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Doctoral Dissertation

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Abstract

The pectenotoxins (PTXs) are a family of marine macrolactones produced by *Dinophysis* dinoflagellates and found in coastal areas worldwide. The PTXs have drawn considerable attention not only because of their complex structure and toxicity but also because of their potential medical applications. Pectenotoxins have shown selective cytotoxicity against a variety cancer cell lines and they are known to interact with the actin cytoskeleton by unique mechanism. These properties could be of great clinical importance for the development of new cancer chemotherapy agents. The scarcity of the PTXs has hampered further studies into their biological activity, and as such access to synthetic PTXs would be immensely helpful.

The exquisitely complex structure of the PTXs presents a considerable challenge for a synthetic chemist. One of the most challenging structural elements is the AB spiroketal ring fragment that is in the more unstable and less easily accessible nonanomeric configuration. Importantly, the PTX congeners that contain this nonanomeric spiroketal ring system, has been reported to be the most biologically active. In the literature part, a short discussion of the anomeric effect is presented. The previously published syntheses of the AB spiroketal ring fragment of PTXs are discussed. And finally, a brief insight into other natural products containing nonanomeric spiroketals and their recent syntheses are presented.

In this work the objective was to synthesize the ABCDE ring fragment of PTX2 using a highly convergent strategy. Three advanced ring fragments corresponding to the A, C and DE ring systems were synthesized. The A ring lactone was also used for the synthesis of the AB spiroketal ring fragment of PTX2. During these studies we developed kinetic spiroketalization conditions that delivered for the first time the desired nonanomeric spiroketal isomer of the PTXs as the major product. For the C ring fragment an efficient synthesis was developed that delivered the key center peace with the right stereochemistry in excellent 46% total yield over nine steps. The connection of the C ring aldehyde with the DE ring fragment using Mukaiyama aldol reaction gave access to the CDE ring system in highly stereoselective manner. The CDE ring allylic alcohol was connected with the A ring fragment via cross-metathesis. As the final step, the kinetic spiroketalization delivered a 3:1 mixture of the nonanomeric and the anomeric spiroketal. Unfortunately, it was discovered that the final ABCDE ring product had the wrong stereochemistry at C10. Studies targeting the inversion of this stereocenter are under way, which would finally give access to the natural ABCDE ring fragment of PTX2.

Keywords pectenotoxin, total synthesis, spiroketal, nonanomeric, anomeric

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Tiivistelmä

Pektenotoksiinit (PTX) ovat myrkyllisiä luonnonaineita, joita tuottavat *Dinophysis*-sukuun kuuluvat panssarisiimalevät. Pektenotoksiinit ovat mielenkiintoisia niiden monimutkaisen rakenteen, myrkyllisyytensä ja mahdollisten lääketieteellisten sovellusten vuoksi. Pektenotoksiinien tiedetään häiritsevän solun aktiinitukirangan toimintaa ja tällä tavoin selektiivisesti ehkäisevän erilaisten syöpäsolujen kasvua. Tämä ominaisuus voi osoittautua erittäin hyödylliseksi uusien kemoterapia-aineiden kehityksessä. Pektenotoksiineja pystytään eristämään luonnosta vain pieniä määriä ja siksi lääketieteellisten tutkimusten edistämiseksi olisikin tärkeää kehittää toimiva menetelmä niiden synteettiseen valmistukseen.

Synteettisesti pektenotoksiinit ovat erittäin haastava kohde. Yksi haastavimmista rakenteellisista ominaisuuksista on epäanomeerinen AB-spiroketaaliyksikkö joka on termodynaamisesti epästabiilimpi ja vaikeammin syntetisoitavissa kuin vastaava anomeerisesti stabiloitu spiroketaali. Epäanomeerisen spiroketaalin omaavien pektenotoksiinien on lisäksi todettu olevan kaikkein biologisesti aktiivisimpia. Kirjallisuusosassa esitellään ensin lyhyesti anomeerinen efekti, minkä jälkeen esitellään pektenotoksiinien AB-spiroketaalifragmentille aikaisemmin julkaistut synteesit. Lopuksi esitellään lyhyesti muita epäanomeerisen spiroketaaliyksikön omaavia luonnonaineita sekä niiden uusimpia synteesimenetelmiä.

Tässä työssä oli tavoitteena kehittää synteesi PTX2:en ABCDE-rengasfragmentille. Rengasfragmentit A, C sekä DE syntetisoitiin erikseen ja sitten kytkettiin yhteen. A-rengaslaktonia käytettiin myös pektenotoksiinien AB-rengasrakenteen syntetisoinnissa. Näissä tutkimuksissa kehitimme kineettiset spiroketalisointiolosuhteet, joilla pystyttiin muodostamaan ensimmäistä kertaa haluttua epäanomeerista AB-spiroketaali-isomeeria päätuotteena. C-renkaalle kehitimme tehokkaan synteesimenetelmän, jolla saatiin muodostettua yhdeksässä reaktiovaiheessa haluttua avain rakenneyksikköä oikealle stereokemialla ja erinomaisella 46 %:n kokonaissaannolla. C-rengasaldehydi kytkettiin erittäin stereoselektiivisesti DE-rengasfragmentin kanssa käyttäen Mukaiyama aldolireaktiota. CDE-rengasfragmentti kytkettiin edelleen A-rengasfragmentin kanssa käyttäen ristimetateesia. Viimeisenä reaktiovaiheena kineettinen spiroketalisointi muodosti 3:1 seoksen epäanomeerista ja anomeerista spiroketaalia. Ikäväksemme havaitsimme, että näin saadussa ABCDE-rengastuotteessa oli väärä stereokemia hiilessä C10. Tutkimukset tämän stereokeskuksen invertoimiseksi ovat meneillään, mikä lopulta mahdollistaisi luonnollisen PTX2:en ABCDE-rengasfragmentin synteesin.

Asiasanat pektenotoksiini, kokonaissynteesi, spiroketaali, epäanomeerinen, anomeerinen	
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– There is no obstacle too difficult to overcome in your life,
as long as you know what you want. –

Espoo, September 2009
Jatta Aho

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ABBREVIATIONS AND DEFINITIONS

Ac	acetyl
AcOH	acetic acid
AD	asymmetric dihydroxylation
AE	asymmetric epoxidation
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
br	broad
Bu	butyl
*t*Bu	*tert*-butyl
Bz	benzoyl
calcd	calculated
CAN	cerium(IV) ammonium nitrate
cat.	catalytic amount
CB	catecholborane
m-CPBA	*meta*-chloroperbenzoic acid
CSA	camphorsulfonic acid
CTX	ciguatoxin
D.	*Dinophysis*
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DET	diethyl tartrate
$(DHQ)_2AQN$	hydroquinine anthraquinone-1,4-diyl diether
$(DHQ)_2PYR$	dihydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
$(DHQD)_2PYR$	dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether
DIBAL-H	diisobutyl aluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DSP	diarrhetic shellfish poisoning

DTX	dinophysistoxin
ee	enantiomeric excess
EE	ethoxyethyl
equiv	equivalent
E_{rel}	relative energy
Et	ethyl
h	hour(s)
i.p.	intraperitoneal injection
imid.	imidazole
inv	inversion
KHMDS	potassium hexamethyldisilazane
LD_{50}	lethal dose, 50% (is the dose that kills half of the animals tested)
LDA	lithium diisopropylamide
LiDBB	lithium di-*tert*-butylbiphenylide
lut.	2,6-lutidine
m	*meta*
Me	methyl
min	minute(s)
Ms	methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
NMP	*N*-methyl-2-pyrrolidone
Nu	nucleophile
OA	okadaic acid
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
PIFA	phenyliodonium bis(trifluoroacetate)
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
*i*Pr	iso-propyl
PTX	pectenotoxin
PTXsa	pectenotoxin seco acid
pyr	pyridine
R	arbitrary substituent
ret	retention
rt	room temperature
sat.	saturated
SM	starting material

TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
thexyl	1,1,2-trimethylpropyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TS	transition state
p-TSOH	*para*-toluenesulfonic acid
YTX	yessotoxins

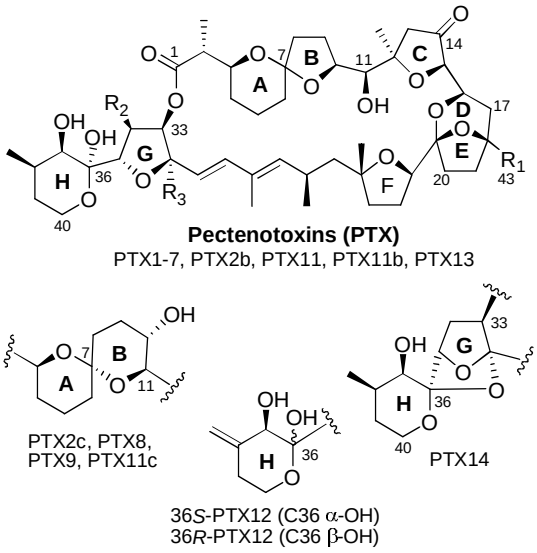
AUTHOR'S CONTRIBUTION

The author designed and carried out the experiments and analyses and interpreted the results that are presented in this work. This work is also written by the author.

1 PECTENOTOXINS

1.1 Isolation and Structure

In 1985, the Yasumoto group reported the isolation and characterization of a family of polyether macrolactones, the pectenotoxins (PTXs).[1] The pectenotoxin family has since grown to comprise over 20 structurally related compounds (Figure 1, Figure 2). Originally isolated from scallops (*Patinopecten yessoensis*),[1a] the actual producers of PTXs are *Dinophysis* dinoflagellates, found in coastal areas worldwide.[2]

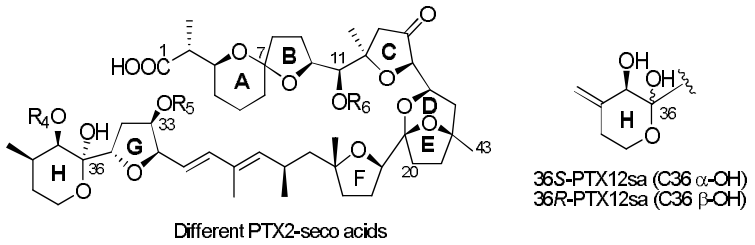


	R_1	R_2	R_3	C7
PTX1	CH_2OH	H	H	*R*
PTX2	CH_3	H	H	*R*
PTX2b	CH_3	H	H	*S*
PTX2c	CH_3	H	H	*S*
PTX3	CHO	H	H	*R*
PTX4	CH_2OH	H	H	*S*
PTX5	Structures not determined			
PTX6	COOH	H	H	*R*
PTX7	COOH	H	H	*S*
PTX8	CH_2OH	H	H	*S*
PTX9	COOH	H	H	*S*
PTX10	Structures not determined			
PTX11	CH_3	OH	H	*R*
PTX11b	CH_3	OH	H	*S*
PTX11c	CH_3	OH	H	*S*
36*S*-PTX12	CH_3	H	H	*R*
36*R*-PTX12	CH_3	H	H	*R*
PTX13	CH_3	H	OH	*R*
PTX14	CH_3	H	-	*R*

Figure 1. Structures of pectenotoxins. White: biosynthesis products, grey: produced by metabolism of shellfish, red: artificial products formed by acid catalysis.

The complex structure of the PTXs consist of a closed macrolactone containing a spiroketal ring unit, three differently substituted tetrahydrofurans, a bicyclic acetal ring system, a cyclic hemiketal and two sites of unsaturation in the form of

carbon-carbon double bonds. The PTXs carry a total of 19-20 stereocenters of which 7 are quaternary and several prone to epimerization under acidic conditions. The main structural differences between the PTXs are the oxidation state of C43 and the configuration of the C7 spiroketal center. More recently, open-chained analogues, PTX seco acids (PTXsa),[3] and analogues containing variations at the GH ring system have also been isolated and characterized (Figure 1, Figure 2). A series of fatty acid esters of PTX2sa has been identified, which are similar to those reported to exist for example brevetoxins.[3b-d]



	R_4	R_5	R_6	C7
PTX2sa and 7-epi-PTX2sa	H	H	H	*R* and *S*
37-O-Acyl PTX2sa	Fatty acid ester	H	H	*R* and *S*
33-O-Acyl PTX2sa	H	Fatty acid ester	H	*R* and *S*
11-O-Acyl PTX2sa	H	H	Fatty acid ester	*R* and *S*
PTX11sa	CH_3	OH	H	*R* and *S*
36*S*-PTX12sa	CH_3	H	H	*R* and *S*
36*R*-PTX12sa	CH_3	H	H	*R* and *S*

Figure 2. Structures of pectenotoxin seco acids. All of them are produced by metabolism of shellfish.

The most commonly found PTX in algae is PTX2, which is reported to be produced by many different dinoflagellate species of the genera *Dinophysis* and found in various parts of the world.[4] Initially PTX2 was detected in *D. fortii*,[5] and later also in *D. acuta*,[6] *D. acuminata*,[5e,7] *D. caudata*,[8] *D. rotundata*,[6b] *D. norgevica*[5e, 7b] and *D. infundibulus*.[5e] Other PTX derivatives, such as PTX11,[6b, 9] PTX12,[7b] and PTX13[10] have also been identified from samples of *Dinophysis*. It is generally accepted that PTX2 is the parent compound, and a product of a natural biosynthesis.[11] In addition, PTX11, PTX12 and PTX13 are also considered to be biosynthetically derived, where as the remaining PTXs are either produced by metabolism in shellfish or are artifacts of the extraction process and have not been

isolated from natural sources[1b, 12] (see Figure 1 and Figure 2). However, the factors controlling the biosynthesis and accumulation of PTXs in shellfish appear to be more complicated than suggested thus far. Miles et al. have detected presumed C43 oxidized analogues of PTX2 in *D. acuta* sample from New-Zealand.[10] Also, PTX2b,[6a] PTX14[10] and PTX2sas[8b, 13] together with other PTXs[14] have been identified in algae as minor compounds. These however, are most likely just chemically converted from PTX2 and PTX13 during extraction and storage. It has been proposed that enzymes released from disturbed cells during the extraction process could account for these transformations.[6a, 7b] PTX1 has been identified as the major component in *D. acuminata* sample harvested in the western North Sea.[15] Even if quite a strong evidence was presented that PTX1 is at least partially, if not entirely, of biosynthetic origin, the writers could not entirely rule out the possibility that metabolic activity of heterotrophic organisms could effect the transformation of PTX2 to PTX1 in algae.

When digested by shellfish, PTX2 can metabolize to other PTX derivatives. Enzymatic hydrolysis to an open-chained derivative PTX2 seco acid occurs in most shellfish species (Figure 2).[3a-b, 16] Similar transformation takes place also with PTX11 and PTX12,[5d, 6c] however, they appear to be much more resistant to hydrolysis and thus these compounds accumulate in shellfish to a greater extent than does PTX2.[7b, 9a] PTX11 is at least two orders of magnitude more resistant to hydrolysis than PTX2 by the enzymes of mussels, probably due to steric hindrance induced by the C34-OH and hydrogen bonding between C34-OH and the carbonyl oxygen.[9a]

Enzyme-mediated oxidation at C43 methyl group gives C43-hydroxy (PTX1), aldehyde (PTX3) and carboxylic acid (PTX6) derivatives (Figure 1).[4a, 4c, 12a] These oxidized PTXs, together with PTX4 and PTX7, have been observed to accumulate especially in the Japanese scallops, *Patinopecten yessoensis*.[12, 17] The reason why these oxidized derivatives are rarely detected elsewhere might be that in other shellfish the conversion of PTX2 to PTX2sa is very rapid.[18] This is supported by

the fact that often PTX2 is the most abundant toxin in *Dinophysis*, whereas in shellfish, PTX2sas predominate with only traces of PTX2.[5d, 19]

Another important transformation occurring in shellfish is epimerization of the C7 spiroketal center.[6c, 12b] Most of the PTXs isolated from natural sources contain a nonanomeric [6,5]-spiroketal ring system with *R* configuration, which easily epimerizes into a thermodynamically more stable anomeric spiroketal with *S* configuration (Figure 3). It is still unclear whether this transformation is mediated by a shellfish-derived enzyme or random acid catalysis. Miles et al. reported that PTX2sa and 7-epi-PTX2sa were found in shellfish in ratios that probably depend on the time since exposure of the shellfish to the algae, the shellfish species and the procedures used for extraction, treatment and storage of the sample.[20] However, this may not be the case with PTX4 and PTX7 as the formation of C7 spiroketal epimers appears to occur much more rapidly with seco acids than with the corresponding lactones. It has been proposed that the carboxylic acid group in the seco acids could intramolecularly catalyze the epimerization of the spiroketal center.[7b] The acid-catalyzed equilibrium between the anomeric and the nonanomeric PTX congeners is discussed in more detail in Chapter 2.2.

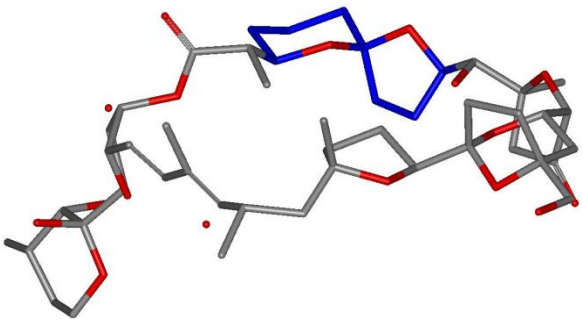


Figure 3. Crystal structure of PTX1 (CCDC: DIKHEK). The structure is enantiomeric to that of natural pectenotoxin. The nonanomeric spiroketal with *R* configuration is highlighted in blue.[1a]

Despite increasing research during the past few years, very little is known about the dynamics of the toxin production by the dinoflagellate cells. The toxin content of a same dinoflagellate species has been reported to vary during the investigation

period even within specimens collected in the same locality.[7a,b] However, it has also been reported that the toxin profiles of the same species in the same locality stays very stable and the toxin content remains in narrow limits.[21] Usually PTXs coexist with other toxins, such as okadaic acid (OA) and dinophysistoxins (DTXs).[4] Blanco et al. reported that no trace of these other toxins was found in *D. acuminata* samples, where the cellular content of PTX2 was exceptionally high.[7c] In other cases, however, *D. acuminata* specimens appear to contain only very small amounts of any of the pectenotoxins.[5d] Until very recently, there was no proof that PTXs are produced by *Dinophysis* dinoflagellates, because the *Dinophysis* species had not been successfully cultured.[22] Recent results by Suzuki and Kamiyama strongly suggest that *D. acuminata* can produce PTXs in laboratory cultures.[23] However, they did not completely deny the possibility that bacteria or prey organisms may be responsible for some roles in the production of these toxins. The PTX2 content in the field *D. acuminata* was 1.5 times higher than in the *D. acuminata* from laboratory culture. This implies that environmental conditions are at least one of the reasons for variable cellular toxicities in *Dinophysis* species.

1.2 Activity

The consumption of shellfish contaminated with toxins, produced by a number of naturally occurring phytoplankton species, can lead to human illness of different nature and severity depending on the toxin class. Pectenotoxins were initially classified and regulated along with the other diarrhetic shellfish poisoning (DSP) group of toxins, including okadaic acid (OA), dinophysistoxins (DTXs) and yessotoxins (YTXs), because of their co-occurrence and biological origin.[2b] Recently, it has been agreed that marine biotoxins are classified based on chemical structure, as opposed to classification based on clinical symptoms.[24] Due to potential threat to human health from consumption of contaminated shellfish and the economic impacts brought by human intoxication incidents, many countries have developed monitoring and regulatory systems.[2b] For

example, the European Union requires monitoring of shellfish for these toxins, including PTX1 and PTX2.[25]

The inclusion of PTXs in the DSP group was long under debate, until recent studies with different PTXs failed to show any signs of diarrhetic activity even with high doses (5 mg/kg).[6c, 9a] Quite recently, PTX2 seco acids were suggested to be responsible for outbreaks of severe diarrhetic illness in Australia.[2b] However, later studies reveled that neither PTX2sa nor 7-epi-PTX2sa cause diarrhea.[6c, 26] Most likely the samples were contaminated with okadaic acid esters, as the presence of even small amounts of these toxins might be sufficient to account for the observed effects.[27]

Even though PTX2 is of very low toxicity by the oral route, it is highly toxic by intraperitoneal injection.[2b, 6c, 12a] LD_{50} toxicities have been determined for some of the PTXs, showing that the most toxic congeners are PTX1, PTX2 and PTX11 (Table 1). PTX2sa and 7-epi-PTX2sa are of low toxicity both orally and intraperitoneally.[3a, 20] This indicates that the closed macrocyclic structure is required for cytotoxicity and thus hydrolytic cleavage of the macrolactone of PTX2 to PTX2sa may be protective for detoxification in shellfish.

Also, oxidation of C43 and epimerization of C7 spirocenter appear to be a result of a detoxification process. Oxidation of PTX2 to PTX1, then to PTX3 and finally to PTX6 is accompanied by a toxicity decrease in a mouse bioassay.[12] Not surprisingly, the 7*S* epimer PTX4 was much less toxic than the 7*R* epimer PTX1 and the toxicities of the [6,6]-spiroketal containing members, PTX8 and PTX9, were further diminished.[12] However, oxidation at C34 does not seem to change intraperitoneal toxicity, as PTX11 has nearly the same LD_{50} toxicity as PTX2 and has been reported to produce the same symptom of intoxication in mice as PTX2.[9a]

The protective detoxification systems in fish and shellfish have been postulated to be effected by a specific enzyme or a toxin-binding protein.[28] It has also been

suggested that the algae are themselves subject to the toxicity and have their own metabolising enzymes to combat and detoxify different toxins.[2b]

Table 1. Toxicity concentrations for various PTXs in mice.

Toxin	LD_{50} [μg/kg] (i.p.)	Reference
PTX1	250	12a
PTX2	216-260	12a, 6c
PTX3	350	12a
PTX4	770	12a
PTX6	500	12a, 29
PTX7-8	>5000	12b
PTX11	244	9a
PTX2sa	>5000	3a, 20
7-epi-PTX2sa	>5000	3a, 20

Terao et al. were the first to demonstrate that an intraperitoneal injection of PTXs into mice produces high hepatotoxicity as the principal symptom.[30] This was supported by subsequent studies, indicating that liver seems to be the target organ of PTXs.[31] Also Fladmark et al. observed hepatocyte death in freshly isolated rat and salmon hepatocytes, however in this study PTX1 induced apoptosis rather than necrosis.[32]

PTX2 has found to be potently cytotoxic against a variety of lung, colon, and breast cancer cell lines.[2b, 33] Research in marine natural products has revealed that toxic mechanisms and anticancer effects of many compounds involves modification of the actin cytoskeleton.[34] Actin is one of the most abundant and common cytoskeletal proteins for cell growth, motility, signaling, and maintenance of cell shape.[35] It has been shown that the actin cytoskeleton is also the principal molecular target of the PTXs. Spector et al. demonstrated that PTX2 disrupts the organization of actin in several cell types by G-actin monomer sequestration.[34] Also, PTX6-induced disruption of F-actin cytoskeleton was observer, although at higher doses than those reported for PTX2. [36, 37] More recent data showed that also PTX11 triggered a remarkable depolymerizing effect on actin cytoskeleton and modifications in the shape of cells.[38] In contrast, PTX2sa

did not evidence the same effects on F-actin and the depolymerizing activity of PTX1 was about half that of PTX2.[38] These results indicate that the diminished ability to disrupt F-actin is again related to structural changes in C43 oxidation state and that the macrolactone ring is essential for the action of PTXs on actin cytoskeletal dynamics. Again, it seems that oxidation at C34 does not affect the potency of PTXs.

Most recent studies on the mechanism of action at a molecular level have shown that PTX2 does not induce severing of F-actin but that it very efficiently inhibits actin polymerization by capping the fast-growing barber-end.[39] However, based on the previous studies, G-actin sequestering effect cannot be ruled out as another possible mode of action. Kim et al. have investigated PTX2-induced anticancer mechanism in human leukemia cells and found that PTX2 inhibited the growth of leukemia cells and caused a marked increase in apoptosis.[40] Chae et al.[41] and Botane et al.[42] independently discovered a higher sensitivity of cancerous cells to PTXs compared to normal cells, which could be of great clinical importance for the development of new cancer chemotherapy agents.

However, further studies are still needed, because much of the toxicological effects, the mechanism of action and also the potential impacts the PTXs may have on public health in the long term are not yet fully understood. This is where the total synthesis comes into play, aiming to provide access to higher quantities of material than would ever be available from the marine sources. Further, in order to obtain reliable results, the purity of PTXs isolated from the natural sources may at times not be sufficient enough, especially due to potential contamination with the DSP toxins.

2 NONANOMERIC SPIROKETALS IN NATURAL PRODUCTS

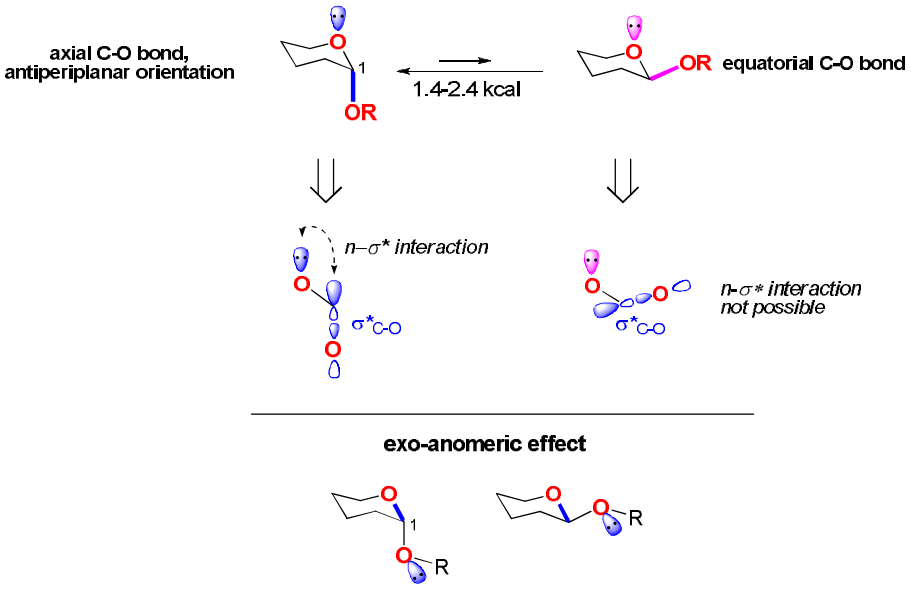
The majority of the naturally occurring spiroketal systems appear to be in the thermodynamically most stable anomeric configuration. There are, however, a number of naturally occurring spiroketal systems that contain the more unstable and less easily accessible nonanomeric configuration. These nonanomeric spiroketal systems have been found in natural products from a wide variety of sources: insect pheromones, different kinds of polyketide antibiotics and in marine toxins. Due to their fragile nature, nonanomeric spiroketals have often been the stumbling blocks of natural product syntheses, requiring a lot of work and determination before a successful synthesis has been achieved.[43]

The fact that PTXs contain this challenging and intriguing nonanomeric spiroketal system is one of the major reasons why we became interested in the PTXs. We have recently published a thorough review covering nonanomeric spiroketals in natural products and the synthetic strategies used to access these structures.[43] In this chapter, a short discussion of the anomeric effect is first presented. In the following section, the previously published syntheses of the AB spiroketal ring system of the PTXs are discussed. Finally, the most recent results with the syntheses of [6,5]-nonanomeric spiroketals in other natural products are presented.[44]

2.1 Anomeric Effect

The term anomeric effect[45] describes the tendency of an electronegative substituent at the anomeric center C1 of a pyranose ring to prefer axial rather than equatorial orientation despite unfavorable steric interactions. The anomeric effect

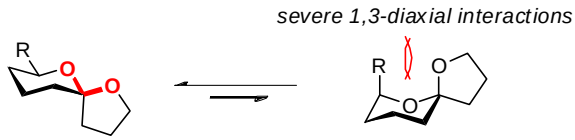
is believed to arise from a stabilizing interaction between one of the lone pairs on the endocyclic oxygen and the antibonding σ*-orbital of the exocyclic C-O bond. For the overlap to be efficient, the lone pair on the oxygen has to be antiperiplanar to the C-O bond (Scheme 1).[46] The contribution of anomeric stabilization to the total energy has been estimated to be in the range of 1.4-2.4 kcal/mol per interaction.[47] The lone pair of the exocyclic oxygen can also exert similar effects to the antibonding orbital of the bond between the anomeric carbon (C1) and the ring oxygen. This is called the exo-anomeric effect, where also the conformation of the substituent must be such that a lone pair orbital is antiperiplanar to the antibonding orbital in the pyranose ring (Scheme 1).[48] The exo-anomeric effect can also be stabilizing with equatorial substituents, and is also stronger with equatorial than with axial substituents.[49]



Scheme 1. Molecular orbital model for the anomeric effect.

The anomeric-nonanomeric configurational dichotomy becomes meaningful only if there is a clear difference between the anomeric and the nonanomeric substituent. The clearest case is the six-membered ring, where the difference between axial and equatorial substituents is clear-cut. Given the rapid pseudorotation in five-membered ring systems,[50] nonanomeric relationships cannot be stabilized in five-membered rings. It is, however, reasonable to assume

that suitably substituted seven-membered rings or larger ring systems might display the anomeric-nonanomeric dichotomy. In addition, conformational locking by ring fusion or suitable placed equatorial substituent on the six-membered ring is required to prevent access to the anomeric configuration by simple ring flipping. Not surprisingly, nearly all nonanomeric spiroketals, including the PTXs, bear an alkyl substituent in the 6-position of the tetrahydropyran ring, which prevents ring flipping due to unfavorable 1,3-diaxial interactions (Scheme 2).



Scheme 2. Unfavorable 1,3-diaxial interactions.

In addition to the anomeric effect, steric interactions, intramolecular hydrogen bonding and other effects influence the conformation of a spiroketal.[51] In natural products, the nonanomeric configuration may be stabilized by these additional factors, which override the thermodynamic preference for the anomeric configuration. In addition, the constraints imposed by the macrocyclic structures may favor the nonanomeric configuration. As such, for the anomeric stabilization to effect the conformation at all, it must be more stabilizing than the sum of all these other factors.

In many syntheses of nonanomeric spiroketal ring systems, acid-catalyzed spiroketalization, typically accompanied with the release of acid-labile protecting groups has been used.[43] The downside of this approach is that a thermodynamic mixture of the spiroketal isomers is formed, favoring in most situations the thermodynamically more stable anomeric configuration. The key thermodynamic question is how to stabilize the nonanomeric structure and thus favor it in the equilibrium? Quite a few synthetic approaches have built upon the utilization of solvent effects, intramolecular hydrogen bonding or related chelation effects using different metal salts. However, most of these examples are case specific and the

selectivities are only moderate in many instances.[43] Better selectivities can be obtained if the spiroketalization can be carried out under kinetic control, an approach that we have used successfully.[52] The acid-catalyzed kinetic spiroketalization is a relatively mild method, giving it an advantage in complex settings with many functionalities. Also, the generation of nonanomeric spiroketals under mild acid catalysis may be sufficient to explain the formation of nonanomeric spiroketals in nature. It has been reported that the biogenesis pathway of certain spiroketals involves hemiketal-type precursors.[53] In an alternative approach, the acid-catalyzed spiroketalization can be avoided altogether.[43] Recently, Rychnovsky has disclosed a general and practical method for a kinetic formation of nonanomeric spiroketals using reductive cyclization.[54]

2.2 Nonanomeric [6,5]-Spiroketal Ring of Pectenotoxins

The spiroketal unit of the PTXs has been observed to undergo isomerization under acid catalysis.[12b] Upon treatment with trifluoroacetic acid, the nonanomeric PTX6 isomerized into an equilibrium mixture of the anomeric isomer PTX7, PTX6, and a third isomer PTX9. In PTX9, the [6,5]-spiroketal unit is expanded into a [6,6]-spiroketal system, having the thermodynamically most stable doubly anomeric configuration (Figure 4). The proportions of different isomers after equilibration were 40:16:44 (PTX6:PTX7:PTX9). A slightly different equilibrium mixture was obtained with PTX1, giving a mixture of PTX1, PTX4 and PTX8 in a ratio of 29:14:57.[12b] More recently, Suzuki et al. reported very similar equilibration ratios with PTX1 (PTX1:PTX4:PTX8, 26:16:58) and PTX6 (PTX6:PTX7:PTX9, 48:14:38).[6b] Also PTX2 was observed to undergo isomerization giving a 29:15:59 equilibration mixture of PTX2, PTX2b and PTX2c, comparable to that for PTX1, PTX4 and PTX8.[6b] Interestingly, the Evans group reported that they had obtained an equilibration ratio of 11:10:79 with PTX1:PTX4:PTX8, starting from synthetic PTX4. Apparently, the macrocyclic structure helps in stabilizing the nonanomeric structure enough that it is still detectable after equilibration. However, both Yasumoto and Evans report that they only isolated PTX8 from the equilibrium mixture of PTX1:PTX4:PTX8.[12b, 55b]

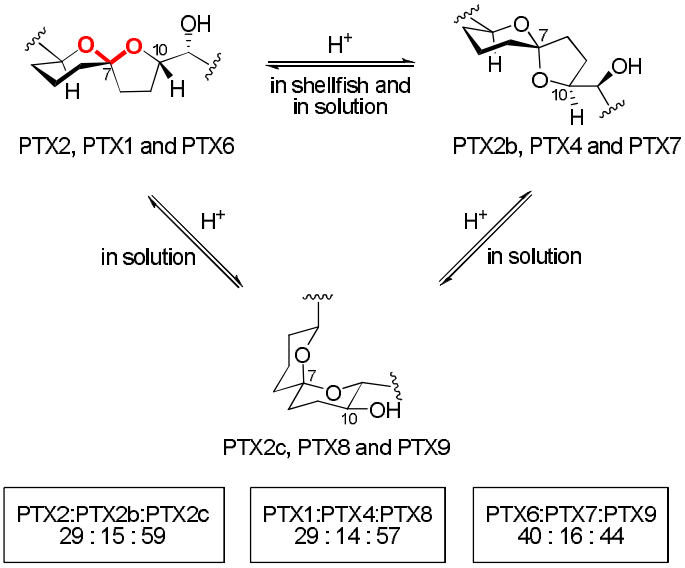


Figure 4. Acid-catalyzed equilibration.

2.3 Previous Syntheses of AB Spiroketal Ring Fragment of PTXs

The exquisitely complex structure of the PTXs presents a considerable challenge for a synthetic chemist. By virtue of the structural complexity, natural scarcity and biological activity, many groups have chosen PTXs as their synthetic target. Despite the growing amount of research during the past decade, the first total synthesis by Evans and co-workers in 2002 still remains the only one.[55] However, the next total syntheses are most likely just around the corner, as several groups, including Brimble,[56] Paquette,[57] and Murai and Fujiwara[58] have already most of the carbon backbone completed, lacking connection and the final finishing touch.

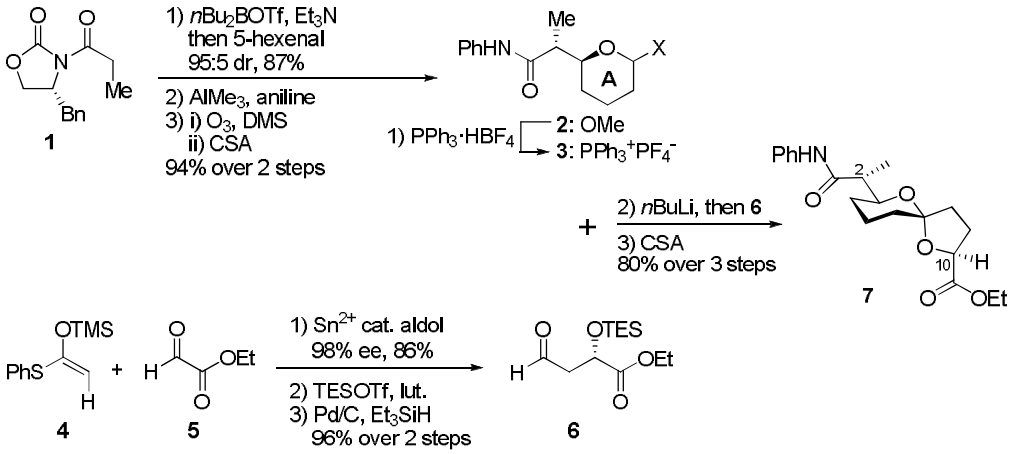
The AB spiroketal ring system is one of the most studied targets of the PTXs. Especially during the past few years the spiroketal fragment has attracted more and more attention, resulting new fresh ideas and excellent syntheses. However, even though the nonanomeric PTX congeners appear to be the most cytotoxic and most biologically active, not to mention the extreme synthetic challenge provided by the thermodynamically less stable nonanomeric spiroketal, they have not attracted the attention they would deserve. Instead, most of the synthetic approaches have targeted PTXs with anomeric spiroketals. However, many

groups have envisaged that the corresponding PTXs with nonanomeric spiroketal configuration could be formed under equilibrium conditions in later stages of the synthesis, taking advantage of the constraints imposed by the macrocyclic ring.

The synthetic studies towards pectenotoxins have been recently reviewed by Brimble and Halim.[59] In the following discussion, the most recent advances in the AB spiroketal ring synthesis are presented and discussed in detail. Also, all of the earlier syntheses are shortly introduced to enable comparison.

2.3.1 Synthesis by Evans et al. 2002

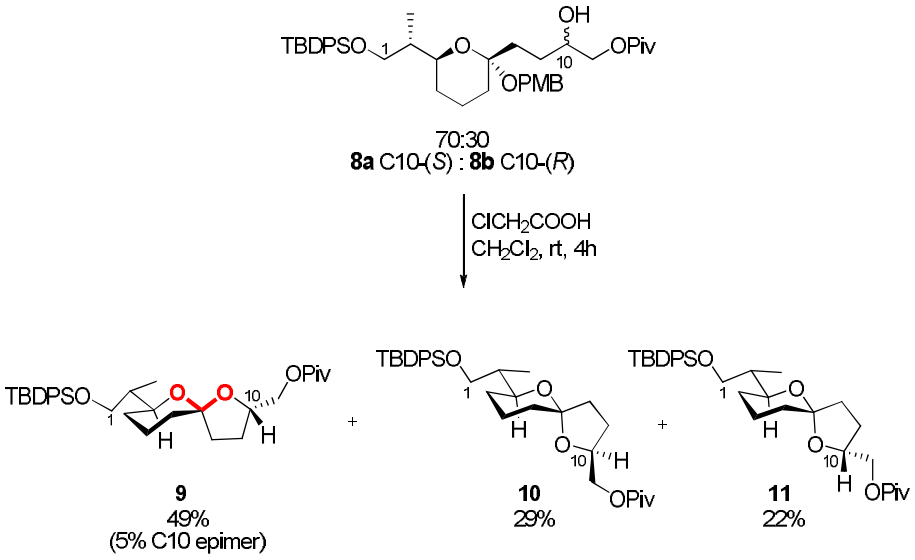
In 2002, Evans group published the first synthesis for the AB spiroketal ring fragment of PTX4, together with the total synthesis.[55] The key steps are boron-mediated oxazolidinone aldol reaction to form the C2-C3 *syn* stereochemistry and tin-catalyzed aldol reaction to form the C10 stereocenter (Scheme 3). Wittig reaction was applied to connect aldehyde **6** and the A ring phosphonium salt **3**. For the removal of the TES protection, camphor sulfonic acid was used which also effected cyclization of the ketal precursor to give the anomeric spiroketal product **7**. This synthesis is quite an amazing achievement in the sense that incomparable 54% total yield was achieved over the 9 synthetic steps.



Scheme 3. Synthesis of the AB spiroketal fragment of PTX4 by Evans et al.[55a]

2.3.2 Synthesis by Pihko and Aho 2004

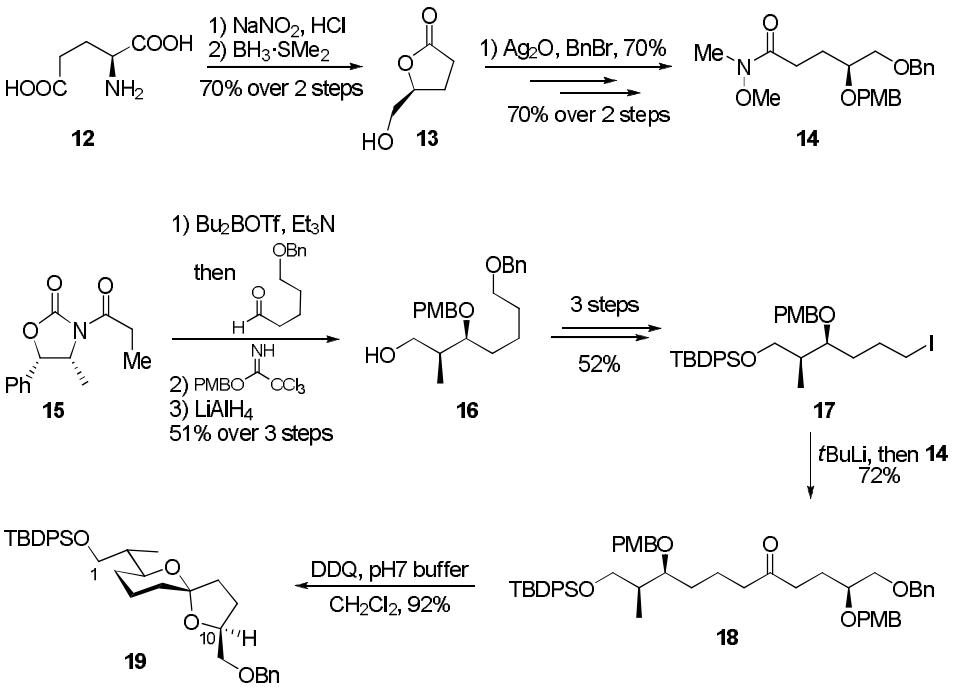
In our synthesis for the AB spiroketal ring fragment of PTX2 kinetic spiroketalization conditions were developed (Scheme 4).[52] After screening different acids to effect the spiroketalization of a PMB ketal precursor **8**, chloroacetic acid was found to be the best, delivering the desired nonanomeric spiroketal isomer **9** as the major product in 49% yield. Our synthesis of the AB spiroketal ring fragment is fully presented in Chapter 3.3.



Scheme 4. Synthesis of the AB spiroketal fragment of PTX2 by Pihko and Aho.[52]

2.3.3 Synthesis by Paquette et al. 2005

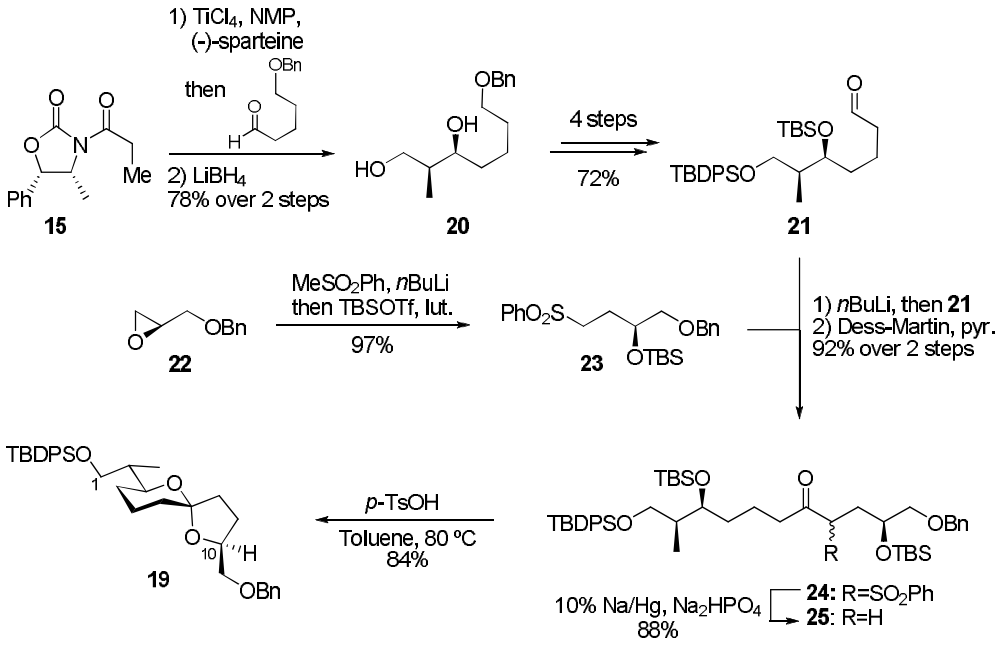
Paquette group also used a boron-mediated oxazolidinone aldol to form the desired C2-C3 *syn* product in stereoselective manner (Scheme 5).[57c] The B ring side of the carbon chain was synthesized starting from L-glutamic acid **12** in five steps. Connection of an organolithium species of **17** and Weinreb amine **14**, furnished ketone **18**, which under the conditions used for removal of the PMB protection groups (DDQ, pH7 buffer) cyclized to give the anomeric spiroketal **19** in 92% yield.



Scheme 5. Synthesis of the AB spiroketal fragment of PTX2b by Paquette et al.[57c]

2.3.4 Synthesis by Brimble et al. 2006

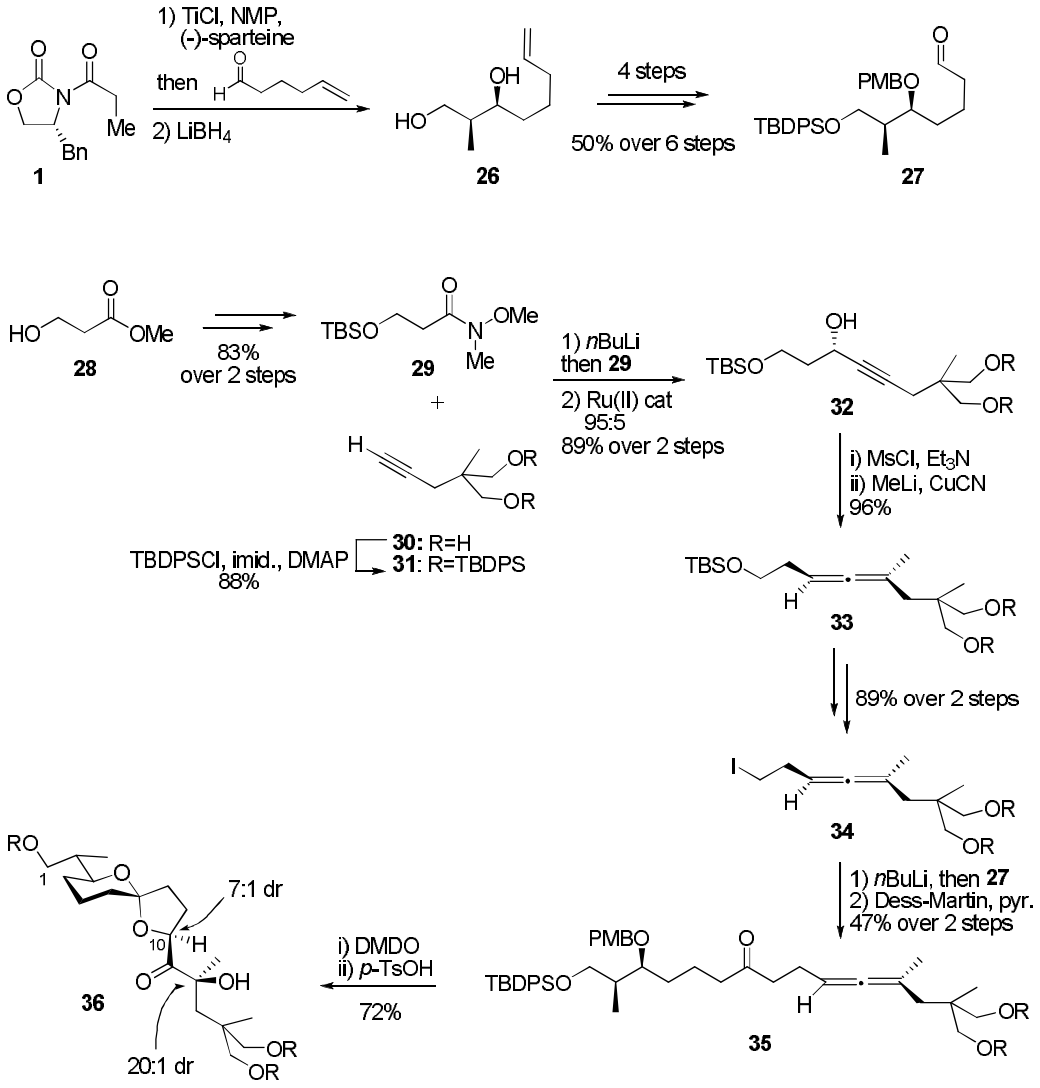
In a similar manner, Brimble group applied oxazolidinone aldol for the construction of the C2-C3 *syn* stereochemistry (Scheme 6).[56b, c] This time the C8-C7 connection was constructed using Julia olefination between the anion of sulfone **23** and aldehyde **21**. After oxidation and reductive elimination of the sulfone, *p*-toluenesulfonic acid induced the removal of the TBS protections and ring closure to give the anomeric spiroketal product **19** in 85% yield.



Scheme 6. Synthesis of the AB spiroketal fragment of PTX7 by Brimble et al.[56b, c]

2.3.5 Synthesis by Williams et al. 2007

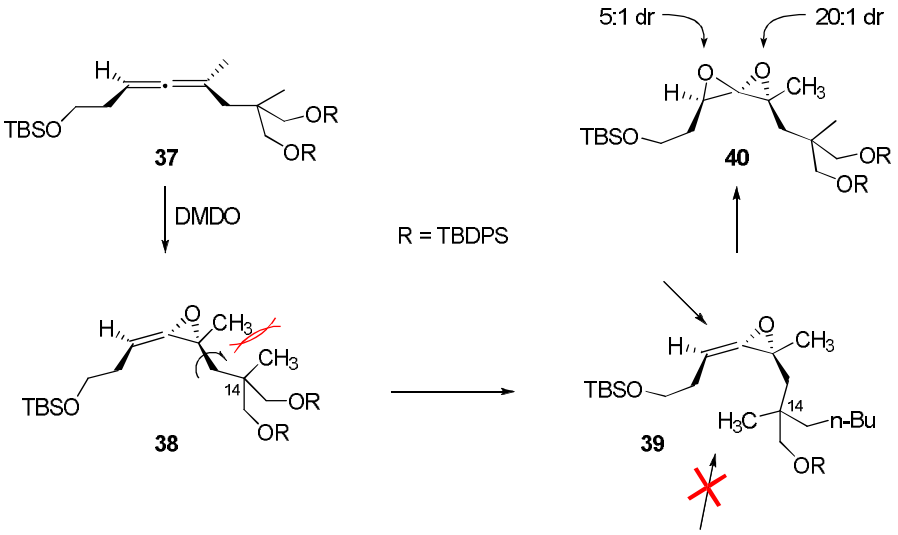
In comparison to the previous syntheses, Williams group developed quite a different approach to synthesize the AB spiroketal ring fragment of PTX4.[60] In their synthesis, also the C12 quaternary center is selectively formed by using an intramolecular spirodiepoxide cyclization as the key step (Scheme 7). The C2-C3 *syn* stereochemistry of the A ring building block was once again formed by utilizing the ever so popular oxazolidinone aldol reaction. The other building block was synthesized from a Weinreb amide **29** and a TBDPS protected alkyne diol **31** to give propargyl alcohol **32** after enantioselective reduction. Conversion to the corresponding mesylate and then to allene **33** proceeded in excellent 96% yield. Alkylation of aldehyde **27** with the organolithium species derived from **34**, followed by oxidation furnished ketone **35**. Finally, an optimized single flask procedure effected the removal of the PMB protection group, oxidation to form a spirodiepoxide and acid-catalyzed spirodiepoxide opening together with spiroketal ring closure to give the anomeric spiroketal product **36** in 89% yield and 7:1 diastereoselectivity.



Scheme 7. Synthesis of the AB spiroketal fragment of PTX4 by Williams et al.[60]

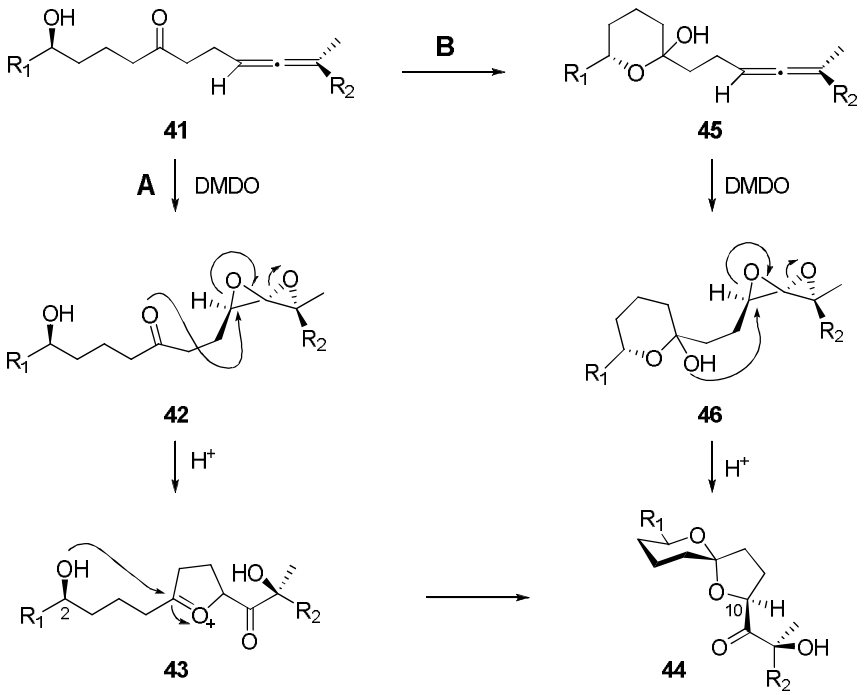
The key allene oxidation was first studied with a model compound **37** to show that a mixture of two diastereomeric spirodiepoxides could be formed in >5:1 diastereoselectivity (Scheme 8). The writers propose that the first oxidation takes place on the more highly substituted double bond, giving high diastereoselectivity (20:1) due to unfavourable steric interaction. These *syn*-pentane interactions together with the bulky substituents in C14 were also considered to control the facial selectivity of the second oxidation by enforcing a preference for a top face approach. The increased reactivity of the allene oxide **39** compared to that of an allene **37** was proposed to be the reason for the lower selectivity obtained for the

second oxidation. Fortunately, a slight improvement in the selectivity was obtained with the actual substrate.



Scheme 8. Stereoselectivity of the allene oxidation.

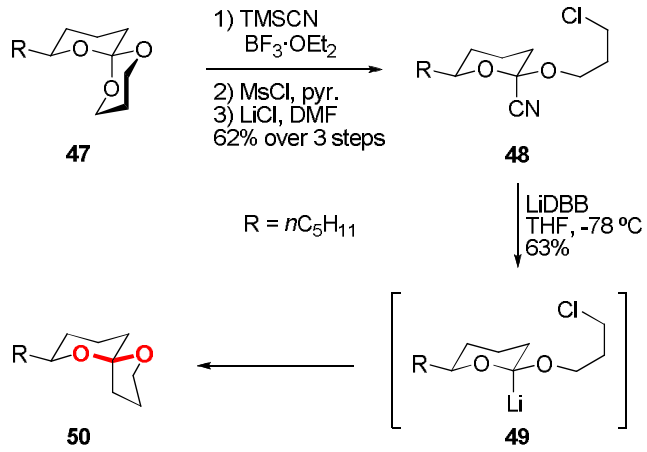
For the spiroketal formation the writers proposed two alternative pathways (Scheme 9). Either A) the ketone attacks the spirodiepoxide, followed by trapping of the formed oxocarbenium ion with the C2 hydroxyl to give spiroketal **44**, or B) a six-membered lactol **45** is formed before the spirodiepoxide, and the lactol hydroxyl then attacks the spirodiepoxide to form spiroketal **44**.



Scheme 9. Two possible pathways for the formation of spiroketals via intramolecular spirodiepoxide cyclization.

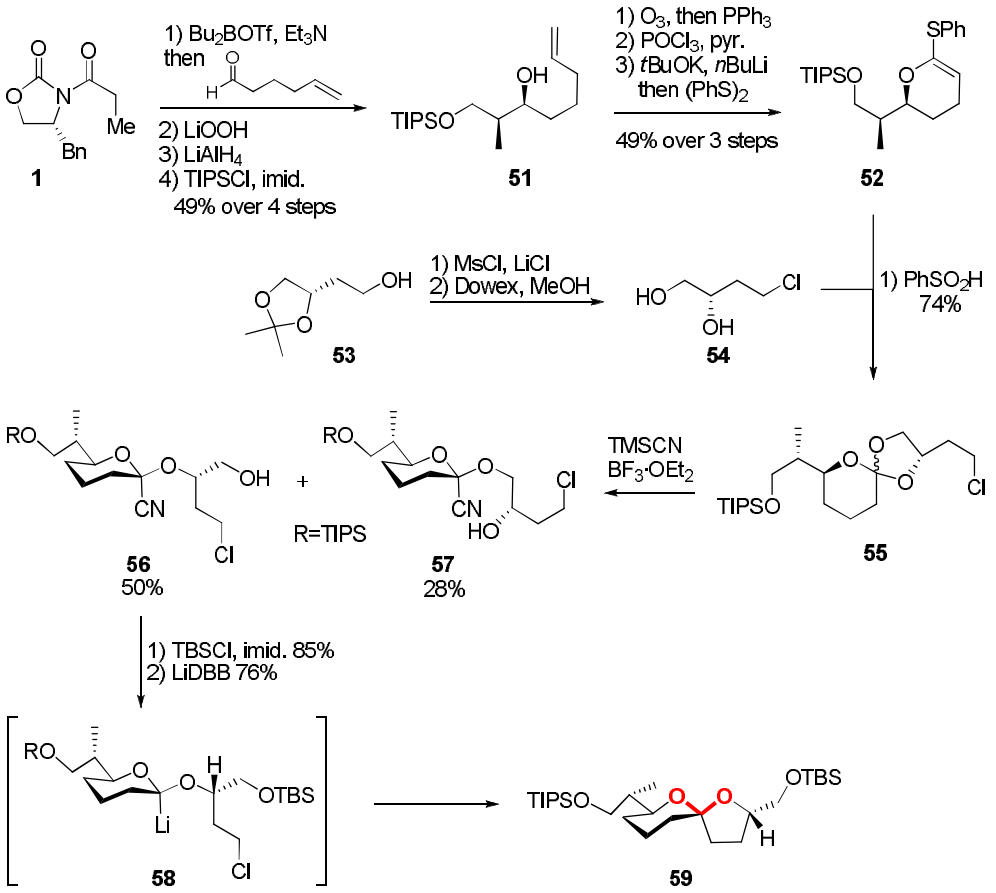
2.3.6 Synthesis by Rychnovsky et al. 2007

Rychnovsky and co-workers have developed a method that constitutes a significant breakthrough in the synthesis of nonanomeric spiroketals. By reversing the usual roles of the nucleophile and the electrophile in spiroketal synthesis, the normal preference for the anomeric isomer is effectively suppressed.[54] A sequence of stereoselective reductive lithiation followed by cyclization, gives different kinds of nonanomeric spiroketal structures, including [6,5]-spiroketals, as single diastereomers (Scheme 10). Upon treatment of the ortho ester-derived axial nitrile **48** with lithium di-*tert*-butylbiphenylide (LiDBB), the resulting lithium species **49** retains its axial configuration. The lithiated acetal can now act as a nucleophile, displacing the primary chloride and generating the nonanomeric spiroketal **50**.



Scheme 10. Synthesis of nonanomeric spiroketals by stereoselective reductive lithiation and cyclization.

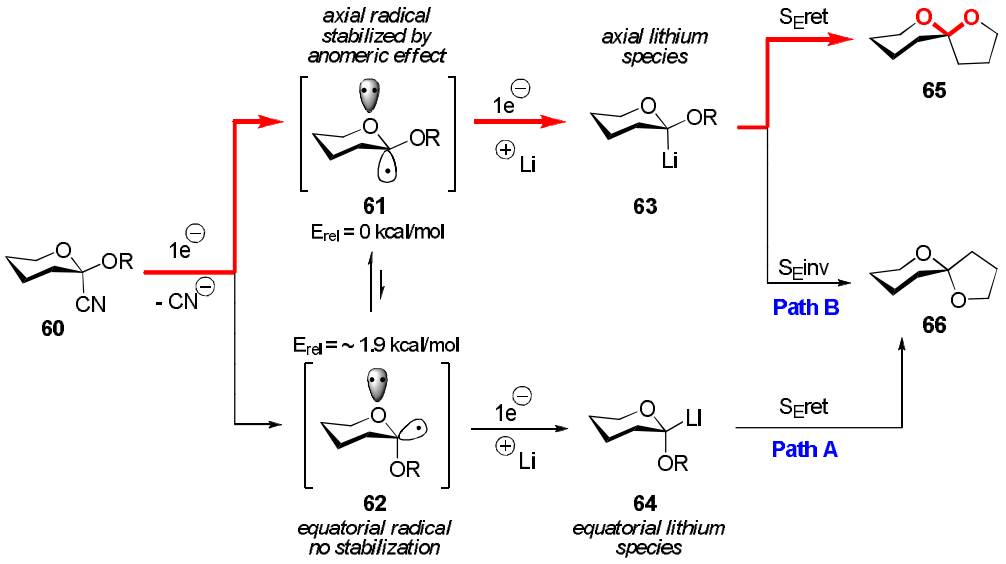
Taking advantages of this methodology, a successful synthesis of the AB spiroketal ring fragment of PTX2 was achieved (Scheme 11).[61] Again, the synthesis began with the well-tried and reliable boron-mediated oxazolidinone aldol reaction. The requisite ortho ester was formed from thio-phenyl dihydropyran **52** and diol **54**, itself derived from a commercially available alcohol **53**. Cleavage of the orthoester with TMSCN and $BF_3{\cdot}OEt_2$ produced two regioisomers, with the preferred isomer **56** formed in 50% yield. In previous cases this cleavage had been very regioselective for the primary group.[54] The lack of selectivity in this case was attributed to the fact that **55** was less sterically hindered than the previously studied intermediates. After TBS protection, the reductive cyclization using freshly prepared LiDBB furnished the nonanomeric spiroketal **59** as a single diastereomer in 76% yield.



Scheme 11. Synthesis of the nonanomeric AB spiroketal fragment of PTX2 by Rychnovsky et al.[61]

Based on recent studies with the synthesis of related spiroketals, Rychnovsky and co-workers proposed a detailed mechanism for the cyclization and provided two different explanations for the origin of the anomeric spiroketals that have occasionally been identified as minor products (Scheme 12).[62] The radical intermediate, generated by single electron transfer and the subsequent C-CN bond fission from **60**, can still undergo inversion of stereochemistry. The preference for the radical to occupy an axial position (**61**) has been calculated to be ~1.9 kcal/mol, apparently as a result of anomeric effect.[63, 62] When the second electron is added in the reduction, the corresponding alkyllithiums **63** and **64** are formed in precisely the same ratio. In an alternative rationalization, the radical can undergo inversion to equatorial configuration **62** giving access to larger amounts of the anomeric isomer **66** (path A).[62, 64] In addition, the anomeric isomer could arise from a cyclization with partial inversion of configuration (path B). However, the

configurational stability of α-oxygenated alkyllithiums is well documented,[65] and thus the inversion pathway B would presumably be far less facile.



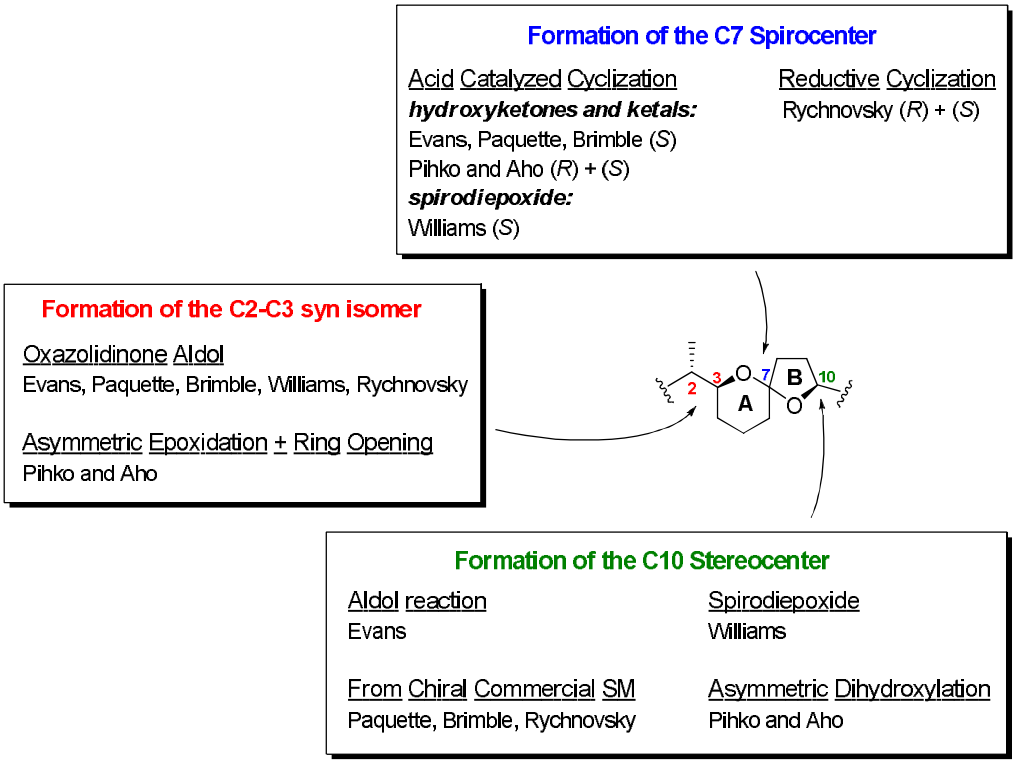
Scheme 12. Mechanism of the reductive cyclization. The preferred route to the nonanomeric spiroketal in red.

2.3.7 Strategies in Comparison

The different methods that have been used to construct the stereocenters in the AB spiroketal ring fragment of PTXs are summarized in Scheme 13. From the six syntheses developed for this fragment, five of them utilize oxazolidinone aldol chemistry to form the C2-C3 *syn* stereochemistry. With new modern methods for asymmetric catalysis breaking ground, the use of chiral auxiliaries is often considered to be old-fashioned and rather inefficient. However, chiral auxiliary-based aldol reactions are still one of the best and most reliable ways to synthesize *syn*-α-methyl-β-hydroxy structures in highly stereoselective fashion.

As expected, an acid-catalyzed cyclization to form the C7 spiroketal center was by far the most popular method of choice. The thermodynamic conditions delivered the anomeric spiroketals in good yields. With the kinetic spiroketalization, the nonanomeric spiroketal could be formed as the major product, although substantial amounts of the anomeric isomer was still formed.

Further research is needed, as the factors controlling the kinetic selectivity towards the nonanomeric isomers are still poorly understood. In terms of selectivity towards the nonanomeric isomer, the reductive cyclization method developed by Rychnovsky et al. stands out from all other protocols. However, in order to avoid epimerization of the extremely fragile nonanomeric spiroketal, it should be formed as one of latest steps of the total synthesis. The acid-catalyzed kinetic spiroketalization is a relatively mild method giving it an advantage with complex substrates, whereas the applicability of the reductive cyclization protocol in such demanding conditions still remains to be seen.



Scheme 13. Comparing different methods used to construct the stereocenters.

2.4 Other Natural Products with a Nonanomeric [6,5]-Spiroketal

The nonanomeric [6,5]-spiroketal is a quite rare structure in natural products compared to the nonanomeric [6,6]-spiroketals. Two of the largest groups containing nonanomeric [6,5]-spiroketals are insect pheromones and ionophore

antibiotics (Figure 5).[43, 66] An extensive selection of naturally occurring spiroketals have been isolated as pheromones from several insect species and the nonanomeric [6,5]-spiroketal systems have been identified as the minor components. However, there are only few synthetic studies addressing these structures[67] whereas the corresponding nonanomeric [6,6]-spiroketals of insect pheromones have attracted more attention and there are multiple synthesis examples.[43]

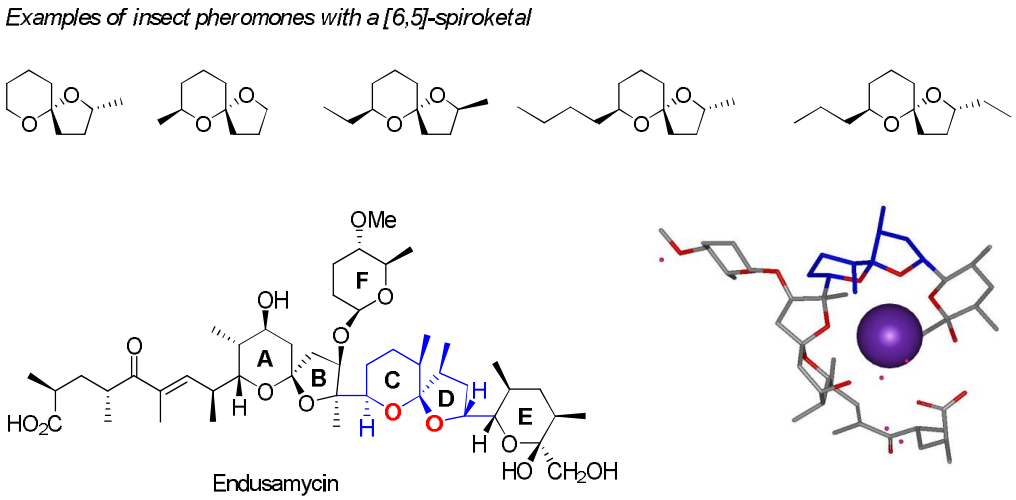


Figure 5. Insect pheromones with [6,5]-spiroketals, endusamycin (CP-63.517) and crystal structure of endusamycin rubidium salt (CCDC: SAWGIG).

A total of 13 members of the dianemycin/endusamycin class of antibiotics have been identified, all having a nonanomeric configuration in the CD spiroketal ring system (Figure 5).[68] However, neither total synthesis of these natural products, nor synthesis for the nonanomeric CD spiroketal ring system has been reported.

Two other natural products bearing a nonanomeric [6,5]-spiroketal have attracted more attention from the synthetic community, namely the ciguatoxins and the aculeatins.

2.4.1 Ciguatoxins

The spiroketal ring system is relatively common structural feature in marine natural products. However, in addition to pectenotoxins, only ciguatoxins (CTXs) have been identified to contain a nonanomeric [6,5]-spiroketal ring unit. Over 20 members of the CTXs have been identified, and four of the CTX congeners have been assigned to contain a nonanomeric LM spiroketal ring system (Figure 6).

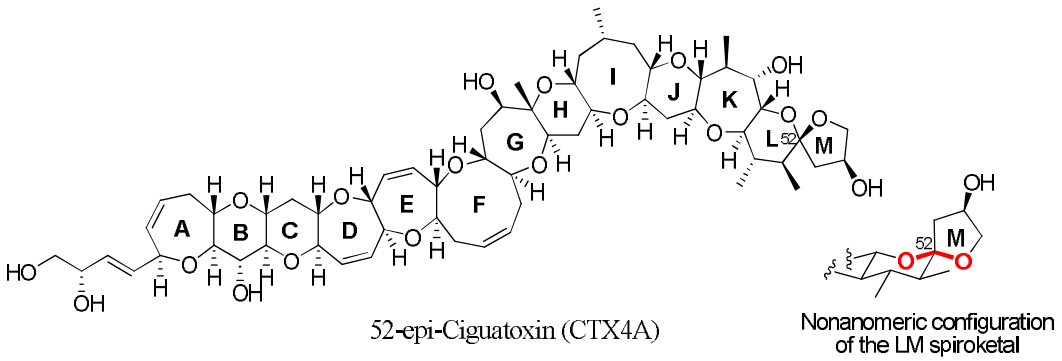
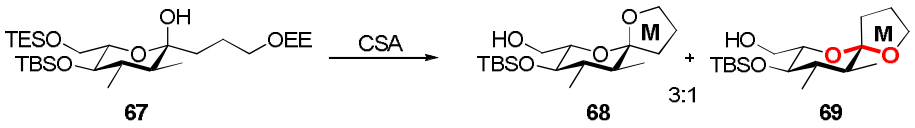


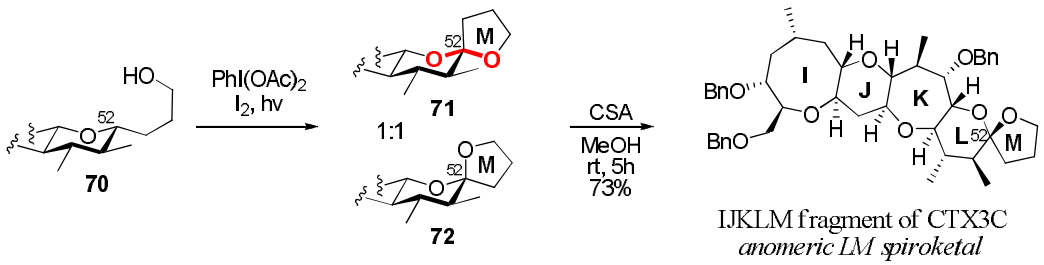
Figure 6. 52-epi-Ciguatoxin (CTX4A).

Several research groups have studied the synthesis of different CTXs,[69] but once again the nonanomeric congeners have not been set as the primary targets. Recently Fujiwara et al. obtained the nonanomeric isomers as unwanted side products in their synthetic studies towards CTX3C.[70, 71] Hemiacetal **67** was used as a substrate in the model studies, which upon treatment with CSA underwent deprotection of the ethoxyethyl and TES protection groups and subsequent spiroketalization to form a 3:1 mixture of the spiroketal products **68** and **69**, in favour of the anomeric isomer **68** (Scheme 14).



Scheme 14. Synthesis of a model compound of the LM spiroketal of CTX3C.

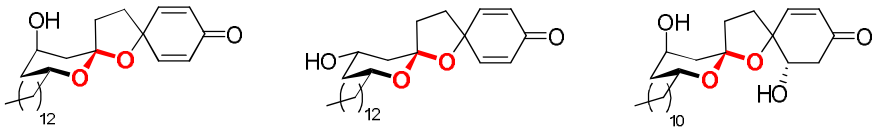
In the actual synthesis of the IJKLM ring fragment of CTX3C, a photochemical hypoiodite oxidation[72] was used to give a 1:1 mixture of the anomeric (**72**) and nonanomeric (**71**) spiroketal (Scheme 15).[70b] This mixture was equilibrated with CSA in MeOH to give the desired IJKLM fragment with an anomeric spiroketal in 73% yield.



Scheme 15. The synthesis of the IJKLM fragment of CTX3C.

2.4.2 Aculeatins and Aculeatols

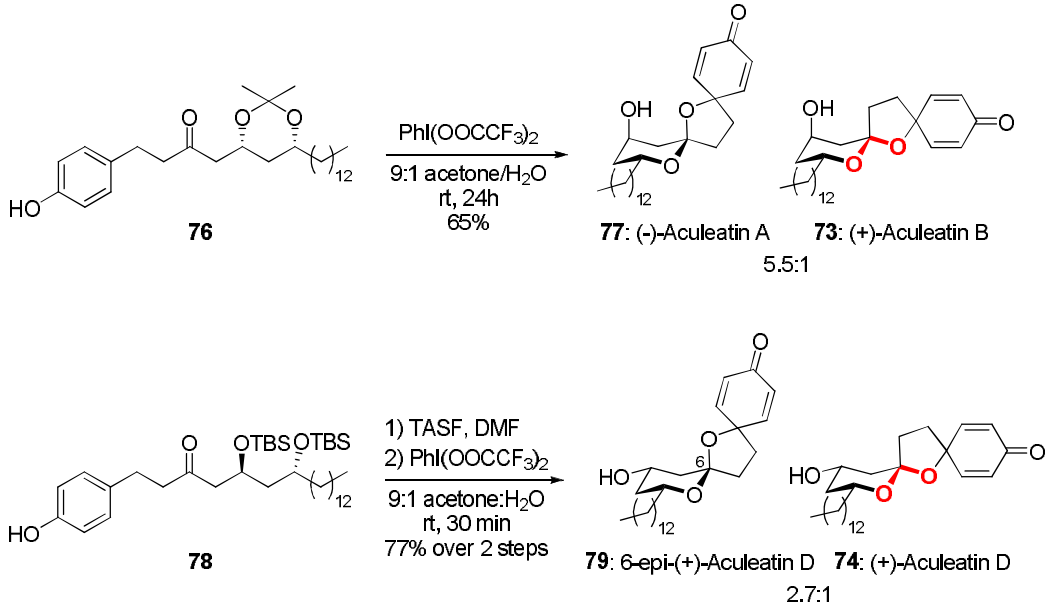
One of the most recently identified group of natural products possessing a nonanomeric [6,5]-spiroketal are the aculeatins.[73] Aculeatins A-D were isolated from the herbaceous plant *Amonum aculeatum* distributed in Malaysia, Indonesia and Papua New Guinea, where it is used as a folk medicine against fever and malaria. Initial studies have shown the aculeatin compounds to display antiprotozoal and antibacterial activity. Not surprisingly, one of the nonanomeric spiroketal containing aculeatins, aculeatin D, is found to be the most biologically active.[73] Even more recently, four new aculeatin derivates, aculeatols A-D were isolated and characterized.[74] The structures of the nonanomeric aculeatin congeners are presented in Figure 7. The aculeatins have been the target of several synthetic studies in the recent years. However, the creativity has been quite low, as all of the syntheses have applied similar kinds of protected ketophenols as substrates for the key oxidative spiroketalization with hypervalent iodine reagent.[75]



73: (+)-Aculeatin B **74**: (+)-Aculeatin D **75**: (+)-Aculeatol D

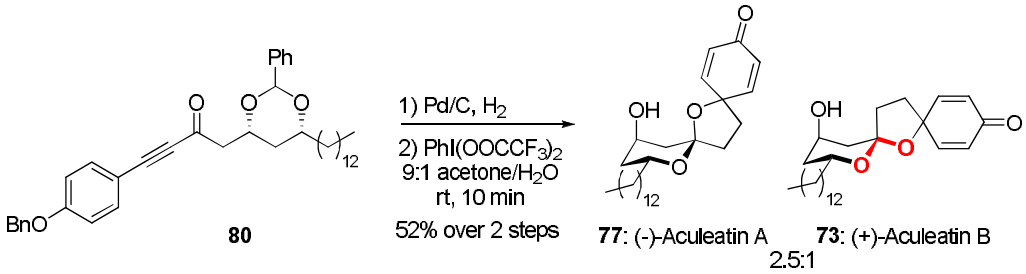
Figure 7. The nonanomeric aculeatin congeners: aculeatin B, aculeatin D and aculeatol D.

Marco et al. achieved the first enantioselective synthesis of aculeatins A, B and D.[76, 77] Treating acetonide **76** with phenyliodonium bis(trifluoroacetate) (PIFA) triggered phenolic oxidation together with acetonide hydrolysis and spiroketalization to form a 5.5:1 mixture of the anomeric aculeatin A (**77**) and nonanomeric aculeatin B (**73**) (Scheme 16). In a similar manner, a 2.7:1 mixture of the anomeric 6-epi-aculeatin D (**79**) and the nonanomeric aculeatin D (**74**) was formed starting from a TBS protected ketone **78**. (Scheme 16).



Scheme 16. The synthesis of aculeatins A, B, D and 6-epi-aculeatin D by Marco et al.[76]

Chandrasekhar et al. synthesized aculeatins A and B using a ketophenol **80** as substrate.[78] After catalytic hydrogenolysis of the benzylidene, benzyloxy and acetylene groups, treatment of the crude product with PIFA furnished a 2.5:1 mixture of aculeatin A and aculeatin B (Scheme 17).

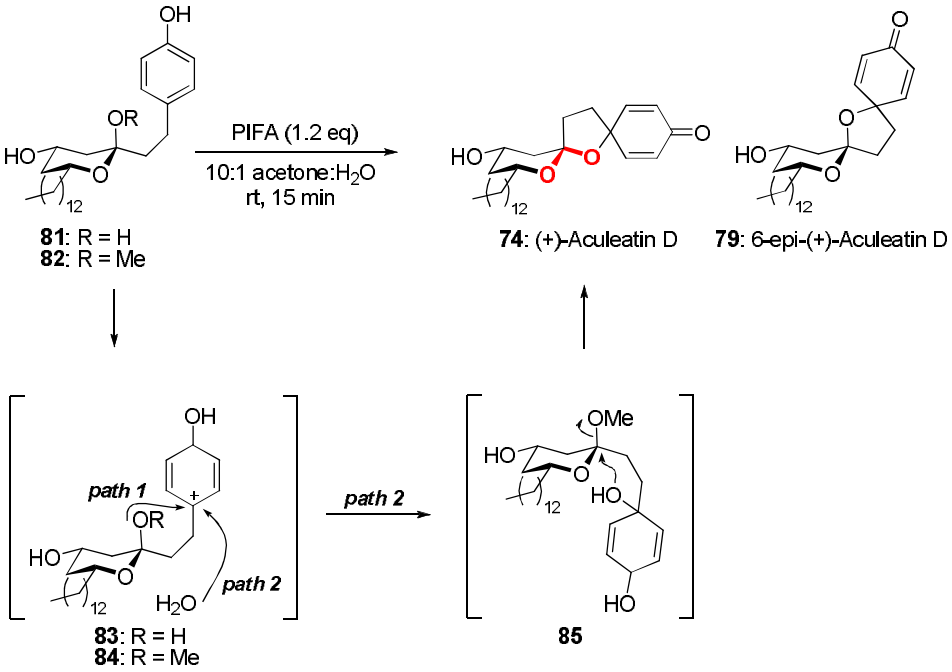


Scheme 17. Synthesis of aculeatins A and B by Chandrasekhar et al.[78]

Wong et al. screened two different kinds of substrates for the synthesis of aculeatin D (Table 2).[79] Oxidative cyclization with PIFA gave a 2:3 mixture of the nonanomeric and anomeric isomers when lactol **81** was used as a substrate (entries 1-3), whereas with methoxy ketal **82**, a 1:1 mixture was formed (entries 4-6). TFA and zinc chloride had neither influence on the selectivity nor the yield of the reaction. It was proposed that the oxygen of the methoxy group in ketal **82** might be less nucleophilic than the free hydroxyl group in **81**, allowing a competitive intermolecular addition of water leading to the nonanomeric isomer **74** via path 2. In an alternate pathway (path 1) intramolecular attack by the free hydroxyl group of lactol (**83**) on the phenoxonium cation leads to prefential formation of the anomeric isomer **79** (Table 2).

Table 2. Synthesis of aculeatin D and 6-epi-aculeatin D by Wong et al.

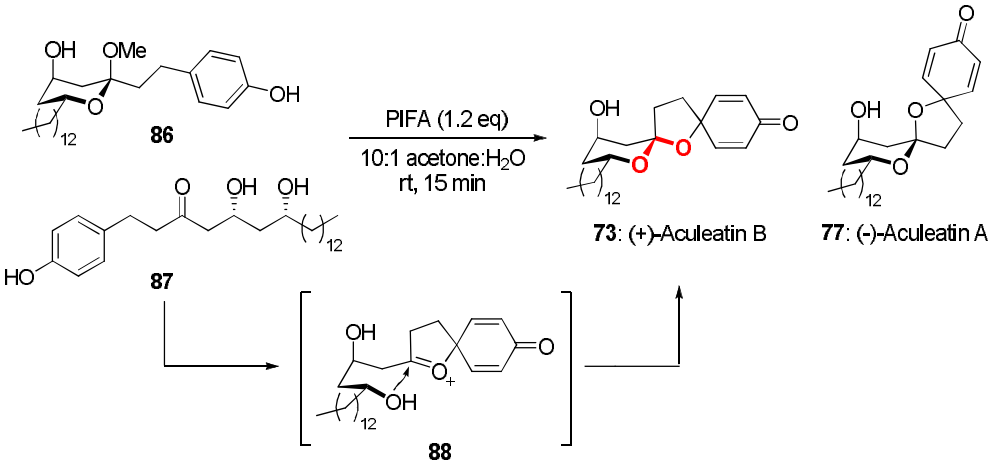
Entry	Substrate	Additive	Ratio 74:76	Total yield [%]
1	81		41:59	64
2	81	TFA (0.4 equiv)	44:56	71
3	81	$ZnCl_2$ (1.2 equiv)	42:58	69
4	82		51:49	69
5	crude 82		52:48	65 (over 2 steps)
6	crude 82	$ZnCl_2$ (1.2 equiv)	49:51	51 (over 2 steps)



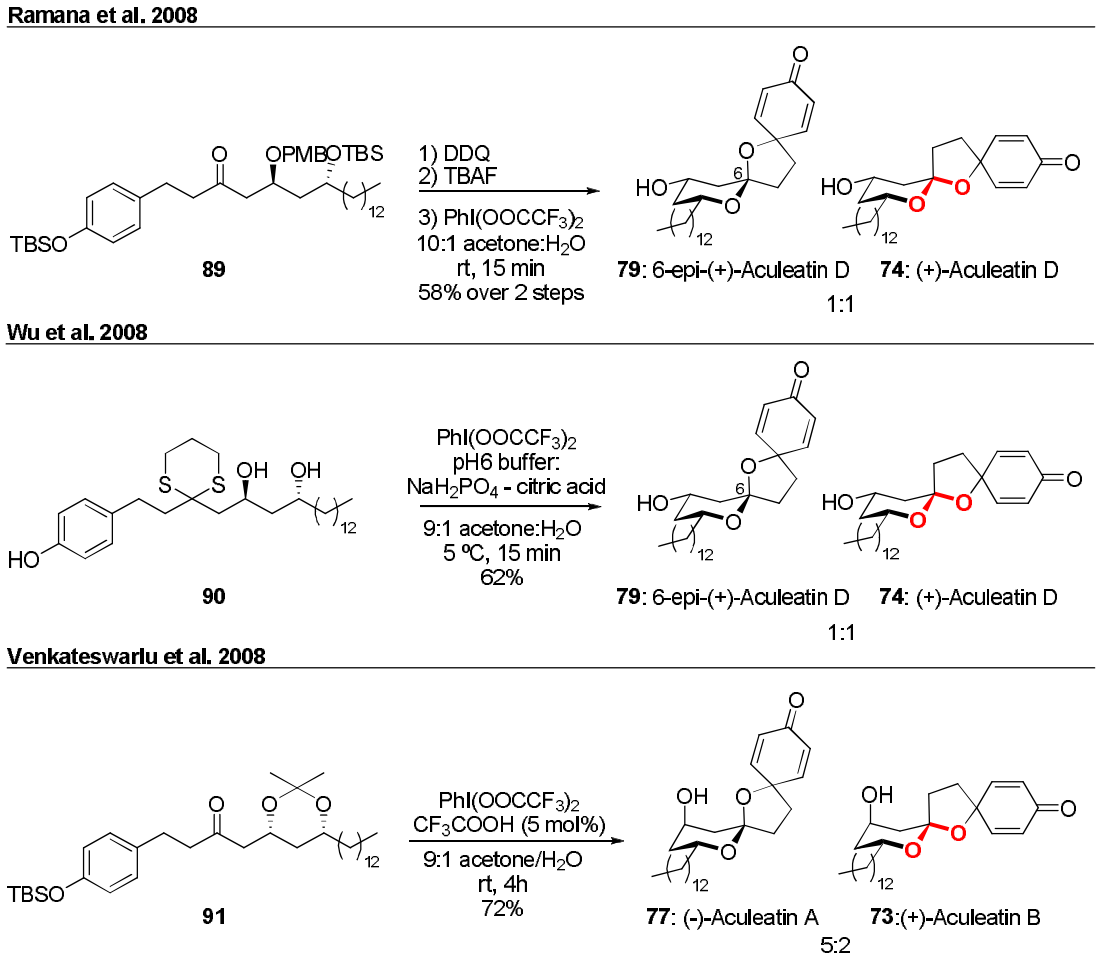
Similar spiroketalization conditions were screened for the formation of aculeatins A and B (Table 3). When an open-chained ketodiol precursor **87** was used as a substrate, a 2:3 ratio in favor of the anomeric isomer, aculeatin A, was obtained (entries 2-4). With methoxy ketal **86**, a ~1:1 product ratio was again obtained (entry 1). The reaction with the open-chained ketodiol **87** was proposed to proceed via oxonium ion intermediate **88** (Table 3).

Table 3. Synthesis of aculeatins A and B by Wong et al.

Entry	Reactant	Additive	Ratio 73:77	Total yield [%]
1	86		47:53	68
2	87	TFA (0.4 equiv)	42:58	82
3	87	$ZnCl_2$ (1.2 equiv)	43:57	57
4	87		38:62	71



The three most recent syntheses developed for different aculeatin congeners are presented in Scheme 18. Ramana et al.[80] and Wu et al.[81] also obtained a 1:1 mixture of 6-epi-aculeatin D and aculeatin D. With the thioketal protected substrate **90**, pH6 buffer was needed to obtain the nonanomeric product, when without any buffer the anomeric isomer was obtained as a single product in 74% yield. Venkateswarlu et al.[82] used a similar acetonide protected ketone **91** as Falomir et al. in their previous studies (Scheme 16). By adding TFA and reducing the reaction time to 4 hours, a slight increase in the selectivity in favor of the nonanomeric isomer was obtained (5.5:1 vs. 5:2)



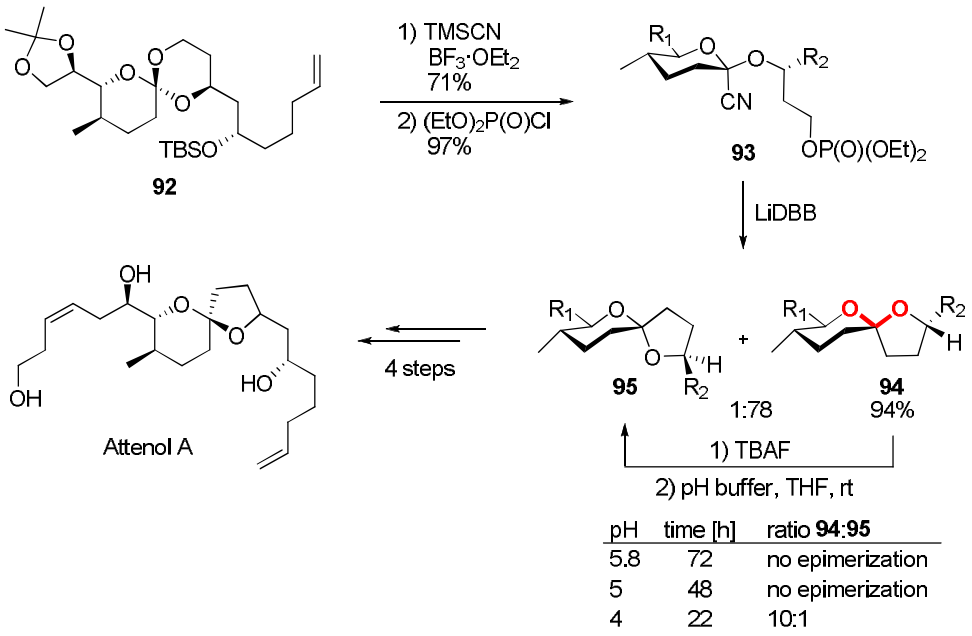
Scheme 18. Aculeatin syntheses by Ramana,[80] Wu[81] and Venkateswarlu[82].

For a comparison, under most circumstances the anomeric isomer is formed as the major product. At best, a 1:1 mixture of the spiroketal isomers has been obtained. Surprisingly little work has been done in screening different conditions for these reactions. In order to gain more information about the selectivity issues with these systems, at least a thorough study covering different reaction temperatures and different solvent systems should be implemented.

2.4.3 Unnatural Nonanomeric Spiroketal of Attenol A

Rychnovsky et al. have applied their reductive cyclization protocol also for the synthesis of other nonanomeric spiroketals. The most recent example, in which excellent yield and selectivity for the nonanomeric spiroketal isomer was obtained, is the synthesis of Attenol A (Scheme 19).[62] Attenol A was isolated from Chinese bivalve *Pinna attenuate* in 1999, and have shown moderate cytotoxicity against various tumor cell lines.[83] The spiroketal in Attenol A is really in an anomeric configuration, but it was envisaged that the corresponding compound with a nonanomeric spiroketal could be used as a pro-drug for its natural isomer. It was proposed that the acidic media of solid tumors (pH ca. 6.8) could trigger the isomerization of the nonanomeric isomer, and this property could be used to selectively target tumor cells.[62]

Spiro orthoester **92** was opened as usual, now with good regioselectivity to give the desired cyanoacetal in 71% yield (Scheme 19). In this synthesis the electrophile had to be installed after the cyanoacetal and a phosphate ester was chosen to serve the purpose, because it could be installed under reaction conditions mild enough to preserve the cyanoacetal and the TBS protection. Reductive cyclization of the intermediate phosphate **93** produced the nonanomeric spiroketal **94** as the major product in remarkable 94% yield! This intermediate was further equilibrated to the more stable anomeric spiroketal **95** (PPTS, MeOH) and then carried on the final three steps to Attenol A. As such, the reductive cyclization method is a powerful strategy for the construction of spiroketal containing natural products, as it opens access selectively to form either of the spiroketal isomers.



Scheme 19. Synthesis of the unnatural nonanomeric spiroketal ring of Attenol A.

To investigate the possible use of the nonanomeric isomer as a pro-drug, epimerization of the spiroketal **94** in aqueous buffer solutions (NaOAc/AcOH) were evaluated (Scheme 19). This spiroketal precursor, however, turned out to be impractical for the use as a pro-drug, because under normal physiological conditions the nonanomeric spiroketal would be stable indefinitely. Only partial epimerization occurred in a pH 4.0 buffer, leading to 10:1 ratio of the nonanomeric and anomeric isomers.

3 SYNTHESIS OF 10-EPI-ABCDE RING FRAGMENT OF PECTENOTOXIN 2

3.1 Introduction

The pectenotoxins came to my life already during my undergraduate studies, as I came to choose the A ring lactone structure for my synthesis design assignment. At that point, however, I was not aware that my long lasting journey with the PTXs had begun. Later, I had the opportunity to try out my design in a lab course and since then my work in the lab has been all for the PTXs. During these years I have learned that natural product synthesis is probably one of the most challenging areas of organic chemistry. An understanding of a wide range of chemical principles in combination with experimental skills and most importantly imagination is required to achieve the synthetic goals.

Natural products have found many uses in medicinal chemistry and the exceptional structural and chemical diversity of these compounds promises new discoveries also in the future.[84] For this very reason, natural product synthesis is often rationalized through the biological activity of these compounds. In my opinion however, the reaction chemistry, both at strategic and operational levels, that provides new information and solutions, and in some cases new methods for organic synthesis, is more than a sufficient rationale.

3.2 Retrosynthetic Design

Our retrosynthetic analysis for the ABCDE ring fragment of PTX2 is presented in Figure 8. This fragment contains the bicyclic acetal, the *cis*-fused THF ring and the nonanomeric spiroketal as challenging and interesting structural motifs that may need special attention from a synthetic point of view due to their stereochemical features and fragile nature. In order to allow easy scale-up and provide an efficient route to the desired target, our strategy was to use a highly convergent synthesis using three advanced fragments **96-98** (Figure 8). The carbon framework was envisioned to be assembled via aldol addition and Suzuki-Miyaura coupling. The key feature of the strategy was the need to form the delicate nonanomeric AB spiroketal ring structure in the late stages of the synthesis. In the following chapters the syntheses of fragments **96-98** and their assembly to form the ABCDE ring system of PTX2 are presented and discussed.

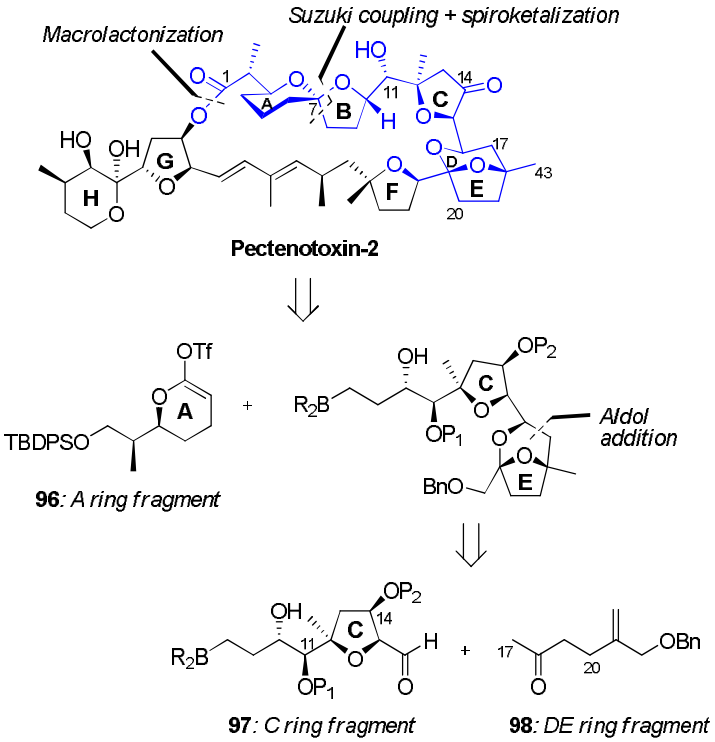
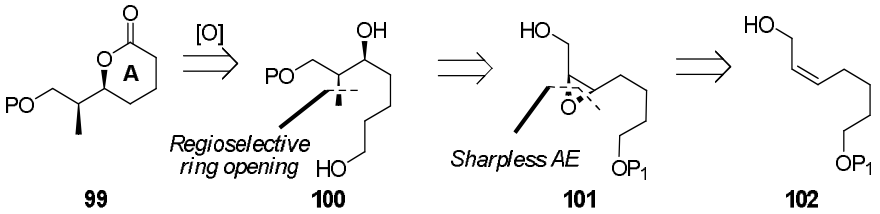


Figure 8. Retrosynthetic analysis for the ABCDE ring fragment of PTX2.

3.3 Synthesis of A Ring Fragment

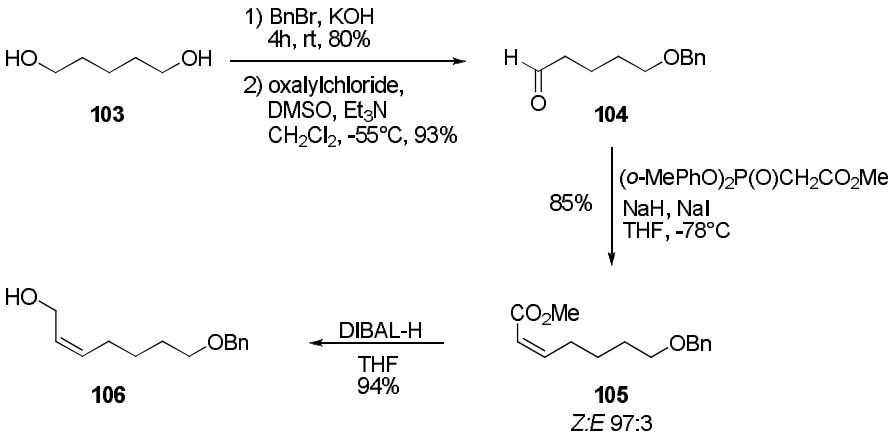
3.3.1 Epoxidation Strategy

Among several possible routes for the construction of the A ring fragment, we selected a strategy wherein the lactone ring structure **99** would arise from allylic alcohol **102** through a sequence of Katsuki-Sharpless asymmetric epoxidation[85] and regioselective epoxide ring opening (Scheme 20).



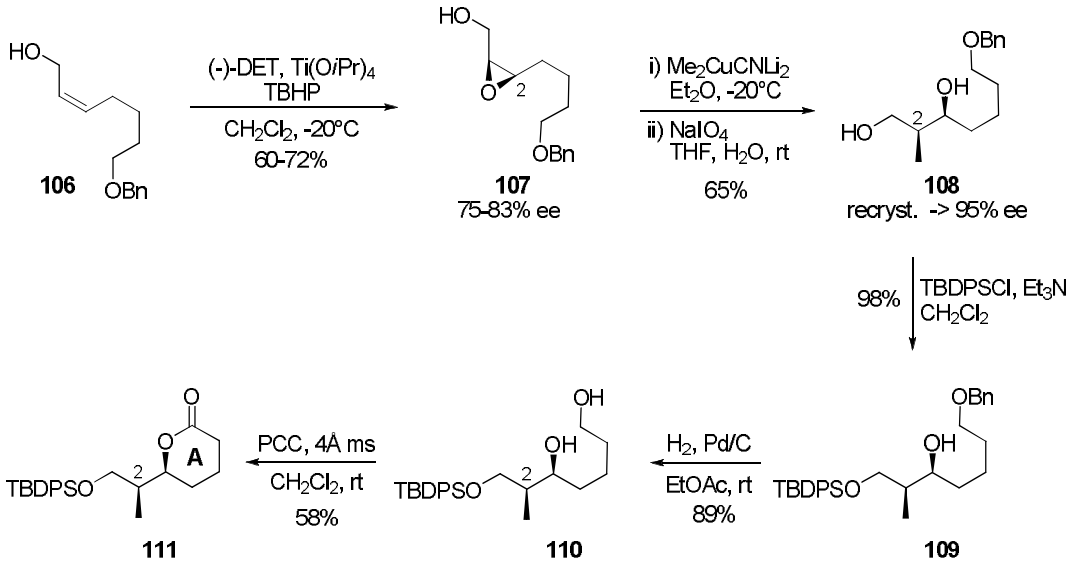
Scheme 20. Retrosynthetic analysis for the A ring fragment.

Commercially available 1,5-pentanediol **103** was monobenzylated using a procedure by Kiddle et al.,[86] followed by Swern oxidation using the standard conditions[87] to afford a known aldehyde **104**.[88] (Scheme 21) Horner-Wadsworth-Emmons olefination[89] by using the Ando phosphonate[90] and a combination of NaH/NaI as the base, an improved protocol developed previously in our group,[91] gave the desired (*Z*)-enoate **105** in excellent 97:3 *Z*:*E* selectivity. The remaining *E* isomer was easily removed by column chromatography and the subsequent DIBAL-H reduction furnished pure *Z* allylic alcohol **106** in 94% yield.



Scheme 21. Synthesis of allylic alcohol **106**.

The construction of the C2-C3 *syn* stereochemistry commenced with a Katsuki-Sharpless asymmetric epoxidation to deliver the desired *cis* epoxide **107** in 60-72% yield and 75-83% ee. (Scheme 22) Epoxide ring opening with a higher order mixed cuprate[92] and subsequent cleavage of the 1,2-diol side product with $NaIO_4$ furnished a crystalline diol **108** in 65% overall yield after recrystallization. The enantiomeric purity, which could be determined only after conversion to diol **110**, had improved to 95% ee upon recrystallization. Monosilylation of the diol **108** and subsequent reductive debenzylation cleanly afforded diol **110**. Finally, oxidation with PCC afforded the A ring lactone **111** in 58% yield. Recently, TEMPO oxidation was discovered to be a much better in effecting the oxidation of **110**, giving 89% yield of the lactone **111**.[93] Overall, 9 steps were required to synthesize the A ring fragment in 14% overall yield (22% if TEMPO oxidation is used).



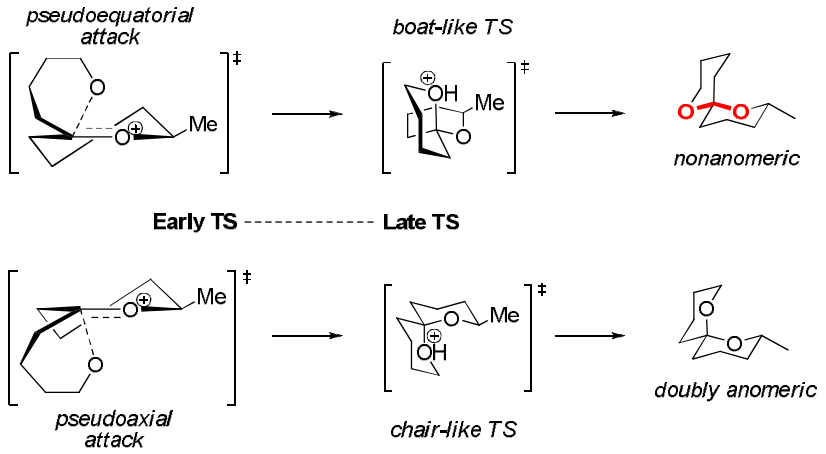
Scheme 22. The synthesis of the A ring lactone **111**.

3.3.2 Synthesis of AB Spiroketal Ring Fragment

Before going forward with the strategic plan presented in Figure 8, the A ring lactone was used to synthesize the AB spiroketal ring fragment of PTX2. In the initial studies, the main objective was to develop suitable kinetic conditions for the spiroketalization to deliver the desired nonanomeric isomer as the major product. Also, we were expecting to obtain indispensable information regarding the sensitivity of the spiroketal ring structure that would be useful in later stages of the synthesis.

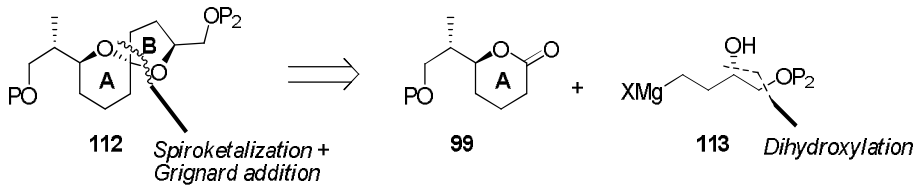
Deslongchamps and co-workers were first to study the formation of nonanomeric spiroketal isomers under kinetic control in the [6,6]-spiroketal series.[51b] They suggest that the formation of the nonanomeric spiroketal isomers can be explained by assuming an early transition state (TS) for the spiroketalization. In the early TS the formation of the C-O bond would not be sufficiently advanced to generate significant energy differences between the pseudoequatorial and pseudoaxial attacks (Scheme 23). On the contrary, a late transition state would become more and more boat-like and thus would be expected to suffer from severe stereoelectronic strain. As we started our studies with the pectenotoxin

spiroketals, kinetically controlled spiroketalization to give nonanomeric isomers as the major product in the [6,5]-series had not been reported.



Scheme 23. Pseudoequatorial and pseudoaxial attacks.

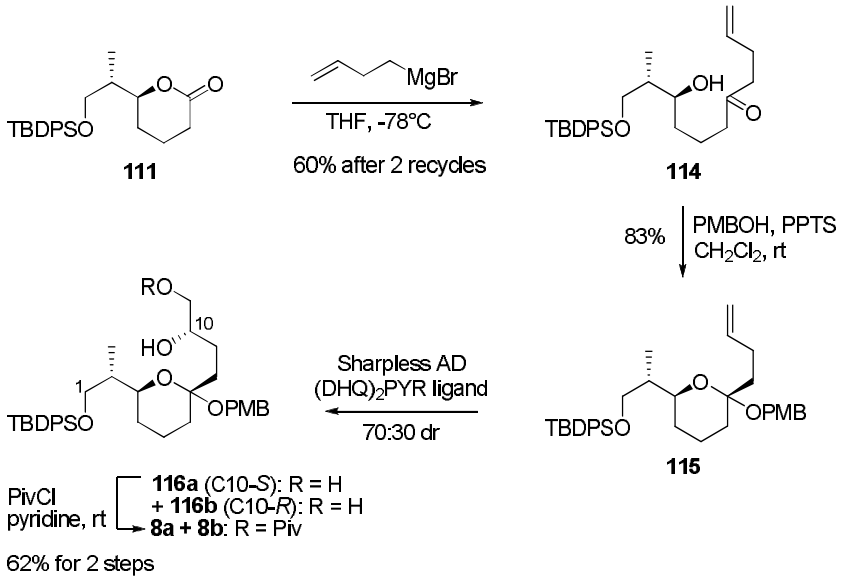
The AB spiroketal ring fragment **112** was envisioned to arise from the A ring lactone **99** by Grignard addition and asymmetric dihydroxylation[94] (Scheme 24).



Scheme 24. Retrosynthetic analysis for the AB spiroketal ring fragment of PTXs.

To this end, lactone **111** was treated with 4-butenylmagnesium bromide to afford ketoalcohol **114** in total yield of 60% after two recycles of the starting material (Scheme 25). Acid-catalyzed methanolysis (MeOH, PPTS) failed to give the desired methoxy ketal as it readily decomposed to give a mixture of elimination products. However, benzyl and especially *p*-methoxybenzyl (PMB) ketals were stable enough and PMB ketal **115** could be obtained in 83% yield after purification by column.

Dihydroxylation using the Sharpless ligand $(DHQ)_2PYR$[94b, 95] cleanly afforded the diol product in 70:30 diastereoselectivity (Scheme 25). $(DHQ)_2AQN$ was also tested for this dihydroxylation, but this ligand gave no improvement to the selectivity.[96] Protection of the crude diol furnished a mixture of the monopivalates **8a** and **8b** in 62% yield over two steps. The protection was crucial in order to prevent the formation of the thermodynamically more stable but undesired [6,6]-spiroketals.[6b, 12b]

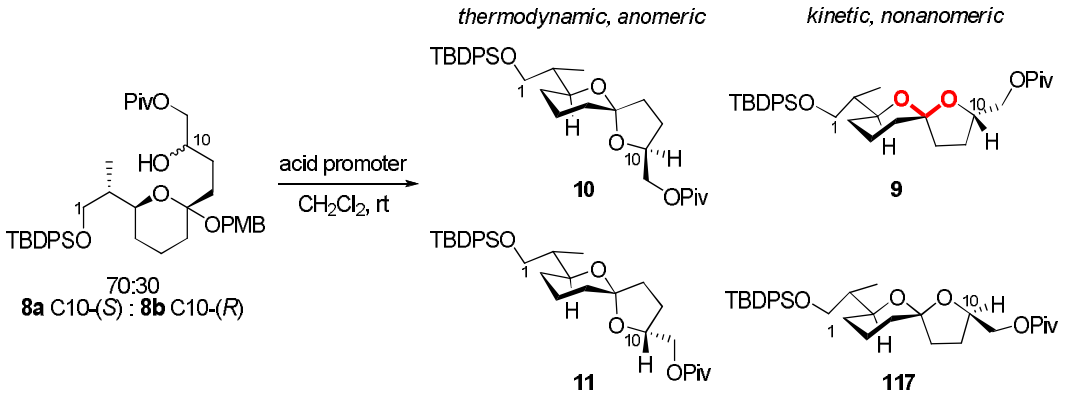


Scheme 25. Synthesis of the spiroketalization substrate.

Now that we had the spiroketalization substrate at hand, all that remained was to close the ring. For this key reaction, different acid promoters were screened (Table 4). The use of a strong acid (*p*-TsOH) led to a rapid formation of a mixture of four spiroketal isomers (entries 2-3). The two anomerically stabilized spiroketals **10** and **11** (C10 epimer of **10**) were identified as the major products. The more polar nonanomeric isomers **9** and **117** (C10 epimer of **9**) were only observed in the initial stages of the reaction. Further equilibration afforded the anomeric spiroketals **10** and **11** almost exclusively, demonstrating that the desired nonanomeric spiroketal **9** appears to be a kinetic product.

With weaker acids such as acetic acid, formic acid and chloroacetic acid (entries 4-7), progressively larger amounts of the desired nonanomeric spiroketal isomer **9** was afforded. Surprisingly, PPTS gave similar results with those of *p*-TsOH, thus appearing to be effectively stronger acid than any of the carboxylic acids in the reaction medium. This indicates that in this case, pK_a values in DMSO are more reliable guides to reactivity than those measured in H_2O, presumably because the spiroketalizations were performed in an aprotic solvent (CH_2Cl_2). Chloroacetic acid was found to be the optimal acid catalyst for the kinetic spiroketalization (entry 4), affording the nonanomeric spiroketal **9** as the major product in 49% yield. Interestingly, under these conditions, less than 5% of the minor C10 epimer **117** was formed.

Table 4. Spiroketalizations with different acid promoters.



Entry	Acid promoter	pKa H_2O (DMSO)	Reaction time	10	11	9 (+117)
1	PPTS (20 mol-%)	5.21 (3.4)	10 min	53	18	29[b]
2	*p*-TsOH (20 mol-%)	-1.3	10 min	50	20	30
3	*p*-TsOH (20 mol-%)	-1.3	90 min	69	29	<2
4	$ClCH_2CO_2H$ (80 mol-%)	2.86	4 h	29	22	49[c]
5	HCOOH (40 mol-%)	3.77	4 h	29	28	43
6	AcOH (200 mol-%)[a]	4.76 (12.3)	6 h	35	25	40
7	AcOH (3300 mol-%)	4.76 (12.3)	21 h	64	34	<2

[a] For entries 2-3 and 5-6, product ratios were determined by HPTLC after the reaction had reached >90% conversion. Spiroketals 9-11 and 117 were the only products identified, isolated yields were not determined. For entries 1, 4 and 7, the ratios represent isolated yields [%] of the products. [b] Including 10% of 117. [c] Including 5% of 117. [d] With 20 or 40 mol-% of AcOH, the reaction failed to go to completion within 24 h.

The configurations of the different spiroketal isomers were assigned by NOESY experiments. Several diagnostic NOESY cross-peaks clearly identified spiroketal **9** as the nonanomeric isomer (Figure 9). Also, ^{13}C NMR chemical shift of the spiro carbon (C7) in **9** was shifted downfield relative to **10** and **11** (109.4 ppm in **9** vs. 107.2 in **10** and 107.3 in **11**), a trend that is also seen in the pectenotoxins[12b] and in the [6,6]-spiroketal series[51b]. In addition, ^{1}H NMR coupling constant data clearly indicates a chair conformation for the A ring (Figure 9).

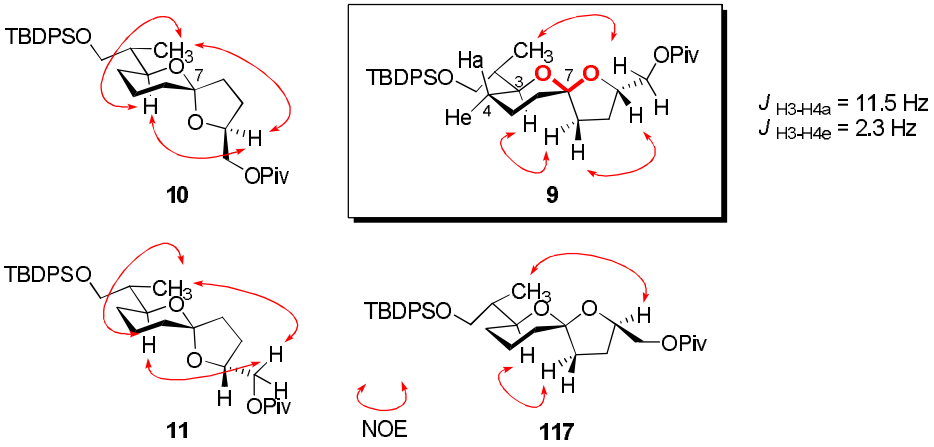
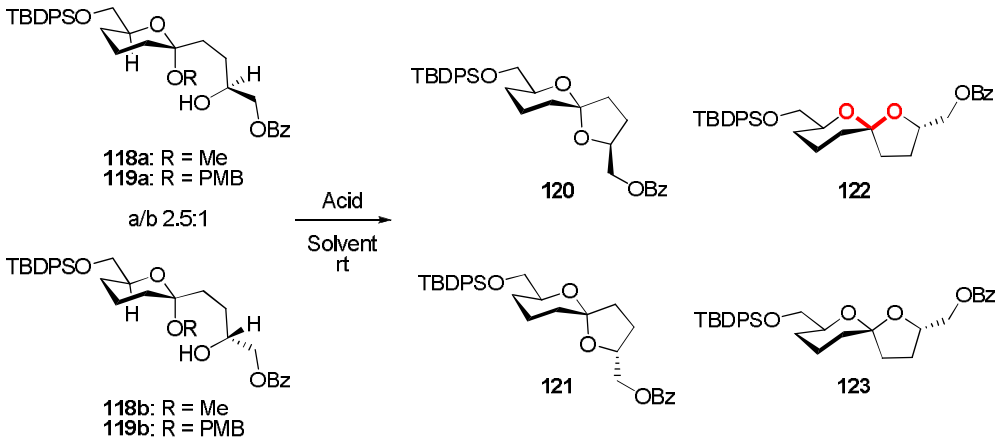


Figure 9. The NOESY cross-peaks and the coupling constants.

More recently, additional studies were conducted in our group by Daniele Castagnolo to further examine the kinetic formation of nonanomeric [6,5]-spiroketals.[97] By using different mixed ketal-alcohol precursors for the spiroketalization the anomeric isomers were formed as the major products (Table 5). However, also nonanomeric spiroketal isomers were observed when the reaction was performed under kinetic conditions using an appropriately tuned acid. Surprisingly, water had a dramatic accelerating effect when THF was used as a solvent, and the highest yields of the nonanomeric products were obtained in aqueous THF (Table 5, entries 4-5).[98] In addition, the product ratio was strongly affected by the substituents and the stereochemistry of the starting alcohol. Similar to our results with the AB spiroketal ring system, the C10 epimer that corresponds to the natural PTX gave rise to both nonanomeric (**122**) and anomeric (**120**) spiroketals, whereas the unnatural C10 epimer afforded the anomeric

spiroketal **121** as the major product with only trace amounts of the nonanomeric isomer **123**.

Table 5. Spiroketalization with simple ketal-alcohol precursors.



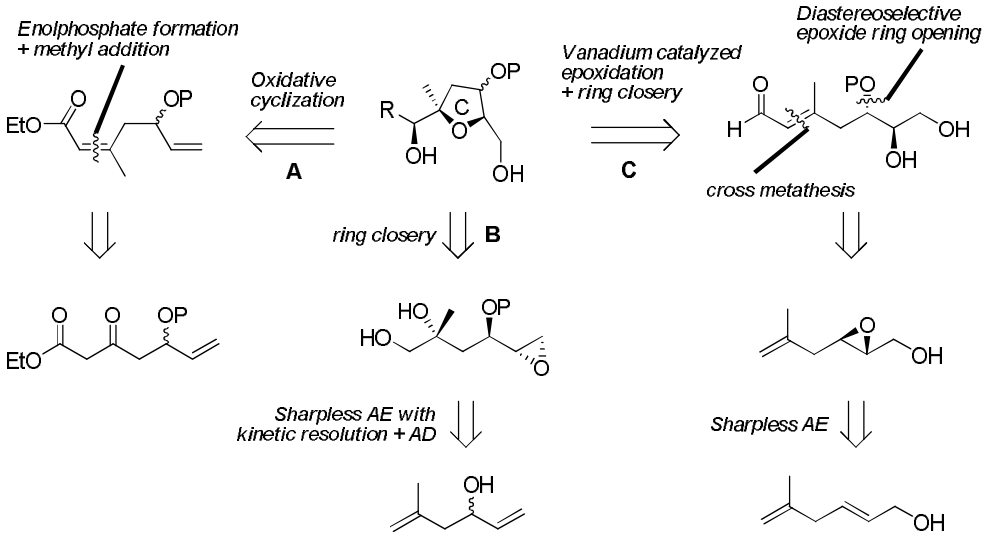
Entry	R	Acid (60 mol-%)	pK_a	Solvent	Time [h]	120[a]	121[a]	122[a]
1	Me	$ClCH_2COOH$[b]	2.86	CH_2Cl_2	4	40[c]	24[c]	26[c]
2	Me	Cl_3CCOOH	0.65	THF	28	23	19	25[d]
3	Me	$ClCH_2COOH$	2.86	THF/H_2O 4:1	16			
4	Me	Cl_3CCOOH	0.65	THF/H_2O 4:1	5.5	23[c]	23[c]	49[c]
5	PMB	Cl_3CCOOH	0.65	THF/H_2O 4:1	5	24	21	44
6	Me	$ClCH_2COOH$	2.86	CH_3CN/H_2O 4:1	1	44	29	26
7	Me	$ClCH_2COOH$	2.86	CH_3CN/H_2O 4:1[e]	5	29	26	43
8	Me	Cl_3CCOOH	0.65	CH_3CN/H_2O 4:1	0.25	55	33	16

[a] For entries 2-3 and 5-8, product ratios were determined by HPTLC. Isolated yields were not determined. [b] 80 mol-% of catalyst was used. [c] The ratios represent isolated yields [%] of the products. [d] Recovered starting material 32%. [e] The reaction was done at 0 °C.

According to the late transition state model presented by Deslongchamps (Scheme 23), the anomeric isomers should always predominate over the nonanomeric isomers. However, our group's results with the pectenotoxin spiroketal system and with the above mentioned simplified spiroketal units, clearly indicate that the model is applicable only when there are no sterically hindering substituents. As such, it is tempting to speculate that the formation of nonanomeric spiroketals in nature could be simply explained by kinetic preference rather than some sort of sophisticated directed spirocyclization. Or, is the nature still one step ahead?

3.4 Synthesis of C Ring Fragment

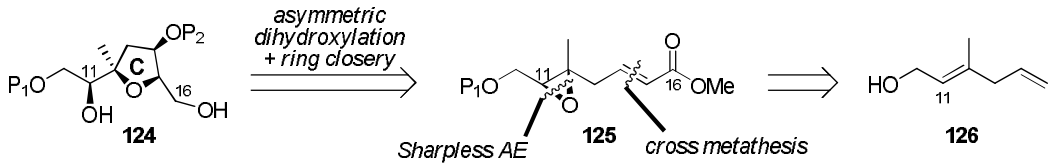
The synthesis of the C ring fragment, a structural unit common to all PTXs, proved to be the most challenging part of the whole project. Many different synthetic strategies were elaborated and tested (Scheme 26) before arriving at the final efficient and reliable synthesis. The C ring is the central subunit of the ABCDE ring system: it incorporates a handle towards the A ring, from which the spiroketal unit is constructed, and a functional group at C16 that can be used in the synthesis of the DE bicyclic acetal. These handles must be built in during the synthesis. Above all, the objective was to develop an efficient synthesis that could be easily conducted on a large scale, thus providing quantities of material to continue the synthesis in both directions of the PTX skeleton.



Scheme 26. Different synthetic strategies that failed to give the C ring fragment.

3.4.1 AE-AD-Metathesis Strategy

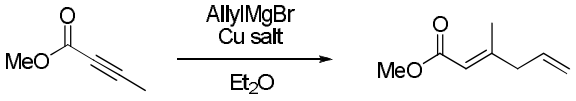
Transformations that had proven to be efficient and reliable in previous studies were combined in the successful synthesis of the C ring fragment. Namely, cross-metathesis[99] combined with Sharpless asymmetric epoxidation and dihydroxylation, were used as the key steps to reach the final target (Scheme 27).



Scheme 27. Retrosynthetic analysis of the AE-AD-metathesis strategy.

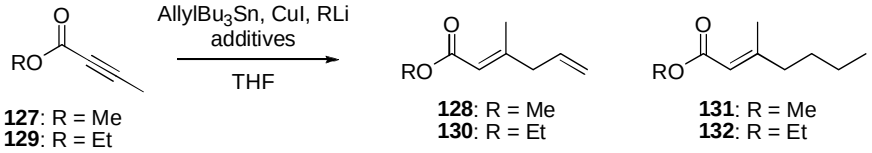
The synthesis started with an addition of an allylcopper reagent to a commercially available tetrolate **129**, a reaction that had already been screened and optimized previously (Table 6-7). When allylmagnesium bromide was used as a starting material to form the allylcopper reagent[100] no desired product **128** was formed. Mostly unreacted starting material **127** was recovered (Table 6, entries 1-3). When the reaction was repeated using allyltributyltin and butyllithium to form the cuprate[101] the desired product **128** could be obtained (Table 7, entry 1), but especially in large scale substantial amounts of an undesired side product **131** was formed (entry 2). Replacing butyllithium with methyllithium and addition of lithium chloride[100,102] slightly improved the reaction outcome by suppressing the formation of the side product (entry 3). Further improvement was achieved by using a larger excess of the allylcopper reagent (entry 4). Finally, a considerable improvement in yield was obtained by using ethyl-2-butynoate **129** as a starting material and 3 equivalents of the allylcopper reagent to provide the desired conjugated ester **130** in excellent 92% yield (entry 5).

Table 6. Allylcopper addition screens using allylMgBr to form the cuprate.



Entry	AllylMgBr equiv	Cu salt	Scale [mmol]	Yield [%]
1	2	CuI	0.5	SM recovered
2	1.25	CuBr·Me_2S	0.8	SM recovered
3	2	CuBr	0.5	SM recovered

Table 7. Allylcopper addition screens using allylBu_3Sn to form the cuprate.



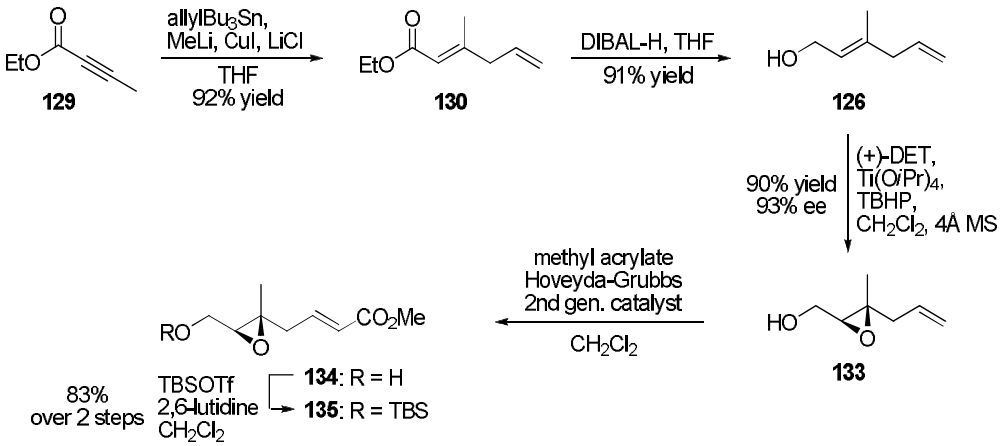
127: R = Me
129: R = Et

128: R = Me
130: R = Et

131: R = Me
132: R = Et

Entry	R	AllylBu_3Sn equiv	RLi	Additivies	Scale [mmol]	Yield [%] (128:131)
1	Me	1.6	*n*BuLi		0.6	60 (9:1)
2	Me	1.6	*n*BuLi		2.0	65 (1:1)
3	Me	1.6	MeLi	LiCl	0.5	23 (1:0)
4	Me	3.0	MeLi	LiCl	1.0	67 (no 132)
5	Et	3.0	MeLi	LiCl	1.0	92 (no 132)
6	Et	3.0	MeLi	LiCl	50.0	85 (no 132)

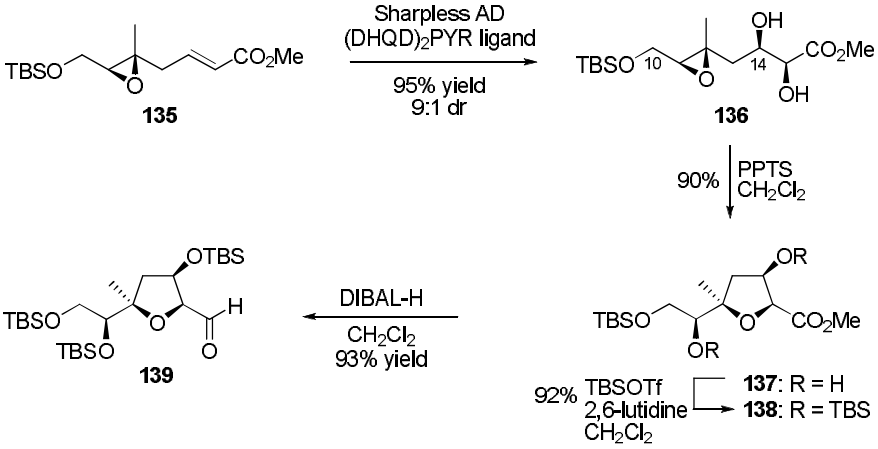
Reduction of ester **130** was efficiently achieved by DIBAL-H to give allylic alcohol **126**, which under Katsuki-Sharpless asymmetric epoxidation conditions furnished epoxide **133** in 90% yield and excellent 93% ee (Scheme 28). The terminal olefin was reacted with methyl acrylate in the presence of Hoveyda-Grubbs 2nd generation catalyst[103] followed by TBS protection to afford ester **135** in 83% yield over 2 steps.



Scheme 28. Synthesis of ester **135**.

Asymmetric dihydroxylation was used to introduce the remaining two stereocenters at C14 and C15. (Scheme 29) After screening different ligands and conditions, the Sharpless' ligand $(DHQD)_2PYR$ proved to be the best, giving the

desired diol **136** in excellent 95% yield and 9:1 diastereoselectivity. However, ten mol-% of the ligand and eleven mol-% of the oxidant were required for the reaction to proceed in a reasonable time. Exposure of the diol mixture to catalytic PPTS resulted in cyclization to give the desired tetrahydrofuran ring system. At this stage the diastereomers could be easily separated by column chromatography to give crystalline **137** in 90% yield as a single diastereomer. X-ray crystallographic analysis confirmed the stereochemistry of **137** (Figure 10). Finally, TBS protection of the secondary hydroxyl groups, followed by DIBAL-H reduction furnished aldehyde **139** in 46% overall yield for 9 steps. The entire synthetic sequence was successfully scaled up to nearly 20 gram scale.



Scheme 29. The final steps of the C ring fragment synthesis.

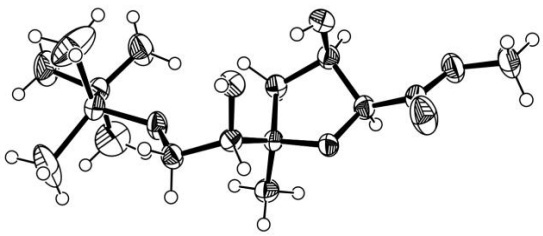
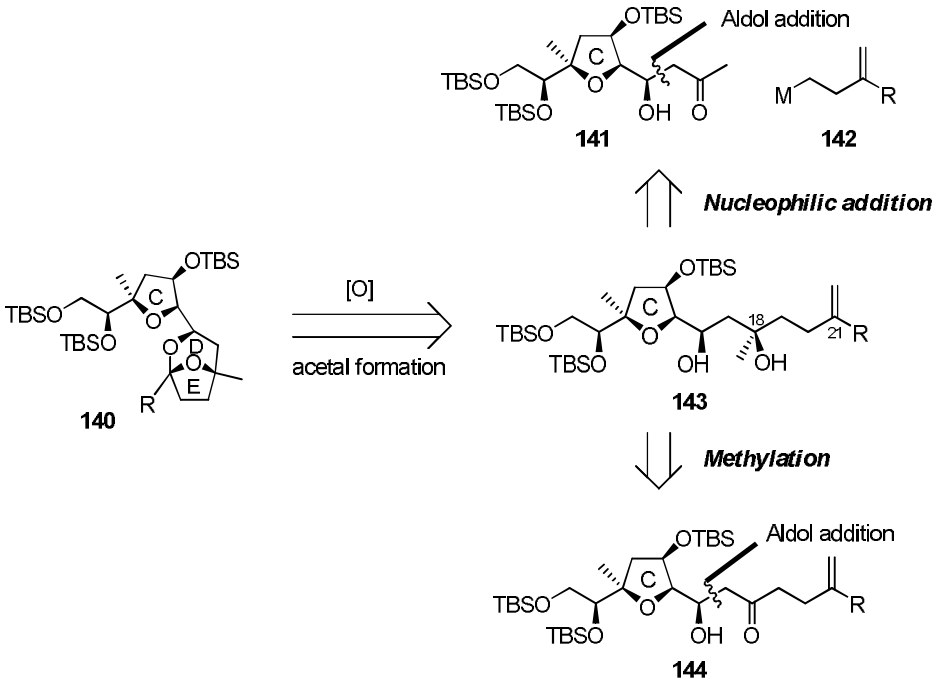


Figure 10. Crystal structure of the C10-C16 tetrahydrofuran ring system **137**.

3.5 Synthesis of CDE Ring Fragment

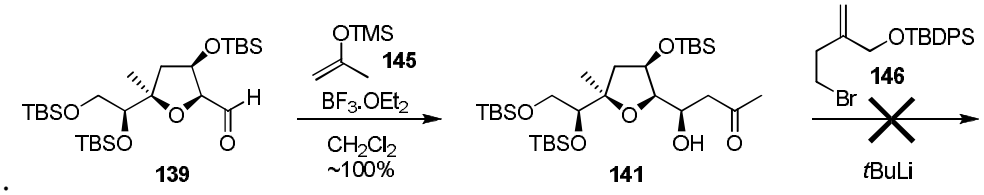
With quantities of the C ring fragment in hand, it was time to move forward. From the very beginning we had two optional strategies planned for the CDE ring synthesis (Scheme 30). In the *methylation strategy*, the carbon chain incorporating the DE ring system was to be introduced using an aldol addition followed by methylation to form the C18 quaternary center. In the *nucleophilic addition strategy*, an enol equivalent of acetone was to be added in the aldol step followed by C-alkylation using an organometallic reagent **142** incorporating rest of the DE ring carbon chain. A key feature of both strategies is that after a mild ozonolytic cleavage of the C21 masking olefin, the ketalization to form the DE ring would take place under very mild conditions, without a need to unmask any protecting groups. In regard of selectivity the formation of the C18 quaternary center was our major concern as only few literature precedents for hydroxyl-directed alkylations of β-hydroxyketones were found.[104]



Scheme 30. Retrosynthetic analysis for the synthesis of the CDE ring fragment.

3.5.1 Nucleophilic Addition Strategy

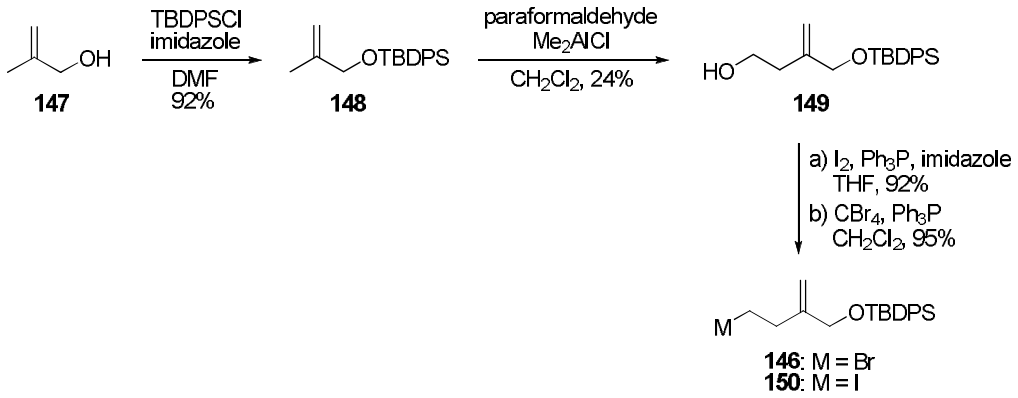
A $BF_3 \cdot OEt_2$ mediated Mukaiyama aldol reaction[105] between the C ring aldehyde **139** and commercially available (isopropenyloxy)trimethylsilane **145** furnished the desired β-hydroxyketone **141** in quantitative yield as the only observed diastereomer (Scheme 31). The rationale behind this selectivity is discussed in more detail in Chapter 3.5.2.



Scheme 31. The nucleophilic addition strategy in action.

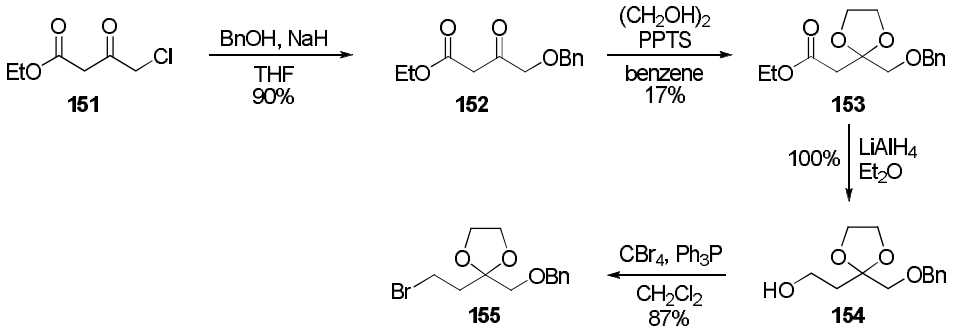
Many different kinds of functionalized organometallic compounds have been successfully used in total synthesis with a variety of complex substrates.[106] Encouraged by these literature precedents, a group of alkylation reagents were synthesized and screened.

Bromide **146** was synthesized starting from a commercially available β-methallyl alcohol **147** (Scheme 32). After TBDPS protection, regiospecific formaldehyde-ene reaction furnished homoallylic alcohol **149**, which under standard bromination conditions (CBr_4, Ph_3P) furnished bromide **146**. The corresponding iodide **150** was synthesized in a similar manner from the intermediate alcohol **149** using standard iodination conditions (I_2, Ph_3P, imidazole).



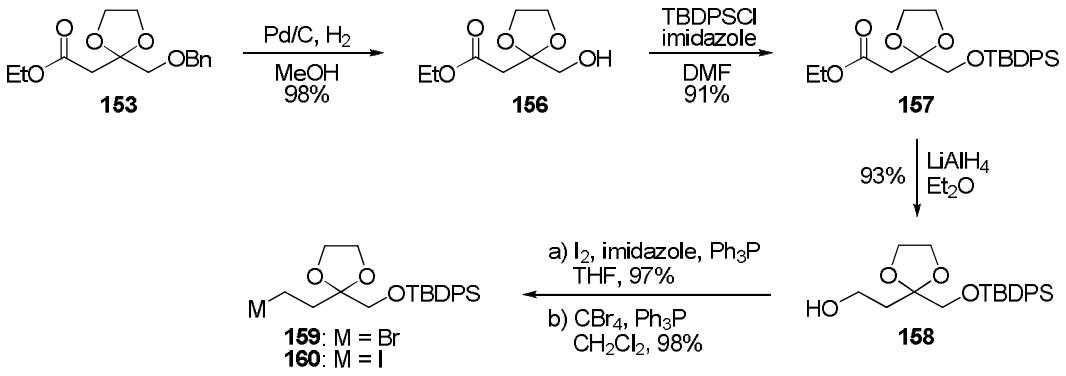
Scheme 32. Synthesis of alkylation reagents **146** and **150**.

The synthesis of bromide **155** commenced with alkylation of a commercially available ethyl 4-chloroacetoacetate **151** to give ester **152** in 90% yield (Scheme 33). Acetal protection furnished **153** in very low yields giving rise to significant amounts of side products. Reduction was initiated with $LiAlH_4$ to afford alcohol **154**, which under standard bromination conditions furnished bromide **155**.



Scheme 33. Synthesis of alkylation reagent **155**.

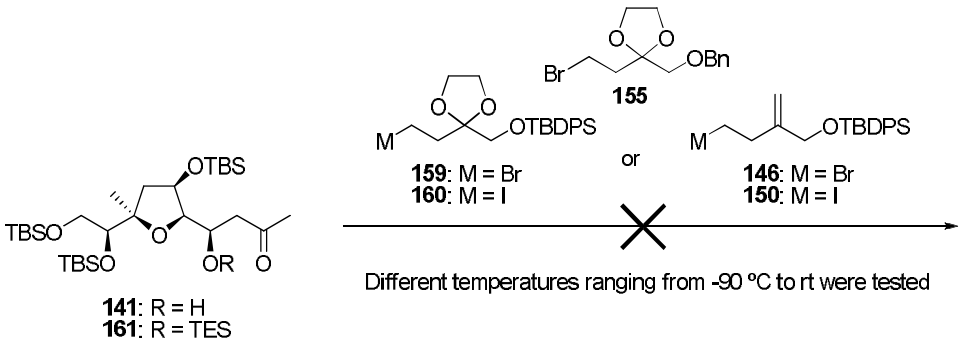
The corresponding reagents **159** and **160** with TBDPS protection were synthesized starting from ester **153**. Two additional protection group manipulations outlined in Scheme 34 were needed. After $LiAlH_4$ reduction, both the bromide **159** and the iodide **160** were accessed using the standard conditions as above.



Scheme 34. Synthesis of the alkylation reagents **159** and **160**.

The different alkylation reagents were tested both as lithium and Grignard organometallic species to effect the C-alkylation of two different ketones **141** and **161** (Table 8). Also, different methods for the lithium-halogen exchange[107], different solvent systems (Et_2O, THF, 2:3 Et_2O/pentane[108]) and different reaction temperatures, times and addition times were investigated (Table 8). To our disappointment, however, nucleophilic addition to β-hydroxyketones **141** and **161** could not be effected. All the reactions failed to deliver any detectable amount of the desired products. In some cases the starting ketone was recovered, also significant decomposition occurred especially when lithium metal was used. With *t*BuLi the reduction of the alkylation reagent was the major reaction observed (Scheme 35).[107c]

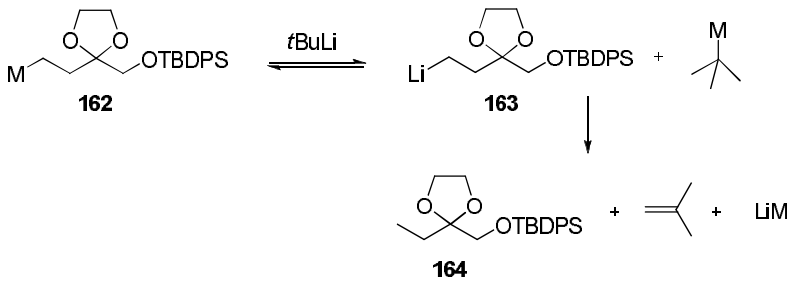
Table 8. Unsuccessful alkylation screens.



Entry	Substrate	Reagent	Li/Grignard forming reagent	Solvent
1	141	160	*t*BuLi	2:3 Et_2O:pentane
2	141	159	*t*BuLi	2:3 Et_2O:pentane
3	141	159	Mg	THF
4	141	146	Mg	THF
5	161	155	*t*BuLi	THF
6	161	155	*t*BuLi	Et_2O
7	161	155	*t*BuLi	2:3 Et_2O:pentane
8	161	160	*t*BuLi	2:3 Et_2O:pentane
9	161	159	*t*BuLi	2:3 Et_2O:pentane
10	161	150	*t*BuLi	Et_2O
11	161	150	*t*BuLi	Et_2O TMEDA
12	161	146	*t*BuLi	Et_2O
13[a]	161	150	Li	Et_2O
14[a]	161	146	Li	Et_2O

a) The reaction was also tested using microwave.

Besides reduction, also other known side reactions such as β-elimination and self-coupling together with the reversible nature of the lithium-halogen exchange might have made the generation of the organolithium reagents impossible.[107d, 109] On the other hand, the problem may well be in the electrophile, which could simply be too unreactive or readily enolizable.

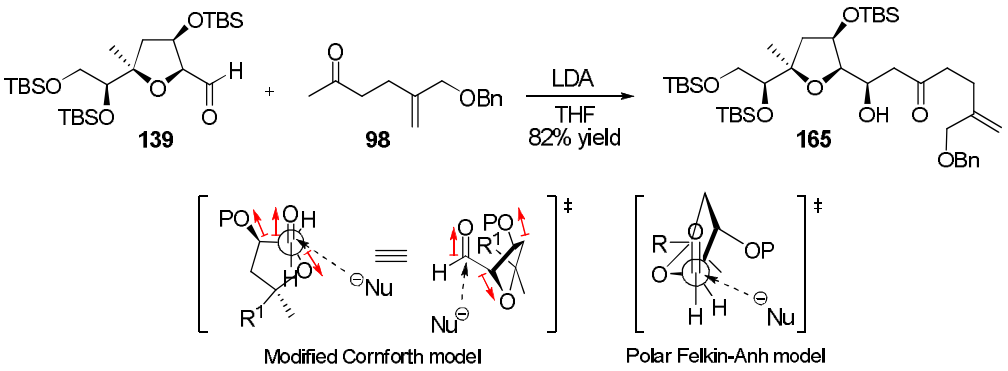


Scheme 35. The unwanted reduction of the alkylation reagents.

After significant amount of the intermediate ketones **141** and **161** were lost to baseline during the alkylation screens, our attention was directed to the alternative construction of the CDE ring fragment by means of the methylation strategy.

3.5.2 Methylation Strategy

To this end, the aldol partner **98** was synthesized according to previously published procedure.[110, 111] Aldol addition between aldehyde **139** and lithium enolate of ketone **98** proceeded nicely to give a single *anti* product **165** in 82% yield (Scheme 36). The *anti* selectivity is in agreement with the modified Cornforth[112] transition state model, although the polar Felkin-Anh[113] model also predicts the same outcome (Scheme 36). Furthermore, the high level of diastereoselection observed suggests that the α,β-*syn* relationship of the oxygen substituents in **139** represents a stereochemically matched case. Similar selectivities, albeit reduced yields (61%), were obtained by using a related enolsilane (TMS/$BF_3 \cdot OEt_2$).



Scheme 36. Cornforth selective aldol addition between aldehyde **139** and ketone **98**.

Based on the precedent by Fujisawa,[104a] titanium reagents were considered as prime candidates for the hydroxyl-directed methylation to obtain the desired *anti* product. There are two possible modes to achieve 1,3-induction in hydroxyl-directed additions: either the nucleophile is delivered externally (from an external reagent) or internally (directed addition) (Figure 11).[114]

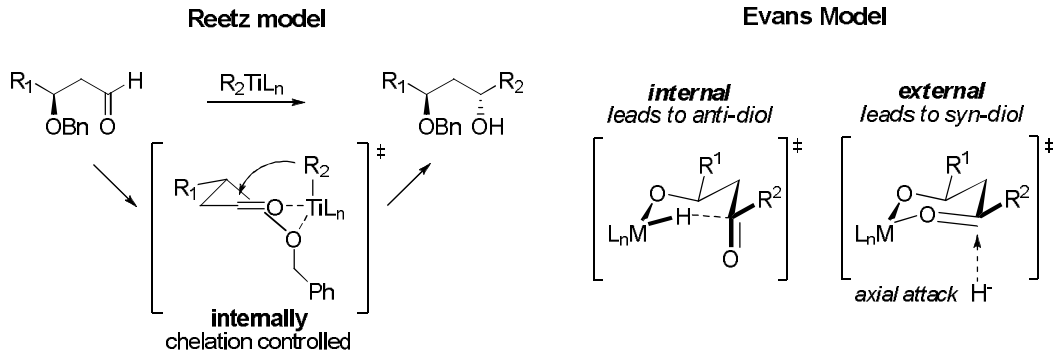
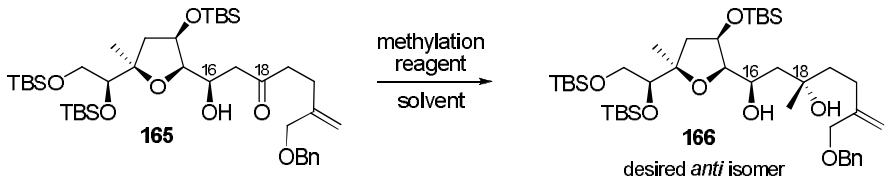


Figure 11. Reetz model for chelation controlled 1,3-induction and Evans model for internal and external addition (in hydride reduction of β-hydroxyketones).

To our delight, initial experiment in 0.25 mmol scale with MeTi(O*i*Pr)$_3$ gave the desired *anti*-diol product **166** in 8:1 diastereoselectivity (Table 9). However, considerable difficulties were encountered in reproducing this result. With determination to resolve this complication, experiments to screen different conditions for this key transformation were conducted (Table 9).

In comparison with methyltitanium reagents, Mg and Zn reagents gave inferior selectivity (entries 2-3). Surprisingly, predistilled MeTi(O*i*Pr)$_3$[115] turned out to be very unreactive, even with 15 equiv of the reagent (entry 4). More Lewis acidic reagents, MeTiCl$_3$ or MeTi(O*i*Pr)$_2$Cl (entries 5-6) gave no progress under comparable conditions, neither did the use of more reactive Me$_2$Ti(O*i*Pr)$_2$ or less hindered MeTi(OMe)$_3$ (entries 7-9). An excess of Ti(O*i*Pr)$_4$ has been suggested to facilitate the removal of the product from the metal center thus promoting the formation of an active complex.[116] In our hands, using excess Ti(O*i*Pr)$_4$ did not afford any improvement in selectivity or reproducibility (entry 10). Eventually, the best reproducible selectivities (9:1) and yields (91%) were obtained using an excess of the *in situ* prepared MeTi(O*i*Pr)$_3$ at –78 °C followed by quick warming to 0 °C (entry 11). The two diastereomers could be separated by a careful column chromatography after cyclization of the DE ring system. Further details, including screens with different solvents and additives in the methylation step are presented in the experimental section under Chapter 5.5.2.8.

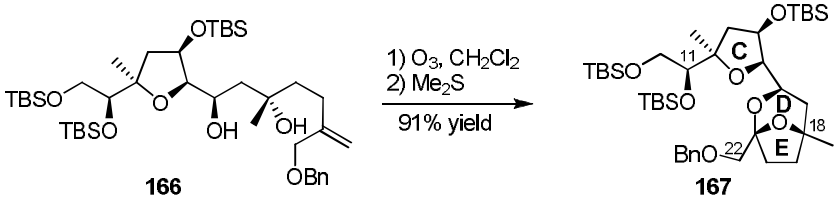
Table 9. *Anti* selective addition of methyl nucleophiles with different reagents.



Entry	Methylation reagent[a]	Equiv	Solvent	T [°C]	Time [min at –78/0°C]	dr[b]	Conversion [%][b]
1	$MeTi(OiPr)_3$	5	Et_2O	–78 to 0	10/10	8:1 – 2:3	100
2	$MeLi/ZnBr_2$	4	CH_2Cl_2	–78	240	3:2	100
3	MeMgBr	1	Et_2O	–78	15	2:1	100
4	$MeTi(OiPr)_3$[c]	15	Et_2O	–78 to 0	10/10	4:1	80
5	$MeTiCl_3$	15	Et_2O	–78 to 0	10/10	1:1	20
6	$MeTi(OiPr)_2Cl$	15	Et_2O	–78 to 0	10/10	3:1	100
7	$Me_2Ti(OiPr)_2$	15	Et_2O	–78 to 0	10/10	6:1	100
8	$Me_2Ti(OMe)_2$	15	Et_2O	–78 to 0	10/10	2:1	100
9	$MeTi(OMe)_3$	15	Et_2O	–78 to 0	10/10	4:1	100
10	$MeTi(OiPr)_3$[d]	15	Et_2O	–78 to 0	10/10	4:1	100
11	$MeTi(OiPr)_3$	15	Et_2O	–78 to 0	10/10	9:1	100

[a] Reagents were prepered *in situ*. [b] Determined by ^1H NMR from the crude reaction mixture. [c] $MeTi(OiPr)_3$ was distilled prior to use. [d] Excess $Ti(OiPr)_4$ (15 equiv) was used.

Having found a solution to the methylation problem, all that remained was ozonolysis of the double bond followed by ketalization to furnish the CDE ring system. Fortunately, using the mild reductive work-up for the ozonolysis (Me_2S at –78 ºC to rt, for 3h), trickered also the ketalization to afford the desired CDE ring fragment **167** in 91% yield (Scheme 37).



Scheme 37. The synthesis of the CDE ring fragment **167**.

NOESY cross-peaks confirmed both the selectivity of the aldol step and the methylation step (Figure 12). Furthermore, analysis of the relevant coupling

constants clearly indicated a chair conformation for the D ring and close to an antiperiplanar orientation between H15 and axial H16 (Figure 12).

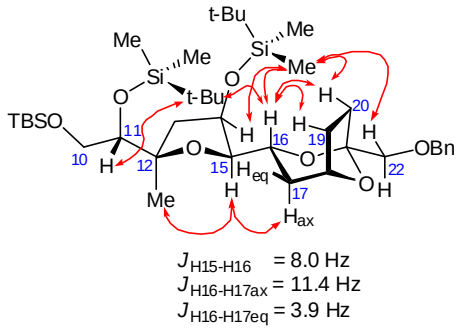
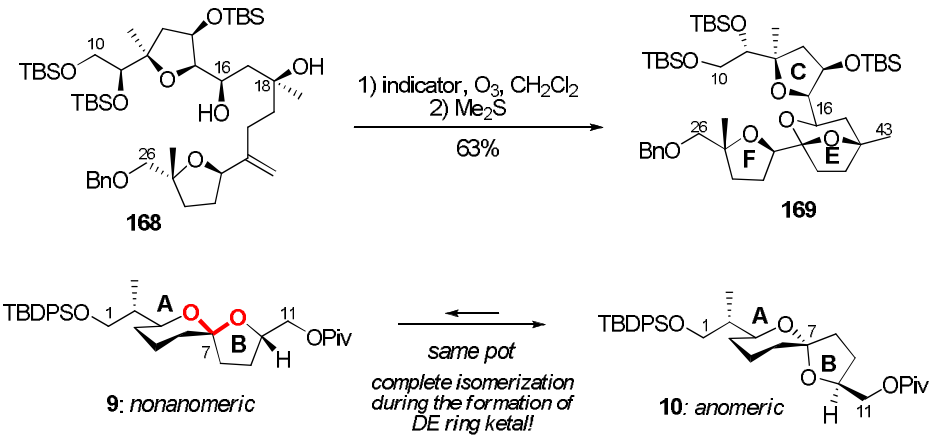


Figure 12. Selected NOESY cross-peaks and coupling constants.

The final step of the CDE ring synthesis was also used in the CDEF ring synthesis by my co-worker Hannes Helmboldt.[117] In his study the ozonolysis – ketal cyclization sequence was tested using a mixture of diol **168** and a small amount of the nonanomeric AB spiroketal **9** (Scheme 38). To our surprise, even these conditions were not mild enough to preserve the nonanomeric AB spiroketal, which underwent fast and complete isomerization into the more stable anomeric isomer **10** during the Me_2S work-up. This result further confirmed our assumption that a key strategic issue in this total synthesis venture is the stability of the ever-enthralling nonanomeric AB spiroketal ring system.

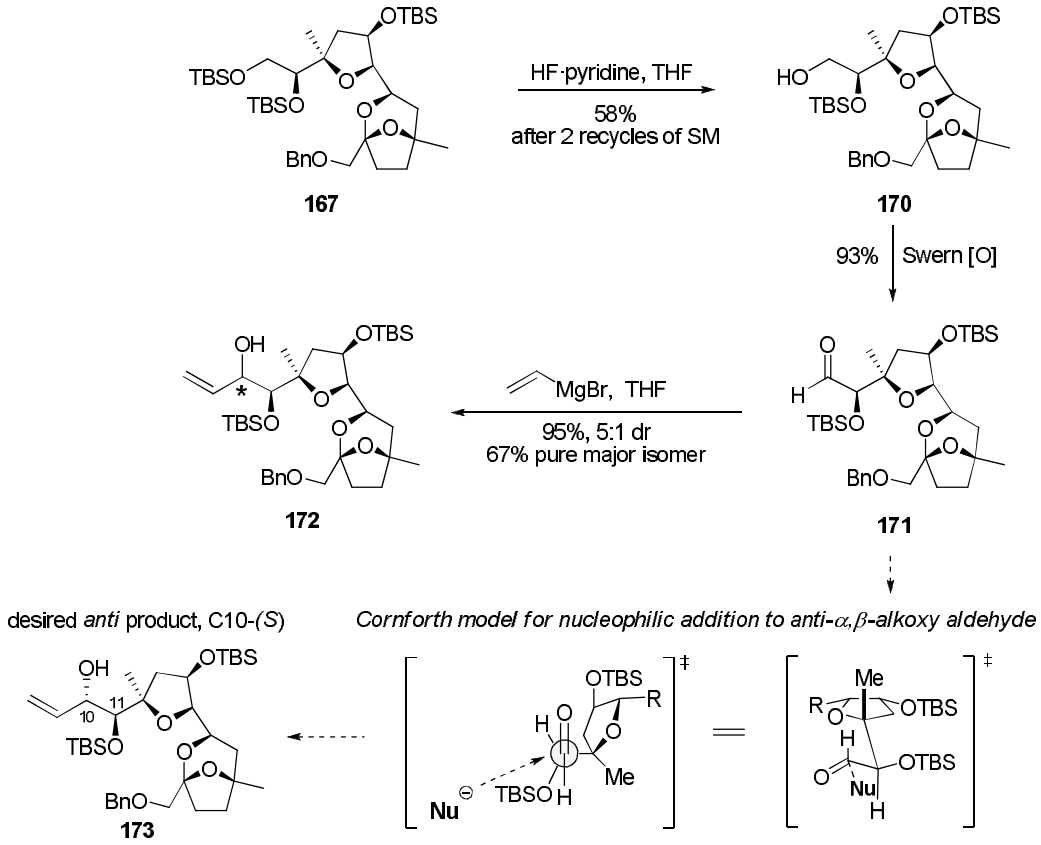


Scheme 38. Testing the stability of the nonanomeric AB spiroketal during the CDEF ring synthesis.

Selective deprotection of the primary TBS group in **167** turned out to be problematic. Eventually, HF·pyridine served this purpose best, giving alcohol **170** in moderate 58% yield after two recycles of the starting material (Scheme 39). In addition, the over-deprotected products could be separated and further recycled. Other methods (PPTS, *p*-TsOH, TASF, CAN on silica[118]) either afforded recovered starting material, or gave similar yields with HF·pyridine accompanied with decomposition of the starting material. While the yields obtained with HF·pyridine were not excellent, being so close to the end, the decision was made to proceed rather than attempt to optimize the reaction any further.

Having secured the targeted CDE ring fragment, it was time to add two carbons required to form the B ring of the PTX2 structure. Grignard addition into an aldehyde was chosen to deliver the desired *anti* relationship between C10 and C11 hydroxyl groups (Scheme 39). Sequential oxidation of alcohol **170** using the Swern protocol, followed by addition of vinyl Grignard delivered a 5:1 mixture of isomeric allylic alcohols in nearly quantitative yield (Scheme 39). The two isomers were readily separated with column chromatography to furnish the major isomer **172** in 67% yield. When vinyllithium was used for this reaction, slightly better selectivities (6:1) were obtained albeit much lower yields (~45%) due to considerable formation of a side product (see Experimental Section 5.6.3).

Although the stereochemistry of the addition step was not determined at this stage, we were confident that the stereochemistry could be confirmed after the formation of the ABCDE ring system. We predicted however, that the addition would follow the modified Cornforth model for *anti*-α,β-alkoxy aldehydes, and thus would deliver the desired *anti* product **173** (Scheme 39).[112b] As such we were confident enough that we had the right isomer to move ahead with the synthesis.



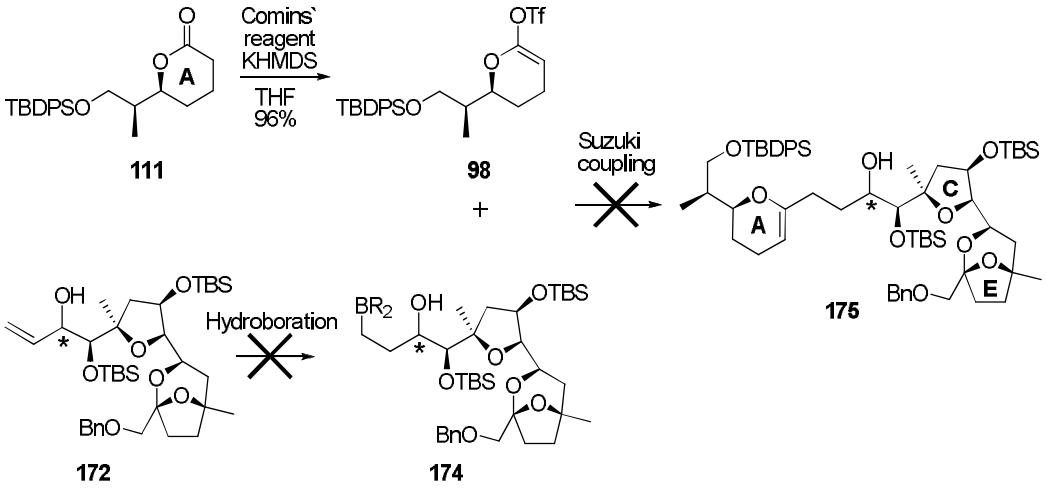
Scheme 39. Synthesis of allylic alcohol **172**.

3.6 Synthesis of ABCDE Ring Fragment

With efficient syntheses for the A ring lactone and the CDE ring fragment accomplished, we now turned our attention to the construction of the ABCDE ring system as defined by the retrosynthetic analysis in Figure 8. To set the stage for the planned Suzuki-Miayura coupling[119], all that was needed was conversion of the A ring lactone into the corresponding enol triflate and hydroboration[120] of the CDE ring allylic alcohol.

Trapping the enolate of the A ring lactone **111** using Comins` reagent[121] cleanly afforded the desired enol triflate **98** (Scheme 40). However, hydroboration failed completely to give the desired coupling partner **174**. Extensive screening of different reagents (9-BBN,[122] CB,[123] thexylborane,[124] $BH_3 \cdot SMe_2$[125])[120b] turned out unsuccessful, giving either recovered starting material together with

decomposition or a large number of products, none of which resembled the desired borates.

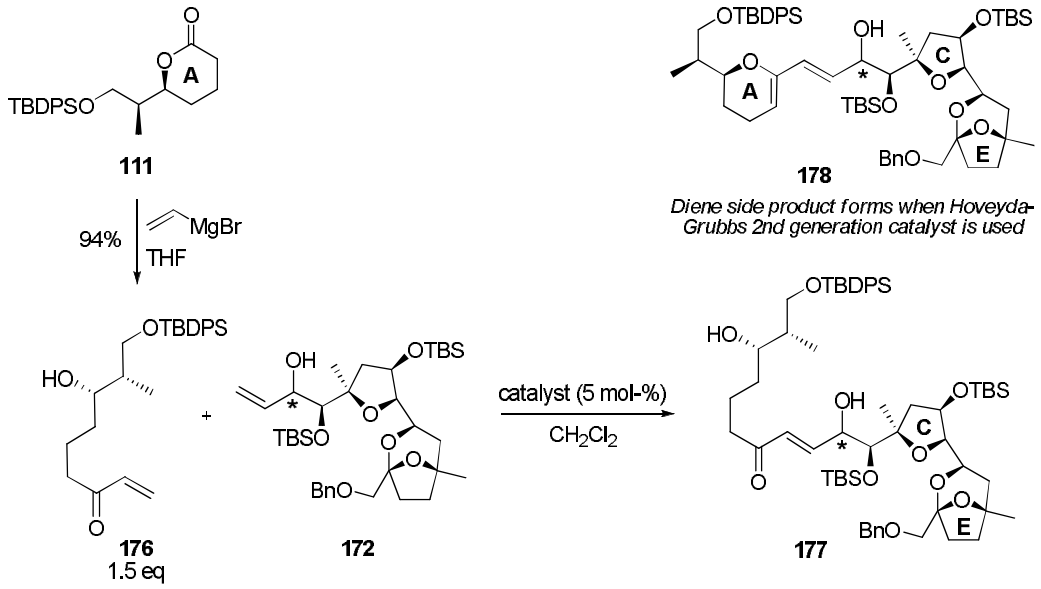


Scheme 40. Suzuki coupling in action.

Despite the double bond was found entirely unreactive towards hydroboration, we decided to give it another change and once again turned our attention to metathesis. As a bit of a surprise, cross-metathesis between an open-chained ketone **176** and the CDE ring allylic alcohol **172** initiated by Hoveyda-Grubbs 2nd generation catalyst furnished the desired product **177** in moderate 50% yield (Table 10, entry 1). We were quite pleased with this result as the two olefins are not exactly a perfect match to achieve a selective cross-metathesis.[126] Unfortunately, however, reproducibility problems were once again encountered. Repeating the reaction under precisely similar conditions, as were used for the initial successful reaction, only furnished an undesired product **178** (entry 2). Nonetheless, encouraged by the first positive result we set of to explore this protocol further. As matters turned out, the metathesis product exhibits a considerable tendency to undergo ring closure followed by elimination of water to give diene **178** under the reaction condition. This diene is extremely unstable and significant decomposition occurs within few hours at 8 ºC. Also, when subjected to a variety of hydrogenation conditions it totally decomposes.

The mild Lewis-acidic nature of Hoveyda-Grubbs 2nd generation catalyst[127] was considered as the potential source of these complications. This hypothesis was tested by buffering the reaction mixture with pyridine. Under these conditions, the desired product **177** could again be isolated in 48% yield with no trace of diene **178** (entry 3). Further experimentation revealed that Grubbs 2nd generation catalyst[128] is ideal for this coupling, affording the desired metathesis product **177** in reproducible yields (48-55%, plus 36-45% recovered **172**), without a need for a basic buffer (entry 4). As such, metathesis once again proved to be a reliable construction tool in a total synthesis venture with complex and highly functionalized substrates.[129]

Table 10. Cross-metathesis.



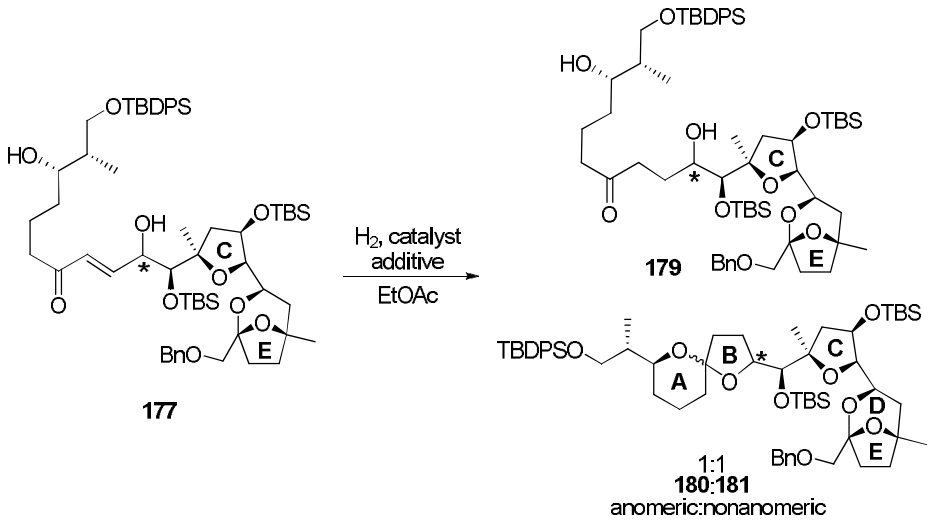
Entry	Catalyst	Product (yield [%])
1	Hoveyda-Grubbs 2nd gen. catalyst	177 (50)
2	Hoveyda-Grubbs 2nd gen. catalyst	178 (52)
3	Hoveyda-Grubbs 2nd gen. cat. + pyridine	177 (48)
4	Grubbs 2nd gen. catalyst	177 (48-55)

The metathesis product **177** included all the carbon atoms required for the targeted ABCDE ring fragment, and we were only two steps away from the final destination. It was time to confront the hydrogenation challenge. To avoid an

uncontrolled closure of the spiroketal ring system under the hydrogenation conditions, two sets of experiments were needed (Table 11). The Wilkinson catalyst was selected as the first candidate, mainly because it was easily accessible and operationally simple to test. However, when ketone **177** was hydrogenated in the presence of Wilkinson catalyst, after a few hours a substantially less polar product mixture was formed, that was characterized as a 1:1 mixture of the anomeric and the nonanomeric spiroketals (entry 1). The Wilkinson catalyst was also tested using 2,6-lutidine as a buffer, but under these conditions only starting material was recovered (entry 2).

The classical reduction using catalytic palladium on charcoal was chosen as the second candidate also for its reliability and simplicity. As was the case with the Wilkinson catalyst, Pd/C cleanly hydrogenated the double bond, but also effected ring closure to give a 1:1 mixture of the spiroketal isomers **180** and **181** (entry 3). Ultimately, it was found that Pd/C poisoned with pyridine[130] gave the desired product **179** in almost quantitative yields (entry 4).

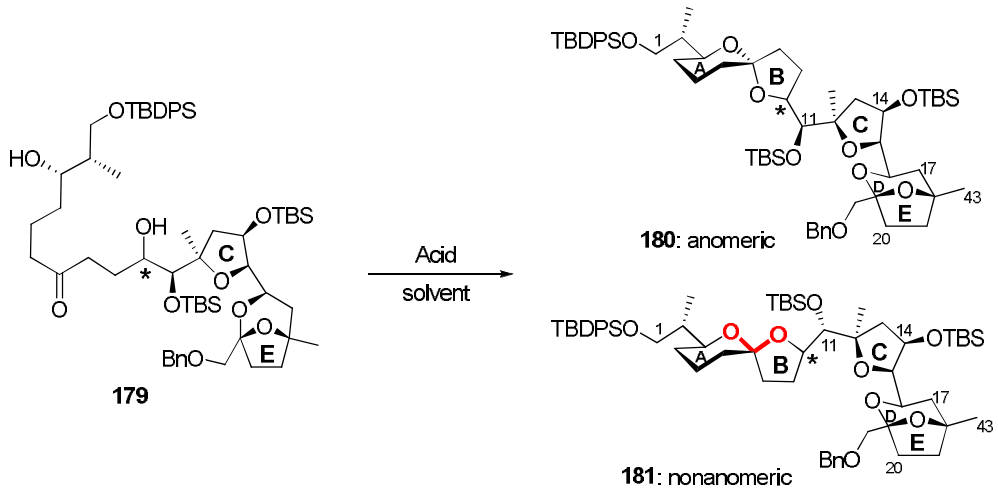
Table 11. Hydrogenation screens.



Entry	Catalyst	Additive	Product (conversion [%])
1	Wilkinson	-	180 and 181 (100)
2	Wilkinson	2,6-lutidine	No reaction
3	Pd/C	-	180 and 181 (100)
4	Pd/C	pyridine	179 (100)

Finally, it was time to test the kinetic spiroketalization, and above all reach for the final target, the ABCDE ring fragment of PTX2. The optimal conditions developed in the AB spiroketal ring synthesis ($ClCH_2COOH$, CH_2Cl_2) gave a clean conversion into a 1:3 mixture of the anomeric **180** and the nonanomeric **181** spiroketal isomers (Table 12, entry 1). Even though this result was all that we could ever have expected, we still needed to dig further. It is known that the anomeric effect decreases with increasing dielectric constant of the medium.[47a, 98] This effect was also demonstrated by my co-workers with the simple spiroketalization substrates.[97] Surprisingly, the aqueous conditions (Cl_3CCOOH, 4:1 THF:H_2O) that gave the best results with the simpler systems, furnished an unsatisfying 1:1 mixture of the spiroketal isomers (entry 2). In addition, when chloroacetic acid was used in THF:H_2O a significant decrease in the reaction rate was observed compared to CH_2Cl_2 as the medium (entry 3).

Table 12. Kinetic spiroketalizations to form the ABCDE ring fragment.



Entry	Acid	Solvent	Time [h]	180:181 (conversion [%])
1	$ClCH_2COOH$	CH_2Cl_2	0.5	1:3 (100)
2	Cl_3CCOOH	4:1 THF:H_2O	4	1:1 (100)
3	$ClCH_2COOH$	4:1 THF:H_2O	20	1:1 (20)

In contrast to our previous experience, the nonanomeric isomer was less polar than the anomeric isomer and the difference in the polarities was very small. For

this reason, significant difficulties were encountered in purification. The pure nonanomeric isomer **181** could be isolated in 29% yield after careful column chromatography. After equilibrating a mixture of the spiroketal isomers with PPTS a 3:1 mixture of the anomeric and the nonanomeric isomer was formed, giving after purification the pure anomeric isomer **180** in 67% yield.

The configurations of the spiroketal isomers were confirmed by NOESY experiments. Based on a NOE between H3 and H8, spiroketal **182** was clearly identified as the nonanomeric isomer (Figure 13, the ABCDE ring fragments are presented as the desired C10-(*S*) isomers). Further confirmation was again obtained from the ^{13}C NMR, where the chemical shift of the spiro carbon (C7) was shifted downfield for the nonanomeric isomer relative to the anomeric isomer (108.0 ppm in **182** vs. 105.8 in **183**).[12b, 51b] The 2D-NOESY spectra of the anomeric spiroketal **183** showed a surprising and slightly alarming correlation between H11 and C41 methyl group, which could indicate that we have the wrong stereochemistry at C10 (Figure 13).

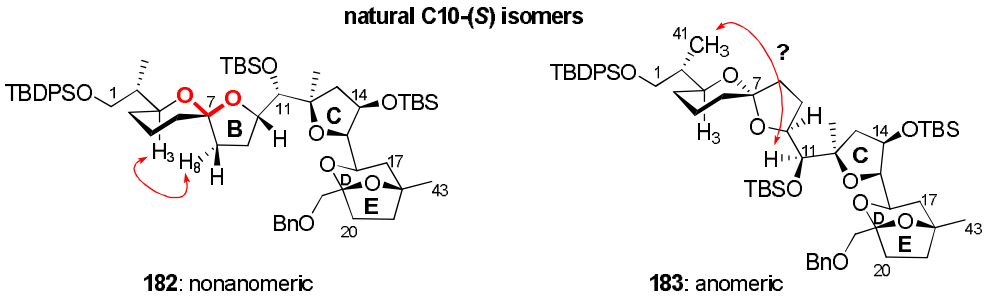
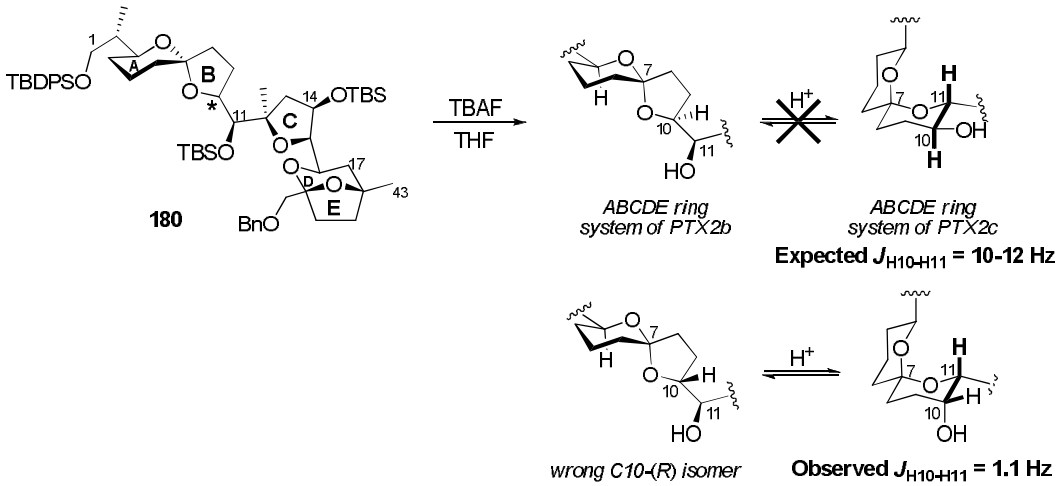


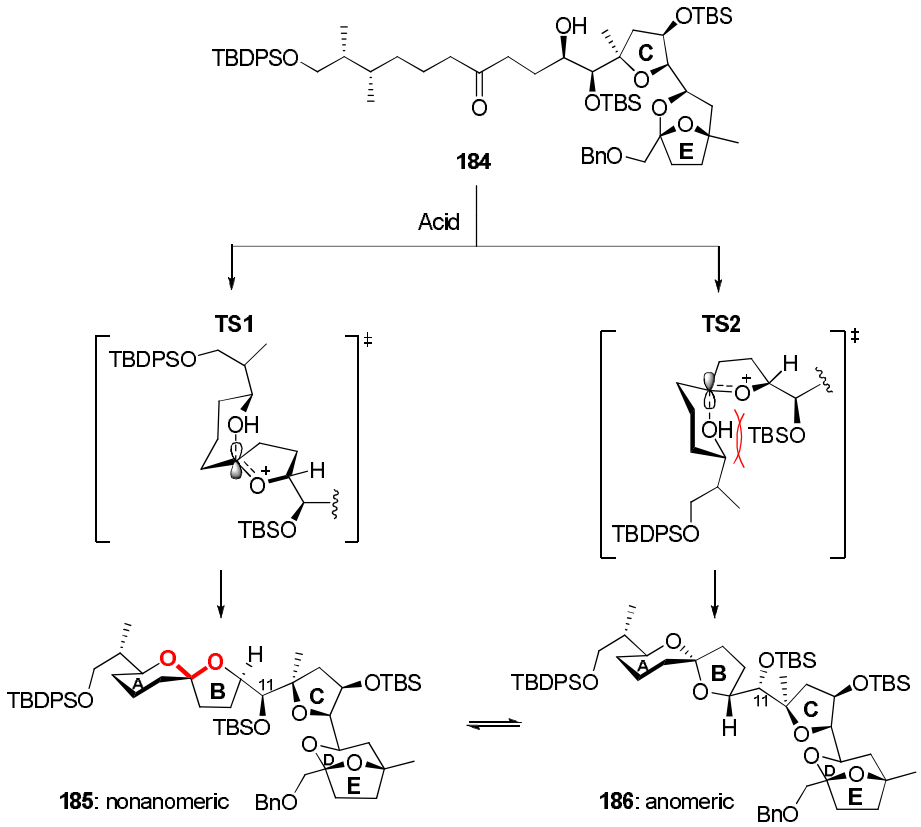
Figure 13. The most important NOESY cross-peaks.

In order to confirm this suspicion, the anomeric spiroketal isomer **180** was treated with TBAF which cleanly removed the TBS and TBDPS protection groups. Acid-catalyzed equilibration of the crude product with *p*-TsOH in CH_2Cl_2 then delivered the corresponding [6,6]-spiroketal product in 86% yield (Scheme 41). We were expecting to see a large coupling constant characteristic to diaxial hydrogens, however to our great disappointment a very small coupling constant of 1.1 Hz was observed, indicating that we had the wrong C10 isomer! (Scheme 41).



Scheme 41. Checking the C10 stereochemistry.

In all of our previous studies, the unnatural C10-(*R*) isomer only gave very small amounts, if any, of the nonanomeric product. For this reason we were very surprised to discover the wrong stereochemistry at C10. As such, a model to explain the formation of the nonanomeric spiroketal **185** as the major product was developed (Scheme 42). Under acidic conditions the five-membered ring is expected to close first. Also, the reaction is assumed to proceed via oxonium ion intermediate, from which follows that the five-membered ring becomes almost flat in the transition state. The incoming nucleophile should prefer the less hindered top face (TS1), giving the nonanomeric isomer **185**. Whereas, TS2 should have higher activation energy, and thus smaller amounts of the anomeric isomer **186** should be formed under kinetic conditions.



Scheme 42. Proposed transition states for the formation of the anomeric and nonanomeric 10-epi-ABCDE ring fragments.

4 CONCLUSION AND FUTURE STUDIES

The objective of this work was to synthesize the ABCDE ring fragment of PTX2. Towards this objective, three advanced fragments corresponding to the A, C and DE rings were synthesized and connected in highly convergent manner. As a key feature, the delicate nonanomeric AB spiroketal ring structure was formed as the last synthetic step.

The A ring lactone was synthesized in 9 steps with 14% overall yield, using Sharpless asymmetric epoxidation and regioselective epoxide ring opening as the key steps. The A ring lactone was also used for the synthesis of the AB spiroketal ring fragment of the PTXs. Importantly, as a result of kinetic control in the spiroketalization reaction, the nonanomeric isomer could be formed as the major product.

For the synthesis of the C ring fragment, Sharpless asymmetric epoxidation and dihydroxylation were used as the key steps, to give the important central unit with high stereocontrol in 9 steps and 46% overall yield. An aldol union of the C ring aldehyde with the DE ring fragment furnished the desired β-hydroxyketone intermediate with excellent stereoselectivity. After extensive screening and optimization, methylation of this ketone to form the C18 quaternary center was achieved with reproducible 9:1 selectivity, giving access to the CDE ring fragment of PTX2 with the correct stereochemistry.

For the extension of the carbon chain towards the A ring, an addition of a vinyl organometallic reagent to the CDE ring aldehyde was used, affording a mixture of two diastereomeric allylic alcohols in 5:1 selectivity. The major isomer was connected with the A ring building block by cross-metathesis. Finally, the kinetic

spiroketalization conditions afforded the ABCDE ring product as a 3:1 mixture of the nonanomeric and anomeric isomers. Unfortunately, it was observed that the vinyl organometallic addition step had favored the undesired C10 diastereomer. Thus, instead of the natural ABCDE ring system, we had synthesized the 10-epi-ABCDE ring fragment of PTX2.

Needless to say, I was of course very disappointed with this result, but not totally discouraged. A long the way, I have come to realize, that as the substrates become more and more complex and highly functionalized, there is little room for predictions. Most of the models that apply with the simple substrates might give an entirely the opposite result when more complex substrates are used. Overall, every total synthesis project is a high-risk endeavor. Negative results are expected, they are a fundamental part of the process and also critical to success. When we discover a reaction that doesn't work, we gain knowledge that eventually will help us learn and discover new reactions and methods that do work.

The correction of the C10 stereocenter will be studied in the near future. As primary solutions, Mitsunobu inversion and a sequence of oxidation and stereoselective reduction will be tested. These methods would provide a quick access to the spiroketalization substrate, allowing further research on the key kinetic spiroketalization step. However, also the possibility of altering the selectivity of the vinyl organometallic addition step will be evaluated in due course. In any case, we are confident that the stereochemistry of the C10 can be inverted, finally giving access to the natural ABCDE ring fragment of PTX2.

5 EXPERIMENTAL SECTION

5.1 General Experimental

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. Nonaqueous reagents were transferred under argon *via* syringe or cannula and dried prior to use. Et_3N and *i*-Pr_2NH were distilled from Na. THF and Et_2O were distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2 and DMF was distilled from molecular sieves (4 Å). A stock sample of dry TBHP was dried by the procedure of Sharpless and co-workers.[85c] All batches of TBHP were also dried on 4 Å molecular sieves immediately prior to use. Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230-400 mesh) plates and analyzed by UV light or by staining upon heating with vanillin solution (6 g vanillin, 5 mL conc. H_2SO_4, 3 mL glacial acetic acid, 250 mL EtOH) or $KMnO_4$ solution (1 g $KMnO_4$, 6.7 g K_2CO_3, 1.7 mL 1M NaOH, 100 mL H_2O). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230-400 mesh) and p.a. grade solvents unless otherwise noted.

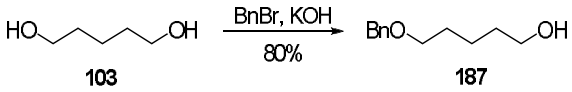
The ^1H NMR and ^{13}C NMR spectra were recorded in either $CDCl_3$, CD_3CN or C_6D_6 on a Bruker Avance 400 (^1H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26), CHD_2CN (δ 1.94) or C_6D_5H (7.16) for ^1H NMR. For the ^{13}C NMR spectra, the residual $CDCl_3$ (δ 77.0), CD_3CN (δ 118.26) or C_6D_6 (128.06) were used as the internal standards. The enantiomeric excess (ee) of the products were determined by HPLC in comparison to the corresponding racemic samples using Waters 501 pump and

Waters 486 detector. Melting points (mp) were determined in open capillaries using Gallenkamp melting point apparatus. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter. High resolution mass spectrometric data were measured using MicroMass LCT Premier Spectrometer. Some of the high resolution mass spectrometric data was obtained by the University of Oulu on Micromass LCT spectrometer. Elemental analyses were recorded on a Perkin-Elmer 2400 CHN by the Elemental Analytical Services of the Department of Chemistry.

The racemic samples corresponding to compound **107** were prepared using *m*-CPBA (120 mol-% in CH_2Cl_2) as the oxidant for **106**. All racemic samples were purified and all subsequent reactions were performed in a manner identical to their enantioenriched counterparts.

5.2 Synthesis of A Ring Fragment

5.2.1 5-Benzyloxypentanol 187[86]

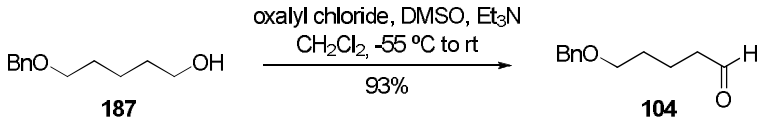


103 187

To neat 1,5-pentanediol **103** (47.3 mL, 46.9 g, 450 mmol, 349 mol-%) at rt was added both benzyl bromide (15.3 mL, 22.1 g, 129 mmol, 100 mol-%) and powdered KOH (30.4 g, 542 mmol, 420 mol-%) in four equal portions over 1 h. After the last addition the solution was stirred for an additional 4 h. H_2O (75 mL) was then added. The layers were separated and the aqueous phase was extracted with EtOAc (4 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (initially 30% EtOAc/hexanes, finally 70% EtOAc/hexanes) afforded 5-benzyloxypentanol

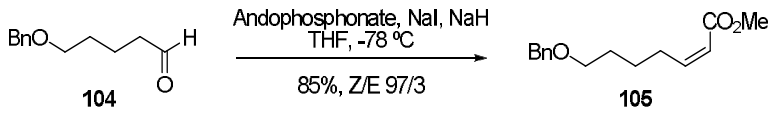
187 (20.1 g, 80%) as pale yellow oil. IR- and ^{1}H NMR-data match those reported in literature.[88]

5.2.2 5-(Benzyloxy)pentanal 104



A solution of oxalyl chloride (1.9 mL, 2.74 g, 21.6 mmol, 110 mol-%) in CH_2Cl_2 (20 mL) was cooled to –55 °C and DMSO (3.1 mL, 3.37 mg, 43.1 mmol, 220 mol-%) was added. After 5 min, a solution of 5-benzyloxypentanol **187** (3.81 g, 19.6 mmol, 100 mol-%) in CH_2Cl_2 (45 mL) was added. The resulting mixture was stirred for 15 min. Triethylamine (13.1 mL, 9.52 g, 94.1 mmol, 480 mol-%) was then added dropwise. Stirring was continued at –55 °C for an additional 10 min and then the mixture was allowed to warm to rt. H_2O (100 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic extracts were washed with brine (2 x 60 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (30% EtOAc/hexanes) afforded 5-(benzyloxy)pentanal **104** (3.5 g, 93%) as pale yellow oil. IR- and ^{1}H NMR-data match those reported in the literature.[88]

5.2.3 7-(Benzyloxy)-methyl-2-(*Z*)-hepteonate 105

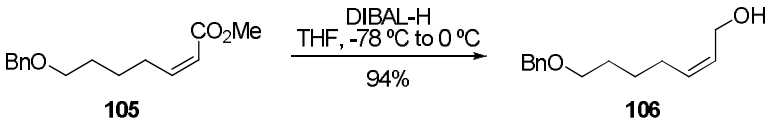


To a solution of bis(*o*-cresyl) phosphonoacetate[90a] (7.4 mL, 9.03 g, 27.0 mmol, 130 mol-%) in THF (150 mL) at 0 °C was added NaI (3.12 g, 20.8 mmol, 100 mol-%). After 5 min, NaH (60% dispersion in mineal oil, 0.65 g, 27 mmol, 130 mol-%) was slowly added and the resulting mixture was cooled to –78 °C. A

solution of 5-(benzyloxy)pentanal **104** (4.0 g, 20.8 mmol, 100 mol-%) in THF (15 mL) was added dropwise *via* cannula. The resulting solution was stirred at –78 ºC for an additional 8 h, after which time half-saturated NH_4Cl (120 mL) was added. H_2O (50 mL) was added to obtain a clear solution and the mixture was allowed to warm to rt. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 80 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (5% EtOAc/hexanes) afforded 7-(benzyloxy)-methyl-2-(*Z*)-heptenoate **105** (4.39 g, 85%, *Z*/*E* 97/3) as pale yellow oil.

R_f (50 % EtOAc/hexanes) = 0.63; IR (film, cm^{-1}): 2944, 2859, 1723, 1645, 1438, 1199, 1170, 1103, 736, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 6.22 (dt, 1H, *J* = 11.5, 7.5 Hz), 5.78 (dt, 1H, *J* = 11.5, 1.7 Hz), 4.50 (s, 2H), 3.70 (s, 3H), 3.49 (t, 2H, *J* = 6.4 Hz), 2.68 (dq, 2H, *J* = 7.5, 1.7 Hz), 1.70-1.63 (m, 2H), 1.60-1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 150.4, 138.6, 128.3, 127.6, 127.5, 119.4, 72.9, 70.0, 51.0, 29.3, 28.7, 25.6; HRMS (ESI^+): *m/z* calcd for $[C_{15}H_{20}O_3Na]$ 271.1310, found 271.1307, Δ = 1.1 ppm.

5.2.4 7-(Benzyloxy)-methyl-2-(*Z*)-hepten-1-ol 106



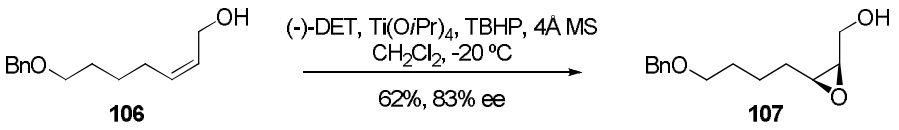
105 **106**

A solution of enoate **105** (2.86 g, 11.5 mmol, 100 mol-%) in THF (150 mL) was cooled to –78 ºC and DIBAL-H (28.8 mL of 1M solution in toluene, 28.8 mmol, 250 mol-%) was added dropwise over a period of 10 min. The resulting solution was stirred at –78 ºC for an additional 45 min and then warmed to 0 ºC. After 1.5 h, the reaction was quenched with sat. aq. Rochelle's salt (100 mL). The mixture was warmed to rt and stirred for an additional 1.5 h. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with H_2O, sat. aq. $NaHCO_3$ and brine

(60 mL each), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (40% MTBE/hexanes) afforded 7-(benzyloxy)-methyl-2-(*Z*)-hepten-1-ol **106** (2.39 g, 94%) as pale yellow oil.

R_f (50 % EtOAc/hexanes) = 0.33; IR (film, cm^{-1}): 3369, 2935, 2859, 1454, 1102, 1027, 735, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 5.65-5.50 (m, 2H), 4.50 (s, 2H), 4.18 (d, 2H, *J* = 6.6 Hz), 3.47 (t, 2H, *J* = 6.4 Hz), 2.10 (q, 2H, *J* = 7.3 Hz), 1.66-1.59 (m, 2H), 1.50-1.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 132.8, 128.7, 128.3, 127.6, 127.5, 72.9, 70.2, 58.5, 29.2, 27.2, 26.2; HRMS (ESI^+): *m/z* calcd for [$C_{14}H_{20}O_2Na$] 243.1361, found 243.1360, Δ = 0.4 ppm.

5.2.5 Epoxide 107[85c]

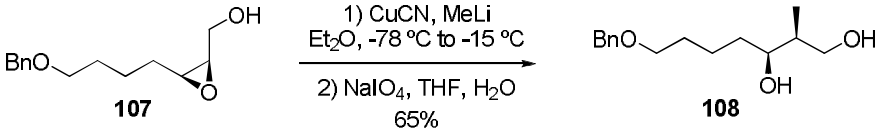


To a stirred 0 °C solution of crushed 4Å molecular sieves (0.6 g) in CH_2Cl_2 (20 mL) were added D-(-)-diethyltartrate (0.23 mL, 0.28 g, 1.36 mmol, 30 mol-%) and $Ti(OiPr)_4$ (0.27 mL, 0.26 g, 0.91 mmol, 5 mol-%). This mixture was cooled to –20 °C and *tert*-butyl hydroperoxide (1.8 mL of a ~5.0 M solution in isooctane, ~9.08 mmol, 200 mol-%) was added. The resulting mixture was stirred for 20 min before a solution of allylic alcohol **106** (1.0 g, 4.54 mmol, 100 mol-%) in CH_2Cl_2 (5 mL) was added dropwise via cannula. The allylic alcohol was first azeotropically dried with toluene and then dissolved in CH_2Cl_2 and dried over 4Å molecular sieves. The resulting mixture was stirred at –20 °C for an additional 70 h and then warmed to 0 °C. H_2O (4 mL) was added and stirring was continued at 0 °C for an additional 1 h. The mixture was allowed to warm to rt. A solution of 30% NaOH in saturated aqueous NaCl (1 mL) was added and the resulting mixture was stirred for 45 min. The solution was diluted with H_2O (4 mL) and filtered to get a better separation of the two layers. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic

extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (40% EtOAc/hexanes) afforded epoxide **107** (0.67 g, 62%, 83% ee) as colorless oil.

R_f (70 % EtOAc/hexanes) = 0.27; $[\alpha]_D$ = +2.5 (*c* 0.59, CH_2Cl_2); IR (film, cm^{-1}): 3436, 2932, 2861, 1727, 1454, 1101, 1044, 737, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.50 (s, 2H), 3.82 (ddd, 1H, *J* = 12.0, 7.4, 4.5 Hz), 3.68 (ddd, 1H, *J* = 12.0, 6.8, 5.1 Hz), 3.49 (t, 2H, *J* = 6.2 Hz), 3.14 (dt, 1H, *J* = 6.8, 4.3 Hz), 3.03 (m, 1H), 1.71-1.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 128.4, 127.7, 127.6, 73.0, 70.0, 60.8, 57.2, 56.6, 29.4, 27.7, 23.5. These data match those reported in literature.[131] HRMS (ESI^+): *m/z* calcd for [$C_{15}H_{20}O_3Na$] 259.1310, found 259.1336, Δ = 10 ppm. The enantiomeric purity was determined by HPLC (Daicel Chiralcel AD column, 15 % *i*PrOH/hexanes, flow rate 0.5 mL/min): τ_{major} = 14.94 min; τ_{minor} = 16.85 min.

5.2.6 (2*S*, 3*S*)-7-(Benzyloxy)-2-methyl-heptane-1,3-diol 108[132]

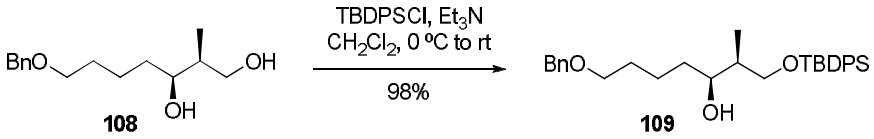


A mixture of CuCN (1.25 g, 14.0 mmol, 600 mol-%) in Et_2O (35 mL) was cooled to –78 °C and methyllithium (17.0 mL of a 1.48 M solution in Et_2O, 25.1 mmol, 1080 mol-%) was added dropwise. The resulting mixture was warmed to –20 °C and stirred vigorously for 1 h. The color of the solution turned pale green (some CuCN remained undissolved). A solution of epoxide **107** (0.55 g, 2.33 mmol, 100 mol-%) in Et_2O (15 mL) was added *via* cannula and the stirring was continued at –15 °C for 2.5 h. Et_2O (15 mL) and sat. aq. NH_4Cl (20 mL) were added. The resulting mixture was warmed to rt and filtered. The layers were separated. The organic phase was washed with sat. aq. NH_4Cl, H_2O and brine (2 x 25 mL each). The combined aqueous phases were back-extracted with Et_2O (25 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated to yield the

crude **108**. To this crude material were added THF (15 mL), H_2O (15 mL) and $NaIO_4$ (0.16 g, 0.77 mmol) at rt. The resulting solution was stirred for 1.5 h and then diluted with Et_2O (20 mL). The layers were separated. The organic phase was washed with sat. aq. $NaHCO_3$ (25 mL) and brine (25 mL). The combined aqueous phases were back-extracted with Et_2O (25 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (50% MTBE/hexanes), followed by recrystallization of the product from EtOAc/hexanes (1:10) afforded diol **108** (0.38 g, 65%) as white crystalline solid.

R_f (70 % EtOAc/hexanes) = 0.23; mp 50-52 ºC; $[\alpha]_D$ = –5.7 (*c* 0.42, CH_2Cl_2, 95 % ee); IR (film, cm^{-1}): 3370, 2937, 2864, 1455, 1101, 1028, 736, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.50 (s, 2H), 3.82 (m, 1H), 3.69 (m, 2H), 3.49 (dt, 2H, *J* = 12.7, 0.9 Hz), 2.22 (s, 2H), 1.82-1.36 (m, 7H), 0.90 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 128.4, 127.7, 127.5, 74.5, 72.9, 70.3, 67.2, 39.1, 33.8, 29.6, 22.9, 10.1. These data match those reported in literature.[133] HRMS (ESI^+): *m/z* calcd for [$C_{15}H_{24}O_3Na$] 275.1623, found 275.1628, Δ = 1.8 ppm; Anal. calcd for [$C_{15}H_{24}O_3$] C: 71.39, H: 9.59, found C: 71.62, H: 9.64.

5.2.7 Alcohol 109

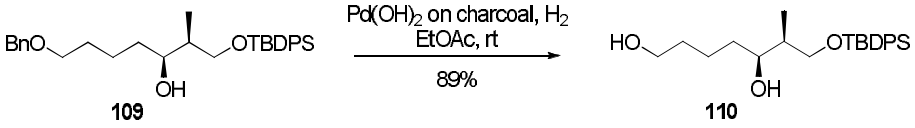


To a stirred 0 ºC solution of diol **108** (0.38 g, 1.51 mmol, 100 mol-%) in CH_2Cl_2 (6 mL) were added triethylamine (0.48 mL, 1.35 g, 3.46 mmol, 229 mol-%) and TBDPSCl (0.47 mL, 0.5 g, 1.81 mmol, 120 mol-%). The reaction mixture was allowed to warm to rt and stirring was continued for 14 h. The mixture was diluted with Et_2O (5 mL). The layers were separated and the organic phase was washed with H_2O (5 mL). The aqueous phase was back-extracted with Et_2O (5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated.

Purification of the residue by flash chromatography (30% EtOAc/hexanes) afforded alcohol **109** (0.73 g, 98%) as pale yellow viscous oil.

R_f (70 % EtOAc/hexanes) = 0.69; $[\alpha]_D$ = –3.4 (*c* 0.44, CH_2Cl_2); IR (film, cm^{-1}): 3460, 2932, 2858, 1472, 1428, 1112, 740, 702; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.46-7.27 (m, 11H), 4.51 (s, 2H), 3.86 (m, 1H), 3.75 (dd, 1H, *J* = 10.1, 4.2 Hz), 3.66 (dd, 1H, *J* = 10.1, 6.0 Hz), 3.49 (dt, 2H, *J* = 6.5, 1.0 Hz), 2.77 (d, 1H, *J* = 2.9 Hz), 1.79-1.36 (m, 7H), 1.06 (s, 9H), 0.90 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 135.7, 135.6, 133.1, 133.0, 129.83, 129.79, 128.3, 127.8, 127.6, 127.5, 74.1, 72.9, 70.4, 68.7, 39.1, 34.0, 29.8, 26.9, 22.9, 19.2, 10.2; HRMS (ESI^+): *m/z* calcd for [$C_{31}H_{42}O_3NaSi$] 513.2801, found 513.2823, Δ = 4.3 ppm.

5.2.8 (5*S*, 6*S*)-6-Methyl-7-(*tert*-butyl-diphenylsilyl)-heptane-1,5-diol 110

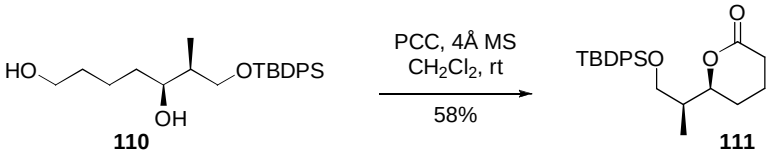


To a stirred solution of alcohol **109** (0.66 g, 1.34 mmol, 100 mol-%) in EtOAc (20 mL) was added $Pd(OH)_2$ on charcoal (0.10 g of 20% Pd catalyst, 0.15 mmol, 11 mol-%) under argon flow. The reaction flask was repeatedly evacuated and flushed with H_2. The suspension was vigorously stirred under H_2 atmosphere for 13 h and then filtered through Celite. The filter pad was washed with EtOAc (3 x 20 mL) and the combined filtrates were concentrated. Purification of the residue by flash chromatography (40% EtOAc/hexanes) afforded 6-methyl-7-(*tert*-butyl-diphenylsilyl)-heptane-1,5-diol **110** (0.46 g, 89%) as colorless viscous oil.

R_f (70 % EtOAc/hexanes) = 0.33; $[\alpha]_D$ = –3.4 (*c* 0.61, CH_2Cl_2, 95% ee); IR (film, cm^{-1}): 3339, 2931, 2585, 1428, 1112, 740, 701; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.46-7.38 (m, 6H), 3.87 (m, 1H), 3.76 (dd, 1H, *J* = 10.1, 4.2 Hz), 3.69-3.65 (m, 3H), 2.02 (br s, 2H), 1.80-1.71 (m, 1H), 1.66-1.35 (m, 6H),

1.06 (s, 9H), 0.92 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 135.6, 133.1, 132.9, 129.9, 129.8, 127.8, 74.2, 68.7, 62.9, 39.2, 33.8, 32.7, 26.9, 22.5, 19.2, 10.3; HRMS (ESI$^+$): *m/z* calcd for [$C_{24}H_{36}O_3NaSi$] 423.2331, found 423.2345, Δ = 3.3 ppm. The enantiomeric purity was determined by HPLC (Daicel Chiralcel OD column, 1:9 *i*PrOH/hexanes, flow rate 0.5 ml/min): τ_{major} = 11.15 min; τ_{minor} = 14.82 min, 95% ee.

5.2.9 Lactone 111



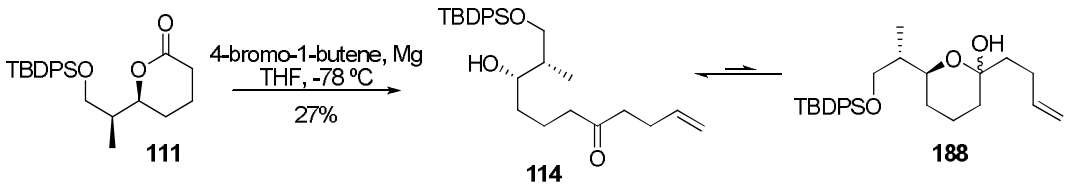
To a stirred solution of diol **110** (0.70 g, 1.75 mmol, 100 mol-%) in CH_2Cl_2 (20 mL) were added crushed 4 Å molecular sieves (0.75 g) and pyridinium chlorochromate (PCC, 0.66 g, 3.06 mmol, 175 mol-%) at rt. After 3 h, second portions of molecular sieves (0.25 g) and PCC (0.66 g, 3.06 mmol, 175 mol-%) were added. Stirring was continued for an additional 13 h and a third portion molecular sieves (0.2 g) and PCC (0.57 g, 2.63 mmol, 150 mol-%) were added. After 3 h, a fourth portion of PCC (0.18 g, 1.88 mmol, 106 mol-%) was added. This mixture was stirred for an additional 3 h before the mixture was filtered through silica gel with EtOAc and then concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded lactone **111** (0.40 g, 58%) as colorless oil.

R_f (70 % EtOAc/hexanes) = 0.56; $[\alpha]_D$ = +26.3 (*c* 1.15, CH_2Cl_2); IR (film, cm^{-1}): 2958, 2931, 2883, 2857, 1736, 1428, 1239, 1112, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.63 (m, 4H), 7.45-7.37 (m, 6H), 4.49 (ddd, 1H, J = 11.5, 4.1, 3.0 Hz), 3.73 (dd, 1H, J = 10.2, 7.0 Hz), 3.61 (dd, 1H, J = 10.2, 5.3 Hz), 2.58 (m, 1H), 2.41 (dt, 1H, J = 8.8, 7.2 Hz), 1.96-1.77 (m, 4H), 1.70-1.59 (m, 1H), 0.98 (s, 9H), 0.97 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 135.6, 135.5,

133.7, 133.5, 129.7, 127.7, 80.4, 65.1, 40.4, 29.5, 26.9, 25.5, 19.3, 18.7, 11.1; HRMS (ESI^+): *m/z* calcd for [$C_{24}H_{32}O_3NaSi$] 419.2018, found 419.2011, Δ = 1.6 ppm.

5.3 Synthesis of AB Spiroketal Ring Fragment

5.3.1 Ketoalcohol 114

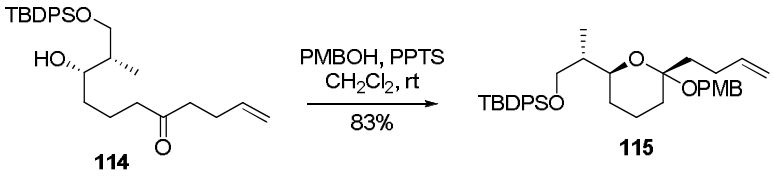


To a stirred mixture of Mg powder (36 mg, 1.46 mmol, 290 mol-%) in THF (3 mL) was added 4-bromo-1-butene (0.15 mL, 1.19 g, 1.46 mmol, 290 mol-%). Heat was evolved and the formation of the Grignard reagent was evident from the darkening of the reaction mixture. After 50 min, 1.55 mL of this Grignard reagent solution was added dropwise to a –78 °C solution of lactone **111** (0.2 g, 0.50 mmol, 100 mol-%) in THF (3 mL). The resulting solution was stirred at –78 °C for an additional 40 min and then sat. aq. NH_4Cl (1.5 mL) and H_2O (1.5 mL) were added. The mixture was warmed to rt and the layers were separated. The aqueous phase was extracted with MTBE (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue twice by flash chromatography (initially 20% EtOAc/hexanes, finally 15% EtOAc/hexanes) afforded ketoalcohol **114** (60.7 mg, 27%) as pale yellow oil and lactone **111** (132.8 mg, 66%). This process was repeated twice to obtain **114** in 60% overall yield.

R_f (40 % EtOAc/hexanes) = 0.44; $[\alpha]_D$ = +0.5 (*c* 0.42, CH_2Cl_2); IR (film, cm^{-1}): 3469, 2930, 2857, 1713, 1428, 1275, 1261, 1112, 912, 824, 750, 702; ^1H NMR

(400 MHz, $CDCl_3$): For **114**: δ 7.69-7.66 (m, 4H), 7.48-7.39 (m, 6H), 5.82 (ddt, 1H, *J* = 17.1, 10.3, 6.6 Hz), 5.01 (dq, 1H, *J* = 17.1, 1.8 Hz), 4.94 (dtd, 1H, *J* = 10.3, 2.0, 1.3 Hz), 3.72-3.68 (m, 1H), 3.67 (dd, 1H, *J* = 10.0, 6.7 Hz), 3.57 (dd, 1H, *J* = 9.8, 5.7 Hz), 2.62 (d, 1H, *J* = 5.5 Hz), 2.49 (t, 2H, *J* = 7.3 Hz), 2.41 (t, 2H, *J* = 7.3 Hz), 2.28-2.22 (m, 2H), 1.78-1.27 (m, 5H), 1.03 (s, 9H), 0.84 (d, 3H, *J* = 7.0 Hz); For **188**: δ 5.86 (m), 4.99 (dq, *J* = 17.2, 5.5 Hz), 4.90 (m), 3.56 (dd), 0.95 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): For **114**: δ 211.0, 136.44, 136.40, 134.7, 134.6, 130.8, 128.75, 115.3, 71.9, 67.9, 43.0, 42.2, 41.4, 34.8, 28.8, 27.2, 21.2, 19.8, 10.9; For **188**: δ 140.3, 138.7, 130.7, 128.70, 114.5, 96.9, 71.0, 67.0, 43.1, 41.7, 34.0, 28.8, 28.4, 20.0, 12.7; HRMS (ESI^+): *m/z* calcd for [$C_{28}H_{40}O_3NaSi$] 475.2644, found 475.2667, Δ = 4.8 ppm.

5.3.2 Ketal 115

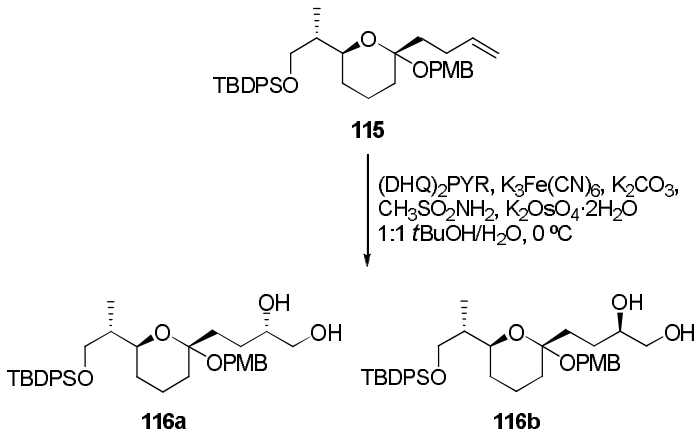


To a stirred solution of ketoalcohol **114** (50 mg, 0.11 mmol, 100 mol-%) in CH_2Cl_2 (4 mL) at rt was added *p*-methoxybenzyl alcohol (0.1 mL, 0.11 g, 0.77 mmol, 700 mol-%) and pyridinium *p*-toluenesulfonate (5.5 mg, 0.022 mmol, 20 mol-%). The resulting solution was stirred for 3 h and then sat. aq. $NaHCO_3$ (2 mL) and H_2O (4 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (3% MTBE/hexanes, using silica gel containing ca. 0.1% Ca (Fluka)) afforded ketal **115** (53 mg, 83%) as pale yellow oil.

R_f (60 % EtOAc/hexanes) = 0.56; $[\alpha]_D$ = +7.4 (*c* 1.04, CH_2Cl_2); IR (film, cm^{-1}): 3070, 2958, 2931, 2857, 1726, 1472, 1428, 1239, 1112, 1027, 931, 824, 741, 702; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65-7.63 (m, 4H), 7.46-7.36 (m, 6H), 7.23-7.20

(m, 2H), 6.82-6.78 (m, 2H), 5.86 (ddt, 1H, *J* = 17.1, 10.3, 6.6 Hz), 5.02 (dq, 1H, *J* = 17.1, 1.7 Hz), 4.93 (dtd, 1H, *J* = 10.3, 1.6, 1.2 Hz), 4.36 (dd^{AB}, 2H, $|J_{AB}|$ = 11.1 Hz, Δv = 31.9 Hz), 3.78- 3.76 (m, 1H), 3.74 (s, 3H), 3.72 (dd, 1H, *J* = 10.0, 5.1 Hz), 3.61 (dd, 1H, *J* = 10.0, 6.0 Hz), 2.11-2.02 (m, 2H), 1.85-1.16 (m, 9H), 1.01 (obscured d, 3H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 139.9 136.4, 134.84, 134.82, 132.2, 130.71, 130.69, 130.0, 128.7, 114.7, 114.5, 100.4, 71.8, 67.0, 61.9, 55.8, 41.8, 37.3, 33.4, 28.8, 28.7, 27.3, 19.9, 19.8, 12.8; HRMS (ESI^+): *m/z* calcd for [$C_{36}H_{48}O_4NaSi$] 595.3220, found 595.3209, Δ = 1.8 ppm.

5.3.3 Dihydroxyketals 116a and 116b[94b]

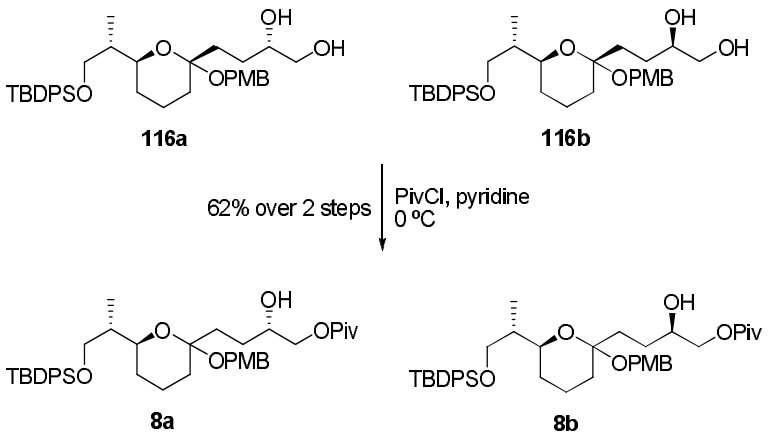


$(DHQ)_2PYR$ (5.6 mg, 0.006 mmol, 6.7 mol-%), $K_3Fe(CN)_6$ (89 mg, 0.27 mmol, 300 mol-%), K_2CO_3 (37 mg, 0.27 mmol, 300 mol-%), $CH_3SO_2NH_2$ (8.6 mg, 0.09 mmol, 100 mol-%) and $K_2OsO_4 \cdot 2H_2O$ (0.3 mg, 0.0009 mmol, 1 mol-%) were dissolved in 1:1 *tert*-butanol/H_2O (1.5 mL each) at rt. The resulting mixture was vigorously stirred for 20 min and then cooled to 0 °C. A solution of ketal **115** (52 mg, 0.09 mmol, 100 mol-%) in *tert*-butanol (0.5 mL) was added *via* cannula. Stirring was continued at 0 °C for an additional 17.5 h before Na_2SO_3 (0.14 g) was added. The resulting mixture was vigorously stirred and allowed to warm to rt. The mixture was diluted with EtOAc (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with H_2O (10 mL), dried over Na_2SO_4 and concentrated.

The crude product was immediately used in the next reaction without further purification.

R_f (60 % EtOAc/hexanes) = 0.16; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.63 (m, 4H), 7.47- 7.37 (m, 6H), 7.23-7.20 (m, 2H), 6.81-6.79 (m, 2H), 4.36-4.26 (m, 2H), 3.77-3.76 (m, 1H), 3.74 (s, 3H), 3.72 (dd, 1H, *J* = 9.9, 5.0 Hz), 3.61 (dd, 1H, *J* = 9.9, 5.8 Hz), 3.49 (m, 1H), 3.41 (m, 1H), 3.30 (m, 1H), 2.82 (m, 1H), 2.69 (m, 1H), 1.81-1.23 (m, 11H), 1.01 (obscured d, 3H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 136.4, 134.82, 134.80, 132.3, 130.69, 130.68, 130.0, 128.7, 114.5, 100.5, 72.8, 71.8, 67.1, 67.0, 61.8, 55.8, 41.8, 34.1, 33.4, 28.8, 28.2, 27.3, 19.9, 19.8, 12.8; For **116b**, the following signals were also observed in ^{13}C NMR: δ 72.8, 67.1, 61.9, 34.2, 28.9, 28.1.

5.3.4 Pivalates 8a and 8b

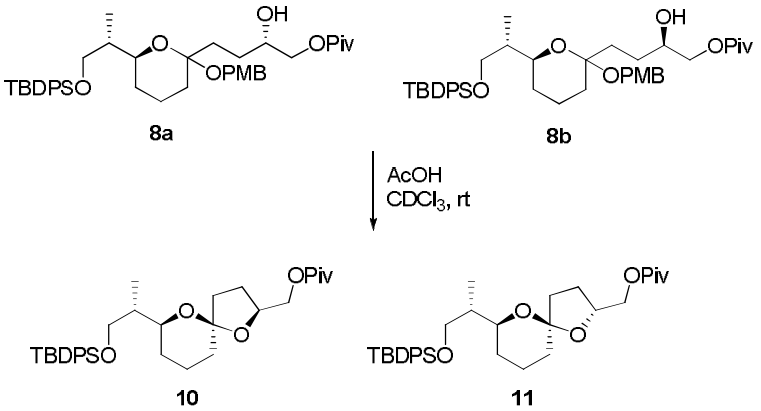


To a stirred 0 °C solution of dihydroxyketal **116** (0.05 g, 0.082 mmol, 100 mol-%) in pyridine (0.5 mL) was added pivaloyl chloride (12 µl, 12 mg, 0.1 mmol, 122 mol-%). The resulting solution was stirred at 0 °C for an additional 2 h 15 min. Sat. aq. $NaHCO_3$ (1 mL) and H_2O (5 mL) were added and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with H_2O (5 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (15%

EtOAc/hexanes) afforded a mixture of pivalates **8a** and **8b** (40.1 mg, 62% over 2 steps) as pale yellow viscous oil.

R_f (40 % EtOAc/hexanes) = 0.47; $[\alpha]_D$ = +12.4 (*c* 0.27, CH_2Cl_2); IR (film, cm^{-1}): 3469, 2930, 2957, 1713, 1428, 1275, 1261, 1112, 912, 824, 750, 701; ^1H NMR (400 MHz, $CDCl_3$): For **8a**: δ 7.65-7.62 (m, 4H), 7.46-7.36 (m, 6H), 7.22-7.20 (m, 2H), 6.80-6.78 (m, 2H), 4.35 (dd, 1H, *J* = 11.1, 3.0 Hz), 4.28 (dd, 1H, *J* = 11.1, 4.6 Hz), 3.96-3.91 (m, 2H), 3.77-3.76 (m, 1H), 3.74 (s, 3H), 3.72 (dd, 1H, *J* = 10.0, 4.9 Hz), 3.61 (dd, 1H, *J* = 10.0, 5.9 Hz), 2.97 (d, 1H, *J* = 5.5 Hz), 1.80-1.21 (m, 11H), 1.17 (s, 9H), 1.01 (obscured d, 3H), 1.00 (s, 9H); For **8b**, the following additional resonances could be observed: δ 2.97 (d, *J* = 5.3 Hz), 1.17 (s); ^{13}C NMR (100 MHz, $CDCl_3$): For **8a**: δ 178.93, 159.8, 136.4, 134.83, 134.81, 132.3, 130.70, 130.69, 130.0, 129.9, 128.7, 114.5, 100.4, 71.8, 70.1, 68.9, 67.0, 61.85, 55.8, 41.9, 39.4, 34.0, 33.4, 28.8, 28.4, 27.4, 27.2, 19.9, 19.8, 12.8; For **8b**, the following additional resonances could be observed: δ 178.91, 100.5, 70.0, 68.8, 61.89, 28.5; HRMS (ESI^+): *m/z* calcd for [$C_{41}H_{58}O_7NaSi$] 713.3850, found 713.3872, Δ = 3.0 ppm.

5.3.5 Spiroketals 10 and 11



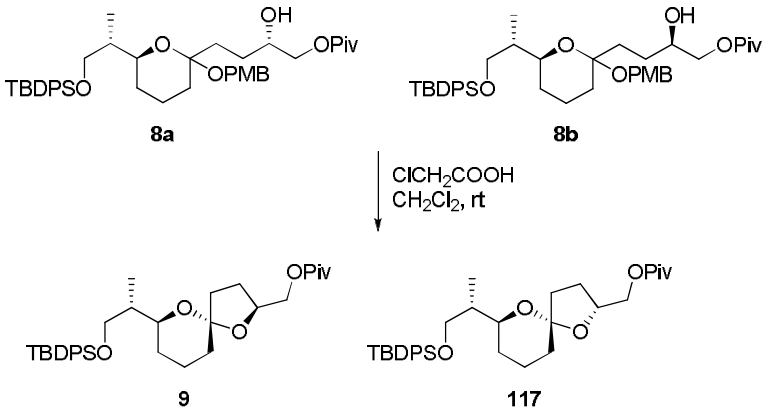
To a solution of pivalate **8** (3.5 mg, 0.005 mmol, 100 mol-%) in $CDCl_3$ (1 mL) was added AcOH (1 drop, ca 10 µL, 3300 mol-%) at rt. After 21 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (0.5 mL) and H_2O (0.5 mL).

The layers were separated and the aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (3% EtOAc/hexanes) afforded fraction A: spiroketal **10** (1.5 mg, 54%), fraction B: a mixture of spiroketals **10** and **11** (0.5 mg, 17%), fraction C: spiroketal **11** (0.8 mg, 29%).

10: R_f (10 % EtOAc/hexanes) = 0.33; $[\alpha]_D$ = +2.6 (*c* 0.53, CH_2Cl_2); IR (film, cm^{-1}): 2930, 2857, 1732, 1460, 1367, 1282, 1153, 1113, 1075, 1023, 824, 742, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.64 (m, 4H), 7.48-7.38 (m, 6H), 4.19-4.12 (m, 1H), 4.03 (dd, 1H, *J* = 11.4, 3.9 Hz), 3.97 (dd, 1H, *J* = 11.4, 5.0 Hz), 3.83 (ddd, 1H, *J* = 11.7, 2.1, 5.3 Hz), 3.66 (dd, 1H, *J* = 9.9, 6.0 Hz), 3.52 (dd, 1H, *J* = 9.9, 6.0 Hz), 2.05-1.98 (m, 1H), 1.79-1.57 (m, 7H), 1.49-1.44 (m, 1H), 1.36-1.22 (m, 2H), 1.15 (s, 9H), 1.04 (s, 9H), 0,90 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8, 136.41, 136.39, 134.89, 134.84, 130.7, 128.7, 107.2, 76.3, 71.4, 67.0, 66.7, 41.4, 39.4, 38.1, 33.5, 28.7, 27.4, 27.3, 26.6, 21.4, 19.8, 12.4; HRMS (ESI^+): *m/z* calcd for [$C_{33}H_{48}O_5NaSi$] 575.3169, found 575.3176, Δ = 1.2 ppm.

11: R_f (10 % EtOAc in hexanes) = 0.30; $[\alpha]_D$ = +1.4 (*c* 0.14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.64 (m, 4H), 7.47-7.38 (m, 6H), 4.21- 4.13 (m, 1H), 3.99 (dd, 1H, *J* = 11.0, 7.3 Hz), 3.94 (dd, 1H, *J* = 11.0, 5.3 Hz), 3.73 (ddd, 1H, *J* = 7.8, 5.7, 2.1 Hz), 3.70 (dd, 1H, *J* = 9.9, 4.6 Hz), 3.54 (dd, 1H, *J* = 9.9, 6.9 Hz), 2.11-2.10 (m, 1H), 1.86-1.47 (m, 10H), 1.15 (s, 9H), 1.03 (s, 9H), 0,97 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 136.4, 134.9, 134.8, 130.69, 130.67, 128.7, 107.3, 78.3, 72.2, 69.0, 67.1, 41.9, 39.0 (2 C), 34.1, 28.6, 27.8, 27.4, 27.3, 21.2, 19.8, 13.4. HRMS (ESI^+): *m/z* calcd for [$C_{33}H_{48}O_5NaSi$] 575.3169, found 575.3157, Δ = 2.1 ppm.

5.3.6 Spiroketal 9



To a solution of pivalate **8** (10.0 mg, 0.014 mmol, 100 mol-%) in CH_2Cl_2 (1 mL) was added chloroacetic acid (0.27 mg, 0.0029 mmol, 20 mol-%) in CH_2Cl_2 (0.8 ml) at rt. After 30 min, another portion of chloroacetic acid (0.27 mg, 0.0029 mmol, 20 mol-%) in CH_2Cl_2 (0.8 ml) was added. The resulting solution was stirred at rt for an additional 4h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (0.5 mL) and H_2O (0.5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (3% EtOAc/hexanes) afforded fraction A: spiroketal **10** (1.9 mg, 24%), fraction B: a mixture of spiroketals **10** and **11** (1.6 mg, 21%), fraction C: spiroketal **11** (0.5 mg, 6%), fraction D: spiroketal **9** (containing ca 5% of **117**) (3.8 mg, 49%).

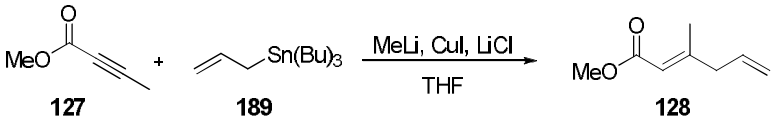
Fraction D: R_f (10 % EtOAc/hexanes) = 0.20; $[\alpha]_D$ = +5.4 (*c* 0.28, CH_2Cl_2); IR (film, cm^{-1}): 2929, 2857, 1732, 1463, 1277, 1263, 1156, 1113, 1009, 896, 824, 748, 703; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.48-7.39 (m, 6H), 4.17 (dt, *J* = 7.3, 4.6 Hz), 4.02 (dd, 1H, *J* = 11.1, 4.6 Hz), 3.92 (dd, 1H, *J* = 11.1, 7.3 Hz), 3.67 (dd, 1H, *J* = 9.9, 6.8 Hz), 3.61 (ddd, 1H, *J* = 11.5, 4.5, 2.3 Hz), 3.52 (dd, 1H, *J* = 9.9, 6.0 Hz), 2.42-2.37 (m, 1H), 1.79-1.24 (m, 10H), 1.17 (s, 9H), 1.04 (s, 9H), 0.89 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 136.4, 134.8, 130.7, 128.7, 109.4, 78.1, 75.0, 69.2, 67.0, 41.4, 39.3, 34.8, 32.2,

28.9, 27.6, 27.4, 27.2, 22.9, 19.8, 12.3; HRMS (ESI^+): *m/z* calcd for [$C_{33}H_{48}O_5NaSi$] 575.3169, found 575.3159, Δ = 1.7 ppm.

Spiroketalization with PPTS (Table 1, entry 1) afforded **9** accompanied by ca. 10% of the inseparable C10 epimer **117**. For spiroketal **117**, the following additional resonances could be observed: δ 4.29-4.22 (m), 4.05 (dd, *J* = 3.8 Hz), 3.95 (dd, *J* = 5.1 Hz), 3.69-3.65 (m), 1.18 (s), 0.89 (d, *J* = 6.8 Hz).

5.4 Synthesis of C Ring Fragment

5.4.1 (*E*)-Methyl 3-methylhexa-2,5-dienoate 128[102]



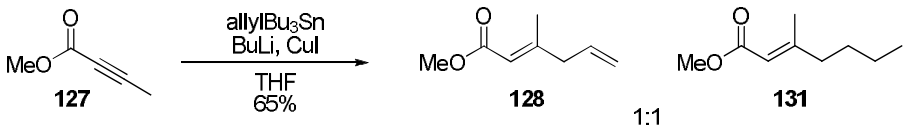
127 **189** **128**

A mixture of CuI (0.29 g, 1.5 mmol, 150 mol-%) and LiCl (64 mg, 1.5 mmol, 150 mol-%) in THF (2.0 mL) was stirred at rt for 5 min to give a yellow suspension and was then cooled to –78 ºC and stirred for 20 min before cooling to –100 ºC. Allyllithium solution was prepared at the same time by adding methyllithium (1.6M in Et_2O, 1.88 mL, 3.0 mmol, 300 mol-%) to a solution of allyltributyltin **189** (0.93 mL, 1.0 g, 3.0 mmol, 300 mol-%) in THF (3.0 mL) at –78 ºC. The resulting yellow solution was stirred at –78 ºC for 15 min before cooling to –100 ºC. The allyllithium solution was slowly transferred to the CuI/LiCl suspension via dry ice-cooled cannula. The resulting yellow mixture was warmed to –78 ºC and a solution of methyl-2-butynoate **127** (98 mg, 1.0 mmol, 100 mol-%) in THF (2.0 mL) was added. The resulting brownish mixture was stirred at –78 ºC for 30 min before sat. aq. NH_4Cl (10 mL) was added. The mixture was allowed to warm to rt and was then diluted with H_2O (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts was washed with sat. aq. NH_4Cl (3 x 20 mL)

and brine (20 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 100% hexanes, finally 5% EtOAc/hexanes, 2 columns) afforded diene **128** (95 mg, 67%) as light yellow liquid.

R_f (30% EtOAc/hexanes) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (ddt, 1H, *J* = 17.0, 10.2, 6.8 Hz), 5.70 (q, 1H, *J* = 1.3 Hz), 5.14-5.08 (m, 2H), 3.69 (s, 3H), 2.87 (dd, 2H, *J* = 6.8, 1.1 Hz), 2.16 (d, 3H, *J* = 1.3 Hz).

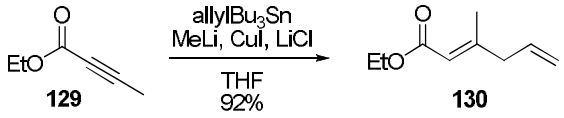
When butyllithium was used instead of methyllithium substantial amounts of the side product **131** was formed.



To a solution of allyltributyltin (0.96 mL, 3.1 mmol, 155 mol-%) in THF (10 mL) was slowly added *n*BuLi (1.68 M, 1.90 mL, 3.1 mmol, 158 mol-%) at –78 °C. The solution was stirred at –78 °C for 30 min and was then cannulated to a suspension of CuI (0.57 g, 3.0 mmol, 150 mol-%) in THF (4 mL) at –78 °C. During the addition the reaction mixture turned grey and then to black. The reaction mixture was allowed to warm to –45 °C during stirring for 45 min. The reaction mixture was cooled back to –78 °C and a solution of methyl-2-butynoate **127** (0.20 mL, 2.0 mmol, 100 mol-%) in THF (4 mL) was added via cannula. The resulting mixture was stirred for further 20 min at –78 °C. The reaction was quenched by addition of sat. aq. NH_4Cl (10 mL) at –78 °C and the mixture was allowed to warm to rt. H_2O (20 mL) and Et_2O (20 mL) were added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with sat. aq. NH_4Cl (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (initially 100% hexanes, finally 5% EtOAc/hexanes) afforded a 1:1 mixture of esters **128** and **131** as light yellow oil (0.18 g, 65 %).

For **131**: R_f (30% EtOAc/hexanes) = 0.58; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 (dt, 1H, *J* = 2.5, 1.2 Hz), 3.68 (s, 3H), 2.15 (d, 3H, *J* = 1.3 Hz), 2.13 (dd, 2H, *J* = 7.8, 0.8 Hz), 1.49-1.42 (m, 2H), 1.36-1.27 (m, 2H), 0.91 (t, 3H, *J* = 7.3 Hz). The data is in agreement with the data presented in literature.[134]

5.4.2 (*E*)-Ethyl 3-methylhexa-2,5-dienoate 130[102]



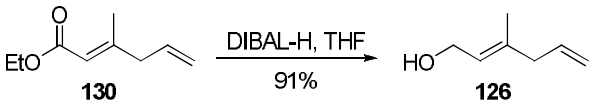
A suspension of LiCl (0.14 g, 3.4 mmol, 150 mol-%) and CuI (0.64 g, 3.4 mmol, 150 mol-%) in THF (5 mL) was stirred at rt for 5 min to get a clear yellow solution. The solution was cooled to –78 °C and stirred for 20 min. Simultaneously, MeLi (1.6 M in Et_2O, 4.19 mL, 6.7 mmol, 300 mol-%) was added to a –78 °C solution of allyltributyltin (2.08 mL, 6.7 mmol, 300 mol-%) in THF (7 mL). This solution was stirred at –78 °C for 15 min, before it was cannulated to the LiCl/CuI solution via dry ice-cooled cannula over a period of 25 min. A solution of ethyl-2-butynoate **129** (0.26 mL, 2.23 mmol, 100 mol-%) in THF (5 mL) was added and the resulting red brownish reaction mixture was stirred for further 35 min at –78 °C. The reaction was quenched by addition of sat. aq. NH_4Cl (20 mL) at –78 °C and the mixture was allowed to warm to rt. H_2O (20 mL) and Et_2O (20 mL) were added, and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with sat. aq. NH_4Cl (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (initially 100% hexanes, then 30% EtOAc/hexanes, and finally 50% EtOAc/hexanes) afforded ester **130** as light yellow oil (0.32 g, 92 %).

The reaction was also done in bigger scale (51.6 mmol of ethyl-2-butynoate **129**). The product was purified by distillation under reduced pressure (8 mmHg,

80-88 °C) to afford ester **130** that contained some tin impurities. This material was used in the following reaction after which the impurities were easily separated.

R_f (50% EtOAc/hexanes) = 0.71; IR (film, cm^{-1}): 3081, 2981, 2930, 1718, 1652, 1221, 1147; ^1H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddt, 1H, *J* = 17.0, 10.1, 6.8 Hz), 5.69 (q, 1H, *J* = 1.3 Hz), 5.14-5.08 (m, 2H), 4.15 (q, 2H, *J* = 7.1 Hz), 2.87 (dd, 2H, *J* = 6.9, 1.1 Hz), 2.16 (d, 3H, *J* = 1.3 Hz), 1.28 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 157.9, 134.4, 118.0, 116.5, 59.7, 45.1, 19.0, 14.5; HRMS (ESI^+): *m/z* calcd for [$C_9H_{14}O_2Na$] 177.0891, found 177.0879, Δ = 6.8 ppm.

5.4.3 (*E*)-3-Methyl-2,5-hexadien-1-ol 126



130 **126**

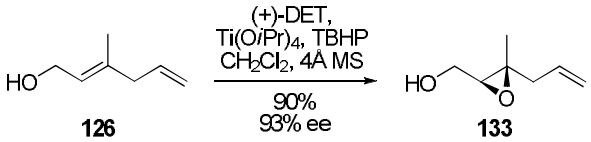
To a solution of ester **130** (1.65 g, 10.7 mmol, 100 mol-%) in THF (50 mL) at –78 °C was added DIBAL-H (1 M in toluene, 21.4 mL, 21.4 mmol, 200 mol-%). The cooling bath was removed and the reaction mixture was stirred at rt for 2 h 40 min. Sat. aq. Rochelle salt (50 mL) was added and the reaction mixture was stirred at rt for further 1 h. The layers were separated and the aqueous phase was extracted with Et_2O (20 mL). The combined organic extracts were washed with H_2O (30 mL), sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (initially 20% EtOAc/hexanes, finally 30% EtOAc/hexanes) afforded alcohol **126** as colorless oil (1.09 g, 91%).

On a larger scale, the reaction was performed using unpurified ester **130** and $LiAlH_4$ as the reductant as follows: To a suspension of $LiAlH_4$ (2.63 g, 69.3 mmol, 120 mol-%) in Et_2O (100 mL) at –78 °C was added a solution of crude ester **130** (8.9 g, 57.7 mmol, 100 mol-%) in Et_2O (40 mL). The cooling bath was

removed and the reaction mixture was stirred at rt for 25 min. The reaction was quenched by addition of H_2O (2.63 mL) at –78 °C, followed by 15% NaOH (2.63 mL) and H_2O (7.9 mL). The reaction mixture was allowed to warm to rt and stirred for 30 min. The white precipitate was filtered and solvent was evaporated. Purification of the residue by distillation under reduced pressure (7 mmHg, 71 °C) afforded alcohol **126** as colorless oil (5.1 g, 78 % over 2 steps). It should be noted that DIBAL-H in toluene should not be used in this procedure, because toluene cannot be separated from the product by distillation.

R_f (50% EtOAc/hexanes) = 0.44; IR (film, cm^{-1}): 3326, 3078, 2978, 2918, 1671, 1637, 995, 913; ^1H NMR (400 MHz, $CDCl_3$): δ 5.79 (ddt, 1H, *J* = 16.9, 10.2, 6.8 Hz), 5.44 (tq, 1H, *J* = 6.9, 1.3 Hz), 5.09-5.03 (m, 2H), 4.17 (d, 2H, *J* = 6.8 Hz), 2.76 (d, 2H, *J* = 6.8 Hz), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 136.2, 124.4, 116.5, 59.6, 44.1, 16.4; The data is in agreement with the data presented in literature.[135]

5.4.4 3-Methyl-2(S),3(S)-epoxy-5-hexen-1-ol 133[85c]

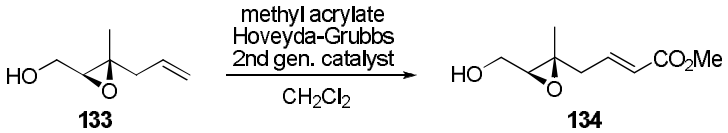


To a suspension of crushed 4Å molecular sieves (1.1 g) in CH_2Cl_2 (20 mL) at 0 °C was added L-(+)-diethyltartrate (0.5 mL, 2.94 mmol, 30 mol-%) and titanium(IV) isopropoxide (0.58 mL, 1.96 mmol, 20 mol-%). After 5 min, the mixture was cooled to –20 °C and *tert*-butylhydroperoxide (~5M in iso-octane, 3.92 mL, 19.61 mmol, 200 mol-%) was added dropwise. The reaction mixture was stirred at –20 °C for 20 min and a solution of alcohol **126** (1.1 g, 9.81 mmol, 100 mol-%) in CH_2Cl_2 (10 mL) was added. Stirring was continued at –20 °C for further 2 h before the reaction was quenching by addition of H_2O (8 mL) at 0 °C. The mixture was vigorously stirred for 1 h and 30% aq. solution of NaOH saturated with NaCl (2.5 mL) was added. The mixture was allowed to warm to rt,

stirred for further 1 h, and filtered through a sintered funnel. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 30% EtOAc/hexanes, finally 50% EtOAc/hexanes) afforded epoxide **133** as light yellow oil (1.13 g, 90%, 93% ee).

R_f (50% EtOAc/hexanes) = 0.29; $[\alpha]_D$ = –4.3 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3401, 3079, 2979, 2930, 1642, 1029; ^1H NMR (400 MHz, $CDCl_3$): δ 5.82-5.72 (m, 1H), 5.15-5.12 (m, 1H), 5.11-5.09 (m, 1H), 3.84 (dd, 1H, *J* = 12.1, 4.2 Hz), 3.70 (dd, 1H, *J* = 12.1, 6.6 Hz), 3.01 (dd, 1H, *J* = 6.6, 4.3 Hz), 2.37 (ddt, 1H, *J* = 14.4, 7.3, 1.0 Hz), 2.26 (ddt, 1H, *J* = 14.3, 6.8, 1.2 Hz), 1.81 (br s, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.0, 118.5, 62.3, 61.5, 60.8, 42.9, 17.0; HRMS (ESI^+): *m/z* calcd for [$C_7H_{12}O_2Na$] 151.0735, found 151.0736, Δ = 0.7 ppm. The enantiomeric purity was determined after the next reaction.

5.4.5 Ester 134

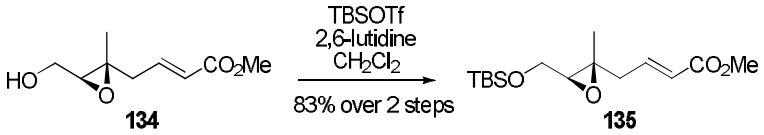


133 **134**

To a solution of epoxide **133** (0.66 g, 5.15 mmol, 100 mol-%) in CH_2Cl_2 (32 mL) was added methyl acrylate (11.6 mL, 128.8 mmol, 2500 mol-%) and a solution of Hoveyda-Grubbs 2nd generation catalyst (0.16 g, 0.26 mmol, 5 mol-%) in CH_2Cl_2 (32 mL) at rt. Stirring was continued at rt for 3.5 h. The mixture was concentrated, and the residue was purified by flash chromatography (initially 100% hexanes, then 25% and 40%, and finally 50% EtOAc/hexanes) to afford ester **134** as black oil. This product was used as such in the following reaction. However, to remove the ruthenium impurities another column (40% EtOAc/hexanes) was needed to afford ester **134** as colorless oil (0.82 g, 86%).

R_f (50% EtOAc/hexanes) = 0.18; $[\alpha]_D$ = –8.0 (*c* 1.00, CH_2Cl_2, 93% ee); IR (film, cm^{-1}): 3438, 2997, 2954, 2850, 1723, 1658; ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (dt, 1H, *J* = 15.6, 7.4 Hz), 5.91 (dt, 1H, *J* = 15.7, 1.5 Hz), 3.84 (dd, 1H, *J* = 12.1, 4.3 Hz), 3.73 (s, 3H), 3.70 (dd, 1H, *J* = 12.3, 6.6 Hz), 3.00 (dd, 1H, *J* = 6.4, 4.4 Hz), 2.51 (ddd, 1H, *J* = 14.9, 7.5, 1.4 Hz), 2.41 (ddd, 1H, *J* = 14.9, 7.1, 1.5 Hz), 1.90 (br s, 1H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 143.2, 124.3, 62.2, 61.3, 60.0, 51.7, 41.1, 17.3; HRMS (ESI^+): *m/z* calcd for [$C_9H_{14}O_4Na$] 209.0790, found 209.0778, Δ = 5.7 ppm. The enantiomeric purity was determined by HPLC (Daicel Chiralcel AD column, 5 % *i*PrOH/hexanes + 0.01% TFA, flow rate 0.8 mL/min): τ_{major} = 30.80 min; τ_{minor} = 36.89 min.

5.4.6 Ester 135



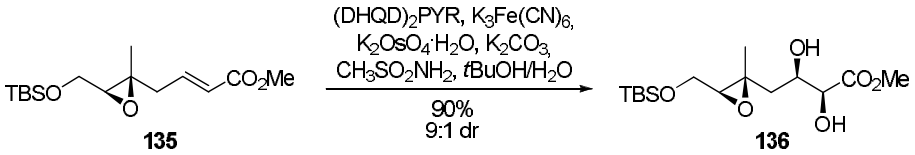
134 **135**

To a solution of ester **134** (11.2 g, 60.2 mmol, 100 mol-%) in CH_2Cl_2 (200 mL) was added 2,6-lutidine (14.0 mL, 120.4 mmol, 200 mol-%) and TBSOTf (14.5 mL 63,2 mmol, 105 mol-%) at –78 °C. The reaction mixture was stirred at –78 °C for 1h and then quenched by addition of 2M NaOH (80 mL). The solution was allowed to warm to rt. The layers were separated, and the organic phase was washed with 2 M HCl (80 mL) and brine (80 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded the desired product **135** as light yellow viscous oil (15.5 g, 86% over 2 steps).

R_f (50% EtOAc/hexanes) = 0.64; $[\alpha]_D$ = –3.5 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2954, 2930, 2886, 2858, 1728, 1660, 838; ^1H NMR (400 MHz, $CDCl_3$): δ 6.92 (dt, 1H, *J* = 15.7, 7.2 Hz), 5.92 (dt, 1H, *J* = 15.7, 1.5 Hz), 3.74 (dd, 2H, *J* = 5.4, 1.7 Hz), 3.73 (s, 3H), 2.93 (t, 1H, *J* = 5.4 Hz), 2.50 (ddd, 1H, *J* = 15.0, 7.5, 1.4 Hz), 2.38 (ddd, 1H, *J* = 15.0, 7.0, 1.5 Hz), 1.29 (s, 3H), 0.90 (s, 9H), 0.08 (2 × s,

6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 143.5, 124.1, 62.5, 62.1, 59.4, 51.7, 41.2, 26.0, 18.4, 17.1, –5.1, –5.2; HRMS (ESI^+): *m/z* calcd for [$C_{15}H_{28}O_4NaSi$] 323.1655, found 323.1653, Δ = 0.6 ppm.

5.4.7 Diol 136

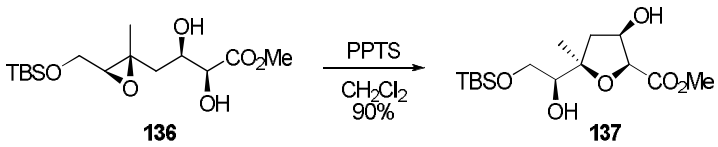


A suspension of potassium hexacyanoferrate(III) (50.8 g, 154.3 mmol, 300 mol-%), K_2CO_3 (21.3 g, 154,3 mmol, 300 mol-%), methanesulfonamide (4.9 g, 51.4 mmol, 100 mol-%), potassium osmate(VI) dihydrate (0.95 g, 2.57 mmol, 5 mol-%) and $(DHQD)_2PYR$ (2.72 g, 3.09 mmol, 6 mol-%) in *tert*-butanol (180 mL) and H_2O (320 mL) was stirred at rt for 45 min until both phases became clear. Ester **135** (15.45 g, 51.4 mmol, 100 mol-%) was added and the reaction mixture was stirred at rt for 3 h. Na_2SO_3 (3.7 g) was added and stirring was continued for further 1 h. The mixture was diluted with Et_2O (100 mL) and the layers were separated. The separated aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (initially 20% EtOAc/hexanes, finally 40% EtOAc/hexanes) afforded diol **136** as light yellow oil (16.4 g, 95%, contains both diastereomers 9:1).

R_f (50% EtOAc/hexanes) = 0.27; $[\alpha]_D$ = –5.1 (*c* 1.00, CH_2Cl_2), $[\alpha]_D$ = +6.7 (*c* 1.00, MeOH); IR (film, cm^{-1}): 3449, 2955, 2930, 2886, 2858, 1744, 1257; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28-4.22 (m, 1H), 4.11 (dd, 1H, *J* = 6.5, 1.8 Hz), 3.84 (s, 3H), 3.78 (dd, 1H, *J* = 11.4, 5.5 Hz), 3.71 (dd, 1H, *J* = 11.5, 5.6 Hz), 3.04-3.00 (m, 2H), 2.66 (d, 1H, *J* = 6.4 Hz), 1.93-1.83 (m, 2H), 1.37 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 73.3, 70.0,

62.8, 61.9, 59.3, 53.0, 41.2, 26.0, 18.4, 17.1, –5.1, –5.3; HRMS (ESI^+): *m/z* calcd for [$C_{15}H_{30}O_6NaSi$] 357.1709, found 357.1705, Δ = 1.1 ppm. It should be noted that the concentration of the ^1H NMR sample affects the positions of the peaks, presumably due to hydrogen bonding–related aggregation effects.

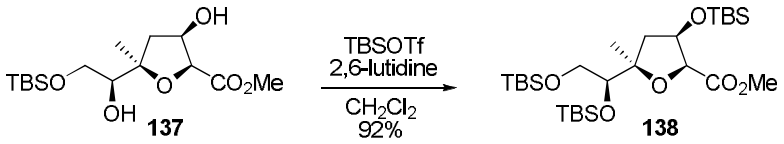
5.4.8 C Ring Diol 137



To a solution of diol **136** (16.3 g, 48.7 mmol, 100 mol-%) in CH_2Cl_2 (250 mL) was added PPTS (1.22 g, 4.9 mmol, 10 mol-%) at rt. The reaction mixture was stirred for 30 min and then quenched by addition of sat. aq. $NaHCO_3$ (80 mL). The layers were separated, and the organic phase was washed with brine (100 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (initially 20% EtOAc/hexanes, finally 35% EtOAc/hexanes) afforded the C ring diol **137** as colorless oil (14.66 g, 90%, only desired diastereomer). For X-ray characterization, the product was further crystallized using Et_2O/pentane to afford white crystalline solid.

R_f (50% EtOAc/hexanes) = 0.51; mp 50-52 ºC; $[\alpha]_D$ = –32.2 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3429, 2955, 2930, 2885, 2857, 1740, 1097; ^1H NMR (400 MHz, $CDCl_3$): δ 4.55 (d, 1H, *J* = 4.2 Hz), 4.51-4.49 (m, 1H), 3.83 (dd, 1H, *J* = 7.2, 3.9 Hz), 3.80 (s, 3H), 3.71 (dd, 1H, *J* = 10.6, 4.0 Hz), 3.53 (dd, 1H, *J* = 10.7, 7.2 Hz), 2.33 (d, 1H, *J* = 14.3 Hz), 1.92 (dd, 1H, *J* = 14.3, 5.8 Hz), 1.27 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 86.6, 82.4, 76.5, 74.5, 64.0, 52.4, 41.7, 26.0, 25.3, 18.4, –5.25, –5.27; HRMS (ESI^+): *m/z* calcd for [$C_{15}H_{30}O_6NaSi$] 357.1709, found 357.1712, Δ = 0.8 ppm; Anal. calcd for [$C_{15}H_{30}O_6Si$] C: 53.86, H: 9.04, found C: 54.17, H: 9.31.

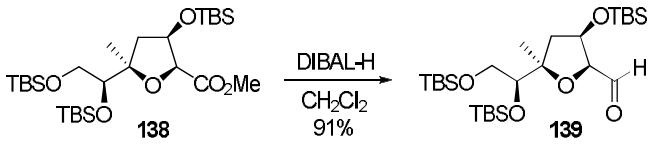
5.4.9 C Ring Ester 138



To a solution of diol **137** (3.05 g, 9.1 mmol, 100 mol-%) in CH_2Cl_2 (50 mL) was added 2,6-lutidine (4.2 mL, 36.5 mmol, 400 mol-%) and TBSOTf (4.4 mL, 19.1 mmol, 210 mol-%) at –78 °C. The reaction mixture was stirred at –78 °C for 1h and then quenched by addition of 2M NaOH (20 mL). The solution was allowed to warm to rt. The layers were separated, and the organic phase was washed with 2M HCl (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (10% MTBE/hexanes) afforded the desired product **138** as light yellow very viscous oil (4.67 g, 91%).

R_f (15% EtOAc/hexanes) = 0.58; $[\alpha]_D$ = –20.5 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2955, 2930, 2886, 2857, 1774, 1740, 1473, 1255, 836, 778; ^1H NMR (400 MHz, $CDCl_3$): δ 4.61 (ddd, 1H, *J* = 5.8, 5.0, 3.6 Hz), 4.51 (d, 1H, *J* = 4.9 Hz), 4.08 (dd, 1H, *J* = 10.5, 1.5 Hz), 3.96 (dd, 1H, *J* = 7.6, 1.4 Hz), 3.70 (s, 3H), 3.53 (dd, 1H, *J* = 10.5, 7.7 Hz), 2.21 (dd, 1H, *J* = 13.4, 3.6 Hz), 1.86 (dd, 1H, *J* = 13.3, 5.9 Hz), 1.12 (s, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 85.9, 82.3, 80.2, 74.4, 65.3, 51.7, 46.2, 26.3, 26.2, 25.8, 21.6, 18.7, 18.5, 18.0, –3.4, –4.5, –4.8, –5.0, –5.2, –5.3; HRMS (ESI^+): *m/z* calcd for $[C_{27}H_{58}O_6NaSi_3]$ 585.3439, found 585.3432, Δ = 1.2 ppm.

5.4.10 C Ring Aldehyde 139



To a solution of compound **138** (4.57 g, 8.1 mmol, 100 mol-%) in CH_2Cl_2 (80 mL) was added dropwise DIBAL-H (1 M in toluene, 8.9 mL, 8.9 mmol, 110 mol-%) at –90 °C. The reaction mixture was stirred at –90 °C for 20 min and then quenched by addition of MeOH (100 mL) at –90 °C. Saturated aq. Rochelle salt (60 mL) was added and the mixture was allowed to warm to rt and stirred for 1 h. H_2O (60 mL) was added to dissolve the precipitate. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (40 mL), dried over Na_2SO_4 and concentrated. The crude ^{1}H NMR showed that the product was a hemiacetal instead of the desired aldehyde. The following procedure was used for the hydrolysis of the hemiacetal: To a solution of the crude product in THF (100 mL) was added acetic acid (0.8 mL). After 30 min another portion of acetic acid (0.6 mL) was added. Stirring was continued for further 1h before sat. aq. $NaHCO_3$ (40 mL) was added. The layers were separated, and the organic phase was washed with brine (40 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (15% EtOAc/hexanes) afforded aldehyde **139** as light yellow viscous oil (4.02 g, 93%).

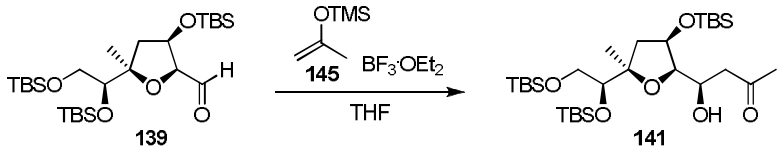
R_f (30% EtOAc/hexanes) = 0.52; $[\alpha]_D$ = –70.6 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2956, 2930, 2886, 2858, 1739, 1255, 836, 778; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (d, 1H, *J* = 2.5 Hz), 4.69 (ddd, 1H, *J* = 6.0, 5.0, 2.9 Hz), 4.16 (dd, 1H, *J* = 4.9, 2.5 Hz), 4.07 (dd, 1H, *J* = 10.7, 1.7 Hz), 3.92 (dd, 1H, *J* = 7.0, 1.7 Hz), 3.57 (dd, 1H, *J* = 10.6, 7.0 Hz), 2.28 (dd, 1H, *J* = 13.6, 2.9 Hz), 1.88 (dd, 1H, *J* = 13.6, 6.0 Hz), 1.14 (s, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 87.0, 86.3, 80.0, 76.3, 65.5, 46.5, 26.2, 26.1, 25.9, 21.7, 18.6,

18.4, 18.1, –3.4, –4.5, –4.8, –5.08, –5.12, –5.3; HRMS (ESI^+): *m/z* calcd for [$C_{26}H_{56}O_5NaSi_3$] 555.3333, found 555.3341, Δ = 1.4 ppm.

5.5 Synthesis of CDE Ring Fragment

5.5.1 Nucleophilic Addition Strategy

5.5.1.1 β-Hydroxyketone 141

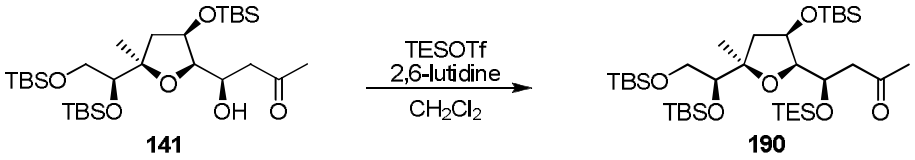


To a solution of aldehyde **139** (2.90 g, 5.44 mmol, 100 mol-%) in CH_2Cl_2 (55 mL) was added $BF_3{\cdot}OEt_2$ (0.75 mL, 0.85 g, 5.98 mmol, 110 mol-%) and (isopropenyloxy)trimethylsilane **145** (1.17 mL, 0.92 g, 7.07 mmol, 130 mol-%) at –78 °C. The reaction mixture was stirred at –78 °C for 20 min and was then quenched by addition of sat. aq. $NaHCO_3$ (20 mL). The reaction mixture was allowed to warm to rt. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated. No purification is needed and the ketone **141** is afforded as yellow viscose oil (3.21 g, 100%). Purification by flash chromatography decreases the yield by ~ 20%.

R_f (15% EtOAc/hexanes) = 0.23; $[\alpha]_D$ = –30.2 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3514, 2956, 2930, 2886, 2857, 1713, 1472, 1463, 1254, 1134, 1104, 1073; ^1H NMR (400 MHz, $CDCl_3$): δ 4.50 (dt, 1H, *J* = 6.1, 4.3 Hz), 4.29-4.23 (m, 1H), 3.90 (dd, 1H, *J* = 10.5, 1.4 Hz), 3.65 (dd, 1H, *J* = 8.2, 6.0 Hz), 3.65 (dd, 1H, *J* = 7.5, 1.4 Hz), 3.47 (dd, 1H, *J* = 10.5, 7.3 Hz), 3.21 (d, 1H, *J* = 3.5 Hz), 2.85 (dd, 1H, *J* = 17.1, 2.4 Hz), 2.59 (dd, 1H, *J* = 17.1, 9.4 Hz), 2.98 (s, 3H), 2.08 (dd, 1H, *J* =

13.4, 4.0 Hz), 1.88 (dd, 1H, *J* = 13.4, 6.1 Hz), 1.06 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.094 (s, 3H), 0.091 (s, 3H), 0.088 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.6, 83.8, 82.6, 80.9, 73.6, 66.8, 65.5, 47.4, 46.5, 30.9, 26.2, 26.1, 26.0, 21.3, 18.7, 18.4, 18.1, –3.4, –4.3, –4.9, –5.1, –5.2 (2H); HRMS (ESI^+): *m/z* calcd for [$C_{29}H_{62}O_6NaSi_3$] 613.3752, found 613.3781, Δ = 4.7 ppm.

5.5.1.2 TES Protected Ketone 190

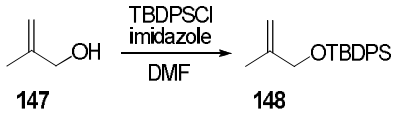


To a solution of ketone **141** (0.63 g, 1.06 mmol, 100 mol-%) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.25 mL, 0.23 g, 2.12 mmol, 200 mol-%) and TESOTf (0.36 mL, 0.42 g, 1.60 mmol, 150 mol-%) at –78 °C. The reaction mixture was stirred at –78 °C for 45 min before 2M NaOH (3 mL) was added. The layers were separated and the organic phase was washed with 1M HCl (3 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (3% EtOAc/hexanes) afforded the desired product **190** as light yellow viscose oil (0.73g, 98%).

R_f (15% EtOAc/hexanes) = 0.67; $[\alpha]_D$ = –17.8 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2955, 2931, 2883, 2858, 1722, 1472, 1463, 1255, 1135, 1098, 1072; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.50 (ddd, 1H, *J* = 8.3, 2.7, 1.7 Hz), 4.29 (ddd, 1H, *J* = 5.6, 3.8, 1.7 Hz), 4.05 (dd, 1H, *J* = 10.5, 1.2 Hz), 3.83 (dd, 1H, *J* = 3.7, 1.6 Hz), 3.71 (dd, 1H, *J* = 7.9, 1.0 Hz), 3.50 (dd, 1H, *J* = 10.4, 8.0 Hz), 2.84 (dd, 1H, *J* = 16.8, 8.4 Hz), 2.77 (dd, 1H, *J* = 17.1, 3.0 Hz), 2.11 (s, 3H), 2.04 (dd, 1H, *J* = 13.8, 1.4 Hz), 1.80 (dd, 1H, *J* = 13.8, 5.8 Hz), 1.07 (s, 3H), 0.92 (t, 9H, *J* = 7.9 Hz), 0.92 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.60 (q, 6H, *J* = 8.0 Hz), 0.12 (s, 3H), 0.01 (s, 3H), 0.09 (s, 3H), 0.051 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.3,

86.4, 83.4, 80.9, 74.1, 68.1, 65.6, 47.9, 47.6, 31.3, 26.3, 26.1, 26.0, 20.8, 18.7, 18.5, 18.0, 7.0, 5.3, –3.2, –4.6, –4.9, –5.0, –5.04 (2H); HRMS (ESI^+): *m/z* calcd for [$C_{35}H_{76}O_6NaSi_4$] 727.4617, found 727.4606, Δ = 1.5 ppm.

5.5.1.3 tert-Butyl(2-methylallyloxy)diphenylsilane 148

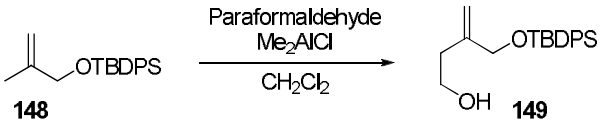


147 148

To a solution β-methallyl alcohol **147** (4.2 mL, 3.61 g, 50 mmol, 100 mol-%) in DMF (50 mL) was added imidazole (6.81 g, 100 mmol, 200 mol-%) and TBDPSCl (14.3 mL, 15.1 g, 55 mmol, 110 mol-%) at rt. The reaction mixture was stirred at rt for 3.5 h. Another portion of TBDPSCl (2.6 mL, 2.75 g, 10 mmol, 20 mol-%) was added. After stirring for an additional 2 h, the reaction mixture was poured into 1M HCl (20 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by distillation under reduced pressure (14-12 mmHg, bp. 195-197 °C) afforded **148** as colorless viscose oil (14.2 g, 92%).

R_f (15 % EtOAc/hexane) = 0.58; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.68 (m, 4H), 7.45-7.36 (m, 6H), 5.14-5.13 (m, 1H), 4.86 (dt, 1H, *J* = 3.7, 1.4 Hz), 4.08-4.07 (m, 2H), 1.69 (d, 3H, *J* = 1.3 Hz), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 135.9, 134.1, 130.0, 128.0, 109.5, 67.7, 27.2, 19.7, 19.4. ^{1}H and ^{13}C-NMR-data match those reported in literature.[136]

5.5.1.4 3-((tert-Butyldiphenylsilyloxy)methyl)but-3-en-1-ol 149[137]

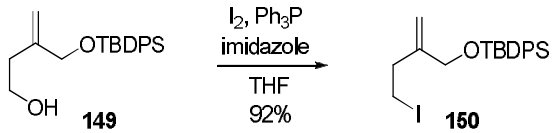


148 **149**

To a solution of **148** (1.0 g, 3.2 mmol, 100 mol-%) in CH_2Cl_2 (8 mL) was added paraformaldehyde (96 mg, 3.2 mmol, 100 mol-%) and crushed 4Å molecular sieves (0.1 g) at rt. The mixture was cooled to –78 °C and dimethylaluminum chloride (1M in hexanes, 3.2 mL, 3.2 mmol, 100 mol-%) was added. The reaction mixture was allowed to warm to rt and stirred for 5h. After filtration, the mixture was washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (15% EtOAc/hexanes) afforded alcohol **149** as yellow oil (0.27 g, 24%).

R_f (15 % EtOAc/hexane) = 0.10; IR (film, cm^{-1}): 3368, 3071, 3050, 2958, 2931, 2892, 2858, 1428, 1113; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71-7.66 (m, 4H), 7.47-7.38 (m, 6H), 5.22 (dd, 1H, *J* = 3.7, 1.5 Hz), 5.00 (dd, 1H, *J* = 2.0, 1.0 Hz), 4.13 (s, 2H), 3.68 (t, 2H, *J* = 6.2 Hz), 2.32 (t, 2H, *J* = 5.9 Hz), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 135.7, 133.4, 129.9, 127.9, 112.7, 66.8, 61.2, 36.8, 26.9, 19.4; HRMS (ESI^+): *m/z* calcd for [$C_{21}H_{28}O_2NaSi$] 363.1756, found 363.1765, Δ = 2.5 ppm.

5.5.1.5 tert-Butyl(4-iodo-2-methylenebutoxy)diphenylsilane 150



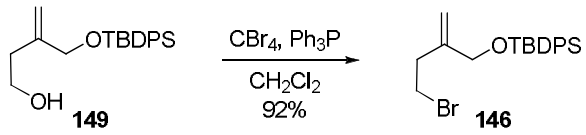
149 **150**

To a solution of alcohol **149** (0.23 g, 0.68 mmol, 100 mol-%) in THF (7 mL) was added imidazole (0.10 g, 1.5 mmol, 220 mol-%) and triphenylphosphine (0.20 g, 0.75 mmol, 110 mol-%) at rt. After 5 min, the reaction mixture was cooled to 0 °C

and iodine (0.19 g, 0.75 mmol, 110 mol-%) was added. The reaction mixture was allowed to warm to rt and stirred for 30 min. Hexanes (15 mL) was added. A white insoluble precipitate (triphenylphosphine oxide) and yellow oil separated from the solution. These were separated from the solution by filtration and the filtrate was concentrated. If white precipitate still formed, the residue was triturated again with hexanes, filtrated and concentrated. Purification of the residue by flash chromatography (5% EtOAc/hexanes) afforded iodide **150** as colorless oil (0.28 g, 92%).

R_f (15 % EtOAc/hexane) = 0.59; IR (film, cm^{-1}): 3070, 3049, 2958, 2930, 2856, 1427, 1112; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70-7.66 (m, 4H), 7.46-7.37 (m, 6H), 5.23 (d, 1H, J = 1.5 Hz), 4.94 (q, 1H, J = 1.3 Hz), 4.12 (s, 2H), 3.21 (t, 2H, J = 7.7 Hz), 2.62 (t, 2H, J = 7.6 Hz), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 135.7, 133.5, 129.9, 127.9, 111.6, 66.1, 37.5, 27.0, 19.5, 3.6.

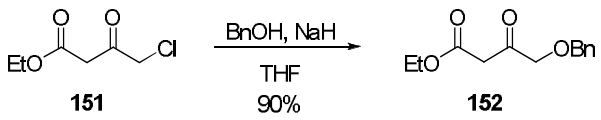
5.5.1.6 4-Bromo-2-methylenebutoxy-tert-butyldiphenylsilane 146



To a solution of alcohol **149** (1.08 g, 3.17 mmol, 100 mol-%) in CH_2Cl_2 (16 mL) was added tetrabromomethane (1.47 g, 4.4 mmol, 140 mol-%) and triphenylphosphine (1.16 g, 4.4 mmol, 140 mol-%) at rt. The reaction mixture was stirred at rt for 50 min. Hexanes (10 mL) was added. A white insoluble precipitate (triphenylphosphine oxide) and yellow oil separated from the solution. These were separated from the solution by filtration and the filtrate was concentrated. If white precipitate still formed, the residue was triturated again with hexanes, filtrated and concentrated. Purification of the residue by flash chromatography (5% EtOAc/hexanes) afforded bromide **146** as colorless oil (1.22 g, 95%).

R_f (15 % EtOAc/hexane) = 0.59; IR (film, cm^{-1}): 3050, 3071, 2959, 2931, 2893, 2857, 1429, 1113; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.67 (m, 4H), 7.47-7.38 (m, 6H), 5.24 (d, 1H, *J* = 1.5 Hz), 5.00 (q, 1H, *J* = 1.3 Hz), 4.12 (s, 2H), 3.43 (t, 2H, *J* = 7.5 Hz), 2.60 (t, 2H, *J* = 7.5 Hz), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 135.7, 133.5, 129.9, 127.9, 112.0, 66.3, 36.5, 31.1, 27.0, 19.5; HRMS (ESI^+): *m/z* calcd for [$C_{21}H_{27}ONaSiBr$] 425.0912, found 425.0896, Δ = 3.8 ppm.

5.5.1.7 Ethyl-4-benzyloxy-3-oxobutanoate 152[138]

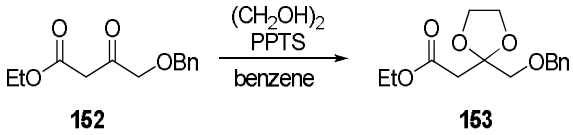


151 **152**

Sodium hydride (60% dispersion in mineral oil, 0.59 g, 25 mmol, 250 mol-%) was washed tree times with pentane and then suspended in THF (10 mL). Benzyl alcohol (1.14 mL, 1.2 g, 11 mmol, 110 mol-%) and ethyl 4-chloroacetoacetate **151** (1,36 mL, 1.65 g, 10 mmol, 100 mol-%) were added to the suspension at rt. (CAUTION, heat and gas formation during the addition!) The orange reaction mixture was stirred at rt for 21h. The mixture was poured into ice-cold 1M HCl (5 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (5 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (20% EtOAc/hexanes) afforded ethyl-4-benzyloxy-3-oxobutanoate **152** as yellow oil (2.13 g, 90%).

R_f (50 % EtOAc/hexane) = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.30 (m, 5H), 4.59 (s, 2H), 4.17 (q, 2H, *J* = 7.1 Hz), 4.14 (s, 2H), 3.54 (s, 2H), 1.25 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 167.1, 137.1, 128.7, 128.3, 128.0, 75.0, 73.7, 61.6, 46.2, 14.2; ^{1}H and ^{13}C-NMR-data match those reported in literature.[139]

5.5.1.8 Ethyl 2-(2-(benzyloxymethyl)-1,3-dioxolan-2-yl)acetate 153[140]

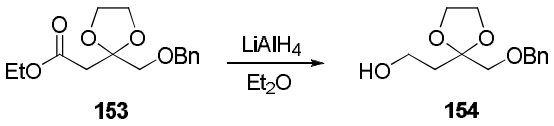


152 **153**

To a solution of ethyl-4-benzyloxy-3-oxobutanoate **152** (2.12 g, 9.0 mmol, 100 mol-%) in benzene (60 mL) was added ethylene glycol (1.51 mL, 1.67 g, 26.9 mmol, 300 mol-%) and PPTS (0.56 g, 2.2 mmol, 25 mol-%) at rt. The reaction mixture was heated to reflux and stirred for 19h. The water formed in the reaction was removed using a Dean-Stark trap. Another portion of ethylene glycol (1.0 mL, 1.1 g, 17.9 mmol, 200 mol-%) and PPTS (0.56 g, 2.2 mmol, 25 mol-%) were added. Refluxing was continued for a further 24h. Solvent was evaporated and the residue was diluted with Et_2O (10 mL). The solution was washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried over over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (initially 10% EtOAc/hexanes, then 30% and 50% EtOAc/hexanes, and finally 100% EtOAc) afforded the desired product **153** as yellow oil (0.43 g, 17%). The product can also be used without purification in the following reactions. The unreacted ethyl-4-benzyloxy-3-oxobutanoate and the side products are more easily separated from the product after the reduction/benzyl deprotection step.

R_f (50 % EtOAc/hexane) = 0.55; IR (film, cm^{-1}): 2981, 2897, 1736, 1106; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.27 (m, 5H), 4.61 (s, 2H), 4.13 (q, 2H, J = 7.1 Hz), 4.03-3.99 (m, 4H), 3.58 (s, 2H), 2.80 (s, 2H), 1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 138.3, 128.5, 127.83, 127.76, 108.2, 73.8, 72.2, 65.5 (2H), 60.7, 40.6, 14.3; HRMS (ESI^+): *m/z* calcd for $[C_{15}H_{20}O_5Na]$ 303.1208 found 303.1205, Δ = 1.0 ppm.

5.5.1.9 2-(2-(Benzyloxymethyl)-1,3-dioxolan-2-yl)ethanol 154[140]

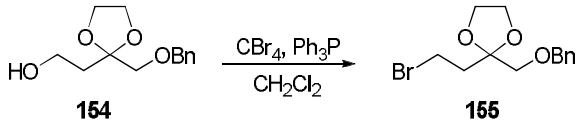


153 **154**

To a suspension of $LiAlH_4$ (67 mg, 1.8 mmol, 120 mol-%) in Et_2O (2 mL) at 0 °C was added dropwise a solution of ester **153** (0.41 g, 1.5 mmol, 100 mol-%) in Et_2O (2 mL). After stirring at 0 °C for 1h, the reaction was quenched by addition of H_2O (70 µL) at 0 °C, followed by 15% NaOH (70 µL) and H_2O (0.2 mL). The reaction mixture was allowed to warm to rt and stirred for 10 min or until white precipitate appeared. $MgSO_4$ was added. The precipitate and the drying agent were filtrated and the filtrate was concentrated. Purification of the residue by flash chromatography (20% EtOAc/hexanes) afforded the desired product **154** as colorless oil (0.34g, 100%).

R_f (50 % EtOAc/hexane) = 0.29; IR (film, cm^{-1}): 3437, 2960, 2890, 1454, 1100; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.60 (s, 2H), 4.02 (s, 4H), 3.76 (t, 2H, J = 5.4 Hz), 3.44 (s, 2H), 2.60 (br s, 1H), 2.04 (t, 2H, J = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 128.6, 127.9, 127.8, 110.4, 73.7, 72.1, 65.4 (2H), 58.6, 37.2; HRMS (ESI^+): *m/z* calcd for $[C_{13}H_{18}O_4Na]$ 261.1103, found 261.1104, Δ = 0.4 ppm.

5.5.1.10 2-(Benzyloxymethyl)-2-(2-bromoethyl)-1,3-dioxolane 155



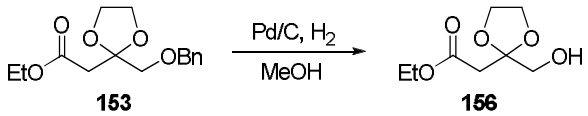
154 **155**

To a solution of alcohol **154** (0.34 g, 1.4 mmol, 100 mol-%) in CH_2Cl_2 (7 mL) was added tetrabromomethane (0.66 g, 2.0 mmol, 140 mol-%) and triphenylphosphine (0.52 g, 2.0 mmol, 140 mol-%) at rt. The reaction mixture was stirred at rt for 30 min and then quenched by addition of sat. aq. NH_4Cl (5 mL).

The layers were separated, and the organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded bromide **155** as colorless oil (0.37 g, 87%).

R_f (50 % EtOAc/hexane) = 0.54; IR (film, cm^{-1}): 3030, 2889, 1453, 1102; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 4.59 (s, 2H), 4.01-3.94 (m, 4H), 3.43-3.39 (m, 2H), 3.38 (s, 2H), 2.38-2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 128.6, 127.9, 127.8, 109.2, 73.7, 72.0, 65.6 (2H), 39.2, 26.6; HRMS (ESI^+): *m/z* calcd for [$C_{13}H_{17}O_3NaBr$] 323.0259, found 323.0266, Δ = 2.2 ppm.

5.5.1.11 Ethyl 2-(2-(hydroxymethyl)-1,3-dioxolan-2-yl)acetate 156



153 **156**

To a solution of ester **153** (1.64 g, 5.9 mmol, 100 mol-%) in MeOH (120 mL) was added Pd on charcoal (1.26 g of 5% Pd catalyst, 0.6 mmol, 10 mol-%) under argon flow. The reaction flask was repeatedly evacuated and flushed with H_2. The suspension was vigorously stirred under H_2 atmosphere for 18 h and then filtered through Celite. The filter pad was washed with EtOAc (3 x 20 mL) and the combined filtrates were concentrated. Further filtration through a short pad of silica with EtOAc afforded the desired product **156** as colorless oil (1.1 g, 98%).

R_f (50 % EtOAc/hexane) = 0.21; IR (film, cm^{-1}): 3480, 2982, 2898, 1733, 1132; ^1H NMR (400 MHz, $CDCl_3$): δ 4.16 (q, 2H, *J* = 7.1 Hz), 4.08-4.00 (m, 4H), 3.69 (d, 2H, *J* = 7.0 Hz), 2.76 (s, 2H), 2.09 (t, 1H, *J* = 7.0 Hz), 1.27 (t, 3H, *J* = 7.1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 108.3, 65.7 (2H), 65.4, 60.9, 40.5, 14.2; HRMS (ESI^+): *m/z* calcd for [$C_8H_{14}O_5Na$] 213.0739, found 213.0754, Δ = 7.0 ppm.

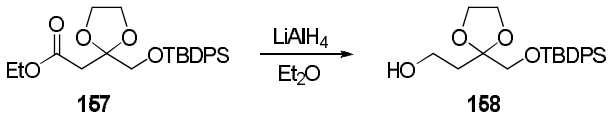
5.5.1.12 Ester 157

156 **157**

To a solution of ester **156** (0.48 g, 2.5 mmol, 100 mol-%) in DMF (3 mL) was added imidazole (0.34 g, 5.0 mmol, 200 mol-%), TBDPSCl (0.79 mL, 0.83 g, 3.0 mmol, 120 mol-%) and DMAP (60 mg, 0.5 mmol, 20 mol-%). The reaction mixture was stirred at rt for 2h. After dilution with CH_2Cl_2 (10 mL), the mixture was washed with 1M HCl (2 x 5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with brine (15 mL), dried over over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (30% EtOAc/hexanes) afforded the desired product **157** as light yellow viscose oil (0.98 g, 91%).

R_f (50 % EtOAc/hexane) = 0.61; IR (film, cm^{-1}): 3072, 3050, 2958, 2931, 2892, 2858, 1738, 1113; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73-7.70 (m, 4H), 7.44-7.36 (m, 6H), 4.14 (q, 2H, *J* = 7.1 Hz), 4.02-3.89 (m, 4H), 3.68 (s, 2H), 2.85 (s, 2H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 135.8, 135.5, 134.9, 133.4, 129.8, 127.9, 127.8, 108.7, 66.3, 65.6 (2H), 60.6, 40.4, 26.9, 26.7, 19.4, 14.3; HRMS (ESI^+): *m/z* calcd for [$C_{24}H_{32}O_5NaSi$] 451.1917, found 451.1926, Δ = 2.0 ppm.

5.5.1.13 Alcohol 158



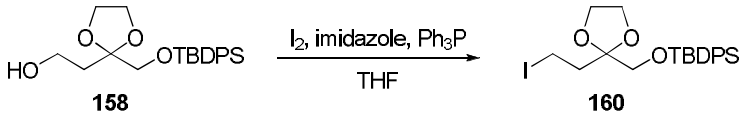
157 **158**

To a suspension of $LiAlH_4$ (29 mg, 0.8 mmol, 120 mol-%) in Et_2O (1 mL) at 0 °C was added dropwise a solution of ester **157** (0.27 g, 0.6 mmol, 100 mol-%) in Et_2O (1 mL). After stirring at 0 °C for 1h, the reaction was quenched by addition

of H_2O (30 μL) at 0 °C, followed by 15% NaOH (30 μL) and H_2O (90 μL). The reaction mixture was allowed to warm to rt and stirred for 30 min or until white precipitate appeared. $MgSO_4$ was added. The precipitate and the drying agent were filtrated and the filtrate was concentrated. Purification of the residue by flash chromatography (initially 20% EtOAc/hexanes, finally 40% EtOAc/hexanes) afforded the desired product **158** as yellow viscose oil (0.23g, 93%).

R_f (50 % EtOAc/hexane) = 0.29; IR (film, cm^{-1}): 3451, 3071, 3049, 2959, 2931, 2890, 2858, 1428, 1113; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72-7.68 (m, 4H), 7.46-7.37 (m, 6H), 4.01-3.87 (m, 4H), 3.79 (t, 2H, *J* = 5.4 Hz), 3.56 (s, 2H), 2.80 (br s, 1H), 2.06 (t, 2H, *J* = 5.4 Hz), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 133.2, 129.9, 127.9, 111.1, 66.3, 65.4 (2H), 58.7, 36.7, 26.9, 19.3; HRMS (ESI^+): *m/z* calcd for [$C_{22}H_{30}O_4NaSi$] 409.1811, found 409.1818, Δ = 1.7 ppm.

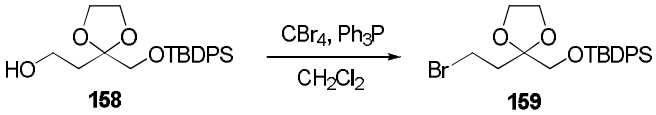
5.5.1.14 Iodide 160



To a solution of alcohol **158** (0.33 g, 0.85 mmol, 100 mol-%) in THF (9 mL) was added imidazole (0.15 g, 2.1 mmol, 220 mol-%) and triphenylphosphine (0.25 g, 0.94 mmol, 110 mol-%) at rt. After 5 min, the reaction mixture was cooled to 0 °C and iodine (0.24 g, 0.94 mmol, 110 mol-%) was added. The reaction mixture was allowed to warm to rt and stirred for 30 min. Hexanes (5 mL) was added. A white insoluble precipitate (triphenylphosphine oxide) and yellow oil separated from the solution. These were separated from the solution by filtration and the filtrate was concentrated. If white precipitate still formed, the residue was triturated again with hexanes, filtrated and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded iodide **160** as white powdery solid (0.41 g, 97%).

R_f (50 % EtOAc/hexane) = 0.68; mp 83-84 ºC; IR (film, cm^{-1}): 2967, 2929, 2899, 2856, 1427, 1228, 1112; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70-7.68 (m, 4H), 7.46-7.37 (m, 6H), 3.96-3.87 (m, 4H), 3.49 (s, 2H), 3.19-3.15 (m, 2H), 2.43-2.39 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 133.2, 129.9, 127.9, 110.6, 66.2, 65.6 (2H), 40.4, 26.9, 19.3, –2.5; HRMS (ESI^+): *m/z* calcd for [$C_{22}H_{29}O_3NaSiI$] 519.0828, found 519.0839, Δ = 2.1 ppm.

5.5.1.15 Bromide 159

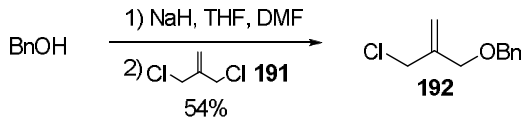


To a solution of alcohol **158** (0.43 g, 1.10 mmol, 100 mol-%) in CH_2Cl_2 (5 mL) was added tetrabromomethane (0.51 g, 1.54 mmol, 140 mol-%) and triphenylphosphine (0.40 g, 1.54 mmol, 140 mol-%) at rt. The reaction mixture was stirred at rt for 1 h 15 min and then quenched by addition of sat. aq. NH_4Cl (5 mL). The layers were separated, and the organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded bromide **159** as white powdery solid (0.48 g, 98%).

R_f (50 % EtOAc/hexane) = 0.60; mp 85-86 ºC; IR (film, cm^{-1}): 2962, 2930, 2900, 2856, 1427, 1231, 1112; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71-7.68 (m, 4H), 7.46-7.37 (m, 6H), 3.95-3.86 (m, 4H), 3.50 (s, 2H), 3.45-3.41 (m, 2H), 2.40-2.36 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 133.3, 129.9, 127.9, 109.9, 66.4, 65.6 (2H), 39.0, 26.9, 26.8, 19.3; HRMS (ESI^+): *m/z* calcd for [$C_{22}H_{29}O_3NaSiBr$] 471.0967, found 471.0982, Δ = 3.2 ppm.

5.5.2 Methylation Strategy

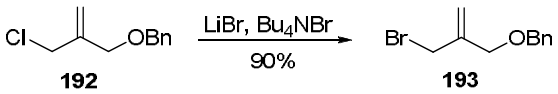
5.5.2.1 3-Benzyloxy-2-chloromethyl-1-propene 192[141]



Sodium hydride (60% suspension in mineral oil, 1.92 g, 48 mmol, 120 mol-%) was washed with hexanes (2 × 60 mL). After evaporation of the residual hexanes, THF (60 mL) was added. To this suspension was added benzyl alcohol (4.97 mL, 5.2 g, 48 mmol, 120 mol-%) at rt and after stirring for 30 min DMF (13 mL) was added. The reaction mixture was warmed to reflux and stirred for 1 h. The color changed from yellow to orange during warming. The mixture was allowed to cool to rt and then transferred via cannula into a dropping funnel. This solution was added dropwise over 30 min to a solution of 3-chloro-2-chloromethyl-1-propene **191** (4.63 mL, 5.0 g, 40 mmol, 100 mol-%) in THF (40 mL) at rt. The reaction mixture was stirred at rt for 18 h, during which time a white precipitate had formed. The mixture was quenched by addition of H_2O (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O/hexanes/pentane (2:1:1.3, 50 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (5% Et_2O/hexanes) afforded the desired product **192** as colorless oil (4.9 g, 62%).

R_f (50 % EtOAc/Hex) = 0.71; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 5.33 (d, 1H, *J* = 1.0 Hz), 5.27 (q, 1H, *J* = 1.0 Hz), 4.53 (s, 2H), 4.14 (d, 2H, *J* = 1.0 Hz), 4.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 138.0, 128.4 (2C), 127.6 (2C), 116.8 (2C), 72.3, 70.2, 45.2. The data is in agreement with the data presented in literature.[142]

5.5.2.2 3-Benzyloxy-2-bromomethyl-1-propene 193[143]

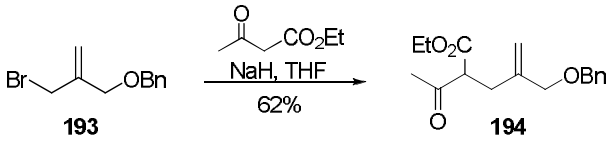


192 **193**

Lithium bromide (4.42 g, 50.9 mmol, 200 mol-%) was flame dried under vacuum before it was added to a mixture of 3-benzyloxy-2-chloromethyl-1-propene **192** (5.0 g, 25.5 mmol, 100 mol-%) and tetrabutylammoniumbromide (0.41 g, 1.3 mmol, 5.0 mol-%). The reaction mixture was stirred at 60 °C for 1.5 h and was then allowed to cool to rt. The mixture was filtered through florisil. Concentration afforded the desired product **193** as light yellow oil (5.9 g, 97%).

R_f (50 % EtOAc/Hex) = 0.72; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 5.36 (d, 1H, *J* = 0.8 Hz), 5.27 (q, 1H, *J* = 1.3 Hz), 4.54 (s, 2H), 4.15 (s, 2H), 4.05 (d, 2H, *J* = 0.8); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 137.9, 128.3 (2C), 127.5 (2C), 117.2 (2C), 72.1, 70.8, 33.0. The data is in agreement with the data presented in literature.[143]

5.5.2.3 2-Acetyl-4-benzyloxymethyl-pent-4-enoic acid ethyl ester 194



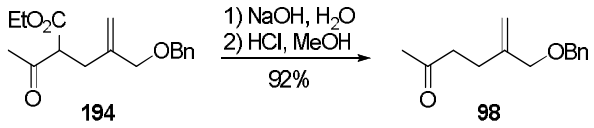
193 **194**

Sodium hydride (60% suspension in mineral oil, 1.96 g, 48.9 mmol, 200 mol-%) was washed with hexanes (2 × 10 mL). After evaporation of the residual hexanes, THF (10 mL) was added. To this suspension at rt was added dropwise ethyl acetoacetate (distilled prior to use, 6.2 mL, 48.9 mmol, 200 mol-%). The reaction mixture was stirred at rt for 30 min and then a solution of 3-benzyloxy-2-bromomethyl-1-propene **193** (5.9 g, 24.5 mmol, 100 mol-%) in THF (5 mL) was added. Stirring was continued at rt for 1.5 h. The mixture was diluted with Et_2O (20 mL) and washed with H_2O (2 x 50 mL). The separated aqueous phases were

back-extracted with Et_2O (30 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (15% MTBE/hexanes) afforded the desired product **194**, containing small amounts of ethyl acetoacetate (5.0 g).

R_f (10 % EtOAc/toluene) = 0.41; IR (film, cm^{-1}): 2983, 2858, 1742, 1716, 1651, 1454, 1359, 1247, 1148, 1074, 911, 739, 699; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.10 (s, 1H), 4.96 (s, 1H), 4.48 (s, 2H), 4.18 (dq, 2H, *J* = 7.1, 0.6 Hz), 3.98-3.96 (m, 2H), 3.74 (t, 1H, *J* = 7.6 Hz), 2.66 (d, 2H, *J* = 7.6 Hz), 2.22 (s, 3H), 1.25 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 169.3, 142.4, 138.1, 128.4 (2C), 127.7 (2C), 127.6, 114.3, 72.9, 72.0, 61.4, 58.0, 31.5, 28.9, 14.0; HRMS (ESI^+): *m/z* calcd for $[C_{17}H_{22}O_4Na]$ 313.1416, found 313.1406, Δ = 3.2 ppm.

5.5.2.4 5-Benzyloxymethyl-hex-5-en-2-one 98

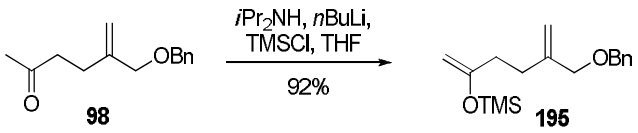


This reaction was not carried out under argon atmosphere. To neat ester **194** (5.0 g, ~17 mmol, 100 mol-%) was added 5 M NaOH in H_2O (15.0 mL, 2.94 g NaOH, 73.5 mmol, ~432 mol-%). After stirring at rt for 21 h, the mixture was poured into a separation funnel charged with 2 M HCl (20 mL) and H_2O (60 mL). The mixture was extracted with Et_2O (3 × 50 mL). After concentration, the residue was dissolved to methanol (40 mL) and 5 M HCl in methanol (15.0 mL, 73.5 mmol, ~432 mol-%) was added. The reaction mixture was stirred at rt for 25 h. The reaction mixture was poured into a separating funnel containing H_2O (50 mL), Et_2O (50 mL) and pentane (50 mL). The layers were separated. The aqueous phase was extracted with hexane/pentane (1:1, 100 ml) and with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (30%

MTBE/hexanes) afforded the desired product **98** as yellow oil (3.2 g, 60% over 2 steps).

R_f (30 % MTBE/Hex) = 0.28; IR (film, cm^{-1}): 2955, 2855, 1717, 1652, 1453, 1358, 1160, 1095, 1073, 1028, 905, 738, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.07 (d, 1H, *J* = 1.2 Hz), 4.91 (s, 1H), 4.49 (s, 2H), 3.97 (d, 2H, *J* = 0.4 Hz), 2.62 (t, 2H, *J* = 7.6 Hz), 2.37 (t, 2H, *J* = 7.6 Hz), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 144.7, 138.2, 128.4 (2C), 127.7 (2C), 127.6, 112.3, 73.2, 72.0, 41.7, 29.9, 27.1; HRMS (ESI^+): *m/z* calcd for [$C_{14}H_{18}O_2Na$] 241.1204, found 241.1211, Δ = 2.8 ppm.

5.5.2.5 TMS Enolate 195

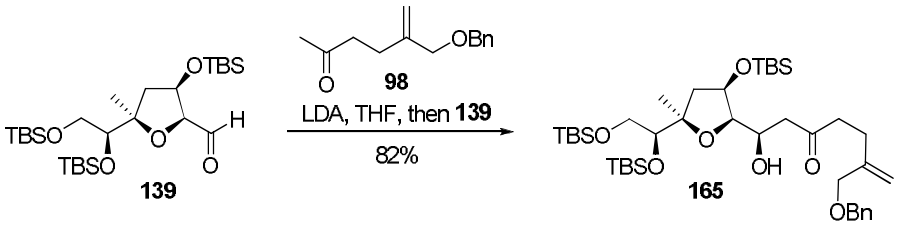


To a solution of diisopropylamine (96 μL, 0.69 mmol, 150 mol-%) in THF (3 mL) was added *n*BuLi (2.2 M in hexanes, 0.31 mL, 0.69 mmol, 150 mol-%) at –78 °C. After stirring for 30 min, a solution of ketone **98** (0.1 g, 0.46 mmol, 100 mol-%) in THF (3 mL) was added. Stirring was continued at –78 °C for further 30 min and TMSCl (88 μL, 0.69 mmol, 150 mol-%) was added. The reaction mixture was stirred for 15 min and then diluted with Et_2O (5 mL) and sat. aq. NH_4Cl (5 mL) was added. The layers were separated, and the organic phase was washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded the desired product **195** as colorless oil (0.11 g, 83%).

R_f (50 % EtOAc/Hex) = 0.60; IR (film, cm^{-1}): 2958, 2925, 2854, 1654, 1635, 1253, 846; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 5.07 (s, 1H), 4.96 (d, 1H, *J* = 0.7 Hz), 4.50 (s, 2H), 4.06 (d, 1H, *J* = 0.7 Hz), 4.05 (d, 1H, *J* = 0.8 Hz), 3.98 (s, 2H), 2.29-2.18 (m, 4H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 159.1, 145.6, 138.6, 128.5, 127.8, 127.7, 112.0, 90.1, 73.3, 72.1, 34.9, 30.7, 0.3; HRMS (ESI^+): *m/z* calcd for [$C_{17}H_{26}O_2NaSi$] 313.1600, found 313.1585, Δ = 4.8 ppm.

5.5.2.6 β-Hydroxyketone 165



A stock solution of LDA (0.5 M) was prepared as follows: To a solution of diisopropylamine (0.66 mL, 5.0 mmol, 176 mol-%) in THF (8 mL) was added *n*BuLi (2.8 M in hexanes, 1.7 mL, 4.8 mmol, 171 mol-%) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min. A portion of the LDA solution (0.5 M, 6.04 mL, 3.02 mmol, 110 mol-%) was transferred via syringe to solution of ketone **98** (0.6 g, 2.8 mmol, 100 mol-%) in THF (15 mL) at –78 °C. After 4 min, a –78 °C solution of aldehyde **139** (1.68 g, 3.2 mmol, 115 mol-%) in THF (15 mL) was cannulated into the reaction mixture. Stirring was continued at –78 °C for 5 min before sat. aq. NH_4Cl (10 mL) was added. The reaction mixture was allowed to warm to rt and then diluted with Et_2O (20 mL) and sat. aq. NH_4Cl (20 mL) was added. The layers were separated, and the organic phase was washed with sat. aq. NH_4Cl (30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded the desired product **165** as yellow viscous oil (1.7 g, 82%). The product contains small amounts of impurities that can be easily separated after the following step. These impurities are the result of the reaction between aldehyde **139** and the undesired thermodynamic enolate of ketone **98**.

R_f (30% EtOAc/hexanes) = 0.42; $[\alpha]_D$ = –20.3 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3514, 2955, 2930, 2885, 2856, 1708, 1254, 1071, 835, 778; ^1H NMR (400 MHz,

$CDCl_3$): δ 7.35-7.26 (m, 5H), 5.07 (d, 1H, *J* = 1.0 Hz), 4.90 (s, 1H), 4.49 (s, 3H), 4.30-4.25 (m, 1H), 3.96, (s, 2H), 3.90 (dd, 1H, *J* = 10.5, 1.4 Hz), 3.67-3.63 (m, 2H), 3.47 (dd, 1H, *J* = 10.5, 7.3 Hz), 3.19 (d, 1H, *J* = 3.8 Hz), 2.79 (dd, 1H, *J* = 16.9, 2.4 Hz), 2.66-2.57 (m, 3H), 2.38 (t, 2H, *J* = 7.5 Hz), 2.09 (dd, 1H, *J* = 13.5, 3.7 Hz), 1.87 (dd, 1H, *J* = 13.4, 6.0 Hz), 1.06 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.092 (s, 3H), 0.091 (s, 3H), 0.087 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 144.9, 138.4, 128.5, 127.9, 127.7, 112.4, 83.9, 82.7, 80.8, 73.6, 73.3, 72.2, 66.7, 65.5, 46.6, 46.5, 41.8, 26.8, 26.2, 26.1, 26.0, 21.3, 18.7, 18.4, 18.2, –3.4, –4.3, –4.9, –5.09, –5.12, –5.2; HRMS (ESI^+): *m/z* calcd for [$C_{40}H_{74}O_7NaSi_3$] 773.4640, found 773.4662, Δ = 2.8 ppm.

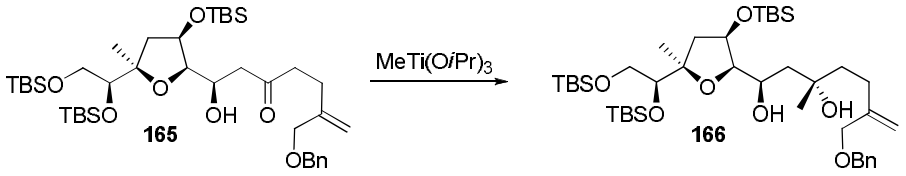
5.5.2.7 Aldol Reaction Screen

The results using different enolate precursors for the aldol reaction are presented in Table 13. Compared to lithium enolate, enolsilane ($TMS/BF_3{\cdot}OEt_2$) gave similar selectivities but reduced yields, which is mainly due to uncompleted reaction. Also, the unreacted ketone was very difficult to separate from the aldol product.

Table 13. Aldol reaction screen

Enolate precursor	Yield [%]
$TMS/BF_3{\cdot}OEt_2$	61
Li	82

5.5.2.8 Diol 166



Optimized procedure:[144]

A stock triisopropoxymethyltitanium solution (0.5 M) was prepared as follows: To a gently cooled (~5 °C) titanium(IV) isopropoxide (2.68 mL, 9 mmol, 2250 mol-%) was added dropwise titanium tetrachloride (0.32 mL, 3 mmol, 750 mol-%). The mixture was allowed to warm to rt and stirred for 5 min. Et_2O (13.5 mL) was added and stirring was continued at rt for 30 min. The reaction mixture was cooled to 0 °C and MeLi (1.6 M in Et_2O, 7.5 mL, 12 mmol, 3000 mol-%) was added. During the addition LiCl precipitates and the color of the suspension changes from orange to bright yellow. After 1 h, a portion of the triisopropoxymethyltitanium solution (0.5 M, 12.0 mL, 6.0 mmol, 1500 mol-%) was transferred to another flask and cooled to –78 °C. A solution of ketone **165** (0.3 g, 0.4 mmol, 100 mol-%) in Et_2O (9 mL) was added. The reaction mixture was stirred at –78 °C for 10 min and then the dry ice bath was changed into an ice bath. Stirring was continued at 0 °C for further 10 min. The reaction mixture was diluted with Et_2O (5 mL) and 2 M HCl (5.0 mL) was added dropwise. The mixture was allowed to warm to rt and stirred vigorously until both phases were clear. The layers were separated, and the organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (15% EtOAc/hexanes) afforded the desired product **166** as light yellow viscous oil (0.28 g, 91%).

R_f (30% EtOAc/hexanes) = 0.31; $[\alpha]_D$ = –28.2 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3429, 2955, 2929, 2885, 2856, 1254, 836, 777; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 5.07 (s, 1H), 4.96 (s, 1H), 4.61 (q, 1H, *J* = 6.0 Hz), 4.51 (s, 2H), 4.21 (dd, 1H, *J* = 10.2, 8.3 Hz), 3.98, (s, 2H), 3.88 (dd, 1H, *J* = 10.3, 1.3 Hz),

3.70 (br s, 1H), 3.64 (dd, 1H, *J* = 8.2, 5.4 Hz), 3,61 (br s, 1H), 3.58 (dd, 1H, *J* = 7.3, 1.3 Hz), 3.48 (dd, 1H, *J* = 10.4, 7.3 Hz), 2.28-2.08 (m, 2H), 1.98 (dd, 2H, *J* = 6.1, 2.4 Hz), 1.89-1.82 (m, 2H), 1.69 (dd, 1H, *J* = 14.7, 10.9 Hz), 1.67-1.61 (m, 1H), 1.20 (s, 3H), 1.06 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 138.6, 128.5, 127.8, 127.7, 111.1, 83.6, 82.3, 81.3, 74.3, 73.3, 72.7, 72.2, 68.8, 65.5, 46.2, 44.3, 38.8, 28.1, 27.9, 26.3, 26.1, 25.9, 21.2, 18.6, 18.4, 18.0, –3.4, –4.1, –4.9, –5.07, –5.13 (2C); HRMS (ESI^+): *m/z* calcd for $[C_{41}H_{78}O_7NaSi_3]$ 789.4953, found 789.4968, Δ = 1.9 ppm.

General procedure for the methylation reactions:[115]

Generally, a stock solution of the methylation reagent (~0.5 M) was prepared in situ. A portion of the reagent was transferred to another flask and ketone **165** in Et_2O or THF (~0.04 M) was added. However, there was no effect whether the methylation reagent was added to the ketone or the other way around. For entry 8 (Table 14), $MeTi(O\textit{i}Pr)_3$ was prepared according to the optimized procedure and then Kugelrohr distilled after removal of solvent directly from the precipitated lithium chloride (0.4 mmHg, 85-90 °C) before used for the methylation as described above. For reaction temperatures and times see Table 14. The work-up was always done according to the optimized procedure. Conversions and diastereoselectivities were determined by ^{1}H NMR from the crude reaction mixture.

Synthesis of $MeTi(O\textit{i}Pr)_3$ using MeMgBr instead of MeLi (Table 14, entry 5):

To a gently cooled (~5 °C) titanium(IV) isopropoxide (0.89 mL, 3 mmol, 300 mol-%) was added dropwise titanium tetrachloride (0.11 mL, 1 mmol, 100 mol-%). The mixture was allowed to warm to rt and stirred for 5 min. THF (4 mL) was added and stirring was continued at rt for 30 min. The solution was cooled to 0 °C and MeMgBr (3.0 M in Et_2O, 1.33 mL, 4 mmol, 400 mol-%) was added. The reaction mixture was stirred at 0 °C for 1 h before used for methylation of ketone **165**.

Methylation with $MeTi(OiPr)_3$ using excess $Ti(OiPr)_4$ (Table 14, entry 9):

To a gently cooled (~5 °C) titanium(IV) isopropoxide (0.89 mL, 3 mmol, 300 mol-%) was added dropwise titanium tetrachloride (0.11 mL, 1 mmol, 100 mol-%). The mixture was allowed to warm to rt and stirred for 5 min. Et_2O (4 mL) was added and stirring was continued at rt for 30 min. The reaction mixture was cooled to 0 °C and MeLi (1.6 M in Et_2O, 2.5 mL, 4 mmol, 400 mol-%) was added. Stirring was continued at 0 °C for 1 h. A portion of the triisopropoxymethyltitanium solution (0.5 M, 0.39 mL, 0.2 mmol, 1500 mol-%) was transferred to another flask and cooled to –78 °C. $Ti(OiPr)_4$ (58 μL, 0.2 mmol, 1500 mol-%) and a solution of ketone **165** (10 mg, 0.013 mmol, 100 mol-%) in Et_2O (0.3 mL) were added consecutively. Work-up according to the optimized procedure.

Synthesis of $MeTi(OMe)_3$ (Table 14, entry 10):

Synthesized according to the optimized procedure using $Ti(OMe)_4$ instead of $Ti(OiPr)_4$.

Synthesis of $MeTi(OiPr)_2Cl$ (Table 14, entries 11-13):

To a gently cooled (~5 °C) titanium(IV) isopropoxide (0.3 mL, 1 mmol, 100 mol-%) was added dropwise titanium tetrachloride (0.11 mL, 1 mmol, 100 mol-%). The mixture was allowed to warm to rt and stirred for 5 min. THF or Et_2O (2.3 mL) was added and stirring was continued at rt for 30 min. The solution was cooled to 0 °C and MeLi (1.6 M in Et_2O, 1.24 mL, 2 mmol, 200 mol-%) was added. The reaction mixture was stirred at 0 °C for 1 h before used for methylation of ketone **165**.

Synthesis of $Me_2Ti(OiPr)_2$ and $Me_2Ti(OMe)_2$ (Table 14, entries 14-17):

To a gently cooled (~5 °C) titanium(IV) isopropoxide (0.3 mL, 1 mmol, 100 mol-%) was added dropwise titanium tetrachloride (0.11 mL, 1 mmol, 100 mol-%). The mixture was allowed to warm to rt and stirred for 5 min. THF or

Et_2O (5.0 mL) was added and stirring was continued at rt for 30 min. The solution was cooled to 0 °C and MeLi (1.6 M in Et_2O, 2.5 mL, 4 mmol, 400 mol-%) was added. The reaction mixture was stirred at 0 °C for 1 h before used for methylation of ketone **165**. $Me_2Ti(OMe)_2$ was prepared in similar manner using $Ti(OMe)_4$ instead of $Ti(O\textit{i}Pr)_4$.

Synthesis of $MeTiCl_3$ (Table 14, entry 18):

Et_2O (1.3 mL) was cooled to –78 °C. Titanium tetrachloride (0.11 mL, 1 mmol, 100 mol-%) and MeLi (1.6 M in Et_2O, 0.63 mL, 1 mmol, 100 mol-%) were added consecutively. The reaction mixture was allowed to warm to 0 °C and stirred for 20 min before used for methylation of ketone **165**.

Methylation using $MeLi/ZnBr_2$ (Table 14, entry 19):

To a solution of ketone **165** (10 mg, 0.013 mmol, 100 mol-%) in CH_2Cl_2 (0.8 mL) was added $ZnBr_2$ (6.1 mg, 0.027 mmol, 200 mol-%). The suspension was stirred at rt for 1 h and was then cooled to –78 °C and MeLi (1.6 M in Et_2O, 33 μL, 0.053 mmol, 400 mol-%) was added. After stirring at –78 °C for 2 h another portion of MeLi (1.6 M in Et_2O, 33 μL, 0.053 mmol, 400 mol-%) was added. Stirring was continued at –78 °C for further 2 h. Work-up according to the optimized procedure.

Methylation using MeMgBr (Table 14, entry 20):

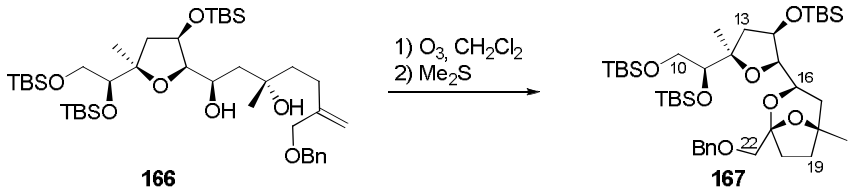
To a solution of ketone **165** (10 mg, 0.013 mmol, 100 mol-%) in Et_2O (0.3 mL) was added MeMgBr (3.0 M in Et_2O, 43 μL, 0.13 mmol, 100 mol-%) at –78 °C. The reaction mixture was stirred at –78 °C for 15 min and then diluted with Et_2O (2.0 mL) and H_2O (0.3 mL) was added. The layers were separated, and the organic phase was washed with brine (2.0 mL), dried over $MgSO_4$ and concentrated.

Table 14. Methylation screens.

Entry	Methylation reagent[a]	Equiv	Solvent	Temperature [°C]	Time [min at –78/0 °C]	dr[b]	Conversion[b] [%]
1	$MeTi(O\textit{i}Pr)_3$	5	THF	0	10	3:1	100
2	$MeTi(O\textit{i}Pr)_3$	5	THF	–78	2h		no reaction
3	$MeTi(O\textit{i}Pr)_3$	5	THF	–30	10	3:1	20
4	$MeTi(O\textit{i}Pr)_3$[c]	5	THF	–30	10		no reaction
5	$MeTi(O\textit{i}Pr)_3$[d]	5	THF	–78 to 0	30/10	2:1	100
6	$MeTi(O\textit{i}Pr)_3$	5	Et_2O	–78 to 0	10/10	8:1 - 2:3	100
7	$MeTi(O\textit{i}Pr)_3$	15	Et_2O	–78 to 0	10/10	9:1	100
8	$MeTi(O\textit{i}Pr)_3$	15	Et_2O	–78 to 0	10/10	4:1	80
9	$MeTi(O\textit{i}Pr)_3$[e]	15	Et_2O	–78 to 0	10/10	4:1	80
10	$MeTi(OMe)_3$	15	Et_2O	–78 to 0	10/10	4:1	100
11	$MeTi(O\textit{i}Pr)_2Cl$[f]	5	THF	–10	30	2:1	100
12	$MeTi(O\textit{i}Pr)_2Cl$	5	THF	–78 to 0	10/15	3:1	100
13	$MeTi(O\textit{i}Pr)_2Cl$	15	Et_2O	–78 to 0	10/10	3:1	100
14	$Me_2Ti(O\textit{i}Pr)_2$	2	THF	0	15	4:1	100
15	$Me_2Ti(O\textit{i}Pr)_2$	15	Et_2O	–78 to 0	10/10	6:1	100
16	$Me_2Ti(OMe)_2$	2	THF	0	12	6:1	100
17	$Me_2Ti(OMe)_2$	15	Et_2O	–78 to 0	10/10	2:1	100
18	$MeTiCl_3$	15	Et_2O	–78 to 0	10/10	1:1	20
19	$MeLi/ZnBr_2$	4	CH_2Cl_2	–78	240	3:2	100
20	MeMgBr	1	Et_2O	–78	15	2:1	100

[a] Reagents were prepared *in situ*, except in entry 8 where $MeTi(O\textit{i}Pr)_3$ was distilled prior to use. [b] Determined by ^1H NMR from the crude reaction mixture. [c] LiI as additive. [d] Prepared using MeMgBr. [e] Excess $Ti(O\textit{i}Pr)_4$ (15 equiv) was used. [f] The methylation reagent was added over a period of 30 min to a solution of ketone using a syringe pump.

5.5.2.9 CDE Ring Fragment 167



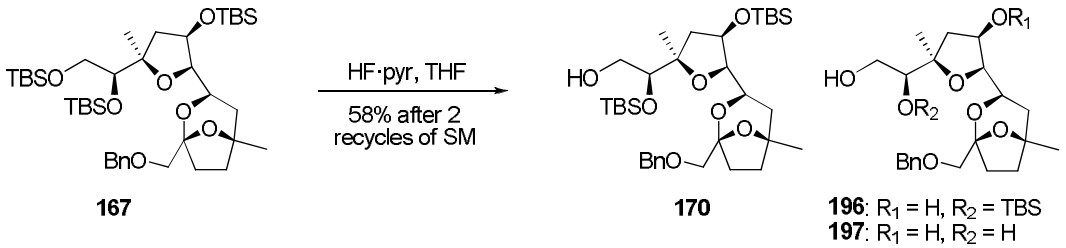
A three-necked flask was charged with diol **166** (0.23 g, 0.3 mmol, 100 mol-%) in CH_2Cl_2 (8 mL) and cooled to –78 °C. Ozone was bubbled through the reaction mixture for 30 sec or until blue color emerged. Oxygen was then allowed to pass through the mixture for 5 min. Dimethylsulfide (0.44 mL, 6.0 mmol, 2000 mol-%) was added and the reaction mixture was allowed to warm to rt. After 1h, another portion of dimethylsulfide (0.88 mL, 12 mmol, 4000 mol-%) was added. Stirring was continued at rt for further 2h. Concentration and purification of the residue by

flash chromatography (initially 5% EtOAc/hexanes, finally 9% EtOAc/hexanes) afforded the desired product **167** as colorless viscose oil (0.28 g, 91%).

R_f (30% EtOAc/hexanes) = 0.60; $[\alpha]_D$ = –13.6 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2955, 2929, 2856, 1471, 1254, 835, 777; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5H), 4.62 (dd^{AB}, 2H, $|J_{AB}|$ = 12.4 Hz, Δv = 33.0 Hz), 4.26 (dd, 1H, *J* = 4.6, 3.1 Hz), 4.13 (ddd, 1H, *J* = 11.4, 7.9, 3.8 Hz), 3.99 (dd, 1H, *J* = 10.7, 1.0 Hz), 3.75 (dd, 1H, *J* = 7.5, 0.9 Hz), 3.57 (dd, 1H, *J* = 8.0, 3.0 Hz), 3.52 (dd^{AB}, 2H, $|J_{AB}|$ = 10.7 Hz, Δv = 22.9 Hz), 3.44 (dd, 1H, *J* = 10.7, 7.6 Hz), 2.18 (dt, 1H, *J* = 13.1, 4.4 Hz), 2.15 (d, 1H, *J* = 13.7 Hz), 2.00 (ddd, 1H, *J* = 13.6, 9.4, 5.2 Hz), 1.85-1.79 (m, 1H), 1.74-1.64 (m, 3H), 1.57 (dd, 1H, *J* = 13.2, 4.0 Hz), 1.39 (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), –0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5 (-Bn, C_q), 128.4 (-Bn, 2 x CH=), 127.9 (-Bn, 2 x CH=), 127.6 (-Bn, CH=), 106.4 (21-C_q), 85.0 (15-CH), 83.6 (12-C_q), 81.1 (18-C_q or 11-CH), 80.9 (18-C_q or 11-CH), 73.8 (Ph, CH_2), 72.4 (14-CH), 71.9 (22-CH_2), 66.6 (16-CH), 65.6 (10-CH_2), 47.0 (13-CH_2), 40.8 (17-CH_2), 34.4 (19-CH_2), 31.8 (20-CH_2), 26.35 (43-CH_3), 26.30 (-TBS, 3 x CH_3), 26.2 (-TBS, 3 x CH_3), 26.1 (-TBS, 3 x CH_3), 21.2 (12a-CH_3), 18.8 (-TBS, C_q), 18.4 (-TBS, C_q), 18.1 (-TBS, C_q), –3.4 (-TBS, -CH_3), –4.4 (-TBS, -CH_3), –4.8 (-TBS, -CH_3), –5.0 (-TBS, -CH_3), –5.07 (-TBS, -CH_3), –5.09 (-TBS, -CH_3); HRMS (ESI^+): m/z calcd for [$C_{40}H_{74}O_7NaSi_3$] 773.4640, found 773.4638, Δ = 0.3 ppm.

5.6 Synthesis of ABCDE Ring Fragment

5.6.1 CDE Ring Alcohol 170



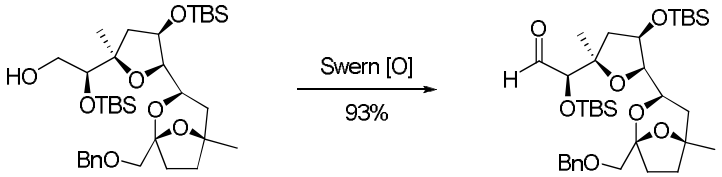
167 **170** **196**: R_1 = H, R_2 = TBS; **197**: R_1 = H, R_2 = H

To a solution of compound **167** (2.0 g, 2.66 mmol, 100 mol-%) in THF (8.0 mL) was added HF·pyridine (70% HF, 2.08 mL, 1.6 g, 80.0 mmol, 3000 mol-%) at rt. The reaction mixture was stirred at rt for 1.5 h before sat. aq. $NaHCO_3$ (50 mL) was added dropwise. The mixture was allowed to stir for 10 min, and then the layers were separated. The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 50 mL). The combined aqueous layers were extracted with Et_2O (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 10% EtOAc/hexanes, finally MeOH) afforded the desired product **170** as light yellow viscous oil (0.76 g, 45%). Other collected fractions contained the starting material **167** (0.64 g) and a mixture of diol **196** and triol **197** (0.26 g). After another reaction with the recycled starting material, the desired product **170** was obtained in 58% combined yield (0.98g).

R_f (30% EtOAc/hexanes) = 0.49; $[\alpha]_D$ = –12.2 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3514, 2955, 2930, 2885, 2857, 1472, 1463, 1254, 1120, 1110, 1067; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.25 (m, 5H), 4.61 (dd^{AB}, 2H, $|J_{AB}|$ = 12.3 Hz, Δv = 29.5 Hz), 4.29 (dd, 1H, *J* = 4.4, 3.0 Hz), 4.15 (ddd, 1H, *J* = 11.5, 8.0, 3.7 Hz), 3.82 (dd, 1H, *J* = 8.0, 3.9 Hz), 3.77 (dd, 1H, *J* = 10.6, 8.0 Hz), 3.60 (dd, 1H, *J* = 8.2, 2.9 Hz), 3.51 (dd^{AB}, 2H, $|J_{AB}|$ = 10.7 Hz, Δv = 22.0 Hz), 3.56-3.50 (m, 1H), 2.94 (s, 1H), 2.19 (dt, 1H, *J* = 13.2, 4.2 Hz), 2.08-1.95 (m, 2H), 1.92-1.83 (m,

2H), 1.74-1.64 (m, 2H), 1.51 (dd, 1H, *J* = 13.1, 3.9 Hz), 1.37 (s, 3H), 1.17 (s, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 128.4, 127.9, 127.6, 106.4, 85.7, 85.2, 81.0, 76.2, 73.8, 71.92, 71.87, 66.1, 64.7, 48.0, 40.7, 34.2, 31.8, 26.3, 26.1, 25.9, 20.5, 18.1 (2H), –3.8, –4.4, –4.5, –5.0; HRMS (ESI^+): m/z calcd for [$C_{34}H_{60}O_7NaSi_2$] 659.3775, found 659.3775, Δ = 0.2 ppm.

5.6.2 CDE Ring Aldehyde 171



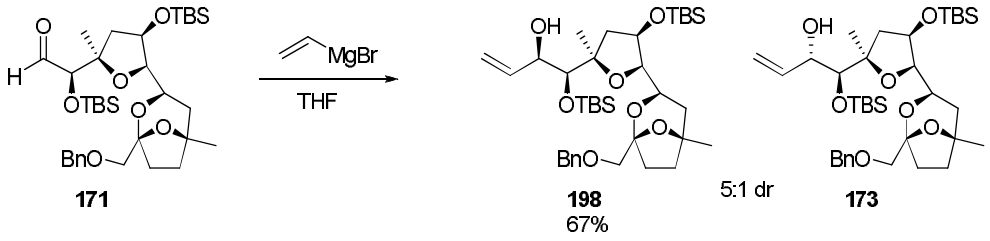
170 **171**

To a solution of oxalyl chloride (21 μL, 30 mg, 0.24 mmol, 120 mol-%) in CH_2Cl_2 (1.5 mL) was added DMSO (36 μL, 40 mg, 0.5 mmol, 250 mol-%) at –50 ºC. After stirring for 8 min, a solution of alcohol **170** (0.13 g, 0.2 mmol, 100 mol-%) in CH_2Cl_2 (2.5 mL) was added. The resulting mixture was stirred for 45 min keeping the temperature below –30 ºC. Triethylamine (0.13 mL, 91 mg, 0.90 mmol, 450 mol-%) was then added dropwise. Stirring was continued at –30 ºC for an additional 10 min and then the mixture was allowed to warm to rt. H_2O (5 mL) was added and the separated aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes) afforded the desired product **171** as light yellow oil (0.12 g, 93%).

R_f (30% EtOAc/hexanes) = 0.70; $[\alpha]_D$ = –64.9 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2954, 2930, 2857, 1736, 1255, 1105; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.34-7.27 (m, 5H), 4.62 (dd^{AB}, 2H, $|J_{AB}|$ = 12.3 Hz, Δv = 30.9 Hz), 4.33 (dd, 1H, *J* = 4.6, 2.9 Hz), 4.25 (s, 1H), 4.18 (ddd, 1H, *J* = 11.0, 8.2, 4.1 Hz), 3.65 (dd, 1H,

J = 8.2, 2.8 Hz), 3.52 (dd^{AB}, 2H, $|J_{AB}|$ = 10.6 Hz, Δv = 21.3 Hz), 2.19 (dt, 1H, J = 13.1, 4.7 Hz), 2.17 (d, 1H, J = 14.0 Hz), 2.01 (ddd, 1H, J = 13.6, 9.2, 4.8 Hz), 1.93-1.89 (m, 1H), 1.85 (dd, 1H, J = 14.0, 5.0 Hz), 1.76-1.57 (m, 4H), 1.39 (s, 3H), 1.13 (s, 3H), 0.901 (s, 9H), 0.900 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H), –0.0002 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 138.5, 128.4, 127.9, 127.6, 106.4, 85.8, 84.1, 82.9, 81.1, 73.8, 72.1, 72.0, 66.4, 47.0, 40.7, 34.3, 31.9, 26.3, 26.1, 26.0, 22.8, 18.5, 18.1, –3.8, –4.4, –4.9, –5.0; HRMS (ESI^+): m/z calcd for [$C_{34}H_{58}O_7NaSi_2$] 657.3619, found 657.3605, Δ = 2.1 ppm.

5.6.3 CDE Ring Allylic Alcohols 198 and 173

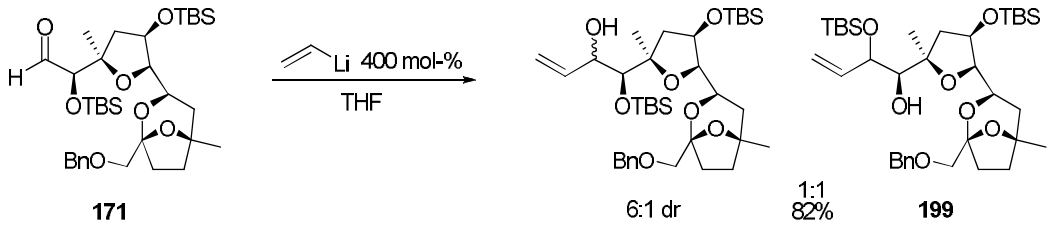


To a solution of aldehyde **171** (0.10 g, 0.16 mmol, 100 mol-%) in THF (3.5 mL) was added vinylmagnesium chloride (1M in THF, 0.64 mL, 0.64 mmol, 400 mol-%) at –78 ºC. The reaction mixture was stirred at –78 ºC for 25 min and then quenched with sat. aq. NH_4Cl (4 mL). The reaction mixture was allowed to warm to rt and H_2O (4 mL) was added to dissolve the precipitate. The separated organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (initially 5% EtOAc/hexanes, then 7%, and finally 10% EtOAc/hexanes) afforded the major product **198** as light yellow oil (71 mg, 67%). Also a mixture containing the major and the minor diastereomers in 1:2 ratio (30 mg) was isolated.

R_f (30% EtOAc/hexanes) = 0.55; $[\alpha]_D$ = –1.9 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3497, 2954, 2929, 2857, 1254, 1100; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 5H), 5.95 (ddd, 1H, J = 17.3, 10.6, 4.3 Hz), 5.31 (dd, 1H, J = 17.2, 1.9 Hz), 5.13 (dd, 1H, J = 10.6, 1.9 Hz), 4.62 (dd^{AB}, 2H, $|J_{AB}|$ = 12.4 Hz, Δv = 30.7 Hz),

4.38 (ddd, 1H, *J* = 9.1, 4.3, 2.2 Hz), 4.29 (dd, 1H, *J* = 4.1, 3.1 Hz), 4.14 (ddd, 1H, *J* = 11.4, 8.0, 3.7 Hz), 3.82 (d, 1H, *J* = 2.4 Hz), 3.56 (dd, 1H, *J* = 8.2, 2.9 Hz), 3.52 (dd^{AB}, 2H, $|J_{AB}|$ = 10.5 Hz, Δv = 22.5 Hz), 2.91 (d, 1H, *J* = 9.1 Hz), 2.20 (dt, 1H, *J* = 13.0, 4.1 Hz), 2.02-1.95 (m, 2H), 1.90-1.85 (m, 1H), 1.84 (dd, 1H, *J* = 13.7, 5.3 Hz), 1.75-1.65 (m, 2H), 1.59-1.56 (m, 1H), 1.39 (s, 3H), 1.23 (s, 3H), 0.902 (s, 9H), 0.896 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 138.5, 128.4, 127.9, 127.6, 114.1, 106.4, 84.8, 84.6, 81.1, 79.2, 3.8, 72.3, 72.1, 72.0, 66.2, 48.9, 40.8, 34.3, 31.8, 26.3, 26.12, 26.06, 22.3, 18.4, 18.1, –3.4, –4.0, –4.3, –5.0; HRMS (ESI^+): m/z calcd for [$C_{36}H_{62}O_7NaSi_2$] 685.3932, found 685.328, Δ = 0.6 ppm.

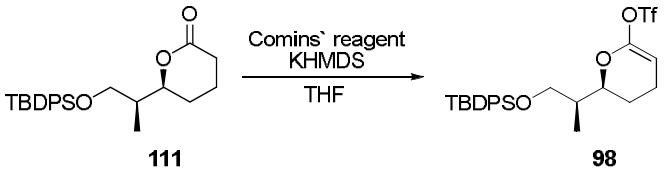
When the reaction was done in a similar manner using vinyllithium, an undesired side product **199** was formed. This product was isolated and characterized as a mixture with the desired product. Only one diastereomer of **199** was observed and the stereochemistry of the C10 was not determined.



171 6:1 dr 1:1 82% **199**

For **199**: R_f (15% EtOAc/hexanes) = 0.55; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.32 (m, 5H), 6.00 (ddd, 1H, *J* = 17.3, 10.4, 7.0 Hz), 5.16 (dt, 1H, *J* = 17.3, 1.5 Hz), 5.09 (ddd, 1H, *J* = 10.3, 1.7, 1.0 Hz), 4.62 (dd^{AB}, 2H, $|J_{AB}|$ = 12.4 Hz, Δv = 28.1 Hz), 4.08 (ddd, 1H, *J* = 9.8, 7.9, 5.3 Hz), 3.58 (t, 1H, *J* = 3.1 Hz), 3.52 (dd^{AB}, 2H, $|J_{AB}|$ = 10.6 Hz, Δv = 21.7 Hz), 3.51-3.47 (m, 1H), 3.40 (d, 1H, *J* = 3.3 Hz), 2.43 (d, 1H, *J* = 14.2 Hz), 2.25-2.15 (m, 2H), 2.04-1.95 (m, 1H), 1.90-1.83 (m 1H), 1.74-1.61 (m, 3H), 1.38 (s, 3H), 1.21 (s, 3H), 0.89 (s, 18H), 0.063 (s, 3H), 0.058 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H). HRMS (ESI^+): m/z calcd for [$C_{36}H_{62}O_7NaSi_2$] 685.3932, found 685.3925, Δ = 1.0 ppm.

5.6.4 A Ring Triflate 98

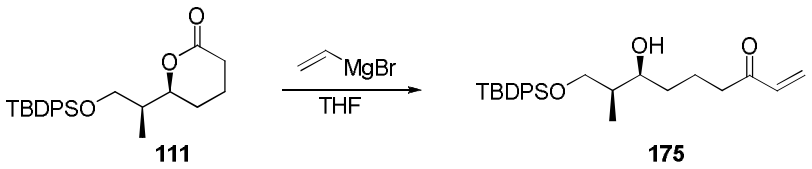


111 **98**

To a solution of lactone **111** (100 mg, 0.25 mmol, 100 mol-%) in THF (5.0 mL) was added Comins` reagent (0.2 g, 0.50 mmol, 200 mol-%) and KHMDS (0.5M in toluene, 1.5 mL, 0.75 mmol, 300 mol-%) at –78 ºC. The reaction mixture was stirred at –78 ºC for 10 min and then quenched with sat. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (4 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (25% EtOAc/hexanes) afforded the desired product **98** as colorless oil (128 mg, 96%).

R_f (50% EtOAc/hexanes) = 0.68; $[\alpha]_D$ = 8.8 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 2931, 2858, 1701, 1426, 1219, 1113; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.48-7.39 (m, 6H), 4.80 (ddd, 1H, *J* = 5.1, 2.5, 0.6 Hz), 4.32 (ddd, 1H, *J* = 11.0, 4.4, 2.0 Hz), 3.68 (dd, 1H, *J* = 10.1, 6.9 Hz), 3.59 (dd, 1H, *J* = 10.1, 5.8 Hz), 2.27-2.10 (m, 2H), 2.03-1.96 (m, 1H), 1.82 (dtdd, 1H, *J* = 14.0, 2.1, 6.2, 0.9 Hz), 1.70 (dd, 1H, *J* = 10.7, 6.1 Hz), 1.03 (s, 9H), 0.95 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 150.4, 141.3, 136.4, 134.52, 134.48, 130.8, 128.77, 128.75, 89.0, 82.2, 66.1, 40.3, 27.2, 25.0, 20.6, 19.8, 11.4; HRMS (ESI^+): m/z calcd for [$C_{25}H_{31}O_5F_3NaSSi_3$] 551.1511, found 551.1517, Δ = 1.2 ppm.

5.6.5 Ketone 175

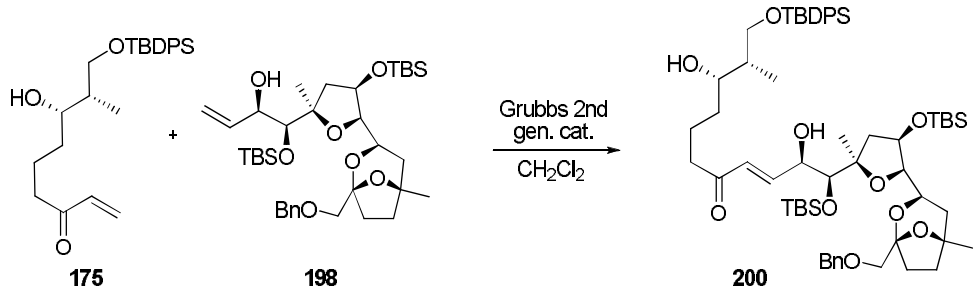


111 **175**

To a solution of lactone **111** (0.11 g, 0.27 mmol, 100 mol-%) in THF (3.0 mL) was added vinylmagnesium chloride (1M in THF, 0.33 mL, 0.33 mmol, 120 mol-%) at –78 ºC. The reaction mixture was stirred at –78 ºC for 30 min and then quenched with sat. aq. NH_4Cl (3 mL). The reaction mixture was allowed to warm to rt and H_2O (3 mL) was added to dissolve the precipitate. The separated organic layer was washed with brine (3 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (20% EtOAc/hexanes) afforded the desired product **175** as light yellow oil (0.11 g, 94%).

R_f (30 % EtOAc/Hex) = 0.29; $[\alpha]_D$ = 0.6 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3503, 2959, 2931, 2858, 1681, 1428, 1112; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.46-7.37 (m, 6H), 6.36 (dd, 1H, *J* = 17.7, 10.5 Hz), 6.23 (dd, 1H, *J* = 17.7, 1.2 Hz), 5,82 (dd, 1H, *J* = 10.5, 1.2 Hz), 3.86 (m, 1H), 3.75 (dd, 1H, *J* = 10.1, 4.2 Hz), 3.66 (dd, 1H, *J* = 10.1, 6.0 Hz), 2.84 (d, 1H, *J* = 4.0 Hz), 2.63 (dt, 2H, *J* = 7.3, 2.3 Hz), 1.85-1.65 (m, 3H), 1.57-1.37 (m, 2H), 1.06 (s, 9H), 0.90 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 133.2, 133.1, 130.0, 129.95, 128.2, 127.92, 127.86, 74.0, 68.7, 39.6, 39.3, 33.7, 27.0, 20.8, 19.3, 10.4; HRMS (ESI^+): *m/z* calcd for [$C_{26}H_{36}O_3NaSi$] 447.2331, found 447.2333, Δ = 0.3 ppm.

5.6.6 Ketodiol 200



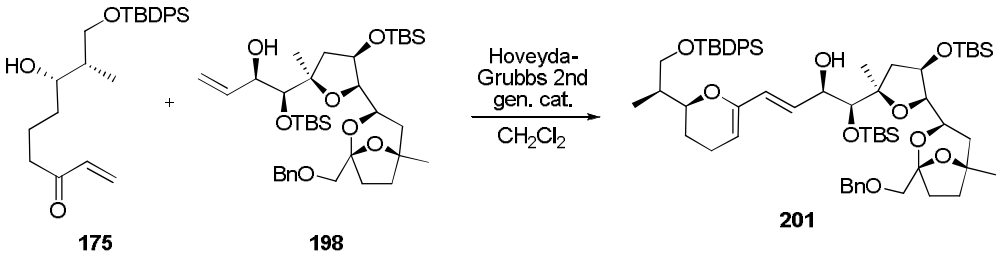
175 **198** **200**

To a solution of ketone **175** (0.15 g, 0.34 mmol, 150 mol-%) and alcohol **198** (0.15 g, 0.23 mmol, 100 mol-%) in CH_2Cl_2 (7 mL) was added Grubbs 2nd generation catalyst (9.8 mg, 0.012 mmol, 5 mol-%). The reaction mixture was warmed to reflux and stirred for 17h. Solvent was evaporated and the residue was purified by flash chromatography (30% MTBE/hexanes, 50 μL Et_3N in 500 mL eluent) to give ketodiol **200** as tanned oil (0.12 g, 52%).

R_f (30% EtOAc/hexanes) = 0.27; $[\alpha]_D$ = –7.9 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3480, 2955, 2931, 2858, 1694, 1472, 1255, 1111; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.46-7.37 (m, 6H), 7.33-7.32 (m, 5H), 6.96 (dd, 1H, *J* = 15.9, 3.5 Hz), 6.41 (dd, 1H, *J* = 15.8, 2.2 Hz), 4.61 (dd^{AB}, 2H, $|J_{AB}|$ = 12.3 Hz, Δv = 28.4 Hz), 4.55-4.51 (m, 1H), 4.29 (dd, 1H, *J* = 4.4, 2.9 Hz), 4.13 (ddd, 1H, *J* = 11.4, 8.0, 3.7 Hz), 3.93 (d, 1H, *J* = 3.2 Hz), 3.87-3.84 (m, 1H), 3.74 (dd, 1H, *J* = 10.4, 4.2 Hz), 3.66 (dd, 1H, *J* = 10.1, 5.9 Hz), 3.56 (dd, 1H, *J* = 8.2, 2.8 Hz), 3.51 (dd^{AB}, 2H, $|J_{AB}|$ = 10.7 Hz, Δv = 21.6 Hz), 3.25 (d, 1H, *J* = 8.5 Hz), 2.84 (d, 1H, *J* = 3.9 Hz), 2.58 (dt, 2H, *J* = 7.5, 1.6 Hz), 2.18 (dt, 1H, *J* = 13.0, 4.2 Hz), 2.02-1.64 (m, 8H), 1.86 (dd, 1H, *J* = 13.9, 5.2 Hz), 1.55 (dd, 1H, *J* = 13.1, 3.9 Hz), 1.52-1.44 (m, 2H), 1.39 (s, 3H), 1.05 (s, 9H), 1.05 (s, 3H), 0.91 (obscured d, 3H), 0.906 (s, 9H), 0.895 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 200.1, 148.4, 138.5, 135.7, 133.2, 133.1, 130.1, 130.0, 129.9, 128.5, 128.4, 128.2, 127.92, 127.89, 126.6, 106.4, 85.0, 84.9, 81.1, 78.5, 74.7, 73.8, 72.0, 71.97, 71.94, 68.8, 66.0, 48.9, 41.0, 40.8, 39.3, 34.2, 33.9, 31.9, 27.0, 26.3, 26.05, 26.01, 22.3, 20.8, 19.3, 18.3, 18.1, 10.3, –3.6, –4.0, –4.3, –

5.1; HRMS (ESI$^+$): m/z calcd for [$C_{60}H_{94}O_{10}NaSi_3$] 1081.6053, found 1081.6072, Δ = 6.3 ppm.

5.6.7 Diene 201

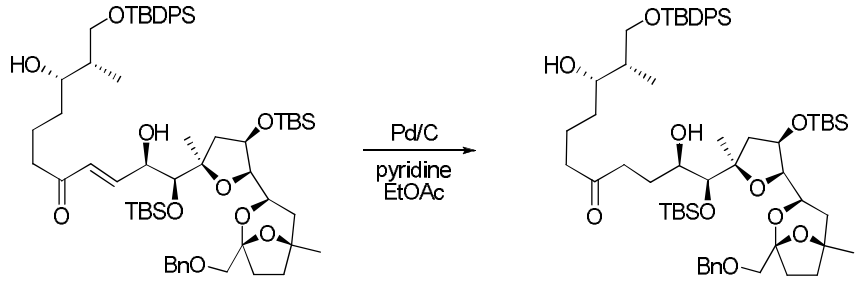


To a solution of ketone **175** (58 mg, 0.14 mmol, 150 mol-%) and alcohol **198** (60 mg, 0.09 mmol, 100 mol-%) in CH_2Cl_2 (3 mL) was added Hoveyda-Grubbs 2nd generation catalyst (2.8 mg, 0.005 mmol, 5 mol-%). The reaction mixture was warmed to reflux and stirred for 20 h. Solvent was evaporated and the residue was purified by flash chromatography (10% EtOAc/hexanes, 50 μL Et_3N in 500 mL eluent) to give diene **201** (49 mg, 52%) as a mixture with the starting alcohol **198**.

For **201**: R_f (30% EtOAc/hexanes) = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (m, 4H), 7.44-7.28 (m, 11H), 5.98 (s, 2H), 4.73 (dd, 1H, J = 4.6, 2.5 Hz), 4.63 (dd^{AB}, 2H, $|J_{AB}|$ = 12.4 Hz, Δv = 31.7 Hz), 4.51 (d, 1H, J = 9.3 Hz), 4.30 (dd, 1H, J = 4.1, 3.0 Hz), 4.15 (ddd, 1H, J = 11.4, 8.1, 3.8 Hz), 3.83 (ddd, 1H, J = 16.4, 5.8, 1.4 Hz), 3.82 (dd, 1H, J = 10.5, 2.1 Hz), 3.74 (dd, 1H, J = 10.1, 5.6 Hz), 3.64 (dd, 1H, J = 10.1, 5.7 Hz), 3.57 (dd, 1H, J = 8.2, 2.9 Hz), 3.54 (dd^{AB}, 2H, $|J_{AB}|$ = 10.7 Hz, Δv = 23.1 Hz), 2.77 (d, 1H, J = 9.4 Hz), 2.20 (dt, 1H, J = 13.0, 4.0 Hz), 2.14-1.56 (m, 12H), 1.37 (s, 3H), 1.23 (s, 3H), 1.06 (s, 9H), 0.91 (obscured d, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 151.2, 138.6, 135.8, 134.1, 130.4, 129.8, 128.5, 128.0, 127.9, 127.8, 127.7, 125.5, 106.4, 101.7, 84.67, 84.66, 81.21, 81.19, 79.7, 79.3, 76.5, 73.9, 72.2, 72.0, 71.5, 66.3, 66.2, 48.8, 40.9, 40.8, 34.4, 31.9, 27.1, 26.4, 26.22, 26.18, 26.1, 25.8, 22.3, 21.8, 19.6, 18.5, 18.2, 12.8,

–3.5, –3.9, –4.2, –5.0; HRMS (ESI$^+$): m/z calcd for [$C_{60}H_{92}O_9NaSi_3$] 1063.5947, found 1063.5996, Δ = 4.6 ppm.

5.6.8 Ketodiol 184

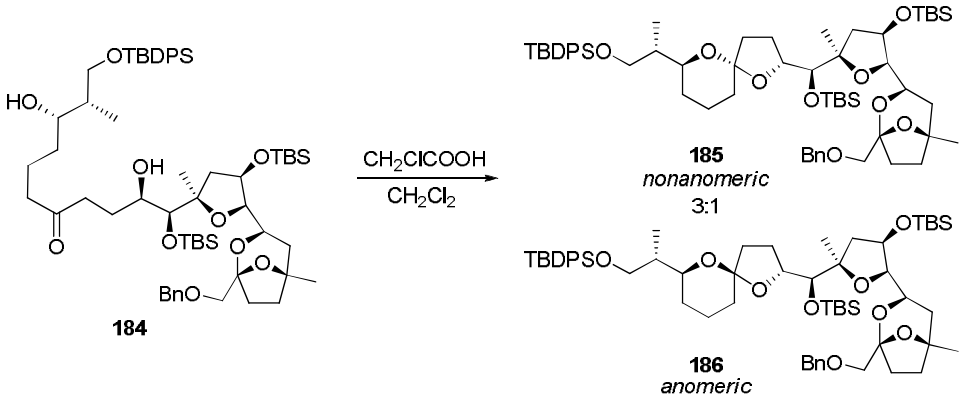


To a solution of ketone **200** (56 mg, 0.053 mmol, 100 mol-%) and pyridine (6.3 μL, 6.3 mg, 0.078 mmol, 150 mol-%) in EtOAc (5 mL) was added Pd on charcoal (11.2 mg of 5% Pd catalyst, 0.005 mmol, 10 mol-%) under argon flow. The reaction flask was repeatedly evacuated and flushed with H_2. The suspension was vigorously stirred under H_2 atmosphere for 4 h and then filtered through Celite. The filter pad was washed with EtOAc (2 x 5 mL) and the combined filtrates were concentrated. Purification of the residue by flash chromatography (30% EtOAc/hexanes, 50 μL Et_3N in 500 mL eluent) afforded the desired product **184** as colorless oil (53 mg, 94%).

R_f (30% EtOAc/hexanes) = 0.25; $[\alpha]_D$ = –5.9 (*c* 1.00, CH_2Cl_2); IR (film, cm^{-1}): 3502, 2954, 2930, 2857, 1713, 1472, 1254, 1111; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.46-7.28 (m, 11H), 4.62 (dd^{AB}, 2H, $|J_{AB}|$ = 12.4 Hz, $\Delta\nu$ = 31.1 Hz), 4.29 (dd, 1H, *J* = 4.2, 3.1 Hz), 4.14 (ddd, 1H, *J* = 12.0, 7.4, 4.0 Hz), 3.85-3.82 (m, 1H), 3.76-3.62 (m, 4H), 3.59-3.55 (m, 1H), 3.52 (dd^{AB}, 2H, $|J_{AB}|$ = 10.6 Hz, $\Delta\nu$ = 22.7 Hz), 2.84 (d, 1H, *J* = 3.8 Hz), 2.65 (ddd, 1H, *J* = 15.9, 8.3, 6.5 Hz), 2.57 (d, 1H, *J* = 8.4 Hz), 2.51-2.42 (m, 3H), 2.19 (dt, 1H, *J* = 13.0, 4.0 Hz), 2.02-1.42 (m, 14H), 1.39 (s, 3H), 1.06 (s, 9H), 1.05 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (obscured d, 3H), 0.131 (s, 3H), 0.129 (s, 3H), 0.04 (s, 3H), –0.02 (s,

3H); ^{13}C NMR (100 MHz, $CDCl_3$): 211.9, 138.5, 135.8, 135.7, 133.2, 133.1, 130.0, 129.9, 128.4, 127.9, 127.89, 127.85, 127.6, 106.4, 84.4, 84.3, 81.1, 79.2, 74.0, 73.8, 72.1, 71.9, 70.8, 68.8, 66.2, 48.5, 43.0, 40.8, 39.8, 39.3, 34.2, 33.9, 31.8, 30.1, 27.0, 26.3, 26.2, 26.1, 22.0, 20.6, 19.3, 18.5, 18.1, 10.4, –3.69, –3.73, –4.4, –5.0; HRMS (ESI$^+$): m/z calcd for [$C_{60}H_{96}O_{10}NaSi_3$] 1083.6209, found 1083.6238, Δ = 9.6 ppm.

5.6.9 Spiroketals 185 and 186

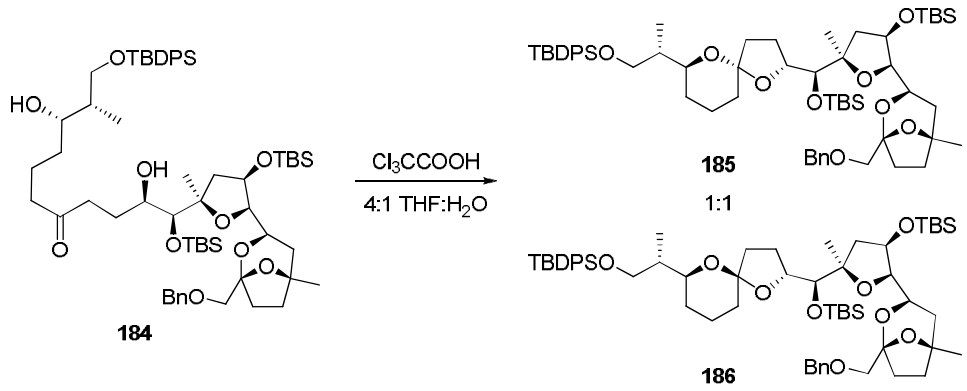


To a solution of ketone **184** (53 mg, 0.049 mmol, 100 mol-%) in CH_2Cl_2 (3.5 mL) was added chloroacetic acid (2.3 mg, 0.024 mol-%, 50 mol-%) at rt. The reaction mixture was stirred at rt for 1 h and then diluted with CH_2Cl_2 (5 mL) and quenched with sat. aq. $NaHCO_3$ (5 mL). The separated organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes, 50 μL Et_3N in 250 mL eluent) afforded the nonanomeric isomer **185** as colorless oil (15 mg, 29%) and a mixture of the nonanomeric and anomeric isomers in (35 mg, combined total yield 98%).

For **185**: R_f (15% EtOAc/hexanes) = 0.38; $[\alpha]_D$ = –13.2 (*c* 0.50, CH_2Cl_2); IR (film, cm^{-1}): 2953, 2929, 2856, 1472, 1106; ^{1}H NMR (400 MHz, C_6D_6): δ 7.82-7.78 (m, 4H), 7.36-7.19 (m, 10H), 7.11-7.07 (m, 1H), 4.54 (dd^{AB}, 2H, $|J_{AB}|$ = 12.3 Hz, $\Delta\nu$ = 23.9 Hz), 4.40-4.34 (m, 2H), 4.22 (dd, 1H, *J* = 4.7, 2.8 Hz), 3.88 (d, 1H, *J* = 8.2 Hz), 3.58 (dd, 1H, *J* = 9.7, 7.3 Hz), 3.80 (s, 2H), 3.62 (dd, 1H, *J* = 11.1, 2.9 Hz),

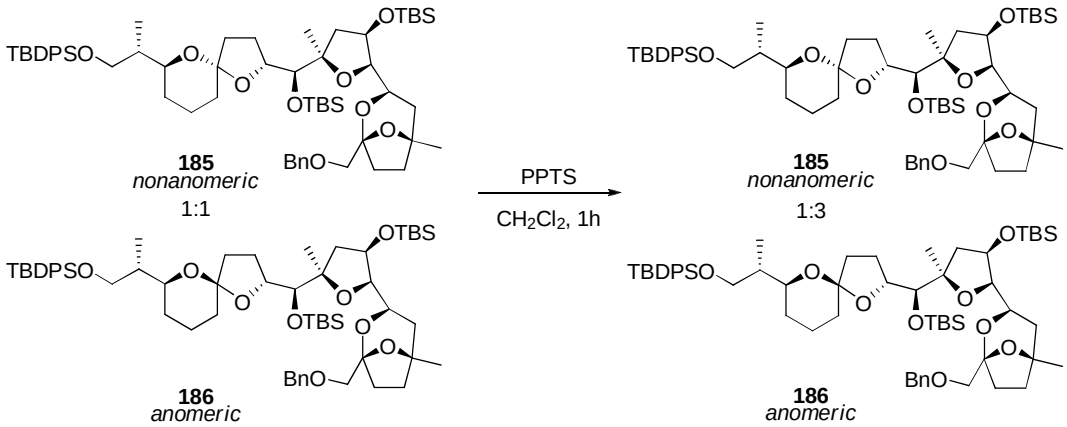
3.60 (dd, 1H, *J* = 9.7, 6.0 Hz), 3.58-3.56 (m, 1H), 2.41 (dt, 1H, *J* = 13.2, 4.5 Hz), 2.32 (d, 1H, *J* = 13.9 Hz), 2.23-1.96 (m, 5H), 1.90-1.49 (m, 12H), 1.29 (s, 3H), 1.24 (s, 3H), 1.19 (s, 9H), 1.10 (s, 9H), 1.04 (s, 9H), 1.00 (d, 3H, *J* = 6.8 Hz), 0.48 (s, 3H), 0.37 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): 139.6, 136.4, 136.3, 134.80, 134.76, 130.6, 130.7, 129.2, 128.8, 128.75, 128.72, 128.4, 108.0, 107.0, 85.9, 84.6, 81.8, 81.4, 80.2, 74.0, 73.5, 72.94, 72.88, 67.2, 66.6, 49.2, 41.6, 41.3, 35.6, 34.7, 33.7, 32.5, 29.3, 28.9, 27.2, 26.7, 26.41, 26.37, 23.0, 21.8, 19.8, 19.3, 18.6, 11.6, –2.7, –4.1, –4.2, –4.9; HRMS (ESI$^+$): m/z calcd for [$C_{60}H_{94}O_9NaSi_3$] 1065.6103, found 1065.6095, Δ = 0.8 ppm.

5.6.10 Spiroketals 185 and 186 (aqueous conditions)



To a solution of ketone **184** (6 mg, 0.006 mmol, 100 mol-%) in THF:H_2O (0.4:0.1 mL) was added Cl_3CCOOH (0.6 mg in 10 μL THF, 0.0034 mol-%, 60 mol-%) at rt. The reaction mixture was stirred at rt for 4 h and then diluted with Et_2O (5 mL) and quenched with sat. aq. $NaHCO_3$ (3 mL). The separated organic layer was dried over Na_2SO_4 and concentrated. The crude ^{1}H NMR showed a 1:1 mixture of the spiroketals **185** and **186**.

5.6.11 Thermodynamic Equilibration of Spiroketals 185 and 186

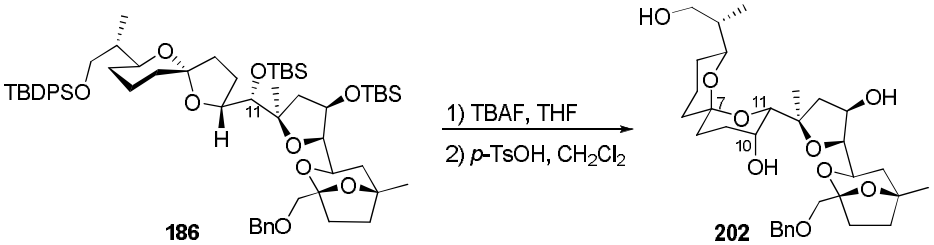


To a solution of 1:1 mixture of spiroketals **185** and **186** (40 mg, 0.038 mmol, 100 mol-%) in CH_2Cl_2 (2.0 mL) was added PPTS (1.9 mg, 0.0075 mmol, 20 mol-%) at rt. After 4h, another portion of PPTS (9.5 mg, 0.038 mmol, 100 mol-%) was added. Stirring was continued at rt for 2h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and then quenched by addition of sat. aq. $NaHCO_3$ (4 mL). The layers were separated and the organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% EtOAc/hexanes, 25 μL Et_3N in 125 mL eluent) afforded the anomeric isomer **186** as colorless oil (26.5 mg, 67%).

For **186**: R_f (15% EtOAc/hexanes) = 0.34; $[\alpha]_D$ = 0.6 (*c* 0.50, CH_2Cl_2); IR (film, cm^{-1}): 2953, 2929, 2856, 1472, 1110; ^1H NMR (400 MHz, C_6D_6): δ 7.85-7.79 (m, 4H), 7.36-7.18 (m, 10H), 7.10-7.06 (m, 1H), 4.54 (dd^{AB}, 2H, $|J_{AB}|$ = 12.3 Hz, Δv = 26.4 Hz), 4.35 (ddd, 1H, *J* = 11.2, 4.7, 2.8 Hz), 4.20 (dd, 1H, *J* = 5.0, 3.2 Hz), 3.96-3.86 (m, 3H), 3.81 (d, 1H, *J* = 7.8 Hz), 3.79 (s, 2H), 3.69 (dd, 1H, *J* = 9.9, 7.0 Hz), 3.64 (dd, 1H, *J* = 8.2, 3.1 Hz), 2.37 (dt, 1H, *J* = 13.1, 4.3 Hz), 2.37-2.28 (m, 1H), 2.28 (d, 1H, *J* = 14.1 Hz), 2.17 (ddd, 1H, *J* = 13.7, 9.2, 4.8 Hz), 1.99-1.83 (m, 5H), 1.74-1.38 (m, 10H), 1.35 (d, 3H, *J* = 6.8 Hz), 1.30 (s, 3H), 1.22 (s, 9H), 1.15 (s, 3H), 1.09 (s, 9H), 1.07 (s, 9H), 0.43 (s, 3H), 0.36 (s, 3H), 0.14 (s, 6H); ^{13}C NMR (100 MHz, CD_3CN): 139.5, 136.42, 136.37, 136.36, 134.8, 130.7, 130.6, 129.2, 128.74, 128.66, 128.62, 128.4, 107.0, 105.8, 85.7, 84.7, 84.6, 83.0,

81.5, 74.0, 73.4, 72.9, 72.7, 67.5, 66.6, 49.7, 42.1, 41.4, 40.4, 34.8, 34.7, 32.5, 28.5, 28.0, 27.3, 26.52, 26.47, 26.41, 21.1, 21.0, 19.8, 19.2, 18.6, 15.1, –2.7, –3.9, –4.4, –4.7; HRMS (ESI^+): m/z calcd for [$C_{60}H_{94}O_9NaSi_3$] 1065.6103, found 1065.6104, Δ = 0.1 ppm.

5.6.12 [6,6]-Spiroketal 202



To a solution of spiroketal **186** (6.0 mg, 0.006 mmol, 100 mol-%) in THF (0.5 mL) was added TBAF (1M in THF, 56 μL, 0.06 mmol, 1000 mol-%) at rt. The reaction mixture was stirred at rt for 24 h and was then diluted with Et_2O (4 mL). Orange oil separated from the solution. The oil was separated from the solution by filtration, and solvent was evaporated. The crude product was dissolved in CH_2Cl_2 (1 mL) and *p*-TsOH (0.5 mg, 0.003 mmol, 50 mol-%) was added. The reaction mixture was stirred at rt for 19h. The reaction mixture was diluted with CH_2Cl_2 (4 mL) and sat. aq. $NaHCO_3$ (2 mL) was added. The layers were separated and the organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (90% EtOAc/hexanes) afforded the [6,6]-spiroketal product **202** as colorless oil (2.8 mg, 86%).

R_f (90% EtOAc/hexanes) = 0.26; $[\alpha]_D$ = 1.7 (*c* 0.23, CH_2Cl_2); IR (film, cm^{-1}) 3401, 2918, 2850, 1454, 1099; ^1H NMR (400 MHz, CD_3CN): δ 7.36-7.28 (m, 4H), 4.56 (s, 2H), 4.19 (d, 1H, *J* = 10.7 Hz), 4.19-4.14 (m, 1H), 4.03-3.99 (m, 1H), 3.81-3.78 (m, 1H), 3.74 (ddd, 1H, *J* = 11.6, 5.1, 2.2 Hz), 3.56-3.53 (m, 1H), 3.51 (d, 1H, *J* = 1.1 Hz), 3.47 (s, 2H), 3.42 (dd, 1H, *J* = 7.9, 2.4 Hz), 3.39-3.33 (m, 1H), 2.77 (d, 1H, *J* = 6.4 Hz), 2.66 (dd, 1H, *J* = 6.5, 4.9 Hz), 2.49 (d, 1H, *J* =

14.5 Hz), 2.12-1.96 (m, 2H), 1.87-1.36 (m, 16H), 1.29 (s, 3H), 1.20 (s, 3H), 0.91 (d, 3H, J = 6.9 Hz); HRMS (ESI$^+$): *m/z* calcd for [$C_{32}H_{48}O_9Na$] 599.3196, found 599.3219, Δ = 3.8 ppm.

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