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MODEL STUDIES TOWARD THE SYNTHESIS OF PHOMOIDRIDES A AND B.

STUDIES TOWARD THE SYNTHESIS OF MYCOEPOXYDIENE.

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in the Graduate School of The Ohio State University

By

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2001

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ABSTRACT

Chapter 1. Two model studies toward the core structure of CP-263,114 (1) have been described. The first approach defined a straightforward synthesis of lactone 76 utilizing highly stereocontrolled transformations such as iodolactonization, epoxide ring opening, alkylation and Wadsworth-Emmons olefination. Despite our successful installation of the C\textsubscript{14} quaternary center, the low yield forced us to abandon this tactic. The second route was an attempted expedient construction of the CP-core. All attempts to bring about intramolecular oxidative cyclization of the dienolate of either 80 or 88 was found to result in preferred formation of the Dieckmann product 86 instead.

Chapter 2. Implementation of the underutilized zirconium-mediated ring contraction of 4-vinyl carbohydrates has been described. Arabinose in both enantiomeric forms, plentiful and inexpensive, is the sugar of choice to conduct in good yield the oxygen extrusion process. Higher temperatures for this reaction resulted in the production of more heavily substituted cyclobutanes without the use of a Lewis acid, which should broaden the range of protecting group used so far; toluene rather than THF was more conductive to the ring contraction when bulky groups reside at the C-2 position. Also, and more importantly, the stereochemical outcome of this transformation can be predicted according to the proposed transition state.
To Kristen.
ACKNOWLEDGMENTS

I would like to express my sincere gratitude to Professor Leo Paquette for his continuous guidance during the course of my graduate journey. His unconditional dedication, endless enthusiasm and exemplary work ethic have irrefutably fostered in me the discipline of Organic Chemistry in many of its facets.

I wish to thank Dr. RajanBabu and Dr. Hart for serving on my dissertation committee, and for being present and helpful at each stage of my graduate studies.

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Finally, I want to thank my parents and my grand-ma, always in my heart, my in-laws to be, Sadie and Kate, and my soul mate and fiancée Kristen for their continuous support and understanding.
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PUBLICATIONS

.Cunière Nicolas “(+/-)-Boc-a-phosphonoglycine trimethyl ester Encyclopedia of
Reagents in Organic Synthesis 2001, accepted for publication.

.Nicolas Cunière and Leo A. Paquette “The case for non competitive cyclizative options
during attempted expedient construction of the core ring system of CP-263,114”
Arkivoc, 2000, 274.
Leo A. Paquette and Nicolas Cunière “Diastereoselectivity Control in the Zirconocene-Mediated Ring Contraction of 4-Vinylfuranosides to Enantiopure Multiply-Functionalized Cyclobutanes”, manuscript in preparation.

FIELDS OF STUDY

Major Field: Chemistry
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<td>Ac</td>
<td>acetate</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>AD</td>
<td>asymmetric dihydroxylation</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azoisobutyronitrile</td>
</tr>
<tr>
<td>[α]</td>
<td>specific rotation</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad (NMR)</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>ºC</td>
<td>degree Celsius</td>
</tr>
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<td>calcd</td>
<td>calculated (MS)</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium (IV) ammonium nitrate</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlated spectroscopy (NMR)</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in part per million, downfield from tetramethylsilane (NMR)</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
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<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
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<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>DEPT</td>
<td>distortionless enhancement by polarization transfer (NMR)</td>
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<td>Dibal-H</td>
<td>diisobutylaluminum hydride</td>
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<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
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<td>DMF</td>
<td>N, N-dimethyl formamide</td>
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<td>DMP</td>
<td>Dess Martin periodinane</td>
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<td>dimethyl sulfoxide</td>
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<td>deoxyribonucleic acid</td>
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<td>e.e.</td>
<td>enantiomeric excess</td>
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<td>EI</td>
<td>electronic ionization (MS)</td>
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<td>eq</td>
<td>equivalent</td>
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<td>ES</td>
<td>electron spray (MS)</td>
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<td>ethyl</td>
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<td>ε</td>
<td>molar absorptivity</td>
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<td>FAB</td>
<td>fast atom bombardment (MS)</td>
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<td>g, mg, μg</td>
<td>gram, milligram, microgram</td>
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<tr>
<td>h</td>
<td>hour</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation (NMR)</td>
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<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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<td>heteronuclear multiple quantum correlation (NMR)</td>
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<td>HR</td>
<td>high resolution (MS)</td>
</tr>
<tr>
<td>Hz, MHz</td>
<td>hertz, megahertz (NMR)</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
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<tr>
<td>IBX</td>
<td>iodoxybenzoic acid</td>
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<td>imid</td>
<td>imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>Infra Red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR)</td>
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<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>L, mL, μL</td>
<td>liter, milliliter, microliter</td>
</tr>
<tr>
<td>LDPTMS</td>
<td>Lithium diphenyltetramethylsilazide</td>
</tr>
<tr>
<td>LHMDS</td>
<td>lithium hexamethyldisilazide</td>
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<tr>
<td>LiTMP</td>
<td>lithium 2,2,6,6-tetramethylpiperidide</td>
</tr>
<tr>
<td>λ</td>
<td>absorption maximum</td>
</tr>
<tr>
<td>M⁺</td>
<td>molecular ion (MS)</td>
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<td>m-CPBA</td>
<td>m-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
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<tr>
<td>min</td>
<td>minute</td>
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<td>MOM</td>
<td>methoxyxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
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<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
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<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>ms</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio (MS)</td>
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<td>n</td>
<td>normal</td>
</tr>
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<td>N</td>
<td>normal</td>
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<td>NBS</td>
<td>N-bromosuccinimide</td>
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<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<td>nOe</td>
<td>nuclear Overhauser enhancement (NMR)</td>
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<td>NOESY</td>
<td>nuclear Overhauser and exchange spectroscopy (NMR)</td>
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<td>o</td>
<td>ortho</td>
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<td>obsd</td>
<td>observed (MS)</td>
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<td>p</td>
<td>para</td>
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<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pH</td>
<td>-log [H+]</td>
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<td>ppm</td>
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<td>Full Name</td>
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<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulfonic acid</td>
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<tr>
<td>Pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>t</td>
<td>tert</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
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<td>TBDPS</td>
<td>t-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBME</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N, N', N'-tetramethylenediamine</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetra-n-propylammonium perruthenate (VII)</td>
</tr>
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CHAPTER 1

MODEL STUDIES TOWARD THE SYNTHESIS OF PHOMOIDRIDES A AND B

1. ISOLATION, BIOLOGY and PROPOSED BIOSYNTHESIS

In 1997, during the course of screening for farnesyl transferase (Ftase) and squalene synthase (SQS) inhibitors, Kaneko and coworkers \(^1\) at Pfizer Central Research identified two new natural products [CP-263,114 or phomoidride B (1) and CP-225,917 or phomoidride A (2)] from a fermentation broth generated from an unidentified fungus (ATCC 74256). Earlier, zaragozic acid A (aka squalestatin 1) from the same CP producing fungus had also been isolated by workers at Merck and Glaxo. \(^2\) The fungus was isolated from twigs of *Juniperus ashei* Bachh collected from a juniper-scrub oak forest located in Dripping Springs, Texas. The high medicinal promise of nonadrides 1 and 2 (Figure 1.1) derives from their impressive inhibitory activity against protein farnesyl transferase (IC\(_{50}\) in rat brain of 6-20\(\mu\)M). This enzyme is widely recognized to be responsible for catalyzing the addition of farnesyl pyrophosphate to a cysteine residue at the carboxyl terminus of protein p21, a product of the *ras* oncogene.
Under normal circumstances, a carcinogenic condition develops because of one amino acid mutation of p21 whose effect is to leave the protein in a permanently active state. Cell division and growth subsequently proceed in an uncontrolled manner. Should the initial addition steps be impeded, the expectation is that the carcinogenic process will not be turned on. \(^3\) In a different context, 2 is also active against squalene synthase in rat liver microsomes (IC\(_{50}\) 43 \(\mu\)M), the enzyme that catalyses the co-condensation of farnesyl pyrophosphate to presqualene pyrophosphate on the way to squalene. Since this process is central to cholesterol synthesis, this agent or analogues thereof are expected
to be serviceable cholesterol-lowering drugs.\(^4\)

Figure 1.2: Biosynthetic proposal for CP-225,917.

The structures and biosyntheses of the related nonadride compounds had previously been investigated by Barton and Sutherland,\(^5\) and later by Baldwin.\(^6\) Based on the biosynthetic pathway for the mold metabolites glaucanic and glauconic acid, the Pfizer group suggested, by extrapolation, the possible operation of a similar route to the CP molecules wherein CP-225,917 is the product of dimerization 7 of the C\(_{16}\) anhydride 8 which in turn is produced from the condensation of oxaloacetyl-CoA (10) and
the C₁₂ carboxylic acid derivative 9. In the dimerization process, three new carbon-carbon bonds are formed and the unique bicyclic system of the CP metabolites is formed. Subsequent decarboxylation and side chain oxidation produces CP-225,917 (2), as illustrated in Figure 1.2. Its cyclodehydration would produce its congener CP-263,114 (1). More recently, Sulikowski ⁷ has determined the origin of all the carbon atoms present in CP-263,114 using ¹³C-labeled biosynthetic precursor. The distinction of a polyketide or fatty acid synthase biosynthetic pathway for the production of the CP compounds is still undetermined and under active investigation.

The related CP compounds present a dense array of diverse, highly oxygenated, and sensitive functionalities mounted onto an unusual bicyclo[4.3.1]dec-1(9)-ene ring system. These rare molecular architectures have inspired many laboratories to develop elegant and efficient approaches. The greatest challenge in the synthesis of the phomoidrides is to gain access to the core structure. The next section will review several approaches focusing on the key step to elaborate the carbon skeleton of either CP-225,917 or CP-263,114.

2. OTHER APPROACHES

Considerable effort has been undertaken to devise synthetic routes toward the phomoidride core skeleton and ultimately to their total synthesis. Shair ⁸ and coworkers have presented a synthesis of CP-263,114.
Earlier studies\(^9\) showed that in a single transformation, four stereochemical issues and the bridgehead double bond can be addressed successfully while assembling the core structure. The key transformation can be described as a tandem alkylation of 11, oxy-Cope rearrangement, followed by spontaneous transannular Dieckmann-like condensation to give rise to 12 as shown in Figure 1.3. The second remarkable step in
Shair’s approach is the one-pot Lewis acid-catalysed Fries-like rearrangement followed by bicyclization and deprotection of 13 to afford 14 (Figure 1.3).

![Chemical structure](image)

Figure 1.4: Nicolaou’s approach to CP-263,114.

During this transformation, the quaternary center at C14 was installed, the pseudo ester cage ring system was assembled, and a free acid was liberated for its homologation. Nicolaou and associates were the first to assign the absolute configuration and to describe the first asymmetric total synthesis of both CP compounds. The core was accessed via a type II Lewis acid-catalysed intramolecular Diels-Alder reaction. Triene 15 was reacted with a very mild and bulky Lewis acid to produce the CP core 16 in high yield (Figure 1.4). The strategy deployed took advantage of the very different reactivity of the two primary alcohols protected as an acetonide in 16. The endo alcohol is so sterically hindered that its reactivity is far less than that of the exo alcohol, so
chemistry can be practiced selectively on the exo-hydroxyl group. Fukuyama et al. reported the first total synthesis of natural phomoidride B ((-)-1).

In a fashion similar to Nicolaou, Fukuyama assembled the core system 18 via Diels-Alder cyclization under mild Lewis catalysis of triene 17 (Figure 1.5). The effect of sulfur is twofold. It enhances the rate of the [4+2] cycloaddition and serves as a masked ketone for most of the synthesis. The synthesis is remarkable in terms of shortness and straightforward transformations.

Danishefsky et al. reported the total synthesis of 1 utilizing a key aldol on 19 and a Heck reaction to furnish 21 (Figure 1.6). The combination of these two steps early in the synthesis in an efficient and convergent manner allowed a straightforward
The synthesis of the natural product. The fused furan ring serves as the masked anhydride moiety. The TBS protecting group is also of prime importance since it prevented premature oxidation of the polysubstituted furan.

![Chemical Structure](image)

Figure 1.6: Danishefsky's approach to CP-263,114.

The next few examples are model studies for the synthesis of the carbocyclic substructure of both CP compounds. Clive\(^{13}\) and coworkers proposed a siloxy-Cope as a key reaction for the transformation of 22 to 23 (Figure 1.7). The strain release associated with the sigmatropy afforded the core structure in quantitative yield. Leighton\(^{14}\) et al. working with an intermediate somewhat close to Clive's substrate, reported an amazing single-pot conversion to gain access to the core structure. The transformation can be described as a tandem palladium-catalyzed carbonylation
of a vinyl triflate followed by a thermal [3,3] siloxy-Cope rearrangement.

Figure 1.7: Clive's model studies toward CP-263,114.

This domino reaction is unprecedented in such a setting (Figure 1.8). In a single step, the [2.2.1] bicyclic system 25 was converted to the [4.3.1] CP core bicyclic system 26, along with proper setting of the C\textsubscript{14} quaternary center and the anti-Bredt double bond. It appeared clear in the synthesis of 25 that the methyl group can be substituted by the real side chain, which would deliver a very advanced intermediate.
Figure 1.8: Leighton's model study.

Davies\textsuperscript{15} proposed a tetrahydrofuran ring opening reaction \textit{en route} to CP-263,114. The ring opening occurred when tetrahydropyran 27 was treated with TMSOTf followed by silica gel to afford 28 (Figure 1.9).

Figure 1.9: Davies' model study.

Wood\textsuperscript{16} described a 10-step access to the CP core. Key steps included a phenolic
oxidation/intramolecular Diels-Alder sequence 29 to 30, the tandem radical cyclization 31 to 32, and a late stage fragmentation of a densely functionalized isotwistane skeleton 33 to 34 (Figure 1.10).

Nagaoka proposed an asymmetric synthesis of the core structure of CP-263,114. The construction was performed through sequential radical fragmentation-reductive olefination 36 to 38 via 37 (Figure 1.11).
3. OUR APPROACH AND RETROSYNTHETIC SCHEME

In early studies, Paquette et al. described an enantioselective synthesis of the complex framework of the CP compound. The synthesis relied on initial elaboration of the two side chains. These fragments were linked to benzoic acid via Birch reduction-alkylation and subsequent cuprate addition. A series of functionalization reactions including dissolving metal reduction, Claisen rearrangement, iodolactonization, regioselective epoxide cleavage, and intramolecular Wadsworth-Emmons olefination took advantage of highly efficient stereocontrol. However, the authors found that quaternization of the C14 center on the fully substituted system proved to be
The advanced lactone 39 was deprotonated with lithium hexamethyldisilazide in the expectation that enolization would occur distal from the oxygen center because of usual inductive contributions. Unfortunately, despite numerous attempts to override kinetic deprotonation from within the butenolide ring, no conditions were found to generate the product 41. The loss of the stereogenic center C_{16} was not an issue, since later on in the synthesis it will be oxidized to the corresponding ketone. Nevertheless, the
destruction of this center influenced the stereochemical outcome of the newly-formed quaternary center. A 2 to 1 ratio of diastereoisomers was found. Both molecules co-migrated on silica gel, impeding their separation. A lot of effort has been engaged to isomerize the double bond to an exo position in order to give rise to 41. Also, gaining access to lactone 39 in 28 linear steps was time ineffective, and finally the C7 stereogenic center was incorrectly installed. The course of the synthesis was redesigned so that C14 would be generated stereospecifically via [3,3] sigmatropic rearrangement. Also for simplicity, a model study was undertaken where the side chains were omitted. The retrosynthetic scheme is shown below in Figure 1.13.

Chung and later Babler have described a new cyclization method based on the intramolecular oxidative cyclization of diester dienolate mediated by a metal salt. Lactone 42, representing the last intermediate of our model study, could be obtainable from the oxidation of the dienolate of 43. In such a system, it was anticipated that the formation of the diradical and thus cyclization would be faster than the Dieckmann or acyloin condensation. The proximity of the two diester groups and then the two radicals should leave no option for other than the system to cyclize and form the bicyclo[4.3.1]dec-1(9)-ene as within the CP core skeleton. The Dieckmann condensation would produce an 8-membered ring system and the acyloin condensation would lead to a 9-membered ring system, processes anticipated to be kinetically slower.
Diester 43 was to be derived from 44, product of the Claisen rearrangement of 45. The lactone moiety resident in 46 would be installed by an intramolecular Horner-Wadsworth-Emmons olefination. Cyclohexenone 48 was intended to serve as starting material for α-hydroxy ketone 47.
4. SYNTHESIS

4.1 ACCESS TO PRECURSOR TO [3,3] SIGMATROPY

The known iodolactone 49 was synthetized in five steps from commercially available cyclohex-2-enone (figure 1.14). Remarkably, the five-step sequence was carried out with only one purification. After recrystallization, racemic 49 was obtained in 55% yield. Reduction of the lactone with Dibal produced a 2:1 mixture of iodolactols 50. Without purification, 50 was subjected to the action of Ag₂O in DCM and afforded the corresponding epoxy aldehyde 51, which was immediately reduced to the primary alcohol 52 by means of NaBH₄ in 85% yield for the last 3 steps. After protection of alcohol 52 as a PMB ether in 91% yield, the epoxide functionality in 53 was smoothly oxidized to the corresponding α-hydroxy ketone 54 in 85% yield. The regioselectivity is explained by the trans-diaxial ring opening of the activated epoxide by DMSO. Triethylamine served to eliminate a molecule of DMS, in a way similar to that seen in a Swern oxidation.
Among the methods available for the clean oxidation of an α-hydroxy ketone to produce an α,α'-dihydroxy ketone, our choice went to a 3-step procedure that appeared clean and reproducible but low yielding (30%). After protection of the free secondary alcohol in 54 as a benzoate, generation of the enolate (LDA, LiHMDS, KHMDS) and oxidation with either the Davis oxaziridine or the molybdenum peroxide reagent (MoO₃-pyridine-HMPA) in a one-pot procedure failed. Trapping of the enolate with TBSCl, followed by epoxidation with dimethyldioxirane and acidic hydrolysis of the enolate produced the α,α'-dihydroxy ketone in less than 10% yield. Ketone 54 was next treated with TBSOTf (Figure 1.15). As expected, the secondary alcohol was protected as a TBS ether under these conditions and, due to the high Lewis acidity of TBSOTf,
the ketone also was masked as a TBS enol ether (see 55). The regioselectivity associated with the introduction of this double bond was anticipated according to a series of observations reported in our laboratories and in the literature. Catalytic dihydroxylation furnished diol 56. The stereocontrol can be explained by the attack of OsO₄ away from the axial OTBS group. Methanolysis of the syn diol with 3 eq of K₂CO₃ afforded the desired α,α'-hydroxy ketone 57 in less than 30 min in 65% yield. The newly formed hydroxy group was protected as an acetate under classical conditions to give 58 in 98% yield.

![Chemical diagrams showing the synthesis steps from 54 to 58 and 57 to 47.]

Figure 1.15: Synthesis of compound 47.

Deprotection of the TBS group appeared to be an unforeseen challenge. Classical methods using fluoride ion sources such as TBAF/THF, CsF/DMF, NH₄F/MeOH led to
extensive decomposition. Acidic media such as PPTS/EtOH or 1% HCl/MeOH had a similar effect. Surprisingly HF.pyr did not affect 58 at rt. After 5 days at 35 °C, the reaction mixture produced 47 in 65% yield along with unidentified products. Phosphonate 61 was prepared in 2 steps from commercially available 59. The first step has been reported. 28 Basic hydrolysis of 60 left phosphonate 61 as a solid, which was used without further purification (Figure 1.16).

The free alcohol in 47 was coupled successfully with phosphonate 61 in 90% yield following recourse to DCC as the activating agent. Use of the corresponding acyl chloride of 61 invariably produced unidentified compounds. The next intramolecular Horner-Wadsworth-Emmons olefination was troublesome. Phosphonate 62 appeared to be highly base-sensitive. The use of conventional bases such as LDA, LHMDS, KHMDS, NaH, K2CO3/18-cr-6 or DBU afforded in high yield the elimination product.
Figure 1.17: Attempted intramolecular olefination.

The success of the olefination resided in the use of the lithium salt (Figure 1.18). Lithium cations most likely form a tight complex with the carbanion derived from 62.

Figure 1.18: Successful intramolecular olefination.

Also the oxophilicity of the lithium cation causes more efficient activation of the
ketone carbonyl in 62. The pKa of phosphonate 62 is by extrapolation approximately 12 in diglyme. This fact suggests that the phosphonate moiety should be deprotonated with an amine such as DBU (pKa 11.6 in water) or DIPEA (pKa 10.5 in water). Whereas recourse to DBU in dry MeCN with 6 eq of LiCl led to a 1 to 1 mixture of 63 and the desired 46, the use of DIPEA delivered olefination product 46 in 92 % yield without any trace of 63.

4.2 FORMATION OF THE QUATERNARY CENTER

The [3,3] sigmatropic rearrangement of an allylic ester as its enolate anion or the corresponding silylketene acetal is known to produce the γ,δ-unsaturated carboxylic acid.

![Diagram]

Figure 1.19: Attempted quaternization of C_{14}.

Acetate 46 possesses the ideal requirement for such a chemical transformation.
Furthermore, due to the high stereospecificity of the rearrangement, the quaternary center would be set with the proper relative configuration. Under the conditions described in the original publication for the Ireland-Claisen rearrangement, acetate 46 failed to deliver the desired carboxylic acid (Figure 1.19). Other milder conditions such as TMSOTf or TBSOTf in the presence of an amine base were tried in an effort to generate the silylketene acetal but without success.

Figure 1.20: Attempted ortho ester and ortho amide Claisen rearrangement.

Acetate 46 reacted in all cases but afforded only unidentified products. The disappointing base-sensitive nature of this acetate prompted us to use other Claisen
rearrangement technologies to install our quaternary center. Acetate 46 was smoothly hydrolysed to the corresponding allylic alcohol 66. The free alcohol was tested for both ortho ester and ortho amide Claisen rearrangement reactivity but without success (Figure 1.20). Finally, alcohol 66 was transformed into its corresponding vinyl ether 69 using ethyl vinyl ether with mercuric trifluoroacetate and DIPEA in quantitative yield (Figure 1.21).

Figure 1.21: Formation of the precursor for Claisen rearrangement.

Compound 69 was heated in a sealed tube under the conditions described below (Table 1.1).
<table>
<thead>
<tr>
<th>solvent</th>
<th>additive</th>
<th>temperature</th>
<th>time</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>decalin</td>
<td></td>
<td>180</td>
<td>1 to 3 days</td>
<td>alcohol 66</td>
</tr>
<tr>
<td>decalin molecular sieve</td>
<td></td>
<td>180</td>
<td>1 to 3 days</td>
<td>SM</td>
</tr>
<tr>
<td>decalin molecular sieve</td>
<td></td>
<td>180</td>
<td>10 days</td>
<td>SM + decomposition</td>
</tr>
<tr>
<td>DMF</td>
<td></td>
<td>180</td>
<td>20 h</td>
<td>aldehyde + alcohol 66</td>
</tr>
<tr>
<td>NMP</td>
<td></td>
<td>180</td>
<td>20 h</td>
<td>two aldehydes + decomposition</td>
</tr>
<tr>
<td>NMP PCS</td>
<td></td>
<td>150</td>
<td>1 to 3 days</td>
<td>decomposition</td>
</tr>
<tr>
<td>NMP NaBF₄</td>
<td></td>
<td>150</td>
<td>3 days</td>
<td>decomposition</td>
</tr>
<tr>
<td>NMP NaBF₄</td>
<td></td>
<td>130</td>
<td>5 days</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 1.1: Summary of attempted Claisen rearrangements of 69.

The polarity of the solvent affected the rate of either decomposition or rearrangement. From the $^1$H NMR, the presence of an aldehyde or two was obvious, but the rest of the spectrum did not correspond to what was expected for the Claisen product. It seemed that elevated temperatures initiated the sigmatropy but the instability of aldehyde 70 precluded its isolation.

A new route via reductive isomerization was then taken. The reduction was intended to produce the $\beta,\gamma$-unsaturated lactone 71 where the double bond would be at its final position in the cyclohexane ring (Figure 1.22). The next step was anticipated to be a simple alkylation of the enolate of 71 to give rise to 72, with the proper setting for C₁₄ since electrophilic capture from the less sterically congested enolate $\pi$-surface.
should operate.

Figure 1.22: Reductive isomerization followed by alkylation to lead to 72.

\[
\text{PMBO} \quad \overset{\text{reduction}}{\longrightarrow} \quad \text{PMBO} \quad \overset{\text{base, then RX}}{\longrightarrow} \quad \text{PMBO}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{CO}_2\text{tBu} & \quad \text{CO}_2\text{tBu} & \quad \text{CO}_2\text{tBu}
\end{align*}
\]

\[
\begin{align*}
\text{46} & \quad \text{71} & \quad \text{72}
\end{align*}
\]

Mg\textsuperscript{0}/MeOH \textsuperscript{33} gave only a 50% yield and MeCu (Li) \textsuperscript{34} gave a 75% yield of 71.

Figure 1.23: Attempted alkylation of 71.

\[
\text{PMBO} \quad \overset{\text{base, then electrophile}}{\longrightarrow} \quad \text{PMBO}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{CO}_2\text{tBu} & \quad \text{CO}_2\text{tBu} & \quad \text{CO}_2\text{tBu}
\end{align*}
\]

\[
\begin{align*}
\text{71} & \quad \text{73}
\end{align*}
\]

Molander \textsuperscript{35} has extensively described that functionalized vinyl oxiranes can be reduced
with isomerization of the double bond using SmI₂. Samarium iodide in MeOH at -78°C gave the desired lactone 71 as a single diastereoisomer in 80% yield with recovery of 20% of starting material. Interestingly, several attempts were made to trap the intermediate samarium(III) enolate. ClSnPh₃, TMSCl, AcCl, Ac₂O or RI were added to

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Co-sovent</th>
<th>Electrophile</th>
</tr>
</thead>
<tbody>
<tr>
<td>KHMDS</td>
<td>THF</td>
<td>18-cr-6</td>
<td>A</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>THF</td>
<td>HMPA</td>
<td>B</td>
</tr>
<tr>
<td>LiTMP</td>
<td>THF</td>
<td>HMPA</td>
<td>B</td>
</tr>
<tr>
<td>LiDPTMS</td>
<td>THF</td>
<td>HMPA</td>
<td>A</td>
</tr>
<tr>
<td>LDA</td>
<td>THF</td>
<td>HMPA</td>
<td>A</td>
</tr>
<tr>
<td>LiHMDS THF</td>
<td>THF</td>
<td>HMPA</td>
<td>C</td>
</tr>
<tr>
<td>DIPEA benzene</td>
<td>THF</td>
<td>HMPA</td>
<td>TBSOTf</td>
</tr>
<tr>
<td>Phosphazene T4 base</td>
<td>THF</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>KH</td>
<td>THF</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>KH</td>
<td>THF</td>
<td>18-cr-6</td>
<td>D</td>
</tr>
<tr>
<td>KH</td>
<td>THF</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>KH</td>
<td>THF</td>
<td>HMPA</td>
<td>F</td>
</tr>
<tr>
<td>KH</td>
<td>DMF</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>tBuOK</td>
<td>THF</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>NaH</td>
<td>DMF</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>DBU</td>
<td>DMF</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>DBU</td>
<td>MeCN</td>
<td>LiI</td>
<td>F</td>
</tr>
<tr>
<td>NaH</td>
<td>DMF</td>
<td>TBAI</td>
<td>F</td>
</tr>
</tbody>
</table>

Table 1.2: Alkylation of compound 71.
the reaction mixture, but protonation invariably occurred. Lactone 71 was then subjected to alkylation (Figure 1.23). Again, various conditions were attempted but not one of them was successful (Table 1.2). Actually, isomerization of the double bond back into conjugation was observed in every case in almost quantitative yield. Various electrophiles were tried during these attempts: 2-bromo-1-(\textit{tert}-butyldimethylsilyloxy)ethane, \textit{tert}-butyldimethylsilyloxy)ethyl iodide, allyl iodide, MeI, 2-(2-bromoethyl)-[1,3]dioxolane and ethyl bromoacetate.

Apparently, \(\alpha\)-alkylation of this conjugated enolate is not kinetically feasible. Only \(\delta\)-protonation, after quenching, was observed. Compound 73 was subjected under the same conditions where lactone 39 gave exclusively the alkylated product 40 and not 41, to produce 74 as a mixture of diastereoisomers (Figure 1.24). As seen previously with 40, loss of the stereogenic center associated with the butenolide was responsible for the 1 to 1 mixture of diastereoisomers.

Figure 1.24: Alkylation of compound 73.
The presence of this unsaturation was evidently the problem so its installation was postponed. The conjugated double bond resident in 66 was reduced by means of NaBH₄/NiCl₂ (Figure 1.25). The corresponding alcohol 75 was protected as MOM ether 76.

Figure 1.25: Successful alkylation of compound 75.

The same study as for alkylation of 71 was conducted. When compound 76 was treated with potassium hexamethyldisilazide in the presence of 18-crown-6 with 2-(tert-
butyldimethylsilyloxy)ethyl iodide, the desired alkylated product 77 was obtained in 5% yield, along with unidentified products. Amazingly, the use of lithiated bases such as LDA, LiHMDS, LiTMP or LiDPTMS in THF or DMF did not affect any transformations.

Looking back to our model study, our approach to 77 was 22 steps from cyclohexenone 48. With this number of steps, Shair and Fukayama were three chemical transformations away from the completion of CP-263,114.

Figure 1.26: Remaining synthetic work for the completion of the model study.
With 77 in hand, we still had to install the bridgehead double bond present in the bicyclo[4.3.1]deca-1(9)-ene ring of the CP core (with the question of regioselectivity during elimination) and had to install the second ester moiety in at least 3 steps prior to attempting the oxidative cyclization to furnish 42 (Figure 1.26).

4.3 NEW MODEL STUDY

In connection with an attempt to achieve a short preparative route to the core ring system of 1 and 2, we have considered a pathway that would eventuate in the delivery of 79 in only five steps from 2-cyclohexenone (Figure 1.27), a rather shorter way than described above.

![Retrosynthetic analysis of target 79.](image)
This new approach can be compared to what Armstrong\textsuperscript{39} has described in order to synthesize the bicyclo[4.3.1]decenone core of CP-263,114. They have developed a short synthesis (6 steps from cyclohexanone) of the CP-core utilizing a Mukaiyama aldol reaction as the key step (Figure 1.28).

![Chemical structure](image)

Figure 1.28: Armstrong's approach to CP-263,114 core structure.

Compound 82 lacked the diester moiety precursor for the anhydride subunit, and the endo ester needed to be homologated. Obviously, the ketone has to be protected in order to complete proper functionalization of the ring. In our new approach, compound 79 possessed all of the necessary functionality. Conjugate addition of cyanide anion using Me\textsubscript{2}AlCN should deliver the missing carbon atom needed for the lactone cage.

The first transformation involved alkylation of the kinetic enolate of 48 with methyl bromoacetate (Figure 1.29).\textsuperscript{40} Keto ester 83, thus obtained in 80\% yield, proved entirely amenable to bromination-dehydrobromination as expected. The bromo enone 84 generated in this manner was conveniently responsive to acetalization.
under the Noyori conditions. Introduction of the diester-containing side chain was accomplished at this stage by stirring 85 with dimethyl \((E)\)-hexenedioate under conventional Heck conditions. Application of this difunctional reagent, directly available from the palladium-catalyzed dimerization of methyl acrylate, provided the key triester 80. Remarkably, the Heck coupling provided 80 exclusively as the \(E\)-isomer. Nevertheless, the turn-over of the catalyst appeared very slow, yielding low conversion after an extensive amount of time.

![Figure 1.29: Forward synthesis to compound 80.](image)

The ability of cupric and ferric ions to bring about the oxidative coupling of ester enolates, recognized more than 20 years ago, has serviced several synthetic objectives.
in both its intermolecular\textsuperscript{45-47} and intramolecular variants.\textsuperscript{20, 21} Comparable success has been realized with elemental iodine as the oxidant.\textsuperscript{48, 49} A variety of possibilities for effecting the conversion of 80 into 79 by these methods failed to achieve the desired carbon-carbon bond formation (Figure 1.30). In those examples where consumption of starting material was evident, keto diester 86 could be isolated in yields up to 60\% (Table 1.3).

According to this table, the ratio between starting material 80 and Dieckmann adduct 86 depended heavily on the strength of the base used as well as the polarity of the solvent, but was independent of the choice of an oxidant like CuCl\textsubscript{2}.

Figure 1.30: Dieckmann condensation vs oxidative cyclization.
As soon as the proton at C₁₁ enolized, Dieckmann condensation occurred very rapidly. Alternative recourse to copper(II) bromide or silver(I) oxide (DMSO, 80 °C, 8 days) fared no better. When 80 failed to respond to the combined action of potassium tert-butoxide and iodine, the decision was made to determine the readiness with which 80 entered into the Dieckmann condensation. Quite remarkably, treatment of 80 with 2.2 equiv of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at -78 °C for 30 min furnished 86 in 70% yield (Figure 1.30). In order to slow down the Dieckmann condensation, the two methyl esters were switched as in di-tert-butyl ester 88 (Figure 1.31). As described earlier, vinyl bromide 85 was coupled to diester 87 under modified conditions.

<table>
<thead>
<tr>
<th>bases (3 equiv)</th>
<th>solvent</th>
<th>oxidant</th>
<th>temp</th>
<th>product composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA</td>
<td>THF-DMF (9:1)</td>
<td>CuCl₂ (neat)</td>
<td>-40 to 0</td>
<td>80 (60%); 86 (40%)</td>
</tr>
<tr>
<td>LDA</td>
<td>THF</td>
<td>CuCl₂ (DMF)</td>
<td>-40 to 0</td>
<td>80 (40%); 86 (60%)</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>THF-TMEDA (9:1)</td>
<td>I₂</td>
<td>-78 to 0</td>
<td>80 (50%); 86 (50%)</td>
</tr>
<tr>
<td>LiTMP</td>
<td>THF-TMEDA (9:1)</td>
<td>CuCl₂ (neat)</td>
<td>-78 to 0</td>
<td>86 (60%)</td>
</tr>
</tbody>
</table>

Table 1.3: Representative oxidations involving 80.
Heck coupling.

Figure 1.31: Synthesis of compounds 87 and 88.

The resulting E-isomer 88 was then treated with LiTMP and CuCl\_2 under the standard conditions for oxidative cyclization. With disappointment, only the Dieckmann adduct was observed.

Quite evidently, the rate of five-ring closure associated with the Dieckmann pathway cannot be overridden by the kinetics associated with formation of the larger ring resident in 79. Beyond that, the conversion of 80 into 86 does not require dienolate
generation. In addition, 86 does not find it possible to return to 80, since deprotonation of the acidic hydrogen positioned in the 1,3-dicarbonyl subunit guarantees irreversibility.

Figure 1.32: Proposed synthesis of compound 91.

A solution to alleviate the exclusive course of the Dieckmann condensation during the attempted oxidative cyclization was to gain access to the Z-isomer of 80, where the two esters involved in the condensation would reside too far apart to interact with each other. Classical conditions for the isomerization of the conjugated double bond were tried but without success. A new route has been designed but never attempted. The zinc homoenolate is anticipated to add to enyne 90 so that the Z-isomer would be
produced exclusively (Figure 1.32). Access to substrate 89 should utilize Sonogashira-coupling of bromoketal 85 with propargylic alcohol. The resulting enyne would be oxidized to the carboxylic acid oxidation state and subsequent protection as a methyl ester would give rise to compound 90.

4.4 CONCLUSION

Two model studies towards the core structure of CP-263,114 (1) have been described. The first approach defined a straightforward synthesis of lactone 76 utilizing highly stereocontrolled transformations such as iodolactonization, epoxide ring opening, alkylation and Wadsworth-Emmons olefination. Despite our successful installation of the C14 quaternary center, the low yield forced us to abandon this tactic. The second route was an attempted expedient construction of the CP-core. The access of triester 80 or 88 was accomplished in 4 steps. All attempts to bring about intramolecular oxidative cyclization of the dienolate of either 80 or 88 was found to result in preferred formation of the Dieckmann product 86 instead. From this study, it was clear that isomerization of the E-double to the Z-double bond should provide the kinetically favored oxidative cyclization product 79.
THF and ether were distilled from sodium benzophenone ketyl under nitrogen just prior to use. For CH₂Cl₂ and benzene, the drying agent was calcium hydride. All reactions were performed under a N₂ atmosphere. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F₂₅₄ aluminum-backed plates. All chromatographic purifications were performed on E. Merck silica gel 60 (230-400 mesh) using the indicated solvent systems. Melting points are uncorrected. ¹H and ¹³C NMR spectra were recorded on Bruker instruments at 300 or 500 and 75 or 125 MHz, respectively, except where noted. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA. IR spectra were recorded with a Perkin-Elmer 1320 spectrometer and optical rotations were measured with a Perkin Elmer Model 241 polarimeter. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.

Compound 50

A solution of iodolactone 49 (20.25 g, 0.075 mol) in 600 mL of DCM stirred at -78 °C was treated with Dibal-H (90 mL, 1M in hexane). After 1 h of stirring at this temperature, the reaction mixture was treated with a 4:1 mixture of H₂O/AcOH and allowed to warm to rt. The separated aqueous layer was extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated.
Flash chromatography of the residue (hexanes/AcOEt 2:1) afforded lactol 50 as a 2:1 mixture of diastereoisomers; colorless oil; IR (neat, cm\(^{-1}\)) 3598, 2992, 2863, 1602, 1451, 1350, 1230, 1152; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.64 (m, 1H), 4.49 (m, 0.33 H), 4.47 (dd, \(J = 5.8, 5.2 \text{ Hz}\), 0.66 H), 4.33 (m, 0.66 ), 4.17 (dd, \(J = 8.3, 6.3 \text{ Hz}, 0.33 \text{ H}\), 3.75 (d, \(J = 3.0 \text{ Hz}, 0.33 \text{ H}\), 3.24 (d, \(J = 3.5 \text{ Hz}, 0.66 \text{ H}\), 2.69-1.39 (m, 9H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (major) 98.2, 82.9, 38.7, 36.5, 35.4, 33.0, 26.4, 22.0; \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (minor) 99.4, 85.4, 38.4, 32.2, 25.5, 22.6; HRMS (El) \(m/z\) (M\(^+\)) calcd for C\(_{13}\)H\(_{13}\)O\(_2\) 267.9960, obsd 268.0005.

*Anal.* Calcd for C\(_{13}\)H\(_{13}\)O\(_2\): C, 35.84; H, 4.89. Found: C, 35.89; H, 4.87.

**Compound 51**

The crude lactol 50 was dissolved in 1 L of DCM and treated with Ag\(_2\)O (26 g, 1.5 eq). After 2 h of stirring at rt, filtration and concentration of the filtrate yielded crude epoxy aldehyde 51 as a colorless oil, which was subjected to the next chemical transformation without further purification: IR (neat, cm\(^{-1}\)) 2986, 2876, 2724, 1724, 1446, 1388, 1352, 1259; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.84 (s, 1H), 3.18 (ddd, \(J = 3.9, 3.9, 1.0 \text{ Hz}, 1H\), 3.12 (dd, \(J = 3.9, 2.2 \text{ Hz}, 1H\), 2.73 (m, 1H), 2.53-2.41 (m, 2H), 1.87-1.80 (m, 2H), 1.51-1.34 (m, 2H), 1.29-1.10 (m,
2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 201.5, 54.6, 53.3, 47.4, 29.4, 25.1, 23.5, 19.3; HRMS (EI) $m/z$ (M$^+$) calcd for C$_8$H$_{12}$O$_2$ 140.0837, obsd 140.0830.

**Compound 52**

To a stirred solution of unpurified aldehyde 51 in 1 L of MeOH cooled to -5°C was added NaBH$_4$ (1.1 g, 0.027 mol). After 20 min, water was added. The volatiles were removed *in vacuo*. The aqueous layer was extracted with Et$_2$O. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated. Flash chromatography on silica gel (AcOEt/hexanes 1:3) of the residue afforded epoxy alcohol 52 as a colorless oil in 85% yield for the last three steps; IR (neat, cm$^{-1}$) 3416, 2860, 1439, 1063, 1048; $^1$H NMR (300 MHz, CDCl$_3$) δ 3.75 (m, 2H), 3.18 (dd, $J$ = 4.0, 4.0 Hz, 1H), 3.10 (dd, $J$ = 4.0, 3.5 Hz, 1H), 1.99 (m, 2H), 1.90-1.72 (m, 2H), 1.63 (m, 1H), 1.47 (m, 1H), 1.34 (m, 1H), 1.26-1.06 (m, 2H), OH not observed; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 60.2, 55.6, 53.4, 36.0, 31.6, 24.9, 23.8, 19.8; HRMS (EI) $m/z$ (M$^+$) calcd for C$_8$H$_{14}$O$_2$ 142.0994, obsd 142.0998.

**Compound 53**

40
To a solution of alcohol 52 (1.0 g, 7.0 mmol) in 20 mL of DMF stirred at 0°C was added NaH (0.319 g, 1.5 eq, 80% in oil). After 20 min of stirring at rt, PMBCl (1.44 mL, 1.4 eq) was added. The reaction mixture was treated with water after 12 h of stirring. The separated aqueous layer was extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The resulting yellowish oil was flash chromatographed on silica gel (hexanes/AcOEt 10:1 to 2:1) to afford 1.2 g (91%) of protected alcohol 53 as a colorless oil; IR (neat, cm⁻¹) 2933, 2857, 1613, 1514, 1455, 1442, 1357, 1302, 1248, 1172, 1100, 1036; ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 4.44 (s, 2H), 3.78 (s, 3H), 3.64-3.51 (m, 2H), 3.15 (dd, J = 3.8, 3.8 Hz, 1H), 3.06 (dd, J = 3.8, 2.5 Hz, 1H), 2.20 (m, 1H), 1.92-1.75 (m, 3H), 1.64 (m, 1H), 1.47 (m, 1H), 1.35 (m, 1H), 1.25-1.06 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 159.0, 130.6, 129.1 (2C), 113.7 (2C), 72.5, 67.4, 55.3, 55.1, 52.9, 33.1, 31.5, 25.0, 23.8, 19.7; HRMS (EI) m/z (M⁺) calcd for C₁₆H₂₂O₃ 262.1569, obsd 262.1560.

*Anal.* Calcd for C₁₆H₂₂O₃: C, 73.25; H, 8.45. Found: C, 73.07; H, 8.35.

**Compound 54**

A solution of epoxide 53 (4.43 g, 0.017 mol) in 33 mL of DMSO containing CSA (3.94 g, 0.017 mol) was stirred for 1 h at rt, diluted with DCM (230 mL), cooled to -78 °C, and treated with NEt₃ (11.8 mL, 5 eq). The reaction mixture was allowed to warm to rt and was stirred for 12 h, dilute with Et₂O, and washed with a saturated solution of
KHSO$_4$. The separated aqueous layer was extracted with DCM. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated. Flash chromatography of the residue on silica gel (AcOEt/hexanes 1:2) afforded 4.0 g (85%) of 54 as a colorless oil; IR (neat, cm$^{-1}$) 3474, 2937, 2861, 1715, 1612, 1513, 1248, 1098; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.24 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 4.44 (d, $J = 11.5$ Hz, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 4.27 (ddd, $J = 5.6$, 4.1, 1.2 Hz, 1H), 3.80 (s, 3H), 3.69 (d, $J = 4.1$ Hz, 1H), 3.48 (dd, $J = 7.2$, 6.2 Hz, 1H), 2.53 (m, 1H), 2.48 (m, 1H), 2.34 (m, 1H), 1.96-1.76 (m, 6H), 1.23 (ddd, $J = 14.4$, 8.9, 6.1, 6.1 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 211.4, 159.1, 130.4, 129.1 (2C), 113.7 (2C), 77.8, 72.5, 68.5, 55.2, 41.0, 39.1, 27.0, 25.7, 22.2; HRMS (EI) m/z (M$^+$) calcd for C$_{16}$H$_{22}$O$_4$ 278.1518, obsd 278.1565.

Compound 55

To a solution of 54 (0.94 g, 3.38 mmol) and NEt$_3$ (10 mL, 10% v/v) in 100 mL of DCM at 0°C was added TBSOTf (3.8 mL, 5 eq). The reaction mixture was stirred for 2 h at 0°C and was allowed to warm to rt. Water was added. The separated aqueous layer was extracted with DCM. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated. Flash chromatography of the residue on silica gel (Et$_2$O/hexanes 1:10) afforded 0.80 g (47%) of 55 as a colorless oil; IR (neat, cm$^{-1}$) 2954, 2930, 1664, 1615, 1514, 1472,
Compound 56

A solution of OsO_4 (30 mg, cat) in 2 mL of THF was added to a stirred solution of silyl enol ether 55 (0.81 g, 1.6 mmol), NMOH_2O (0.77 mg, 5.7 mmol) in 40 mL of a 3:1 mixture of THF/H_2O at rt. The solution was stirred for 12 h and treated with 1 g of NaHSO_3 and 10 mL of water. The suspension was filtered. The filtrate was evaporated and extracted with DCM. The separated aqueous layer was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The diol 56 was isolated as a white solid. A small aliquot was set aside for characterization: mp 102-103°C; IR (neat, cm⁻¹) 3405, 2928, 2855, 1513, 1249; ^1H NMR (300 MHz, C⁶D₆) δ 7.28 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.38 (d, J = 6.0 Hz, 2H), 4.04 (s, 1H), 3.91 (s, 1H), 3.80 (dt, J = 5.9, 4.7 Hz, 1H), 3.46 (dt, J = 8.8, 6.4 Hz, 2H), 3.37 (s, 3H), 3.81 (s, 2H), 3.77 (s, 3H), 3.77 (s, 3H), 3.77 (s, 3H), 3.77 (s, 3H); ^13C NMR (75 MHz, CDCl₃) δ 159.2, 152.0, 130.8, 129.3 (2C), 113.8 (2C), 101.0, 72.6, 71.0, 67.8, 55.2, 37.7, 32.0, 26.0 (3), 24.0, 21.9, 18.5, 18.4, -4.0 (2C), -5.1 (2C); FAB MS m/z (MH⁺) calcd for C_28H_51O_4Si_2 507.33, obsd 507.25.
2.23-2.19 (m, 1H), 1.88-1.77 (m, 2H), 1.66-1.57 (m, 1H), 1.54-1.31 (m, 3H), 1.06 (s, 9H), 0.98 (s, 9H), 0.30 (s, 6H), 0.24 (s, 3H), 0.19 (s, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) $\delta$ 159.4, 130.9, 129.1 (2C), 113.7 (2C), 101.9, 76.0, 72.7, 72.0, 68.0, 54.5, 35.8, 32.6, 31.4, 26.2 (3C), 26.0 (3C), 18.0, 17.9, -2.3, -2.9, -3.7, -4.7.

Compound 57

The resulting solid 56 was dissolved in 40 mL of MeOH and treated with 3 eq of K$_2$CO$_3$ at rt for 30 min. The reaction was stopped by the addition of a saturated solution of NH$_4$Cl. Evaporation of the volatiles left a thick liquid which was extracted with AcOEt. The separated aqueous layer was extracted with AcOEt. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated. Flash chromatography on silica gel (Et$_2$O/hexanes 1:2) of the residue delivered 57 as a colorless oil (424 mg, 65%); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3440, 1710; $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 7.24 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 4.78-4.70 (m, 1H), 4.34 (s, 2H), 4.17 (s, 1H), 3.49 (d, $J = 5.1$ Hz, 1H), 3.38 (s, 3H), 3.37-3.24 (m, 2H), 2.28-2.20 (m, 1H), 1.73-1.53 (m, 4H), 1.26-1.17 (m, 2H), 0.88 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) $\delta$ 211.3, 159.6, 130.7, 129.2 (2C), 113.8 (2C), 77.5, 72.6, 71.9, 67.0, 54.5, 42.6, 36.3, 31.3, 25.5 (3C), 23.4, 17.8, -5.1, -5.6; HRMS (EI) m/z (M$^+$-CH$_3$) calcd for C$_{27}$H$_{33}$O$_7$Si 393.2109, obsd 393.2075.
Compound 58

To a solution of pyridine (0.7 mL, 10 eq) and DMAP (cat) in 80 mL of DCM stirred at 
-30 °C was added AcCl (0.3 mL, 5 eq). A solution of 
57 (0.35 mg, 0.857 mmol) in 10 mL of DCM was next 
introduced via cannula. The reaction mixture was 
stirred at rt for 2 h. The solution was washed with 
saturated solutions of NaHCO₃ and brine, dried over 
Na₂SO₄ and concentrated. Flash chromatography of the residue on silica gel 
(hexanes/Et₂O 2:1) gave 0.38 g (98%) of 58 as a colorless oil: IR (neat, cm⁻¹) 2954, 
2930, 2855, 1751, 1736, 1610, 1512, 1461, 1372, 1235, 1172, 1090, 1071, 1035, 836, 
780;¹H NMR (300 MHz, CDCl₃) δ 7.23 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 
5.65 (dd, J = 12.2, 6.8 Hz, 1H), 4.41 (s, 2H), 4.00 (s, 1H), 3.81 (s, 3H), 3.43 (t, J = 6.3 
Hz, 2H), 2.21-2.16 (m, 1H), 2.15 (s, 3H), 1.87-1.83 (m, 2H), 1.72-1.55 (m, 4H), 0.91 (s, 
9H), 0.04 (s, 3H), 0.01 (s, 3H);¹³C NMR (75 MHz, CDCl₃) δ 206.5, 169.8, 159.3, 
130.4, 129.3 (2C), 113.8 (2C), 78.5, 74.0, 72.7, 67.0, 55.3, 42.0, 31.8, 31.1, 25.7 (3C), 
23.5, 20.7, 18.0, -4.9, -5.4; FAB MS m/z (MH)+ calcd for C₂₄H₃₉O₆Si 451.25, obsd 
451.23.

Anal. Calcd for C₂₄H₃₉O₆Si: C, 63.97; H, 8.51. Found: C, 64.15; H, 8.53.

Compound 47

To a solution of pyridine (6 mL) in 5 mL of THF being stirred at 0 °C was carefully
added HF.pyr (5 mL). A solution of 58 (69 mg, 0.153 mmol) in 5 mL of THF was next introduced. The reaction mixture was stirred at 30 °C for 5 days before the addition of a saturated solution of NaHCO₃ until the pH reached 8. The separated aqueous layer was extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (Et₂O/hexanes 2:1) of the residue delivered 34 mg (67%) of 47 as a colorless oil;

\[ \text{IR (CH₂Cl₂, cm}^{-1}\text{)} 3460, 1735, 1713; \text{ }^1\text{H NMR (300 MHz, CDCl₃) } \delta 7.21 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.79 (dd, J = 11.6, 6.3 Hz, 1H), 4.26 (s, 2H), 4.12 (s, 1H), 3.36 (s, 3H), 3.28-3.17 (m, 2H), 2.88 (br s, 1H), 1.94-1.87 (m, 1H), 1.84 (s, 3H), 1.79-1.65 (m, 3H), 1.58-1.34 (m, 3H); \text{ }^{13}\text{C NMR (75 MHz, CDCl₃) } \delta 204.6, 169.1, 159.6, 130.4, 129.2 (2C), 113.9 (2C), 77.1, 74.1, 72.5, 67.0, 54.5, 41.9, 31.1, 30.4, 23.4, 20.0; \text{HRMS (El) } m/z (M⁺) \text{calcd for } C_{18}H_{24}O_{6} \text{336.1574, obsd 336.1611.}

**Compound 62**

To a solution of acid 61 (0.114 g, 2.5 eq) and DMAP (cat) in 3 mL of DCM stirred at rt was added DCC (0.075 g, 2.5 eq). There followed a solution of 47 (0.045 g, 0.133 mmol) in 3 mL of DCM. The suspension was filtered off after 12 h of stirring. The filtrate was concentrated. Flash chromatography of the residue on silica gel (AcOEt/hexanes 6:1) afforded 62 as a 1:1
mixture of diastereoisomers (colorless oil, 0.083 g, 90%); IR (CH₂Cl₂, cm⁻¹) 735, 1728, 1720, 1710; ¹H NMR (300 MHz, CDCl₃) δ 7.22 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.56 (dd, J = 11.8, 6.8 Hz, 0.5H), 5.48 (dd, J = 11.6, 6.7 Hz, 0.5H), 5.13 (d, J = 0.2 Hz, 1H), 4.40 (d, J = 3.6 Hz, 2H), 4.23-4.08 (m, 4H), 3.79 (s, 3H), 3.48-3.43 (m, 2H), 3.18-3.08 (m, 1H), 2.43-2.13 (m, 4H), 2.11 (s, 0.5x3H), 2.10 (s, 0.3x3H), 1.97-1.88 (m, 1H), 1.85-1.46 (m, 3H), 1.42 (s, 9H), 1.40-1.20 (m, 6H), 1.11-1.07 (m, 1H), 0.89-0.83 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 200.6, 171.5 (0.5C), 171.4 (0.5C), 169.2 (0.5C), 169.1 (0.5C), 167.7 (0.5C), 167.6 (0.5C), 159.2, 130.2 (0.5C), 130.2 (0.5C), 129.3 (0.5x2C), 129.2 (0.5*2C), 113.8 (0.5x2C), 113.7 (0.5x2C), 80.5 (0.5C), 80.5 (0.5C), 79.6 (0.5C), 79.6 (0.5C), 74.1 (0.5C), 73.9 (0.5C), 72.6, 66.6, 63.1 (0.5C), 63.0 (0.5C), 62.8 (0.5C), 62.8 (0.5C), 62.7 (0.5C), 62.7 (0.5C), 51.2, 45.4 (0.5C), 43.6 (0.5), 43.6 (0.5C), 40.6 (0.5C), 40.5 (0.5C), 31.8 (0.5C), 31.7 (0.5C), 28.3 (3C), 24.0 (0.5C), 24.0 (0.5C), 22.6 (0.5C), 22.5 (0.5C), 22.3 (0.5C), 22.2 (0.5C), 20.5, 16.3 (0.5C), 16.2 (0.5C); HRMS (EI) m/z (M⁺-C₄H₉) calcd for C₂₇H₃₈O₁₂P 585.2102, found 585.2135.

Compound 46

To a suspension of LiCl (39.6 mg, 6 eq) in 4 mL of MeCN being stirred at -10 °C was added 62 (109 mg, 0.155 mmol) and DIPEA (54 µL, 2 eq). The reaction mixture was stirred for 12 h. Evaporation of the solvent left a clear residue which was purified by flash chromatography on silica gel (hexanes/AcOEt 1:1) to afford 50 mg (65%) of 46 as
Compound 66

To a solution of acetate 46 (560 mg, 1.14 mmol) in 100 mL of dry MeOH stirred at -10°C was added K$_2$CO$_3$ (300 mg, 1.5 eq). The reaction mixture was stirred overnight. A saturated solution of NH$_4$Cl was added and MeOH was removed in vacuo. The residue was extracted with AcOEt. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated. Flash chromatography on silica gel (hexanes/AcOEt 1:1) gave 430 mg (92%) of alcohol 66 as a clear oil; IR (CH$_2$Cl$_2$, cm$^{-1}$) 3452, 1743, 1731; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.22 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.94 (br s, 1H), 5.01 (dd, $J = 6.5$, 1.4 Hz, 1H), 4.38 (d, $J = 3.6$ Hz, 2H), 3.80 (s, 3H), 3.48-3.39 (m, 2H), 2.79-2.74 (m, 1H), 2.66-2.63 (m, 1H), 2.57-2.43 (m, 3H), 2.05 (s, 3H), 1.92-1.71 (m, 3H), 1.55-1.42 (m, 2H), 1.39 (s, 9H), 1.15-1.07 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.3, 171.7, 169.8, 159.1, 155.8, 130.5, 129.1 (2C), 127.4, 113.7 (2C), 80.4, 79.9, 72.5, 68.1, 66.2, 55.2, 36.3, 32.1, 28 (3C), 25.4, 23.1, 21.6, 20.9, 18.9; HRMS (El) m/z (M$^+$) calcd for C$_{27}$H$_{36}$O$_6$ 488.2409, obsd 488.2434.
2H), 6.85 (d, J = 8.7 Hz, 2H), 5.03 (d, J = 6.7 Hz, 1H), 4.77 (br s, 1H), 4.30 (d, J = 1.5 Hz, 2H), 3.37 (s, 3H), 3.39-3.28 (m, 2H), 2.59-2.55 (m, 1H), 2.46-2.33 (m, 4H), 1.97-1.85 (m, 1H), 1.77-1.65 (m, 1H), 1.60-1.29 (m, 4H), 1.26 (s, 9H), 1.14-1.09 (m, 1H); 

\[^{13}\text{C}\text{ NMR (75 MHz, C}_6\text{D}_6\)] \(\delta\) 173.3, 172.5, 161.1, 159.4, 131.0, 129.1 (2C), 124.2, 113.8 (2C), 80.4, 79.8, 72.4, 68.3, 62.9, 54.5, 36.4, 32.4, 27.6 (3C), 27.2, 23.4, 21.1, 18.4; 

HRMS (EI) \(m/z\) (M^+) calcd for C\(_{25}\)H\(_{34}\)O\(_6\) 446.2304, obsd 446.2329.

**Compound 69**

To a solution of alcohol 55 (100 mg, 0.22 mmol) in 10 mL of freshly distilled ethyl vinyl ether stirred at 0 °C was added DIPEA (50 µL, 1 eq) and Hg(OOCFC\(_3\))\(_2\) (30 mg, 0.22 mmol). The reaction mixture was stirred for 10 h at rt. A solution of 10% KOH in H\(_2\)O and petroleum ether were added. The combined organic phase was washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated. Flash chromatography on silica gel (hexanes/Et\(_2\)O 1:1, 5% NEt\(_3\)) gave 107 mg (98%) of a clear oil: \(^1\text{H}\text{ NMR (300 MHz, C}_6\text{D}_6\)] \(\delta\) 7.23 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 6.12 (dd, J = 14.0, 6.5 Hz, 1H), 4.91 (br s, 1H), 4.87 (d, J = 6.5 Hz, 1H), 4.43 (dd, J = 14.0, 1.7 Hz, 1H), 4.28 (s, 2H), 4.04 (dd, J = 6.5, 1.65 Hz, 1H), 3.37 (s, 3H), 3.35-3.23 (m, 2H), 2.80-2.72 (m, 2H), 2.49-2.26 (m, 4H), 1.83-1.73 (m, 2H), 1.64-1.28 (m, 3H), 1.34 (s, 9H), 1.28-1.03 (m, 1H); 

\[^{13}\text{C}\text{ NMR (75 MHz, C}_6\text{D}_6\)] \(\delta\) 172.4, 171.6, 159.4, 156.6, 149.6, 130.9, 37.4, 32.4, 27.6, 27.2, 23.4, 21.1, 18.4.
Compound 71

To a solution of vinyl acetate 46 (100 mg, 0.2 mmol) in 10 mL of THF stirred at -78 °C was added 0.4 mL of dry MeOH and a solution of SmI₂ (0.1 M in THF, 5 mL) until a dark blue color persisted. A saturated solution of NH₄Cl followed, and the reaction mixture was allowed to warm to rt. Evaporation of the volatiles left a residue that was extracted with AcOEt. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (hexanes/Et₂O 1/1) gave 70 mg (80%) of a clear oil and some starting acetate was recovered (20 mg, 20%); IR (CH₂Cl₂, cm⁻¹) 1754, 1731; ¹H NMR (300MHz, CDCl₃) δ 7.26 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 5.04 (br s, 1H), 4.38 (br s, 1H), 4.32 (d, J = 3.7 Hz, 2H), 3.38- 3.32 (m, 2H), 3.36 (s, 3H), 2.78-2.76 (br s, 1H), 2.60 (t, J = 7.9 Hz, 1H), 2.29-2.23 (m, 1H), 2.26-2.06 (m, 1H), 1.99-1.84 (m, 1H), 1.79-1.55 (m,
Compound 61

Phosphonate 60 (3.5 g, 10 mmol) was added to a solution of KOH (728 mg, 13 mmol) in 4 mL of EtOH and 1 mL of water. The solution was stirred at rt for 24 h, concentrated under reduced pressure and diluted with 30 mL of water. The aqueous solution was washed twice with ether, acidified with 1 N HCl, saturated with solid NaCl, and extracted twice with ether. The combined organic layers were dried over MgSO₄, filtered and concentrated. The crude acid was isolated as a viscous oil (2.45 g, 68 %), which solidified on standing, mp 78-81 °C ; IR (CH₂Cl₂, cm⁻¹) 3056, 2984, 2932, 1728, 1369, 1266, 1220, 1152, 1024, 975; ; ¹H NMR (300 MHz, CDCl₃) δ 11.35 (br s, 1H), 4.22-4.03 (m, 4H), 3.02-2.84 (m, 1H), 2.29-1.95 (m, 4H), 1.27 (s, 9H), 1.19-1.12 (m, 6H); ¹³C NMR (75 MHz, C₆D₆) δ 171.6, 170.1, 80.4, 63.3 and 63.2, 63.0 and 62.9, 45.0 and 43.3, 33.3 and 33.1, 27.8 (3C), 22.2 and 22.1,
16.1 and 16.0. HRMS (EI) m/z (M+)^+ calcd for C_{35}H_{58}O_{9} 673.3742, found 673.3742.

Compound 77

To a solution of KHMDS (0.05 mL, 0.5 M in toluene, 0.025 mmol) in 0.4 mL of THF being stirred at -78 °C was added 18-cr-6 (10 mg, 0.04 mmol) and lactone 76 (10 mg, 0.02 mmol) in 0.5 mL of THF. The reaction mixture was stirred for 1 h at -78 °C prior to the addition of 2-(tert-butyldimethylsilyloxy)ethyl iodide (0.025 mL, xs). The reaction mixture was stirred for 3 h at -78 °C and allowed to warm to 0 °C before 1 mL of a saturated solution of NH_4Cl was added. The aqueous phase was extracted with ether. The combined organic layers were dried over MgSO_4, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 0.7 mg (5%) of the desired product and 95% or unidentified compounds. For 77: ^1H NMR (500 MHz, C_6D_6) δ 7.26 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 4.05 (d, J = 7.3 Hz, 1H), 4.44 (d, J = 7.3 Hz, 1H), 4.40 (br s, 1H), 4.31 (s, 2H), 3.78-3.76 (m, 1H), 3.75-3.73 (m, 1H), 3.33 (m, 1H), 3.29 (s, 3H + 1H), 3.17 (s, 3H), 3.20-3.15 (m, 2H), 2.95-2.92 (m, 1H), 2.57-2.53 (m, 1H), 2.49-2.45 (m, 1H), 2.10-2.03 (m, 2H), 1.90-1.53 (m, 8H), 1.49 (s, 9H), 0.93 (s, 9H), 0.01 (s, 6H); ^13C NMR (75 MHz, C_6D_6) δ 179.0, 173.4, 159.6, 130.9, 128.7 (2C), 113.8 (2C), 96.5, 79.3, 78.0, 75.9, 72.4, 66.9, 58.6, 55.2, 54.5, 50.2, 45.1, 35.1, 33.8, 33.7, 32.3, 30.9, 29.0 (3C), 27.7 (3C), 27.7, 25.6, 18.0, -5.7 (2C); HRMS (FAB) m/z (M+Na)^+ calcd for C_{35}H_{38}O_{9} 673.3742,
To a solution of LiHMDS (0.016 mL, 0.016 mmol) being stirred at -78 °C was added a solution of lactone 71 (5 mg, 0.011 mmol) in 0.5 mL of DMF. After 1 h at -78 °C, 1 mL of a saturated solution of NH$_4$Cl was added. The aqueous phase was extracted with ether. The combined organic layers were dried over MgSO$_4$, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 5 mg (100%) of 73; $^1$H NMR (300 MHz, CHCl$_3$) $\delta$ 7.22 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 4.76 (d, $J$ = 6.4 H, 1H), 4.40 (d, $J$ = 11.6 Hz, 1H), 4.35 (d, $J$ = 11.6 Hz, 1H), 3.79 (s, 3H), 3.49-3.39 (m, 2H), 2.91 (br d, $J$ =14.0 Hz, 1H), 2.64-2.43 (m, 5H), 2.11 (ddd, $J$ = 13.3, 13.3, 6.2 Hz, 1H), 1.88-1.42 (m, 5H), 1.41 (s, 9H), 1.18 (m, 1H); $^{13}$C NMR (75 MHz, CHCl$_3$) $\delta$ 174.1, 171.8, 161.5, 159.1, 130.5, 129.1 (2C), 123.4, 113.7 (2C), 82.1, 80.4, 72.4, 68.4, 55.2, 36.3, 33.1, 28.0 (3C0, 26.6, 26.0, 23.7, 20.2, 18.7; HRMS (EI) m/z (M$^+$) calcd for C$_{25}$H$_{34}$O$_6$ 373.1250, obsd 373.1633.
Compound 74

To a solution of KHMDS (0.140 mL, 0.5 M in toluene, 0.07 mmol) in 2 mL of DMF cooled at -40 °C was added a solution of lactone 73 (25 mg, 0.058 mmol) in 1 mL of DMF. After the solution had been stirred for 30 min, an excess of t-butyl bromoacetate (0.15 mL) was added. The solution was warmed to rt over 30 min prior to addition of water, the separated aqueous layer was extracted with ether, and the combined organic phases were washed with brine, dried and concentrated. The residue purified by flash chromatography on silica gel (elution with 5:1 hexanes/ether) to give 74 as a 1:1 mixture of epimers (19 mg, 61%); IR (neat, cm⁻¹) 2976, 2934, 2862, 1797, 1730, 1613, 1514, 1368, 1249, 1152; ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.44 (m, 2H), 3.80 (s, 3H), 3.57 (m, 2H), 2.79 (d, J = 15.0 Hz, 0.5xH), 2.65-2.56 (m, 1H), 2.42 (d, J = 15.0 Hz, 0.5xH), 2.41 (d, J = 14.8 Hz, 0.5xH), 2.13-1.43 (m, 12H), 1.26 (s, 9H), 1.39 (s, 0.5x9 H), 1.38 (s, 0.5x9H); HRMS (FAB) m/z (M⁺) calcd for C₃₁H₄₄O₈ 544.3036, obsd 544.4200.

Compound 83

Methyl 2-Oxo-3-cyclohexene-1-acetate. To a solution of diisopropylamine (16 mL, 0.11 mol) in dry THF (150 mL) cooled to -78 °C was added n-butyllithium (97 mL of 1.17 M in hexanes, 0.11 mol). After 15 min, a solution of 2-cyclohexenone (10.0 g,
0.104 mol) in dry THF (50 mL) was introduced dropwise over a period of 15 min. After 3 h of stirring at -78 °C, the reaction mixture was quenched with saturated NH₄Cl solution, the separated aqueous layer was extracted with ether, and the combined organic phases were washed with brine, dried and concentrated. The residue was distilled and further purified by flash chromatography on silica gel (elution with 1:1 hexanes/ether) to give 83 as a colorless oil (14 g, 80%); bp 90 °C at 0.05 Torr; IR (neat, cm⁻¹) 1735, 1681; ¹H NMR (300 MHz, CDCl₃) δ 6.98-6.92 (m, 1H), 6.03-5.99 (m, 1H), 3.69 (s, 3H), 2.93-2.81 (m, 2H), 2.48-2.39 (m, 2H), 2.32-2.23 (m, 1H), 2.15-2.09 (m, 1H), 1.88-1.78 (m, 1H); ¹³C NMR (75MHz, CDCl₃) δ 199.3, 172.9, 149.8, 129.2, 51.6, 43.6, 34.2, 28.6, 25.9; HRMS (El) m/z (M⁺) calcd for C₉H₁₂O₃ 168.0786, obsd 168.0774.

Compound 84

Methyl 3-Bromo-2-oxo-3-cyclohexene-1-acetate. To a solution of 83 (2.60 g, 0.015 mol) in CH₂Cl₂ (30 mL) at -10 °C was added dropwise a solution of bromine (0.78 mL, 1.05 equiv) in the same solvent (30 mL). After 30 min, triethylamine (2.59 mL, 1.2 equiv) was introduced during 5 min, and the reaction mixture was stirred at rt for 3 h and quenched with saturated NaHCO₃ solution. The organic phase was washed with water and brine, dried, and concentrated. Flash chromatography of the residue on
silica gel (elution with 2:1 hexanes/ether) afforded 3.25 g (85%) of 84 as an acid-sensitive colorless oil; IR (neat, \text{cm}^{-1}) 1735, 1687; \textsuperscript{1}H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}) \delta 6.61-6.57 (m, 1H), 3.38 (s, 3H), 2.76 (dd, J =16.5, 5.5 Hz, 1H), 2.60-2.50 (m, 1H), 2.06 (dd, J =16.5, 6.9 Hz, 1H), 1.62-1.37 (m, 3H), 1.28-1.14 (m, 1H); \textsuperscript{13}C NMR (75 MHz, C\textsubscript{6}D\textsubscript{6}) \delta 190.7, 171.6, 149.9, 122.9, 50.9, 44.0, 34.5, 27.9, 27.4; HRMS (El) \textit{m/z} (M\textsuperscript{+}) calcd 247.9891, obsd 247.9882.

\textit{Anal.} Calcd for C\textsubscript{9}H\textsubscript{11}BrO\textsubscript{3}: C, 43.72; H, 4.48. Found: C, 43.69; H, 4.46.

**Compound 85**

\textbf{Methyl 10-Bromo-1,4-dioxaspiro[4.5]dec-9-ene-6-acetate.} To a solution of trimethylsilyl triflate (0.33 mL, 30 mol%) in 5 mL of CH\textsubscript{2}Cl\textsubscript{2} at -78 °C was added 1,2-bis(trimethylsiloxy)ethane (2.23 mL, 1.5 equiv) and 84 (1.50 g, 6.07 mmol). The reaction mixture was left to stand for 5 days at rt, quenched with pyridine (3 mL), and diluted with ether and water. After the separated aqueous layer had been extracted with ether, the combined organic phases were washed with saturated NaHCO\textsubscript{3} solution and brine, dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 4:1 hexanes/ether) furnished 1.5 g (85%, 100% based on recovered 84) of 85 as a colorless oil; IR (CH\textsubscript{2}Cl\textsubscript{2}, \text{cm}^{-1}) 1731; \textsuperscript{1}H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}) \delta 5.96-5.94 (m, 1H), 4.06-4.01 (m, 1H), 3.99-3.92 (m,
1H), 3.62-3.60 (m, 2H), 3.42 (m, 3H), 2.67-2.56 (m, 2H), 2.17-2.09 (m, 1H), 1.79-1.71
(m, 1H), 1.63-1.57 (m, 3H); $^{13}$C NMR (75MHz, C$_6$D$_6$) δ 172.3, 134.3, 125.0, 107.5,
66.6, 66.4, 50.8, 41.8, 33.9, 25.6, 25.1; HRMS (EI) m/z (M$^+$) calcd 292.0130, obsd
292.0098.


Compound 80

(E)-3-[10-(Carboxymethyl)-1,4-dioxaspiro[4.5]dec-6-en-6-yl]-2-hexenedioic acid,
Trimethyl Ester. A mixture of 85 (123 mg, 0.422 mmol), dimethyl (E)-2-hexenedioate
(0.17 mL, 2.5 equiv), triethylamine (0.11 mL, 2 equiv), dichloropalladium
bis(triphenylphosphine) (3 mg, 1 mol%), and triphenylphosphine (6.6 mg, 6 mol%) in DMF (0.1 mL)
was heated at 80 °C for 5 days, cooled, poured into water, and shaken with ether. The organic phase was
washed with saturated NaHCO$_3$ solution and brine, dried and concentrated. Flash chromatography of the residue
on silica gel (elution with 1:1 ether/hexanes) gave 40 mg (25%, 90% based on
recovered 85) of 80 as a colorless oil; IR (CH$_2$Cl$_2$, cm$^{-1}$) 1731, 1729, 1713; $^1$H NMR
(300 MHz, C$_6$D$_6$) δ 6.08 (s, 1H), 5.49 (t, J = 3.6 Hz, 1H), 3.77-3.69 (m, 1H), 3.61-3.36
(m, 4H), 3.44 (s, 3H), 3.42 (s, 3H), 3.39 (s, 3H), 3.31-3.24 (m, 1H), 2.70-2.63 (m, 2H),
2.60-2.50 (m, 2H), 2.11-2.05 (m, 1H), 1.98-1.92 (m, 1H), 1.75-1.70 (m, 2H), 1.61-1.57
Compound 86

10-(4-Carboxy-3-oxo-1-cyclopenten-1-yl)-1,4-dioxaspiro[4.5]dec-9-ene-6-acetic acid, Dimethyl Ester. A cold (-78 °C), magnetically stirred solution of lithium 2,2,6,6-tetramethylpiperidide (2.2 equiv) in dry THF (1.2 mL) was treated dropwise with a solution of 80 (8 mg, 0.02 mmol) in THF (0.5 mL). After 30 min at -78 °C, saturated NaHCO₃ solution was introduced, to be followed by ether once warming to rt had occurred. The separated aqueous layer was extracted into ether, and the combined organic phases were washed with saturated NaHCO₃ solution and brine, dried, and freed of solvent. Purification of the residue by flash chromatography on silica gel (elution with 1:1 ether/hexanes) afforded 86 (5.2 mg, 70%) as a 1:1 mixture of diastereomers; IR (CH₂Cl₂, cm⁻¹) 1742, 1699, 1264; ¹H NMR (300 MHz, CDCl₃) δ 6.58-6.55 (m, 1H), 6.20 (brs, 1H), 4.12-4.04 (m, 5H), 3.81 (s, 3H), 3.75-3.66 (m, 1H), 3.69 (s, 3H), 3.20 (dd, J =18.2, 1.2 Hz, 1H) (a), 3.12 (dd, J =18.2, 1.0 Hz, 1H) (b), 2.61-2.51 (m, 2H), 2.35-2.30 (m, 2H), 2.22-2.16 (m, 1H), 2.04-2.01 (m, 1H), 1.78-1.72 (m, 1H); ¹³C NMR (75MHz, CDCl₃) δ 197.6 (a), 197.4 (b), 173.2 (a + b), 168.6
Compound 87

To a solution of KOH (11.26 g, 0.170 mol) in a 3:1 mixture of 400 mL of MeOH/water was added at rt dimethyl (E)-2-hexenedioate (14 g, 0.081 mol). After 4 h of stirring the volatiles were evaporated. The residue was taken up in water and extracted with ether. The aqueous phase was acidified to pH 1 and extracted overnight with ether. The ether phase was dried over MgSO₄, filtered and concentrated. The residue was dissolved in 100 mL of dioxane and transferred in a pressure flask. H₂SO₄ (10 mL) was added and 50 mL of isobutene was condensed into the flask which was immersed in a 10 °C bath. After 4 h of mechanical shaking the reaction mixture was quenched with a saturated solution of NaHCO₃. The volatiles were evaporated under reduced pressure. The residue was taken up in water and extracted with EtOAc. The combined organic phases were washed with saturated NaHCO₃ solution and brine, dried, and freed of solvent to leave the di-tert-butyl ester 87 pure enough to bypass purification (20.7 g, quant); IR (neat, cm⁻¹) 1717, 1653; ¹H NMR (300 MHz, CDCl₃) δ 6.87-6.77 (m, 1H), 5.75 (d, J = 15.6 Hz, 1H), 2.48-2.41 (m, 2H), 2.38-2.33 (m, 2H), 1.46 (s, 9H), 1.46 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 171.6, 165.7, 145.5, 123.7, 80.6, 80.1, 33.7, 28.1, 28.0, 27.3; FAB MS m/z (M⁺ + H) calcd for C₁₈H₂₃O₇ 351.15, obsd 351.25.
To a solution of bromo ketal 85 (300 mg, 1.01 mmol) in 2 mL of DMF was added diester 87 (390 mg, 1.52 mmol), n-Bu₄NCI (280 mg, 1.01 mmol), K₂CO₃ (240 mg, 2.55 mmol), PPh₃ (26 mg, 0.1 mmol) and finally Pd(OAc)₂ (11 mg, 0.05 mmol). The reaction mixture was heated to 80 °C for 5 days before 1 M HCl was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with saturated solutions of NaHCO₃ and brine, dried over MgSO₄ and concentrated. Flash chromatography of the residue on silica gel (hexanes/Et₂O 2:1) gave 120 mg (26%) of 88 as a colorless oil along with recovery of starting material (218 mg, 74%); IR (neat, cm⁻¹) 2978, 2931, 2919, 1731, 1725, 1713; ¹H NMR (300MHz, CDCl₃) δ 5.76-5.73 (m, 1H), 6.67 (s, 1H), 4.10-3.90 (m, 4H), 3.63 (s, 3H), 3.25-3.15 (m, 1H), 2.83-2.70 (m, 1H), 2.66-2.20 (m, 5H), 2.20-1.80 (m, 4H), 1.50 (s, 9H), 1.43 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 157.4, 139.0, 131.9, 126.0, 121.4, 108.4, 79.9 (2C), 65.5, 64.8, 51.6, 38.5, 33.6, 33.3, 28.2 (3C), 27.9 (3C), 27.0, 24.3, 22.4; EI HRMS m/z (M⁺) calcd for C₂₅H₃₈O₈ 466.2566, found 466.2564.
CHAPTER 2

STUDIES TOWARD THE SYNTHESIS OF MYCOEPOXYDIENE

1) ISOLATION AND STRUCTURE

In 1999, Houch et al. uncovered a novel epoxycyclooctadiene, mycoepoxydiene (1), from the solid-state fermentation of a fungus designated as OS-F66617. The producing fungus, a sterile dematiaceous culture, was isolated from twig litter collected from a deciduous alluvial forest near Curitiba, in the state of Parana, Brazil. Mycoepoxydiene (1) was obtained as colorless needle-shaped crystals. Its structure and relative stereochemistry were established using spectroscopic studies, including X-ray diffraction analysis. The only natural products before mycoepoxydiene (1) containing oxygen-bridged cyclooctadiene were the dibenzocyclooctadiene lignans related to kadsulignans (2-4) and neokadsuranin (5) (Figure 2.1).
In an anti-HIV screen, kadsulignan M (3) exhibits significant *in vitro* activity against HIV (IC$_{50}$ 1.19 $10^{-4}$ M, EC$_{50}$ 6.03 $10^{-6}$ M). There is no precedent for the mycoepoxydiene skeleton existing without the fused biphenyl system. Houck and coworkers speculated that mycoepoxydiene (1) may originate from a polyketide. With Cl of the attached δ-lactone as a starting unit, mycoepoxydiene could be produced from seven acetate units. No biological data concerning mycoepoxydiene is currently available. It may be speculated that mycoepoxydiene (1) acts as an anti-HIV agent,
since its structure is related to kadsulignan M (3). Also, the absolute stereochemistry of mycoepoxydiene remains unknown. The present synthetic endeavor is therefore designed to distinguish 1 from 1' and thereby resolve the absolute configurational status of the six stereogenic centers (Figure 2.2).

![Diagram of two enantiomers of mycoepoxydiene](image)

**Figure 2.2:** The two enantiomers of mycoepoxydiene.

2) RETROSYNTHETIC ANALYSIS

The target molecule could be accessible from ketone 6 after transformation of the ketone carbonyl to the exo methyl group and dehydration within the δ-lactone ring, along with appropriate protecting group manipulation. Ketone 6 would be derived from an aldol condensation involving ketone 7 and aldehyde 8. The pivotal enantiopure bicyclic ketone 7 should emerge after a tandem cyclization/oxy-Cope rearrangement of
fully substituted cyclobutanol 9, available from alcohol 10. The key cyclobutanol 10 could be prepared via zirconocene-mediated ring contraction of the properly functionalized vinyl carbohydrate 11 derived from arabinose, a widely available and inexpensive starting material (Figure 2.3).

Figure 2.3: Retrosynthetic analysis.

Particular emphasis in this chapter will be placed on gaining proper understanding of those factors that control the stereoselectivity of the oxygen extrusion process in the conversion 11→10.
The unusual structural features incorporated in mycoepoxydiene (1) are well suited to be rapidly and efficiently constructed via zirconocene-mediated carbohydrate ring contraction.

The discovery that the highly reactive complex 13 can be readily generated in situ simply by warming a solution of 12 in toluene or THF \(^5^4\) has greatly facilitated access to this useful reagent, often referred to as "zirconocene" and depicted simply as "Cp₂Zr". \(^5^5^5^8\) One of the key properties of 13 is its ability to enter ligand exchange with
unsaturated compounds. If the substrate is an allylic ether, the high oxophilicity of the zirconium atom subsequently manifests itself via β-elimination of the alkoxy group as reflected in 14 with formation of the nucleophilic allylzirconocene 15 (Figure 2.4). This process has been touted as an effective and practical method for the deprotection of allyl groups.

![Chemical structures](image)

**Figure 2.5**: Ring contraction of 16 and 19.

The Taguchi group has demonstrated in a clever extrapolation of this reaction that 5-vinylpyranosides such as 16 are chemically transformed under the influence of “Cp₂Zr”
and boron trifluoride etherate into cis-vinylcyclopentanols.\(^{63}\) The diastereodifferentiation is believed to be operational in intermediate 17, where the stereoselectivity is apparently dictated by nonbonded steric interactions (Figure 2.5).\(^{63}\)

This promising chemical transformation encouraged us to examine the capacity of this process to transform 4-vinylfuranosides into vinylcyclobutanols such as 19→20 and 21. The low yields and modest stereocontrol sometimes seen in the few examples heretofore reported must obviously be improved if applications to targeted synthesis are to be accomplished (Figure 2.5). In their initial work involving vinylpyranosides such as 16, Taguchi et al. convincingly demonstrated that the substituents residing in C-3, C-4 and C-5 exert significant control over the stereochemical course of the ring contraction due to the preference for the quasi-equatorial positions of the substituents in the product-determinative transition state (see 17). Their examination of vinylfuranosides was substantially less defining, a fact that led us to clarify matters for this particular process. Substrates similar to 19 were designed in order to clarify several important features of this useful enantioselective method for obtaining enantiopure functionalized cyclobutanes.

4) OPTIMIZATION OF THE RING CONTRACTION REACTION

Vinyl carbohydrates 22 and 23 possess cis substituents at C-2 and C-4, contrary to 19 where these substituents offer a trans relationship (Figure 2.6). It was therefore
interesting to investigate this cis relationship and its effect on both the selectivity and yield. D-glucose was transformed into diol 24 in five steps. Application of the Filkenstein reaction to ditosylate 25 afforded the terminal olefin 26. Stepwise introduction of the methyl acetal (see 27) and SEM group was next accomplished efficiently, giving rise to 22. D-arabinose was converted in two steps into alcohol 28, which was deoxygenated to give 31. Oxidation to the corresponding aldehyde followed by Wittig olefination produced olefin 32.

![Figure 2.6: Access to vinyl carbohydrates 22 and 23.](image-url)
Vinyl carbohydrate 22 was then submitted to the ring contraction conditions. Upon exposure of 22 to \( \text{Cp}_2\text{Zr} \), a 1:3 mixture of 33 and 33' was generated in 64% combined yield. Since both anomers react, it would appear reasonable to rationalize this product distribution in terms of the faster rate of cyclization within transition state 34 relative to 35 (Figure 2.7).

Figure 2.7: Ring contraction of 22.

The similar ratio obtained between 33 and 33' in comparison to 20 and 21 suggests that the relative position of the substituents at C-2 and C-4 is not determining the stereochemical outcome of the ring contraction. It was anticipated that the ring
The contraction of 23 would have given the same diastereoselectivity with \textit{ent-33} and \textit{ent-33'} as products. The major element of diastereocontrol might be the substituent at C-3 for the formation of cyclobutanol. A case where a \(\beta\)-oriented OPMB substituent at C-3 was next examined. Diacetonide 36 was readily available from \(D\)-glucose. \(^{69}\) Careful hydrolysis \(^{70}\) of 36 gave diol 37, which was subsequently converted into the corresponding olefin 39 \textit{via} ditosylate 38. Stepwise introduction of the methyl acetal (see 40) and SEM groups afforded the desired vinyl carbohydrate 41 (Figure 2.8).

When vinyl carbohydrate 41 was subjected to the ring contraction, two important features emerged (Figure 2.9). The first was that only the \(\alpha\)-anomer reacted. Secondly,
the process was highly stereoselective, giving rise to 42 (98% de) in 35% yield. Since equilibration of the β-anomer of 41 with its α form occurs readily, the overall conversion to 42 after one additional recycling operation yields the desired product in an acceptable yield. These results brought into focus the fact that transition states 43 and 44 are no longer balanced energetically as in the case of 34 and 35. Presumably the adoption of 44 is totally disfavored as a consequence of nonbonded interactions between the newly introduced OPMB substituent and the allylic methylene group positioned α to zirconium. A relative point made evident in Figure 2.9 is that a 3β-oxygenated substituent as in 41 promotes reaction via 43, a transition state otherwise disfavored at a lower level of functionalization (cf 34).

![Figure 2.9: Ring contraction of 41](image-url)
It appeared that the glucose configuration at C-2 and C-3 was a mismatch for the favored transition state 43. A highly matched scenario was possible with recourse to D-arabinose, where the C-2 and C-3 substituents are respectively opposite to the C-2 and C-3 substituents in D-glucose. The known alcohol 28 was protected as its PMB ether 45. Deprotection of the TBDPS ether (see 46), oxidation and Wittig olefination provided olefin 47. Formation of the methyl acetal 48 and SEM protection of the corresponding alcohol afforded vinyl carbohydrate 49 (Figure 2.10).

When 49 was exposed to “Cp₂Zr” and boron trifluoride etherate, it underwent a
smooth ring contraction to deliver only alcohol 50 in an unoptimized yield of 54%. As predicted, a reversal in the configurations at C-2 and C-3 leads to a switchover in the operational transition state for cyclobutane bond formation. We now see that 51 is so sterically disadvantaged relative to 52 that is inoperative at a detectable level (Figure 2.11).

The yield for the conversion of 49→50 has been improved to 61% by omitting the boron trifluoride etherate co-reagent and stirring the reaction mixture at 45 °C for an additional 3 hours (see Experimental). This optimized procedure may extend the range
of protecting groups that may be employed and lead to enhancement of the reaction efficiency.

In conclusion it was found that the use of arabinose rather than glucose as a precursor to a 4-vinyl carbohydrate such as 49 doubled the yield for the ring contraction to 70% (further optimization will be discussed later). Since both enantiomers of arabinose are available at similar costs both enantiomers of cyclobutanols may be obtained.

5) EN ROUTE TO THE BICYCLIC KETONE

The stability of the PMB and SEM groups is essential in our case for the completion of the synthesis.

Figure 2.12: Synthesis of 54.
The SEM ether should serve via prior coordination as a directing group in order to accomplish the desired stereoconversion to acetylene 54 (Figure 2.12). This type of eventuality has been observed previously in rather different contexts. Numerous attempts to oxidize cyclobutanol 22 to ketone 53 failed. The mildness and the neutrality of those conditions associated with o-iodoxybenzoic acid (IBX) proved to be the most efficient for the oxidation to 53 in quantitative yield. Our intent at this point was to take advantage of the well recognized kinetic stability of 2-vinylcyclobutanones to acidic conditions and the ability of this class of molecules to react smoothly with organometallic reagents without double bond migration. The triple bond was introduced by means of lithium trimethylsilylacetylide and the resulting alkoxide was quenched with PMBCl in 54% yield. Only one diastereoisomer was detected by $^1$H NMR and TLC analysis during this transformation. However extensive nOe studies could not prove the configurational status of the quaternary carbon. For our purposes, alcohol 22 was not an ideal substrate to proceed with in the synthesis, since it was the minor product in the ring contraction process. Enough cyclobutanol 42 led us to start our quest for the bicyclic ketone 7. Alcohol 42 was oxidized with DMP in the presence of NaOAc and molecular sieves to provide the corresponding ketone in quantitative yield (Figure 2.13). Interestingly, IBX led to extensive decomposition. The resulting ketone was attacked by lithium trimethylsilylacetylide to produce tertiary alcohol 55. Again, the stereochemistry of the newly formed quaternary center could not be assigned by NMR. Nevertheless, the SEM protecting group was removed by means of MgBr$_2$ and nitromethane in ether to afford 56 in 95% yield. The TMS group was removed with K$_2$CO$_3$/MeOH in 98% yield and gave rise to the key diol 57. The stage for the
silver ion-catalysed ring closure had now been set. Alkali metal hydroxides and basic silver salts have been reported to serve as efficient catalysts for the regiospecific intramolecular addition of various acetylenic alcohols.\(^{81-83}\) In our case the 5-endo-dig cyclization is feasible because the acetylenic system provides an orbital that is available for the nearly planar mode approach.\(^{84,85}\) The success of this utilitarian transformation relies on the proper setting of the quaternary center.

![Diagram](image)

Figure 2.13: Access to 57.

If the acetylenic moiety added syn to the OSEM substituent, alcohol 57 under the influence of \(\text{Ag}_2\text{CO}_3\) should give rise to 3-hydroxy-2,3-dihydrofuran 58. The heat associated with the cyclization should also promote a [3,3]sigmatropic rearrangement.
to afford the desired ketone 7. If the same addition occurs anti to the OSEM substituent, the silver salt would have no effect and diol 57 should rearrange thermally to ketone 59 via a retro-ene reaction (Figure 2.14). Experimentally, upon heated in refluxing benzene, diol 57 was quantitatively rearranged to 59. This disappointment underlined the fact that the SEM ether is not an appropriate directing group. Thus, it was apparent that installation of the quaternary center required an alternative approach.

![Figure 2.14: Fate of compound 57.](image)

For this purpose other substrates and conditions were designed and tried. In order to optimize yields, the PMB ether was replaced by a TBDPS ether, a notorious stable protecting group. Hence the known alcohol 60 was protected as a TBDPS ether. Deprotection of the pivaloate ester followed by oxidation and Wittig olefination
provided olefin 63. Formation of the methyl acetal and protection of the remaining hydroxy group as a SEM ether afforded vinyl carbohydrate 65. The SEM ether was chosen once again for its stability towards the ring contraction conditions and for its ease of removal.

\[ \text{D-arabinose} \rightarrow \begin{array}{c} \text{OPiv} \\ \text{60} \end{array} \xrightarrow{\text{TBDPSCI}} \begin{array}{c} \text{61} \\ \text{DIBAL-H} \rightarrow 93\% \end{array} \]

\[ \begin{array}{c} \text{OTBDPS} \\ \text{62} \end{array} \xrightarrow{\text{1) Swern}} \begin{array}{c} \text{HCl/MeOH} \rightarrow 99\% \end{array} \xrightarrow{\text{2) Wittig}} \begin{array}{c} \text{OTBDPS} \\ \text{63} \end{array} \xrightarrow{\text{HCl/MeOH}} \begin{array}{c} \text{OMe} \\ \text{64} \end{array} \]

\[ \text{SEMCI, iPr}_{2}\text{NEt} \rightarrow \begin{array}{c} \text{OMe} \\ \text{OSEM} \\ \text{OTBDPS} \\ \text{65} \end{array} \xrightarrow{\text{"Cp}_2\text{Zr"}, \text{then BF}_3\text{OEt}_2 \text{ 61\%}}} \begin{array}{c} \text{TBDPSO} \\ \text{OSEM} \\ \text{66} \end{array} \]

Figure 2.15: Access to cyclobutanol 66.

Classical conditions for the ring contraction yielded cyclobutanol 66 as a single diastereoisomer in 61% yield, whereas an optimized reaction without the Lewis acid afforded 66 in 68% yield (Figure 2.15).
<table>
<thead>
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<th>Nucleophile</th>
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<th>Temperature</th>
<th>Additive</th>
<th>Results</th>
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<td></td>
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<tr>
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<td>MAD</td>
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<td>-40</td>
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<td>20% of 69, 15% of 68</td>
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</tbody>
</table>

Table 2.1: Formation of 68 vs 69.
Alcohol 66 was oxidized to ketone 67, thereby setting the stage for the nucleophilic attack of lithium trimethylsilylacetylide. Various conditions were examined in an attempt to reverse the diastereoselectivity previously observed (Table 2.1). This study suggested that methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide (MAD) may play a role in the diastereoselectivity. The bulky Lewis acid coordinates to the carbonyl of the ketone on the less hindered face of the molecule at low temperature. It was necessary to warm the reaction mixture to see some additional product appearing. Nevertheless it seemed that MAD, at higher temperatures, had more affinity for the oxygen atoms present on the SEM ether.

![Chemical Structures](image.png)

Figure 2.16: Formation of compound 72.

This shift permitted the attack of the nucleophile on the undesired face of the ketone. The diastereoselectivity was improved by operating at -40°C. The increased
diastereoselectivity was met with a reduction in yield to an unsatisfactory 15%. The stereochemistry of alcohol 69 was assigned chemically. The SEM ether protecting group was removed using MgBr₂ (see 70) and the TMS ether was removed using K₂CO₃ in methanol to give rise to diol 71 which upon heating gave the retro-ene product 72 (Figure 2.16).

Employment of MAD seemed obvious for enabling access to alcohol 68. The SEM ether, with its two coordinating oxygen atoms was not compatible with MAD at temperatures conductive to obtaining the desired diastereocontrol and was replaced by a TBS ether. Its steric hindrance should force the MAD complexing agent to chelate the ketone carbonyl on the opposite side, thereby causing the nucleophilic attack to occur on the desired face of the double bond. Alcohol 64 was protected with TBSOTf to give rise to vinyl carbohydrate 73. Interestingly, the ring contraction using “Cp₂Zr” followed by BF₃.OEt₂ in THF afforded 74 in a consistent 10% yield. The use of toluene as solvent and quenching of the reaction mixture at -20 °C (rather than at 0 °C) with boron trifluoride etherate increased the yield of alcohol 74 to 58% and an unexpected 15% yield of diastereoisomer 75 (Figure 2.17). The diastereoselectivity observed in this case suggested that in toluene the ring contraction operates via the transition states 76 and 76’. The kinetically favored product 74 (4:1 ratio) now suffers from the largest nonbonded interactions. The OTBS substituent is far bulkier than an OSEM or OBn appendage. The consequence is that the enthalpy of activation for 76 and 76’ are now very close in energy, which bring into consideration the influence of the C-2 substituent. It is also important to understand the role of the solvent. Toluene appeared to be superior to THF when both transitions state are very high in energy.
(like 76 and 76*). Nevertheless, the use of toluene rather than THF in the ring contraction of 28 and 49 did not change the yields or the diastereoselectivity.

Figure 2.17: Ring contraction of compound 73.

In an earlier study, compound 77 failed to undergo ring contraction in THF. At that time it was difficult to rationalize this unsuccessful reaction. It would be interesting to attempt the same reaction in toluene. Without any C-3 substituent and a very bulky
OTBDPS substituent at C-2, would the transition state 78 be kinetically favored over 79 (Figure 2.18) and deliver exclusively cyclobutanol 80 rather than 81?

![Chemical structures](image)

Figure 2.18: Ring contraction of compound 77.

We then examined an alternative approach for the installation of the quaternary center. From the study conducted with alcohol 66, it was clear that employing MAD would be mandatory. It is known from the literature that MAD favors axial attack on cyclohexanone systems, contrary to cyclopentanone system where its addition does not influence the diastereoselectivity. No example has been described with cyclobutanones such as 82 (Figure 2.19). Also of principle concern was the choice of
solvent. As in other cases,⁹¹ the reaction diastereoselectivity in this instance could vary as a function of co-solvents (such as tertiary amines) and additives (LiBr), both of which are known to play a role in controlling the state of aggregation of the lithium nucleophile.⁹² Diamine ligands such as TMEDA and donating solvents like THF promote dimer formation, whereas tetrameric aggregates prevail when ether and tertiary amines are employed. Unlike Carreira, we were unable to prevent the exclusive equatorial attack of lithium trimethylsilylacetylide when switching solvent systems from THF/TMEDA to ether/Me₃N. Nevertheless, when recourse was made to the combination MAD/toluene, 8₃ and 8₄ were formed equally in a combined 50% yield. The use of a lanthanide metal such as Ce or Yb⁹³ did not affect the stereoselectivity as anticipated, but increased the overall yield. Finally, premixing MAD and ketone 8₂ exclusively at -78 °C for one minute followed by cannulation of this bright orange solution into ten equivalents of cerium trimethylsilylacetylide afforded in 40% isolated yield of alcohol 8₃, in addition to a 20% yield of 8₄. Increasing the premixing time of MAD and 8₂ lowered the diastereoselectivity of the reaction. The 2:1 ratio of alcohols 8₃ and 8₄ indicates that MAD plays a substantial role to override the kinetically favored equatorial attack. The bigger methylaluminum bis(2,4,6-tri-tert-butylphenoxide (MAT) Lewis acid ⁴⁰ did not improve this ratio. The stereochemistry of alcohol 8₃ was assigned chemically when it underwent oxy-Cope rearrangement upon heating to give rise to ketone 8₅. With the proper stereochemistry of the quaternary center established in this way, few steps remained to gain access to our precursor for the cyclization. Removal of the TBS proved to be an unexpected challenge: fluoride ion sources such as TBAF, TBAF/silica gel, HF.pyr, CsF, KF/18-cr-6, NH₄F/MeOH were ineffective on
either TMS, TBS or TBDPS. Low yields of the desired alcohol 86 were obtained when TBAF/BF$_3$.OEt$_2$ was employed. Deprotection via acidic conditions such as 1% HCl/MeOH afforded the desired diol 86 in quantitative yield. Noteworthily PPTS/MeOH had no effect. Again, TMS was cleanly cleaved with K$_2$CO$_3$ to provide the cyclization precursor 87.

![Chemical structures](image)

Figure 2.19: Formation of compounds 85 and 87.

The silver mediated cyclization was then examined on diol 87. Many silver salts were used in order to initiate the transformation 87→88 such as Ag$_2$CO$_3$, 85
AgNO₃, AgOAc, AgOBz or Ag₂O, but none of them produced the desired alcohol 88 (Figure 2.20). The only observed product was the heat-induced oxy-Cope product 89. Addition of HgCl₂ or Hg(OAc)₂ to 89 to induce a Michael addition of the free alcohol to provide the desired bicyclic ketone 90 was an illustration of the limitation of this process.

Figure 2.20: Attempted silver-mediated cyclization.
6) SYNTHESIS OF THE SIDE CHAIN

In our first approach, consideration was given to the completion of the lactone ring via palladium-catalysed carbonylation of vinyl iodide 91 to obtain lactone 92 (Figure 2.21). For this purpose, aldehyde 93 was synthetized from protected D-glyceraldehyde 94 available in two steps from mannitol. Stork-Wittig olefination of 94 provided the light-sensitive Z-vinyl iodide 95 in 70% yield. Acidic hydrolysis of the acetonide with TFA gave diol 96. The primary alcohol of diol 96 was selectively protected as a pivaloate ester and the secondary alcohol was then protected as its TBS ether to give rise to iodide 98. Reductive cleavage of the ester group produced alcohol 99, which was oxidized to the corresponding aldehyde 93 with Dess-Martin periodinane. Unfortunately, the base sensitivity of this highly functionalized aldehyde precluded us for employing this building block for the lactone moiety.

A new aldehyde 100 was prepared, which was believed to be more tolerant toward basic reagents. Thus, (-)-menthyl-(S)-p-toluenesulfinate (101) was transformed into thiazolyl ester in a manner parallel to that developed by Solladié in the enantiomeric series. The β-keto sulfoxide 102 was next stereoselectively reduced with Dibal-H and the resulting (R) alcohol 103 was protected by a TBS group to give compound 104. After a Pummerer rearrangement, the product 105 was subjected to desulfurization with Raney
nickel to yield acetate 106. Finally, the acetate was reduced with Dibal-H and oxidized to the corresponding aldehyde 107. The known Dondoni method, involving the addition of 2-(trimethylsilyl)thiazole (2-TST) to α-hydroxy aldehydes usually gives mainly the anti-1,2-diol. However previous work in Solladié's laboratory as well as a more recent report from Dondoni showed indeed that the syn-1,2-diol could also be obtained. Treatment of aldehyde 107 with 2-TST gave exclusively the syn diol 108.
Further protection of syn-1,2-diol 108 by reaction with TBSOTf not only effected the protection of the secondary alcohol but also facilitated a transesterification from tert-butyl ester into TBS ester. Reductive elimination of the thiazole moiety with Mel/NaBH₄ and HgCl₂ in sequence provided crude aldehyde 100 which was used without purification (Figure 2.22).

Figure 2.22: Synthesis of aldehyde 100.
It was important at this stage to ensure the effectiveness of the aldol condensation between aldehyde 100 and norcamphor, a model substrate which is related to our desired

![Chemical Structure]

\[ \text{100} \xrightarrow{\text{LiHMDS}} \text{110} \]

nOe from NOESY experiment

Figure 2.23 : Synthesis and nOe of compound 110.

ring system. While there is virtually no information concerning oxabicyclo[4.2.1]nonanones, a considerable array of facts surrounds their more highly strained 7-oxanorbornanone counterparts. When norcamphor was treated with
LiHMDS at $-5 \, ^\circ C$ followed by the addition of aldehyde \textbf{100} at $-78 \, ^\circ C$, only one aldehyde product was detected in an unoptimized 40% yield. Extensive NOe studies agreed with structure \textbf{110} (Figure 2.23).

8) CONCLUSION AND FUTURE WORK

It was found that ketone \textbf{7} might be accessible via silver-catalyzed ring contraction of cyclobutanol \textbf{110}, followed by thermal [3,3] sigmatropy (Figure 2.24). Only few data, such as IR and $^1$H NMR were collected which of course is the beginning of the full characterization of this new ketone \textbf{7}. It is not clear why would \textbf{110} gave \textbf{7} when under the same condition \textbf{87} produced \textbf{89} and not \textbf{90}. The only difference is a PMB ether \textit{versus} a TBDPS ether.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure224.png}
\caption{Access to 7.}
\end{figure}
It is not the first time that a protecting group affects the course of a reaction and the fate of a synthesis. Future effort should focus on the reproducibility of gaining access to 7. The end game has the benefit of being approachable from several directions. For example, one option is to introduce the conjugated diene subunit from 7 (Figure 2.25). The protocol involves initial deprotection of the alcohol and subsequent reaction with 2,4-dinitrobenzenesulfenyl chloride.\textsuperscript{113, 114}

Figure 2.25: Proposed end game for the completion of mycoepoxydiene (1).

A [2,3]sigmatropic rearrangement will be set into motion, thereby generating an allylic sulfoxide that will experience \textit{in situ} elimination. The end product would be
dienone 111. The subsequent aldol coupling of the lithium enolate of 111 can be expected to utilize the sterically least congested transition state alignment depicted as 112 and result directly in the formation of 113 via cyclization as observed for 109. Sodium borohydride reduction of this advanced intermediate will proceed from the exo direction to establish an endo carbinol that will be triflated and displaced in Sn2 fashion by lithium dimethylcuprate to produce 114. Subsequent conversion to the diacetate will allow for the β-elimination of acetic acid and formation of mycoepoxydiene (1).

Implementation of the underutilized zirconium-mediated ring contraction of 4-vinyl carbohydrates has been described. Arabinose in both enantiomeric forms, plentiful and inexpensive, is the sugar of choice to conduct in good yield the oxygen extrusion process. Higher temperatures for this reaction resulted in the production of more heavily substituted cyclobutanes without the use of a Lewis acid, which should broaden the range of protecting group used so far; toluene rather than THF was more conductive to the ring contraction when bulky groups reside at the C-2 position. Also and more importantly, the stereochemical outcome of this transformation can be predicted according to the proposed transition state. During this partial synthesis, it was showed that MAD could be effective on cyclobutanone systems to direct 1,2-addition. Also, if 7 could be accessed via 110, it would be the first example of tandem 5-endo dig cyclization/oxy-Cope rearrangement. The last sigmatropy has no parallelism at present with past application of this isomerization process.
Compound 25

To a solution of 1,2-O-isopropylidene-3-deoxy-α-D-xylo-hexofuranose (24) (20 mg, 0.095 mmol) in 1 mL of pyridine was added TsCl (110 mg, 6 eq). The solution was stirred at 40 °C for 20 h. Water and EtOAc were added. The separated aqueous layer was extracted with EtOAc. The combined organic phases were washed with 1M HCl, saturated NaHCO₃ solution and brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/ether 1:1). The product 25 was obtained as a white foam (30 mg, 57%) : [α]°D
-39 (c 1.8, CHCl₃), IR (CH₂Cl₂, cm⁻¹) 1265; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 5.64 (d, J = 3.8 Hz, 1H), 4.95-4.91 (m, 1H), 4.71-4.67 (m, 1H), 4.34-4.21 (m, 3H), 2.46 (s, 3H), 2.44 (s, 3H), 2.23-2.28 (m, 1H), 2.08-2.01 (m, 1H), 1.45 (s, 3H), 1.28 (s, 3H) ; ¹³C NMR (75 MHz, CDCl₃) δ 145.2, 144.8, 133.4, 132.1, 129.9 (2C), 129.5 (2C), 128.2 (2C), 128.0 (2C), 113.1, 106.2, 80.2, 79.0, 77.6, 68.4, 32.7, 26.8, 21.6 (2C) ; HRMS (El) m/z (M-CH₃)⁺ calcd for C₂₂H₂₅O₅S₂ 497.0938, obsd 497.0943.

Compound 26

To a solution of ditosylate 25 (1.3 g, 2.5 mmol) in 10 mL of dry acetone was added NaI (3.8 g, 10 eq). The clear solution turned dark red upon being heated at reflux overnight. The mixture was poured into water and ether was added. The separated aqueous layer was extracted with ether. The combined dark organic phases were washed with saturated solutions of Na₂S₂O₅, NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography (hexanes/ether 5:1).

The product was obtained as a colorless oil (388 mg, 90\%); \([\alpha]_D^{21} -20\) (c 2.1, CHCl₃); IR (neat, cm⁻¹) 3055, 2986, 2940, 1476, 1374, 1265, 1240, 1212; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 6.16-6.04 (m, 1H), 5.78 (d, \(J = 3.9\) Hz, 1H), 5.20 (d, \(J = 18.4\) Hz, 1H), 5.08 (d, \(J = 11.5\) Hz, 1H), 4.75-4.72 (m, 1H), 4.59-4.54 (m, 1H), 2.32-2.22 (m, 1H), 2.07 (ddd, \(J = 13.6, 2.8, 1.3\) Hz, 1H), 1.53 (s, 3H), 1.30 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 139.3, 115.6, 112.3, 106.5, 81.5, 81.0, 37.3, 26.8, 26.1; HRMS (El) \(m/z\) (M⁻) calcd for C₉H₁₄O₃ 169.0863, obsd 169.0854.

Compound 27

A solution of acetonide 26 (388 mg, 2.28 mmol) in 10 mL of a 5% solution of HCl in MeOH was heated at reflux for 2 h. The reaction mixture was cooled to rt and NaHCO₃ was added until no more bubbling was observed. The suspension was dried under...
vacuum. The solid was taken up in CH2Cl2 and MgSO4 was added. After filtration and concentration, the resulting residue was purified by flash chromatography (hexanes/Et2O 10:3). The product was obtained as a colorless oil (266 mg, 80%); [α]D^21-27 (c 0.9, CHCl3); IR (neat, cm^-1) 3454; ^1H NMR (300 MHz, CDCl3) δ 6.04-5.93 (m, 1H), 5.31 (d, J = 17.4 Hz, 1H), 5.15 (d, J = 10.3 Hz, 1H), 4.91 (s, 1H), 4.60-4.54 (m, 1H), 4.24-4.21 (m, 1H), 3.37 (s, 3H), 2.54-2.45 (m, 1H), 1.72-1.63 (m, 1H + 1 OH); ^13C NMR (75 MHz, CDCl3) δ 139.3, 115.5, 109.6, 78.8, 76.3, 54.6, 38.8.

Compound 28

To a suspension of KH (35 % in mineral oil, 164 mg, 3 eq) in 5 mL of THF stirred at 0 °C was added via cannula a solution of alcohol 27 (70 mg, 0.48 mmol) in 5 mL of THF. After 1 h at rt, SEMCl was added neat (0.254 mL, 3 eq). The red suspension turned yellow after the addition. After 1 h at rt, a saturated solution of NaHCO3 was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with a saturated solutions of NaHCO3 and brine, dried over Na2SO4 and concentrated. The residue was purified by flash chromatography (hexanes/ether 20:1). The product 28 was obtained as a colorless oil (102 mg, 80% for β-anomer, and 10 mg, 8% for the α-anomer).
For the β anomer:

\[
\alpha^2 -25 \text{ (c 0.9, CH}_2\text{Cl}_2\text{); IR (CH}_2\text{Cl}_2, \text{cm}^{-1}) \text{ 3053, 2986, 1440, 1422, 1264, 1229 ; } ^1\text{H NMR (300 MHz, CDCl}_3\text{) } \delta 5.97-5.85 (m, 1H), 5.23 (d, J = 17.1 Hz, 1H), 5.09 (d, J = 10.2 Hz, 1H), 4.95 (s, 1H), 4.67 (s, 2H), 4.52-4.45 (m, 1H), 4.12 (dd, J = 6.4, 3.2 Hz, 1H), 3.64-3.56 (m, 2H), 3.33 (s, 3H), 2.46-2.37 (m, 1H), 1.66 (ddd, J = 13.2, 6.4, 3.2 Hz, 1H), 0.94-0.88 (m, 2H), 0.00 (s, 9H) ; ^13\text{C NMR (75 MHz, CDCl}_3\text{) } \delta 138.7, 115.9, 108.1, 94.0, 81.5, 78.9, 65.3, 54.5, 37.1, 17.9, -1.5 (3C).
\]

For the α-anomer:

\[
\alpha^2 +12 \text{ (c 1.0, CH}_2\text{Cl}_2\text{); IR (CH}_2\text{Cl}_2, \text{cm}^{-1}) \text{ 3053, 2986, 1440, 1422, 1264, 1229 ; } ^1\text{H NMR (300 MHz, CDCl}_3\text{) } \delta 5.87 (ddd, J = 17.7, 10.3, 7.3 Hz, 1H), 5.23 (d, J = 17.7 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 4.84 (d, J = 4.2 Hz, 1H), 4.77 (s, 2H), 4.448-4.42 (m, 1H), 4.15-4.07 (m, 1H), 3.77-3.57 (s, 3H), 2.44-2.35 (m, 1H), 1.97-1.27 (m, 1H), 0.98-0.92 (2H), 0.03 (s, 9H) ; ^13\text{C NMR (75 MHz, CDCl}_3\text{) } \delta 140.1, 115.9, 101.4, 94.9, 78.1, 77.6, 65.5, 54.6, 34.3, 18.2, -1.5 (3C).
\]
To a solution of alcohol 28 (26 g, 61 mmol) and CS$_2$ (14 mL, 4 eq) in 300 mL of benzene being stirred at 0 °C was added n-Bu$_4$NSO$_4$ (17 g, 1.1 eq) and carefully 200 mL of a 40% aqueous solution of NaOH. The solution turned dark red. After 30 min, MeI (34 mL, 10 eq) was added. The solution turned yellowish. After 1 h, ether and water were added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with a saturated solution of NaHCO$_3$ and brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash chromatography (hexanes/ether 20:1) and afforded the desired xanthate 29 as a yellowish oil (25 g, 80 %); [α]$^\circ$$_D$-13 (c 3.5, CHCl$_3$); IR (benzene, cm$^{-1}$) 3089, 3070, 3034, 1959, 1815, 1427, 1206, 1112, 1062, 1035; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.73-7.67 (m, 4H), 7.44-7.37 (m, 6H), 6.10 (s, 1H), 5.95 (d, J = 3.9 Hz, 1H), 4.70 (d, J = 4 Hz), 4.45-4.41 (m, 1H), 3.92-3.85 (m, 2H), 2.62 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.08 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 214.5, 135.4 (4C), 133.0 (2C), 129.6 (2C), 127.7 (4C), 112.6, 105.9, 85.2, 84.3, 63.5, 26.8 (3C), 26.4, 25.8, 19.4, 19.1; HRMS (EI) m/z (M$^+$) calcd for C$_{26}$H$_{34}$O$_3$S$_2$Si 518.1616, obsd 518.1621.

Anal. Calcd for C$_{26}$H$_{34}$O$_3$S$_2$Si: C, 60.21; H, 6.61. Found: C, 60.31; H, 6.69.
Compound 30

To a solution of xanthate 29 (25 g, 48 mmol) in 300 mL of refluxing benzene was added a solution of AIBN (1.1 g, 10 mol %) and nBu₃SnH (20 mL, 1.1 eq) in 100 mL of benzene. After 5 h at reflux, the volatiles were evaporated. The residue was purified by flash chromatography (hexanes/ether 20:1) and yielded 16.3 g (80%) of 30 as a colorless oil; \([\alpha]_D^{19} + 14 \ (c 1, \text{CHCl}_3)\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.75-7.69 \text{ (m, 4H)}\), 7.46-7.36 \(\text{ (m, 6H)}\), 5.80 \(\text{ (d, } J = 4 \text{ Hz, 1H)}\), 4.76-4.72 \(\text{ (m, 1H)}\), 4.34-4.28 \(\text{ (m, 1H)}\), 3.89-3.79 \(\text{ (m, 2H)}\), 2.32-2.27 \(\text{ (m, 1H)}\), 2.21-2.11 \(\text{ (m, 1H)}\), 1.35 \(\text{ (s, 3H)}\), 1.30 \(\text{ (s, 3H)}\), 1.09 \(\text{ (s, 9H)}\); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 135.9 \text{ (4C)}\), 133.5 \(\text{ (2C)}\), 129.6 \(\text{ (2C)}\), 127.7 \(\text{ (4C)}\), 114.8, 106.2, 81.6, 80.7, 66.7, 33.9, 26.9, 26.6 \(\text{ (3C)}\), 25.6, 19.30.

Compound 31

To a solution of silyl ether 30 (53 mg, 0.13 mmol) in 5 mL of THF was added a 1M solution of TBAF (1.1 eq) in THF at rt. After 1 h the volatiles were evaporated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 1:1) and afforded alcohol 31 (19 mg, 85%) as a colorless oil; \([\alpha]_D^{21} + 23 \ (c 1, \text{CHCl}_3)\); IR (neat, cm\(^{-1}\)) 3500; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 5.81 \text{ (d, } J = 3.9 \text{ Hz, 1H)}\), 4.77-4.74 \(\text{ (m, 1H)}\), 4.36-4.28 \(\text{ (m, 1H)}\), 3.83 \(\text{ (dd, } J = 11.5, 8 \text{ Hz, 1H)}\), 3.61 \(\text{ (dd, } J = 11.5, 4 \text{ Hz, 1H)}\), 2.35 \(\text{ (br s, 1 OH)}\), 2.25-2.16 \(\text{ (m, 1H)}\), 1.99 \(\text{ (dd, } J = 14.2, 2.6 \text{ Hz, 1H)}\)
Compound 32

To a solution of alcohol 31 (40 mg, 0.30 mmol) in 5 mL of DCM being stirred at 0 °C was added 55 mg of 4Å MS and 55 mg of PCC (2 eq). After 12 h at rt, ether was added. The suspension was filtered and poured into brine. The separated organic layer was dried and concentrated. The crude aldehyde was dissolved in 5 mL of THF and transferred via cannula to a freshly suspension of PPh₃=CH₂ in 5 mL of THF stirred at −20 °C, prepared as follows: to a suspension of PPh₃CH₃I (137 mg, 0.39 mmol) being stirred at 0 °C was added slowly a solution of KHMDS in toluene (0.78 mL, 0.39 mmol). After 30 min at 0 °C, the aldehyde was added. The reaction was completed in 5 min and the mixture was poured in a saturated solution of NH₄Cl. The separated aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/ether 10:1) and afforded 15 mg (30%) of the desired product; [α]₂¹°+13 (c 0.6, CHCl₃); IR (CH₂Cl₂, cm⁻¹) 2987, 2925, 2856, 1612, 1514, 1373, 1248, 1073; ¹H NMR (300 MHz, CDCl₃) δ 6.13 (ddd, J = 17.4, 10.3, 7.3 Hz, 1H), 5.82 (d, J = 3.9 Hz, 1H), 5.23 (d, J = 17.4 Hz, 1H), 5.11 (d, J = 10.3 Hz, 1H), 4.77-4.74 (m, 1H), 4.63-4.57 (m, 1H), 2.29 (ddd, J = 14.2, 8.4, 5.9 Hz, 1H), 2.10-2.05 (m, 2H), 1.55 (s, 1H), 1.55 (s, 3H), 1.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 112.3, 106.4, 81.7, 80.7, 65.0, 33.1, 27.0, 25.9.
Compounds 33 and 33'

To a stirred solution of Cp₂ZrCl₂ (137 mg, 0.486 mmol, 1.3 eq) in 3 mL of THF at -78 °C was added dropwise a solution of nBuLi (0.60 mL, 0.97 mmol, 1.6 M in hexane, 2.6 eq) in hexane. After 1 h, the clear solution had become a yellowish suspension. A solution of 28 (102 mg, 0.372 mmol) in 3 mL of THF was added via cannula. The reaction mixture was allowed to warm to rt, stirred for 3 h, cooled in an ice bath, and treated with a solution of BF₃·OEt₂ (0.1 mL, 0.744 mmol, 2 eq) in 1 mL of THF. After warming to rt with stirring for 15 min, a 1 M solution of HCl was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with a saturated solution of NaHCO₃ and with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/ether 20:1) and afforded 32 as a colorless oil (12.5 mg, 14%) and 33 as a colorless oil (45 mg, 50%).

Minor isomer 33:

\([\alpha]_D^{21} - 11 \ (c \ 0.6, \ CHCl₃) ; \ IR \ (CH₂Cl₂, \ cm^{-1}) 3530, 2951, 1465, 1379, 1250, 1099, 1029, 908 ; \ ^1H \ NMR \ (300 MHz, CDCl₃) \ \delta \ 6.03-5.95 \ (m, 1H), 5.16 \ (d, J = 10.2 \ Hz, 1H), 5.08
(d, $J = 17.3$ Hz, 1H), 4.74-4.67 (m, 2H), 4.39 (br s, 1H), 4.15 (dd, $J = 6.8$ Hz, 6.8 Hz, 1H), 3.71-3.60 (m, 2H), 2.75-2.72 (m, 1H), 2.63 (br s, 1 OH), 2.42-2.37 (m, 1H), 2.20-2.14 (m, 1H), 1.40 (dd, $J = 13.3$, 5.6 Hz, 1H), 0.98-0.93 (m, 1H), 0.03 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 136.0, 116.6, 94.0, 72.0, 71.2, 65.9, 38.2, 31.9, 18.1, -1.4 (3C); HRMS (EI) m/z (M+1)$^+$ calcd for C$_{12}$H$_{25}$O$_3$Si 245.1572, obsd 245.1583.

Major isomer 33$^*$_:

$^\text{[a]}_D^{21}$ -23 (c 2.3, CHCl$_3$); IR (CH$_2$Cl$_2$, cm$^{-1}$) 3416, 2954, 2895, 1449, 1378, 1250, 1099, 1058; $^1$H NMR (300 MHz, CDCl$_3$) δ 6.00-5.88 (m, 1H), 5.25-5.15 (m, 2H), 4.74 (d, $J = 6.8$ Hz, 1H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.12-4.06 (m, 1H), 3.99-3.91 (m, 1H), 3.76-3.68 (m, 1H), 3.66-3.54 (m, 2H), 3.06-2.96 (m, 1H), 2.13-2.05 (m, 1H), 1.84-1.74 (m, 1H), 0.98-0.92 (m, 1H), 0.03 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 136.2, 117.4, 94.1, 79.4, 74.1, 65.4, 37.1, 26.3, 18.0, -1.4 (3C).

Anal. Calcd for C$_{12}$H$_{25}$O$_3$Si: C, 58.98; H, 9.90. Found: C, 59.05; H, 10.04.

Compound 37

To a solution of 36 (10.00 g, 27 mmol) in 200 mL of MeOH was added 2 mL of water and 10 drops of conc. HCl. After 12 h at rt, a saturated solution of NaHCO$_3$ was added. Ether served for extraction. The combined
organic phases were washed with water and brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (1:1 EtOAc/hexanes) afforded 37 (8.72 g, 95%); 

\(^1\)H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.6 Hz, 2H), 5.89 (d, J = 4.8 Hz, 1H), 4.70 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 4.8 Hz, 1H), 4.44 (d, J = 11.0 Hz, 1H), 4.20-4.10 (m, 2H), 4.05-3.99 (m, 1H) 3.80-3.75 (m, 1H), 3.78 (s, 3H), 3.66-3.60 (m, 1H), 2.58-2.55 (m, 1 OH), 2.27-2.23 (m, 1 OH) 1.47 (s, 3H), 1.40 (s, 3H) ; \(^{13}\)C NMR (75 MHz, CDCl₃) δ 159.6, 129.6, 129.0 (2C), 114.1 (2C), 111.8, 105.1, 82.0, 81.5, 79.9, 71.7, 69.3, 64.4, 55.3, 26.7, 21.0.

**Compound 38**

To a solution of 37 (9.7 g, 27.9 mmol) in 100 mL of pyridine was added TsCl (32.6 g, 17.1 mmol). The solution was stirred at 40 °C for 20 h. Water and EtOAc were added. The separated aqueous layer was extracted with EtOAc. The combined organic phases were washed with 1M HCl, saturated solutions of NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 4:1) to give 38 as a white foam (9.0 g, 50%); [α]₂⁰° +47 (c 1.8, CHCl₃) ; IR (CH₂Cl₂, cm⁻¹) 1265 ; \(^1\)H NMR (300 MHz, CDCl₃) δ 7.79 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.75 (d, J = 4.8 Hz, 1H), 5.10 (m, 1H), 4.55-4.47 (m, 3H), 4.37-4.28 (m,
4.12-4.10 (m, 2H), 3.81 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.6, 149.8 (2C), 135.9 (2C), 134.2, 129.8 (2C), 129.7 (2C), 129.7 (2C), 127.7 (2C), 123.7 (2C), 113.9 (2C), 112.4, 105.2, 81.8, 80.6, 78.2, 76.2, 72.0, 55.2, 44.1, 26.9, 26.4, 21.6 (2C).

Compound 39

To a solution of ditosylate 38 (9 g, 0.014 mol) in 100 mL of dry DMF was added NaI (20 g, 10 eq) and zinc dust (10 g, 10 eq). The clear solution turned dark red upon being heated at reflux overnight. The mixture was poured into water and ether was added. The separated aqueous layer was extracted with ether. The combined dark organic phases were washed with a saturated solutions of Na$_2$S$_2$O$_5$, NaHCO$_3$ and brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash chromatography (hexanes/ether 10:1). Product 39 was obtained as a colorless oil (5 g, 98%); [α]$^5$_D +46 (c 2.4, CHCl$_3$); IR (neat, cm$^{-1}$) 2986, 2940, 1475, 1378, 1265, 1244, 1212; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.26 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.05 (ddd, $J = 17.3, 10.2, 7.0$ Hz, 1H), 5.99 (d, $J = 4.8$ Hz, 1H), 5.45 (d, $J = 17.3$ Hz, 1H), 5.35 (d, $J = 10.2$ Hz, 1H), 4.60 (d, $J = 4.8$ Hz, 1H), 4.55 (d, $J = 11.0$ Hz, 1H), 4.47 (d, $J = 11.0$ Hz, 1H), 3.90 (d, $J = 3.7$ Hz, 1H), 3.81 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.3, 132.3, 129.5, 129.2 (2C), 118.9, 113.8 (2C), 1115.5, 104.8, 82.9, 81.5, 71.2, 55.2, 26.7, 26.2.
To a solution of 39 (7.50 g, 0.025 mol) in 100 mL of MeOH was added at 0 °C 1 mL of HCl. After 48 h at rt, a saturated solution of NaHCO₃ was added. Ether served for extraction. The combined organic phases were washed with water and brine, dried over MgSO₄, filtered, and concentrated. Flash chromatography (1:5 ether/hexanes) provided a mixture of anomers (α-anomer 2.26 g, 32% and β-anomer 1.92 g, 27%) as well as recovery of the starting material (3.20 g, 42%).

For β-anomer: [α]ᵢᵇ⁺9 +92 (c 1.0, CHCl₃); IR (neat, cm⁻¹) 3494, 2928, 1611, 1513, 1247, 1032; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.05-5.94 (m, 1H), 5.36 (d, J = 17.2 Hz, 1H), 5.29 (d, J = 10.3 Hz, 1H), 5.00 (d, 4.6 Hz, 1H), 4.63-4.50 (m, 3H), 4.23 (br s, 1H), 3.95 (dd, J = 5.5, 4.0 Hz, 1H), 3.81 (s, 3H), 3.50 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 133.8, 129.9, 129.2 (2C), 118.4, 113.7 (2C), 101.6, 84.2, 79.8, 76.7, 71.6, 71.6, 55.8, 55.2.

For α-anomer: [α]ᵢᵇ⁻23 (c 1, CHCl₃); IR (neat, cm⁻¹) 3428, 2912, 2836, 1613, 1586, 1513, 1462, 1453; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.06 (ddd, J = 17.8, 9.6, 0.7 Hz, 1H), 5.35 (br d, J = 17.8 Hz, 1H), 5.27 (d, J = 9.6 Hz, 1H), 4.80 (d, J = 2.3 Hz, 1H), 4.67-4.62 (m, 1H), 4.52 (s, 2H), 4.20 (dd, J = 4.0, 2.3 Hz, 1H), 3.92 (dd, J = 6.1, 4.0 Hz, 1H), 3.80 (s, 3H), 3.43 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 134.9, 129.7, 129.4 (2C), 105
Compound 41

A solution of alcohol 40 (100 mg, 0.36 mmol) in 5 mL of THF was transferred to a suspension of KH (122 mg, 1.07 mmol, 35% in oil) in 5 mL of THF stirred at 0 °C. After 1 h at rt, SEMCl (0.2 mL, 1.07 mmol) was added neat. After 12 h, a saturated solution of NH₄Cl was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/ether 10:1) and afforded 4 (α-anomer 80 mg (54%) and β-anomer 70 mg (46%));

For α-anomer:

\[
\begin{align*}
[\alpha]_D^{20} & -42 \text{ (c 1, CHCl}_3) ; \\
\text{IR (neat, cm}^{-1}) & 2952, 16.12, 1513, 1248, 1110 ; \\
\text{H NMR (300 MHz, CDCl}_3) & \delta 7.27 (d, J = 8.7 \text{ Hz, 2H}), 6.89 (d, J = 8.7 \text{ Hz, 2H}), 6.15-6.06 (m, 1H), 5.33 (d, J = 17.0 \text{ Hz, 1H}), 5.27 (d, J = 10.3 \text{ Hz, 1H}), 4.87 (d, J = 1.4 \text{ Hz, 1H}), 4.76-4.70 (m, 2H), 4.73-4.46 (m, 3H), 4.21-4.18 (m, 1H), 3.94 (dd, J = 5.7, 2.9 \text{ Hz, 1H}), 3.80 (s, 3H), 3.66-3.57 (m, 2H), 3.44 (s, 3H), 0.98-0.89 (m, 2H), 0.02 (s, 9H); \\
\text{C NMR (75 MHz, CDCl}_3) & \delta 159.2, 134.9, 129.8, 129.3, 118.0, 113.7, 108.2, 94.1, 84.2, 82.6, 81.8, 71.5, 65.6, 55.7, 55.2, 18.0, -1.4.
\end{align*}
\]
For β-anomer:

\[[\alpha]_D^0 +13 \text{ (c 0.4, CHCl}_3) \right\]; \text{ }^1H \text{ NMR (300 MHz, CDCl}_3) \delta 7.23 \text{ (d, } J = 8.6 \text{ Hz, 2H)}, 6.85 \text{ (d, } J = 8.6 \text{ Hz, 2H)}, 6.05-5.93 \text{ (m, 1H)}, 5.34 \text{ (d, } J = 17.1 \text{ Hz, 1H)}, 5.28 \text{ (d, } J = 10.2 \text{ Hz, 1H)}, 4.92 \text{ (d, } J = 4.3 \text{ Hz, 1H)}, 4.76 \text{ (s, 2H)}, 4.60-4.56 \text{ (m, 1H)}, 4.50 \text{ (s, 2H)}, 4.27-4.22 \text{ (m, 1H)}, 4.10 \text{ (dd, } J = 6.3 \text{, 4.3 Hz, 1H)}, 3.81-3.72 \text{ (m, 1H)}, 3.78 \text{ (s, 3H)}, 3.62-3.53 \text{ (m, 1H)}, 3.43 \text{ (s, 3H)}, 0.97-0.90 \text{ (m, 2H)}, 0.01 \text{ (s, 9H)}; \text{ }^{13}C \text{ NMR (75 MHz, CDCl}_3) \delta 159.2, 134.4, 130.0, 129.3 \text{ (2C)}, 118.4, 113.7 \text{ (2C)}, 101.0, 95.2, 81.9, 81.6, 78.1, 72.0, 65.7, 55.2, 55.2, 18.1, -1.4 \text{ (3C)}.

Compound 42

To a solution of Cp₂ZrCl₂ (110 mg, 1.3 eq) in 3 mL of THF being stirred at -78 °C was added dropwise a solution of n-BuLi (0.51 mL, 1.47 M in hexane, 2.6 eq). After 1 h the clear solution had become a yellowish suspension. A solution of 41 (78 mg, 0.20 mmol) in 3 mL of THF was added via cannula. The reaction mixture was allowed to warm to rt, stirred for 3 h, cooled in an ice bath and treated with a solution of BF₃.OEt₂ (0.05 mL, 2 eq) in 1 mL of THF was added. After warming to rt and stirring for 15 min, a 1M solution of HCl was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with saturated solutions of NaHCO₃ and brine, dried over Na₂SO₄ and
The residue was purified by flash chromatography (hexanes/ether 10:1) and afforded 42 as a colorless oil (26 mg, 35%), plus recovery of the β-anomer (41 mg, 50%); \([\alpha]_{D}^{20} = -10 \ (c \ 3.3, \ CHCl_3)\); IR (neat, \text{cm}^{-1}) 3436, 2951, 2836, 1613, 1247; \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.25 (d, \(J = 8.6\) Hz, 2H), 6.86 (d, \(J = 8.6\) Hz, 2H), 6.01 (ddd, \(J = 16.9, 11.0, 7.8\) Hz, 1H), 5.24-5.21 (m, 1H), 5.17 (s, 1H), 4.73 (d, \(J = 6.5\) Hz, 1H), 4.67 (d, \(J = 6.5\) Hz, 1H), 4.50-4.49 (m, 2H), 4.32-4.23 (m, 1H), 4.15 (dd, \(J = 8.2, 6.5\) Hz, 1H), 3.97-3.92 (m, 1H), 3.80 (s, 3H), 3.77-3.59 (m, 2H), 2.59-2.52 (m, 1H), 0.99-0.96 (m, 2H), 0.02 (s, 9H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 159.2, 133.8, 130.1, 129.3, 117.5, 113.7, 101.4, 94.6, 81.7, 77.2, 71.1, 66.2, 66.2, 55.3, 45.1, 44.9, 18.2, -1.5; FAB HRMS \text{m/z} (M+Na) calcd for C\(_{20}\)H\(_{32}\)O\(_{5}\)Si 403.1916, obsd 403.1885.

Compound 45

A solution of alcohol 28 (10 g, 23 mmol) in DMF being stirred at 0 °C was treated portionwise with NaH (1.4 g, 35 mmol, 60% in oil). After 1 h at rt, PMBCl (4.77 mL, 35 mmol) was added. The reaction mixture was stirred overnight. A saturated solution of NH\(_4\)Cl was added. The separated aqueous phase was extracted with ether. The combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated. The residue was purified by flash chromatography (hexanes/ether 10:3) and afforded the desired product 45 (4 g, 30%), and recovery of starting material (7 g, 70%); \([\alpha]_{D}^{21} = +3 \ (c \ 1.9, \ CHCl_3)\); IR (CHCl\(_3\), \text{cm}^{-1})
Compound 46

To a solution of silyl ether 45 (3.10 g, 5.7 mmol) in 20 mL of THF was added a 1M solution of TBAF (1.1 eq) in THF at 0 °C. After 3 h at 0 °C and 1 h at rt the volatiles were evaporated under reduced pressure. The H O residue was purified by flash chromatography (hexanes/EtOAc 1:1) and afforded the alcohol (1.45 g, 87 %) as a colorless oil. \([\alpha]_D^{11}+10 (c 1.4, \text{CHCl}_3)\); \(\text{IR (CHCl}_3, \text{cm}^{-1})\) 3471, 2981, 2937, 1617, 1514, 1462, 1375, 1302, 1248, 1032; \(^1\text{H NMR (300 MHz, CDCl}_3) \delta 7.26 (d, J = 8.6 \text{ Hz}, 2\text{H}), 6.88 (d, J = 8.6 \text{ Hz}, 2\text{H}), 5.90 (d, J = 4.1 \text{ Hz}, 1\text{H}), 4.67 (d, J = 4.1 \text{ Hz}, 1\text{H}), 4.57 (d, J = 11.3 \text{ Hz}, 1\text{H}), 4.49 (d, J = 11.3 \text{ Hz}, 1\text{H}), 4.20-4.15 (m, 1\text{H}), 3.96-3.95 (m, 1\text{H}), 3.81 (s, 3\text{H}), 3.74-3.70 (m, 2\text{H}), 1.53 (s, 3\text{H}), 1.34 (s, 3\text{H}); \(^{13}\text{C NMR (75 MHz, CDCl}_3) \delta 159.4, 129.5, 129.1, 113.9, 112.8, 105.6, 85.5,
Compound 47

To a solution of alcohol 46 (40 mg, 0.13 mmol) in 5 mL of DCM stirred at 0 °C was added 55 mg of 4 Å MS and 55 mg of PCC (2 eq). After 12 h at RT, ether was added. The suspension was filtered off and poured into brine. The separated organic layer was dried and concentrated. The crude aldehyde was dissolved in 5 mL of THF and transferred via cannula to a freshly prepared suspension of PPh₃=CH₂ in 5 mL of THF stirred at −20 °C, prepared as follows: to a suspension of PPh₃CH₃I (137 mg, 0.39 mmol) being stirred at 0 °C was added slowly a solution of KHMDS in toluene (0.78 mL, 0.39 mmol). After 30 min at 0 °C, the aldehyde was added. The reaction was completed in 5 min and the mixture was poured into a saturated solution of NH₄Cl. The separated aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography (hexanes/ether 10:1) and afforded 25 mg (63%) of 47; [α]_D²¹ +15 (c 1.1, CHCl₃); IR (CH₂Cl₂, cm⁻¹) 2987, 2925, 2856, 1612, 1514, 1373, 1248, 1073; ^1H NMR (300 MHz, CDCl₃) δ 7.27 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.00 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.91 (d, J = 4.0 Hz, 1H), 5.32 (ddd, J = 17.2, 1.4, 1.4 Hz, 1H), 5.17 (ddd, J = 10.4, 1.4, 1.4 Hz, 1H).
1H), 4.65 (d, J = 4.0 Hz, 1H), 4.55 (d, J = 7.9 Hz, 2H), 4.52-4.49 (m, 1H), 3.91 (d, J = 3.1 Hz, 1H), 3.81 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 159.4, 136.4, 129.5, 129.3, 116.9, 113.9, 112.9, 105.6, 86.0, 85.6, 85.2, 71.6, 55.3, 26.9, 26.4; HRMS (EI) m/z (M+) calcd for C17H22O5 306.1467, obsd 306.1467.

Compound 48

To a solution of 47 (25 mg, 0.081 mmol) in 1 mL of MeOH was added at 0 °C 4 mL of 5% HCl/MeOH. After warming to rt during 1 h, a saturated solution of NaHCO3 was added. Ether served for extraction. The combined organic phases were washed with water and brine, dried over MgSO4, filtered and concentrated. Flash chromatography (ether/hexanes 1:5) provided 48 as an inseparable mixture of anomers (23 mg, 99%).

Compound 49

A solution of alcohol 48 (100 mg, 0.36 mmol) in 5 mL of THF was transferred to a suspension of KH (122 mg, 1.07 mmol, 35% in oil) in 5 mL of THF being stirred at 0 °C. After 1 h at rt, SEMCl (0.2 mL, 1.07 mmol) was added neat and the reaction mixture was stirred overnight before the addition of a saturated solution
of NH₄Cl. The separated aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/ether 10:1) and afforded 140 mg (99%) of 49; [α]_{D}^{21} = -20 (c 0.6, CHCl₃); IR (CHCl₃, cm⁻¹) 2951, 2834, 1612, 1513, 1301, 1249, 1192, 1172, 1099; ¹H NMR (300 MHz, CDCl₃) δ 7.23 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.94-5.82 (m, 1H), 5.32-5.26 (m, 1H), 5.18-5.14 (m, 1H), 4.86 (d, J = 2.7 Hz, 1H), 4.76 (s, 2H), 4.56 (d, J = 2.4 Hz, 2H), 4.31-4.27 (m, 1H), 4.10-4.08 (m, 2H), 3.79 (s, 3H), 3.78-3.74 (m, 1H), 3.59-3.50 (m, 1H), 3.41 (s, 2H), 2H), 0.01 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 138.7, 136.0, 129.2, 117.3, 113.8, 102.0, 95.3, 84.7, 82.7, 72.3, 65.6, 55.3, 55.0, 18.2, -1.4; FAB HRMS m/z (M⁺) calcd for C₂₁H₃₄O₆Si 433.2022, obsd 433.2035.

Anal. Calcd for C₂₁H₃₄O₆Si: C, 61.43; H, 8.35. Found: C, 61.67; H, 8.23.

Compound 50

To a solution of Cp₂ZrCl₂ (110 mg, 1.3 eq) in 3 mL of THF stirred at -78 °C was added dropwise a solution of n-BuLi (0.51 mL, 1.47 M in hexane, 2.6 eq). After 1 h, the clear solution had become a yellowish suspension. A solution of 49 (78 mg, 0.20 mmol) in 3 mL of THF was added via cannula. The reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was cooled in an ice bath and a solution of BF₃.OEt₂ (0.05 mL, 2 eq) in 1 mL of THF was
added. After warming to rt and stirring for 15 min, a 1 M solution of HCl was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with a saturated solution of NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/ether 10:1) and afforded 50 as a colorless oil (35 mg, 51%). Improvement: to a solution of Cp₂ZrCl₂ (110 mg, 1.3 eq) in 3 mL of THF being stirred at -78°C was added dropwise a solution of n-BuLi (0.51 mL, 1.47 M in hexane, 2.6 eq). After 1 h the clear solution had become a yellowish suspension. A solution of 49 (78.0 mg, 0.20 mmol) in 3 mL of THF was added via cannula. The reaction mixture was allowed to warm to rt, stirred for 1 h and 3 h at 45°C. The reaction was cooled and 10 mL of a 1 M solution of HCl was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with a saturated solution of NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography (hexanes/ether 10%) and afforded the 50 as a colorless oil (48.6 mg, 64%); [α]_D^{21} -10 (c 1.0, CHCl₃); IR (neat, cm⁻¹) 3436, 2951, 2836, 1613, 1514, 1247; ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.01 (ddd, J = 16.9, 11.0, 7.8 Hz, 1H), 5.24-5.21 (m, 1H), 5.18 (s, 1H), 4.75 (d, J = 6.5 Hz, 1H), 4.67 (d, J = 6.5 Hz, 1H), 4.50-4.49 (m, 2H), 4.32-4.29 (m, 1H), 4.15 (dd, J = 8.2, 6.5 Hz, 1H), 3.97-3.93 (m, 1H), 3.80 (s, 3H), 3.77-3.60 (m, 2H), 2.59-2.52 (m, 1H), 2.44 (br s, 1 OH), 0.99-0.96 (m, 2H), 0.02 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 133.8, 130.1, 129.3, 117.5, 113.7, 101.4, 94.6, 81.7, 77.2, 71.1, 66.1, 66.1, 55.3, 45.1, 44.9, 18.2, -1.5, one Cq missing, FAB HRMS m/z (M+Na) calcd for C₂₀H₃₂O₅Si 403.1916, obsd 403.1885.
Compound 53

To a solution of IBX (166 mg, 0.60 mmol) in 1 mL of DMSO was added a solution of cyclobutanol 32 (50 mg, 0.20 mmol) in 1 mL of DMSO. After 5 h of stirring, water was added. The solution was freed of precipitate and diluted with ether. Water was added. The organic phase was washed with water, dried and concentrated to afford crude 53 (50 mg); [α]_D^21 -32 (c 1, CHCl₃); IR (CHCl₃, cm⁻¹) 1733; °H NMR (300 MHz, C₆D₆) δ 5.74-5.63 (m, 1H), 5.09-4.97 (m, 2H), 4.74 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.57-4.49 (m, 1H), 3.78-3.60 (m, 2H), 3.10-2.97 (m, 3H), 3.08-3.00 (m, 1H), 2.98-2.87 (m, 2H), 2.01-1.92 (m, 2H), 0.99-0.91 (m, 2H), -0.03 (s, 9H); ¹³C NMR (75 MHz, C₆D₆) δ 204.1, 133.2, 115.4, 93.9, 84.4, 65.4, 57.4, 25.6, 17.8, -1.6 (3C); HRMS (El) m/z (M-1)^+ calcd for C₁₂H₂₁O₃Si 241.1212, obsd 241.1220.
To a solution of TMS acetylene (0.1 mL, 0.6 mmol) in dry hexane (3 mL) stirred at -78 °C was added n-Buli (0.38 mL, 0.6 mmol, 1.6 M in hexane). After 1 h a solution of ketone 53 (15 mg, 0.06 mmol) in 3 mL of hexane was added via cannula. After 6 h at -20 °C, PMBCl was added neat and the reaction mixture was warmed to rt. After 2 h, a saturated solution of NH₄Cl was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with saturated solutions of NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/ether 20:1) and afforded a single stereoisomer as a colorless oil (14 mg, 54%); [α]°D 21'-17 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.28 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.02-5.90 (m, 1H), 5.22-5.12 (m, 2H), 4.79 (d, J = 6.8 Hz, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.46 (s, 2H), 4.17-4.11 (m, 1H), 3.81 (s, 3H), 3.70-3.60 (m, 2H), 2.76-2.70 (m, 1H), 2.42-2.33 (m, 1H), 2.15-2.05 (m, 1H), 1.01-0.90 (m, 2H), 0.16 (s, 9H), 0.05 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 134.1, 130.4, 129.4 (2C), 117.5, 113.9 (2C), 107.0, 94.1, 75.2, 71.8, 71.4, 65.6, 55.2, 43.0, 30.9, 18.0, 1.0 (3C), -1.4 (3C); HRMS (El) m/z (M+1)+ calcd for C₁₂H₂₁O₅Si 241.1212, obsd 241.1221.
To a solution of cyclobutanol 42 (70 mg, 0.20 mmol) in 14 ml of DCM being stirred at rt was added powdered molecular sieves (190 mg), NaOAc (32 mg, 0.39 mmol) and DMP (190 mg, 0.389 mmol). After 1 h the suspension was filtered and a saturated solution of Na$_2$S$_2$O$_5$ was added to the filtrate. The separated aqueous layer was extracted with DCM. The combined organic phases were washed with saturated solutions of NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated. The residue was dissolved in 10 mL of hexane and chilled at -78 °C. It was added via cannula to a solution of lithium trimethylsilylacetylide (1.95 mmol) at -78 °C. After 10 min a saturated solution of NH$_4$Cl was added. After warming the flask to rt the separated aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue was subjected to flash chromatography (1:10 ether/hexanes) to afford 72 mg (72%) of a clear oil; [α]$_D^{21}$-0.8 (c 0.5, CHCl$_3$); IR (neat, cm$^{-1}$) 3440, 2954, 2924, 2854, 1613, 1513, 1249, 1173, 1109; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.24 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 5.95 (ddd, $J$ = 17.2, 10.4, 8.0 Hz, 1H), 5.29-5.22 (m, 2H), 4.79 (d, $J$ = 6.0 Hz, 1H), 4.68 (d, $J$ = 6.0 Hz, 1H), 4.48 (s, 2H), 4.06 (d, $J$ = 0.8 Hz, 1H), 3.99 (dd, $J$ = 8.1, 1.8 Hz, 1H), 3.82-3.77 (m, 1H), 3.80 (s, 3H), 3.73-3.65 (m, 2H), 3.21 (s, 1 OH), 2.73-2.67 (m, 1H), 1.02-0.98 (m, 2H), 0.15 (s, 9H), 0.02 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 1 Cq not shown, 132.2, 129.8, 129.4, 118.7, 113.7, 94.5, 82.6, 79.6, 77.2, 76.9, 71.2, 65.7, 65.6, 55.2, 31.9, 18.0, -1.4, -1.5, FAB MS m/z (M-1+Na) calcd for
Compound 56

To MgBr₂ (154 mg, 0.838 mmol) was added 3 mL of ether. After 10 min, MeNO₂ (0.045 mL, 0.838 mmol) was added. This solution was added to a solution of 55 (20 mg, 0.042 mmol) in 3 mL of ether. After 6 h, water was added and the separated aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The residue was subjected to flash chromatography (hexanes/ether 10:1) to afford 13 mg (95%) of 56 as a clear oil; [α]₂₁⁰⁻¹₅ (c 0.3, CHCl₃); IR (neat, cm⁻¹) 3415, 2956, 2926, 2854, 1612, 1513, 1249, 1036; °H NMR (300 MHz, CDCl₃) δ 7.27 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.98-5.86 (m, 1H), 5.31-5.24 (m, 2H), 4.51 (s, 2H), 4.11 (d, J = 6.1 Hz, 1H), 3.85-3.78 (m, 1H), 3.81 (s, 3H), 2.77-2.71 (m, 1H), 0.16 (s, 9H); °C NMR (75 MHz, CDCl₃) δ 159.3, 131.5, 130.1, 129.7 (2C), 119.9, 113.8 (2C), 81.7, 77.4, 77.2, 76.2, 71.2, 66.2, 55.2, 51.0, -0.1 (3C); HRMS (ES) m/z (M+Na) calcd for C₁₉H₂₆O₄Si 369.1498, obsd 369.1511.

Compound 57

To a solution of diol 56 (10 mg, 0.036 mmol) in 2 mL of MeOH was added K₂CO₃
(2.0 mg, 0.014 mmol). After 6 h, MeOH was removed. The residue was passed through a pad of silica gel and 9 mg (98%) of desired product was obtained; \([\alpha]_D^{21} -16 (c 1.1, \text{CHCl}_3)\); IR (neat, \text{cm}^{-1}) 3554, 3310, 2952, 2850, 1614, 1428, 1217; \(^1\text{H NMR}\) (300 MHz, \text{CDCl}_3) \(\delta\) 7.28 (d, \(J = 8.6 \text{ Hz}, 2\text{H}\)), 6.88 (d, \(J = 8.6 \text{ Hz}, 2\text{H}\)), 5.98-5.86 (m, 1H), 5.33 (br s, 1H), 5.27 (br d, \(J = 10.1 \text{ Hz}, 1\text{H}\)), 4.52 (s, 2H), 4.14-4.08 (m, 1H), 3.87-3.83 (m, 1H), 3.81 (s, 3H), 2.76-2.74 (m, 1H), 2.63 (d, \(J = 10.7 \text{ Hz}\)), 2.57 (s, 1H), 2.52 (s, 1H); \(^{13}\text{C NMR}\) (75 MHz, \text{CDCl}_3) \(\delta\) 159.3, 131.3, 129.7, 129.5 (2C), 119.5, 113.9 (2C), 81.7, 77.2, 76.7, 72.9, 71.3, 65.8, 55.3, 50.8.

**Compound 7**

To a solution of the diol (2.5 mg, 0.018 mmol) in 5 mL of benzene was added \(\text{Ag}_2\text{CO}_3\) (2.5 mg, 1 eq). After 12 h at 80 °C, the reaction mixture was filtered on a pad of silica gel. Evaporation of the volatile left the almost pure ketone. (2.4 mg, 92%); \([\alpha]_D^{21} -20 (c 0.03, \text{CHCl}_3)\); IR (neat, \text{cm}^{-1}) 1726; \(^1\text{H NMR}\) (300 MHz, \text{CDCl}_3) \(\delta\) 7.13 (d, \(J = 8.6 \text{ Hz}, 2\text{H}\)), 6.89 (d, \(J = 8.6 \text{ Hz}, 2\text{H}\)), 5.80-5.71 (m, 1H), 5.49-5.41 (m, 1H), 4.51 (s, 2H), 4.25 (d, \(J = 8.0 \text{ Hz}, 1\text{H}\)), 4.20-4.10 (m, 1H), 3.80 (s, 3H), 3.51 (d, \(J = 5.1 \text{ Hz}, 1\text{H}\)), 2.44-2.36 (m, 2H), 1.88 (d, \(J = 1.0 \text{ Hz}, 1\text{H}\)), 1.84 (d, \(J = 2.3 \text{ Hz}, 1\text{H}\)).

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Compound 61

To a solution of alcohol 60 (9.5 g, 34.6 mmol) in 150 mL of DMF being stirred at rt was added imidazole (3.5 g, 51.0 mmol) and TBDPSCl (10.8 mL, 41.5 mmol). The reaction mixture was stirred overnight. A 1:1 mixture of water and ether was added (300 mL). The separated aqueous layer was extracted with ether three times. The combined organic phases were washed with water and brine, dried over MgSO₄, filtered and finally concentrated. The residue was purified by flash chromatography (AcOEt/hexanes 1/8) to give 61 as a clear oil (14.0 g, 82%); [α]D²¹ +13 (c 1.1, CHCl₃); IR (neat, cm⁻¹) 2930, 1732, 1472, 1428, 1385, 1282; 

¹H NMR (300 MHz, CDCl₃) δ 7.67-7.63 (m, 4H), 7.46-7.36 (m, 6H), 5.95 (d, J = 3.6 Hz, 1H), 4.48 (d, J = 3.6 Hz, 1H), 4.26-4.20 (m, 2H), 4.04 (dd, J = 11.6, 7.0 Hz, 1H), 3.85 (dd, J = 11.6, 5.6 Hz, 1H), 1.45 (s, 3H), 1.23 (s, 3H), 1.10 (s, 9H), 1.09 (s, 9H); 

¹³C NMR (75 MHz, CDCl₃) δ 177.9, 135.6 (4C), 132.8 (2C), 130.0 (2C), 127.8 (4C), 112.5, 105.9, 86.5, 85.5, 77.3, 63.9, 38.7, 27.0 (3C), 26.8 (3C), 25.9, 19.1; FAB HRMS m/z (M+Na)+ calcd for C₂₉H₄₀O₆Si 535.2486, obsd 535.2511.

Compound 62

To a solution of pivaloate ester 61 (14.0 g, 28.4 mmol) in 150 mL of DCM being stirred at -78 °C was added Dibal-H (42 mL, 42 mmol) via a dropping funnel. After 2 h, a saturated solution of Rochelle’s salt (100 mL) was added. The reaction mixture was warmed to rt and stirred for an additional hour. The separated aqueous layer was extracted with DCM. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (AcOEt/hexanes 1:4) and afforded 62 as a colorless oil (11.3 g, 93%); [α]ᵦ₊₊₁₄ (c 1.1, CHCl₃); IR (neat, cm⁻¹) 3506, 2942, 2860, 1472, 1384; ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.63 (m, 4H), 7.47-7.37 (m, 6H), 5.98 (d, J = 3.8 Hz, 1H), 4.58 (d, J = 3.8 Hz, 1H), 4.18 (br s, 1H), 4.10-4.05 (m, 1H), 3.40 (dd, J = 11.6, 7.9 Hz, 1H), 3.20 (dd, J = 11.6, 3.4 Hz, 1H), 1.75 (br s, 1 OH), 1.43 (s, 3H), 1.27 (s, 3H), 1.10 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 135.7 (4C), 133.0, 132.8, 130.1, 130.0, 127.9 (2C), 127.8 (2C), 112.3, 105.8, 89.2, 87.2, 77.2, 62.3, 26.8 (3C), 26.7, 25.9, 19.1; FAB HRMS m/z (M+Na)+ calcd for C₂₄H₃₂O₅Si 451.1911, obsd 451.1907.

Compound 63

To a solution of oxalyl chloride (2.1 mL, 24 mmol) in 200 mL of DCM being stirred at -78 °C was added dropwise DMSO (1.8 mL, 24 mmol). After 15 min, a solution of alcohol 62 (4.0 g, 10.9 mmol) in 50 mL of DCM was added. After 45 min, NEt₃ (10 ml, xs) was added. After 45 min at -78 °C, the reaction mixture was warmed to rt and stirred for another hour. A saturated solution of NH₄Cl was next added. The separated aqueous layer was extracted with DCM. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was taken up in ether, filtered, concentrated and dissolved in 50 mL of THF. This solution was added to a stirred suspension of PPh₃CH₂ (24 mmol) at -78 °C, prepared from PPh₃CH₃Br (7.8 g, 24 mmol) and LiHMDS (24 mL, 1M in THF). After the addition, the reaction mixture was warmed to 0 °C and quenched with a saturated solution of NH₄Cl. The separated aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (AcOEt/hexanes 1:10) to afford 63 as a colorless oil (2.2 g, 55%) ; [α]ᵢ⁺₊₁₅ (c 0.7, CHCl₃) ; IR (neat, cm⁻¹) 2919, 2860, 1472, 1425, 1378, 1213, 1108, 1072, 1008, 702; ¹H NMR (300 MHz, CDCl₃) δ 7.67-7.63 (m, 4H), 7.48-7.36 (m, 6H), 6.00 (d, J = 3.8 Hz, 1H), 5.71 (ddd, J = 17.3, 10.5, 7.1 Hz, 1H), 4.94-4.83 (m, 2H), 4.56 (d, J = 3.8 Hz, 1H), 4.41 (br d, J = 7.0, 1.2 Hz, 1H), 4.25 (d, J = 0.7 Hz, 1H), 1.44 (s, 3H), 1.27 (s, 3H), 1.10 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ
Compound 64

To a solution of 63 (145 mg, 0.34 mmol) in 40 mL of MeOH was added 1 mL of conc. HCl. After 8 h of stirring at rt, NaHCO₃ was added until gas evolution ceased. After concentration, the residue was dissolved in DCM, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (AcOEt/hexanes 1:5) and afforded 64 as a colorless oil (135 mg, 99%).

For the β-anomer:

[α]ₙ° -39 (c 0.8, CHCl₃); IR (neat, cm⁻¹) 3459, 2931, 2848, 1472, 1425, 1114, 1031, 702; ¹H NMR (300 MHz, CDCl₃) δ 7.74-7.68 (m, 2H), 7.68-7.64 (m, 2H), 7.47-7.34 (m, 6H), 5.53 (ddd, J = 17.3, 10.3, 7.3 Hz, 1H), 5.05 (ddd, J = 17.3, 1.4, 1.4 Hz, 1H), 4.95 (ddd, J = 10.3, 1.1, 1.1 Hz, 1H), 4.89 (d, J = 4.5 Hz, 1H), 4.30-4.26 (m, 1H), 4.20-4.17 (m, 1H), 4.03 (dd, J = 5.5, 5.5 Hz, 1H), 3.41 (s, 3H), 1.09 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 137.1, 135.9 (4C), 134.7 (2C), 129.8 (2C), 127.6 (4C), 116.7, 102.6, 84.9, 82.0, 78.6, 55.5, 26.9 (3C), 19.2; FAB HRMS m/z (M+Na)⁺ calcd for C₂₅H₃₂O₄Si 447.1962, obsd 447.1924.

Anal. Calcd for C₂₅H₃₂O₄Si: C, 70.72; H, 7.60. Found: C, 70.77; H, 7.66.
calcd for $\text{C}_{23}\text{H}_{30}\text{O}_{4}\text{Si} \text{ (M+Na)}^+ 421.1805$, obsd 421.1804.

*Anal.* Calcd for $\text{C}_{23}\text{H}_{30}\text{O}_{4}\text{Si} : \text{C}, 69.31; \text{H}, 7.59$. Found: C, 69.28; H, 7.65.

For the $\alpha$-anomer:

$^1\text{H NMR (300 MHz, CDCl}_3$ δ 7.75-7.67 (m, 4H), 7.50-7.38 (m, 6H), 5.73 (ddd, $J = 17.3, 10.3, 7.1$ Hz, 1H), 5.36 (d, $J = 17.3$ Hz, 1H), 5.20 (d, $J = 10.3$ Hz, 1H), 4.71 (d, $J = 1.7$ Hz, 1H), 4.48-4.44 (m, 1H), 4.06-4.04 (m, 1H), 3.87 (dd, $J = 7.0, 3.9$ Hz, 1H), 3.42 (s, 3H), 1.09 (s, 9H); $^{13}\text{C NMR (75 MHz, CDCl}_3$ δ 135.9 (2C), 135.6, 133.9, 132.9, 130.0, 127.9 (2C), 127.8 (2C), 118.1, 108.6, 84.1, 83.9, 83.6, 55.0, 26.9 (3C), 19.2.

**Compound 65**

To a solution of the alcohols 64 (1.87 g, 4.5 mmol) in 70 mL of DCM stirred at 0 °C was added $i$-Pr$_2$NEt (1.2 mL, 6.9 mmol) and SEMCl (1.2 mL, 6.8 mmol). The reaction mixture was stirred overnight at rt. The volatiles were evaporated. The residue was purified by flash chromatography (3% AcOEt/hexanes) and afforded 65 as a colorless oil (2.26 g, 95%); $[\alpha]_{D}^{20} +56$ (c 0.8, CHCl$_3$); IR (neat, cm$^{-1}$) 2988, 2928, 2853, 1648, 1557, 1248, 1104.
Compound 66

To a solution of Cp₂ZrCl₂ (2.0 g, 6.9 mmol) in 50 mL of THF being stirred at -78 °C was added dropwise a solution of n-BuLi (8.5 mL, 13.7 mmol) in hexane. After 1 h, a solution of vinyl carbohydrate 65 (2.8 g, 5.3 mmol) in 20 mL of THF was added via cannula, and the reaction mixture was warmed to rt. After 3 h, the reaction mixture was cooled to 0 °C and BF₃·OEt₂ (1.4 mL, 10.6 mmol) was added dropwise. After 10 min a saturated solution of NH₄Cl was added as well as 2 mL of a 1M solution of HCl. After 20 min at 0 °C the separated aqueous layer was extracted with ether. The combined organic phases were washed with saturated solutions of NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% AcOEt/hexanes) and afforded compound 66 as a colorless oil (1.6 g, 61%).

Improvement: to a solution of Cp₂ZrCl₂ (465 mg, 1.51 mmol) in 3 mL of THF being stirred at -78°C was added dropwise a solution of n-BuLi (2.17 mL, 1.47 M in
hexane, 3.22 mmol). After 1 h the clear solution has become a yellowish suspension. A solution of 65 (500 mg, 1.22 mmol) in 3 mL of THF was added via cannula. The reaction mixture was allowed to warm to rt and was stirred 3 hours at 45°C. The reaction was cooled and 10 mL of a 1 M solution of HCl was added. The separated aqueous layer was extracted with ether. The combined organic phases were washed with a saturated solution of NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography (hexanes/ether 10%) and afforded 66 as a colorless oil (315 mg, 68%); [α]₁⁰⁺11 (c 0.5, CHCl₃); IR (neat, cm⁻¹) 3461, 3070, 2933, 2848, 1427, 1242, 1110;¹H NMR (500 MHz, CDCl₃) δ 7.73-7.67 (m, 4H), 7.47-7.36 (m, 6H), 5.74 (ddd, J = 18.6, 10.4, 8.6 Hz, 1H), 5.06 (ddd, J = 10.4, 1.9, 0.5 Hz, 1H), 5.01 (ddd, J = 18.6, 1.8, 0.9 Hz, 1H), 4.65 (d, J = 6.5 Hz, 1H), 4.58 (d, J = 6.5 Hz, 1H), 4.39 (dd, J = 8.1, 6.4 Hz, 1H), 4.28 (dd, J = 5.7, 5.6 Hz, 1H), 3.99 (ddd, J = 6.2, 6.2, 0.5 Hz, 1H), 3.72-3.67 (m, 1H), 3.63-3.58 (m, 1H), 2.58-2.56 (m, 1H), 1.09 (s, 9H), 0.97-0.91 (m, 2H), 0.04 (s, 9H);¹³C NMR (75 MHz, CDCl₃) δ 135.8 (4C), 133.6 (2C), 133.2, 129.6 (2C), 127.5 (4C), 117.6, 94.5, 79.0, 77.1, 66.2, 65.9, 47.3, 26.8 (3C), 19.1, 18.2, -1.5 (3C); FAB HRMS m/z (M+Na)⁺ calcd for C₂₈H₄₂O₄Si₂ 521.2513, obsd 521.2467.

Compound 69

IBX (170 mg, 0.64 mmol) was dissolved in 2 mL of DMSO. A solution of alcohol 66 (80 mg, 0.16 mmol) in 1 mL of DMSO was added. After 3 h, 10 mL of ether and 10
mL of water were added. The aqueous phase was extracted with ether. The combined organic phases were washed with water and brine, dried over MgSO₄, filtered, concentrated, and dissolved in 10 mL of THF. To this solution cooled down to -78 °C was added a solution of lithium trimethylsilylacetylide (prepared from trimethylsilylacetylene (0.23 mL, 1.6 mmol) and n-BuLi (0.93 mL, 1.6 mmol)) in 10 mL of hexane. After 1 min, a saturated solution of NH₄Cl was added and the reaction mixture was allowed to reach rt. The aqueous phase was extracted with ether. The combined organic phases were washed with 20 mL of water and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% AcOEt/hexanes) and afforded compound 69 as a colorless oil (71 mg, 75%); [α]D²⁰ +30 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.61 (m, 4H), 7.45-7.31 (m, 6H), 5.71-5.59 (m, 1H), 5.09 (br s, 1H), 5.06-4.96 (m, 1H), 4.72 (d, J = 6.1 Hz, 1H), 4.58 (d, J = 6.1 Hz, 1H), 4.17 (dd, J = 8.2, 8.0 Hz, 1H), 4.08 (d, J = 6.1 Hz, 1H), 3.68-3.60 (m, 2H), 3.00 (br s, 1 OH), 2.68 (dd, J = 8.1, 8.1 Hz, 1H), 1.06 (s, 9H), 0.99-0.84 (m, 2H), 0.17 (s, 9H), 0.01 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 135.9 (4C), 133.8, 131.6 (2C), 129.6 (2C), 127.5 (4C), 118.8, 99.8, 94.2, 84.2, 75.1, 65.7, 65.6, 53.6, 45.0, 26.8 (3C), 19.7, 18.0, -0.0 (3C), -1.4 (3C); FAB HRMS m/z (M+Na)⁺ calcd for C₃₂H₅₀O₃Si₃ 617.2909, obsd 617.2937.
MgBr₂ (246 mg, 1.24 mmol) was dissolved in 2 mL of ether. After 20 min, MeNO₂ (0.074 mL, 1.24 mmol) was added. The one-phase solution was added to a solution of SEM ether 69 (40 mg, 0.064 mmol). The reaction was quenched after 12 h of stirring at rt by the addition of ether. A saturated solution of NaHCO₃ was added. The aqueous phase was extracted with ether. The combined organic phases were washed with 5 mL of water, brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (15% AcOEt/hexanes) and afforded compound 70 as a colorless oil (20 mg, 71%); [α]²⁰ +44 (c 0.9, CHCl₃); \(^1^H\) NMR (300 MHz, CDCl₃) δ 7.74-7.70 (m, 2H), 7.66-7.62 (m, 2H), 7.45-7.33 (m, 6H), 5.65 (ddd, J = 17.5, 10.5, 7.0 Hz, 1H), 5.16 (d, J = 10.5 Hz, 1H), 5.10 (d, J = 17.5 Hz, 1H), 4.10-4.08 (m, 1H), 3.96 (dd, J = 7.9, 6.3 Hz, 1H), 2.74 (dd, J = 8.0, 7.9 Hz, 1H), 2.26 (br s, 1 OH), 1.55 (br s, 1 OH), 1.07 (s, 9H), 0.18 (s, 9H); \(^1^C\) NMR (75 MHz, CDCl₃) δ 135.8 (4C), 133.4, 131.1 (2C), 129.7 (2C), 127.5 (2C), 119.3, 89.1, 79.0, 77.4, 66.0, 53.2, 45.0, 26.8 (3C), 19.0, -0.1(3C); FAB HRMS m/z (M+Na)⁺ calcd for C₂₇H₃₆O₃Si₂ 487.2095, obsd 487.2051.
**Compound 71**

To a solution of 70 (10 mg, 0.021 mmol) in 2 mL of MeOH was added K$_2$CO$_3$ (1 mg, cat). After 3 h at rt, MeOH was evaporated. The residue was purified by flash chromatography (35% AcOEt/hexanes) to afford 71 as a colorless oil (8 mg, 95%); [α]$_D^21$ +55 (c 0.3, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.73-7.70 (m, 2H), 7.65-7.63 (m, 2H), 7.45-7.34 (m, 6H), 5.71-5.59 (m, 1H), 5.17-5.07 (m, 2H), 4.10-4.08 (m, 1H), 4.01-3.96 (m, 1H), 2.77-2.71 (m, 1H), 2.54 (s, 1 H), 1.07 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 135.8 (4C), 130.9, 129.9 (2C), 129.8 (2C), 129.7 (2C), 127.7 (2C), 127.6, 1195, 78.7, 76.9, 72.6, 72.5, 53.0, 26.7 (3C), 19.0.

**Compound 72**

Compound 71 (5 mg, 0.01 mmol) was dissolved in 2 mL of benzene and heated to 80°C for 6 h. Evaporation of benzene left 72 as a yellowish oil (5 mg, 100%); [α]$_D^21$ +78 (c 0.2, CHCl$_3$); IR (neat, cm$^{-1}$) 3495, 3260, 2931, 2869, 2096, 1684, 1425, 1108, 1061, 820; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.60-7.58 (m, 4H), 7.37-7.29 (m, 6H), 5.48-5.43 (m, 1H), 5.30-5.26 (m, 1H), 4.98 (d, $J = 9.2$ Hz, 1H), 4.11 (dd, $J = 8.5$, 2.2 Hz, 1H), 3.30 (s, 1H), 3.28 (d, $J = 8.5$ Hz, 1H), 1.06 (dd, $J = 7.0$, 1.4 Hz, 3H), 0.94 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ
Compound 73

To a solution of alcohol 64 (800 mg, 2.01 mmol) in 5 mL of DCM, stirred at 0 °C was added (i-Pr)_2NEt (0.7 mL, 6.0 mmol) and TBSOTf (1.2 mL, 6.0 mmol). The reaction mixture was stirred overnight at rt, the volatiles were evaporated, and the residue was purified by flash chromatography (3% AcOEt/hexanes) to afford 73 as a colorless oil (800 mg, 81%); [α]_D^21 -22 (c 1.2, CHCl_3); IR (neat, cm⁻¹) 2919, 2860, 1472, 1419, 1249, 1100, 1020, 837; ^1H NMR (300 MHz, CDCl_3) δ 7.70-7.64 (m, 4H), 7.44-7.32 (m, 6H), 5.39-5.27 (m, 1H), 4.78 (d, J = 3.4 Hz, 1H), 4.72 (dd, J = 4.6, 0.8 Hz, 1H), 4.67 (d, J = 0.6 Hz, 1H), 4.24-4.23 (m, 2H), 4.18-4.14 (m, 1H), 3.36 (s, 3H), 1.06 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^13C NMR (75 MHz, CDCl_3) δ 137.1, 136.0 (4C), 133.9, 133.1, 129.7, 129.6, 127.6 (4C), 116.5, 103.4, 84.5, 81.7, 79.5, 55.3, 27.0 (3C), 25.8 (3C), 19.2, 18.2, -4.5, -4.7; FAB HRMS m/z (M+Na)^+ calcd for C_{29}H_{44}O_4Si_2 535.2670, obsd 535.2714.

Anal. Calcd for C_{29}H_{44}O_4Si_2: C, 67.93; H, 8.65. Found: C, 68.20; H, 8.76.
Compounds 74 and 75

To a solution of Cp₂ZrCl₂ (3.2 g, 10.93 mmol) in 100 mL of toluene being stirred at -78 °C was added dropwise n-BuLi (13.6 mL, 21.9 mmol). After 1 h, a solution of vinyl carbohydrate 73 (4.0 g, 7.81 mmol) in 20 mL of THF was added via cannula, and the reaction mixture was warmed to rt. After 3 h, the reaction mixture was cooled to -20 °C and BF₃.OEt₂ (2 mL, 15.60 mmol) was added dropwise. After 10 min, a saturated solution of NH₄Cl was added as well as 5 mL of a 1 M solution of HCl. After 20 min at 0 °C, the separated aqueous layer was extracted with ether.

The combined organic phases were washed with saturated solutions of NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (2% AcOEt/hexanes) and afforded 74 as a colorless oil (2.20 g, 58%) and compound 75 as a colorless oil (0.56 g, 15%).

For 74:

\[[\alpha]_D\] +17 (c 0.1, CHCl₃); IR (neat, cm⁻¹) 3530, 3060, 2931, 2860, 1472, 1425, 1390, 1255, 1172, 1108; ¹H NMR (500 MHz, C₆D₆) δ 7.80-7.74 (m, 4H), 7.25-7.18 (m, 6H), 5.87-5.79 (m, 1H), 4.93-4.90 (m, 1H), 4.90 (s, 1H), 4.42 (dd, J = 5.5, 5.2 Hz, 1H), 3.99-3.95 (m, 2H), 2.35-2.32 (m, 1H), 2.01 (d, J = 3.1 Hz, 1 OH), 1.18 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 136.3 (4C), 134.3, 134.0 (2C), 130.0 (2C), 127.9 (4C), 117.0, 80.4, 74.5, 67.2, 48.3, 27.2 (3C), 25.9 (3C), 19.4, 18.1, -4.9, -5.0; FAB HRMS m/z (M+Na)⁺ calcd for C₂₈H₄₂O₃Si₂ 505.2564, obsd 505.2601.

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Anat. Calcd for C$_{28}$H$_{32}$O$_3$Si$_2$: C, 69.66; H, 8.77. Found: C, 69.64; H, 8.91.

For 75:

\[ \alpha \]$_0$ 21°-37 (c 1.1, CHCl$_3$); IR (neat, cm$^{-1}$) 3436, 3072, 2942, 1848, 1637, 1584, 1472, 1425; $^1$H NMR (500 MHz, CHCl$_3$) $\delta$ 7.74-7.64 (m, 4H), 7.43-7.30 (m, 6H), 6.08-5.96 (m, 1H), 5.36 (dd, $J = 10.3$, 1.9 Hz, 1H), 5.06 (d, $J = 17.3$ Hz, 1H), 4.14-4.09 (m, 1H), 3.88 (dd, $J = 7.1$, 6.9 Hz, 1H), 3.55-3.48 (m, 1H), 2.85-2.82 (m, 1H), 1.06 (s, 9H), 0.93 (s, 9H), 0.14 (s, 6H); $^{13}$C NMR (125 MHz, CHCl$_3$) $\delta$ 135.8 (2C), 135.6 (2C), 134.8, 133.8, 133.4, 129.6, 129.5, 127.5 (2C), 127.4 (2C), 121.2, 84.9, 83.1, 70.2, 69.5, 45.5, 26.8 (3C), 25.8 (3C), 19.2, 8.4, -4.5, -4.9.

Compounds 83 and 84

IBX (170 mg, 0.64 mmol) was dissolved in 2 mL of DMSO. A solution of alcohol 74 (80 mg, 0.16 mmol) in 1 mL of DMSO was added. After 3 h, 10 mL of ether and 10 mL of water were added. The aqueous phase was extracted with ether. The combined organic phases were washed with 20 mL of water and brine, dried over MgSO$_4$, filtered, concentrated, and dissolved in 10 mL of hexanes. This solution was added to a solution of MAD (prepared according to ref 40, 0.48 mmol) in 3 mL of toluene stirred at -78°C for 1 min. This solution was added to a suspension of cerium trimethylsilylacetylide.
(prepared from trimethylsilylacetylene (0.23 mL, 1.6 mmol) and n-BuLi (0.93 mL, 1.6 mmol)) in 10 mL of hexanes, cannulated into a suspension of anhydrous CeCl₃ (1.6 mmol) in 5mL of hexanes at -78 °C. After 45 min, a saturated solution of NH₄Cl and 5 mL of a 1M solution of HCl were added and the reaction mixture was allowed to reach rt. The aqueous phase was extracted with ether. The combined organic phases were washed with saturated solutions of NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% AcOEt/hexanes) and afforded compound 83 as a colorless oil (37 mg, 40%) and compound 84 as a colorless oil (18 mg, 20%).

For 83:

\[
\begin{align*}
\text{[a]}^{21}_{D} &+28 \text{ (c 0.1, CHCl}_{3}) ; \\
\text{IR} \text{ (neat, cm}^{-1}) & 3444, 2953, 2852, 2616, 1426, 1245, 1102, 1014, 838 ; \\
\text{^1}H \text{ NMR (300 MHz, CDCl}_{3} & \delta 7.74-7.61 \text{ (m, 4H), 7.45-7.29 \text{ (m, 6H),} } \\
5.55-5.53 \text{ (m, 1H), 4.95-4.91 \text{ (m, 1H), 4.88 (br s, 1H),} } \\
4.03 \text{ (d, } J = 6.3 \text{ Hz, 1H), 3.70 (dd, } J = 8.1, 6.3 \text{ Hz, 1H), 2.44-2.38 \text{ (m, 1H), 2.28 (s, 1} \\
\text{OH), 1.04 (s, 9H), 0.93 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H), 0.08 (s, 9H); } \\
\text{^13}C \text{ NMR (75 MHz, CDCl}_{3} & \delta 135.8 \text{ (4C), 133.5, 129.5 (2C), 127.5 (2C), 127.3 (4C), 117.7, 102.4,} \\
94.4, 82.2, 73.3, 72.6, 54.2, 26.8 (3C), 25.8 (3C), 19.1, 19.0, -0.23 (3C), -4.0, -5.0; \\
\text{FAB HRMS m/z (M+Na)}^{+} & \text{calcd for C}_{33}H_{50}O_{3}Si}_{3} 601.2959, \text{ obsd 601.2978.}
\end{align*}
\]

\textit{Anal.} Calcd for C_{33}H_{50}O_{3}Si}_{3}: C, 68.45; H, 8.70. Found: C, 68.68; H, 8.88.
For 84:

\[ [\alpha]_D^{21} +34 \text{ (c 0.2, CHCl}_3) \]; \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta 7.66-7.60\) (m, 4H), 7.42-7.30 (m, 6H), 5.53-5.46 (m, 1H), 4.93-4.91 (m, 1H), 4.90-4.89 (m, 1H), 4.16 (dd, \(J = 5.9, 0.7\) Hz, 1H), 4.07 (dd, \(J = 8.0, 5.9\) Hz, 1H), 2.61 (s, 1 OH), 2.58-2.55 (m, 1H), 1.04 (s, 9H), 0.92 (s, 9H), 0.18 (s, 3H), 0.15 (s, 9H), 0.14 (s, 3H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta 135.8\) (2C), 135.8 (2C), 133.6, 133.2, 131.5, 129.6 (2C), 127.5 (2C), 127.5 (2C), 118.4, 106.8, 88.4, 79.2, 77.7, 66.3, 53.5, 26.8 (3C), 25.8 (3C), 19.1, 17.9, -0.14 (3C), -4.2, -4.9; FAB HRMS \(m/z\) (M+Na)= calcd for C\(_{33}\)H\(_{50}\)O\(_3\)Si\(_3\) 601.2959, obsd 601.2978.

Compound 85

Compound 83 (17 mg, 0.029 mmol) was dissolved in 2 mL of benzene and heated to 60 °C for 2 h. Evaporation of benzene left compound 85 as a yellowish oil (17 mg, 100%); \([\alpha]_D^{21} +72 \text{ (c 0.3, CHCl}_3) \]; IR (neat, cm\(^{-1}\)) 2956, 2929, 2856, 1695, 1466, 1249, 1100, 831; \(^1H\) NMR (500 MHz, CDCl\(_3\)) \(\delta 7.72-7.70\) (dd, \(J = 7.9, 1.1\) Hz, 2H), 7.67-7.65 (dd, \(J = 7.9, 1.1\) Hz, 2H), 7.42-7.29 (m, 6H), 6.01 (br s, 1H), 5.48-5.41 (m, 2H), 4.54 (dd, \(J = 6.7, 6.5\) Hz, 1H), 4.29 (d, \(J = 6.7\) Hz, 1H), 2.58 (dd, \(J = 17.8, 7.5\) Hz, 1H), 2.44-2.40 (m, 1H), 1.07 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 133
0.02 (s, 12 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 205.6, 149.6, 136.0 (2C), 136.0 (2C), 135.9, 135.3, 134.1, 134.0, 133.4 (2C), 129.6, 127.5 (2C), 127.4 (2C), 86.7, 73.8, 30.9, 27.0 (3C), 25.7 (3C), 19.2, 18.0, -2.3 (3C), -4.7, -5.0; FAB HRMS m/z (M+Na)$^+$ calcd for C$_{32}$H$_{50}$O$_3$Si$_3$ 601.2959, obsd 601.2943.

Compound 86 and 87

A solution of 83 (45 mg, 0.08 mmol) in 2 mL of 1% HCl/MeOH was stirred for 4 h at rt. A small aliquot was set aside for characterization of 86. K$_2$CO$_3$ (20 mg, 0.14 mmol) was added carefully. After 10 min of stirring a saturated solution of NH$_4$Cl was added along with ether. The aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over MgSO$_4$, filtrated and concentrated. The resulting residue was subjected to flash chromatography (hexanes/EtOAc 5:3) and afforded 87 as a clear oil (30 mg, 99% for 2 steps)

For 86:

[$\alpha$]$^D_{\text{P}}$ -19 (c 0.3, CHCl$_3$); IR (neat, cm$^{-1}$) 3412, 2942, 2929, 2848, 1100, 837; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.74-7.71 (m, 2H), 7.67-7.64 (m, 2H), 7.44-7.33 (m, 6H), 5.60 (ddd, $J$ = 17.7, 10.3, 7.3 Hz, 1H), 5.11-5.07 (m, 1H), 3.96-3.94 (br m, 1H), 3.46 (dd, $J$ = 8.0, 6.5 Hz, 1H), 2.58-2.55 (m, 1H), 2.52 (br s, 1 OH), 2.38 (br m, 1H), 1.06 (s, 9H), 0.10 (s, 9H); $^{13}$C NMR
**For 87:**

\[
[a]^\circ_\text{D} -26 (c 0.4, \text{CHCl}_3); \text{IR (neat, cm}^{-1}) 2956, 2920, 2848, 2345, 1111; \ 'H \text{ NMR (300 MHz, C}_6\text{D}_6 \delta 7.94-7.90 (m, 2H), 7.84-7.81 (m, 2H), 7.34-7.23 (m, 6H), 5.84-5.72 (m, 1H), 5.11-5.02 (m, 2H), 4.11-4.09 (m, 1H), 3.76 (dd, } J = 7.9, 6.5 \text{ Hz, 1H), 2.67-2.62 (m, 1H), 1.94 (br, 1 OH), 1.89 (s, 1H), 1.23 (s, 9H); } ^{13}\text{C NMR (75 MHz, CDCl}_3 \delta 136.0 (4C), 134.1, 133.5 (2C), 129.8 (2C), 127.1 (4C), 117.9, 82.0, 78.0, 74.3, 71.8, 53.9, 45.1, 26.7 (3C), 19.1; } \text{ FAB HRMS (ES}^+\text{) m/z (M+Na})^+ \text{ calcld for } C_{24}H_{28}O_3 \text{ 415.1700, obsd 415.1724.}
\]

**Compound 89**

Compound 87 (5 mg, 0.013 mmol) was dissolved in 2 mL of benzene and heated to 80 °C for 2 h. Evaporation of benzene left compound 89 as a yellowish oil (5 mg,
Compound 109

To a solution of 108 (300 mg, 0.80 mmol) in 5 mL of DCM, being stirred at 0 °C was added (i-Pr)₂EtN (0.3 mL, 2.4 mmol) and TBSOTf (0.5 mL, 2.4 mmol). The reaction mixture was stirred overnight at rt. The volatiles were evaporated. The residue was purified by flash chromatography (3% AcOEt/hexanes) and afforded 109 as a colorless oil (410 mg, 95%); [α]ᵣ⁺1 = -4 (c 1.6, CHCl₃); IR (neat, cm⁻¹) 2942, 2929, 2860, 1719, 1466, 1249, 1119, 837; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, J = 3.0 Hz, 1H), 7.26 (d, J = 3.0 Hz, 1H), 5.11 (d, J = 7.5 Hz, 1H), 4.47-4.39 (m, 1H), 2.87 (dd, J = 16.0, 5.1 Hz, 1H), 2.78 (dd, J = 16.0, 7.1 Hz, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.80 (s, 9H), 0.25 (s, 3H), 0.10 (s, 3H), 0.05 (s, 6H), -0.02 (s, 3H), -0.13 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 171.9, 142.2, 118.6, 74.6, 72.3, 39.4, 25.7 (3C), 25.6 (3C), 15.5 (3C), 18.1, 17.9, 17.5, -2.9, -4.7, -4.7, -4.8, -4.9, -5.0; FAB HRMS m/z (M+Na)+ calcd for C₂₅H₂₁NO₄SSi₃ 568.2738, obsd 568.2698.
Norcamphor (9 mg, 0.081 mmol) was dissolved in 2 mL of THF. The solution was cooled to -78 °C and LiHMDS (0.081 mL, 0.081 mmol) was added. The reaction mixture was warmed to -5 °C and stirred for 30 min.

The solution was cooled to -78 °C and a solution of crude 109 (9 mg, 0.018 mmol) in 0.5 mL of THF was added. After 3 h at -78 °C, a saturated solution of NH₄Cl was added and the reaction mixture was allowed to reach rt. The aqueous phase was extracted with ether. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (25% AcOEt/hexanes) and afforded 110 as a colorless oil (3.5 mg, 40%); IR (neat, cm⁻¹) 2953, 2857, 1746, 1470, 1255, 1090, 837; ¹H NMR (500 MHz, CDCl₃) δ 4.66 (dd, J = 10.1 Hz, 1H), 4.10-4.09 (m, 1H), 3.78 (d, J = 4.8 Hz, 1H), 3.02 (br s, 1H), 2.91 (dd, J = 17.7, 4.4 Hz, 1H), 2.73 (br s, 1H), 2.49-2.23 (m, 3H), 1.95-1.23 (m, 5H), 0.91 (s, 9H), 0.88 (s, 9H), 0.12 (d, J = 3.0 Hz, 6H), 0.08 (d, J = 3.2 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 214.2, 168.4, 168.1, 76.7, 67.9, 67.6, 50.0, 45.8, 38.4, 37.0, 34.9, 29.6, 27.5, 25.7 (3C), 25.6 (3C), 17.9, 17.9, -4.09, -4.74 (2C), -4.8; FAB HRMS m/z (M+Na)^+ calcd for C₂₄H₄₄O₅Si₂ 491.2619, obsd 491.2585.
Compound 95

A suspension of PPH$_3$CH$_2$I$_2$ (10.16 g, 18.5 mmol) in 100 mL of THF being stirred at 0 °C was treated with a solution of NaHMDS (23.4 mL, 0.79 M in THF). After 10 min, the brown reaction mixture was cooled to -78 °C. A solution of 94 (1.85 g, 14.2 mmol) in 20 mL of THF cooled to -78 °C was added to the above mixture via cannula. After 1 h, a saturated solution of NH$_4$Cl was added. The reaction mixture was allowed to reach rt. The separated aqueous layer was extracted with Et$_2$O. The combined organic phases were washed with brine, dried over MgSO$_4$ and concentrated. Flash chromatography of the residue (5% ether/petroleum ether) afforded 2.50 g (70%) of the exclusive Z-iodide 95 as a colorless oil; [\(\alpha\)]$_D$ +10 (c 1, CHCl$_3$); IR (neat, cm$^{-1}$) 2985, 2934, 2872, 1614, 1454, 1373, 1217, 1153, 1061; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.45 (d, $\nu$ = 7.8 Hz, 1H), 6.40 (dd, $\nu$ = 7.8, 7.6 Hz, 1H), 4.80-4.60 (m, 1H), 4.25 (dd, $\nu$ = 8.3, 6.4 Hz, 1H), 3.63 (dd, $\nu$ = 8.3, 7.1 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 139.7, 109.8, 83.8, 78.8, 68.2, 26.5, 25.7.

Compound 96

A solution of 95 (500 mg, 1.96 mmol) in 30 mL of 20% H$_2$O/THF being stirred at 0 °C was treated with 0.5 mL of TFA. After warming to rt, the reaction mixture was stirred for 6 h. Then the volatiles were removed in vacuo. Dichloromethane was added. The separated aqueous layer was
continuously extracted overnight with dichloromethane. The combined organic phases were dried over MgSO₄ and concentrated. Flash chromatography of the residue (50% EtOAc/hexanes) afforded 96 as a colorless oil (420 mg, 99%); [α]°D +16 (c 2.3, CHCl₃); IR (neat, cm⁻¹) 3717, 3278, 2918, 1613, 1462, 1264, 1076 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.45 (dd, J = 7.8, 0.9 Hz, 1H), 6.32 (dd, J = 7.8, 7.6 Hz, 1H), 4.52-4.46 (m, 1H), 3.74-3.46 (m, 2H + 2 OH); ¹³C NMR (75 MHz, CDCl₃) δ 139.5, 84.3, 75.3, 64.6; FAB HRMS m/z (M+Na)⁺ calcd for C₄H₇IO₂ 236.9389, obsd 236.9392.

Compound 97

To a solution of 96 (750 mg, 3.5 mmol) and 1 crystal of DMAP in 10 mL of pyridine was added slowly PVCl (0.47 mL, 3.9 mmol). After 12 h, 30 mL of ether and 10 mL of 1 M HCl were added. The organic layer was washed with saturated solutions of NaHCO₃ and brine, dried over MgSO₄, and concentrated. The residue was purified by flash chromatography (10% ether/hexanes). Product 97 was obtained as a colorless oil (990 mg, 94%); [α]°D +18 (c 1.0, CHCl₃); IR (neat, cm⁻¹) 3443, 2971, 2873, 1731, 1480, 1284, 1158; ¹H NMR (300 MHz, CDCl₃) δ 6.51 (dd, J = 7.8, 0.8 Hz, 1H), 6.31 (dd, J = 7.8, 7.6 Hz, 1H), 4.69-4.63 (m, 1H), 4.18-4.08 (m, 2H), 2.05 (br s, 1 OH), 1.24 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 178.7, 139.3, 84.6, 73.0, 66.2, 38.9, 27.2.

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Compound 98

A solution of 97 (150 mg, 0.50 mmol) and 2,6-lutidine (0.22 mL, 2.00 mmol) in 3 mL of dichloromethane being stirred at 0°C was treated with TBSOTf (0.38 mL, 2.00 mmol). After warming to rt, the reaction was complete in 30 min. A saturated solution of NaHCO₃ was added and the separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine and dried over MgSO₄. The residue was purified by chromatography (5% ether/hexanes) and afforded 98 as a colorless oil (200 mg, 95%); [α]₂⁰⁻² (c 2.2, CHCl₃); IR (neat, cm⁻¹) 2957, 2857, 1728, 1480, 1282, 1154; ¹H NMR (300 MHz, CDCl₃) δ 6.39 (dd, J = 7.7, 0.9 Hz, 1H), 6.20 (dd, J = 7.7, 7.6 Hz, 1H), 4.67-4.60 (m, 1H), 4.07-3.97 (m, 2H), 1.22 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 178.3, 141.0, 82.9, 73.6, 66.3, 38.8, 27.3, 25.7, 18.0, -4.4, -4.7; FAB HRMS m/z (M+Na)⁺ calcd for C₁₅H₂₉IO₃ 435.0828, obsd 435.0822.

Compound 99

A solution of 98 (27 mg, 0.06 mmol) in 2 mL of dichloromethane being stirred at -78 °C was treated with Dibal (0.15 mL, 1M in hexane). After 2 h, a solution of Rochelle’s salt was added. The
reaction mixture was allowed to warm to rt. After 1 h, the separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by flash chromatography (5% ether/hexanes) to give 20 mg (94%) of 99 as a colorless oil; \([\alpha]_{D}^{20} -48 (c 1.1, \text{CHCl}_3); \text{IR} \ (\text{neat, cm}^{-1}) 3447; \text{^1}H \text{NMR} (300 \text{ MHz, CDCl}_3) \delta 6.36 \ (dd, J = 7.8, 0.9 \text{ Hz, 1H}), 6.23 \ (dd, J = 7.8, 7.6 \text{ Hz, 1H}), 4.51-4.45 \ (m, 1H), 3.57 \ (dd, J = 11.1, 3.9 \text{ Hz, 1H}), 3.47 \ (dd, J = 11.1, 6.8 \text{ Hz, 1H}), 2.03 \ (br s, 1 \text{ OH}), 0.91 \ (s, 9H), 0.14 \ (s, 3H), 0.09 \ (s, 3H); \text{^13}C \text{NMR} (75 \text{ MHz, CDCl}_3) \delta 141.0, 82.3, 76.6, 65.2, 25.8 \ (3C), 18.0, -4.2, -4.7; \text{FAB HRMS } m/z (M+Na)^{+} \text{ calcd for C}_{10}H_{21}IO_2 351.0253, \text{ obsd 351.0259.}

Compound 93

To a suspension of 99 (20 mg, 0.06 mmol), NaOAc (20 mg) and powdered molecular sieves (20 mg) in 3 mL of dichloromethane was added Dess Martin periodinane (100 mg, 0.20 mmol). After 12 h at rt, a saturated solution of NaHSO₃ was added. The aqueous layer was extracted with dichloromethane. The combined organic phase were washed with a saturated solutions of NaHCO₃ and brine, dried over MgSO₄ and concentrated. Product 93 was used without purification; \(^1H \text{NMR} (300 \text{ MHz, CDCl}_3) \delta 9.35 \ (s, 1H), 6.01 \ (dd, J = 7.7, 1.1 \text{ Hz, 1H}), 5.75 \ (dd, J = 7.8, 7.8 \text{ Hz, 1H}), 4.87-4.84 \ (m, 1H), 0.98 \ (s, 9H), 0.12 \ (s, 3H), 0.07 \ (s, 3H); \text{^13}C \text{NMR} (75 \text{ MHz, CDCl}_3) \delta 196.1, 136.7, 85.8, 81.4, 29.9, 25.5 \ (3C),
3H), 0.07 (s, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) δ 196.1, 136.7, 85.8, 81.4, 29.9, 25.5 (3C),
-4.8, -4.9; FAB HRMS m/z (M+Na)$^+$ calc for C$_{10}$H$_{19}$IO$_2$Si 349.0097, obsd 349.0093.
REFERENCES


71) Reequilibration using 1% HCl/MeOH at rt for 15 h left a 1:1 mixture in 80% yield. Longer times caused loss of the PMB ether.


103) Jones, A. B.; Villalobos, A.; Linde, R. G.; Danishefsky, S.


115) Close parallelism exists with the stereochemical course of aldolization of norbornanone enolates with aldehydes. Consult, for example: Schaller, C.; Vogel, P. Synlett 1999, 1219-1222.

116) We and others (see “Protecting Groups in Organic Synthesis,” Greene, T. W.; Wuts, P. G. Third Edition, John Wiley and Sons, N. Y., 1999, pp 728-729) have found TBS esters to enjoy a reactivity level closely comparable to that of methyl esters.


APPENDIX

$^1$H NMR SPECTRA FOR CHAPTER 1
\textsuperscript{1}H NMR SPECTRA FOR CHAPTER 2