinyllithium[52] and $ZnCl_2$ following the general procedure (ref. 42a). [d] Prepared from ethereal solutions of RMgBr and $ZnCl_2$ following the general procedure. [e] Prepared from ethereal solutions of RLi (from RCl and Li°) and $ZnCl_2$ following the general procedure (ref. 42a). [f] Prepared from ethereal solutions of RLi and $ZnCl_2$ following the general procedure (ref 42a). [g] Prepared from ethereal solutions of RMgCl and $ZnCl_2$ following the general procedure (ref. 42a). [h] [(*R*)-Tol-BINAP]$PdCl_2$, $Zn(OTf)_2$, DCM; then EtMgBr. [i] $Rh(COD)Cl]_2$, Cs_2CO_3, (S)-(R)-PPF-P^{t}Bu$_2$, H_2O, THF, rt. [j] The same as [i], but without Cs_2CO_3 and H_2O.



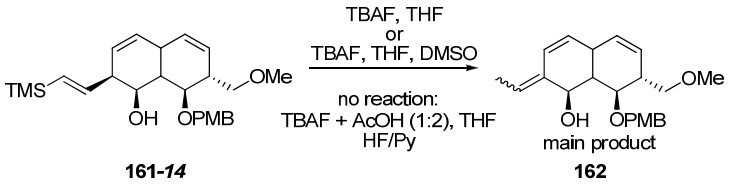
[62] Subsequent addition of $ZnEt_2$ into reaction mixture resulted in conversion into corresponding Et-substituted product, although slower than in a reaction with $ZnEt_2$ as the only nucleophile. This experiment demonstrates that although a partial deactivation of a catalyst occurred, it was still potentially active.

[63] Braun, J.; Normant, H. *Bull. Soc. Chim. Fr.* **1966**, 2557-2564.

[64] Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14(7)*, 3127-3128.

To our great disappointment, divinylzinc (Table 4, Entry 1), $(Me_2PhSiCH_2CH_2)_2Zn$ (entries 2-5) and $Zn(Me_2PhSiCH_2)_2$ (entry 7) gave no reaction even after extended reaction times, whereas $Zn(TMSCH_2)_2$ (entry 6) resulted only in traces of the product together with substantial decomposition.[65] Attempts to perform the oxa-bridge opening with boronic acids under Rh catalysis also gave rather poor results. Thus, reaction with vinylboronic acid (entry 12) or its derivatives (entries 8-11) gave only traces of the desired product together with a mixture of undefined side products.

Employing silyl-substituted vinyl boronic acids (entries 13-14) provided desired product **161-*14*** in 90% yield (45% from 50% theor.). Unfortunately, we were not able to cleave the silyl substituent under variety of conditions (Scheme 47). Employing unbuffered TBAF led to conjugation of the double bond (**162**), whereas change to milder conditions resulted in no reaction.

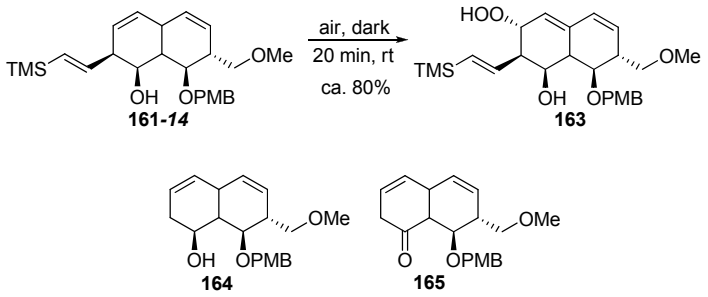


161-*14* **162**

Scheme 47: Attempts to cleave the silicon substituent in **161-*14***

Moreover, it should be noted, that skipped diene **161-*14*** proved to be unexpectedly air sensitive. Exposure of neat **161-*14*** to air for 20 min at room temperature resulted in almost quantitative conversion to dienic hydroperoxide **163** (Scheme 48). Later on a similar oxidation was observed for relative compounds **164** and **165**. For discussion see Supporting Information for the Organic Letters publication, Chapter10.2).

In light of potential instability of products, reactions of oxa-brdige opening with $vinylB(OH)_2$ and $Zn(TMSCH_2)_2$ were reinvestigated. However, in these cases low yields (estimated from crude NMR) most probably cannot be attributed to autooxidation processes, as characteristic signals of diene moiety CH=CC***H***=CH (d, range 6-6.5 ppm) and OO***H*** (s, range 7-7.5 ppm) were not detected.



161-*14* **163** **164** **165**

Scheme 48: Autooxidation of **161-*14***

Although this approach had proved to some extent promising, it became obvious, that for obtaining practically valuable results we would have to invest a substantial amount of additional time and effort to optimize the second oxa-bridge opening. At the same time, parallel investigations in another direction proved more promising. As a result, this approach was abandoned.

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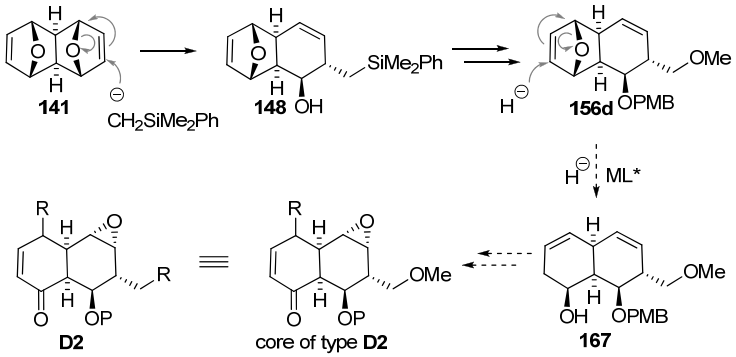
[65] It should be noted, that $Zn(TMSCH_2)_2$ was successfully used in our 1st generation approach; moreover, $ZnEt_2$ prepared *in situ* from EtMgCl and $ZnCl_2$ gave identically good results to commercial $ZnEt_2$. [Therefore our laboratory equipment and skills proved suitable for this rather sensitive area of chemistry.]

10. *cis*-Decalin Core of Branimycin *via* Desymmetrization of Diepoxynaphthalene: 3rd Generation Approach

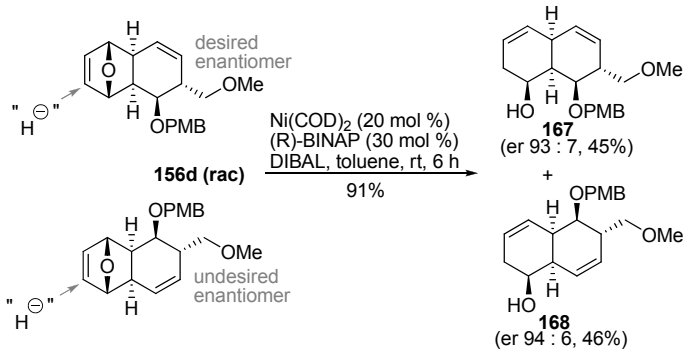
10.1. Synthetic Outline and Initial Attempts Towards Functionalization of Rings A and B

Although openings of the oxa-bridges with carbon nucleophiles gave rather poor results in both opening orders (first ring A, then ring B or *vice versa*) there was still another option: employing formal "H⁻" nucleophile for the second oxa-bridge opening would give us access to *cis*-decalin core of type **D2** (Scheme 49).



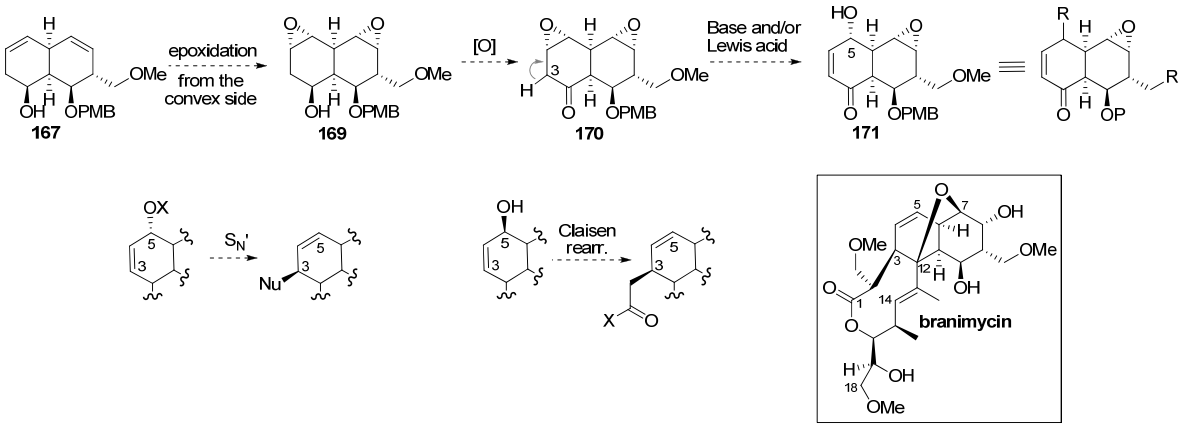
Scheme 49: 3rd Generation approach

As a substrate for the second oxa-bridge opening, we chose PMB-protected compound **156d**. Following the procedure developed by Lautens *et al*.,[48] compound **156d** was treated with DIBAL under chiral nickel-complex catalysis to give the products of S_N' oxa-bridge opening **167** and **168** in a 91 % combined yield (Scheme 50). From two obtained products, **167** and **168**, only the former was suitable for further elaboration.



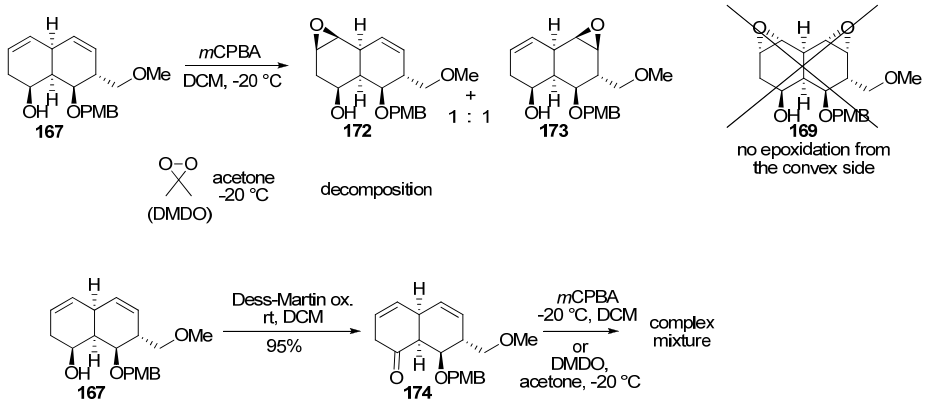
Scheme 50: Opening of the second oxa-bridge with formal hydride anion

As the *cis*-decalin **167** was expected to have a shape of an "open book", we planned to epoxidize both double bonds from the convex side. This would provide bis-epoxide **169**. The alcohol should be then oxidized to ketone **170**. Selective enolization at C3 would lead to opening of one of epoxides to give compound **171** as a representative of targeted **D2**. Similar to the plan discussed earlier in Scheme 35, the oxygen functionality at C5 would have to allow introduction of the C_2-appendage at the C3 position, either *via* S_N'-substitution or *via* Claisen rearrangement. However, in the latter case configuration at C5 would have to be inverted.



Scheme 51: Double epoxidation strategy towards **D2**

Following the outlined plan, diene **167** was epoxidized by treatment with *m*CPBA. To our surprise two regioisomeric mono-epoxides **172** and **173** were isolated, and configuration of epoxides in both cases was opposite to the expected one. Selective epoxidation from the concave side of the *cis*-decalin was attributed to delivery of *m*CPBA by the OH-group. Employing dimethyldioxirane (DMDO) resulted in full decomposition. In order to prevent coordination of the OH-group with *m*CPBA, alcohol **167** was oxidized to ketone **174** by the Dess-Martin reagent. Unfortunately, subjection of **174** to epoxidation with DMDO or *m*CPBA gave a complex mixture of products.



Scheme 52: Attempts towards epoxidation of **167** and **174**

Although room for studies on epoxidation remained, we turned to another option, which at that time proved more promising. The new approach resulted in a publication submitted to Organic Letters (for a copy of the manuscript see Chapter10.2.)

10.2. A Desymmetrization Approach Towards Highly Oxygenated *cis*-Decalins (Publication in Organic Letters)

A Desymmetrization Approach Towards Highly Oxygenated *cis*-Decalins

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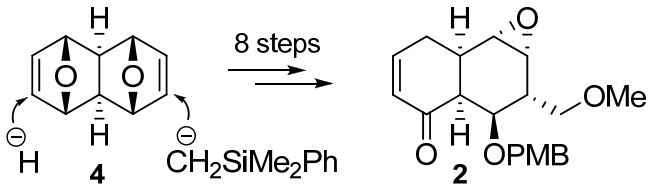
Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT

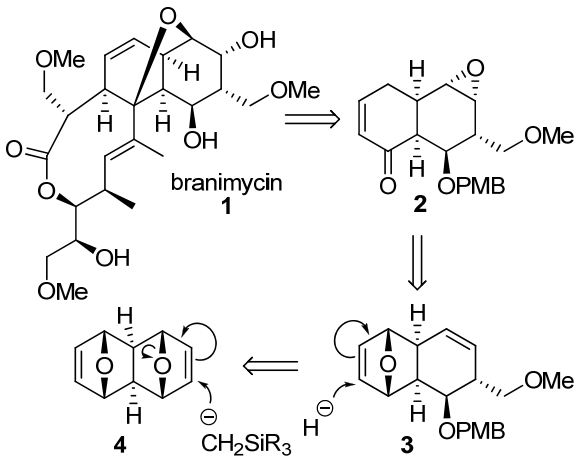


The *cis*-decalin core 2 of the antibiotic branimycin has been prepared by desymmetrization of diepoxy-naphthalene 4. The key steps involve two successive S_N' opening of the oxa-bridges. An improved procedure for the synthesis of 4 is also described.

In recent years our group became interested in the development of various novel approaches towards the synthesis of highly functionalized *cis*-decalins in the context of an ongoing study towards the total synthesis of the highly active antibiotic branimycin[66,67] (**1**).

In our new approach, we envisioned that the construction of the *cis*-decalin core **2** of branimycin (**1**) could be accomplished by desymmetrization[68] of diepoxynaphthalene **4** (Scheme 1) *via* two successive S_N' reactions. First a copper mediated S_N' opening of one of the oxa-bridges was performed with a Grignard reagent containing a silyl group as a latent hydroxy group, followed by an enantioselective S_N' opening of the second oxa-bridge with a formal hydride anion.

Scheme 1. Retrosynthetic Overview of Compound **2**



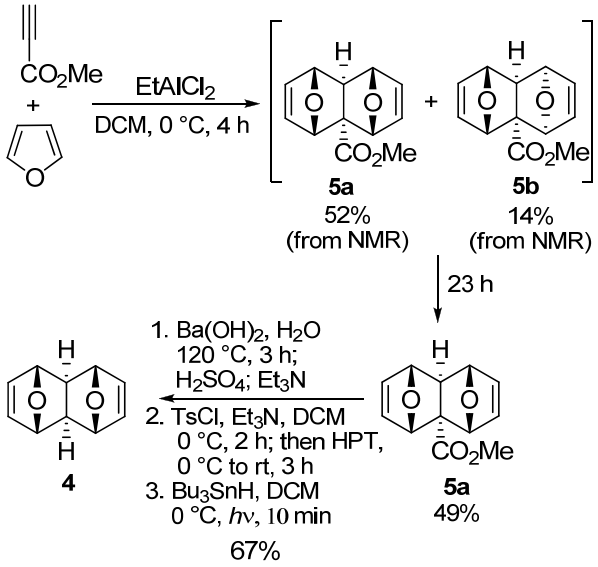
[66] (a) Enev, V. S.; Drescher, M.; Mulzer, J. *Org. Lett.* **2008**, *10,* 413-416. (b) Enev, V. S.; Drescher, M.; Mulzer, J. *Tetrahedron* **2007**, *63*, 5930-5939. (c) Marchart, S.; Mulzer, J.; Enev, V. S. Org. Lett. **2007**, 9, 813−816.(d) Felzmann, W.; Arion, V. B.; Mieusset, J. L.; Mulzer, J. Org. Lett. **2006**, 8, 3849−3851. (e) Review: Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev V. S. *Chem. Eur. J.* **2006**, *12*, 5992 – 6001.

[67] Isolation and biological activity of branimycin: (a) Speitling, M. Ph.D. Thesis, Universität Göttingen, **1998**. (b) Speitling, M.; Grün-Wollny, I.; Hannske, F. G.; Laatsch, H. *12. And 13. IRSEER Naturstofftage der DECHEMA e.V. Irsee* **2000**, **2001**, poster sessions

[68] For similar desymmetrizations, see: (a) Lautens, M.; Fillion, E. *J. Org. Chem.* **1996**, *61,* 7994-7995. (b) Lautens, M.; Fillion, E. *J. Org. Chem.* **1998**, *63,* 647-656

The synthesis of diepoxynaphthalene **4**[69] commenced with the twofold Diels-Alder reaction between methyl propiolate and furan (Scheme 2). When we performed this reaction at 0 °C for 4 h, both diastereomers **5a** (52%) and **5b** (14%) were formed. However, on longer reaction times, the undesired diastereomer **5b** slowly disappeared, leaving **5a** as a single diasteromer along with some decomposition products.[70] This protocol avoids the tedious chromatographic separation of **5a** and **5b** and is suitable for the synthesis of **5a** on a multigram scale.

Scheme 2. Synthesis of Tetracycle **4**

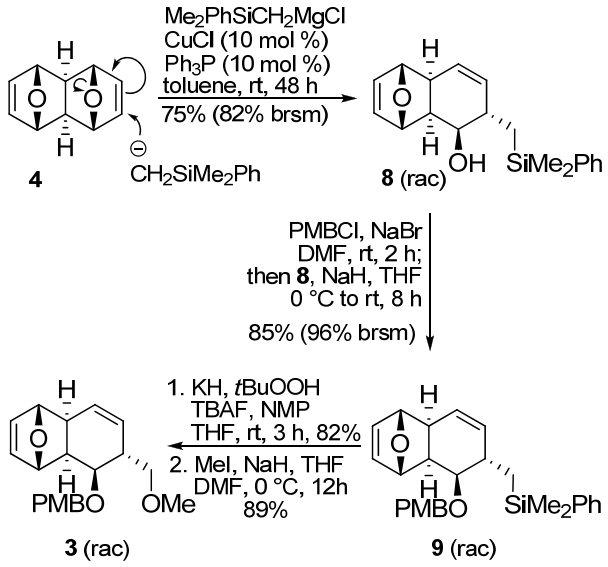


HPT = 1-hydroxypyridine-2(1H)-thione.

The four-step elaboration of ester **5a** to diepoxynaphthalene **4** proved straightforward.[69] Saponification of **5a** provided the corresponding acid, which was isolated as the triethylammonium salt **6**. Activation of the carboxylate *via* the acyl tosylate and conversion to *N*-thionopyridyl ester **7** was followed by reductive Barton decarboxylation to furnish the desired tetracyclic compound **4** in 67% overall yield from **5a**.

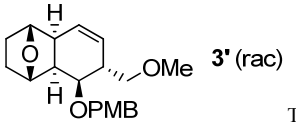
With a reliable route to diepoxynaphthalene **4** in hand, the selective opening of the oxa-bridges could be tested. We were delighted to find that exposure of **4** to $Me_2PhSiCH_2MgCl/CuCl/Ph_3P$ under the conditions described by Carretero *et al.*[71] resulted in an *anti* S_N' opening of only one of the oxa-bridges to give compound **8** in 75% yield (82% brsm). Alcohol **8** was protected as a PMB-ether with PMBBr (prepared *in situ* from PMBCl[72] and NaBr in DMF). Next, the C-Si bond was cleaved oxidatively to deliver the corresponding primary alcohol which was converted to methyl ether **3** in 73% yield over two steps.

Scheme 3. Desymetrization of Compound **4**



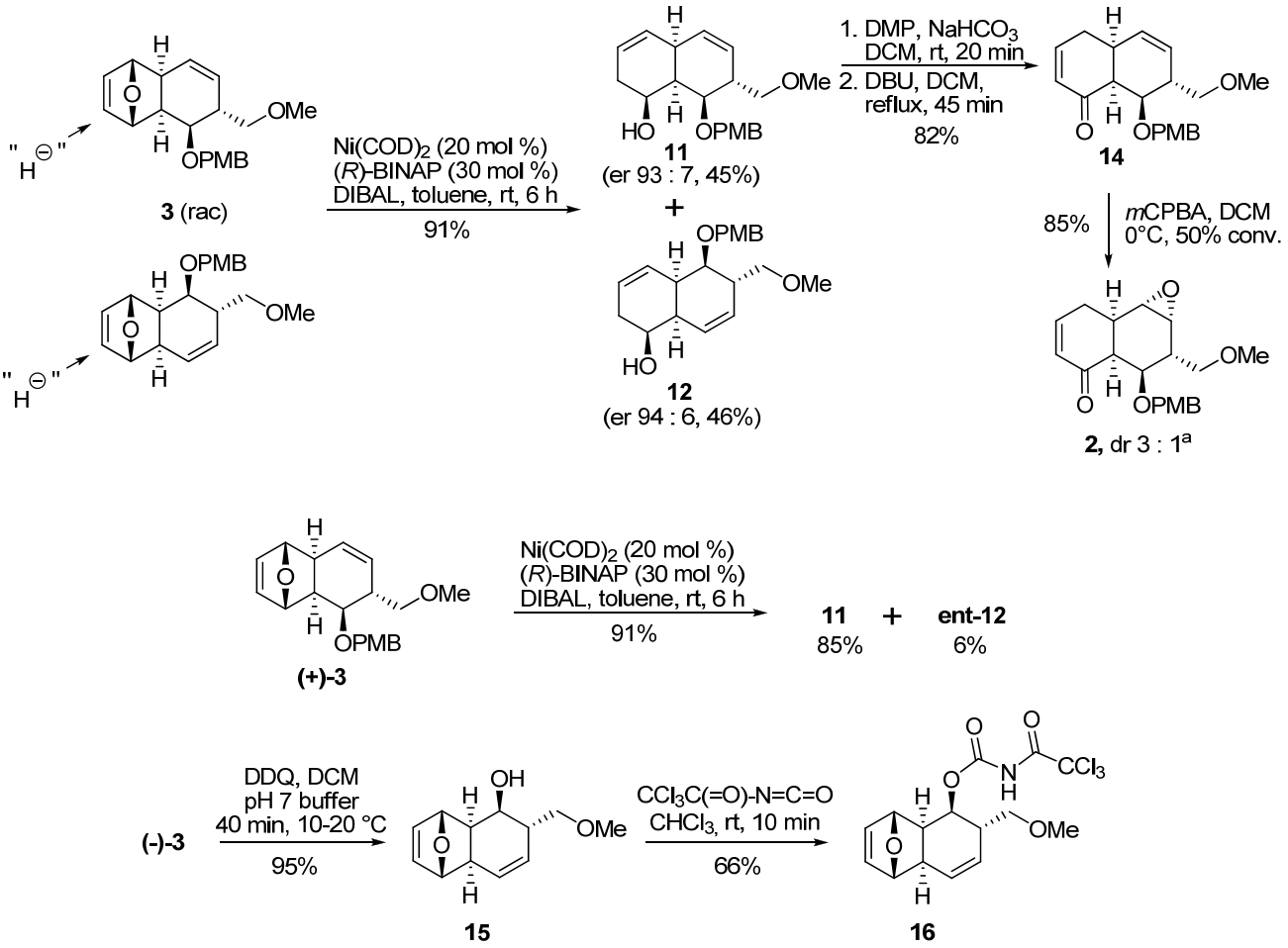
The stage was now set for the conversion of the remaining oxa-bridge into the α,β-unsaturated ketone moiety of **2** (Scheme 4). Following a procedure by Lautens *et al.*[73] racemic compound **3** was treated with DIBAL and $Ni(COD)_2$/(*R*)-BINAP. Indeed, a *pseudo*-enantiotopos-selective hydrogen attack was achieved on both enantiomers of **3** to give the enantiomerically enriched regioisomers **11**[74] and **12** in 91% yield, easily separable by chromatography.[75]

[69] For preliminary studies on the synthesis of **4** see: Gromov, A.; Enev, V.; Mulzer, J. *Syn. Comm*. in press.
[70] For a discussion of this phenomenon see comment 1 in the Supporting Information.
[71] Arrayás, R., G.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2003**, *5*, 1333-1336.
[72] A reliable scalable procedure for preparation of PMBCl: Chaudhari, S., S.; Akamanchi, K., G. *Synlett* **1999**, *11*, 1763–1765.
[73] Lautens, M.; Rovis, T. *Tetrahedron* **1998**, *54*, 1107-1116.
[74] It has to be pointed out that skipped dienes **11** and **13** (not shown, see Supporting Information) proved to be air sensitive to give dienyl hydroperoxides (for a discussion see comment 2 in the Supporting Information).
[75] Toluene as a solvent was essential for a high yield of the desired products. Performing the reaction in THF resulted in the formation of ca



50% of compound **3'**. This solvent effect might be attributed to the higher Lewis acidity of aluminum species in the non-coordinating toluene. An increase in Lewis acidity presumably favors coordination of Al with the oxa-bridge and therefore facilitates the C-O bond cleavage. For other examples of Lewis acids influence on oxa-bridges opening see: Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc*. **1995**, *117*, 532-533 and ref. cited therein.

Scheme 4. Opening of the Second Oxa-Bridge and Synthesis of Compound **2**



[a] The major diastereomer is shown.

The synthesis of **2** was continued with a Dess-Martin oxidation of **11**, followed by base catalyzed double bond isomerization to provide α,β-unsaturated ketone **14** in 88% yield. Regioselective epoxidation of diene **14** with *m*CPBA gave a 3:1 mixture of diastereomeric epoxides, easily separable by chromatography. To avoid competitive Bayer-Villiger oxidation, the reaction was stopped at *ca.* 50% conversion. The relative configuration of the major diastereomer **2** was determined by single crystal diffraction (see Supporting Information).

To secure the absolute configuration of our products racemic compound **3** was separated into the enantiomers by chiral HPLC. Under the same conditions used for the racemate, enantiomer **(+)-3** gave **11**. On the other hand, (-)-**3** was converted into alcohol **15** and then into crystalline urethane **16**, the X-ray analysis of which allowed the determination of the absolute configuration based on the anomalous dispersion of chlorine atoms.

In conclusion, we have demonstrated that organometallic catalysis can be used for a successive desymmetrization of diepoxynaphthalene **4**. This opens a direct access to highly functionalized *cis*-decalin systems as exemplified by the core of branimycin.

Acknowledgment We thank Dr. Hanspeter Kählig, Dr. Lothar Brecker, and Susanne Felsinger for NMR analysis, Prof. Vladimir Arion for X-ray analysis (all Universitiy of Vienna), and Dr. Neil Sheddan (LOBA Feinchemie GmbH) for help in the preparation of the manuscript.

Supporting Information Available Experimental procedures and analytical data for all new compounds (see Experimental Section for Chapter 10.2 (Publication in Organic Letters). For comments 1 and 2 for footnotes 70 and 74 see the next page (quoted from Supporting Information).

A Desymmetrization Approach Towards Highly Oxygenated *cis*-Decalins

SUPPORTING INFORMATION

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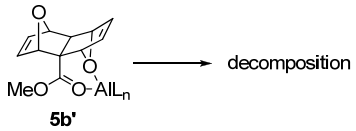
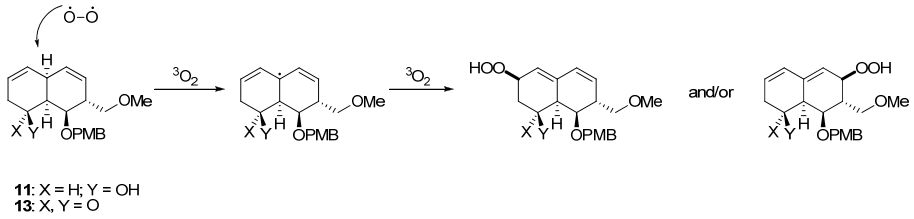
Comment 1. The disappearing of **5b** could be explained by decomposition, facilitated by a possible formation of cyclic complex **5b′** (Scheme S1) which is not possible in the case of **5a**. A similar difference in decomposition rates was observed[76] earlier for the corresponding ethyl esters in the presence of $AlCl_3$, but even for the more stable isomer degradation was still very substantial.



Scheme S1

Comment 2. Skipped dienes **11** and **13** proved to be relatively unstable when exposed to air even at -20 °C in the absence of light, giving rise to a mixture of hydroperoxides (Scheme S2). These dienyl hydroperoxides have characteristic signals in ^{1}H NMR ($CDCl_3$): a doublet at ca. 6.0-6.5 ppm (CH=C-C*H*=CH) and a singlet at ca. 7.5-8.0 (OOH).

As was proposed earlier,[77] oxidation presumably proceeds *via* initial abstraction of a hydrogen radical by $^3O_2$ and formation of a corresponding stabilized allylic C-radical (Scheme S2). As not all alkenes and skipped dienes are equally sensitive to oxygen, facile oxidation of **11** and **13** could be explained by conformationally fixed alignment of the allylic C-H bond to the π-system.



Scheme S2

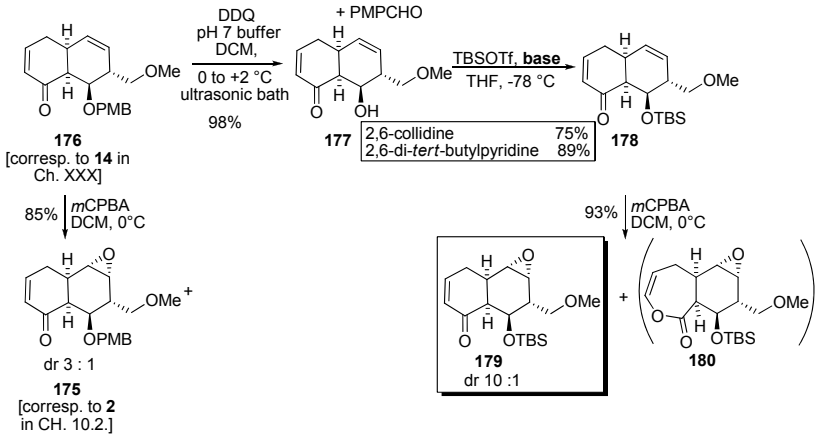
For other examples of autooxidation of alkenes and dienes see ref. 3.[78]

10.3. Further Studies on the Synthesis of the cis-Decalin Core

As was reported in Chapter 10.2 (publication in Organic Letters), our investigations resulted in the development of a reliable route to epoxy ketone **175**, where the final epoxidation resulted in a 3:1 mixture[79] of epoxides. Further investigations[80] also revealed, that a change from OPMB to OTBS-group, results in an increase in diastereomeric ratio to 10:1 (93% yield). The

[76] McCukkoch, A. W.; Smith, D. G.; McInnes, A. G. *Can. J. Chem.* **1974**, *52*, 1013-1018.
[77] Nickon, A.; Mendelson, W. L. *J. Org. Chem.* **1965**, *30*, 2087-2089.
[78] (a) Williams, R. D.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 915 –918. (b) Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223-4226. (c) Smith, A. B.; Ishiyama, N. K. H.; Minakawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 8228-8237. (d) Enev, V. S.; Drescher, M.; Mulzer, J. *Org. Lett.* **2008**, *10,* 413-416.
[79] Diastereomeric epoxides are easily separable by chromatography.
[80] Together with Mag. S. Marchart (Prof. Mulzer research group).

best yields were obtained at ca. 60% conversion, whereas full conversion resulted in decrease in yield down to 77%, mostly due to a competitive Bayer-Villiger oxidation.



Scheme 53: Further studies on the synthesis of the *cis*-decalin core

To synthesize **178**, compound **176** was subjected to PMB deprotection to give **177** in ca. 98% yield. It is worth mentioning, that in this rather trivial transformation, low temperature was important for obtaining a high yield. Crude[81] **177** was further protected with TBSOTf to give **178.** Best results (89%) were obtained with 2,6-di-*tert*-butylpyridine, whereas with 2,6-collidine yield decreased to 75%. Finally, epoxidation of **178** was carried out as discussed in the previous paragraph.

[81] Alcohol **177** was not purified from PMPCHO due to its instability on silica gel.

11. Synthesis of the C13-C18 Side Chain

Earlier investigations in the Mulzer group resulted in development of the very elegant synthesis[82] of side chain **182** (Figure 2). Nevertheless, we found it necessary to undertake certain optimization studies due to high price of starting (*S*)-glycidol and need in large quantities of the side chain. Additionally, we decide to exchange TIPS protecting group with the easier cleavable TBS group.

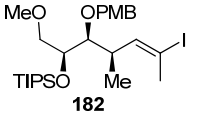
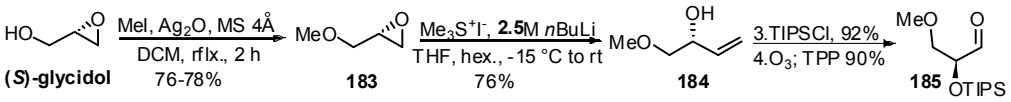


Figure 2: The side-chain synthesized by Muzer group

Methylation of (*S*)-glycidol with MeI/Ag_2O under original[82] conditions required reflux for 24-48 h and never resulted in full conversion, giving isolated yield of **183** ca. 60-65%. To our delight, addition of molecular sieves[83] resulted in full conversion after 2 h and isolated yield of 75-78%.[84,85]



Scheme 54: Synthesis of aldehyde **185**

Opening of **183** with sulfur ylide,[86] followed by TIPS protection of resulting allylic alcohol and ozonolysis were performed in accordance with reported procedures providing aldehyde **185** in 60% over 3 steps.

Unfortunately, the reaction of chiral allenylsilane **186** with aldehyde **185** under reported[82] conditions (1 eq. $TiCl_4$, -78 °C) in our hands gave low yield of the desired product **187** (Table 5). Side product **188**[90] together with products of decomposition comprised material balance. Variations in Lewis acid[87] (Et_2AlCl, $EtAlCl_2$, TMSOTf, TiF_4, $LiClO_4$, $Eu(OTf)_3$, $(CF_3)CHOH$[88]) and quench (aq. NH_4Cl or Et_3N/aq. $NaHCO_3$) resulted in no improvement in the yield. Therefore we decided to come back to $TiCl_4$ and investigate this reaction in details.

---

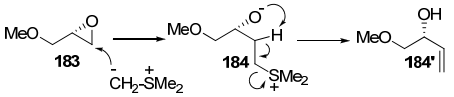
[82] Felzmann, W.; Castagnolo, D.; Rosenbeiger, D.; Mulzer, J. *J. Org. Chem.* **2007**, *72*, 2182-2186.

[83] Reymond, S.; Cossy, J. *Tetrahedron* **2007**, *63*, 5918–5929.

[84] As in the course of the methylation reaction, water liberates as a byproduct, it competes with glycidol in reaction of methylation, producing MeOH, which, in turn, can also compete with glycidol. Therefore, a beneficial effect of molecular sieves 4Å could be attributed to adsorption of water and MeOH, and, therefore, no Ag_2O getting consumed in "side methylations", allowing the desired methylation to go to completion.

[85] This reaction is virtually "quantitative", but volatility of the product **183** resulted in some loss during isolation.

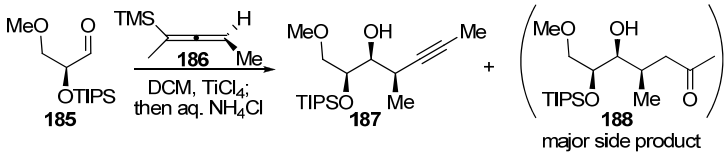
[86] Interestingly, for obtaining of full conversion in this reaction, employing of 2.5 M *n*BuLi was necessary. Use of 1.6 M BuLi resulted in lower solubility of ylide in reaction mixture (due to higher amount of hexane coming from *n*BuLi hexane solution) and consequently much longer reaction times. These results were obtained by Ing. M. Drescher and Univ. Doz. V. Enev (University of Vienna, Prof. Mulzer research group). Mechanism of this reaction:



[87] Other Lewis acids were tested earlier: BF_3*Et_2O, $SnCl_4$, $AlCl_3$ and $TiBr_4$.[82]

[88] Ratnikov, M. O.; Tumanov, V. V.; Smit, W. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 9739-9742.

Table 5: Propargylation of aldehyde **185**

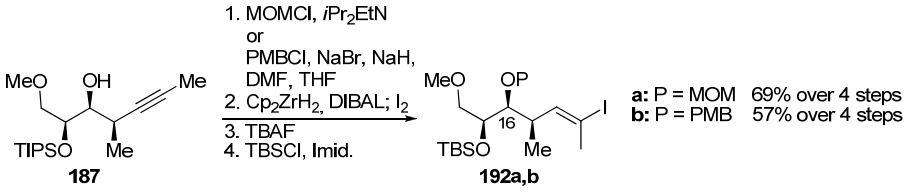


$TiCl_4$ (eq.)	T (°C)	Yield[a,b] of **187**, %	Yield[a,b] of **188**, %
1.0	-78	8	40
1.2	-78	40	32
1.7	-78	82	18
1.7	**-95 to -78**	**89 (85, dr 20 :1)**	**11**
1.7	-50	68	32
3.0	-78	79	21

[a] Yields were estimated from NMR using 4,4′-*di-tert-butyl-biphenyl* as an internal standard. Isolated yields are given in parentheses. [b] Although absolute values of yields determined from NMR are obviously affected by a certain measurement error, the tendency of yields changes is apparent.

Itis known, that titanium species can exist in aggregated forms[89]. Consequently, an outcome of reactions in principle could be sensitive to concentration. With this idea in mind, we decided to vary amount of $TiCl_4$. As can be seen from Table 5, changes in the number of equivalents of $TiCl_4$ had dramatic effect on products distribution. To our great delight, yield of the desired product **187** increased up to 85% employing 1.7 eq. of $TiCl_4$ at low temperatures. Noteworthy, the latter results were obtained on 12 mmol scale, what allowed us preparation of **187** in large quantities.

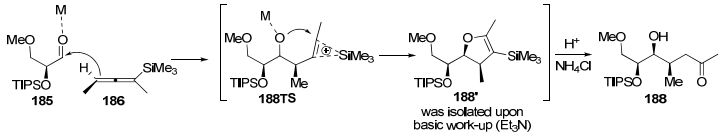
The subsequent four-step elaboration of side chain **192** proved straight forward (Scheme 55). Alcohol **187** was protected with MOMCl/*i*Pr_2EtN; the triple bond was hydrozirconated, followed by iodination to give the corresponding vinyl iodide.



Scheme 55: Synthesis of side-chains **192a,b**

Finally, the TIPS protecting group was exchanged with TBS in two steps to obtain **192a** in 69% over four steps. In a similar manner derivative side chain **192b** was prepared employing PMBBr instead of MOMCl.

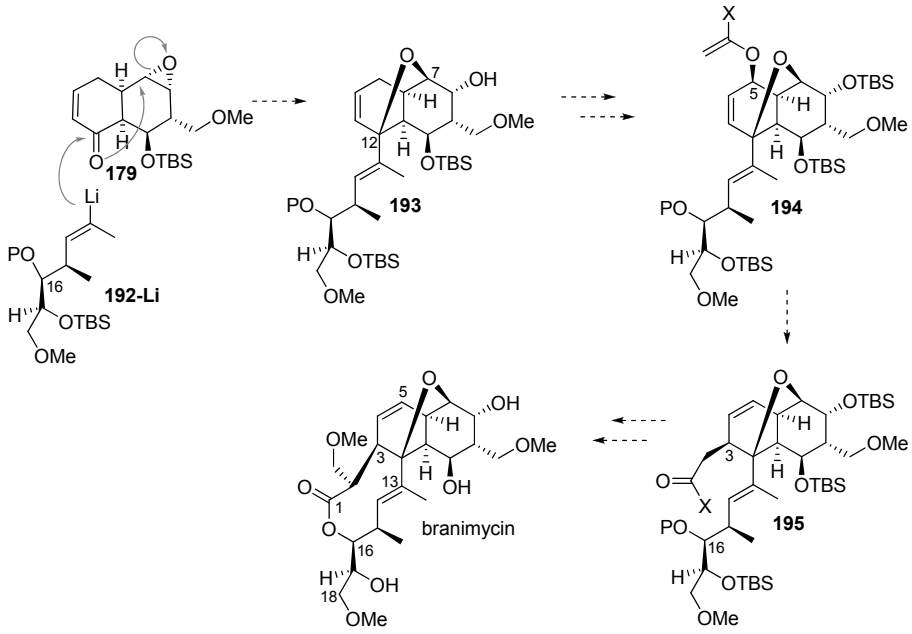
[89] M. Santelli and J.-M. Pons. Lewis Acids and Selectivity in Organic Synthesis, CRC Press, Boca Raton, FL (1995).
[90] Formation of **188** was also reported earlier.[82] Proposed mechanism for formation of **188**:



12. Connection of the *cis*-Decalin Core and the Side Chain and Further Transformations

12.1. The synthetic plan

Development of the syntheses of epoxy ketone **179** and side chain **192a,b** set the stage for connection of these two fragments. Our plan was similar to the strategy described earlier by Kallmerten (Scheme 6): metallated side chain **192-Li** should be added to the carbonyl of **179** and the resultant alkoxide should open the epoxide to give the desired compound **193** with the oxa-bridge.

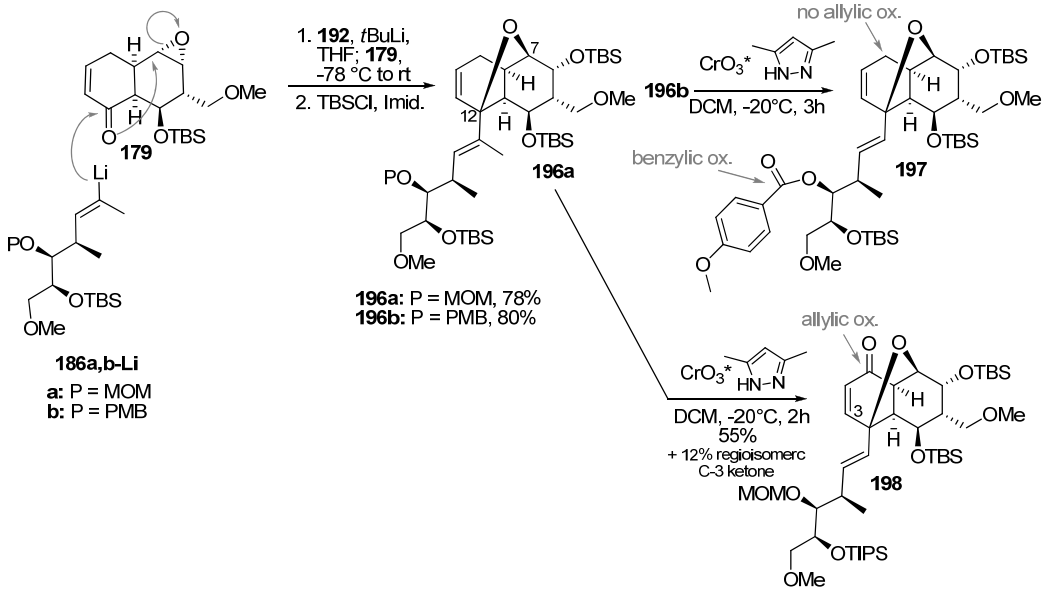


Scheme 56: Further synthetic plans

Next, we planned introduction of the alcohol functionality at the C5 position and perform a Claisen rearrangement to introduce C_2-apendix at the C3 position. Subsequent macrolactonization, introduction of CH_2OMe at the α–position to the carbonyl (at C2) and global deprotection should finish the synthesis. As a further option, the sequence: macrolactonization - introduction of CH_2OMe could be reversed.

12.2. Coupling of the *cis*-Decalin Core with the Side Chain, and Introduction of the C5-Oxygen Functionality

Synthesis of two side chains described in Chapter 11 requires some comments. According to our synthetic plan, one of transformations had to include an allylic oxidation to obtain the oxygen functionality required at the C5 position. We believed, that one of the most suitable protecting group at 16-OH is PMB, as its deprotection at later stage of the synthesis could be achieved under very mild conditions, orthogonal to other present functionalities. On the other hand, concerns about behavior of the PMB-group under allylic oxidation conditions prompted us to secure the approach by preparation of alternative side chain **192a** with MOM protecting group, which should be more stable towards oxidation.

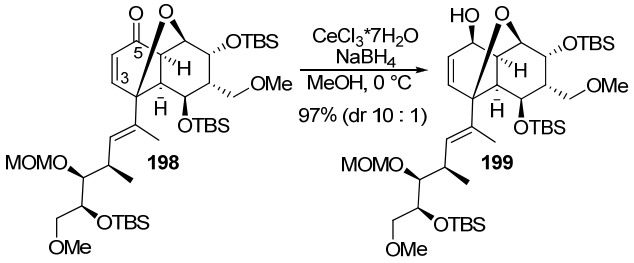


Scheme 57: Coupling of the side-chain with the *cis*-decalin core; allylic oxidation

Vinyliodide **186a** was metallated with *t*BuLi, followed by reaction with epoxy ketone **179**, what resulted in clean conversion into desired compound **195** (shown in Scheme 56) possessing the oxa-bridge. Formation of the oxa-bridge was demonstrated by observation of a $^{3}J_{C\text{-}H}$ between C12 and H7. The newly formed C8 alcohol was protected as its TBS ether, to give **196a**. In the same, way compound **196b** was synthesized starting from **186b**. The stage was now set for an allylic oxidation at the C5 position. Unfortunately, only decomposition was observed upon subjection of **196b** to $Mn(OAc)_3$*$2H_2O$/*t*BuOOH.[91] Employing an excess of CrO_3*3,5-dimethylpirazole[92] resulted in oxidation of PMB-ether to its corresponding *p*-methoxybenzoic ester **197,** but no products of the allylic oxidation were observed in the crude reaction mixture[93] even after extended reaction times.

In contrast, substrate **196a** bearing a MOM-group instead of a PMB-group gave the desired product of the allylic oxidation **198** in a 55% together with 12% of regioisomeric C3 ketone. Studyingof the influence of solvents showed that performing the reaction in EtOAc, CH_3CN or PhCl gave almost no difference with respect to CH_2Cl_2, whereas no reaction was observed in DMF or THF. Conducting oxidation in DCM at -78 °C gave no reaction even if the reaction mixture was subsequently warmed to the standard temperature -20 °C.[94] At -60 to -40 °C ratio of regioisomers improved to 7:1, but the reaction stopped at ca. 50% conversion, and no substantial difference in yield of the desired regioisomer (brsm) was observed. Employing $PhIO_2$/$(PhSe)_2$ led to decomposition, and $Mn(OAc)_3$*$2H_2O$/*t*BuOOH gave the desired product **198** in very low yield (ca. 30%). Therefore, original conditions (CrO_3*3,5-dimethylpirazole , CH_2Cl_2, -20 °C) so far gave the best results for this transformation.

[91] Mn oxidation
[92] Salmond, W. G.; Rarta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057-2059.
[93] α,β-Unsaturated ketones could be easily distinguished from crude ^{1}H NMR by appearing of characteristic low field C=CH-signals.
[94] Complex CrO_3*3,5-dimethylpirazole is prone to polymerization in solution at temperatures above -20°C.[92] Too low temperatures could result in precipitation of the complex from solution and subseqent polymerization.

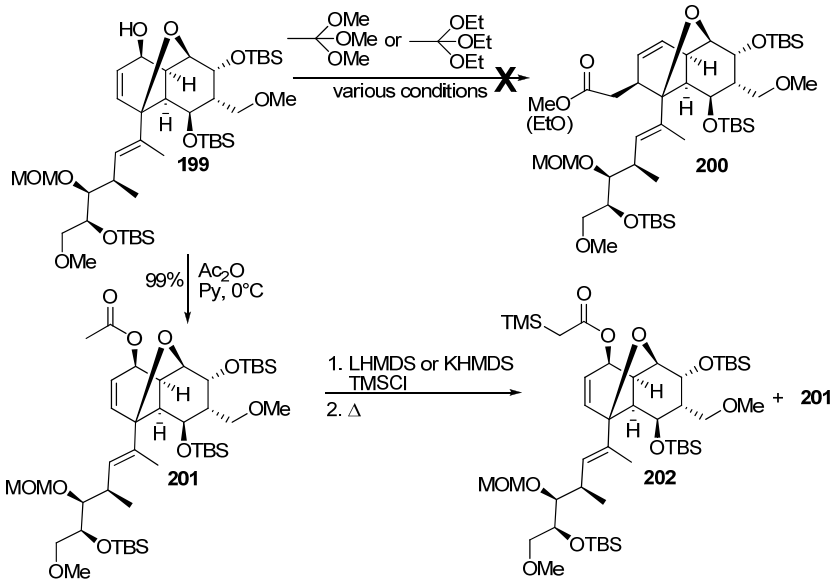


Scheme 58: Stereoselective Luche reduction of **198**

Mixture[95] of ketones **198** and its isomer was reduced under Luche conditions, to give desired allylic alcohol **199** in high yield and diastereoselectivity. Exact reason for high stereoselectivity of the reduction is not totally understood. Complexation of cerium with the carbonyl group and the oxa-bridge is unlikely, as the lone pairs of these two oxygen atoms are not suitably oriented. Transfer of the hydride anion from the less sterically hindered side could be considered as a possible explanation.

12.3. Claisen Rearrangemets

The stage was now set for the crucial introduction of the C_2-appendage at C3, which was planned *via* one of variations of the Claisen rearrangement. To this end, **199** was subjected to a number of conditions for the Johnson-

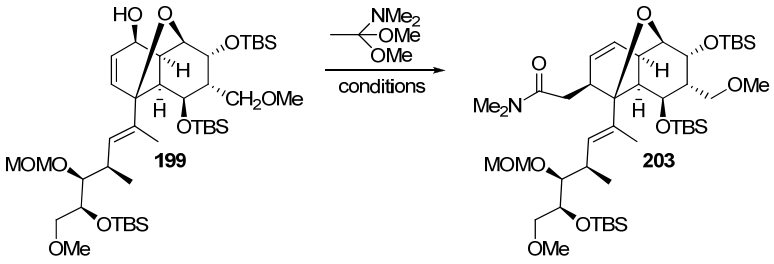


Scheme 59: Attempts towards Johnson-Claisen and Ireland-Claisen rearrangements

Claisen rearrangement. Unfortunately, in all cases no desired product **200** was detected. At lower temperatures, reactions led to recovery of some starting material and formation of the corresponding acetate; and at higher temperatures, decomposition took place. All attempts to perform the Ireland-Claisen rearrangement from the corresponding acetate **201** also proved fruitless. Formation of a lithium enolate, with LHMDS, followed by reaction with TMSCl resulted in prevailed formation of C-silylation product **202.** Changing to KHMDS/TMSCl, with subsequent heating at 60 °C, resulted in recovery of starting acetate **201** with and ca. 30 mol % of C-silylation product **202.**

[95] Isomeric ketones **198** and **198'** in our hands proved inseparable by conventional flash column chromatography. However, after reduction to their corresponding alcohols in the next step, regioisomers could easily be separated.

Table 6: Eschenmoser-Claisen rearrangement in a closed vessel



Entry	Solvent	4Å MS	Temp. (Time)	Yield [a,b]
1	Xylenes[c]	+	oil bath, 130 →150 °C (12 h)	traces
2	Tetralin	-	oil bath, 130 → 170 °C (open vessel)	no product
3	DMF[c]	+	µW, 150 °C (5h)	30%
4	DMF[c]	+	µW, 190 (20 min)	72%
5	DMF[c]	-	µW, 220 °C	41%
6	**DMF**[c]	+	**µW, 220 °C (4 min)**	**72% (64%)**
7	DMF[c]	+[d]	µW, 220 °C	72%
8	DMF[c]	+	µW, 250 °C	68%

[a] Yields were estimated from NMR using 4,4′-*di-tert-butyl-biphenyl* as an internal standard. Isolated yields are given in parentheses. [b] Although absolute values of yields determined from NMR are obviously affected by a certain measurement error, the tendency of yields changes is apparent. [c] Reaction was conducted in a **closed vessel**. [d] 4Å MS were used in 1.5 time higher than in the entry 6 (see experimental part).

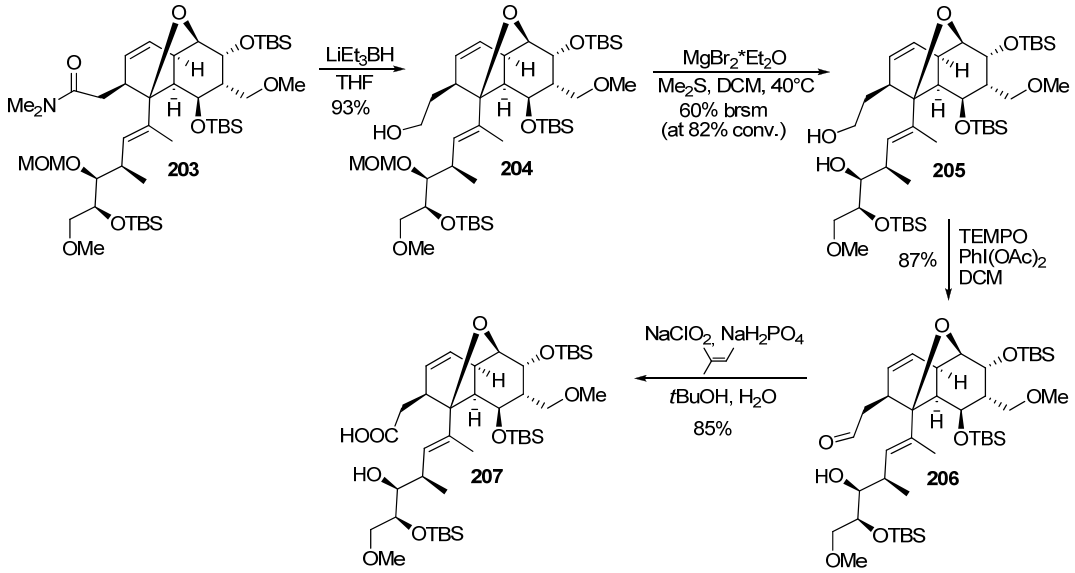
Although room for optimization of the Ireland-Claisen rearrangement remained, at this time the Eschenmoser-Claisen rearrangement gave much more promising results (Table 6). Initial attempts to carry out the rearrangement in an open vessel in tetralin gave no product at all. Conducting the reaction in a sealed tube in xylenes in the presence of 4Å MS[20] (beads) resulted to formation of traces of **203** after 12 h ad 150 °C. However, the product was detected in substantial amount when the reaction was performed in DMF in a closed vessel in the presence of powdered 4Å MS (entry 3). Increasing the temperature to 190 °C and shortening of the reaction time, to 20 min, resulted in pronounced improvement in the yield; up to 72% (from NMR). The most practical conditions were found to be irradiation at 220 °C for 4 min to obtain the desired product in 64% isolated yield (72% from NMR) on 100 mg scale. Increasing the amount of molecular sieves by a factor of 1.5,with respect to the "standard" amount (see Experimental Section for Chapter 12), did not result in any significant difference. Finally, the beneficial effect of molecular sieves was demonstrated (entry 5 *vs.* 6). An exact reason as to why molecular sieves are beneficial for the reaction remains unclear. We believe that 4Å MS could shift equilibrium towards reactive species in the Eschenmoser-Claisen rearrangement by adsorption of MeOH. Nevertheless, additional effects could not be *a priori* excluded, e.g. overheating on the surface of molecular sieves.[96]

[96] It was observed that reaction mixtures containing MS adsorb microwave irradiation much more efficient. From this, we hypothesized, that MS strongly adsorb microwave irradiation (due to their ionic character) and therefore their surface could be overheated, whereas the temperature in media would be lower. As the beneficial effect of higher temperatures was demonstrated (entrie 4 *vs.* 3), reaction could proceed or become initiated on the surface of overheated MS, whereas the product could be preserved in the "cold" solvent.

The beneficial effect of higher temperatures and shorter reaction times could be explained by possibly higher activation enthalpy $\Delta H^{\neq}$ for the rearrangement compared to $\Delta H^{\neq}$ for side reactions. Follows on from the Eyring equation,[97] with increase in temperature, a reaction with a higher activation enthalpy will be accelerated more than a reaction with a lower activation enthalpy.

Although it is too early to generalize, obtained results demonstrate, however, that *developed conditions for the Eschenmoser-Claisen rearrangement (4Å MS, DMF, high temperatures and short reaction times) can be highly beneficial for unreactive substrates, with respect to the conventional reaction performed in an open vessel.*[98]

12.4. Synthesis of the Seco Acid and Macrolactonization



Scheme 60: Synthesis of seco acid **207**

Amide **203** was reduced to alcohol **204** by treatment with Super-Hydride®. Selective MOM-deprotection in the presence of three OTBS groups was achieved under very mild conditions ($MgBr_2$*Et_2O/Me_2S).[99] The resulting diol **205** was subjected to oxidation with TEMPO/$PhI(OAc)_2$. To our delight, only the primary alcohol was oxidized providing aldehyde **206** in high yield, and no products of oxidation of the secondary alcohol were detectable in crude ^{1}H NMR. Finally, aldehyde **206** was oxidized to its corresponding carboxylic acid **207**, and thus the stage was set for the crucial macrolactonization step.

Molecular modeling of the desirable macrolactone showed that it should be significantly strained, which is to be expected taking into consideration its size (9 membered ring); and the presence of the *trans*-double bond! Following the conclusion from our theoretical approach to the effect of the temperature on cyclizations into strained and hindered cycles (see Chapter13), we conducted the cyclization at high temperature.

---

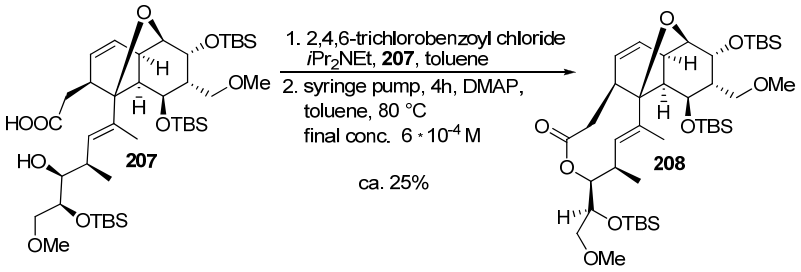
[97] Eyring equation:

$$k = \frac{k_b}{h} T e^{\left(\frac{-\Delta H^{\neq}}{RT}\right)} e^{\left(\frac{\Delta S^{\neq}}{R}\right)} \qquad (eq.1)$$

Where k = reaction rate constant, k_B = Boltzmann's constant [$1.381 \cdot 10^{-23}$ J K^{-1}]; T = absolute temperatures in degrees Kelvin (K); R = gas constant [8.314 J K^{-1} · mol^{-1}]; h = Plank constant [$6.626 \cdot 10^{-34}$ J s]; $\Delta H^{\neq}$ = activation enthalpy [J mol^{-1}]; $\Delta S^{\neq}$ = activation entropy [J K^{-1} mol^{-1}].

[98] *The Meerwein–Eschenmoser–Claisen Rearrangement*; Gradl, S. N.; Trauner, D. In *Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH, Weinheim, 2007; Chapter 7, pp 367–396.

[99] Onoda, T.; Shirai, R., Iwasaki, S. *Tetrahedron Lett.* **1997**, *38*, 1443-1446.



Scheme 61: Macrolactonization

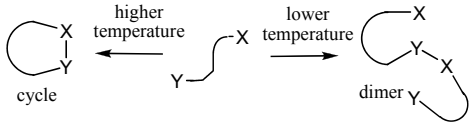
Initial attempts to perform macrolactonization under Boden-Keck conditions (EDCI[100], DMAP, DMAP*HCl, $CHCl_3$, reflux) resulted in formation of no product at all. However, employing modified Yamaguchi lactonization conditions at 80°C gave the desired lactone **208,** albeit in rather low ca. 25% yield, together with undefined side products. *Although these preliminary investigations produced a low yield of the desired product **208**, they demonstrate that a 9-membered macrolactone with a trans-double bond could be, in principle, formed via a macrolactonization reaction. This is a very rare, if not the first example of, lactonization to provide suck kind of macrolactone.*

[100] 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

13. Effect of the Temperature on Cyclization Reactions in Competition with Side Reactions

The beneficial effect of higher temperatures for the intramolecular [3+2] cycloaddition (Chapter 4.4) encouraged us to carry out a literature investigation and generalize this observation to virtually all types of cyclizations. Obtained results are discussed in Chapter 13.1 and are in preparation for publication.

13.1. Intramolecular Cyclization *vs.* Oligomerization: Effect of Temperature[101]



Analysis of a number of literature examples shows that higher temperatures are often beneficial for intramolecular cyclizations. Explanations of this effect which were proposed in literature for selected reactions are discussed. A possible kinetic background of this phenomenon is proposed in terms of enthalpy, in contrast to entropy factors suggested by some authors. Thus, cyclizations often can be characterized by higher apparent enthalpy of activation (e.g. due to strain and rotational barriers), than some common side reactions such as intermolecular dimerizations or radical terminations. As follows on from Eyring equation, increase in temperature should more accelerate a reaction with higher enthalpy of activation (cyclization) than a reaction with lower enthalpy of activation (dimerization etc.).

Intramolecular cyclization reactions, especially those leading to strained cycles or macrocycles, are often considered as key steps in the course of a synthesis, as there are many precedents when such kind of intramolecular cyclizations gave rather poor results. Therefore, it is not surprising that so much attention is paid to the development of new methods of intramolecular cyclizations. The other direction of intensive investigations is the determination of the best conditions for cyclizations, under which impact of side reactions would be minimal. To date studies deal with the influence of concentrations of reagents and substrates. Surprisingly, less studies were directed on the effect of the temperature on intramolecular cyclizations. In the present work we discuss the influence of the temperature on the competition between intramolecular cyclizations and oligomerizations or other "side"[102] reactions. Analysis of a number of literature examples shows that higher temperatures are often beneficial for intramolecular cyclizations. To the best of our knowledge this phenomenon is not generalized in synthetic organic literature. In this work we also discuss explanations of this effect which were proposed in literature for selected reactions and propose a possible kinetic background of this phenomenon in terms of enthalpy, in contrast to entropy terms proposed by some authors.

1. Influence of temperature on rate constants. Eyring equation (Eq. 1) describes the temperature dependence of a reaction rate constant:

$$k = \frac{k_b}{h} T e^{\left(\frac{-\Delta H^{\neq}}{RT}\right)} e^{\left(\frac{\Delta S^{\neq}}{R}\right)} (c^{o})^{1-n} \qquad (Eq.1)$$

[101] Compounds numbering is kept independently from the previous numbering.
[102] For clarity we choose cyclizations as desired reactions, whereas any other competitive reactions are regarded as "side" reactions. Of course, which reaction is "desired" depends on the purpose of the investigations.

k = reaction rate constant, k_B = Boltzmann's constant [$1.381 \cdot 10^{-23}$ J · K^{-1}]; T = absolute temperatures in degrees Kelvin (K); R = gas constant [8.314 J · K^{-1} · mol^{-1}]; h = Plank constant [$6.626 \cdot 10^{-34}$ J · s]; $\Delta H^{\neq}$ = activation enthalpy [J · mol^{-1}]; $\Delta S^{\neq}$ = activation entropy [J · K^{-1} · mol^{-1}], c^o = standard-state concentration[103] [mol · L^{-1}], n = molecularity of the reaction.

Increase in a rate constant upon rising the temperature from T_1 to T_2 ($T_2 > T_1$) can be expressed by the ratio[104] of rate constants at temperatures T_2 and T_1:

$$\frac{k_{(T_2)}}{k_{(T_1)}} = \frac{T_2}{T_1} e^{\left(\frac{\Delta H^{\neq}(T_2 - T_1)}{RT_1T_2}\right)} \qquad (Eq. 2)$$

$k_{(T_1)}, k_{(T_2)}$ = rate constants at T_1 and T_2 respectively.

Consequence 1 from Eq. 2. The ratio $k_{(T2)}/k_{(T1)}$ increases with $\Delta H^{\neq}$. In other words, with increase in temperature a reaction with higher activation enthalpy will be higher accelerated, than a reaction with lower activation enthalpy.

Consequence 2 from Eq. 2. Although activation entropy $\Delta S^{\neq}$ influences the absolute value of a rate constant k (Eq. 1) and therefore can be responsible for a chemical outcome of a reaction,[105] it does not have influence on temperature dependence of a rate constant.[106] Consider two reactions: a reaction #1 ($\Delta H_1^{\neq}$,$\Delta S_1^{\neq}$) and a reaction #2 ($\Delta H_2^{\neq}$,$\Delta S_2^{\neq}$), where $\Delta H_1^{\neq} > \Delta H_2^{\neq}$. As follows on from Eq. 2, increase in temperature will result in higher acceleration of the reaction #1, than of the reaction #2 independently from relation of activation entropies (i.e. whether $\Delta S_1^{\neq} > \Delta S_2^{\neq}$ or $\Delta S_1^{\neq} < \Delta S_2^{\neq}$).

For a reversible reaction (Eq. 3):

$$A_1 + A_2 + \ldots \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B_1 + B_2 + \ldots \quad (Eq. 3)$$

products distribution is determined by the ratio of rate constants for a forward (k_1) and a backward (k_{-1}) reaction (Eq. 4):

$$K = \frac{k_1}{k_{-1}} = \frac{[B_1][B_2]\ldots}{[A_1][A_2]\ldots} \qquad (Eq. 4)$$

K = equilibrium constant

Combining Eq. 2 and Eq. 4 we obtain the ratio of equilibrium constants at temperatures T_2 and T_1 (Eq. 5):

$$\frac{K_{(T_2)}}{K_{(T_1)}} = e^{\frac{(\Delta H_1^{\neq} - \Delta H_{-1}^{\neq})(T_2 - T_1)}{RT_1T_2}} \qquad (Eq. 5)$$

$\Delta H_1^{\neq}$, $\Delta H_{-1}^{\neq}$ = activation enthalpy for the forward and the backward reactions;

Consequence 1 from Eq. 5. At higher temperatures equilibrium shifts towards products with higher enthalpy of formation.

Consequence 2 from Eq. 5. The direction and the value of an equilibrium shifts with change of the temperature depends only on enthalpy parameters and does not depend on entropy[106] (cf. consequence 2 from Eq. 2).

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[103] IUPAC Compendium of Chemical Terminology 2nd Edition (1997): http://www.iupac.org/goldbook/E02142.pdf

[104] In this range of temperatures T_1-T_2 values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are assumed to be almost constant. This is a common assumption in kinetic investigations of reactions in a relatively narrow temperature window. Nevertheless, if a reaction is studied in a broader temperature range, a rate constants can become influenced by changes in $\Delta H^{\neq}$ and/or $\Delta S^{\neq}$ if changes are substantial. To the best of our knowledge an extent of these changes is case sensitive and to date is not generalized. From this, all theoretical descriptions discussed in this work should be taken as an approximation valid for a certain range of temperature, which is in turn case sensitive.

[105] So called "entropy driven reactions".

[106] Unless entropy parameter substantially changes within the studying range of temperature, which cannot be generalized (see ref.104).

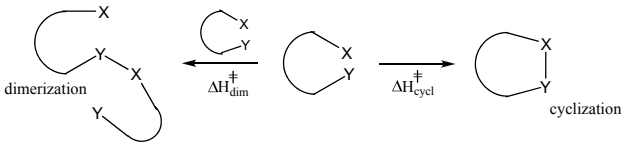
Noteworthy, reactions under thermodynamic control will give different product distribution at different temperatures, and with certain relation of ΔS and ΔH parameters[107] this may result in a switch in selectivity.

In principle, any reaction can be considered as a combination of irreversible and reversible (e.g. conformational changes) processes. Consequently, as follows on from the discussion above, temperature dependence of reaction rate constants (or equilibrium constants) are determined rather by enthalpy term, whereas entropy in general has no influence on it.[106] This could be described in other words, if to recall physical meanings of $\Delta H^{\neq}$ and $\Delta S^{\neq}$.[108] Thus, roughly speaking, activation enthalpy is connected with energies of breaking and creating bonds in the transition state. At different temperatures a probability (i.e. a rate constant) for reacting partners to surpass the required barrier is different. Therefore, the enthalpy term should be highly temperature dependent. In contrast, the meaning of $\Delta S^{\neq}$ is a probability to meet an appropriate orientation of reacting partners (i.e. reactants and solvent) in the transition state. Apparently, this term should be much less temperature dependent.

2. Intramolecular cyclization vs. dimerization and other "side"[102] reactions.

We believe that an *increase in a reaction temperature will likely favor cyclizations (with strain and/or slow conformational changes) over dimerizations and some other intermolecular reactions with low activation enthalpy.*

Consider a competition between a cyclization and a linear dimerization of a bi-functional substrate (Scheme 1). Each reaction (cyclization and dimerization) in reality can involve a few processes e.g. a series of conformational changes, coordination with a reagent (catalyst) etc. Nevertheless, each overall reaction (cyclization and dimerization) has apparent rate constant with corresponding apparent activation parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$). To assess relative values of $\Delta H^{\neq}_{cycl}$ vs. $\Delta H^{\neq}_{dim}$ we have to consider some possible factors influencing them.



Scheme 1: Competition between a cyclization and a dimerization

Strain. Illuminati *et al*.[109] demonstrated, that the activation enthalpy $\Delta H^{\neq}_{cycl}$ of the cyclization of unsubstituted aliphatic substrates (Table 1) are in most cases higher, then activation enthalpy of intermolecular alkylations ($\Delta H^{\neq}_{dim}$), where the latter ones were chosen as a model reaction to mimic a corresponding linear dimerization.

Based on these results it is reasonable to anticipate that the activation enthalpy of a cyclization ($\Delta H^{\neq}_{cycl}$) is often higher than activation enthalpy of a linear dimerization ($\Delta H^{\neq}_{dim}$), which can be attributed to strain and some other unfavorable intramolecular stereoelectronic interactions resulting in the course of cyclization, especially in case of hindered substrates.

For cyclizations under thermodynamic control (products are in equilibrium) enthalpies of formation of a cyclic product vs. a dimeric (oligomeric) product should be considered. In this case the strain in a cyclic product apparently will favor the latter at higher temperatures (consequence 1 from Eq. 5).

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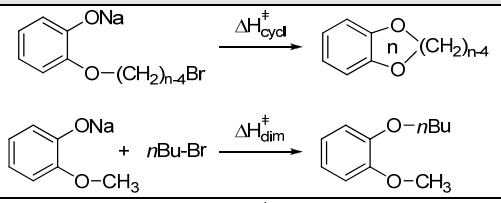
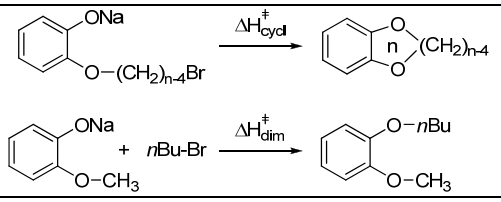
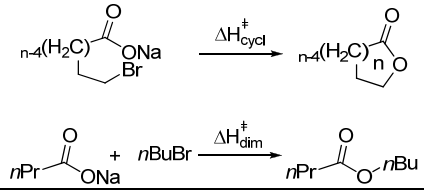
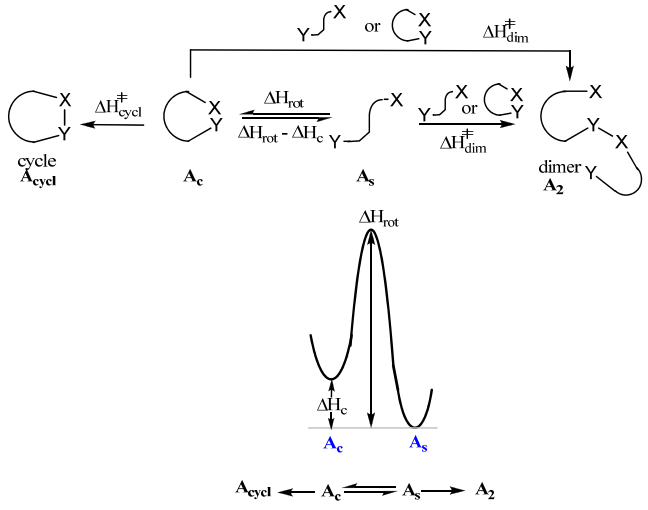
[107] $\Delta H^{\neq}_{1} > \Delta H^{\neq}_{-1}$ and $\Delta S^{\neq}_{1} > \Delta S^{\neq}_{-1}$ or $\Delta H^{\neq}_{1} < \Delta H^{\neq}_{-1}$ and $\Delta S^{\neq}_{1} < \Delta S^{\neq}_{-1}$.
[108] Schmid, R., Sapunov, V. N. *Non-formal Kinetics*; Verlag Chemie: Weinheim, 1982.
[109] For a review see: Illuminati, G.; Mandolini, L. *Acc. Chem. Res.*, **1981**, *14*, 95-102.

Table 1: Activation enthalpy for cyclizations

Entry	Reaction	size of the ring (n) with $\Delta H^{\neq}_{cycl} > \Delta H^{\neq}_{dim}$	size of the ring (n) with $\Delta H^{\neq}_{cycl} < \Delta H^{\neq}_{dim}$
1		6-11, 14, 16,	24[a]
2		8-10	5 6[a],7[a]
3		7-13, 14[a], 16, 18, 23[a]	-

[a] difference between $\Delta H^{\neq}_{cycl}$ and $\Delta H^{\neq}_{dim}$ is in the range of the sum of experimental errors.

Rotational barriers. Consider a substrate **A** (Scheme 2) which can exist in two conformations: $\mathbf{A^s}$-conformation (X and Y are remote from each other, i.e. the conformation looks like the letter "**S**") and $\mathbf{A^c}$-conformation (X and Y are close to each other, i.e. the conformation looks like the letter "**C**"). Apparently cyclization reaction can occur only from the conformation $\mathbf{A^c}$. In contrast, it is intuitively clear, that dimerization reaction should be much less sensitive to in which conformation[110] reacts **A** (unless a remote part of the molecule substantially hinders the reacting center). If conformational changes are necessary for cyclization[111] and their rates are comparable to rates of chemical reactions,[112] then rotational barier ($\Delta H^{\neq}_{rot}$) can have more impact in increase of an apparent activation enthalpy of cyclization $\Delta H^{\neq}_{cycl}$ rather than $\Delta H^{\neq}_{dim}$.



Scheme 2[a]:

[110] Although here we discuss only two conformation, the general point is that among all possible conformations of a substrate, the number of conformations suitable for the dimerization is much higher than a number of conformations leading to the intramolecular cyclization.
[111] I. e. if the conformation $\mathbf{A^c}$ does not substantially prevail.
[112] At given concentrations.

[a] Relative enthalpies of $\mathbf{A^c}$ and $\mathbf{A^S}$ here are shown arbitrarily.

Population of conformers. If conformational changes are fast and rate of cyclization from conformer $\mathbf{A^c}$ is comparable[112] to the rate of dimerization, then population of conformers will influence competition between cyclization and dimerization.[113] As geometry of conformer $\mathbf{A^c}$ resembles the product of cyclization $\mathbf{A_{cycl}}$ and both ends are brought into proximity, it is reasonable to assume that conformer $\mathbf{A^c}$ can experience some "transannular" repulsion and other strain forces, especially in case of hindered substrates. Therefore it is probably not an unusual situation when enthalpy of formation for $\mathbf{A^c}$ is higher than for $\mathbf{A^s}$. Consequently, higher temperatures will favor conformer $\mathbf{A^c}$ with respect to conformer $\mathbf{A^s}$ (consequence 1 from eq. 5, *vide supra*).

Summarizing, it seems to be a not uncommon situation when apparent activation enthalpy of cyclization $\Delta H^{\neq}_{cycl}$ is higher than $\Delta H^{\neq}_{dim}$ due to strain or rotational barriers. Applying consequence 2 from eq. 2 we can conclude that increase in temperature will likely favor cyclization over dimerization.

For consistency, we should note that besides discussed strain or rotational barriers, other points may play a role in products distribution:

1. Thermal stability. For example, if the dimer is more stable towards decomposition at higher temperatures as the corresponding monomer, then a yield and a proportion of the monomer will decrease.
2. Template or chelate driven cyclizations. Increase in temperature will likely lead to dissociation, although the outcome will depend on relative values of ΔH (see e.g. an example shown in Table 4, *vide infra*).
3. Change in reaction mechanism upon change in temperature. For example, in a two step process each reaction is rate limiting but at different temperatures. The other possibility is a change of a reaction mechanism (e.g. activated acid derivative *vs.* ketene).
4. As was mentioned above, for Eq. 2 we assumed that values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are constant within the temperature range studied. Nevertheless, for some reactions this assumption can become unvalid; however it is rather unpredictable as well as the influence of this effect.

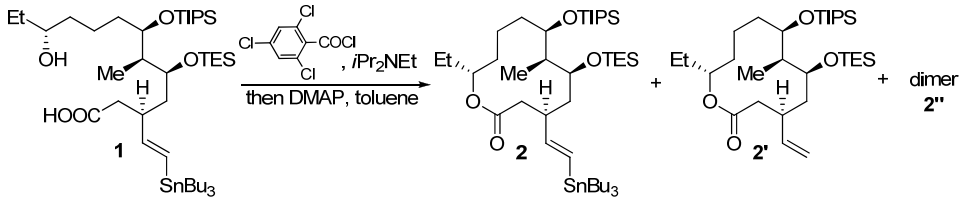
So far we discussed only a competition of cyclization with dimerization. Nevertheless, similar considerations can be applied to competition with any other "side" reaction, although relative ranking of $\Delta H^{\neq}_{cycl}$ *vs.* $\Delta H^{\neq}_{dim}$ should be considered separately for each type of competition. Presented discussion of course is not comprehensive and it is called here just to illustrate a possible nature of the favoring of cyclizations at higher temperatures, what is exemplified by a number[114] of literature precedents presented below.

3. Literature survey.

Yamaguchi macrolactonization. In the course of synthesis of (+)-A83543A Evans *et al.*[115] showed a beneficial effect of higher temperatures for cyclization of **1** to **2** (Table 2). As can be seen, the amount of monomeric macrocycle **2** substantially increased upon increase of the temperature.

[113] I.e. with this conditions Curtin-Hammett principle is not applicable.
[114] It should be noted, that in this work we discuss all literature examples on influence of temperature on cyclizations found during the survey. However, the conducted literature search cannot pretend to be exhaustive due to its non-triviality, and therefore further examples will show the generality of the discussed phenomena.
[115] Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513.

Table 2: Yamaguchi Macrolactonization (**1** → **2**)[a]

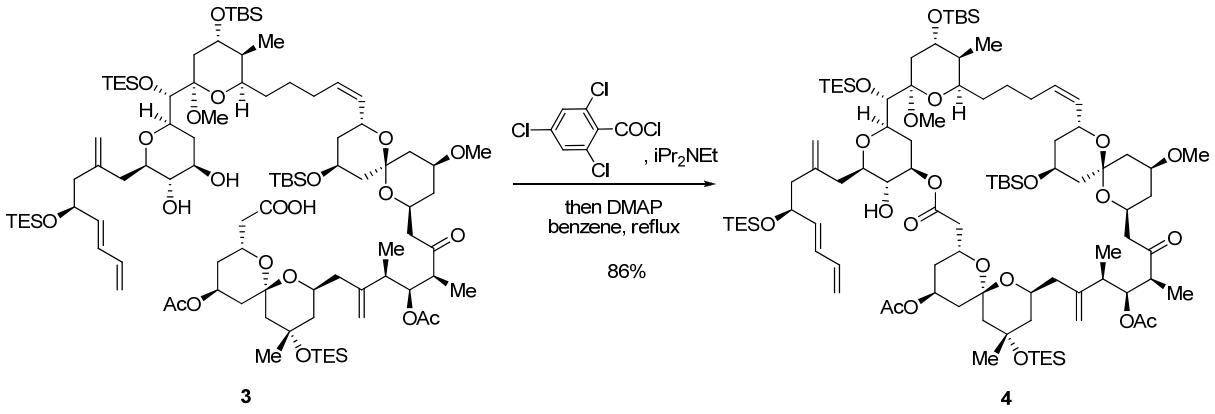


T (°C)	addn time (h)	macrocycle prod. **2** (%)	destannylated monomer **2'** (%)	dimer (%)
25	0.5	13	-	33
70	0.5	63	7	10
110	10	10	63	1
110	**1**	**78**	**3**	**3**

[a] Final cyclization concentration was 0.007 M in toluene

Noteworthy, as the product **2** proved to be sensitive to prolonged heating due to destannylation, the best results were obtained at shorter reaction times.

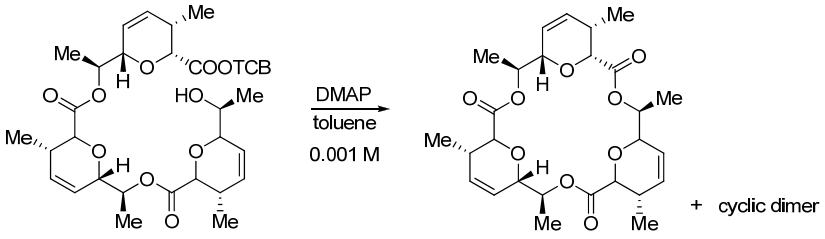
A similar trend was observed for macrolactonization of **3** to **4** (Scheme 3).[116] Although in this case no detailed temperature studies were not provided, the authors mentioned that for optimal results high temperatures (refluxing benzene) were required.



Scheme 3: Yamaguchi macrolactonization **3** to **4**

Cyclization of **5** in refluxing toluene was shown to yield the monomeric lactone **6** as the major product, whereas at lower temperatures formation of cyclic dimers was prevailed.[117]

[116] Evans, D. A.;Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671-8726.
[117] Burke, S. D.; Heap, C. R.; Porter, W. J.; Song, Y. *Tetrahedron Lett.* **1996**, *37*, 343-346.



5 **6** **6'**

22 °C	13%	52%
111 °C	61%	17%

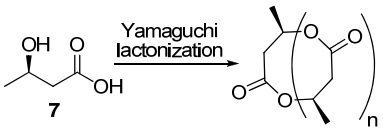
TCB = 2,4,6-trichlorobenzoyl

Scheme 4 Yamaguchi macrolactonization **5** to **6**

The authors provided the following explanation for the observed temperature effect: "Based upon the assumption that dimerization to the larger ring is the entropically less-favored pathway, it was reasoned that the yield of **6'** might increase if lactonization was attempted at lower temperature." Although reported results are undoubtedly valuable, the proposed explanation seems to us rather questionable in view of the consequence 2 from Eq. 2 or consequence 2 from Eq. 5[118] (*vide supra*).

In studies of cyclooligomerization of acid **7** Seebach *et al.*[119] observed that at higher temperatures distribution of products shifts towards formation of smaller rings (Table 3).

Table 3: Ratio of oligomers at different temperatures[a]



7

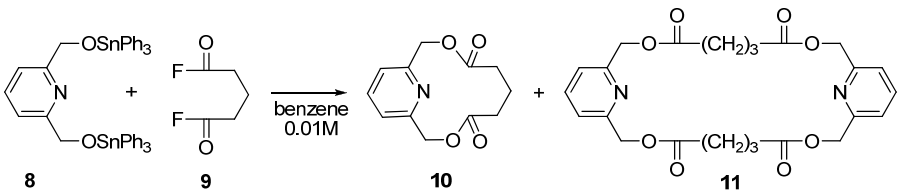
Temp.	n = 5	n = 6	n = 7
rt	1	1	1
110 °C	6	3	1

[a] Yield at rt was 50%. Yield at 110° C was not reported.

Tin mediated macrolactonization. Picard *et al.*[120] reported the formation of macrodiolide **10** from diacid fluoride **9** and tin alcoholates **8**. It was demonstrated that although selectivity of the formation of monomer **10** *vs.* dimer **11** decreased at higher temperature, the yield of the desired diolide **10** slightly increased (Table 4).

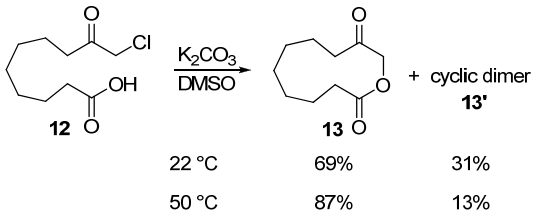
[118] An eveidence for certain degree of reversibility of formation of ester bond under Yamaguchi conditions were reported (ref. 16).
[119] Seebach,D.; Brändli, U.; Schnurrenberger, P.; Przybylski, M. *Helv. Chim. Acta* **1988**, *71*, 155–167.
[120] Picard, C.; Cazaux, L.; Tisnes, P. *Tetrahedron* **1986**, 42, 3503–3519.

Table 4: Tin mediated macrolactonization



T (°C)	Yield of **10** (%)	Yield of **11** (%)	Ratio **10**/**11**
20	73	3	24
80	80	4	20

The decrease in selectivity is explained by the authors based on a template directed nature of cyclization. Presumably, at higher temperatures constant of coordination with tin is lower. This example shows that although temperature does have promoting effect on cyclization (the combined yield of cyclic products **10** and **11** increased at the expense of side reaction e.g. oligomerization or decomposition), there are other factors (such as complexation) which sometimes also influence product distribution.



Scheme 5: S_N2 macrolactonization **12** to **13**

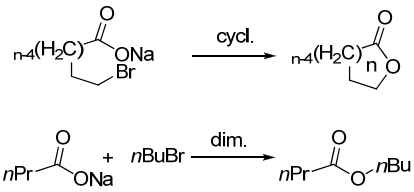
S_N2 macrolactonization. Sampson and Karim[121] developed a new method for a macrolactonization via intramolecular cyclization of chloro keto acids under basic conditions (Scheme). Performing the reaction at 22 °C led to formation of a substantial amount of the diolide **13'**, whereas at 50 °C the yield of the desired lactone **13** increased, and the proportion of the dimer **13'** decreased.

As mentioned above (Table 1, entry 3), Illuminati *et al.* studied the kinetics of cyclizations of ω-bromo acids sodium salts into corresponding lactones.[109,122] Obtained activation parameters were compared with corresponding activation parameters for linear dimerization reaction (intermolecular esterification). The latter reaction was not studied for each substrate, but a model reaction of sodium *n*-butyrate with *n*-BuBr was taken instead (Table 5).

Reaction rate constants were measured at different temperatures which allows the use of these data for the discussion of influence of temperature on relative rate constants of intramolecular cyclizations and the intermolecular esterification (i.e. "dimerization").

[121] Karim, M. R.; Sampson, P. *J.* Org. *Chem.* **1990**, *55*, 598-605.
[122] (a) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.***1977**, *99*, 2591-2597; (b) Galli, C.; Illuminati, G.; Mandolini, L. *J. Am. Chem. Soc.*, **1973**, *95*, 8374-8379.

Table 5: S_N2 macrolactonization



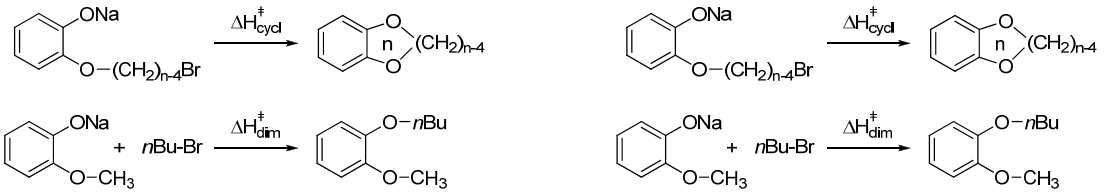
n[a]	T °C	Rate constant [b,c] k_T, s^{-1}	Acceleration k_{50}/k_{35}	$\Delta H^{\neq}$ [c] kcal mol^{-1}	$\Delta S^{\neq}$ [c] cal K^{-1} mol^{-1}
13	35	$1.1x10^{-3}$	3.3	15.3	-22.5
	50	$3.6x10^{-3}$			
7	35	$3.0x10^{-3}$	3.6	17.4	-13.6
	50	$1.1x10^{-2}$			
8	35 [d]	$2.2\ x10^{-5}$ [d]	5.0	21.8	-9.2
	50	$1.1\ x10^{-4}$			
intermolecular alkylation	35	$6.7x10^{-2}$ [b]	3.0	14.1	-18.4
	50	$2.0x10^{-1}$ [b]			

[a] Ring size of the ring to be formed. [b]For intermolecular alkylation rate constant has dimention mol s^{-1} L^{-1}. [c] All values here have certain experimental errors which are not presented here, but given in the original publications.[122] The values of accelerations were calculated from average values of $\Delta S^{\neq}$ and $\Delta H^{\neq}$. [d] A rate constant at 35 °C is not reported by authors, therefore it was estimated from $\Delta S^{\neq}$ and $\Delta H^{\neq}$ values via Eyring eq. (Eq. 1).

As can be seen from the Table 5, the activation entropy of the cyclization into 13-membered lactone is more negative than the activation entropy of the intermolecular alkylation. On the other hand, the activation entropy of cyclization into the 7-membered lactone is substantially less negative than the activation entropy of the intermolecular alkylation. Nevertheless, in both cases increase in temperature from 35 to 50 °C results in higher acceleration of the intramolecular cyclizations, compared to the intermolecular esterification. These examples clearly demonstrate that, as follows on from Eyring equation (Eq. 2), activation entropy $\Delta S^{\neq}$ in general does not have an impact in the temperature dependence of rate constants.[106] In contrast, a rate constant is sensitive to temperature rather due to the activation enthalpy term. And the higher the activation enthalpy $\Delta H^{\neq}$, the higher the temperature sensitivity of the rate constant. For example, upon rising the temperature from 35 to 50 °C the acceleration of the cyclization into 8-membered lactone ($\Delta H^{\neq}$ = 21.8 kcal mol^{-1}) is ca. 5 times, whereas intermolecular esterification ($\Delta H^{\neq}$ = 14.1 kcal mol^{-1}) is accelerated in only ca. 3 times. As cyclizations into 7-13, 16 and 18 membered lactones have values $\Delta H^{\neq}_{cyc} > \Delta H^{\neq}_{dim}$, for all these reactions observed accelerations[123] are higher than the acceleration of "dimerizations". Cyclizations into unsubstituted 14 and 23 membered lactones have values of $\Delta H^{\neq}_{cycl}$ very close to $\Delta H^{\neq}_{dim}$. As a result, in these cases almost no difference in accelerations was observed.

Williamson synthesis of cyclic ethers. The same authors also carried out kinetic studies of cyclizations of ω-bromophenolates into the corresponding cyclic ethers (Table 1, entries 1, 2).[109] Data obtained show the same trend as outlined in Table 5. Thus, for most substrates $\Delta H^{\neq}_{cycl} > \Delta H^{\neq}_{dim}$, and therefore accelerations[123] upon rising the temperature for these cyclizations are higher than for the intermolecular alkylation ("dimerization"). The only distinct exception is the cyclization into 5-membered ether (Table 1, entry 2), for which $\Delta H^{\neq}_{cycl} < \Delta H^{\neq}_{dim}$.

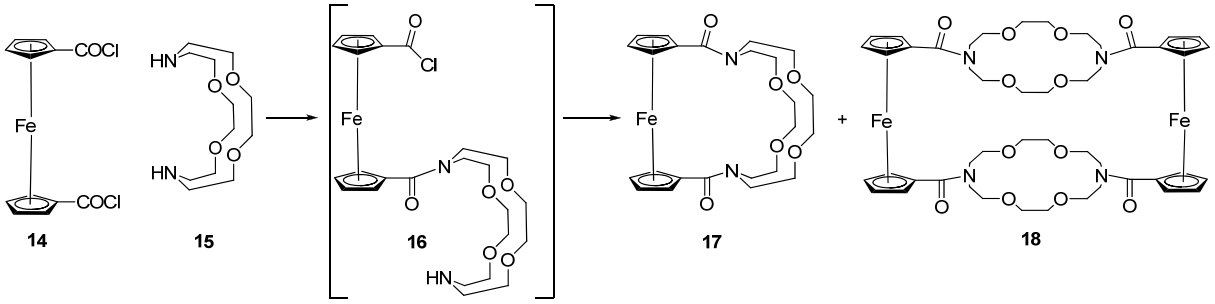
[123] In the original publication reported rate constants were not measured in all cases at the same temperatures, therefore for comparing rate constants should be recalculated.



Scheme 6: Williamson synthesis of cyclic ethers

Macrolactamization. Hall *et al.*[124] revealed a remarkable effect of temperature in the synthesis of cryptands **17** and **18**. Dropwise addition of the reactants to vigorously stirred toluene over 3h (final concentration of 1.7 x 10^{-3} M in monomer) at -70 °C gave only 6% of the desired monomeric amide **17**, together with 20% of the dimer **18** (Table 6, entry 5). Increase of the reaction time at the same temperature did not improve the overall yield of **17** and **18** and high molecule weight oligomeric products comprised the material balance (entry 6). In contrast, rising of the temperature to 20 °C resulted in an improvement of the yield of **17** up to 65%, and the yield of the dimeric macrocycle decreased to 5% (Table 6, entry 2).

Table 6: Yields of **17** and **18** as a function of temperature



Entry	T, °C	Yield of **17**, %	Yield of **18**, %
1	100	63	2
2	20	65	5
3	-20	62	9
4	-40	17	15
5	-70	6	20
6	-70 (8 h); -40 (8 h)	no improvement in the overall yield of **17** + **18**	

An explanation of this phenomenon by the authors is based on presumably hindered rotation about the N-CO bond in intermediate **16**, which at higher temperatures is faster.

We would like to note, that for validity of this explanation (from our point of view), it should be specified, that the rotation about the N-CO bond is hindered **namely with respect to** dimerization (i.e. $\Delta H_{rotation} > \Delta H^{\neq}_{dim}$).

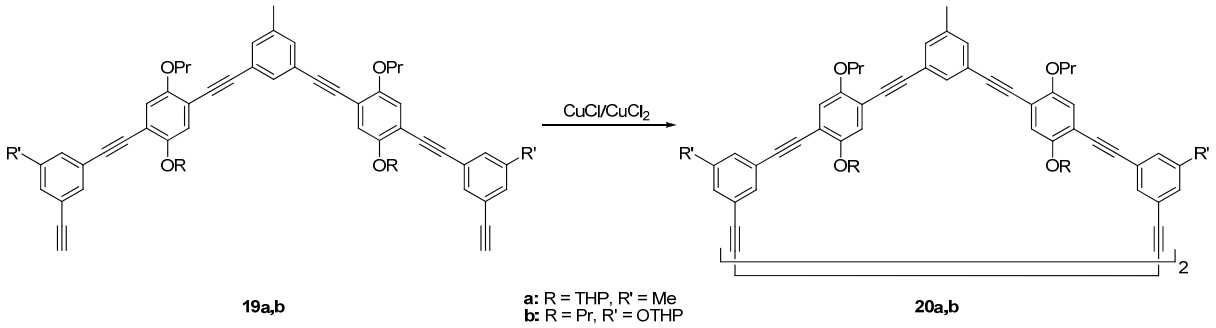
Formation of macrocyclic phosphodiester (oligonucleotide cyclization). Studies[125] on the cyclization of oligonucleotide 5'-d(pGCCCG)rG showed that the reaction at 0 °C in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and imidazole gave the desired product with substantial amount of a dimerized oligonucleotide (12-mer). When the cyclization was performed at 25 °C, the yield of the dimerized product became negligible (Eq. 6).

[124] Hammond, P. J.; Beer, B. D.; Hall, C. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1161–1163.
[125] Kawamura, K.; Nakahara, N.; Okamoto, F.; Okuda, N. *Viva origino* **2003**, *31*, 221-232.

5'-d(pGCCCG)rG	→	monomeric cyclic oligonucleotide	+	dimerized oligonucleotide	(Eq. 6)

Oxidative cyclizations of bis-acetylenes. The outcome of oxidative cyclodimerization of bis-acetylenes **19a,b** with copper salts was shown to be temperature dependent (Table 7).[126] Thus, the yield of macrocycle **20a** increased

Table 7: Oxidative Cyclodimerization of Bis-acetylenes **19a,b → 20a,b**

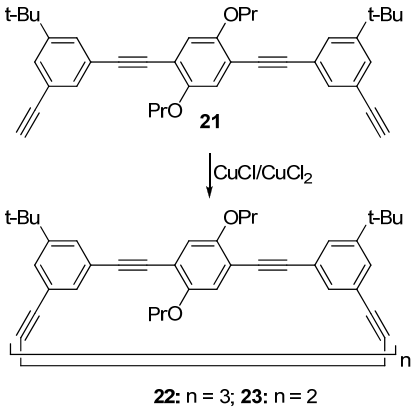


19a,b **a:** R = THP, R' = Me **b:** R = Pr, R' = OTHP **20a,b**

T (°C)	Yield of **20a** (%)	Yield of **20b** (%)
20	40-45	30-35
60	65-70	45-50
90	25-30	45-40

from 40-45% to 65-70% upon rising the temperature from 20 to 60 °C, and accordingly the amount of oligomeric side products decreased. In this example conditions had to be carefully controlled as extended reaction times or too high temperatures lead to a decrease in yield. A similar trend was observed for oxidative cyclodimerization of **19b**.

Cyclization of related bis-acetylene **21** gave constant amount of cyclic trimer **22** in about 35% yield (Scheme 7) together with higher oligomers and polymeric material independently from the reaction temperature (rt or 65 °C).



22: n = 3; **23:** n = 2

Scheme 7 Oxidative Cyclooligomerization of Bis-acetylene **21**

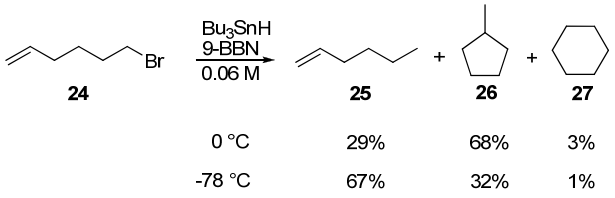
[126] Höger, S.; Bonrad, K.; Karcher, L.; Meckenstock, A.-D. *J. Org. Chem.* **2000**, *65,* 1588-1589.

However, at 65 °C approximately 15-20% of the cyclic dimer **23** was formed, whereas at room temperature its formation was negligible.

The authors attribute the observed temperature effect to "an increased mobility of the intermediate formed after the first coupling reaction."

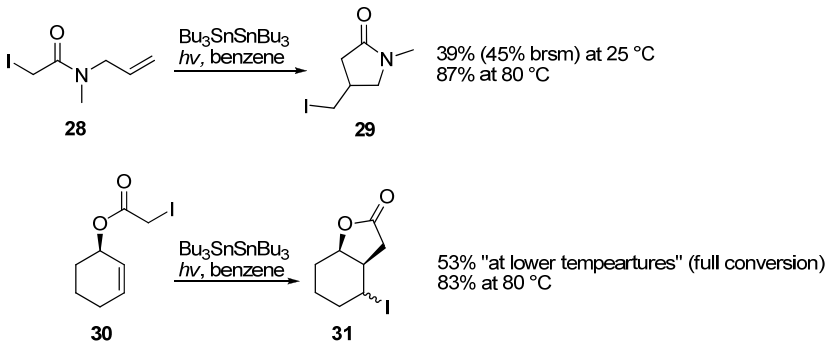
Strictly speaking, we believe, that increase in mobility at higher temperatures could be observed for any molecule. Therefore it should be specified, that only if the enthalpic barrier of "mobility" is higher than the enthalpic barrier for intermolecular reaction, only in this case higher temperatures should favor the cyclizations.

Reductive radical cyclization. Cyclization of hexenyl radical under reductive conditions[127] was demonstrated to give mainly acyclic product **25** at -78 °C. In contrast, at 0 °C products of cyclization **26** and **27** were prevailed (Scheme 8).



Scheme 8: Reductive radical cyclization

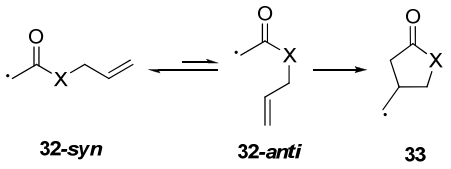
Atom transfer radical cyclizations. The efficiency of atom transfer cyclization of α-iodoacetamide **28** proved to be highly temperature dependent (Scheme 9).[128] At 25 °C, **28** showed the signs of a poor chain, as it required excess of ditin reagent to prevent the reaction from stopping and long reaction times for considerable conversion. At 80 °C, **28** cyclized much more cleanly and rapidly to give 87% of the desired product **29**. A similar trend was observed for cyclization of ester **30**, where cyclization gave higher yields at higher temperature.



Scheme 9: Atom transfer radical cyclizations

The explanation of authors is based on the fact that typical esters and amides exist mainly in the **32-*syn*** rotamer (Scheme 10), which is topologically prohibited from cyclizing. The barriers to rotation are much higher than the activation energy for typical radical cyclizations. Therefore, lifetime of **32-*syn*** is probably too short to surpass the barrier for ester bond rotation to **32-*anti***. Thus, in a tin hydride reaction (not discussed here), direct reduction is observed, and

[127] V. Tamara Perchyonok and Carl H. Schiesser Tetrahedron Letters 39 (1998) 5437-5438
[128] Dennis P. Curran, and John Tamine *J. Org. Chem.*, **1991**, 56 (8), 2746-2750

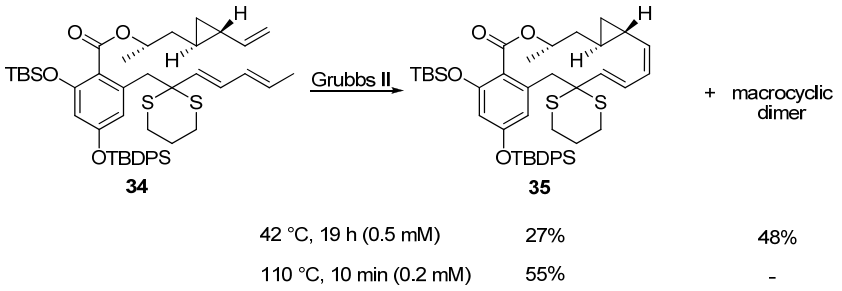


Scheme 10: Interconversion of rotamers

in the atom-transfer reaction, chains will not propagate. At 80 °C rotation of bonds is quick enough and **32-*syn*** can isomerize (at least partly) to **32-anti**, what is followed by the rapid cyclization to **33**.

As a conclusion authors say: "Changing solvents[129] or substituents can effect either the rotamer population or the barrier to rotation; however, temperature is an effective, easily altered variable. If an amide or ester radical cyclization reaction fails, heat it up."

Ring closing metathesis (RCM). Optimization studies of RCM in course of syntheses of different natural products revealed[130] that higher temperatures and shorter reaction times lead to increase of yields of monomeric cycles.



Scheme 11: Ring Closing Metathesis

For example, cyclization of diene **34** (Scheme 11) in toluene at 42 °C (19 h) gave desired monomer **35** in 27% yield, together with 48% of dimers. Performing this reaction at 110 °C (10 min) improved the yield of **35** up to 55%, and no dimers were observed.[131]

Authors provide the following explanation of this phenomenon: "The observations described above may be explained by the difference of entropy in activation energy leading to each product. If the formation of the monomer is entropically favored over that of the dimer the kinetic ratio of the two products should shift toward the monomer at higher temperature. In fact, the ratio obtained after 5–10 min appears to be a kinetic ratio, since runs with longer reaction times resulted in the formation of more dimer."

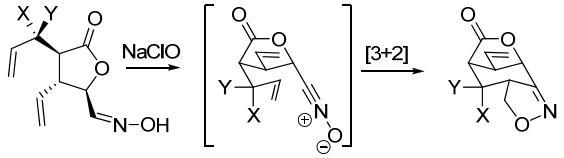
---

[129] Jung, M. E.; Cervay, J. *J. Am. Chem. Soc*. **1989**, *111*, 5469-5470.
[130] Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett*. **2003**, *44*, 3297–3299.
[131] Apparently this dramatic change cannot be fully attributed to difference in concentrations.

This explanation is similar to the explanation proposed by other authors[117] for the example shown in Scheme 4. Although the synthetic value of this study is really high, the explanation seems to us rather questionable in view of the consequence 2 from Eq. 2 and consequence 2 from Eq. 5 (*vide supra*).

Intramolecular [3+2] cycloaddition. Earlier we reported[132] a remarkable effect of temperature on intramolecular [3+2] cycloaddition (Table 8). Thus, cyclization of **36a,b** at 0°C resulted in constantly low yield of ca. 30 % independently from the cyclization reagent (not shown, see ref. 132) what was attributed to a competitive intermolecular [3+2] cycloaddition leading to formation of polymers. Although dilution did result in increase in the yield, the most pronounced effect was observed upon conducting the reaction at higher temperatures. The yield of the desired products **37a,b** raised from 51% at 0 °C to 76 % at 80 °C.

Table 8: Intramolecular [3+2] Cyclization



36a,b **37a,b** **38a,b**

36a:**36b** 1:3

a X = H; Y = OTBS
b X = OTBS; Y = H

Conc., M	Temp.	Solvent	Yield[a]; d.r. **2b : 2a**
$1.5x10^{-2}$	0 °C	DCM	37%; 32 : 5 (31%; 28 : 3)
$1.5x10^{-3}$	0 °C	DCM	51%; 46 : 5
$1.5x10^{-3}$	22 °C	DCM or DCE	63%; 53 : 10
$1.5x10^{-3}$	40 °C	DCM or DCE	70%; 59 : 11
$1.5x10^{-3}$	60 °C	DCE	74%; 59 : 15
$1.5x10^{-3}$	80 °C	DCE	76%; 60 : 16
$0.8x10^{-3}$	80 °C	DCE	79%; 61 : 18 (75%; 60 : 15)

[a] Yields were estimated from NMR using 4,4′-*di-tert-butyl-biphenyl as an internal standard*. Isolated yields and diastereoselectivity are given in parentheses.

Conclusions. A number of the literature examples discussed clearly demonstrate that in many[114] cases increase in temperature favors cyclizations over oligomerizations and some other side reactions. Although in each case various effects can play a role, we believe that there is one effect which could be common for all these examples. Cyclizations can often be characterized by higher apparent enthalpy of activation (e.g. due to strain and rotational barriers), with respect to some side

[132] Gromov, A.; Enev, V.; Pilger, C.; Mulzer, J. *Tetrahedron Lett.* submitted.

reactions such as intermolecular dimerization or radical termination. As follows on from Eyring equation (Eq. 1, 2), increase in temperature should more accelerate a reaction with higher enthalpy of activation (i.e. cyclization) than a reaction with lower enthalpy of activation (dimerization etc.).

With this work we would like to encourage synthetic chemist during the course of optimization studies to vary not only reagents, but also temperature of a cyclization. According to examples and conclusions discussed in this work examples, there is a big chance that cyclization will work better at higher temperatures.

14. Conclusions and Outlook

The aim of this Ph.D. research was the study towards the total synthesis of branimycin. This general goal included several sub-goals:

1. Development of novel approaches towards highly functionalized *cis*-decalins applicable to the core of branimycin.
2. Improvement of the synthesis of the C13-C18 side-chain; and its subsequent coupling with the *cis*-decalin core, leading to the completion of branimycin.
3. Investigating the viability of the macrolactonization approach for formation of the highly strained 9-membered lactone containing the *trans* double bond.
4. Improvement of certain low-yielding reactions and formulation of "take home messages" for the chemical community.

Results achieved for each listed sub-goal together with outlook are briefly discussed in the following chapter.

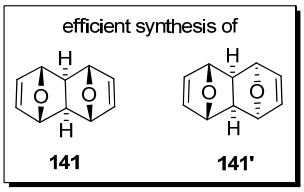
14.1. Development of Novel Approaches Towards Highly Functionalized *cis*-Decalins Aiming the Core of Branimycin

In the present work six approaches towards the *cis*-declin core of branimycin were studied, which could be divided into two major groups:

- RCM-based approaches.
- Approaches *via* desymmetrization of diepoxynaphthalene **141**.

Although interesting results were obtained in all approaches, the most significant results were achieved in approaches based on the desymmetrization of diepoxynaphthalene **141**.

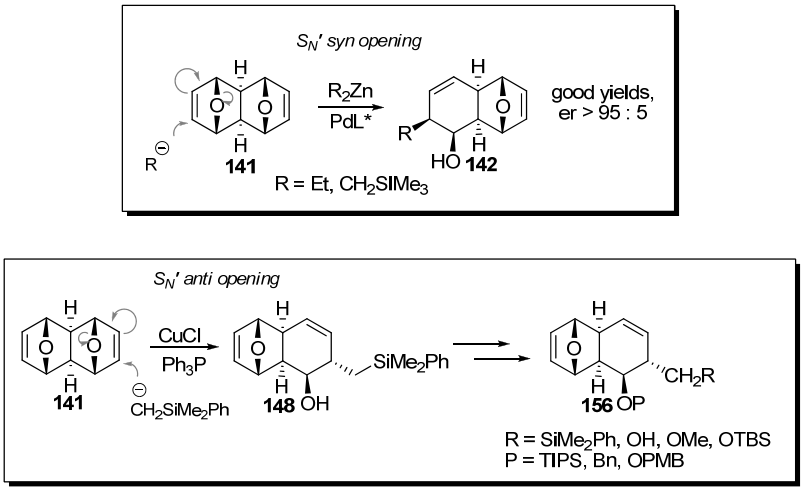
✓ An efficient synthesis of diepoxynaphtalene **141** (and also of its isomer **141'**) was developed.



Scheme 62

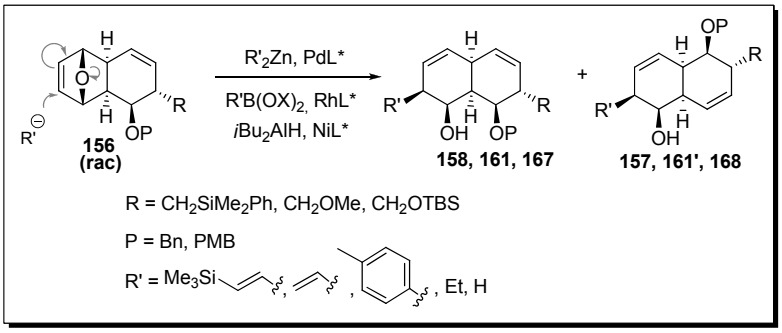
✓ It was demonstrated that although diepoxynaphthalene **141** possess two oxa-bridges, a selective mono-opening of only one of them could be carried out under certain conditions (Scheme 63):

- enantioselective in a *syn*-fashion with aliphatic organozinc nucleophiles under chiral palladium catalysis.
- in an *anti* fashion (although racemic) employing $Me_2PhSiCH_2MgCl$, as nucleophile, under copper catalysis, which introduces the silicon bearing substituent suitable for further elaboration.



Scheme 63

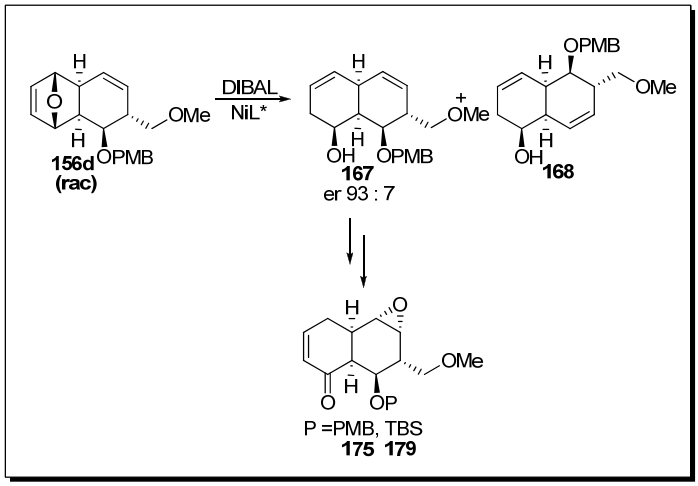
✓ We demonstrated (Scheme 64) that compounds of the type **156** can be used for the synthesis of highly functionalized *cis*-decalins of type **158**, **161** and of type **157**, **161'**. Different types of substituents can be introduced at this stage: alkyl, vinyl, aryl or hydrogen. Moreover, it was shown that, *at least*, in the case of DIBAL ("H^-"-nucleophile) and (presumably) in the case of $ZnEt_2$ ("Et^-"-nucleophile); racemic substrate **156** could be converted to their corresponding products, with high enantioselectivity.



Scheme 64

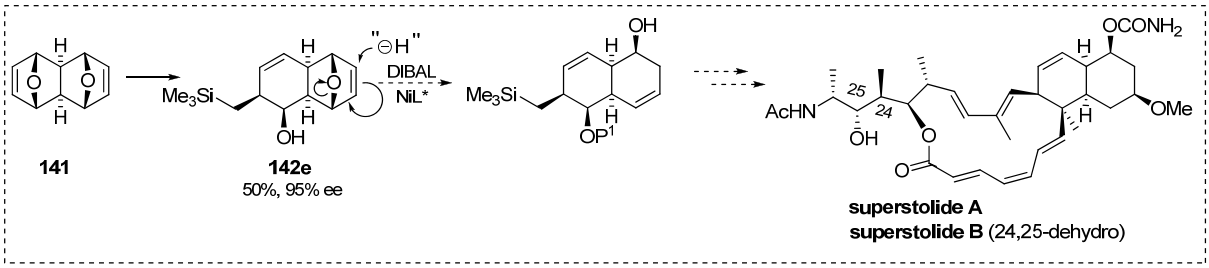
It was also revealed, that remote substituents in **156** can have a somewhat surprising crucial effect on the efficiency of the oxa-bridge opening.

✓ *cis*-Decalin **167** was synthesized in enantioenriched form (er 93:7) and was further converted to the *cis*-decalin core(s) (**175** and **179**) of branimycin.



Scheme 65

Outline. The developed approach to functionalize *cis*-decalins seems to be an attractive way to access the various cores of the members of the Nargenicin family. Moreover, this approach could be tested for the construction of *cis*-decali moieties of other natural products. For example, superstolides[133] core could be synthesized starting from enantioenriched mono-opened product **142e** (Scheme 66):

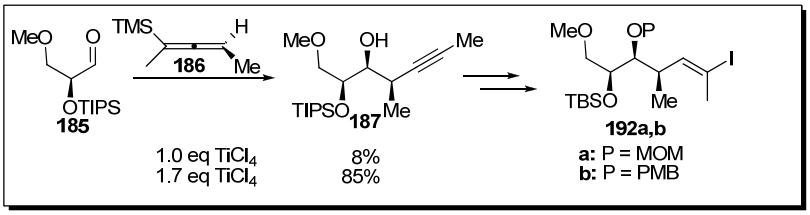


Scheme 66

14.2. Improvement of the C13-C18 Side-Chain Synthesis and its Coupling with the *cis*-Decalin Core Followed by Subsequent Elaboration Towards Branimycin

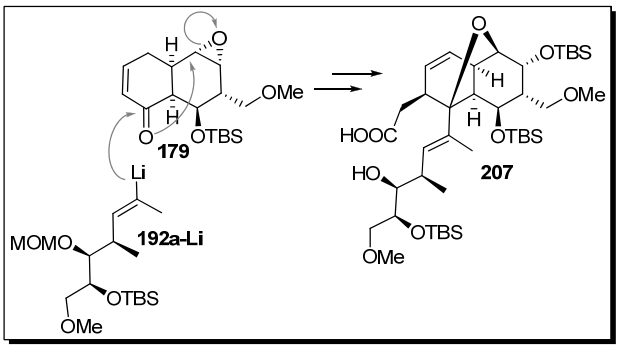
- ✓ Side-chains **192a,b** were synthesized and preparation of their precursor **187** was substantially optimized. The crucial improvement came with the discovery that $TiCl_4$ concentration had a critical effect on the key propargylation (with chiral allene **186**) of aldehyde **185**. The yield for this reaction was improved from 8% to 85% (Scheme 67):

[133] D'Auria, M. V.; Debitus, C.; Paloma, L. G.; Minale, L.; Zampella, A. *J. Am. Chem. Soc*. **1994**, *116*, 6658. (b) D'Auria, M. V.; Paloma, L. G.; Minale, L.; Zampella, A.; Debitus, C. *J. Nat. Prod*. **1994**, *57*, 1595.



Scheme 67

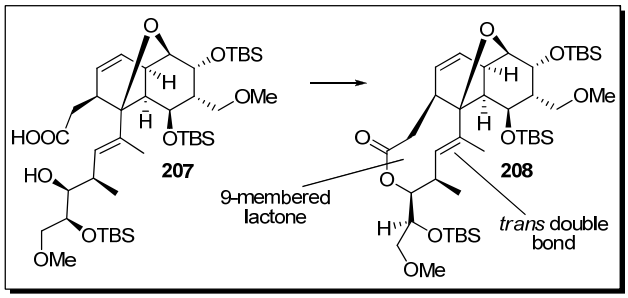
Synthesized *cis*-decalin core **179** and side-chain **192a** were coupled, which after a few steps resulted in highly advanced synthetic intermediate **207** (Scheme 68).



Scheme 68

14.3. Viability of the Macrolactonization Approach for Formation of the 9-Membered Lactone with a *trans*-Double Bond

A possibility to carry out the macrolactonization of **207** to **208** and close the highly strained 9-membered lactone with the *trans*-double bond was questionable from the beginning of the synthesis. However, we were able to demonstrate the viability of this thesis (Scheme 69).

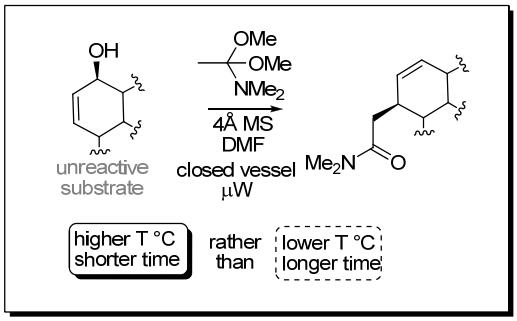


Scheme 69

14.4. Miscellaneous "Take Home Messages" for the Chemical Community

Besides the achievements discussed above, the following "take home messages" could be suggested for the chemical community.

✓ Although it too early to generalize, the new[134] developed conditions for the Eschenmoser-Claisen rearrangement (4Å MS, DMF, closed vessel, high temperatures and short reaction times) could be highly beneficial with respect to the conventional procedure for this reaction in an open vessel for rearrangement of unreactive substrates. The yield of transformation of **199** to **203** was improved from "traces" to 64%.

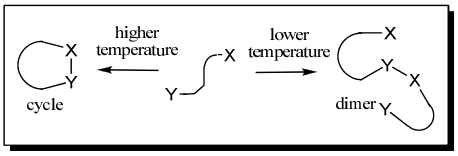


Scheme 70

1. A new procedure for the *in situ* preparation of PMBBr from PMBCl and NaBr in DMF was proposed (Scheme 71). This procedure avoids isolation of the unstable PMBBr; and for sensitive substrates gave better results with respect to the conventional employing $PMBCl/Bu_4NI_{(cat.)}$.

Scheme 71

2. A beneficial effect of higher temperatures was revealed in favour of an intramolecular [3+2] cyclization with competition side reactions. These results coupled with literature examples lead to a rather general conclusion:



Scheme 72

Higher temperatures will likely favor virtually any kind of cyclization of strained or hindered substrates over competitive oligomerization or some other side processes with relatively low activation enthalpy.

A plausible explanation of this effect was proposed.

[134] These results are partly based on results obtained in the Prof. Mulzer group by Univ.-Doz. Dr. V. Enev (see ref. 20).

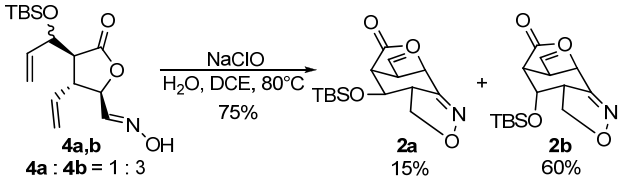
15. Experimental Section

15.1. General Information

All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates. Plates were visualized by dipping into ceric sulfate mixture [H_2SO_4 (10 vol %, 100 mL), phosphormolybdic acid (4.5 g), $Ce(IV)SO_4$ (0.1 g)] followed by heating with a heat gun. Flash column chromatography was carried out with silica gel 60 (0.040-0.063 μm, 240-400 mesh). Dichloromethane was dried by storage over MS 4Å. THF, diethyl ether, benzene and toluene were distilled from Na/benzophenone. Dry DMF and NMP (over molecular sieves) were purchased from Fluka. Molecule sieves 4Å (Aldrich) in powder (5 μ) or in beads (Merck) 4Å or 3Å were activated by heating at 350 °C in high vacuum for 8 h. All reactions were performed under atmosphere of Ar with flame-dried glassware unless otherwise stated. Microwave experiments were carried out on a Biotage Initiator (Biotage, Sweden) with reaction times specified as the ramp time and hold times at the final temperature. Temperatures were measured at the vessel surface by IR-sensors.

NMR spectra were recorded at 250, 400 or 600 MHz in $CDCl_3$ or C_6D_6 at 300 K. Chemical shift values were quoted in parts per million (ppm), and coupling constants were quoted in hertz. Residual signal of $CHCl_3$ (δ = 7.26 ppm) or C_6H_6 (δ = 7.16 ppm) were used as an internal reference for ^1H chemical shifts; signals of $CDCl_3$ (δ = 77.16 ppm) or C_6D_6 (δ = 128.06 ppm) were used as an internal reference for ^{13}C chemical shifts. ^{13}C NMR spectra were measured *J*-modulated and proton decoupled unless otherwise stated. Abbreviations for multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded with a FTIR spectrometer and are reported in wave numbers (cm^{-1}). All compounds were measured as a thin film on a silicon single crystal plate (Si-pellet).

15.2. Experimental Section for Chapter 4.4 (Publication)



Isoxazolines 2a and 2b. An aq. solution of NaClO (available chlorine 10-13%; 50 mL) was heated to 80 °C and added at once to a preheated to 80 °C solution of oximes **4a,b** (**4a** : **4b** = 3 : 1; 51.1 mg, 0.157 mmol) in dichloroethane (100 mL). The mixture was vigorously stirred at 80 °C for 8 min and cooled to rt. The organic phase was separated and the water phase was extracted with dichloromethane (30 mL). The combined organic phases were washed with brine, passed through a plug of cotton and solvents were removed *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane) to give **2b** (30.6 mg, 60%) and **2a** (7.6 mg, 15%).

2a: ^1H NMR ($CDCl_3$, 400MHz): δ = 5.93-5.83 (m, 1H), 5.36-5.22 (m, 3H), 4.49-4.41 (m, 2H), 4.24 (dd, *J* = 8.0, 11.9 Hz, 1H), 3.68 (ddd, *J*=5.2, 11.6, 11.6 Hz, 1H), 3.32 (d, *J* = 7.0 Hz, 1H), 2.87 (d, *J* = 4.7 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 6H);

^{13}C NMR ($CDCl_3$, 100MHz): δ = 174.2, 154.9, 133.0, 119.0, 77.2, 68.7, 65.0, 52.5, 49.5, 47.1, 25.7, 18.2, -4.6, -5.0.

HRMS (ESI): calc. for $C_{16}H_{25}NNaO_4Si$ $[M+Na]^+$ 346.1451; found: 346.1455.

2b: ^{1}H NMR ($CDCl_3$, 400MHz): δ = 5.92-5.82 (m, 1H), 5.35-5.23 (m, 3H), 4.02-3.96 (m, 2H), 3.64 (ddd, *J*=7.8, 10.9, 11.8 Hz, 1H), 2.72 (d, *J* = 3.1 Hz, 1H), 2.66 (d, *J* = 6.8 Hz, 1H), 0.91 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H);
^{13}C NMR ($CDCl_3$, 100MHz): δ = 172.6, 156.2, 132.2, 119.4, 75.4, 74.3, 74.2, 54.3, 52.0, 50.1, 25.6, 18.0, -4.4, -4.7.
HRMS (ESI): calc. for $C_{16}H_{25}NNaO_4Si$ $[M+Na]^+$ 346.1451; found: 346.1456.

15.3. Experimental Section for Chapter 7 (Publication in Synthetic Communications)

Diels-Alder adducts 3 and 4

To a stirred solution of methylpropiolate (2.00 g, 23.8 mmol) in dry dichloromethane (60 mL) at 0 °C, $EtAlCl_2$ (22.6 mL of 1 M solution in hexanes, 22.6 mmol) was added within 3 min and the resulting yellowish solution was stirred for 10 min followed by cooling to -21 °C (ice-salt bath) and a solution of furan (9.70 g, 143 mmol) in dichloromethane (20 mL) was added within 5 min. The resulting solution was kept in a freezer at -22 °C for 32 h. The reaction was quenched by pouring into a vigorously stirred saturated solution of K,Na-tartrate (100 mL) and stirred for 2 h. The organic phase was separated and the water phase was extracted with dichloromethane (2 x 50 mL). Combined organic phases were washed with brine, passed through a plug of cotton and solvents were removed *in vacuo* (*CAUTION: distilled off solvents may contain furan which is toxic*). The crude products were purified by column chromatography (1 g of mixture on 10 g of silica gel, gradient elution with Et_2O / DCM (0-14 vol % of Et_2O)) to yield **3** (2.78 g, 53%; ca. 98 wt % purity from ^{1}H NMR) and **4** (1.20 g, 23%; ca. 99 wt % purity from NMR).

NMR data of **3** and **4** was in accordance with the literature.[5a]

3: m.p. 186-187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.63 (dd, *J* =1.7, 5.8 Hz, 2H), 6.30 (dd, *J* =1.6, 5.8 Hz, 2H), 5.06 (bs, 2H), 4.88 (bd, *J* =1.7 Hz, 2H), 3.61 (s, 3H), 2.38 (s, 1H); ^{13}C (100 MHz, $CDCl_3$): δ = 171.8, 140.6, 136.9, 81.6, 81.5, 66.3, 52.9, 52.2.

4: m.p. 134-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56 (dd, *J* = 1.8, 5.8 Hz, 1H), 6.47 (dd, *J* = 1.8, 5.8 Hz, 1H), 6.41 (dd, *J* = 1.8, 5.8 Hz, 1H), 6.34 (dd, *J* = 1.5, 5.6 Hz 1H), 4.92 (m, 1H), 4.90 (bd, *J* = 4.7 Hz, 1H), 4.62 (d, *J* = 1.4 Hz, 1H), 4.47 (d, *J* = 1.6 Hz, 1H), 3.72 (s, 3H), 3.06 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 140.5, 137.3, 136.0, 133.6, 83.1, 79.5, 77.8, 77.3, 66.1, 52.5, 52.4.

Triethylammonium salts 5 or 8

A suspension of ester **3** (or **4**) (3.65 g, 16.6 mmol) and $Ba(OH)_2$*$8H_2O$ (7.85 g, 24.9 mmol) in 40 mL of water was heated on an oil bath at 120 °C for 3 h (30 min for **4**). The cloudy mixture was cooled and washed with dichloromethane (2x20 mL). To the stirred water phase (together with insoluble residue) an aqueous solution of H_2SO_4 (1.00 M, 24.9 mL, 24.9 mmol) was added and the resulting white suspension was stirred for 1 h at rt. Then ca. 1 mL of Et_3N was added and the mixture was concentrated *in vacuo* at 40 °C to almost dryness (if in the course of evaporation the water solution starts foaming, addition of ca. 10 vol % of *n*-BuOH is recommended, finally, if necessary, traces of *n*-BuOH can be removed by co-evaporation with small portions of water).

The resulted solid residue was stirred at rt with acetonitrile (50 mL) and Et_3N (ca. 4 g, 40 mmol) for 5 min, followed by addition of dichloromethane (100 mL) and further stirred for 1 h. Then the suspension was dried over Na_2SO_4 for 5 min, filtered through a plug of Celite® and solvents were removed *in vacuo* to yield ca. 4.5 g of **5** (or **8**) as pale brownish solid, which was used without further purification. *NOTE:* The title salt **5** (or **8**) are not very stable and can lose some Et_3N upon

concentration or storage, yielding a non-stoichiometric ratio of acid : Et_3N and even give certain amount of the corresponding acid, which is poorly soluble in dichloromethane. The acid can be redissolved by addition of some Et_3N.

5: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (bs, 1H), 6.61 (dd, *J* = 1.7, 5.8 Hz, 2H), 6.37 (dd, *J* = 1.5, 5.8 Hz, 2H), 5.07 (bs, 2H), 4.84 (bd, *J* = 1.7, 2H), 2.99 (q, *J* = 7.4, 14.8 Hz, ca. 4H), 2.29 (s, 1H), 1.21 (t, 7.4 Hz, ca. 6H); ^{13}C (100 MHz, $CDCl_3$): δ = 175.0, 138.7, 136.8, 81.2, 80.7, 66.1, 51.4, 43.7, 7.5.

8: ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.82 (bs, 1H), 6.52 (dd, *J* = 5.6, 1.7 Hz, 1H), 6.46 (dd, *J* = 5.6, 1.7 Hz, 1H), 6.43 (bs, 2H), 4.96 (bs, 1H), 4.88 (d, *J* = 4.9 Hz, 1H), 4.63 (d, *J* = 1.1 Hz, 1H), 4.43 (d, *J* = 1.7 Hz, 1H), 3.07(q, *J* = 7.2 Hz, ca. 4H), 2.99 (d, *J* = 4.8 Hz, 1H), 1.26 (t, *J* = 7.3 Hz, ca. 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 139.5, 138.3, 135.4, 134.3, 83.8, 79.6, 77.8, 77.6, 66.4, 52.3, 45.1, 8.6.

N-Thionopyridyl esters 6 or 9

*NOTE: Compound **6** is photo- and thermosensitive, therefore all further manipulations were performed with glassware covered with aluminum foil and at temperatures below 30 °C.*

To a solution of **5** or **8** (ca. 14 mmol, synthesized from 14.0 mmol of ester **3** or **4**) in dry dichloromethane (75 mL) was added TsCl (2.79 g, 14.7 mmol) at 0 °C and the resulting solution was stirred for 2 h (4.5 h for **8**). Then 1-hydroxypyridine-2(1H)-thione **7** (1.86 g, 4.7 mmol) was added and stirring was continued for 2 h (3 h for **8**) at 0 °C followed by 1 h at rt. The reaction mixture was washed with 5% $NaHCO_3$ (100 mL), 2M NaH_2PO_4 (2x200 mL, until water phase pH <5), 5% $NaHCO_3$ (50 mL)and brine (50 mL). The organic phase was passed through a plug of cotton and solvents were removed *in vacuo* (bath temperature 25-27°C) to yield crude **6** (or **9**) as a brownish solid.

6: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 1.6, 8.9 Hz, 1H), 7.33 (bd, *J* = 6.8 Hz, 1H), 7.18 (ddd, *J* = 8.9, 6.8, 1.5 Hz, 1H), 6.73 (dd, *J* = 1.3, 5.8 Hz, 2H), 6.69 (dd, *J* = 1.6, 5.8 Hz, 2H), 6.60 (bt, *J* = 6.8 Hz, 1H), 5.39 (bs, 2H), 4.96 (bs, 2H), 2.52 (s, 1H).

9: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.68 (dd, *J* = 1.5, 8.8 Hz, 1H) 7.47 (dd, *J* = 1.2, 6.9 Hz, 1H), 7.20 (ddd, *J* = 1.5, 6.8, 8.9 Hz, 1H), 6.73 (dd, *J* = 1.6, 5.6 Hz, 1H), 6.59-6.66 (m, 2H), 6.53 (dd, *J* = 1.6, 5.8 Hz, 1H), 6.48 (dd, *J* = 1.7, 5.8 Hz, 1H), 5.64 (bs, 1H), 4.96 (d, *J* = 5.0 Hz, 1H), 4.88 (d, *J* = 1.4 Hz, 1H), 4.54 (d, *J* = 1.6 Hz, H), 3.21 (d, *J* = 5.0 Hz, 1H).

Products of decarboxylation 1 or 2

A solution of Bu_3SnH (6.1 g, 5.7 mL, 21 mmol) in dry degased dichloromethane (150 mL) was transferred *via* cannula to a flask (covered with aluminum foil) charged with crude **6** or **9**(prepared from ca. 14 mmol of **5** or **8**). The resulting clear solution was cooled to 0 °C (ice cold water), the aluminum foil was removed and the reaction mixture was irradiated with a 500 Watt halogen lamp for ca. 20 min until TLC (DCM/Et_2O 1:1) showed full conversion of the starting material. The solvents were removed *in vacuo*.

For compound **1**: The residue was dissolved in acetonitrile (200 mL), transferred to a separation funnel and extracted with hexane (4x30 mL) to remove excess of Bu_3SnH and some of tin byproducts. The combined hexane fraction was washed

once with acetonitrile (20 mL). The combined acetonitrile fractions were concentrated *in vacuo* and the residue was passed through a short column of silica gel (6 g SiO_2/1 g of mixture; gradient elution with Et_2O / DCM (0-30 vol % of Et_2O)). After removal of solvents *in vacuo* the residue was triturated with Et_2O (50 mL) for 1 h. The resulting white crystals (1.10 g) are 95 wt % pure **1** (from NMR). The ether fraction was evaporated to dryness *in vacuo* and the residue subjected to column chromatography (50 g SiO_2/ 1 g of mixture; gradient elution with Et_2O / DCM (0-30 vol % of Et_2O)) to obtain additional 0.42 g of **1**. The combined yield of **1** is 67% (1.52 g, ca. 95 wt % pure from NMR) starting from ester **3**. Further purification can be achieved *via* recrystallization from EtOAc (ca. 99 wt. % pure from 1H NMR).

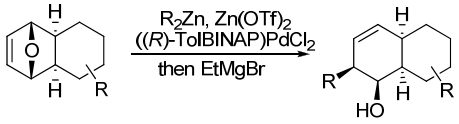
(NOTE: the described procedure was developed for relatively big scale reactions to decrease scale for final column chromatography. For small scale reactions the procedure can be simplified and after removal of acetonitrile a residue can be directly subjected to column chromatography (5 g SiO_2/ 100 mg of mixture; gradient elution with Et_2O / DCM (0-30 vol % of Et_2O)).

For compound **2:** T he residue was dissolved in a mixture acetonitrile (200 mL) and water (7 mL), transferred to a separation funnel and extracted with hexane (4x30 mL) to remove excess of Bu_3SnH and some of tin byproducts. The combined hexane fraction was washed once with acetonitrile/water (20 mL/0.6 mL). The acetonitrile-water fractions were combined, the solvents were removed *in vacuo,* ethanol (200 mL) was added and distilled off *in vacuo* to remove residual water. The residue was subjected to column chromatography (100 g SiO_2/ 1 g of mixture; gradient elution with Et_2O / DCM (0-7 vol % of Et_2O)) to obtain **2** (194 mg, 60%, ca. 97 wt. % pure from NMR) as white solid.

1: m.p. 170-172 °C (Lit.[4] m.p. 152-155 °C). ^{1}H NMR (400MHz, $CDCl_3$): δ = 6.43 (s, 4H), 4.84 (s, 4H), 1.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 79.9, 49.0.

2: m.p. 80-82 °C (Lit.[4] m.p. 68-70 °C). ^{1}H NMR (400MHz, $CDCl_3$): δ = 6.33 (dd, *J* = 0.6, 0.6, 2H), 6.28 (dd, *J* = 0.8, 0.8 Hz, 2H), 4.69 (m, 2H), 4.40 (bs, 2H), 2.49 (dd, *J* = 1.5, 1.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 134.0, 78.8, 76.3, 48.2.

15.4. Experimental Section for Chapters 9 and 10



General procedure for opening of oxa-bridged compounds with diorganozinc nucleophiles. Based on literature described procedures.[42]

[(*R*)-Tol-BINAP]$PdCl_2$. To a mixture of $PdCl_2$*2CH_3CN (26 mg, 0.1 mmol) and (*R*)-Tol-BINAP (68 mg, 0.1 mmol) was added dichloromethane (2 mL) and the reaction was stirred at rt for 3h. Volatiles (CH_3CN and CH_2Cl_2) were removed *in vacuo* and the residue was dissolved in dichloromethane (10.0 mL) to obtain a 0.010M stock solution of [(*R*)-Tol-BINAP]$PdCl_2$.

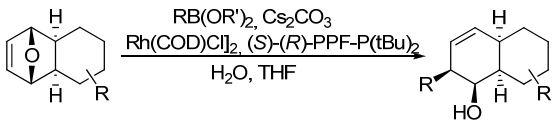
Diorganozinc nucleophile. To a solution of $ZnCl_2$ (1.0 mmol, 1.0 M in ether) in ether at 0 °C was added slowly a solution of alkyllithium or alkylmagnesium halide (titrated, in ether or pentane, 2.0 mmol). The mixture was stirred at 0 °C for 30 min, and then pentane added and stirring stopped to allow precipitated salts to settle. The cloudy solution was transferred *via* a syringe to another flask, volatiles were removed *in vacuo* or blown away with Ar-stream at 0 °C and the residue was dissolved in hexane or toluene to obtain ca. 1 M solution.

Oxa-bridge opening. To a solution of a corresponding substrate (0.2 mmol) in dichloromethane (4 mL) was added $Zn(OTf)_2$ (0.032 mmol) and [(*R*)-Tol-BINAP]$PdCl_2$ (0.01 M solution in dichloromethane, 1.4 mL, 0.014 mmol) and the resulting mixture was stirred at rt or 0 °C for 1 h. A solution of a corresponding diorganozinc nucleophile (ca. 1 M in pentane, 0.3 mL, 0.3 mmol) and the mixture was stirred at the same temperature until TLC analysis shows full consumption of the substrate or no further progress in conversion. A solution of EtMgBr (3.0M in ether, 0.2 mL, 0.6 mmol) was added and the mixture was stirred for an additional 15 min at rt. The reaction was quenched by addition of several drops of water. This was stirred vigorously for 10 min to allow the precipitation of salts. MgSO4 was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography. Enantiomeric excess was determined from NMR of corresponding Mosher esters.

142d: Yield: 68% (at 86% conv.). ^{1}H (400 MHz, $CDCl_3$): δ = 6.48 (dd, *J*=1.8, 6.0 Hz, 1H), 6.33 (dd, *J*=1.7, 6.0 Hz, 1H), 5.90 (ddd, *J*=2.5, 2.5, 9.8 Hz, 1H), 5.55 (dm, *J*= 9.7 Hz, 1H), 5.09 (bs, 1H), 4.66 (bs, 1H), 4.18-4.12 (m, 1H), 2.62 (d, *J*=9.7 Hz, 1H), 2.10-2.05 (m, 1H), 2.03 (dd, *J*= 5.2, 8.3 Hz, 1H), 1.87-1.80 (m, 1H), 1.68-1.48 (m, 2H), 0.99 (dd, *J*= 7.4, 7.4 Hz, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.7, 134.1, 132.3, 129.4, 82.3, 80.7, 68.3, 43.3, 41.1, 37.9, 24.5, 12.0.

143d: Yield: 10% (at 86% conv.). ^{1}H (400 MHz, $CDCl_3$): δ = 5.69 (dm, *J*= 10.5 Hz, 2H), 5.56 (bd, *J*= 10.5 Hz, 2H), 3.87-3.83 (m, 2H), 3.03 (s, 2H), 2.66-2.59 (m, 2H), 2.12-2.04 (m, 2H), 1.66-1.41 (m, 4H), 1.02 (dd, *J*= 7.3, 7.3 Hz, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 130.3, 128.5, 67.5, 42.7, 39.6, 24.6, 11.8.

142e: Yield: 50%. ^{1}H (400 MHz, $CDCl_3$): δ = 6.48 (dd, *J*= 1.7, 5.8 Hz, 1H), 6.33 (dd, *J*= 1.7, 5.8 Hz, 1H), 5.86 (dm, *J*= 9.6 Hz, 1H), 5.51-5.46 (dm, *J*= 9.6 Hz, 1H), 5.08 (bs, 1H), 4.65 (bs, 1H), 3.99-3.94 (dm, *J*= 9.6 Hz, 1H), 2.60 (d, *J*= 9.6 Hz, 1H), 2.15-2.08 (m, 1H), 2.07-2.01 (m, 2H), 0.89 (dd, *J*= 9.4, 14.9 Hz, 1H), 0.81 (dd, *J*= 6.0, 14.9 Hz, 1H), 0.03 (s, 9H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.6, 134.3, 134.2, 129.1, 82.3, 80.6, 71.6, 41.3, 37.7, 19.9, -0.7.

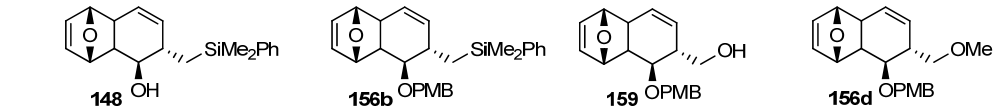


General procedure for opening of oxa-bridged compounds with diorganozinc nucleophiles.
Based on literature described procedures.[43]

To a solution of [Rh(COD)Cl]2 (4.9 mg, 0.010 mmol), (*R*)-(*S*)- PPF-P(t-Bu)2 ligand (10.8 mg, 0.020 mmol) and a corresponding substrate (0.20 mmol) in THF (1.7 mL) was added a corresponding boronic acid derivative (2.6 mmol). A solution of Cs_2CO_3 (5M in water, 0.1 mmol, 20 µL) was added and the reaction was stirred at rt or 40 °C until TLC showed full conversion of the substrate. Reaction mixture was diluted with EtOAc (30 mL) and washed with water (5 mL) and brine (5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography.

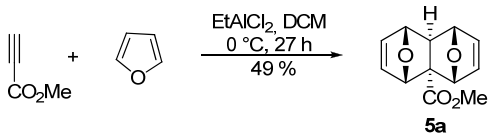
161-9: Yield: 24% (12% from 50% theor.). ^{1}H (250 MHz, $CDCl_3$): δ = 7.30 (dm, *J*=8.7 Hz, 2H), 6.89(dm, *J*=8.7 Hz, 2H), 5.97 (ddd, *J*=6.8, 10.5, 17.3 Hz, 1H), 5.83 (ddd, *J*=2.9, 4.1, 10.0 Hz, 2H), 5.69-5.51 (m, 3H), 5.23-5.12 (m, 2H), 4.60 (d, *J*=11.5 Hz, 1H), 4.45 (d, *J*=11.5 Hz, 1H), 4.30 (dm, *J*=7.9 Hz, 1H), 3.86-3.77 (m, 1H), 3.81 (s, 3H), 3.51 (m, 2H), 3.29 (s, 3H), 3.09-3.84 (m, 3H), 2.30 (dd, *J*=6.0, 6.0 Hz, 1H), 1.63 (d, 8.3Hz, OH).

161-14: Yield: 94% (47% from 50% theor.).^{1}H (250 MHz, $CDCl_3$): δ = 7.31 (dm, *J*=8.6 Hz, 2H), 6.89 (dm, *J*=8.6 Hz, 2H), 6.17 (dd, *J*=6.2, 18.9 Hz, 1H), 5.89-5.77 (m, 2H), 5.68-5.53 (m, 3H), 4.61 (d, *J*=11.4 Hz, 1H), 4.46 (d, *J*=11.4 Hz, 1H), 4.33 (bd, *J*=6.0 Hz, 1H), 3.87-3.77 (m, 1H), 3.81 (s, 3H), 3.59-3.44 (m, 2H), 3.29 (s, 3H), 3.10-2.89 (m, 3H), 2.41 (bdd, *J*=5.7, 5.7 Hz, 1H), 1.59 (d, *J*=7.0, Hz, 1H), 1.26 (dd, *J*=7.2, 7.2 Hz, 1H), 0.06 (s, 9H).



Procedures for preparation of **148**, **156b**, **156d** and **159** see: experimental section for Chapter 10.2, compounds **8**, **9**, **10** and **3** respectively.

15.5. Experimental Section for Chapter 10.2 (Publication in Organic Letters)



Compound 5a. To a stirred solution of methylpropiolate (1.00 g, 11.9 mmol) in dry dichloromethane (30 mL) at 0 °C, $EtAlCl_2$ (11.3 mL of 1 M solution in hexanes, 11.3 mmol) was added within 3 min and the resulting yellowish solution was stirred for 10 min. Then a solution of furan (4.90 g, 72 mmol) in dichloromethane (10 mL) was added within 5 min. The resulting solution was kept in a fridge at 0 °C for 27 h. The reaction was quenched by pouring into a vigorously stirred saturated solution of sodium-potassium-tartrate (100 mL) and stirred for 2 h. The organic phase was separated and the water phase was extracted with dichloromethane (2 x 50 mL). The combined organic phases were washed with brine, passed through a plug of cotton and the solvents were removed *in vacuo* (*CAUTION: distilled off solvents may contain furan which is toxic*). The residue was stirred with Et_2O (50 mL) for 30 min and filtered. The obtained crude **5a** (filter cake) was purified by passing it through a short plug of silica gel (1 g / 10 g SiO_2 ; DCM, then DCM + 1 vol % MeOH) to obtain **5a** (1.21 g,

45%) as white solid. Additional 3-5% of **5a** can be obtained from the Et_2O- filtrate by column chromatography (DCM/Et_2O). NMR data of **5a** were in accordance with the literature.[135]

5a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.63 (dd, *J* =1.7, 5.8 Hz, 2H), 6.30 (dd, *J* =1.6, 5.8 Hz, 2H), 5.06 (bs, 2H), 4.88 (bd, *J* =1.7 Hz, 2H), 3.61 (s, 3H), 2.38 (s, 1H);

^{13}C (100 MHz, $CDCl_3$): δ = 171.8, 140.6, 136.9, 81.6, 81.5, 66.3, 52.9, 52.2.

m.p. 186-187 °C (ethyl acetate).

5b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56 (dd, *J* = 1.8, 5.8 Hz, 1H), 6.47 (dd, *J* = 1.8, 5.8 Hz, 1H), 6.41 (dd, *J* = 1.8, 5.8 Hz, 1H), 6.34 (dd, *J* = 1.5, 5.6 Hz 1H), 4.92 (m, 1H), 4.90 (bd, *J* = 4.7 Hz, 1H), 4.62 (d, *J* = 1.4 Hz, 1H), 4.47 (d, *J* = 1.6 Hz, 1H), 3.72 (s, 3H), 3.06 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 140.5, 137.3, 136.0, 133.6, 83.1, 79.5, 77.8, 77.3, 66.1, 52.5, 52.4.

Compound 6. A suspension of ester **5a** (3.65 g, 16.6 mmol) and $Ba(OH)_2$*$8H_2O$ (7.85 g, 24.9 mmol) in 40 mL of water was heated on an oil bath at 120 °C for 3 h. The cloudy mixture was cooled and washed with dichloromethane (2x20 mL). To the stirred water phase (together with the insoluble residue) an aqueous solution of H_2SO_4 (1.00 M, 24.9 mL, 24.9 mmol) was added and the resulting white suspension was stirred for 1 h at rt. Then ca. 1 mL of Et_3N was added and the mixture was concentrated *in vacuo* at 40 °C to almost dryness (if in the course of evaporation the water solution starts foaming, addition of ca. 10 vol % of *n*-BuOH is recommended, finally, if necessary, traces of *n*-BuOH can be removed by co-evaporation with small portions of water).

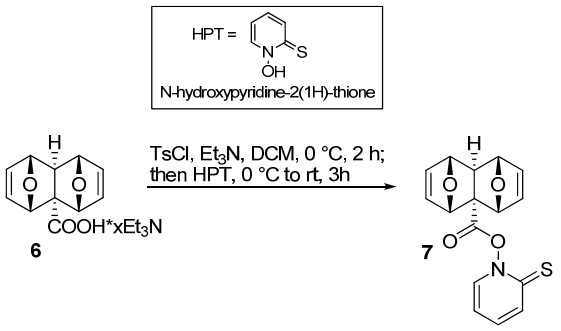
The resulting solid residue was stirred at rt with acetonitrile (50 mL) and Et_3N (ca. 4 g, 40 mmol) for 5 min, followed by addition of dichloromethane (100 mL) and stirred for 1 h. Then the suspension was dried over Na_2SO_4 for 5 min, filtered through a plug of Celite® and the solvents were removed *in vacuo* to yield ca. 4.53 g (100 %, corresponding to RCOOH*0.66Et_3N from ^{1}H NMR) of **6** as pale brownish solid, which was used without further purification. *NOTE:* The title salt **6** is not very stable and can lose some Et_3N upon concentration or storage, yielding a non-stoichiometric ratio of acid : Et_3N and even give a certain amount of the corresponding acid, which is poorly soluble in dichloromethane. The acid can be redissolved by addition of some Et_3N.

*NMR data are given for RCOOH*0.66Et_3N:*

6: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (bs, 1H), 6.61 (dd, *J* = 1.7, 5.8 Hz, 2H), 6.37 (dd, *J* = 1.5, 5.8 Hz, 2H), 5.07 (bs, 2H), 4.84 (bd, *J* = 1.7, 2H), 2.99 (q, *J* = 7.4, 14.8 Hz, 4H), 2.29 (s, 1H), 1.21 (t, 7.4 Hz, 6H);

^{13}C (100 MHz, $CDCl_3$): δ = 175.0, 138.7, 136.8, 81.2, 80.7, 66.1, 51.4, 43.7, 7.5.

[135] Lasne, M.-C.; Ripoll, J.-L. *Bull. Soc. Chim. Fr.* **1986**, *5*, 766-770.



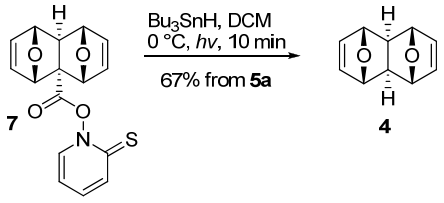
Compound 7

NOTE: Compound 7 is photo- and thermosensitive, therefore all further manipulations were performed with glassware covered with aluminum foil below 30 °C.

To a solution of **6** (ca. 14 mmol, synthesized from 14.0 mmol of ester **5a**) in dry dichloromethane (75 mL) was added TsCl (2.79 g, 14.7 mmol) at 0 °C and the resulting solution was stirred for 2 h. Then HPT (1-hydroxypyridine-2(1H)-thione; 1.86 g, 4.7 mmol) was added and stirring was continued for 2 h at 0 °C followed by 1 h at rt. The reaction mixture was washed with 5% $NaHCO_3$ (100 mL), 2M NaH_2PO_4 (2x200 mL, until water phase pH <5), 5% $NaHCO_3$ (50 mL), brine (50 mL). The organic phase was passed through a plug of cotton and the solvents were removed *in vacuo* (bath temperature 25-27°C) to yield crude **7** as a brownish solid.

NOTE: Purification of **7** by column chromatography led to substantial decomposition, therefore crude **7** was used directly in the next step.

7: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 1.6, 8.9 Hz, 1H), 7.33 (bd, *J* = 6.8 Hz, 1H), 7.18 (ddd, *J* = 8.9, 6.8, 1.5 Hz, 1H), 6.73 (dd, *J* = 1.3, 5.8 Hz, 2H), 6.69 (dd, *J* = 1.6, 5.8 Hz, 2H), 6.60 (bt, *J* = 6.8 Hz, 1H), 5.39 (bs, 2H), 4.96 (bs, 2H), 2.52 (s, 1H).



Compound 4. A solution of Bu_3SnH (6.1 g, 5.7 mL, 21 mmol) in dry degassed dichloromethane (150 mL) was transferred *via* a cannula to a flask (covered with aluminum foil) charged with crude **7** (prepared from 14 mmol of **5a**). The resulting clear solution was cooled to 0 °C (ice cold water), the aluminum foil was removed and the reaction mixture was irradiated with a 500 Watt halogen lamp for ca. 20 min until TLC (DCM/Et_2O 1:1) showed full conversion of the starting material. The solvents were removed *in vacuo* and the residue was dissolved in acetonitrile (200 mL), transferred to a separation funnel and extracted with hexane (4x30 mL) to remove an excess of Bu_3SnH and some tin byproducts. The combined hexane fraction was washed once with acetonitrile (20 mL). The combined acetonitrile phases were concentrated *in vacuo* and the residue was passed through a short column of silica gel (6 g SiO_2/1 g of mixture; gradient elution with Et_2O / DCM (0-30 vol % of Et_2O)). After removal of solvents *in vacuo* the residue was triturated with Et_2O (50 mL) for 1 h. The resulting white

crystals (1.10 g) are ca. 97% pure **4** (from NMR). The ether fraction was evaporated to dryness *in vacuo* and the residue subjected to column chromatography (50 g SiO_2/ 1 g of mixture; gradient elution with Et_2O / DCM (0-30 vol % of Et_2O)) to obtain additional 0.42 g of **4**. The combined yield of **4** is 67% (1.52 g, ca. 97% pure from NMR) starting from ester **5a**. Further purification can be achieved *via* recrystallization from EtOAc.

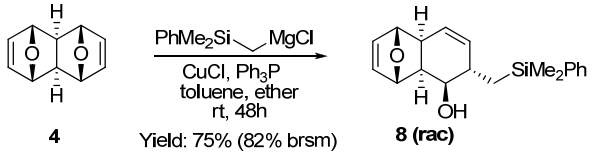
(NOTE: For small scale reactions the procedure can be simplified and after removal of acetonitrile a residue can be directly subjected to column chromatography: 5 g SiO_2/ 100 mg of mixture; gradient elution with Et_2O / DCM (0-30 vol % of Et_2O)).

m.p. 170-172 °C (ethyl acetate).

NMR data were in agreement with lit.[136]

4: ^{1}H NMR (400MHz, $CDCl_3$): δ =6.43 (s, 4H), 4.84 (s, 4H), 1.90 (s, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 79.9, 49.0.



Compound 8.

Grignard reagent.[137] A dry, 100 mL, two-necked, round-bottomed flask was equipped with a septum and a reflux condenser, the top of which was connected to an argon line. The flask was charged with magnesium turnings (0.84 g, 35 mmol) and dry diethyl ether (40 mL) and immersed into an ultrasound bath at 32-35° C. To the sonicated mixture was added 0.05 mL dibromoethane and then a solution of $PhMe_2SiCH_2Cl$ (10 g, 30 mmol) in dry diethyl ether (10 mL) was added in a rate keeping the reaction mixture at reflux (ca. 1 h). At the end of the addition the mixture was kept in the ultrasound bath at reflux for additional 1 hour.

Oxa-bridge opening. CuCl (153 mg, 1.54 mmol) and Ph_3P (444 mg, 1.69 mmol) in dry toluene (160 mL) were sonicated in an ultrasonic bath at 20-40 °C for ca. 1 h until a milky white opalescent solution was formed. Diepoxynaphthalene **4** (2.5 g, 15.4 mmol) was added and the mixture was further sonicated for additional 30 min to obtain a fine suspension. The flask was removed from the ultrasonic bath, charged with a stirring bar and the reaction mixture was cooled to rt under stirring. Then a solution of the Grignard reagent (30 mmol) was added, and the reaction mixture was stirred for 48 h at rt until no more progress could be observed (TLC). The reaction mixture was quenched with saturated NH_4Cl (100 mL) and stirred for 2 h. The water phase was separated and extracted with DCM (2x30 mL). The combined organic phases were washed with brine, passed through a plug of cotton and concentrated *in vacuo* to dryness. (NOTE: If required, the residue can be directly

[136] a) Gromov, A.; Enev, V.; Mulzer, J. *Syn. Comm.* in press; b) Maksimović, L.; Novak, N.; Eckert-Maksić, M. *Synth. Comm.* **1993**, 23(22), 3119-3125.

[137] Based on: Enev, V.; Drescher, M.; Mulzer, J. *Org. Lett*. **2008**, *10*, 413–416.

subjected to flash column chromatograph (SiO_2, EtOAc/toluene, then EtOAc/DCM to elute **4**)). The crude product was stirred with Et_2O (75 mL), and filtered from the insoluble residue (mostly contains **4**). The filtrate was concentrated *in vacuo* to dryness and triturated with hexane (50 mL) for 2 h. The resulting white crystals were filtered, washed with hexane (2x10 mL) and dried *in vacuo* to obtain a mixture of **8** (3.1-3.5 g) and **4** (5-10 mol %). The hexane fraction was concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc/toluene, then EtOAc/DCM to elute **4**) to get pure **8** (ca. 0.3-0.7 g). Combined **8** was used in the next step without further purification. The yield of **8** is 3.60 g (75%, 82 % brsm).

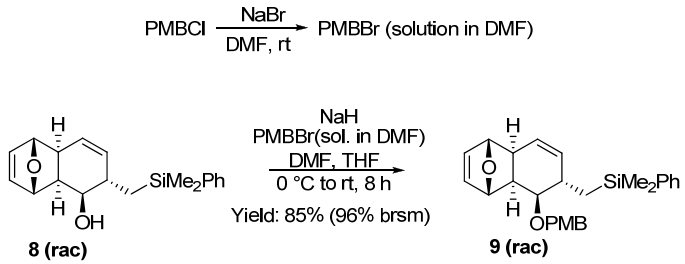
8: ^{1}H NMR (400MHz): δ = 7.54-7.49 (m, 2H), 7.37-7.33 (m, 3H), 6.40 (dd, *J*=1.5, 5.8 Hz, 1H), 6.35 (dd, *J*=1.5, 5.8 Hz, 1H), 5.76 (dd, *J*=2.5, 10.0 Hz, 1H), 5.72 (ddd, *J*=1.7, 4.1, 10.0 Hz, 1H), 5.05 (bs, 1H), 4.65 (bs, 1H), 3.83 (ddd, *J*=5.5, 5.5, 7.6 Hz, 1H), 2.66 (bd, *J*=7.6 Hz, 1H, *OH*), 2.50-2.41 (m, 1H), 2.13 (bd, *J*=8.2 Hz, 1H), 2.08 (dd, *J*=5.5, 8.2 Hz, 1H), 0.96 (dd, *J*=4.2, 14.4 Hz, 1H), 0.96 (dd, *J*=10.7, 14.4 Hz, 1H), 0.33 (s, 3H), 0.32 (s, 3H);

^{13}C NMR (100 MHz): δ = 139.5, 136.6, 135.4, 133.8, 133.6, 129.1, 128.2, 128.0, 83.6, 79.6, 73.5, 39.0, 38.0, 37.7, 19.6, -1.8, -2.2;

HRMS (ESI): calc. for $C_{21}H_{27}NNaO_2Si$ $[M+Na+CH_3CN]^+$ 376.1709; found: 376.1717.

M.p. 94-95 °C

IR (film): 3468, 2930, 820 cm^{-1}.



Compound 9.

Solution of PMBBr in DMF. Dry NaBr (3.44 g, 33.4 mmol) was suspended in dry DMF (8 mL) at 25 °C, PMBCl (2.62 g, 16.7 mmol) was added and the reaction mixture was stirred for 2 h at 25 °C. NMR-analysis showed ca. 90 % conversion. (*NOTE:* extension of the reaction time did not result in improvement of conversion.)

PMB-protection. A stirred solution of PMBBr in DMF (prepared from 16.7 mmol of PMBCl, ca. 15.0 mmol) was diluted with DMF (10 mL), cooled to 0 °C and NaH (60 % in mineral oil, 0.61 g, 15.2 mmol) was added. A solution of **8** (2.40 g, 7.6 mmol) in DMF (11 mL) was added within 5 min and stirring was continued for 6 h at 0°C and 2 h at rt. Then $NH_2CH_2CH_2NH_2$ (5 mL) was added and the mixture was stirred for 1 h at 0 °C and 1 h at rt until no more PMBBr and PMBCl could be detected by TLC. [138] Volatiles were removed *in vacuo* at rt, the reaction mixture was diluted with EtOAc (200 mL) and washed repeatedly with 1N HCl until pH 5-6 was reached. The combined water phases were extracted with EtOAc (3x100 mL). The combined organic phases were washed with water (3x100 mL), brine (50 mL) and passed through a plug of cotton. Solvents were removed *in vacuo* and the residue was subjected to flash column chromatography

[138] PMBCl and PMBBr converts into PMB-NH-$CH_2CH_2NH_2$.

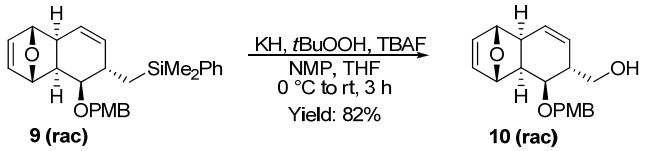
(EtOAc/hexane) to give **9** (clear oil; 2.75 g, 85%, 96% brsm) and **8** (0.31 g, 13 %). (*NOTE:* Extension of reaction times did not improve conversion. Equal results were obtained when pure PMBBr was used instead of material prepared *in situ*).

9: ^{1}H NMR (400MHz): δ = 7.56-7.50 (m, 2H), 7.36-7.31 (m, 3H), 7.28 (bd, *J*=8.7 Hz, 2H), 6.89 (bd, *J*=8.7 Hz, 2H) 6.32 (d, *J*=1.6, 5.8 Hz, 2H), 6.25 (d, *J*=1.6, 5.8 Hz, 2H), 5.64 (ddd, *J*=2.8, 4.8, 9.9 Hz, 1H), 5.72 (dd, *J*=1.3, 9.9 Hz, 1H), 5.07 (bs, 1H), 4.65 (bs, 1H), 4.54 (d, *J*=11.6 Hz, 1H), 4.44 (d, *J*=11.6 Hz, 1H), 3.82 (s, 3H), 3.31 (dd, *J*=6.1, 9.8 Hz, 1H) 2.53 (bdd, *J*=10.4, 10.4 Hz, 1H), 2.23-2.18 (m, 1H), 2.05 (dd, *J*=6.3, 7.6 Hz, 1H), 1.44 (dd, *J*=3.02, 14.7 Hz, 1H), 0.59 (dd, *J*=11.1, 14.7 Hz, 1H), 0.33 (s, 3H), 0.20 (s, 3H);

^{13}C NMR (100 MHz): δ = 159.2, 140.4, 137.7, 134.8, 134.4, 133.7, 131.4, 129.3, 128.8, 127.8, 127.4, 113.9, 85.4, 83.9, 78.3, 71.4,55.4,39.5, 39.2, 34.8, 19.0, -1.71, -1.73;

HRMS (ESI): calc. for $C_{27}H_{32}NaO_3Si$ $[M+Na]^+$ 455.2018; found: 455.2012.

IR (film): 2952, 1612, 1513, 1248, 836 cm^{-1}.



9 (rac) **10 (rac)**

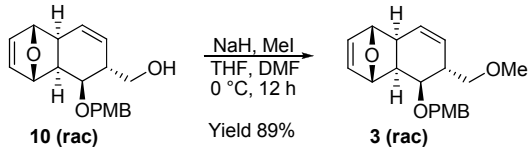
Compound 10. Potassium hydride (30 wt % suspension in mineral oil, 0.83 g, 20.8 mmol) was placed in a dried 200 mL flask under Ar. Mineral oil was removed by washing the suspension with dry hexane (3x5 mL), *N*-Methyl-2-pyrrolidone (NMP, 25 mL) was added and the flask was cooled to 0 °C. Under vigorous stirring *t*BuOOH (5-6 M in decane, 4.2 mL, ≥20.8 mmol) was added dropwise over 10 min, followed by addition of a solution of **9** (1.50 g, 3.5 mmol) in NMP (10 mL) over 5 min. The reaction mixture was warmed to rt, TBAF (1 M in THF, 7.5 mL, 7.5 mmol) was added and the stirring was continued for 3 h. The reaction mixture was quenched with aq. $Na_2S_2O_3$ (5 M, 50 mL), stirred for 30 min, diluted with water (1 L) and extracted EtOAc/toluene 2:1 (5x200 mL). The combined organic phase was washed with water (2x200 mL), brine (200 mL) and dried over $MgSO_4$. Solvents were removed *in vacuo* and the residue was subjected to a flash column chromatography (toluene/EtOAc) to yield **10** as a colorless oil (0.89 g, 82 %).

10: ^{1}H NMR (400MHz): δ = 7.30 (bd, *J*=8.8 Hz, 2H), 6.90 (bd, *J*=8.8 Hz, 2H), 6.38 (dd, *J*=1.7, 5.8 Hz, 1H), 6.31 (dd, *J*=1.6, 5.8 Hz, 1H), 5.86-5.81 (m, 1H), 5.47 (dd, *J*=1.5, 9.9 Hz, 1H), 5.14 (bs, 1H), 4.71 (bs, 1H), 4.64 (d, *J*= 11.3 Hz, 1H), 4.49 (d, *J*=11.3 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, *J*= 6.5, 10.5 Hz, H), 3.63 (dd, *J*=7.3, 10.5 Hz, 1H), 2.64-2.56 (m, 1H), 2.32-2.67 (m, 1H), 2.17 (dd, *J*=6.2, 7.6 Hz, H);

^{13}C NMR (100 MHz): δ = 159.4, 137.4, 134.9, 130.1, 129.7, 129.4, 129.0, 114.0, 85.4, 81.2, 77.9, 70.6, 66.2, 55.3, 40.1, 39.2, 38.8;

HRMS (ESI): calc. for $C_{19}H_{22}NaO_4$ $[M+Na]^+$ 337.1416 ; found: 337.1412.

IR (film): ca. 3460, 3822, 3676, 3651, 3629, 3448, 2931, 1701, 1513, 1249, 1033, 821 cm^{-1}.



Compound 3. To a suspension of NaH (60 % in mineral oil, 300 mg, 7.6 mmol) in dry THF (12 mL) at 0 °C was added dry DMF (12 mL) and MeI (5.4 g, 2.5 mL, 38 mmol), followed by **10** (1.2 g, 3.8 mmol) in dry THF (5 mL). The reaction mixture was stirred at 0 °C for 12 h. Then saturated aq. NH_4Cl (1 mL) was added carefully and the volatiles were removed *in vacuo* at rt (*CAUTION: distillate contains MeI, which is toxic!*). The residue was diluted with water (70 mL) and extracted with toluene (5x50 mL). The combined organic phase was washed with water (3x20 mL), brine (30 mL) and passed through a plug of cotton. The solvents were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexane) to yield 1.11 g of **3** (89 %) as a colorless oil.

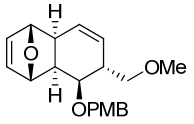
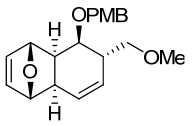
3: ^{1}H NMR (400MHz): δ = 7.30 (bd, *J*=8.8 Hz, 2H), 6.90 (bd, *J*=8.8 Hz, 2H), 6.38 (dd, *J*=1.6, 5.8 Hz, 2H), 6.28 (dd, *J*=1.5, 5.8 Hz, 1H), 5.83 (ddd, *J*=2.9, 4.6, 9.9 Hz, 1H), 5.71 (dd, *J*=1.5, 9.9 Hz, H), 5.14 (bs, 1H), 4.68 (bs, 1H), 4.57 (d, *J*=11.4 Hz, 1H), 4.50 (d, *J*=11.4 Hz, 1H), 3.81 (s, 3H), 3.74 (d, *J*=6.3, 10.4 Hz, 1H), 3.58 (d, *J*=4.5, 9.0 Hz, 1H), 3.50 (d, *J*=3.0, 9.0 Hz, 1H), 3.33 (s, 3H), 2.57-2.49 (m, 1H), 2.29-2.23 (m, 1H), 2.08 (bt, 1H);

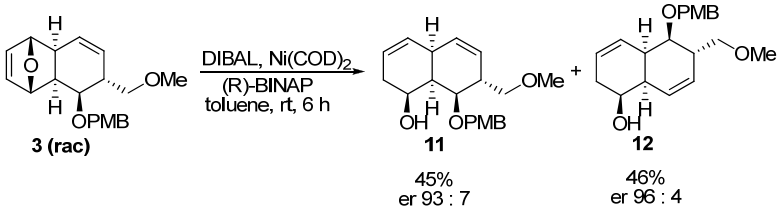
^{13}C NMR (100 MHz): δ = 159.3, 137.7, 134.9, 131.2, 130.8, 129.5, 129.1, 113.9, 85.6, 78.2, 76.8, 72.8, 71.4, 59.2, 55.4, 39.4, 39.4, 39.3.

HRMS (ESI): calc. for $C_{20}H_{24}NaO_4$ $[M+Na]^+$ 351.1572 ; found: 351.1570.

IR (film): 2928, 1612, 1513, 1249, 1117, 1079, 822cm^{-1}.

A sample of racemic **3** was separated by preparative chiral HPLC: Chiracel OD, hexane/*i*PrOH 9:1, 22 °C.

		
retention time	7.1 min	10.2 min
$[\alpha]_D^{20}$ (c 7.05, $CHCl_3$)	+ 31.7	- 31.7



Compounds 11 and 12. A solution of $Ni(COD)_2$ (420 mg, 1.52 mmol) in toluene (dry and degassed; 25 mL) was added to (*R*)-BINAP (1.43 g, 2.29 mmol) and the mixture was stirred at rt for 4 h. (*NOTE:* the solution became dark burgundy red.

Green or brown colors indicate presumably a partial oxidation of Ni° species and may result in lower enantioselectivity).[139] To this burgundy red solution a solution of **3** (2.50 g, 7.62 mmol) in toluene (43 mL) was added (the color stayed dark burgundy red, but a weak green-brown shade appeared) and the mixture was stirred for 30 min. Then DIBAL (1.0 M in hexanes, 8.8 mL, 8.8 mmol) was added over 6 h at 22 °C *via* a syringe pump. The reaction was allowed to stir for 1 h, then saturated aq. sodium-potassium-tartrate (100 mL) was added and the mixture was stirred for 30 min. The organic phase was separated and the water phase was extracted with Et_2O (4x50 mL). The combined organic phase was washed with brine, passed through a plug of cotton and the solvents were removed *in vacuo*. The solid residue was triturated with MeOH (50 mL), the solution was filtered to remove undissolved BINAP and its oxides, and the filtrate was concentrated *in vacuo*. The residue was subjected to flash column chromatography (EtOAc/hexane) to obtain **12** (1.16 g, 46%) as yellowish crystals and a mixture of **11** with (R)-BINAP monooxide. The latter mixture was resubjected to flash column chromatography (EtOAc/toluene) to yield **11** (1.13 g, 45%) as a colorless oil. (*NOTE:* **11 is air sensitive!** Oxidation happens even at -20 °C. See the comment 2 in Supporting Information).

11: ^{1}H NMR (400MHz): δ = 7.29 (bd, *J*=8.9 Hz, 2H), 6.88 (bd, *J*=8.9 Hz, 2H), 5.80-5.74 (m, 1H), 5.69-5.58 (m, 3H), 4.58 (d, *J*=11.4 Hz, 1H), 4.43 (d, *J*=11.4 Hz, 1H), 4.45-4.39 (m, 1H), 3.81 (dd, *J*=5.3, 9.7 Hz, 1H), 3.81 (s, 3H), 3.53-3.46 (m, 2H), 3.30 (s, 3H), 3.06-2.98 (m, 1H), 2.98-2.91 (m, 1H), 2.39-2.34 (m, 1H), 2.26-2.22 (m, 2H), 1.90 (d, *J*=10.3 Hz, 1H, *OH*).

^{13}C NMR (100 MHz): δ = 159.3, 131.0, 129.5, 128.8, 128.7, 128.5, 123.6, 113.9, 75.5, 73.3, 70.9, 64.2, 59.1, 55.4, 40.5, 37.5, 35.2, 34.8.

The enantiomeric ratio was determined by chiral HPLC: Chiracel OD-H, 22 °C, hexane/*i*PrOH 9:1, 0.95 mL/min, 100 mL/min, 8.2 min (major enantiomer), 11.0 min (minor enantiomer).

$[\alpha]_D^{20}$ = +146.2 (c = 1.10, $CHCl_3$).

HRMS (ESI): calc. for $C_{20}H_{26}NaO_4$ $[M+Na]^+$ 353.1729; found: 353.1733.

IR (film): ca. 3480, 2890, 1513, 1247, 772 cm^{-1}.

12: ^{1}H NMR (400MHz): δ = 7.25 (bd, *J*=8.7 Hz, 2H), 6.87 (bd, *J*=8.7 Hz, H), 5.79-5.74 (m, 1H), 5.72-5.66 (m, 2H), 5.64-5.59 (m, 1H), 4.56 (d, *J*=11.3 Hz, 1H), 4.47 (d, *J*=11.3 Hz, 1H), 4.00-3.94 (m, 1H), 3.79 (s, 3H), 3.69 (dd, *J*=3.6, 6.5 Hz, 1H), 3.45-3.33 (m, 2H), 3.31 (s, 3H), 2.91-2.84 (m, 1H), 2.69-2.63 (m, 1H), 2.26-2.10 (m, 2H);

^{13}C NMR (100 MHz): δ = 159.3, 130.3, 129.6, 128.3, 126.2, 113.9, 75.7, 73.6, 71.2, 67.7, 59.0, 55.4, 40.5, 39.8, 36.0, 32.4;

$[\alpha]_D^{20}$ = -151.3 (c 1.6, $CHCl_3$).

m.p. 104-106 °C.

IR (film): ca. 3400, 2874, 1612, 1514, 1248, 1077, 671 cm^{-1}.

The enantiomeric ratio was estimated from the ^{1}H-NMR spectra of the corresponding Mosher esters.

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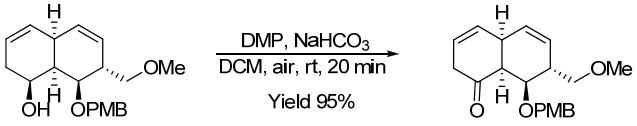
[139] Lautens, M.; Rovis, T. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Heidelberg, 1999; Vol. I, Chapter 8, pp 8-9.



11 **13**

Compound 13. A solution of **11** (330 mg, 1.0 mmol) in dry DCM (10 mL) was added to a suspension of $NaHCO_3$ (1.7 g, 20 mmol) and Dess-Martin periodinane (DMP, 509 mg, 1.2 mmol) in dry DCM (16 mL) and stirred in an open vessel for 10-20 min until full conversion was observed (TLC; EtOAc/hexane 1 : 1.5). The reaction was quenched with $Na_2S_2O_3$ (2M aq., 5 mL) and stirred for 1 h at rt. The organic phase was separated and the water phase was extracted with DCM (3x20 mL). The combined organic phase was washed with brine (20 mL), passed through a plug of cotton and the volatiles were removed *in vacuo*. The residue was passed through a short plug of silica gel (25% EtOAc/hexane) to give **13** (305 mg, 93%). (*NOTE:* **13 is air sensitive**, see the comment 2 in Supporting Information).

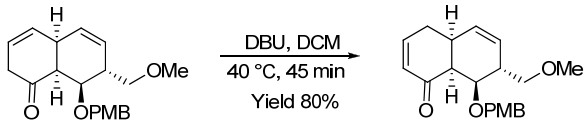
13: ^{1}H NMR (400MHz): δ = 7.22 (bd, *J*=8.6 Hz, 2H), 6.84 (bd, *J*=8.6 Hz, H), 5.86-5.80 (m, 1H), 5.72-5.66 (m, 1H), 5.57 (d, *J*=11.1 Hz, 1H), (d, *J*=11.1 Hz, 1H), 4.48(d, *J*=11.9 Hz, 1H), 4.46(d, *J*=11.9 Hz, 1H), 3.78 (s, 3H), 3.71 (dd, *J*= 3.7, 7.8 Hz, H), 3.47 (dd, *J*=4.6, 9.3 Hz, 1H), 3.39 (dd, *J*=4.4, 9.3 Hz, 1H), 3.37-3.32 (m, 1H), 3.26 (s, 3H), 3.02-2.97 (m, 2H), 2.92 (bd, *J*=21.1 Hz, 1H), 2.77 (bd, *J*= 21.1 Hz, 1H);

^{13}C NMR (100 MHz): δ = 208.3, 159.2, 130.8, 129.4, 129.1, 127.7, 127.2, 123.6, 113.8 75.1, 72.9, 71.6, 59.0, 55.3, 47.3, 41.2, 39.7, 39.6;

HRSM: calc. for [$C_{20}H_{24}NaO_4$] 351.1572 ; found: 351.1582.

IR (film): 2874, 1720, 1612, 1513, 1248, cm^{-1}.

$[\alpha]_D^{20}$ = +85.4 (c 2.40, $CHCl_3$)



13 **14**

Compound 14. To a solution of **13** (110 mg, 0.34 mmol) in dry DCM (9.5 mL) at 40 °C was added DBU (139 mg, 0.92 mmol) and the resulted green-brown mixture was stirred at 40 °C for 45 min (conversion monitored by ^{1}H NMR). The reaction mixture was washed with NaH_2PO_4 (2 M aq.) until pH 6-7 was reached. The combined water phase was extracted with EtOAc (4x30 mL). The combined organic phase was washed with brine (30 mL), dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. The residue was subjected to column chromatography (EtOAc/toluene) to yield **14** as a clear pale yellow oil (99 mg, 88 % yield)

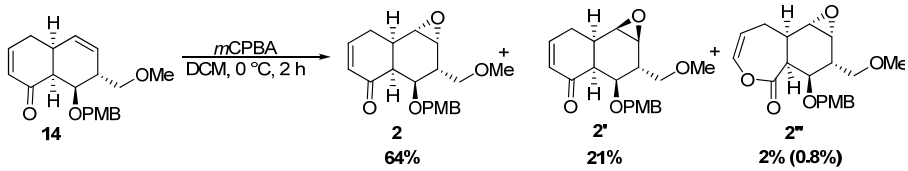
14: ^{1}H NMR (400MHz): δ = 7.11 (bd, *J*=8.7 Hz, 2H), 7.01-6.95 (m, 1H), 6.81 (bd, *J*=8.7 Hz, 2H), 6.15-6.09 (m, 1H), 5.84 (ddd, *J*=1.7, 4.5, 10.1 Hz, 1H), 5.65 (bdd, *J*=4.5, 10.1 Hz, 1H), 4.42 (d, *J*=11.4 Hz, 1H), 4.29 (d, *J*=11.4 Hz, 1H), 4.11 (bs, 1H), 3.78 (s, 3H), 3.36 (d, *J*=4.8, 9.5 Hz, 1H), 3.33 (s, 3H), 3.24 (d, *J*=7.7, 9.5 Hz, 1H), 2.83-2.75 (m, 1H), 2.72-2.66 (m, 1H), 2.60 (dd, *J*=3.0, 6.6 Hz, 1H), 2.55 (dddd, *J*=2.6, 2.6, 10.4, 18.4 Hz, 1H), 2.38 (dddd, *J*=0.8, 5.7, 5.7, 18.4 Hz, 1H);

^{13}C NMR (100 MHz): δ = 201.4, 159.1, 150.5, 131.0, 130.5, 130.2, 128.9, 126.0, 113.7, 78.3, 74.5, 71.8, 59.1, 55.4, 45.9, 40.4, 33.5, 31.4.

$[\alpha]_D^{20}$ = -70.0 (c 0.30, $CHCl_3$)

HRMS calc. for $C_{20}H_{24}NaO_4$ $[M+Na]^+$ 351.1572 ; found: 351.1578.

IR (film): 2899, 1667, 1613, 1513, 1248 cm^{-1}.



Compounds 2, 2′ and 2′′. A solution of **14** (40.0 mg, 0.12 mmol) in DCM (2.3 mL) was cooled to 0 °C and *m*CPBA (70 wt %, 147 mg, 0.60 mmol) was added. The reaction was stirred at 0 °C for 2 h (until TLC analysis shows ca. 50% conversion). Then aq. sat. $Na_2S_2O_3$ (10 mL.) and aq. sat. $NaHCO_3$ (10 mL) were added, and the mixture was stirred for 10 min. The water phase was extracted with EtOAc (5x20 mL), the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc/hexane) yielded **14** (19.5 mg), **2** (white solid, 13.1 mg, 64% brsm), **2'** (oil, 4.3 mg, 21% brsm) and **2′′** (0.2 mg, 0.8%; *NOTE:* **2′′** is presumably unstable towards column chromatography on silica gel, as the crude yield estimated from NMR was ca. 2%. The ratio of **2′′** and **2** was determind by NMR before and after chromatography.

2: ^{1}H NMR (400MHz): δ = 7.08 (d, *J*=8.7 Hz, 2H), 7.02 (ddd, *J*=1.9, 6.2, 9.9 Hz, 1H), 6.81 (d, *J*=8.8Hz, 2H), 6.13 (bd, *J*=9.9 Hz, 1H), 4.36 (d, *J*=11.2 Hz, 1H), 4.15 (d, *J*=11.2 Hz, 1H), 3.78 (s, 3H), 3.70 (m, 1H), 3.56 (dd, *J*=6.5, 9.4 Hz, 1H), 3.39 (s, 3H), 3.34-3.28 (m, 2H), 3.22 (dd, *J*=1.4, 3.8 Hz, 1H), 2.85-2.70 (m, 2H), 2.62-2.56 (m, 1H), 2.40 (dd, *J*=2.8, 5.9 Hz, 1H), 2.38-2.30 (m, 1H).

^{13}C NMR (100 MHz): δ = 200.5, 159.2, 150.1, 130.7, 130.4, 129.0, 113.7, 76.1, 71.58, 71.56, 59.3, 55.4, 55.3, 51.8, 43.2, 38.1, 32.2, 28.3.

M.p. 94-95 °C (EtOAc/hexane)

$[\alpha]_D^{20}$ = +110.8 (c 2.60, $CHCl_3$).

HRMS (ESI): calc. for $C_{20}H_{24}NaO_5$ $[M+Na]^+$ 367.1521 ; found: 367.1533.

IR (film): 2919, 2857, 2835, 1673, 1514, 1250 cm^{-1}.

For X-ray data see the enclosed CIF file

2′: ^{1}H NMR (400MHz): δ = 7.22 (d, *J*=8.4 Hz, 2H), 6.85 (d, *J*=8.8 Hz, 2H), 6.82-6.85 (m, 1H), 6.02 (ddd, *J*=1.9, 1.9, 10.3 Hz, 1H), 4.47 (bd, *J*=11.8 Hz, 1H), 4.42 (d, *J*=11.8 Hz, 1H), 3.80 (s, 3H), 3.57 (dd, *J*=4.1, 9.3 Hz, 1H), 3.53 (bs, 1H), 3.49 (dd, *J*=3.7, 9.3 Hz, 1H), 3.27 (s, 3H), 3.12-3.06 (m, 2H), 2.67 (bs, 2H), 2.64-2.57 (m, 3H).

^{13}C NMR (100 MHz; CPD mode): δ = 159.2, 130.9, 130.5, 129.4, 113.7, 77.2, 75.7, 71.7, 71.0, 59.0, 55.3. 53.7, 42.9, 37.1, 34.9, 29.2. *NOTE:* two signals of ^{13}C were not visible even with a large number of scans. Chemical shifts at 29.2 and 42.9 were obtained from HSQC spectra. Some of ^{13}C signals are broad and of very low intensity (compared to the corresponding

carbons of diastereomeric **2**). This phenomenon could be attributed to slow conformational changes or to long relaxation times).

$[\alpha]_D^{20}$ = + 12.6 (c 0.135, $CHCl_3$).

HRMS (ESI): calc. for $C_{20}H_{24}NaO_5$ $[M+Na]^+$ 367.1521 ; found: 367.1516.

IR (film): 2925, 1683, 1514, 1246 cm^{-1}.

2'': ^{1}H NMR (400MHz): δ = 7.19 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8.9 Hz, 2H), 6.32 (dd, *J*=2.2, 5.9 Hz, 1H), 5.49-5.43 (m, 1H), 4.47 (d, *J*=11.7 Hz, 1H), 4.37 (d, *J*=11.7 Hz, 1H), 3.47 (s, 3H), 3.72 (dd, *J*= 3.1, 8.9 Hz, 1H), 3.56 (dd, *J*= 7.5, 9.1 Hz, 1H), 3.49 (dd, *J*= 2.0, 3.8 Hz, 1H), 3.39 (s, 3H), 3.12 (dd, *J*= 3.8, 8.3 Hz, 1H), 2.84 (d, *J*= 3.8 Hz, 1H), 2.66-2.58 (m, 1H), 2.37-2.27 (m, 1H), 2.24-2.16 (m, 1H).

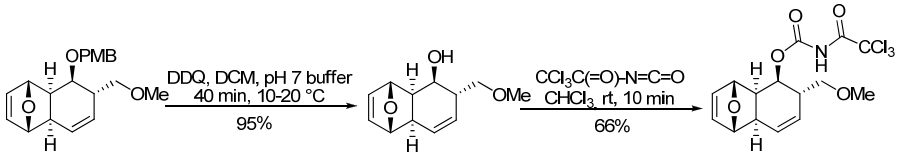
^{13}C NMR (100 MHz): δ = 169.9, 159.5, 141.6, 130.4, 129.4, 113.9, 112.2, 73.8, 72.6, 71.8, 59.1, 57.2, 55.3, 54.0, 42.7, 42.5, 37.3, 26.1.

The configuration of epoxide **2''** was proven by reaction of **2** with *m*CPBA.

HRMS (ESI): calc. for $C_{20}H_{24}NaO_6$ $[M+Na]^+$ 383.3907 ; found: 383.3895.

IR (film): 1758, 1513, 1248, 1100 cm^{-1}.

$[\alpha]_D^{20}$ = + 101.5 (c 0.065, $CHCl_3$).



(-)-3 **15** **16**

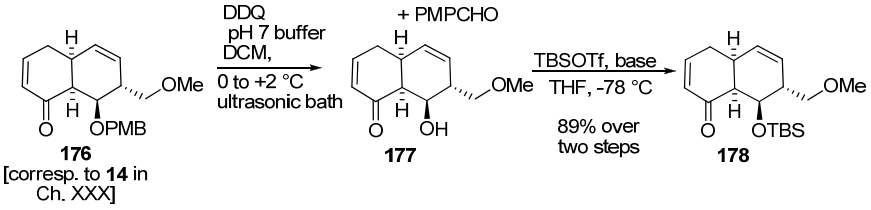
Compound 15. A flask was charged with **(-)-3** (30 mg, 0.09 mmol), DCM (2 mL) and aq. pH 7 buffer (2 mL) was placed in an ultrasound bath at 10 °C. DDQ (41 mg, 0.18 mmol) was added and the mixture was sonicated for 40 min at 10-20 °C. Then aq. $Na_2S_2O_3$ (2 M , 1 mL) and DCM (30 mL) were added. The organic phase was washed with saturated aq. $NaHCO_3$ (4x20 mL), brine (5 mL), passed through a plag of cotton and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexane) to yield compound **15** (18 mg).

Compound 16. Compound **A** (18 mg) was dissolved in dry $CHCl_3$ (1 mL) at rt, and $CCl_3C(=O)$-N=C=O (0.1 mL) was added under stirring. After 10 min water (5 mL) was added and the mixture was extracted with EtOAc (3x10 mL). The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography to yield **16** (21 mg) as a white foam. (*NOTE:* **16** is unstable on silica gel, therefore chromatography should be done as quickly as possible).

Crystals of **16** suitable for X-ray were obtained by slow diffusion of pentane vapors into a solution of **16** in EtOAc at 0 °C.

For X-ray data see the attached CIF file.

15.6. Experimental Section for Chapter 10.3

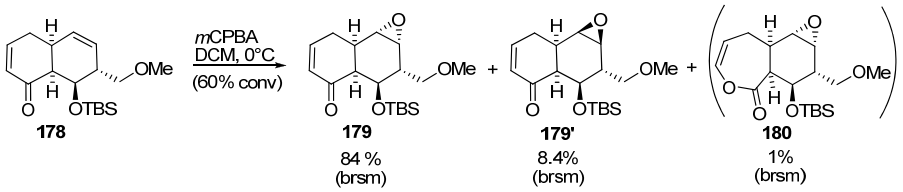


Compound 177. To a solution of **176** (50.0 mg, 0.151 mmol) in dichloromethane (1.2 mL) was added aq. pH 7.0 buffer (1 mL). The mixture was immersed in an ultrasonic bath and sonicated at +1 to + 3 °C for 5 min. To this mixture DDQ (69.1 mg, 0.305 mmol) was added and the reaction mixture was sonicated for 30 min at +1 to + 3 °C (maintaining the temperature in the bath by adding ice). The mixture was transferred into a separation funnel, saturated aq. $Na_2S_2O_3$ (3 mL) was added and the flask was vigorously shacked for 20 sec. Saturated aq. $NaHCO_3$ (30 mL) was added and the flask was vigorously shacked for 1 min. The mixture was phase was extracted with EtOAc (2x30 mL), the origin phase was washed with saturated aq. $NaHCO_3$ (30 mL). The combined water phases were extracted with EtOAc (4x30 mL). The combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. Solvents were removed *in vacuo* below 30 °C to obtain crude **177** in a mixture with PMPCHO. The yield from NMR is ca. 98% (with CH_2Br_2 and dichloroethane as internal standards).

177 (in a mixture with PMPCHO)**:** ^{1}H NMR (400MHz, $CDCl_3$): 6.85-6.79 (m, 1H), 5.96 (bdd, *J*=2.9, 10.0 Hz, 1H), 5.70 (ddd, *J*=2.7, 2.7, 10.0 Hz, 1H), 5.4 (bd, *J*=10.0 Hz, 1H), 4.09 (d, *J*=11.0 Hz, 1H, *OH*), 3.75-3.67 (m, 1H), 3.60 (dd, *J*=3.7, 9.0 Hz, 1H), 3.53 (dd, *J*=5.6, 9.0 Hz, 1H), 3.34 (s, 3H), 3.00 (bs, 1H), 2.87 (dd, *J*=4.5, 4.5 Hz, 1H), 2.74-2.65 (m, 1H), 2.5-2.42 (m, 1H), 2.43 (bdd, *J*=6.4, 19.4 Hz, 1H);
^{13}C NMR (100 MHz): 203.2, 147.9, 131.1, 129.8, 129.7, 77.3, 77.0, 76.6, 72.9, 70.6, 59.0, 49.0, 42.6, 35.4, 31.2 29.6;

Compound 178. Crude mixture of **177** (ca. 0.15 mmol) and PMPCHO obtained from the previous step was dissolved in THF (1.4 mL) and cooled to -78 °C. To this solution 2,6-di-*tert*-butylpyridine (115 mg, 129 µL, 0.60 mmol) was added and the mixture was stirred until a clear solution was obtained. Then TBSOTf (86 µL, 99 mg, 0.375 mmol) was added dropwise and the mixture was stirred at -78 °C for 1h. The reaction was quenched by pouring into a vigorously stirred saturated aq. $NaHCO_3$ (30 mL), stirred for 5 min and extracted with EtOAc (3x30 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/toluene) to obtain **178** in 89% (43.6 mg) over two steps.

178: ^{1}H NMR (400MHz, $CDCl_3$): δ = 6.99 (ddd, *J*=2.1, 6.1, 10.2 Hz, 1H), 6.09 (ddd *J*=1.0, 2.7, 10.2 Hz, 1H), 5.87 (ddd, *J*=1.6, 4.8, 10.2 Hz, 1H), 5.64 (dddd *J*=1.3, 4.8, 10.2 Hz, 1H), 4.37 (bs, 1H), 3.33 (s, 3H), 3.31 (dd, *J*=5.1, 9.6 Hz, 1H), 3.21 (dd, *J*=7.8, 9.6 Hz, 1H), 2.87-2.72 (m, 1H), 2.61 (dddd *J*=2.5, 11.3, 18.4 Hz, 1H), 2.47 (dd, *J*=2.6, 6.9 Hz, 1H), 2.48-2.40 (m, 1H), 2.38 (dddd, *J*=0.8, 5.8, 5.8, 18.3 Hz, 1H), 0.79 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 150.9, 130.5, 130.2, 125.3, 74.8, 71.7, 59.2, 46.8, 45.0, 33.1, 31.5, 25.8, 17.9, -4.9, -5.2.
$[\alpha]_D^{20}$ = -91.88 (c 0.690, $CHCl_3$).
HRMS (ESI): calc. for $C_{18}H_{30}NaO_3Si$ $[M+Na]^+$ 345.1862; found: 345.1862.



Compounds 179, 179' and 180. To a solution of **178** (700 mg, 2.17 mmol) in dichloromethane (40 mL) at 0 °C was added *m*CPBA (77%, 2.43 g, 10.8 mmol). The mixture was stirred for 2 h at 0 °C, washed with saturated aq. $Na_2S_2O_3$ (20 mL) and saturated aq. $NaHCO_3$ (2x20 mL). The combined water phases were extracted with dichloromethane (5x50 mL). The combined organic phases were washed with brine, passed through a plug of cotton and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexanes) to obtain starting **178** (281 mg), **179** (371 mg, 84% brsm), **179'** (36 mg, 8.4% brsm) and **180** (3 mg, 1% brsm).

179: ^{1}H NMR (400MHz): 7.00 (ddd, *J*=1.6, 6.1, 10.2 Hz, 1H), 6.08 (bd, *J*=10.2 Hz, 1H), 3.94 (bs, 1H), 3.50 (dd, *J*=7.1, 9.5, 1H), 3.16 (s, 3H), 3.34-3.28 (m, 2H), 3.25 (dd, *J*=1.0, 3.8, 1H), 2.87-2.76 (m, 2H), 2.45-2.33 (m, 2H), 2.28 (dd, *J*=2.4, 5.6, 1H), 0.8 (s, 9H), 0.14 (s, 3H), -0.14 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 149.9, 131.0, 71.6, 69.5, 59.4, 55.4, 51.5, 43.9, 42.7, 32.0, 28.5, 25.9, -5.0, -5.3.
$[\alpha]_D^{20}$ = -100.47 (c 0.645, $CHCl_3$).
HRMS (ESI): calc. for $C_{18}H_{30}NaO_4Si$ $[M+Na]^+$ 361,1811; found: 361,1817.
IR (film): 2928, 1733, 1674, 1557, 1388, 1326, 1253, 1212, 1067, 1035, 1006, 912, 828, 796, 778 cm^{-1}.

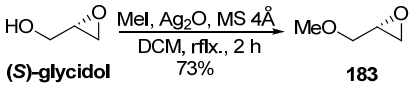
179': ^{1}H NMR (400MHz, $CDCl_3$): δ = 6.90 (bs, 1H), 6.00 (ddd, *J*=2.0, 2.0, 10.2 Hz, 1H), 3.97 (bs, 1H), 3.58-3.49 (m, 1H), 3.46 (dd, *J*=4.8, 9.4 Hz, 1H), 3.34 (s, 3H), 3.22-3,12 (m, 2H), 2.88-2.76 (m, 1H), 2.76-2.67 (m, 1H), 2.60-2.51 (m, 1H), 2.48 (dd, *J*=4.7, 9.7 Hz, 1H), 2.35 (dd, *J*=2.8, 3.4 Hz, 1H), 0.83 (s, 9H), 0.02 (s, 3H), -0.09 (bs, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.6, 112.7, 72.4, 67.6, 59.3, 55.3, 46.6, 25.8, 18.0, -4.8, -4.9. (NOTE: similar to compound **2'**,few signals (in this case 5 signals) are not visible in ^{13}C spectra even at large number of scans, and some of signals are relatively broad (up to 20 Hz for the signal at 130.6 ppm). This phenomenon could be attributed to slow conformational changes or to long relaxation times)
HRMS (ESI): calc. for $C_{18}H_{30}NaO_4Si$ $[M+Na]^+$ 361,1811; found: 361,1815.
IR (film): 2928, 2363, 1672, 1557, 1473, 1418, 1388, 1328, 1254, 1213, 1108, 976, 876, 862, 837, 791, 775, 638, 611 cm^{-1}.

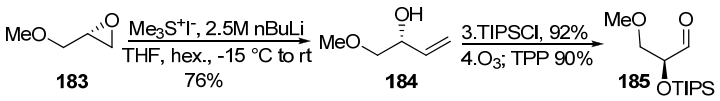
180: ^{1}H NMR (400MHz): δ = 6.45 (dd, *J*= 2.2, 5.8 Hz, 1H), 5.56-5.50 (m, 1H), 3.70 (dd, *J*= 4.3, 10.0 Hz, 1H), 3.67 (dd, *J*= 3.4, 9.0 Hz, 1H), 3.58 (dd, *J*= 7.4, 9.0 Hz, 1H), 3.49 (dd, *J*= 2.2, 3.6 Hz, 1H), 3.41-3.33 (m, 1H), 3.40 (s, 3H), 3.12 (dd, *J*= 4.3, 8.2 Hz, 1H), 2.85 (d, *J*= 3.8 Hz, 1H), 2.73 (ddd, *J*= 6.3, 8.2, 14.8 Hz, 1H), 2.42-2.31 (m, 1H), 2.23 (ddd, *J*= 6.3, 8.2, 14.4 Hz, 1H), 0.85 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 141.7, 112.5, 72.0, 67.0, 59.2, 57.6, 54.0, 46.8, 43.0, 38.4, 26.2, 25.7, 18.0, -4.5, -4.9.
HRMS (ESI): calc. for $C_{18}H_{30}NaO_5Si$ $[M+Na]^+$ 377.1760; found: 377.1764.

IR (film): 2847, 1843, 1760, 1558, 1233, 1207, 1100, 1029, 847, 791, 778, 700, 610, 458, 427, 420, 415, 412 cm^{-1}.

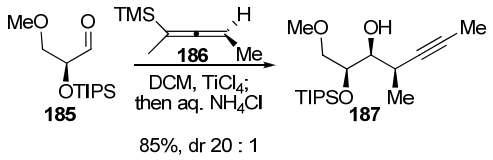
15.7. Experimental Section for Chapter 11



Compound 183. A mixture of (*S*)-glycidol (11.0 g, 0.149 mol), silver oxide[140] (34.5 g, 0.149 mol), methyl iodide (211.0 g, 1.49 mol) and molecular sieves 4 Å (powder, 13.5 g) in dichloromethane (90 mL) was refluxed for 2h (conversion was monitored by NMR). After cooling to rt, the mixture was passed through a short plug of Celite, the filter cake was washed with dichloromethane (80 mL). Fractional distillation of the combined organic phases gave **183** in 73% yield (9.6 g).
Analytical data for **183** were in agreement with literature reported.[82]**Error! Bookmark not defined.**
^{1}H NMR (, 250 MHz, CDCl3): δ = 3.69 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.41 (s, 3H), 3.34 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.16 (m, 1H), 2.81 (dd, *J* = 9.1, 4.2 Hz, 1H), 2.61 (dd, *J* = 5.0, 2.7 Hz, 1H).
^{13}C NMR (CDCl3, 75 MHz): δ = 73.1, 59.1, 50.7, 44.1.



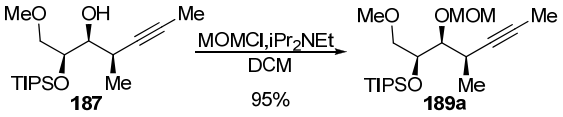
Conversion of **183** into **185** was carried out as previously described.[25]



Compound 187. Chiral allene **186** was synthesized as previously described.[141]
A solution of aldehyde **185** (3.0 g, 11.5 mmol) in dichloromethane (78 mL) was cooled to -90 °C and a solution of $TiCl_4$ (3.78g, 19.9 mmol) in dichloromethane (8.7 mL) was added slowly. The mixture was warmed to -80 °C over 20 min and then cooled to -95 °C. Allene **186** was added dropwise over 20 min, the reaction mixture allowed to warm to -78°C over 1 h, and stirred at -78°C for 2 h. The reaction mixture was quenched by pouring into a vigorously stirred saturated aq. NH_4Cl (0.5 L). The organic phase was separated and the water phase was extracted with Et_2O (4 x 100 mL). The combined organic phases were washed with saturated aq. $NaHCO_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexanes) to obtain 3.22 g of **187** (85%, dr 20 : 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (dd, *J*=6.7, 5.7 Hz, 1H), 3.48 (dd, *J*=9.3, 6.7 Hz, 1H), 3.41 (dd, *J*=9.3, 5.7 Hz,1H), 3.35 (s, 3H), 2.49 (m, 1H), 2.36 (bd, *J*= 9.9 Hz, 1H), 1.77 (d, *J*=2.6 Hz, 3H), 1.26 (d, *J*=6.8 Hz, 3H), 1.21 (m, 21H). 13C NMR (100 MHz, CDCl3): δ = 81.4, 78.5, 75.6, 75.1, 71.4, 59.3, 30.8, 18.5, 18.2, 13.4, 3.9.

[140] Tanabe, M.; Peters, R. H.*Organic Syntheses,* Coll. Vol. 7, p.386 (1990); Vol. 60, p.92 (1981).
[141] Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc* .**2005**, *127*, 3694-3695.



Compound 189a

To a mixture of alcohol **187** (4.73 g, 14.4 mmol), *i*Pr_2NEt (7.0 g, 54.5 mmol) and dichloromethane (2 mL, *NOTE:* dichloromethane was used in this small amount make the final mixture not too viscous) was added MOMCl (5.8 g, 72.0 mmol). The mixture was stirred at rt over 12 h. Reaction was quenched by stirring with aq. $NaHCO_3$ (100 mL) over 30 min. The water phase was extracted with Et_2O (3x50 mL). The combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo* (CAUTION: distillate can contain MOMCl, which is toxic!) and the residue was subjected to column chromatography (EtOAc/hexanes) to obtain **189a** in 95% yield (5.10 g).

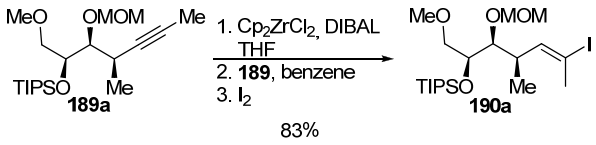
^{1}H NMR (400MHz, $CDCl_3$): δ = 4.73 (d, *J*=6.5 Hz, 1H), 4.70 (d, *J*=6.5 Hz, 1H), 4.30 (ddd, *J*=3.0, 6.1, 6.1 Hz, 1H), 3.53 (dd, *J*=6.1, 9.3 Hz, 1H), 3.49 (dd, *J*=3.0, 7.7 Hz, 1H), 3.41 (dd, *J*=6.1, 9.3 Hz, 1H), 3.40 (s, 3H), 3.32 (s, 3H), 2.88-2.78 (m, 1H), 1.74 (d, *J*=2.4 Hz 3H), 1.20 (d, *J*=7.0 Hz 3H), 1.12-1.02 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.1, 82.9, 82.0, 77.2, 74.5, 72.5, 58.8, 56.1, 27.7, 18.4, 18.3, 18.1, 13.0, 3.7.

HRMS (ESI): calc. for $C_{20}H_{40}NaO_4Si$ $[M+Na]^+$ 395.2594; found: 395,2597.

IR (film): 2943, 2881, 2867, 1464, 1417, 1384, 1344, 1152, 1079, 1037, 983, 974, 938, 921, 902, 883, 836, 774, 714, 679, 419 cm^{-1}.

$[\alpha]_D^{20}$ = +8.68 (c 2.50, $CHCl_3$).



Compound 190a. To a solution of Cp_2ZrCl_2 (5.0 g, 17.1 mmol) in THF (120 mL) at 0 °C was added DIBAL (1.0 M in hexanes, 17.1 mL, 17.1 mmol). The reaction mixture was warmed to rt and the resulting slurry was stirred for 2 h. Then the stirring was stopped, and after 10 min the supernatant liquid was removed with a syringe. To the white precipitate a solution of **189a** (2.20 g, 5.9 mmol) in benzene (160 mL) was added, and the mixture was stirred at rt over 12 h. Then the reaction mixture was cooled to 0 °C, and a solution of I_2 (5.0 g, 20 mmol) in benzene (100 mL) was added over 5 min. The reaction was quenched by pouring into a vigorously stirred aq. 3M $Na_2S_2O_3$ (100 mL). After both layers became colorless, the organic phase was separated, and the water phase was extracted with Et_2O (4x50 mL). The combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes) to obtain **190a** in 83% yield (2.45 g).

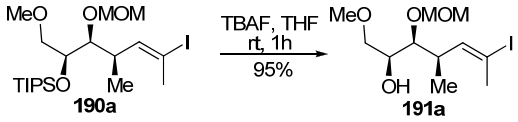
^{1}H NMR (400MHz, $CDCl_3$): δ = 6.23-6.18 (m, 1H), 4.74 (d, *J*=6.8 Hz, 1H), 4.63 (d, *J*=6.8 Hz, 1H), 4.01-4.02 (m, 1H), 3.53 (dd, *J*=3.9, 9.6 Hz, 1H), 3.44 (dd, *J* =4.8, 5.8 Hz, 1H), 3.40 (s, 3H), 3.35 (dd, *J* =6.0, 9.6 Hz, 1H), 3.32 (s, 3H), 2.77-2.66 (m, 1H), 2.38 (d, *J*=1.5 Hz, 1H), 1.10-1.06 (m, 21H), 1.00 (d, *J*=6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 98.0, 92.7, 82.9, 74.9, 73.5, 58.9, 56.0, 36.4, 27.8, 18.3, 16.4, 12.9.

HRMS (ESI): calc. for $C_{20}H_{41}INaO_4Si$ $[M+Na]^+$ 523.1716; found: 523.1721.

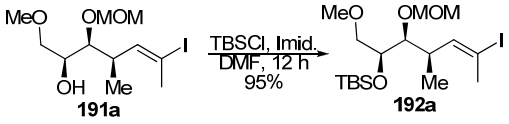
IR (film): 2943, 2906, 2866, 1465, 1112, 1076, 1039, 937, 919, 882, 766, 679, 415, 406 cm^{-1}.

$[\alpha]_D^{20}$ = +15.36 (c 2.80, $CHCl_3$).



Compound 191a. To a solution of **190a** (2.50 g, 5.00 mol) in THF (18 mL) at rt was added TBAF (1.0 M in THF, 7 mL, 7 mmol) and the mixture was stirred for 1 h. A saturated aq. NH_4Cl (5 mL) was added and volatiles were removed *in vacuo*. The residue was dilueted with half-saturated NH_4Cl (50 mL) and extracted with EtOAc (5x30 mL). The combined organic phases were washed with brine (30 mL) and dried over $MagSO_4$. Solvents were removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes) to obtain **191a** in 95% yield (1.63 g).

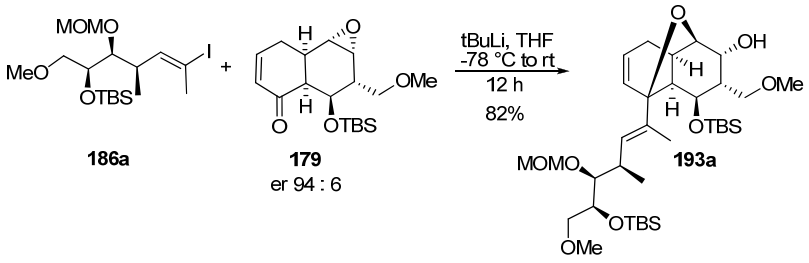
^{1}H NMR (400MHz, $CDCl_3$): δ = 6.08-6.03 (m, 1H), 4.65 (d, *J*=6.6 Hz, 1H), 4.62 (d, *J*=6.6 Hz, 1H), 3.75-3.69 (m, 1H), 3.43-3.40 (m, 2H), 3.41 (s, 3H), 3.36 (dd, *J*=4.1, 6.1 Hz, 1H), 3.36 (s, 3H), 2.81-2.73 (m, 1H), 2.79 (d, *J*=5.8 Hz, 1H, O*H*), 2.40 (d, *J*=1.5 Hz, 3H), 1.00 (d, *J*=6.8 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 98.6, 94.8, 83.1, 74.1, 70.4, 59.2, 56.3, 37.4, 28.0, 15.7.
HRMS (ESI): calc. for $C_{11}H_{21}INaO_4$ $[M+Na]^+$ 367.0382; found: 367.0381.
IR (film): 3460, 3165, 2931, 2363, 1457, 1326, 1126, 1070, 1029, 809, 671, 611, 590, 587, 458, 452, 449, 434, 421, 410, 406, 403 cm^{-1}.
$[\alpha]_D^{20}$ = +44.43 (c 3.00, $CHCl_3$).



Compound 192a. A mixture of **191a** (1.5 g, 4.36 mmol), imidazole (1.20 g, 20 mmol), TBSCl (1.4 g, 9 mmol) and DMF (3.0 mL) was stirred over 12 h at rt. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (10 mL), stirred for 20 min, diluted with water (200 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were washed with water (2x30 mL), brine (30 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo*, and the residue was subjected to column chromatography (EtOAc/hexanes) to obtain 1.90 g of **192a** (95%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 6.22-6.17 (m, 1H), 4.73 (d, *J*=6.8 Hz, 1H), 4.62 (d, *J*=6.8 Hz, 1H), 3.89-3.84 (m, 1H), 3.47 (dd, *J*=4.0, 9.9 Hz, 1H), 3.41 (s, 3H), 3.39 (dd, *J* =5.3, 5.3 Hz, 1H), 3.33 (dd, *J* =5.8, 9.7 Hz, 1H), 3.33 (s, 3H), 2.73-2.63 (m, 1H), 2.38 (d, *J*=1.5 Hz, 1H), 1.00 (d, *J*=6.9 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 98.1, 93.0, 82.5, 74.8, 73.2, 59.1, 56.1, 36.6, 27.8, 26.1, 18.3, 16.1, -4.4, -4.5.
HRMS (ESI): calc. for $C_{17}H_{35}INaO_4Si$ $[M+Na]^+$ 481.1247; found: 481.1253.
IR (film): 2929, 2911, 2888, 2868, 2857, 2356, 1636, 1557, 1473, 1418, 1378, 1318, 1253, 1229, 1196, 1182, 1105, 1069, 1037, 999, 980, 836, 818, 778, 665, 631 cm^{-1}.
$[\alpha]_D^{20}$ = -0.41 (c 2.45, $CHCl_3$).

15.8. Experimental Section for Chapter 12



Compound 193a. A solution of *t*BuLi (1.74 M in pentane, 1.13 mL, 1.96 mmol) was added within 10 min to THF (1.7 mL) cooled to -90 °C. The resulted yellow slurry was warmed to -80 °C, and a solution of **186a** (451 mg, 0.98 mmol) in THF (1.2 mL) was added within 1.5 h. After stirring for additional 1 h, a solution of **179** (185 mg, 0.55 mmol, er 94 : 6) in THF (1.2 mL) was added within 5 min. The reaction mixture allowed to warm to rt overnight and stirred at rt for additional 3 h. Saturated aq. NH_4Cl (5 mL) was added and the mixture was concentrated to half its volume *in vacuo*. The mixture was extracted with EtOAc (3x20 mL), the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and solvents were removed *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexanes) to obtain 282 mg of **193a** (82% yield based on the amount of the desired enantiomer).

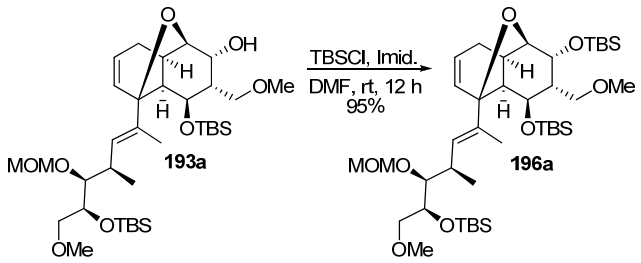
^{1}H NMR (400MHz, C_6D_6): δ = 6.12 (d, *J*=9.8 Hz, 1H), 5.96 (ddd, *J*=1.7, 1.8, 9.3 Hz, 1H), 5.51 (ddd, *J*=3.2, 3.2, 9.3 Hz, 1H), 4.76 (d, *J*=6.5 Hz, 1H), 4.64 (d, *J*=6.5 Hz, 1H), 4.33-4.26 (m, 2H), 4.18-4.09 (m, 2H), 3.72-3.66 (m, 2H), 3.62 (dd, *J*=5.4, 5.4 Hz, 1H), 3.57 (dd, *J*=3.5, 9.7 Hz, 1H), 3.43 (dd, *J*=6.6, 9.7 Hz, 1H), 3.33 (dd, *J*=3.0, 9.3 Hz, 1H), 3.31 (s, 3H), 3.14 (s, 3H), 3.06-2.96 (m, 1H), 2.92 (s, 3H), 2.81 (d, *J*=5.4 Hz, 1H), 2.78-2.71 (m, 1H), 2.41-2.32 (m, 1H), 2.37 (d, *J*=2.5 Hz, 1H), 2.09 (d, *J*=18.3 Hz, 1H), 1.93 (s, 3H), 1.27 (d, *J*=6.8 Hz, 1H), 1.06 (s, 9H), 0.99 (s, 3H), 0.224 (s, 3H), 0.216 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6): δ = 139.1, 133.6, 128.2, 127.9, 98.4, 85.5, 85.1, 83.4, 75.8, 74.2, 73.8, 72.6, 72.2, 58.7, 58.4, 55.9, 49.6, 41.1, 38.0, 33.8, 33.6, 26.5, 26.4, 18.6, 18.5, 17.0, 16.4, -3.1, -4.0, -4.3, 5.6.

IR (film): 3468, 2930, 1473, 1423, 1388, 1349, 1253, 1223, 1103, 1083, 1039, 928, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

$[\alpha]_D^{20}$ = +22.11 (c 0.90, $CHCl_3$).

HRMS (ESI): calc. for $C_{35}H_{66}NaO_8Si_2$ $[M+Na]^+$ 693.4194; found: 693.4200.



Compound 196a. A mixture of **193a** (200 mg, 0.30 mmol), TBSCl (230 mg, 1.5 mmol), imidazole (200 mg, 3 mmol) and DMF (0.3 mL) was stirred over 12 h at rt. Saturated aq. $NaHCO_3$ (5 mL) was added and stirring was continued for 10 min. The mixture was diluted with water (30 mL) and the water phase was extracted with EtOAc (3x30 mL). The combined

organic phases were washed with brine (20 mL), dried over $MgSO_4$ and solvents were removed *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexanes) to obtain **196a** in 95% yield (222 mg).

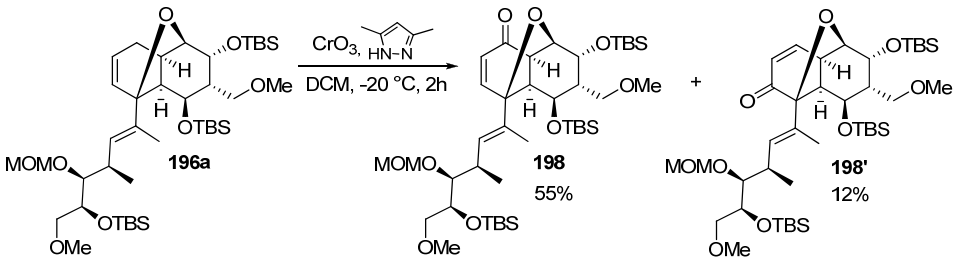
^{1}H NMR (400MHz, C_6D_6): δ = 6.20 (dd, *J*= 1.1, 9.8 Hz, 1H), 6.02 (ddd, *J*= 1.8, 1.8, 9.2 Hz, 1H), 5.55 (ddd, *J*= 3.1, 3.1, 9.2 Hz, 1H), 4.76 (d, *J*= 6.5 Hz, 1H), 4.64 (d, *J*= 6.5 Hz, 1H), 4.26 (dd, *J*= 4.5, 4.5 Hz, 1H), 4.19-4.14 (m, 2H), 3.79 (dd, *J*= 2.7, 11.0 Hz, 1H), 3.64-3.53 (m, 4H), 3.44 (dd, *J*= 6.8, 9.6 Hz, 1H), 3.31 (s, 3H), 3.23 (s, 3H), 3.14 (s, 3H), 3.16-3.00 (m, 2H), 2.70 (d, *J*= 5.4 Hz, 1H), 2.47-2.38 (m, 1H), 2.37 (d, *J*= 2.4 Hz, 1H), 2.10 (bd, *J*= 18.8 Hz, 1H), 1.96 (d, *J*= 1.1 Hz, 3H), 1.32 (d, *J*= 6.9 Hz, 3H), 1.06 (s, 9H), 1.00 (s, 9H), 0.96 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (100MHz, C_6D_6): δ = 139.4, 133.2, 128.5, 127.5 98.4, 85.6, 85.3, 83.4, 75.9, 74.3, 73.9, 71.0, 70.6, 58.7, 58.3, 55.9, 49.8, 41.2, 38.0, 33.9, 33.6, 26.5, 26.4, 26.2, 18.6, 18.5, 18.4, 17.0, 16.3, -3.1, -3.9, -4.3, -4.6, -5.1, -5.3.

IR (film): 2955, 2944, 2929, 2911, 2889, 2871, 1557, 1388, 1253, 1117, 1030, 874, 836, 776, 705, 676, 619 cm^{-1}.

$[\alpha]_D^{20}$ = +44.30 (c 1.00, $CHCl_3$).

HRMS (ESI): calc. for $C_{41}H_{80}NaO_8Si_3$ $[M+Na]^+$ 807.5059; found: 807.5067.



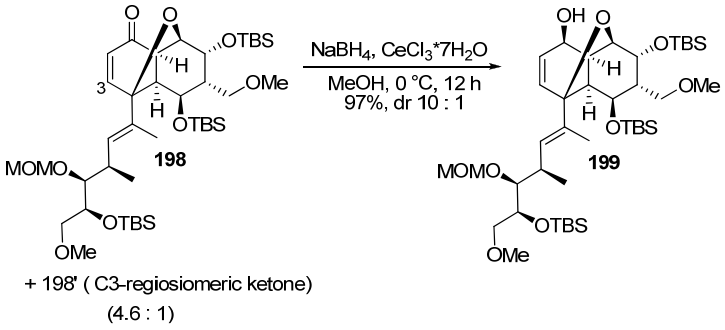
Compound 198. To a suspension of CrO_3 (1.02 g, 10.2 mmol, dried overnight over P_2O_5) in dichloromethane (7.5 mL) at -20 °C was added at once 3,5-dimethylpyrazole (0.98 g, 10.2 mmol) and the mixture was stirred until all solids dissolved to give a dark cherry-red solution. To this solution of CrO_3*3,5-dimethylpyrazole complex, a solution of **196a** (0.200 g, 0.255 mmol) in dichloromethane (2 mL) was added slowly and the mixture was stirred at -20 °C for 2h until TLC analysis showed full conversion of **196a**. The reaction mixture wad diluted with hexanes (10 mL) and washed with portions of aq. NaOH (3M, 30 mL) until the water phase stayed colorless. The combined water phase was extracted with EtOAc (3x30 mL). The combined organic phases were washed with aq. HCl (1M, 3x30 mL), saturated aq. $NaHCO_3$ (30 mL), brine (30 mL) and dried over $MgSO_4$. Concentration *in vacuo* and purification by column chromatography gave 204 mg (67%) of **198** as a mixture of regioisomeric ketones (4.6 : 1 from NMR).

NMR data are given for the major regioisomer.

198: ^{1}H NMR (400MHz, C_6D_6): 7.03 (d, *J*=9.4 Hz, 1H), 6.40 (d, *J*=9.7 Hz, 1H), 6.15 (dd, *J*=1.2, 9.4 Hz, 1H), 4.88 (d, *J*=6.6 Hz, 1H), 4.72 (d, *J*=6.6 Hz, 1H), 4.55 (dd, *J*=4.5 Hz, 1H), 4.29-4.20 (m, 2H), 3.82 (bs, 1H), 3.79-3.58 (m, 5H), 3.53 (dd, *J*=6.2, 9.7 Hz, 1H), 3.40 (s, 3H), 3.28 (s, 3H), 3.25 (s, 3H), 3.2-3.02 (m, 2H), 2.63 (d, *J*=2.6 Hz, 1H), 1.93 (bs, 3H), 1.78 (s, 3H), 1.40 (d, *J*=6.8 Hz, 3H), 1.16 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.33 (s, 3H), 0.32 (s, 3H), 0.19 (s, 3H), 0.15 (s, 3H), 0.02 (s, 3H), -0.01 (s, 3H).

^{13}C NMR (100MHz, C_6D_6): 197.9, 159.9, 130.5, 130.4, 130.1, 98.4, 86.9, 83.3, 80.7, 78.4, 75.7, 74.4, 72.1, 70.5, 70.0, 58.7, 58.4, 55.9, 55.5, 53.8, 41.5, 33.8, 26.33, 26.3, 26.2, 18.4, 16.7, 16.0, -3.3, -4.1, -4.3, -4.5, -5.2, -5.5.

HRMS (ESI): calc. for $C_{41}H_{78}NaO_9Si_3$ $[M+Na]^+$ 821.4851; found: 821.4847.



Compound 199. A solution of $CeCl_3*7H_2O$ (746 mg, 2.00 mmol) in MeOH (20 mL) was added to a mixture of ketones **198**+**198'** (4.5 :1, 800 mg, 1.00 mmol). The mixture was cooled to 0 °C, and $NaBH_4$ (230 mg, 6 mmol) was added. The reaction was stirred at 0 °C for 12 h. Saturated aq. NH_4Cl (20 mL) was added, the mixture was warmed to rt, stirred for 30 min. Aq. HCl (1M, 5Most of volatiles were remove *in vacuo* and the reaction was diluted with saturated aq. NH_4Cl (50 mL). The water phase was extracted with EtOAc (5x50 mL), combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. Volatiles were removed *in vacuo*, and the residue was repeatedly concentrated from MeOH (7x30 mL) *in vacuo*. The residue was subjected to column chromatography (EtOAc/Hex) to obtain **199** in 97% yield (638 mg) as a mixture of diastereomers (dr 10 : 1).

NMR data are given for the major diastereomer.

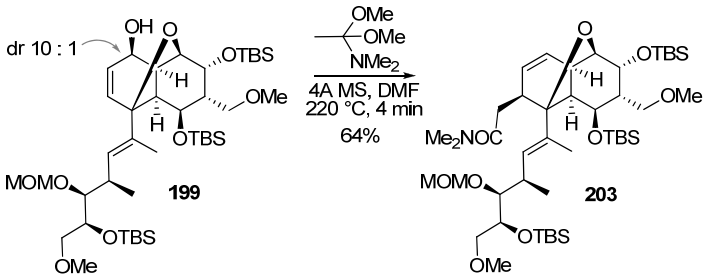
^{1}H NMR (400MHz, $CDCl_3$): δ = 5.90 (dd, *J*=1.3, 9.3 Hz, 1H), 5.73 (dd, *J*=1.2, 9.6 Hz, 1H), 5.67-5.62 (m, 1H), 4.73 (d, *J*=6.4 Hz, 1H), 4.69-4.64 (m, 1H), 4.62 (d, *J*=6.4 Hz, 1H), 4.40 (d, *J*=5.1 Hz, 1H), 4.09 (dd, *J*=4.6, 4.6 Hz, 1H), 3.89-3.84 (m, 1H), 3.56 (dd, *J*=2.6, 11.0 Hz, 1H), 3.47 (dd, *J*=4.2, 9.7 Hz, 1H), 3.40-3.29 (m, 4H), 3.38 (s, 3H), 3.30 (s, 3H), 3.24 (s, 3H), 2.79 (d, *J*=5.7 Hz, 1H), 2.79-2.68 (m, 2H), 2.32 (d, *J*=2.4 Hz, 1H), 1.67 (s, 3H), 1.58 (d, *J*=7.2 Hz, 1H), 1.02 (d, *J*=6.9 Hz, 3H), 0.90 (s, 9H), 0.897 (s, 3H), 0.88 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.055 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 132.1, 129.7, 128.0, 98.3, 84.4, 83.2, 76.7, 75.3, 73.3, 72.9, 70.7, 70.5, 69.4, 58.9, 58.4, 56.1, 51.9, 45.4, 41.2, 33.3, 26.3, 26.2, 26.1, 18.4, 18.3, 18.2, 16.6, 15.8, -3.11, -4.18, -4.24, 4.38, -5.24,-5.27.

IR (film): 3470, 2932, 1471, 1422, 1387, 1349, 1253, 1223, 1103, 1083, 1039, 928, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

Optical rotation for the mixture of diastereomers (10:1): $[\alpha]_D^{20}$ = +66.63 (c 2.05, $CHCl_3$).

HRMS (ESI): calc. for $C_{41}H_{80}NaO_9Si_3$ $[M+Na]^+$ 823.5008; found: 823.5014.



Compound 203. A microwave vial (2-5 mL) was charged with a stirring bar and 4Å molecular sieves (powder, 1.20 g), sealed with a cap and a septa, and subjected to 5 cycles of evacuation - filling with Ar.[142] A solution of **199** (100 mg, 0.125 mmol, dr 10 : 1) in DMF (dry, degassed, 1.4 mL) followed by N,N-dimethylacetamide dimethyl acetal (1.2 mL, 8.2 mmol). The mixture was irradiated at 220 °C for 2 min. Additional N,N-dimethylacetamide dimethyl acetal (0.3 mL, 2.05 mmol) was added and the mixture was irradiated for additional 2 min. All volatiles were removed *in vacuo*, the solid residue was suspended in EtOAc (10 mL) and passed through a plug of Celite. The filter cake was washed repeatedly with EtOAc (5x10 mL). The combined fractions were concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc/haxanes) to yield a mixture of regioisomer **203** (58 mg, 64%).

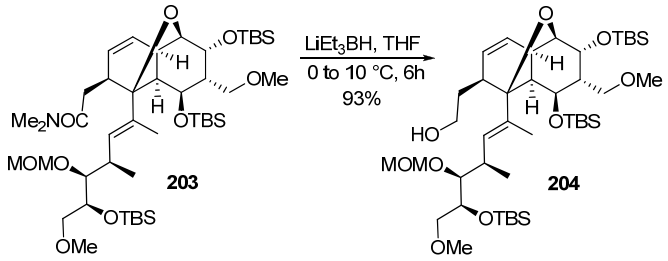
^{1}H NMR (400MHz, C_6D_6): δ = 6.28 (dd, *J*=0.8, 10.1 Hz, 1H), 6.12 (dd, *J*=2.4, 9.5 Hz, 1H), 6.00-5.95 (m, 1H), 6.12 (ddd, *J*=1.2, 3.0, 9.2 Hz, 1H), 4.76 (d, *J*=6.7 Hz, 1H), 4.62 (d, *J*=6.7 Hz, 1H), 4.34 (d, *J*=4.8 Hz, 1H), 4.30 (dd, *J*=4.0, 4.6 Hz, 1H), 4.15-4.10 (m, 1H), 3.81 (dd, *J*=2.5, 10.9 Hz, 1H), 3.74-3.69 (m, 1H), 3.60-3.55 (m, 3H), 3.52 (dd, *J*=3.7, 9.7 Hz, 1H), 3.41 (dd, *J*=6.6, 9.7 Hz, 1H), 3.31 (s, 3H), 3.24-3.16 (m, 1H), 3.22 (s, 3H), 3.09 (s, 3H), 3.08-3.01 (m, 1H), 2.85 (d, *J*=6.5 Hz, 1H), 2.78-2.71 (m, 1H), 2.75 (s, 3H), 2.63 (s, 3H), 2.57-2.51 (m, 2H), 1.91 (d, *J*= 0.9 Hz, 3H), 1.34 (d, *J*=6.8 Hz, 3H), 1.05 (s, 9H), 0.98 (s, 9H), 0.97 (s, 9H), 0.20 (s, 6H), 0.13 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6): δ = 170.7, 131.4, 131.1, 130.1, 127.6, 97.3, 89.4, 89.3, 85.2, 83.0, 74.6, 73.4, 72.0, 69.9, 69.3, 57.6, 57.4, 54.7, 49.6, 42.3, 39.9, 39.0, 35.6, 34.2, 33.1, 31.8, 25.5, 25.3, 25.1, 17.6, 17.5, 17.4, 15.90, 15.4, -4.1, -5.0, -5.4, -5.5, -6.1, -6.3.

IR (film): 2931, 1662, 1474, 1422, 1387, 1349, 1253, 1223, 1103, 1083, 1039, 928, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{45}H_{87}NNaO_9Si_3$ $[M+Na]^+$ 892.5586; found: 892.5581.

$[\alpha]_D^{20}$ = +98.9 (c 0.37, $CHCl_3$).



Compound 204. To a flask charged with amide **203** (179 mg, 0.206 mmol) under stirring was added dropwise Super-Hydride (1.0 M in THF, 3.2 mL, 3.2 mmol) at 0°C, and the reaction was stirred for 5 h at 0 °C, 30 min at 5°C and 30 min at 10 °C. Saturated aq. NH_4Cl (5 mL) followed by MeOH (2mL) were added carefully and the mixture was stirred for 10 min at rt. Most of organic solvents were removed *in vacuo* and the water phase was extracted with EtOAc (5x30 mL). Combined organic phases were diluted with toluene (40 mL), washed with brine (40 mL) and concentrated *in vacuo*. The residue was concentrated repeatedly from methanol (5x5 mL) and then subjected to column chromatography (EtOAc/hexanes) to give 159 mg (93%) of **204**.

[142] A needle (0.8x80mm) was injected into the vial's septa, the vial with the needle was placed in a flask (250 mL, joint 29/42) and the system was subjected to evacuation - filling with Ar cycles.

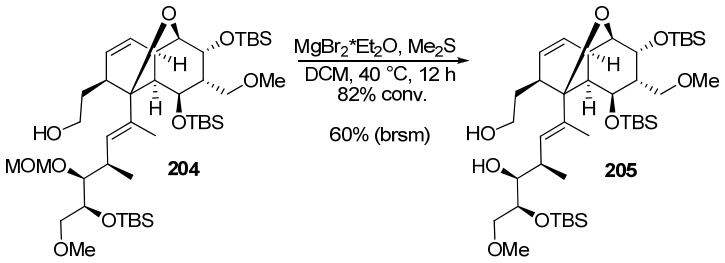
^{1}H NMR (400MHz, $CDCl_3$): δ = 5.92 (ddd, *J*=2.1, 6.7, 9.2 Hz, 1H), 5.74 (dd, *J*=1.0, 10.0 Hz, 1H), 5.57 (dd, *J*=2.4, 9.5 Hz, 1H), 4.74 (d, *J*=6.7 Hz, 1H), 4.66 (d, *J*=6.7 Hz, 1H), 4.05 (d, *J*=5.0 Hz, 1H), 3.97 (dd, *J*=4.3, 4.3 Hz, 1H), 3.94-3.89 (m, 1H), 3.71-3.61 (m, 1H), 3.62 (dd, *J*=2.5, 11.0 Hz, 1H), 3.53-3.44 (m, 2H), 3.43-3.27 (m, 4H), 3.41 (s, 3H), 3.33 (s, 3H), 3.23 (s, 3H), 2.84-2.73 (m, 2H), 2.73-2.68 (m, 1H), 2.68-2.63 (m, 2H), 2.30 (d, *J*=2.3 Hz, 1H), 1.75-1.66 (m, 1H), 1.68 (s, 3H), 1.55-1.45 (m, 1H), 1.04 (d, *J*=6.7 Hz, 1H), 0.903 (s, 9H), 0.900 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ = 132.1, 130.1, 130.4, 129.0, 98.0, 90.1, 85.8, 83.0, 75.7, 73.6, 72.5, 70.5, 69.4, 60.8, 58.9, 58.4, 56.0, 50.4, 43.1, 40.2, 39.3, 34.4, 32.4, 26.4, 26.1, 26.0, 18.5, 18.4, 18.2, 17.1, 16.5, -3.1, -4.2, -4.3, -4.5, -5.20, -5.22.

IR (film): 3460, 1470, 1422, 1387, 1349, 1252, 1223, 1103, 1083, 1039, 921, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

$[\alpha]_D^{20}$ = +93.8 (c 0.305, $CHCl_3$).

HRMS (ESI): calc. for $C_{43}H_{84}NaO_9Si_3$ $[M+Na]^+$ 851.5321; found: 851.5320.



Compound 205. A flask was charged with magnesium turning (400 mg, 16.6 mmol) and diethyl ether (10 mL), equipped with a reflux condenser and immersed in an ultrasound bath (20 °C). Dibromoethane (0.65 mL, 7.6 mmol) was added and the mixture was sonicated at 20 to 40 °C for 1h. The sonication was stopped and the mixture was allowed to stay at rt for 20 min. The separated bottom layer was transferred into a Schlenk flask (10 mL) *via* a syringe. Most of the solvent was blown away with Ar-stream and finally dried *in vacuo* for 2-3min to obtain a white powder. Into this flask Me_2S (2 mL) and a solution of substrate **204** (152 mg, 0.183 mmol) in 1.5 mL were added. The flask was immersed in an oil bath (40 °C), heated to reflux and the stop-cock to Ar-line was closed. The closed flask was heated at 40 °C for 12 h. Saturated aq. $NaHCO_3$ (5 mL) was added and the organic solvents were removed *in vacuo*. The water phase was extracted with EtOAc (4x15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/toluene) to obtain starting **204** (27 mg, 18%) and **205** (70 mg, 60% brsm).

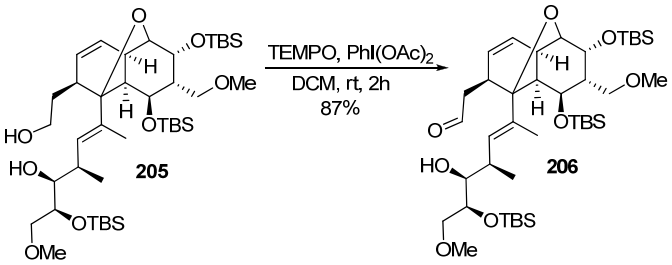
^{1}H NMR (400MHz, $CDCl_3$): δ = 5.94 (ddd, *J*=2.2, 6.7, 9.3 Hz, 1H), 5.57 (dd, *J*=2.3, 9.5 Hz, 1H), 5.53 (dd, *J*= 0.9, 10.0 Hz, 1H), 4.08 (d, *J*=5.0 Hz, 1H), 4.00 (dd, *J*=4.3 Hz, 1H), 3.88 (ddd, *J*=1.2, 4.4, 7.0 Hz, 1H), 3.72-3.61 (m, 1H), 3.63 (dd, *J*=2.5, 10.9 Hz, 1H), 3.54-3.45 (m, 1H), 3.43 (dd, *J*=4.4, 9.8 Hz, 1H), 3.37 (dd, *J*=7.1, 9.7 Hz, 1H), 3.35-3.30 (m, 2H), 3.32 (3H), 3.22 (s, 3H), 3.20 (dd, *J*=0.9, 9.4 Hz, 1H), 2.82 (dd, *J*=5.3, 7.6 Hz, 1H), 2.84-2.74 (m, 1H), 2.74-2.68 (m, 1H), 2.69 (d, *J*=6.6 Hz, 1H), 2.56 (d, *J*=9.4 Hz, 1H), 2.58-2.50 (m, 1H), 2.33 (d, *J*= 2.2 Hz, 1H), 1.79 (d, *J*= 0.90 Hz, 1H), 1.66-1.47 (m, 2H), 1.09 (d, *J*=6.7 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ = 133.4, 130.3, 129.9, 129.2, 90.3, 86.1, 76.5, 75.4, 72.4, 72.2, 70.3, 69.2, 60.3, 58.9, 58.4, 50.5, 43.1, 40.2, 39.3, 37.1, 32.4, 26.4, 26.1, 26.0, 18.5, 18.4, 18.2, 17.4, 17.0, -3.1, -3.7, -4.5, -4.6, -5.19, -5.22.

IR (film): 3470, 1474, 1422, 1387, 1349, 1252, 1223, 1103, 1083, 1039, 921, 898, 880, 835, 797, 775, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{80}NaO_8Si_3$ $[M+Na]^+$ 807.5059; found: 807.5063.

$[\alpha]_D^{20}$ = +105.4 (c 0.280, $CHCl_3$).



Compound 206. To substrate **205** (46 mg, 0.060 mmol) at rt was added a solution of TEMPO (3.0 mg, 0.019 mmol) and $PhI(OAc)_2$ (45 mg, 0.140 mmol) in dichloromethane (0.45 mL) and the clear solution was stirred at rt for 2 h. Then a mixture EtOAc/hexanes (1:1, 3 mL) was added and the solution was passed through a short plug of silica gel (elution with EtOAc/hexanes 1:1) to remove $PhI(OAc)_2$. The resulting solution was concentrated, the residue was dissolved in toluene (3 mL) and passed through a short silica gel column (1.5 g SiO_2, elution with toluene; 2% EtOAc/toluene) to separate from most of TEMPO. The fractions containing **206** were concentrated and subjected to column chromatography to (EtOAc/toluene) to obtain **206** (40 mg, 87%).

(NOTE: test experiments showed that a commonly used quench procedure with saturated aq. $Na_2S_2O_3$ or $Na_2S_2O_3$/$NaHCO_3$ does not result in reduction of neither $PhI(OAc)_2$ nor TEMPO after 5 min of stirring or shaking. Concentration of the crude mixture ($PhI(OAc)_2$,TEMPO and product **206**) followed by loading on silica gel column resulted in partial oxidation **206** to carboxylic acid **207**. TEMPO on TLC appears as a yellowish spot, UV-visible at 254 nm if its concentration is high enough).

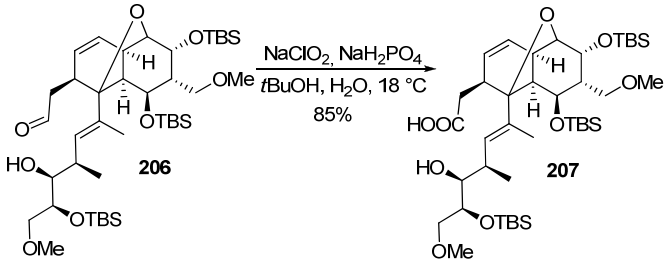
206: ^{1}H NMR (400MHz, $CDCl_3$): δ = 9.75 (d, *J*=1.9 Hz, 1H), 5.96 (ddd, *J*=2.2, 6.8, 9.4 Hz, 1H), 5.62 (dd, *J*=0.8, 9.6 Hz, 1H), 5.54 (dd, *J*=2.5, 9.4 Hz, 1H), 4.05 (d, *J*=5.0 Hz, 1H), 4.00 (dd, *J*=4.5, 4.5 Hz, 1H), 3.80 (ddd, *J*=1.4, 4.9, 6.5 Hz, 1H), 3.63 (dd, *J*=2.5, 11.0 Hz, 1H), 3.41 (dd, *J*=4.9, 9.5 Hz, 1H), 3.36 (dd, *J*=6.6, 9.5 Hz, 1H), 3.33-3.25 (m, 3H), 3.32 (s, 3H), 3.23 (s, 3H), 3.13-3.09 (m, 1H), 2.79-2.72 (m, 1H), 2.70 (d, *J*=6.3 Hz, 1H), 2.58-2.50 (m, 1H), 2.48-2.43 (m, 2H), 2.40 (dd, *J*=2.5, 8.4 Hz, 1H), 2.32 (d, *J*=2.2 Hz, 1H), 1.67 (d, *J*=0.8 Hz, 1H), 1.09 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.082 (s, 3H), 0.079 (s, 3H), 0.044 (s, 3H), 0.036 (s, 3H), 0.03 (s, 3H), 0.02(s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ = 202.1, 132.8, 130.3, 129.9, 129.5, 89.5, 86.1, 75.6, 75.3, 72.2, 72.1, 70.2, 69.1, 58.9, 58.4, 50.2, 43.4, 41.1, 40.1, 39.1, 36.6, 26.3, 26.0, 25.9, 18.3, 18.1, 16.9, 16.8, -3.3, 3.8, -4.6, -4.7, -5.3.

IR (film): 3464, 1730, 1479, 1421, 1387, 1345, 1252, 1223, 1103, 1082, 1039, 921, 898, 885, 835, 797, 770, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{78}NaO_8Si_3$ $[M+Na]^+$ 805.4902; found: 805.4898.

$[\alpha]_D^{20}$ = +92.0 (c 0.275, $CHCl_3$).



Compound 207. To a solution of aldehyde **206** (25 mg, 0.032 mmol) in *t*BuOH (0.6 mL) was added 2-methyl-2-betene (1.4 mL) and the mixture was cooled to 17 °C. A solution of $NaClO_2$ (80%, 40 mg, 0.356 mmol) and NaH_2PO_4*H_2O (80mg, 0.580 mmol) in water (0.4 mL) was added and the mixture was stirred at 17 °C for 40 min. Chloroform (20 mL) was added and the organic phase was washed with water (2x5 mL). Combine organic phases were extracted with chloroform (4x15 mL). Combined organic phases were washed with brine (20 mL), passed through a plug of cotton and concentrated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexanes + 1% *i*PrOH) to obtain acid **207** (21.9 mg, 85%).

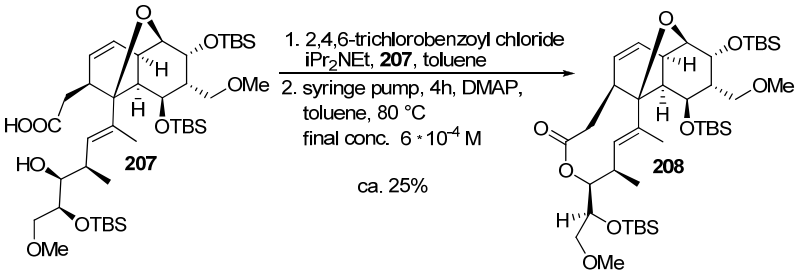
^{1}H NMR (400MHz, $CDCl_3$): δ = 5.97 (ddd, *J*=2.0, 6.9, 9.4 Hz, 1H), 5.60 (dd, *J*=0.8, 9.6 Hz, 1H), 5.54 (dd, *J*=2.5, 9.4 Hz, 1H), 4.11 (d, *J*=5.0 Hz, 1H), 4.04 (dd, *J*=4.5, 4.5 Hz, 1H), 3.82 (dd, *J*=1.1, 6.1 Hz, 1H), 3.46-3.36 (m, 2H), 3.34-3.27 (m, 3H), 3.33 (s, 3H), 3.23 (s, 3H), 3.07 (m, 1H), 2.82-2.72 (m, 1H), 2.70 (d, *J*=6.6 Hz, 1H), 2.60-2.49 (m, 2H), 2.32 (d, *J*=2.2 Hz, 1H), 2.21 (dd, *J*=6.8, 16.0 Hz, 1H), 1.72 (bs, 3H), 1.08 (d, *J*=6.7 Hz, 3H), 0.92 (s, 9H), 0.82 (s, 9H), 0.78 (s, 3H), 0.08 (s, 3H), 0.044 (s, 3H), 0.036 (s, 3H), 0.025 (s, 3H), 0.017(s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ = 175.5, 133.0, 130.4, 130.2, 129.7, 89.8, 86.2, 75.3, 74.6, 72.4, 71.9, 70.3, 69.2, 59.0, 58.5, 50.5, 42.4, 40.3, 39.0, 36.7, 34.2, 26.4, 26.1, 26.0, 18.42, 18.39, 18.2, 17.3, 16.9, -3.1, -3.7, -4.5, -4.7, -5.20, -5.23.

IR (film): 3460, 1710, 1479, 1421, 1387, 1345, 1252, 1223, 1103, 1082, 1039, 921, 898, 885, 835, 797, 770, 722, 671, 649, 611, 419 cm^{-1}.

HRMS (ESI): calc. for $C_{41}H_{78}NaO_9Si_3$ $[M+Na]^+$ 821.4851; found: 821.4857.

$[\alpha]_D^{20}$ = +80.0 (c 0.48, $CHCl_3$).



Compound 208. To acid **207** (2.5 mg, 0.003 mmol) was added a solution of *i*Pr_2NEt (0.4M in toluene, 200 µL, 0.080 mmol) and a solution of 2,4,6-trichlorobenzoyl chloride (0.4M in toluene, 130 µL, 0.052 mmol), and the mixture was stirred at rt for 4 h. The mixture was diluted with toluene (2.2. mL) and added *via* syringe pump to a solution of DMAP (17.0 mg, 0.14 mmol) in toluene (2.9 mL) at 80 °C over 4 h. Saturated aq. $NaHCO_3$ (10 mL) was added and the mixture was stirred for 15 min until phases became clear. The mixture was extracted with Et_2O (3x20 mL). The combined organic phases were washed with saturated aq. $NaHCO_3$ (20 mL), aq. NaH_2PO_4 (2M, 30 mL), saturated aq. $NaHCO_3$ (20 mL), brine (20 mL) and dried over Mg_2SO_4. The solvents were removed *in vacuo* and the residue was subjected to column chromatography to obtain lactone **208** (0.6 mg, ca. 25%).

The structure of the lactone was confirmed by ^{1}H, DQF-COSY, NOESY, ROESY, HSQC and HMBC NMR experiments.

^{1}H NMR (400MHz, C_6D_6): δ = 6.18 (dd, *J*=1.0, 9.3 Hz, 1H), 5.83 (ddd, *J*=2.2, 6.7, 9.3 Hz, 1H), 5.22 (dd, *J*=2.2, 9.4 Hz, 1H), 5.18 (dd, *J*=6.0, 7.2 Hz, 1H), 4.33-4.29 (m, 1H), 4.24-4.18 (m, 2H), 3.89 (dd, *J*=2.1, 11.4 Hz, 1H), 3.62-3.49 (m, 2H), 3.41-3.34 (m, 2H), 3.31 (dd, *J*=3.2, 9.8 Hz, 1H), 3.18 (s, 3H), 3.07 (s, 3H), 3.95-2.96 (m, 1H), 2.87-2.78 (m, 2H), 2.51 (d, *J*=1.6 Hz, 1H), 2.02 (dd, *J*=2.1, 12.9 Hz, 1H), 1.99 (d, *J*=1.0 Hz, 3H), 1.12 (s, 9H), 1.03 (d, *J*=6.9 Hz, 3H), 0.97 (s, 9H), 0.96 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H), 0.13 (s, 3H), 0.05 (s, 3H), 0.03 (2s, 6H).

^{13}C NMR shifts were obtained from HSQC and HMBC spectra (C_6D_6): δ = 173.9, 135.7, 131.6, 129.6, 89.0, 84.7, 79.6, 75.6, 72.7, 71.8, 70.3, 69.6, 58.4, 57.9, 49.6, 49.92, 41.4, 40.1, 36.5, 32.7, 26.0, 25.86, 25.9, 17.0, 15.0, -3.90, -3.89, -5.10, -5.12, -5.4.

HRMS (ESI): calc. for $C_{41}H_{76}NaO_8Si_3$ $[M+Na]^+$ 803.4746; found: 803.4742.

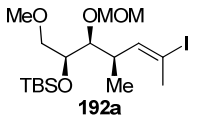
16. Appendices

16.1. List of Abbreviations

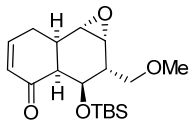
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Ar	aryl, aromatic
Bn	benzyl
Bu	butyl
cat.	catalyst, catalytic amount
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DDQ	2,3-dichloro-5,6-dicyano-p-quinone
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylaminopyridine
EE	1-ethoxyethyl
eq.	equvalent
Et	ethyl
er	enantiomeric ratio
et al.	latin: "et alii", meaning "and others"
EtOAc	ethyl acetate
Imid.	imidazole
INOC	intramolecular nitrile oxide cyclization
IR	infra red
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
*m*CPBA	*meta*-chloro peroxybenzoic acid
Me	methyl
min	minute
MOM	methoxymethyl
mp	melting point
MS	mass spectroscopy
4Å MS or 3Å MS	molecular sieves with pores 4 or 3 angstrom
NBS	N-bromosuccinamide
NMR	nuclear magnetic resonance spectroscopy
P or PG	unspecified protecting group
ppm	part per million
R, R', R'', R^1, R^2, R^3	unspecified substituents
RCM	ring closing metathesis
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofurane
TBS	dimethyl-*tert*-butylslyl
TBDPS	*ter*-butyldiphenylsilyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl

16.2. Selcted NMR Spectra

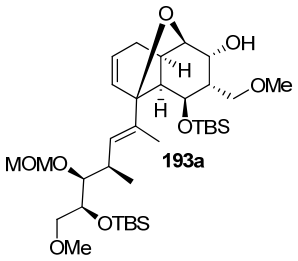
Spectra are given for the following key synthetic intermediates:



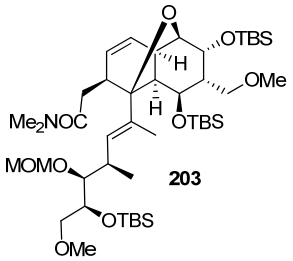
192a in $CDCl_3$



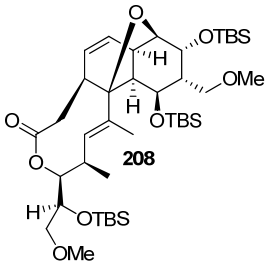
179 in $CDCl_3$



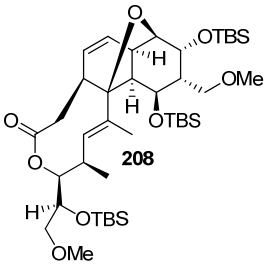
193a in C_6D_6



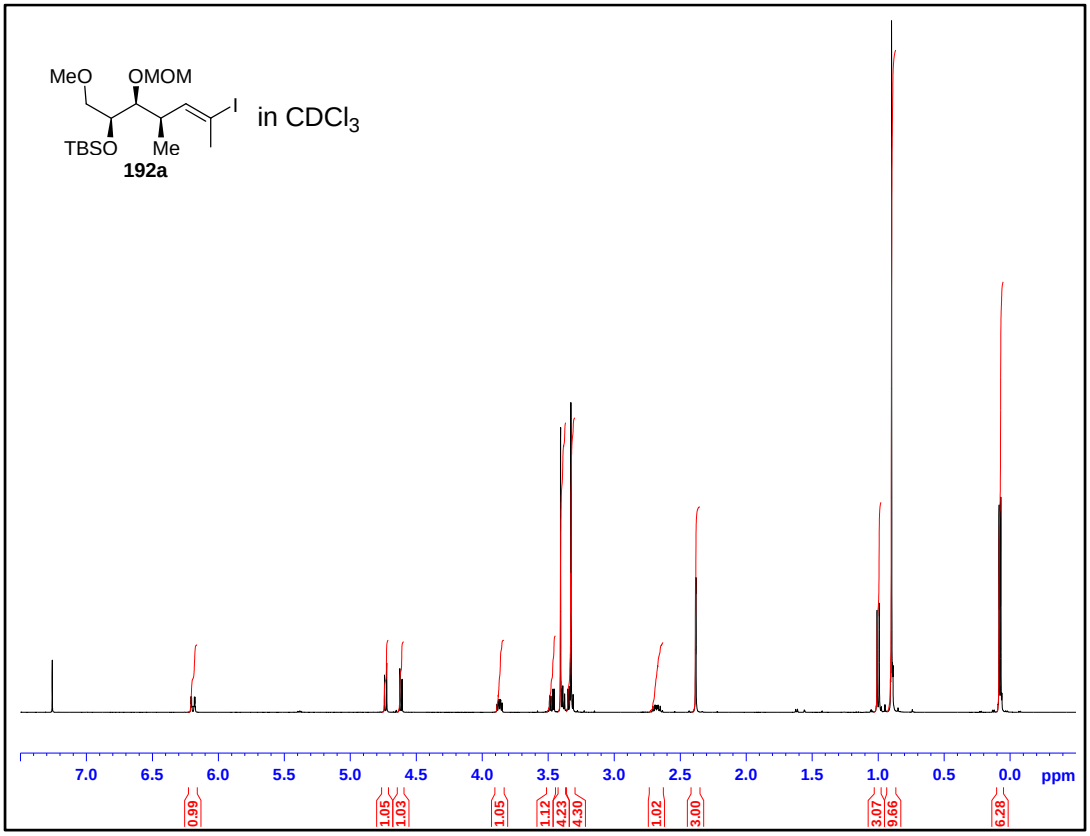
203 in C_6D_6

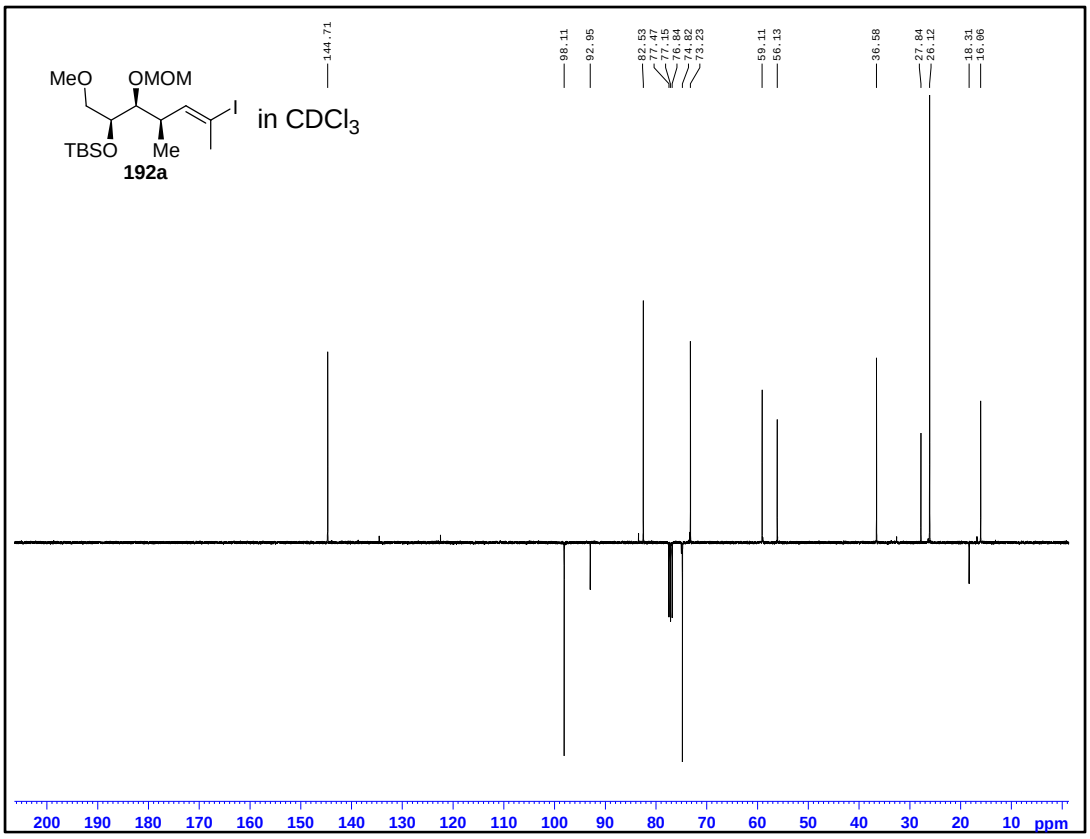


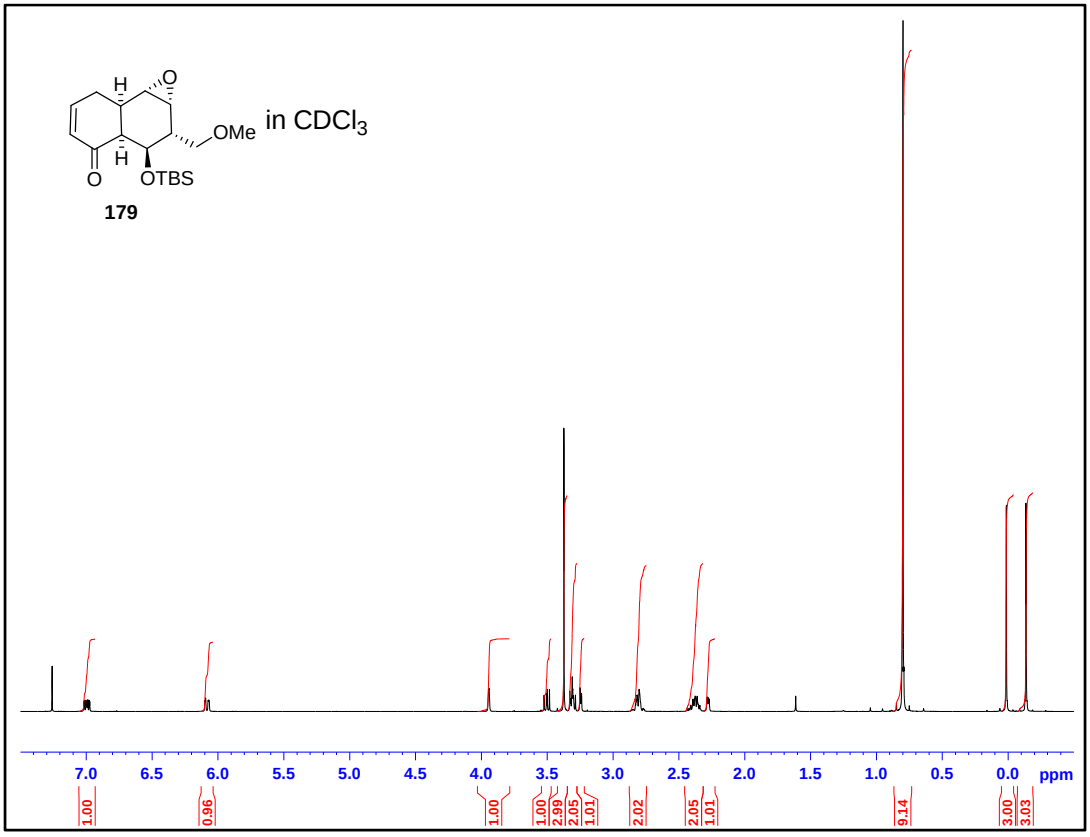
208 in $CDCl_3$

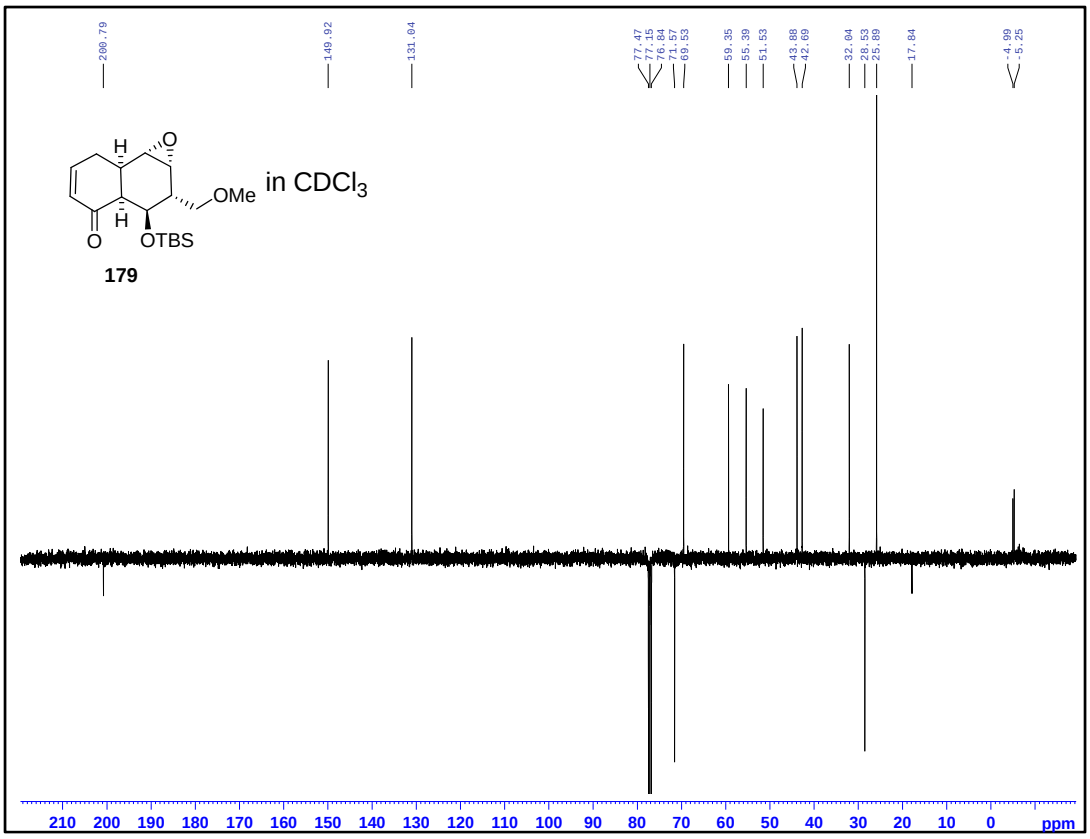


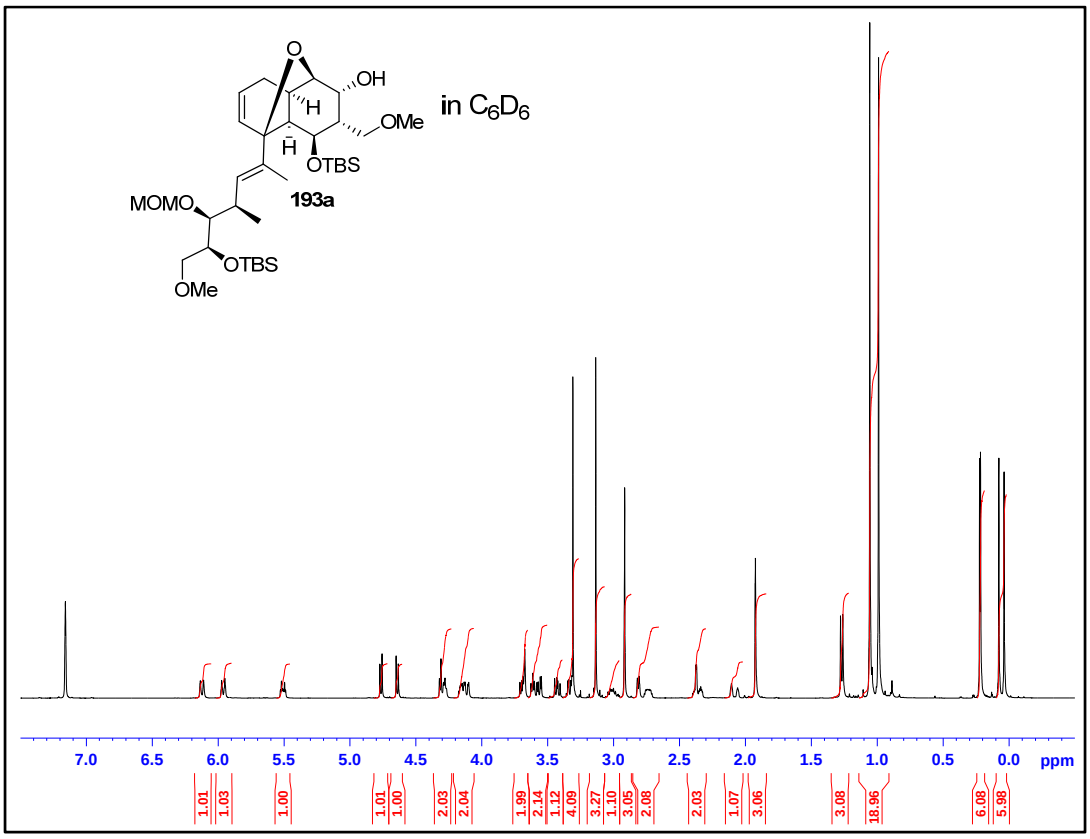
208 in C_6D_6

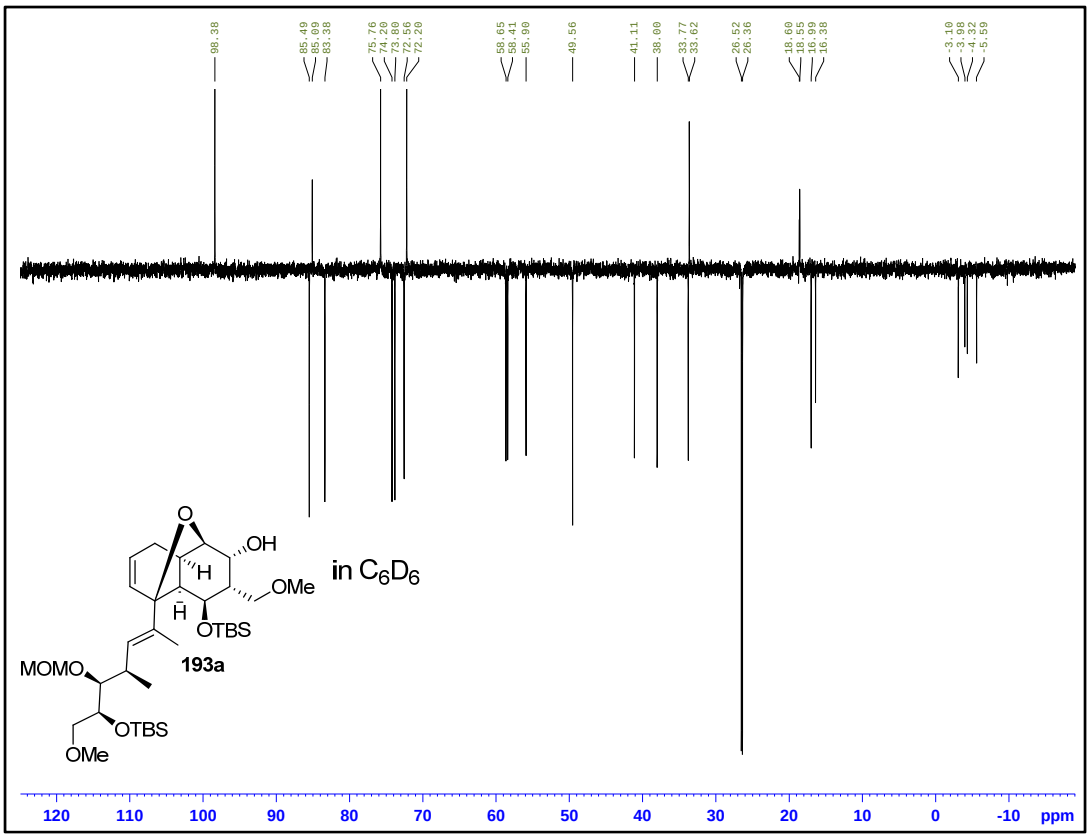

MeO
OMOM
TBSO
Me
I
192a
in CDCl3
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.99 1.05 1.03 1.05 1.12 4.23 4.30 1.02 3.00 3.07 9.66 6.28

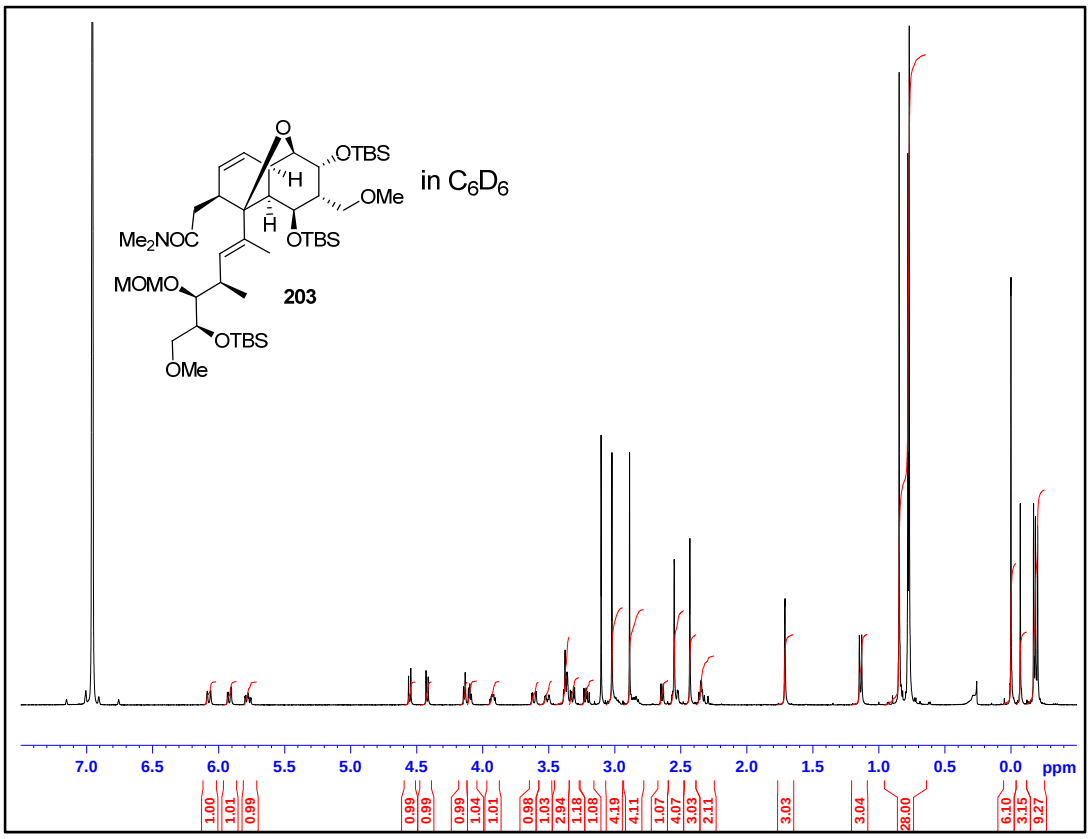

MeO
OMOM
TBSO
Me
I
192a
in CDCl3
144.71
98.11
92.95
82.53
77.47
77.15
76.84
74.82
73.23
59.11
56.13
36.58
27.84
26.12
18.31
16.06
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

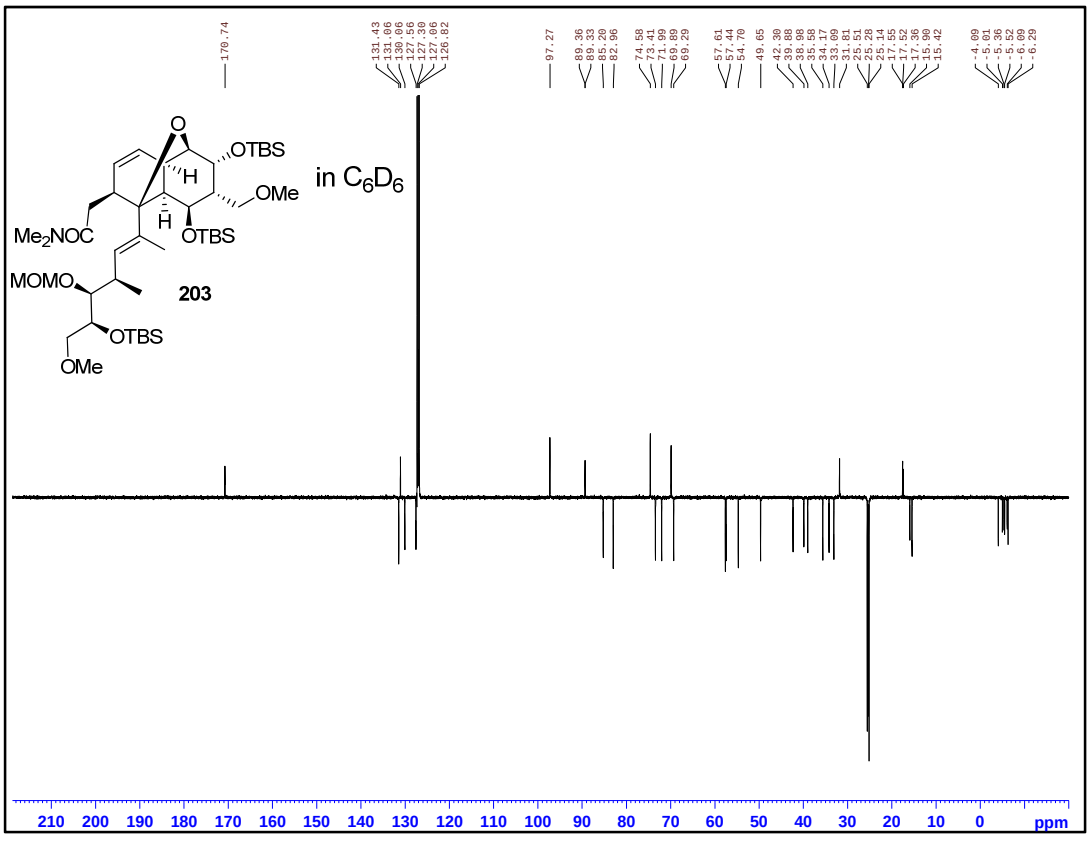

H
O
OMe
in CDCl3
H
O
OTBS
179
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 0.96 1.00 1.00 2.99 2.05 1.01 2.02 2.05 1.01 9.14 3.00 3.03

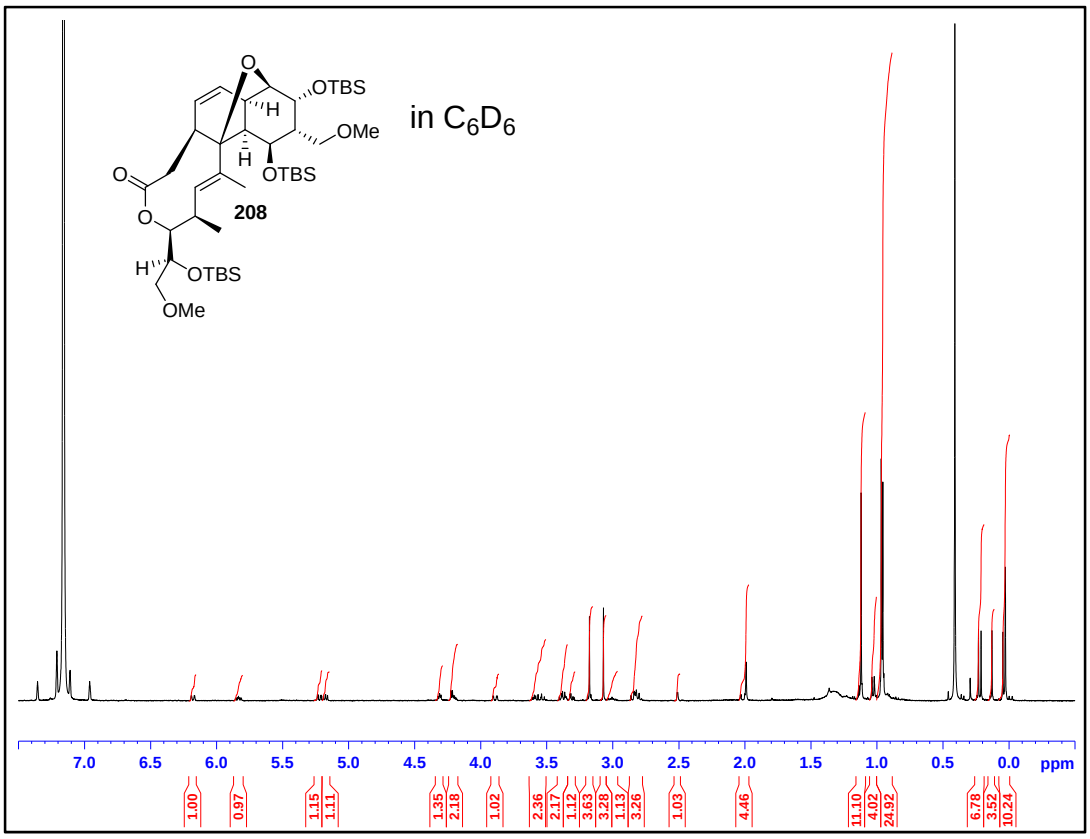

200.79
149.92
131.04
77.47
77.15
76.84
71.57
69.53
59.35
55.39
51.53
43.88
42.69
32.64
28.53
25.89
17.84
-4.99
-5.25
H
O
OMe
in CDCl3
H
O
OTBS
179
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

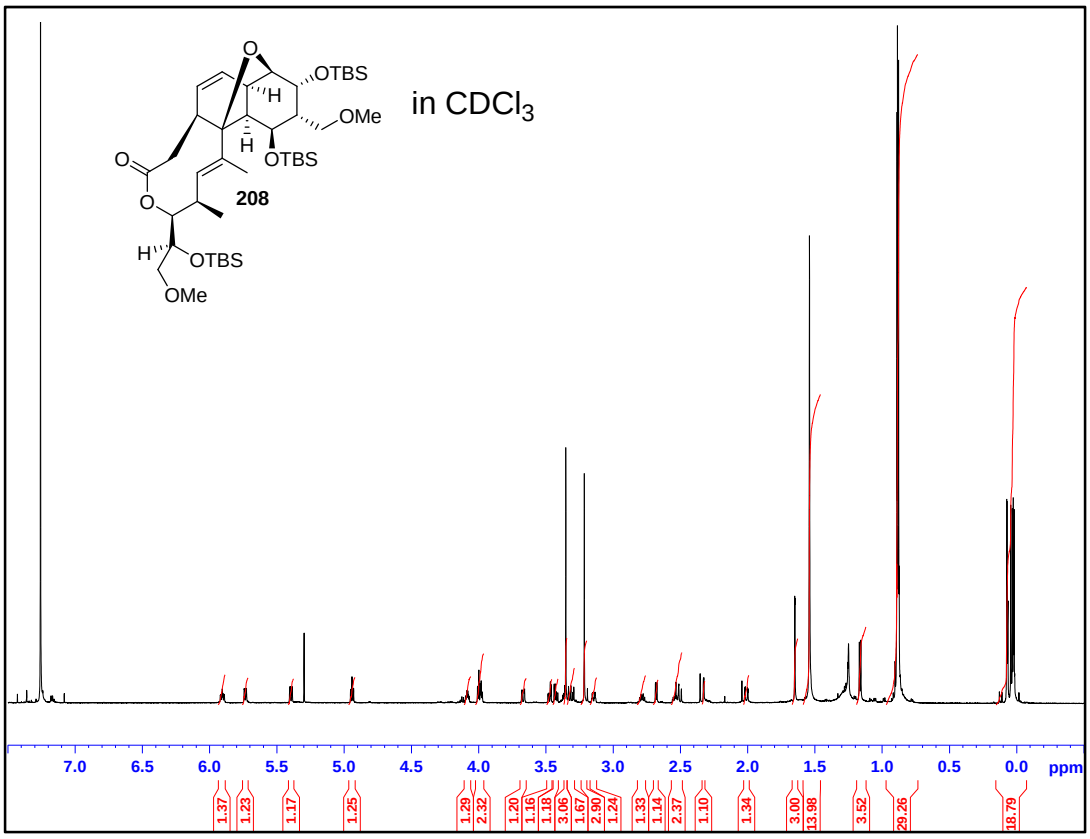

O
OH
H
OMe
H
OTBS
MOMO
193a
OTBS
OMe
in C6D6
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.01
1.03
1.00
1.01
1.00
2.03
2.04
1.99
2.14
1.12
4.09
3.27
1.10
3.05
2.08
2.03
1.07
3.06
3.08
18.96
6.08
5.98


98.38
85.49
85.09
83.38
75.76
74.26
73.80
72.56
72.20
58.65
58.41
55.90
49.56
41.11
38.00
33.77
33.62
26.52
26.36
18.60
18.55
16.99
16.38
-3.10
-3.98
-4.32
-4.59
O
OH
H
OMe
H
OTBS
MOMO
193a
OTBS
OMe
in C6D6
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


O
OTBS
H
OMe
in C_6D_6
Me_2NOC
H
OTBS
MOMO
203
OTBS
OMe
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 1.01 0.99 0.99 0.99 0.99 1.04 1.01 0.98 1.03 2.94 1.18 1.08 4.19 4.11 1.07 4.07 3.03 2.11 3.03 3.04 28.00 6.10 3.15 9.27


170.74
131.43 131.06 130.66 127.56 127.30 127.06 126.82
97.27
89.36 89.33 85.20 82.96
74.58 73.41 71.99 69.89 69.29
57.61 57.44 54.70
49.65
42.30 39.88 38.98 35.58 34.17 33.09 31.81 25.51 25.28 25.14 17.55 17.52 17.36 15.90 15.42
-4.09 -4.81 -5.36 -5.52 -6.09 -6.29
O
OTBS
H
OMe
in C_6D_6
Me_2NOC
H
OTBS
MOMO
203
OTBS
OMe
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OTBS
H
OMe
H
OTBS
O
O
208
H
OTBS
OMe
in C_6D_6
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00 0.97 1.15 1.11 1.35 2.18 1.02 2.36 2.17 1.12 3.63 3.28 1.13 3.26 1.03 4.46 11.10 4.02 24.92 6.78 3.52 10.24


OTBS
H
OMe
H
OTBS
O
O
208
H
OTBS
OMe
in $CDCl_3$
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.37 1.23 1.17 1.25 1.29 2.32 1.20 1.16 1.18 3.06 1.67 2.90 1.24 1.33 1.14 2.37 1.10 1.34 3.00 13.98 3.52 29.26 18.79

Curriculum Vitae

Personal Data:

Date of Birth:	25th December 1979
Birth Place:	Moscow, Russia
Marital Status:	Married
Nationality:	Russian

Ph. D. Theis

Summer 2009	Ph.D *viva*, Department of Organic Chemistry, University of Vienna
2004 Spring - Summer 2009	Ph.D studies, Department of Organic Chemistry, University of Vienna
2004 Autumn- Spring 2009	Ph.D research under supervision of Prof. J. Mulzer and Univ.-Doz. Dr. V. Enev (co-supervisor) "**Studies Towards the Total Synthesis of Barnimycin"**

University Studies

1997-2003	Full time student at The Higher Chemical College of the Russian Academy of Sciences. Diploma thesis under Supervision of Prof. W. Smit: **"Adducts of ArSCl with vinyl ethers as equivalents of 1,1-bis-electrophylic synthons in reactions of geminal alkylation"**

Education

1994 – 1997	Moscow Chemical Lyceum, Moscow

Publications and Awards not derived from the Ph.D research

- Smit, William A.; Gromov, Alexei V.; Yagodkin, Elisey A. *Mendeleev Communications* **2003**, *1*, 21-23. **"Adducts of ArSCl with vinyl ethers or esters as synthons in geminal alkylation"**

- Gromov, Alexey V.; Smit, William A. *European Journal of Organic Chemistry* **2006**, *5*, 1317-1322 **"β-Arylthio-α-chloroalkyl ethers - novel 1,1-bis-electrophiles for geminal alkylation"**

- Awarded by www.InnoCentive.com for a theoretical proposal of the synthesis of 1-phenyl-1,3,8-triaza-spiro[4,5]decan-4-one oriented on tone scale production