CHAPTER-3

Synthesis of 6-Substituted-5,6-Dihydro-2H-Pyran-2-Ones

Section A:- Total Synthesis of Umuravumbolide and Hyptolide via Silicon-Tethered Ring Closing Metathesis

Section B:- Attempted Synthesis of Hypurticin via Temporary Silicon Tethered-Ring Closing Metathesis
Chapter 3: Section A

3.1 Section A

TOTAL SYNTHESIS OF UMURAVUMBOLIDE AND HYPTOLIDE VIA SILICON-TETHERED RING CLOSING METATHESIS

3.1.1. Introduction

Protozoal diseases, particularly malaria, leishmaniasis and Chagas disease, represent major causes of mortality in various tropical and subtropical regions. These diseases remain significant health problems in many developing countries, and this situation is compounded by increasing treatment failures using current drugs.

Malaria causes more than 300 million acute illnesses and at least one million deaths annually. Resistance of the malaria parasites, *Plasmodium spp.*, to drugs such as chloroquine (and, more lately, quinine) occurs with increasing frequency.1,2 This resistance underlies the necessity of developing new agents for malaria chemotherapy, with new modes of action to replace current ineffective drugs.

Leishmaniasis is a major health problem that affects approximately 12 million people worldwide, with 2 million new cases diagnosed every year.3 The causative agents of this disease are parasites of the genus *Leishmania*, which infect and replicate in macrophages of the vertebrate host. Recently, a dramatic increase in the number of cases of leishmaniasis has been observed in patients with compromised T-cell function, such as those infected with the human immunodeficiency virus.4 The chemotherapy of leishmaniasis has been based on pentavalent antimonials, sodium stibogluconate (pentostam) and meglumine antimonite (glucantime). These drugs contain multiple uncharacterized molecular structures with variable efficacies and toxicities, they are associated with moderate and severe side effects,5,6,7 prone to induce resistance8,9 and require parenteral administration over a long period.10 Second-line drugs, such as amphotericin B and its lipid formulations, are either more toxic and expensive for routine use in developing countries.
Trypanosoma cruzi is a protozoa that causes Chagas disease (American trypanosomiasis); it is an obligate intracellular protozoan parasite that causes acute and chronic infection in several mammalian species including humans. This illness affects approximately 16 to 18 million people in tropical and sub-tropical Americas leading to the death of approximately 400,000 people per year. Nifurtimox and benznidazole, the drugs currently in use against this disease, present several side effects and have limited efficacy. Gentian violet, another compound for the prevention of Chagas disease by blood transfusion, leads to purple colouring of the blood and staining of patients' tissues. The use of gentian violet is limited due to its toxicity and other side effects such as alteration of skin color, mucous membranes and urine.

The development of new, effective, non-toxic and less expensive drugs is required to contribute to the world-wide control of these diseases. 6-Substituted 5,6-dihydro-α-pyrones, so-called α,β-unsaturated δ-lactones (see Fig 1) of both natural and nonnatural origin have been found to exhibit relevant pharmacological activities.

**Figure 1:** Structures of α,β-unsaturated δ-lactones
We cite a few examples: pironetin (1)\textsuperscript{15} has been found to inhibit cell cycle progression in the M phase. Callystatin A (2),\textsuperscript{16} gonodiol (3),\textsuperscript{17} obolactone (4),\textsuperscript{18} and spicigerolide (5)\textsuperscript{19} exhibit cytotoxic activity. Goniothalamin (6)\textsuperscript{20} induce the apoptotic process. Pectinolides A-C (7) exhibit significant antimicrobial and cytotoxic activity.\textsuperscript{21} Umuravumbolide (8b), hyptolide (9) and hypurticin (10) also show a wide range of pharmacological activities. In an effort to discover new compounds for infectious diseases treatment, several $\alpha,\beta$-unsaturated $\delta$-lactones were evaluated and found to have high antiprotozoal activity.

Desacetyllumuravumbolide (8a),\textsuperscript{22a} umuravumbolide (8b),\textsuperscript{22a} structurally related hyptolide (9)\textsuperscript{22b} were isolated from species of Tetradenia and Hyptis respectively are representative members of family Lamiaceae (Figure 1).

These compounds have a common structural feature, the polyacetylated-6-heptenyl-5,6-dihydro-2H-pyran-2-ones framework containing an $\alpha,\beta$-unsaturated $\delta$-lactone and are known to bind protein thiol groups as a result of their ability to act as a Michael acceptor. They show a wide range of pharmacological activities such as cytotoxicity against human tumor cells, antimicrobial and antifungal activity etc.

They inhibit HIV protease,$^{23}$ induce apoptosis,$^{24}$ and have even been shown to be antileukemic\textsuperscript{25} and anticancer agents.$^{26}$ Further, they have shown a variety of biological activities, such as plant-growth inhibitors, pheromones, and antifeedant, antifungal, and antibacterial reagents.$^{27}$

Although biological activities of umuravumbolide (8b) are not known so far, but several compounds from Lamiaceae family have been shown to be an emetic to treat loss of appetite.

The structures of (–)-deacetyllumuravumbolide (8a) and (+)-umuravumbolide (8b) were revised by Davies-Coleman and Rivett, and they determined the absolute configuration on the basis of NMR and CD spectral studies and also reported the optical rotations of these compounds.$^{28}$
3.1.2. Review of Literature

Synthetic studies toward the aforementioned molecules (8, 9) have been described. To the best of our knowledge, all attempts have been in linear fashion involving semi-hydrogenation of the alkyne part using Lindlar’s catalyst to generate the side chain olefin and ring-closing metathesis reaction for the construction of lactone ring. A detailed report of these syntheses is described below.

3.1.2.1 Synthesis of Umuravumbolide

Ramachandran et al.29 (2001)

Ramachandran and co-workers first synthesized desacetylumuravumbolide and umuravumbolide via asymmetric reduction, allylboration, and ring-closing metathesis and confirmed their revised structures and configurations. They required optically pure (S)-1-heptyn-3-ol (12). Reduction of the corresponding acetylenic ketone 11 with (S)-B-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane)30 provided (S)-12.31 After recrystallization the enantiomeric becomes ≥ 99% ee as determined by the HPLC.32 TBDMS protection of 12, followed by formylation, provided the acetylenic aldehyde 13. This was converted to the required Z-olefinic aldehyde 6 by hydrogenation under Lindlar catalysis. Allylboration of 14 with B-allyldiiso-2-caranylborane33 provided enantiomerically pure 15.34 Esterification with acryloyl chloride, followed by ring-closing metathesis using Grubbs ruthenium catalyst,35 provided the lactenone 17.36 The deprotection of TBDMS was achieved by utilizing triethylamine trihydrofluoride.37 Acetylation provided the target molecule 8b.
Scheme 1: Reagents and conditions: (a) Alpine-Borane, 75%; (b) (i) TBDMS-Cl, imidazole, DMF; (ii) BuLi, Me₂NCHO, –78°C to 0°C, 50%; (c) H₂, Lindlar catalyst, 65%; (d) AllylBlpc₂ [from (+)-DIP-Cl], Et₂O, –78°C, 79%, (e) Acryloyl chloride, NEt₃, cat. DMAP, CH₂Cl₂, rt, 70%; (f) 10% PhCH=RuCl₂(PCy₃)₂, CH₂Cl₂, reflux, 65%; (g) triethylamine trihydrofluoride, AcCN; (h) Ac₂O, Et₃N, cat. DMAP, CH₂Cl₂, rt, 98%.

Venkateswarlu et al.²⁸ (2011)

Venkateswarlu and co-workers reported the synthesis of desacetyllumuravumbolide (8a) and umuravumbolide (8b), starting from commercially available valeraldehyde 18. As outlined in Scheme 2, the first stereocenter was generated by the highly enantioselective addition of propargyl alcohol 19 and 18 to give compound 20.³⁹ The secondary hydroxyl group in compound 20 was protected with tert-butylidiphenylsilyl (TBDPS) chloride as TBDPS ether 21. The tetrahydropyranyl group in compound 21 was deprotected with pyridinium p-toluenesulfonate (PPTS)/MeOH to give compound 22, which was oxidized with 2-iodoxybenzoic acid (IBX) to afford aldehyde 23 in 90% yield. Aldehyde 23 was converted into required (Z)-olefinic aldehyde 24 in 85% yield by hydrogenation using Lindlar’s catalyst in dry DCM.

Scheme 2: Reagents and conditions: (a) 19, Et₂Zn, (R)-BINOL, Ti(O’Pr)₄, PhOH, 95%, 93% ee; (b) TBDPS-Cl, imidazole, dry CH₂Cl₂, 6 h, r.t., 93%; (c) PPTS, MeOH,
r.t., 95%; (d) IBX/DMSO, CH$_2$Cl$_2$, 0 °C to r.t., 90%; (e) Lindlar’s catalyst, CH$_2$Cl$_2$, H$_2$, 8 h, 85%. (f) 25, TiCl$_4$, DIPEA, dry CH$_2$Cl$_2$, −78 °C, 77%; (g) MOMCl, DIPEA, 7 h, 0 °C to r.t., 95%; (h) (i) DIBAL-H, dry CH$_2$Cl$_2$, −78 °C, 5 min; (ii) NaH/THF, −78 °C, 30 min, then (CF$_3$CH$_2$O)$_2$P(O)CH$_2$COOCH$_3$, THF, 30–45 min, 82%; (i) 3 m HCl, THF (1:1), 3 h, r.t.; (j) Ac$_2$O, pyridine, CH$_2$Cl$_2$, 18 h, 97%.

Aldehyde 24 was subjected to an aldol reaction under the Crimmins protocol$^{40}$ to give a mixture of diastereomers. Amide 27 was treated with DIBAL-H to give the aldehyde, which was subjected to Horner–Wadsworth–Emmons olefination$^{41}$ to give cis-olefinic ester 28. One-pot deprotection of the protecting groups with concomitant cyclization of the ester and alcohol functionalities with 3.0 m HCl/THF (1:1) at room temperature afforded 8a. Further 8a was acetylated by using acetic anhydride/pyridine to afford the target molecule 8b.

**Sabitha et al.$^{42}$ (2011)**

Sabitha and co-workers reported the stereoselective synthesis of naturally occurring α,β-unsaturated δ-lactones desacetylumuravumbolide and umuravumbolide, starting from commercially available propargyl alcohol. As outlined in Scheme 3, the key steps of this synthesis were alkynylation, a Noyori asymmetric reduction and Still–Gennari olefination.
**Scheme 3** Reagents and conditions: a) Li, liq. NH$_3$, Fe (NO$_3$)$_3$.9H$_2$O, n-BuBr, THF, –33 °C, 8 h, 70%. b) LiAlH$_4$, THF, 0 °C–r.t, 6 h, 85%. c) (+)-DIPT, Ti(iPrO)$_4$, 5 M TBHP in CH$_2$Cl$_2$, 4Å molecular sieves powder, CH$_2$Cl$_2$, –30 °C, 6 h, 85%. d) CCl$_4$, PPh$_3$, NaHCO$_3$, reflux, 6 h, 80%. e) (i) n-BuLi, THF, –78 °C, 3 h, (ii) TBSCl, imidazole, CH$_2$Cl$_2$, 0 °C, r.t, 2 h, (69% overall yield of two steps). f) n-BuLi, THF, -30 °C then add aldehyde 6 at –78 °C, 4 h, 70%. g) IBX, DMSO, CH$_2$Cl$_2$, 0 °C–r.t, overnight, 80%. h) (1R,2R)-Noyori catalyst, HCO$_2$H (10 eq), Et$_3$N (4eq), r.t, overnight, 89%. i) TBSCl, imidazole, CH$_2$Cl$_2$, 0 °C–r.t, 3 h, 92%. j) DDQ, CH$_2$Cl$_2$, pH 7 (10 : 1), r.t, 4 h, 75%. k) (i) IBX, DMSO, CH$_2$Cl$_2$, 0 °C–r.t, overnight, (ii) NaH, Still–Gennari reagent, 30 min at 0 °C, then addition of 14 at –78 °C, 2 h, (75% overall yield of two steps). l) PTSA, MeOH, 0 °C–r.t, overnight, 80%. m) Pd/CaCO$_3$, H$_2$, quinoline (cat.), EtOAc, rt, 6 h, 92%. n) Ac$_2$O, Et$_3$N, DMAP (cat.), CH$_2$Cl$_2$, 0 °C, r.t, 2 h, 85%.

**3.1.2.2 Synthesis of Hyptolide**

Marco *et al.* (2003)
Marco and co-workers first synthesized hyptolide using a chiral pool starting material ethyl L-lactate (scheme 4). Asymmetric allylation of 41 to homoallyl alcohol 42 was performed with Brown’s B-allyl diisopinocampheyloborane. Protection of the hydroxyl group as a TES derivative was followed by oxidative cleavage of the olefinic bond to yield \( \beta \)-silyloxy aldehyde 43. Next by using Carreira’s asymmetric protocol propargyl alcohol 44 was obtained as a single diastereomer. Alcohol silylation followed by selective cleavage of the C-silyl group furnished the terminal acetylene 46, which was formylated to 47 via the intermediate lithium derivative. Semihydrogenation of the C\( \equiv \)C bond in 47 was performed using Lindlar catalyst. Z-Enal 48 was subjected as above to Brown’s asymmetric allylation, which provided alcohol 49. Acylation of 49 with acryloyl chloride furnished acrylate 50, which was then subjected to RCM to form \( \delta \)-lactone. Finally, cleavage of all silyl groups and acetylation of the three hydroxyl functions was achieved to afford (+)-9.

**Scheme 4: Reagents and conditions:** (a) AllylB\( \text{IIpc}_2 \) [prepared from allylmagnesium bromide and (+)-DIP-Cl], Et\( _2 \)O, \(-78^\circ \text{C} \) (82%, 92:8 diastereomeric mixture). (b) TESOTf, 2, 6-lutidine, CH\( _2 \)Cl\(_2 \), rt, 87%. (c) OsO\(_4 \) (cat.), NMO, \( ^1\text{BuOH/THF/H}_2\text{O} \), then NaI\( \text{O}_4 \), aq. THF, 78%. (d) TMSC\( \equiv \text{CH} \), Zn(OTf)\(_2\), Et\(_3\)N, (−)-\( N \)-methylephedrine, toluene, rt. (e) TBSOTf, 2, 6-lutidine, 0°C, CH\( _2 \)Cl\(_2 \). (f) K\(_2\)CO\(_3\)/MeOH, rt, 58% overall. (g) BuLi, THF, 0°C, then DMF, 70%. (h) H\(_2\), Lindlar catalyst, 84%. (i) AllylB\( \text{IIpc}_2 \) [from (+)-DIP-Cl], Et\( _2 \)O, \(-78^\circ \text{C} \), (79%, single diastereomer). (j) Acryloyl chloride, NE\(_3\), cat. DMAP, CH\( _2 \)Cl\(_2 \), rt, 70%. (k) 10% PhCH=RuCl\(_2\)(PC\(_3\))\(_2\), CH\(_2\)Cl\(_2\), reflux, 82%. (l) PPTS, aq. MeOH, 70°C, then Ac\(_2\)O, Et\(_3\)N, cat. DMAP, CH\(_2\)Cl\(_2\), rt, 83%. 

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Chakraborty and co-workers synthesized hyptolide (scheme 5) starting from compound 52, which was prepared from alcohol 51 according to the reported procedure involving Sharpless asymmetric kinetic resolution, followed by protective group manipulations. The chiral epoxy alcohol 52 was subjected to Swern oxidation to afford exclusively the trans enal, (4R, 5S, E)-5-(tert-butyl-dimethylsilyloxy)-4-hydroxy-hex-2-en-1-ol (53). Reduction of the aldehyde functionality with DIBAL-H followed by selective protection of the resultant primary alcohol as a TBDPS-ether furnished compound 54. Stereoselective epoxidation of 54 with mCPBA afforded the epoxide 54. Then compound 55 was treated with Cp₂TiCl₂ to obtain diol 56. Acetonide protection of the 1,3-diol of 56 gave 57. Chemoselective deprotection of the TBDPS-ether afforded the primary alcohol 57a, which was converted to alkene 58 first by oxidation of 57a followed by selective Z-olefination following Still’s protocol.

Scheme 5: Reagents and conditions (a) Ref. 31; (b) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −78°C, 1 h, 90%; (c) DIBAL-H, CH₂Cl₂, −78°C, 0.5 h; (d) TBDPSCl, Et₃N, DMAP (cat), CH₂Cl₂, 0°C to rt, 3 h, 81% over two steps; (e) mCPBA, CH₂Cl₂, 0°C, 12 h,
90% (2:1 in favor of the required isomer); (f) Cp₂TiCl₂, Zn, ZnCl₂, THF, −20°C to rt, 12 h, 85%; (g) 2, 2-dimethoxypropane, CSA (cat), CH₂Cl₂, rt, 1 h; (h) TBAF, THF, 0°C to rt, 1 h, 85%, over two steps; (i) (i) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −78°C, 2 h; (ii) (CF₃CH₂O)₂P(O)CH₂CO₂Me, NaH, THF, −78°C to 0°C, 1.5 h, 80% (Z:E = 95:5) over two steps; (j) (i) step c; (ii) DMP, CH₂Cl₂, 0°C to rt, 0.5 h, 85% over two steps; (k) (+)-Ipc₂B(allyl), Et₂O, −78°C, 1 h, 70%; (l) acryloyl chloride, Et₃N, DMAP, CH₂Cl₂, 0°C; 15 min, 70%; (m) Grubbs’1st generation catalyst, CH₂Cl₂, reflux, 5 h, 85%; (n) (i) PPTS, MeOH, rt, 24 h; (ii) Ac₂O, Et₃N, DMAP (cat), CH₂Cl₂, 0°C to rt, 0.5 h, 80% over two steps.

The α,β-unsaturated aldehyde 59 was obtained from 58 in two steps. Asymmetric allylation of 59 using Brown’s protocol⁵⁸ afforded the secondary alcohol 60. Acylation of 60 with acryloyl chloride furnished acrylate 61, which was then subjected to RCM to form δ-lactone 62. Finally, global deprotection followed by acetylation was achieved to afford (+)-9.
3.1.3. PRESENT WORK

Objective

Numerous strategies have been developed for the synthesis of polyacylated-6-heptenyl-5,6-dihydro-2H-pyran-2-ones with great success. With the development of an efficient approach to the synthesis of various α,β-unsaturated δ-lactones,\(^{59}\) we further considered attempting at the total synthesis of umuravumbolide (8b) and hyptolide (9).

Towards this end, we were interested in a concise and versatile approach exploiting temporary silicon-tethered ring-closing metathesis (TST-RCM)\(^{60}\) and Ando’s protocol\(^{61}\) to construct the olefins. The strategy provides convergent synthetic access to all members of the Lamiaceae family. The general synthetic analysis is depicted in Scheme 6.

\[\text{Scheme 6. Retro-synthetic analysis of umuravumbolide (8b) and hyptolide (9).}\]

We aimed to construct the side chain Z-olefin of both umuravumbolide 8b and hyptolide 9 through ring-closing metathesis of bis-siloxane intermediate 63 and 64 respectively. The intermediates 63 and 64 would originate by the coupling of allylic alcohols 65, 66 and 66, 67 respectively, whereas the requisite fragments 65, 66 and 67...
could be prepared from hexanal 68, 4-(4-methoxybenzoyloxy)butanal 69 and TBS protected L-lactaldehyde 41 respectively.

### 3.1.4. Results and Discussion

#### Synthesis of fragment 65

Our synthesis started with the preparation of fragment 65. The sequence developed to prepare fragment 65 is summarized in Scheme 7. Thus, the aldehyde 68 was exposed to sequential α-aminoxylation catalyzed by D-proline, followed by in situ reduction using NaBH₄ to furnish O-amino-substituted diol, which was subjected to reductive hydrogenation conditions to afford the known diol 70 in 85% yield, which on selective monotosylation and base treatment furnished epoxide 71 in 80% yield. Appearance of multiplet in the range of δ 2.71-2.67, 2.57-2.52, 2.28-2.25 in ¹H NMR and disappearance of OH peak at 3372 cm⁻¹ in IR spectrum confirmed the formation of the epoxide 71. Finally, dimethylsulfoxonium methylide-mediated ring opening of epoxide 71 gave rise the fragment 65 in 72% yield. The IR spectrum of 65 gave broad hydroxyl absorption at 3485 cm⁻¹. The ¹H NMR spectrum of 65 gave olefin peaks at δ 5.88-5.71 (multiplet, one proton) and 5.19-4.99 (multiplet, two protons).

**Scheme 7.** Synthesis of fragment 65.

#### Synthesis of fragment 66

The synthesis of fragment 66 commenced from 4-(4-methoxybenzoyloxy)butanal 69 as illustrated in Scheme 8.

The aldehyde 69 was subjected to α-aminoxylation catalyzed by L-proline, followed by similar set of reaction conditions, used in Scheme 7 to afford diol 72\(^{67}\) in 83% yield and in 97% ee\(^{68}\) which on selective monotosylation and base treatment furnished epoxide 73\(^{67}\) in 83% yield. Appearance of multiplet in the range of δ 3.11-3.02, 2.81-2.76, 2.54-2.50 in \(^1\)H NMR and disappearance of OH peak at 3384 cm\(^{-1}\) in IR spectrum confirmed the formation of the epoxide 73. This epoxide was also opened with dimethylsulfonium methyldie to afford the allylic alcohol fragment 66\(^{69}\) in 75% yield and was confirmed by IR spectrum and \(^1\)H NMR. The IR spectrum of 66 gave broad hydroxyl absorption at 3414 cm\(^{-1}\) and the \(^1\)H NMR spectrum of 66 gave olefin peaks at δ 5.97-5.80 (multiplet, one proton) and 5.33-5.08 (multiplet, two protons) which confirmed the structure.

Synthesis of fragment 67

The sequence developed to prepare fragment 67 is summarized in Scheme 9. As our point of departure, asymmetric allylation of TBS protected L-lactaldehyde 41 to known homoallylic alcohol 42\(^{22}\) was performed with Brown’s B-allyl diisopinocampheylborane, followed by treatment with benzyl bromide (BnBr) to afford 74 in 97% yield. We next examined proline-catalyzed α-aminoxylation reaction of aldehyde to generate the third stereogenic centre. Towards this we converted olefin 74 to alcohol 75 in 95% yield by the hydroboration oxidation technique. Thus compound 75 was oxidized by using IBX to furnish aldehyde, which was directly subjected to α-aminoxylation catalyzed by D-proline, followed by in situ reduction using NaBH\(_4\) to give the required O-amino substituted diol, which on treatment with catalytic amount of copper sulfate afforded the diol 76 in 80% yield along with minor diastereomer (10%), which could be separated easily by chromatography. The
stereochemistry of the major diastereomer 76 was confirmed by $^{13}$C NMR analysis. Diol 76 on selective monotosylation and base treatment furnished 77 in 90% yield. Appearance of multiplet in the range of $\delta$ 3.05-2.95, 2.73-2.61, 2.44-2.35 in $^1$H NMR and disappearance of OH peak at 3412 cm$^{-1}$ in IR spectrum confirmed the formation of the epoxide 77. Finally, dimethylsulfonium methylide mediated (Corey-Chaykovsky’s condition) ring opening of epoxide 77 gave rise the fragment 67 in 80% yield and was confirmed by IR spectrum and $^1$H NMR. The IR spectrum of 67 gave broad hydroxyl absorption at 3290 cm$^{-1}$ and the $^1$H NMR spectrum of 67 gave olefin peaks at $\delta$ 5.83-5.67 (multiplet, one proton) and 5.21-4.96 (multiplet, two protons) which confirmed the structure.


The stereochemistry of compound 76 was confirmed from $^{13}$C NMR spectra by converting compound 67 (derived from 76, Scheme 9) into compound 78 through the following sequence of reaction. Compound 67 was subjected to Birch reaction condition followed by acetonide protection of 1,3-diol into the cyclic moiety 78.

Scheme 10. Synthesis of cyclic acetonide.

The appearance of methyl resonance peaks at $\delta$ 19.8 and 30.0 ppm and acetal carbon resonating at $\delta$ 98.5 ppm confirmed the stereochemistry of syn-acetonide 78.
Coupling of Fragments 65, 66 and Fragments 66, 67 for The Synthesis of Umuravumbolide 8a and Hyptolide 9 Respectively

With the cross coupling partners in hand, the crucial silicon tethered coupling to construct the disiloxane 63 was examined (Table 1). Initial attempts using different silicon tethering reagents such as Me₂SiCl₂ and Ph₂SiCl₂ proved to be unsuccessful. Then we considered using (iPr)₂SiCl₂ as tethering reagent following the reaction conditions as reported by Evans and coworkers. Accordingly, the addition of fragment 65 to (iPr)₂SiCl₂ followed by further addition of second fragment 66 after 24 h led to the exclusive formation of homodimer of 65 (Table 1; entry 1). We attributed this failure to the use of excess tethering reagent and prolonging the reaction mixture for long after the addition of first fragment 65.

Table 1. Optimization of the coupling reaction of fragments 65 and 66

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fragment 65 (equiv)</th>
<th>(iPr)₂SiCl₂ (equiv)</th>
<th>Time[a]</th>
<th>yield of 63 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10</td>
<td>24 h</td>
<td>[b]</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5</td>
<td>24 h</td>
<td>[b]</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1.1</td>
<td>24 h</td>
<td>5[c]</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.1</td>
<td>5 h</td>
<td>5[c]</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1.1</td>
<td>1 h</td>
<td>30[c]</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1.1</td>
<td>15 min</td>
<td>87[d]</td>
</tr>
</tbody>
</table>

[a] time duration between the addition of first fragment and second fragment [b] only homodimer of 65 [c] along with homodimer of 65 [d] along with 5% homodimer of 65 and unreacted 66.
Consequently we performed reaction with 5 equivalents of tethering reagent, but there was no product formation (entry 2). Nevertheless we could isolate 5% of coupled product 63 when the equivalent of tethering reagent was lowered to 1.1 (entry 3). The structure of 63 was proven by the $^1$H NMR and $^{13}$C NMR spectra. We then reduced the time duration between the addition of fragment 65 and fragment 66 from 24 h to 5 h, but we ended with no improvement in the yield of coupled product 63 (entry 4). Yields higher than 25% were obtained when the time gap was reduced to 1 h (entry 5). The best yield 87% could be achieved when we added fragment 66 just after 15 min of the addition of fragment 65 (entry 6).

Thus the coupled product 63 could be synthesized in excellent yield by reducing the equivalent of tethering reagent from previously used 10 to 1.1 as well as time duration between the addition of two fragments from 24 h to 15 min. Reduction in the amount of tethering reagent also takes care the cost effectiveness of the reaction. With disiloxane intermediates 63 and 64 in hand, we turned our attention to its further elaboration to umuravumbolide (8b) and hyptolide (9) by transforming the disiloxane moieties (63 and 64) to the corresponding cyclic intermediates 79 and 80 respectively and subsequent synthetic manipulations (Scheme 11). Eventually the ring closing metathesis reaction of disiloxane 63 using Grubbs second generation catalyst A in toluene at 110 °C proceeded smoothly to get the required cyclic intermediate 79 in 88% yield. The appearance of internal olefin at δ 5.86-5.39 and disappearance of four protons at δ 5.23-5.01 in $^1$H NMR confirmed the product.

![Figure 2: Metal-alkylidene metathesis catalysts.](image)

However cyclization of 64 under similar conditions furnished the required cyclic intermediate 80 only in low yield. Hence we examined the ring closing metathesis (RCM) of disiloxane 64 using Grubbs catalyst under a variety of reaction conditions
to get exclusively the cis-product in appreciable yield (Table 2). The best yield 75% could be achieved when we used Grubbs-Hoveyda second generation catalyst B in toluene at 110 °C (entry 4). The appearance of internal olefin at δ 5.60-4.63 and disappearance of four protons at δ 5.12-4.91 in 1H NMR confirmed the product. Our next objective towards the completion of the synthesis was to form the requisite lactone rings with unsaturation. Towards this end, compounds 79 and 80 were subjected to the removal of PMB groups using DDQ producing the corresponding alcohols 81 and 82 respectively in excellent yields. Subsequent Dess Martin periodinane oxidation of alcoholic group led to the formation of corresponding aldehydes, which were directly subjected to two-carbon homologation under Ando conditions61 to give (Z)-unsaturated ester 83 and 84 in 70% yield with excellent stereoselectivity. The IR spectrum of 83 and 84 showed the ester carbonyl absorption at 1723, 1742 cm⁻¹ respectively and olefin C=C stretching at 1610, 1620 cm⁻¹ respectively.

Table 2. Optimization of RCM condition for disiloxane 64

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst</th>
<th>solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs II A</td>
<td>DCM</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs II A</td>
<td>DCE</td>
<td>84</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Grubbs II A</td>
<td>Toluene</td>
<td>110</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs-Hoveyda II B</td>
<td>Toluene</td>
<td>110</td>
<td>75</td>
</tr>
</tbody>
</table>

With substantial amount of compound 83 and 84 in hand, the platform was then set to construct the lactone ring of the target molecules. At the beginning we attempted the simultaneous deprotection of the silyl groups and cyclization in order to prepare the lactones 8a and 85 using pTSA in MeOH. However the reaction led to the formation
of some unidentified products. Hence the obvious choice was two-step procedure; we
first deprotected the silyl groups using TBAF in THF and the crude polyols thus
obtained was eventually cyclized to give the six-membered lactones
desacetylumuravumbolide (8a) and 85 in 70% yield upon treatment with catalytic
amount of Ti(OiPr)₄ in refluxing benzene.

Scheme 11. Completion of the synthesis of umuravumbolide 8b and hyptolide 9.

The IR spectrum of 8a and 85 showed characteristic carbonyl group absorption of
α,β-unsaturated δ-lactone at 1644 and 1654 cm⁻¹ respectively. The lactone
desacetylumuravumbolide (8a) was further acetylated to furnish umuravumbolide 8b. The spectroscopic and physical data of desacetylumuravumbolide (8a) and umuravumbolide (8b) were identical in all respects to those reported in the literature.22a Towards the synthesis of target molecule 9, compound 85 was subjected to debenzylation followed by acetylation of secondary hydroxyl group to furnish the target molecule hyptolide 9 in excellent yield. The spectroscopic and physical data of compound 9 were identical in all respects to those reported in the literature.22b

### 3.1.5. Conclusion

In conclusion, an efficient synthesis for umuravumbolide (8b) and hyptolide (9) has been achieved via temporary silicon tethered ring closing metathesis (TST-RCM) and Ando olefination reaction. The stereogenic centres were installed by using proline catalyzed α-aminoxylation reactions and by Brown’s asymmetric allyl boration. Further application of this methodology to the synthesis of other structurally related biologically active compounds for the studies of structure activity relationship is currently underway in our laboratory.

### 3.1.6. Experimental Section

General Methods: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. 1H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to CDCl3 as internal standard and 13C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to CDCl3. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.
(S)-Hexane-1,2-diol (70): To a stirred solution of aldehyde 68 (1.0 g, 9.98 mmol) and nitrosobenzene (1.06 g, 9.98 mmol) in DMSO (9 mL) was added D-proline (0.23 g, 1.9 mmol, 20 mol %) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (10 mL) and careful addition of excess NaBH₄ (1.32 g, 35 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et₂O and aqueous HCl (1M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over anhyd Na₂SO₄, concentrated, and purified by column chromatography over silica gel using EtOAc/Pet. Ether (40:60) as eluent to give pure aminoxy alcohol, which was dissolved in EtOAc (10 mL) and to the solution was added 10% Pd/C (0.050 g) and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a celite pad, concentrated, and the crude product was then purified by silica gel chromatography using EtOAc/Pet. Ether (40:60) as eluent to give pure diol 70 as a colourless liquid.

Yield: 1.0 g, 85%

Mol. Formula: C₆H₁₄O₂


IR (CHCl₃, cm⁻¹): νmax 3372, 2925.

¹H NMR (400 MHz, CDCl₃): δ 4.38-3.36 (m, 5H), 1.32-1.22 (m, 6H), 0.84-0.82 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 71.9, 66.2, 33.1, 27.7, 22.6, 13.8.

HRMS (ESI⁺) m/z calcd for C₆H₁₄O₂ [M + Na]⁺ 141.0891, found 141.0893.

(S)-2-Butyloxirane (71): To a mixture of diol 70 (0.21 g, 1.77 mmol), in dry DCM (5 mL) was added dibutyltin oxide (0.008 mg, 0.035 mol) followed by the addition of p-
toluenesulfonyl chloride (0.337 g, 1.77 mmol) and triethylamine (0.25 mL, 1.77 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with DCM (3 x 10 ml) and then combined organic phase was washed with water, dried (Na$_2$SO$_4$) and concentrated. To this crude mixture in MeOH at 0 °C was added K$_2$CO$_3$ (0.5 g, 3.61 mmol) and the resultant mixture was allowed to stir for 1 h at same temp. After completion of reaction as indicated by TLC the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 x 20 mL), the combined organic layer was washed with brine, dried (Na$_2$SO$_4$) and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (70:30) gave the epoxide 71 as a colorless liquid.

**Yield:** 0.14 g, 80%

**Mol. Formula:** C$_6$H$_{14}$O$_2$

[\[\alpha\]$_D$$^{25}$]: $-16.5$ (c 1.0, pentane). lit.$^{64}$ [\[\alpha\]$_D$$^{25}$]: $-18.7$(c 0.93, pentane).

**IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 2989, 2925, 2870.

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 2.71-2.67 (m, 1H), 2.57-2.52 (m, 1H), 2.28-2.25 (m, 1H), 1.34-1.10 (m, 6H), 0.78-0.71 (t, $J$=6.13 Hz, 3H).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 51.9, 46.6, 31.9, 27.8, 22.2, 13.6.

**HRMS** (ESI$^+$) m/z calcd for C$_6$H$_{12}$O [M + Na]$^+$ 123.0786, found 123.0784.

(S)-Hept-1-en-3-ol (65): To a suspension of trimethylsulfonium iodide (5.44 g, 26.5 mmol) in dry THF (10 mL) at −20 °C was added $n$-BuLi (16.68 mL, 1.6 M solution in hexane, 26.5 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide 71 (0.5 g, 4.37 mmol) in dry THF (5 mL) was added to the above reaction mixture and slowly allowed to warm to 0 °C over 1 h. The reaction mixture was then stirred at ambient temperature for 2 h. After consumption of the starting material the reaction
mixture was quenched with H$_2$O (10 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (70:30) gave 65 as a colorless liquid.

**Yield:** 0.45 g, 80%

**Mol. Formula:** C$_7$H$_{14}$O

[α]$_D^{25}$: +9.5 (c 1.4, pentane).

**IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 3485, 1613, 1586.

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 5.88-5.71 (m, 1H), 5.19-4.99 (m, 2H), 4.08-3.96 (m, 1H), 2.34 (s, 1H), 1.48-1.22 (m, 6H), 0.88-0.81 (m, 3H).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 141.3, 114.2, 73.0, 36.6, 27.4, 22.5, 13.8.

**HRMS** (ESI$^+$) m/z calcd for C$_7$H$_{14}$O [M + Na]$^+$ 137.0942, found 137.0945.

(R)-4-(4-Methoxybenzylolxy)butane-1,2-diol (72): Compound 72 was prepared from compound 69 using L-proline as catalyst following the procedure as described for 70 (colorless liquid).

**Yield:** 0.9 g, 83%

**Mol. Formula:** C$_{12}$H$_{18}$O$_4$

[α]$_D^{25}$: −1.03 (c 1.0, CHCl$_3$).

**IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 3384, 2934, 1613, 1514, 1249.

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.27-7.20 (m, 2H), 6.90-6.84 (m, 2H), 4.44 (s, 2H), 3.93-3.82 (m, 1H), 3.79 (s, 3H), 3.69-3.42 (m, 4H), 1.89-1.62 (m, 2H).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 159.3, 129.8, 129.4, 113.8, 72.9, 71.3, 67.8, 66.5, 55.23, 32.7.
HRMS (ESI⁻) m/z calcd for C_{12}H_{16}O_{4} [M + Na]⁻ 249.1103, found 249.1106.

(R)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (73): Compound 73 was prepared following the procedure as described for 71 (colorless liquid).

Yield: 0.16 g, 83%

Mol. Formula: C_{12}H_{16}O_{3}

[α]_D^{25}: +13.82 (c 1.0, CHCl₃), lit.₆⁷ [α]_D^{25} +12.0 (c 1.0, CHCl₃)

IR (CHCl₃, cm⁻¹): νmax 2997, 2924, 2860, 1613, 1513.

¹H NMR (400 MHz, CDCl₃): δ 7.29-7.24 (m, 2H), 6.91-6.85 (m, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.63-3.57 (m, 2H), 3.11-3.02 (m, 1H), 2.81-2.76 (m, 1H), 2.54-2.50 (m, 1H), 1.99-1.71 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 158.7, 128.8, 128.5, 112.3, 73.3, 67.5, 55.5, 50.1, 47.3, 33.8.

HRMS (ESI⁻) m/z calcd for C_{12}H_{16}O_{3} [M + Na]⁻ 231.0997, found 231.0993.

(R)-5-(4-Methoxybenzyloxy)pent-1-en-3-ol (66): Compound 66 was prepared following the procedure as described for 65 (colorless liquid).

Yield: 0.4 g, 75%

Mol. Formula: C_{13}H_{18}O_{3}

[α]_D^{25}: – 10.0 (c 1.4, CHCl₃), lit.₆⁹ [α]_D^{19}: – 9.2 (c 1.0, CHCl₃).

IR (CHCl₃, cm⁻¹): νmax 3414, 1613, 1586.
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\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.31-7.24 (m, 2H), 6.93-6.86 (m, 2H), 5.97-5.80 (m, 1H), 5.33-5.08 (m, 2H), 4.46 (s, 2H), 3.82 (s, 3H), 3.76-3.57 (m, 2H), 2.99 (s, 1H), 1.94-1.79 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 159.1, 140.5, 129.9, 129.2, 114.2, 113.7, 72.8, 71.7, 67.8, 55.1, 36.1.

HRMS (ESI\(^+\)) m/z calcd for C\(_{13}\)H\(_{18}\)O\(_3\) [M + Na]\(^+\) 245.1154, found 245.1158.

((\(2S, 3R\))-3-(Benzyloxy)hex-5-en-2-yl)oxy)(\( tert\)-butyl)dimethylsilane (74): To the known homoallylic alcohol 41 (2 g, 8.67 mmol) in DMF (7.5 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.38 g, 9.54 mmol). After 15 min, benzyl bromide (1.63 g, 1.13 mL, 9.54 mmol) was introduced and the reaction mixture further stirred for 2 h at room temperature. Water was carefully added to the reaction mixture, extracted with diethyl ether, washed with water and dried (Na\(_2\)SO\(_4\)). Silica gel column chromatography of the crude product using petroleum ether/EtOAc (95:5) as eluent afforded benzyl protected compound 74.

Yield: 2.69 g, 97%

Mol. Formula: C\(_{19}\)H\(_{32}\)O\(_2\)Si

\([\alpha]_D^{25}\): +10.16 (c 0.9, CHCl\(_3\)).

IR (CHCl\(_3\), cm\(^{-1}\)): \(v_{\text{max}}\) 2933, 2867, 1613, 1514, 1464, 1248, 1039, 920, 885.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.30-7.19 (m, 5H), 5.92-5.75 (m, 1H), 5.08-4.93 (m, 2H), 4.64-4.45 (m, 2H), 3.92-3.61 (m, 1H), 3.31-3.21 (m, 1H), 2.25 (t, \(J=6.53\) Hz, 2H), 1.13 (d, \(J=6.42\) Hz, 3H), 0.83-0.80 (m, 9H), -0.01-0.06 (m, 6H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 138.9, 135.6, 128.2, 127.8, 127.3, 116.6, 83.6, 72.7, 70.4, 35.7, 33.7, 25.9, 19.3, -4.3, -4.7.

HRMS (ESI\(^+\)) m/z calcd for C\(_{19}\)H\(_{33}\)O\(_2\)Si [M + H]\(^+\) 321.2250, found 321.2254.
(4R, 5S)-4-(Benzyloxy)-5-(tert-butyldimethylsilyloxy)hexan-1-ol (75): A solution of olefin 74 (2.5 g, 7.8 mmol) in dry THF (30 mL) was treated under N\textsubscript{2} with BH\textsubscript{3}.DMS (0.75 mL, 7.8 mmol, d=0.8 g/ml). The reaction mixture was stirred for 4 h at room temperature and then quenched by addition of MeOH (25 mL), 6 M aqueous NaOH (9 mL), and 30% H\textsubscript{2}O\textsubscript{2} (15 mL) and stirred for additional 12 h. The resulting mixture was then stirred for 1 h and worked up (extraction with EtOAc). Column chromatography on silica gel (petroleum ether : EtOAc, 90 : 10) afforded (4R, 5S)-4-(Benzyloxy)-5-(tert-butyldimethylsilyloxy)hexan-1-ol (75) as a light yellow colored oil.

**Yield:** 2.5 g, 95%

**Mol. Formula:** C\textsubscript{19}H\textsubscript{34}O\textsubscript{3}Si

\([\alpha]_D^{25}\): +9.31 (c 0.9, CHCl\textsubscript{3}).

**IR** (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \(\nu_{max}\) 3377, 3019, 2400, 1501, 1427, 1230, 1070, 993, 857, 725.

**\(^1\)H NMR** (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.27-7.18 (m, 5H), 4.73-4.37 (m, 2H), 4.01-3.73 (m, 1H), 3.63-3.47 (m, 2H), 3.35-3.15 (m, 1H), 1.61-1.50 (m, 4H), 1.11 (d, J=6.19 Hz, 3H), 0.81-0.79 (m, 9H), -0.01-0.07 (m, 6H).

**\(^{13}\)C NMR** (100 MHz, CDCl\textsubscript{3}): \(\delta\) 138.7, 128.3, 127.9, 127.5, 83.8, 72.9, 70.8, 63.0, 29.6, 29.0, 27.4, 25.8, 19.2, -4.3, -4.7.

**HRMS** (ESI\textsuperscript{+}) m/z calcd for C\textsubscript{19}H\textsubscript{35}O\textsubscript{3}Si [M + H]\textsuperscript{+} 339.2355, found 339.2354.

(2S, 4R, 5S)-4-(Benzyloxy)-5-((tert-butyldimethylsilyl)oxy)hexane-1,2-diol (76): To a solution of 75 (2 g, 5.9 mmol) in 10 mL EtOAc was added IBX (4.6 g, 17.7 mmol) and it was heated to 80 °C for 3 h. It was cooled to rt and filtered through a pad of Celite. The filtrate was concentrated and the crude aldehyde was used for the next step without purification. To a stirred solution of above aldehyde (1.5 g, 4.45
mmol) and nitrosobenzene (0.48 g, 4.45 mmol) in DMSO (4 mL) was added D-proline (0.1 g, 0.89 mmol, 20 mol %) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (5 mL) and careful addition of excess NaBH₄ (0.6 g, 15.6 mmol). The reaction was quenched after 10 min by sat. NH₄Cl. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over anhyd Na₂SO₄, concentrated, and purified by column chromatography over silica gel using EtOAc/Pet. Ether (40:60) as eluent to give pure aminoxy alcohol (1.5 g, 80%). The aminoxy alcohol (1.5 g, 3.5 mmol) was dissolved in MeOH (10 mL) and to the solution was added 3% copper sulfate and the reaction mixture was stirred for 12 h. After completion of the reaction (monitored by TLC) it was quenched with sat. NH₄Cl. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over anhyd Na₂SO₄, concentrated, and purified by silica gel chromatography using EtOAc/Pet. Ether (50:50) as eluent to give pure diol 76 as a colorless liquid.

**Yield:** 0.66 g, 80%

**Mol. Formula:** C₁₉H₃₄O₄Si

\[ \alpha \] D₂₅: +41.86 (c 0.2, CHCl₃).

**IR** (CHCl₃, cm⁻¹): \( \nu_{\text{max}} \) 3412, 3020, 2978, 1652, 1534, 1248, 1237.

**¹H NMR** (400 MHz, CDCl₃): \( \delta \) 7.31-7.19 (m, 5H), 4.77-4.41 (m, 2H), 3.99-3.78 (m, 3H), 3.56-3.47 (m, 2H), 3.41-3.29 (m, 1H), 1.58-1.54 (m, 2H), 1.10-1.07 (m, 3H), 0.82-0.81 (m, 9H), -0.01 (s, 6H).

**¹³C NMR** (100 MHz, CDCl₃): \( \delta \) 138.0, 128.5, 127.9, 83.0, 72.4, 70.5, 70.1, 66.8, 33.0, 29.6, 25.8, 18.9, -4.8.

**HRMS** (ESI⁺) m/z calcd for C₁₉H₃₅O₄Si [M + H]⁺ 355.2305, found 355.2301.
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(((2S, 3R)-3-(Benzyloxy)-4-((S)-oxiran-2-yl)butan-2-yl)oxy)(tert-butyl)dimethylsilane (77): Compound 77 was prepared following the procedure as described for 71 (colorless liquid).

Yield: 0.18 g, 90%

Mol. Formula: C_{19}H_{32}O_3Si

[α]_D^{25}: +12.8 (c 0.5, CHCl₃).

IR (CHCl₃, cm⁻¹): ν_{max} 2930, 2856, 1620, 1600, 1557, 1501, 1310.

¹H NMR (400 MHz, CDCl₃): δ 7.30-7.21 (m, 5H), 4.74-4.45 (m, 2H), 3.87-3.79 (m, 1H), 3.51-3.30 (m, 1H), 3.05-2.95 (m, 1H), 2.73-2.61 (m, 1H), 2.44-2.35 (m, 1H), 1.92-1.37 (m, 2H), 1.10 (t, J=6.22 Hz, 3H), 0.81-0.79 (m, 9H), 70.02-70.04 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 138.8, 135.6, 128.3, 127.8, 127.5, 81.7, 73.1, 70.5, 50.1, 47.8, 34.5, 34.0, 25.8, 19.2, -4.4, -4.7.

HRMS (ESI⁺) m/z calcd for C_{19}H_{33}O_3Si [M + H] 337.2199, found 337.2196.

(3S, 5R, 6S)-5-(Benzyloxy)-6-((tert-butyldimethylsilyl)oxy)hept-1-en-3-ol (67): Compound 67 was prepared following the procedure as described for 65 (colorless liquid).

Yield: 0.41 g, 80%

Mol. Formula: C_{20}H_{33}O_3Si

[α]_D^{25}: +26.42 (c 1.1, CHCl₃).

IR (CHCl₃, cm⁻¹): ν_{max} 3290, 3032, 2430, 1652, 1561, 1504, 1215, 1012, 901, 876.

¹H NMR (400 MHz, CDCl₃): δ 7.27-7.16 (m, 5H), 5.83-5.67 (m, 1H), 5.21-4.96 (m, 2H), 4.77-4.41 (m, 2H), 4.25-4.18 (m, 1H), 3.93-3.77 (m, 1H), 3.56-3.46 (m, 1H), 1.74-1.59 (m, 2H), 1.09 (d, J=6.42 Hz, 3H), 0.83-0.82 (m, 9H), -0.01 (s, 6H).
\(^{13}\text{C} \text{NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 140.8, 138.2, 128.4, 127.9, 127.7, 114.2, 83.2, 72.5, 71.3, 76.6, 40.1, 37.5, 25.7, 18.9, -4.6, -4.7.

\(\text{HRMS (ESI\(^+\)) m/z calcd for C}_{20}\text{H}_{34}\text{O}_3\text{Si} [\text{M + H}]^+ 351.2355, \text{found 351.2350.}\)

\(\text{tert-Butyl((S)-1-((4R,6S)-2,2-dimethyl-6-vinyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (78):}\) To a dark blue solution of sodium-ammonia prepared from excess sodium and liquid ammonia (30 ml) was added a solution of 67 (0.05 g, 0.14 mmol) in THF (5 ml) at -78 °C. The solution was warmed to -50 °C and was stirred for 1 h. The reaction was quenched with ammonium chloride. The cooling bath was removed, and after all ammonia was evaporated, the mixture was diluted with water and the aqueous layer extracted with EtOAc. The extract was washed with water, and was concentrated under reduced pressure.

To a solution of this compound in DCM (5 mL) at 25 °C was added 2-methoxypropene (40 µL, 0.42 mmol), followed by PPTS (2.5 mg, 10 µmol) portionwise. The reaction mixture was stirred at 25 °C for 15 min, then quenched with solid NaHCO\(_3\) and stirred for 30 min. The reaction mixture was filtered through a pad of celite and concentrated. Silica gel column chromatography using petroleum ether:ethyl acetate (24:1) gave 78 as a colorless liquid.

**Yield:** 0.036 g, 85%

**Mol. Formula:** C\(_{16}\)H\(_{32}\)O\(_3\)Si

\([\alpha]_D^{25}\): +11.50 \((c 0.5, \text{CHCl}_3)\).

**IR (CHCl\(_3\), cm\(^{-1}\)):** \(\nu_{\text{max}}\) 2901, 2823, 1580, 1545, 1309, 745.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 5.92-5.79 (m, 1H), 5.27-5.18 (m, 1H), 5.13-5.04 (m, 1H), 4.39-4.18 (m, 1H), 3.98-3.70 (m, 1H), 3.64-3.55 (m, 1H), 1.92-1.64 (m, 2H), 1.57 (s, 6H), 1.15-1.11 (m, 3H), 0.88-0.86 (m, 9H), 0.05 (m, 6H).
**13C NMR** (100 MHz, CDCl₃): δ 139.0, 115.3, 114.2, 98.5, 73.4, 71.3, 70.2, 32.7, 30.1, 29.7, 25.8, 19.9, -4.4, -4.6.

**HRMS** (ESI⁺) m/z calcd for C₁₆H₃₃O₃Si [M + H]⁺ 301.2199, found 303.2197.

((5R, 9S)-7, 7-Diisopropyl-1-(4-methoxyphenyl)-5,9-divinyl-2,6,8-trioxa-7-silatridecane (63): Dichlorodiisopropylsilane (0.085 ml, 0.48 mmol) was added to imidazole (0.089 g, 1.31 mmol) in DCM (0.24 ml) at 0 ºC. The solution was stirred for 5 minutes, then the fragment 65 (0.05 g, 0.437 mmol) in DCM (0.18 ml) was added dropwise over 1 h period at 0 ºC. After the mixture was stirred for 15 minutes at 0 ºC, a solution of the fragment 66 (0.097 g, 0.437 mmol) in DCM (0.035 mL) was added at 0 ºC. The reaction mixture was warmed to the room temperature and stirred for 14 h. The reaction mixture was filtered and washed with hexane, then concentrated in vacuo to afford the crude oil, which was purified by flash chromatography on silica gel (pet ether:ethyl acetate = 95:5) to afford bisalkoxysilane 63 as a colorless oil.

**Yield:** 0.196 g, 87%

**Mol. Formula:** C₂₆H₄₄O₄Si

[α]₀²⁵ – 1.98 (c 1.3, CHCl₃).

**IR** (CHCl₃, cm⁻¹): νₘₐₓ 2933, 2867, 1613, 1514, 1464, 1248, 1089, 1039, 920, 885.

**¹H NMR** (400 MHz, CDCl₃): δ 7.31-7.24 (m, 2H), 6.92-6.85 (m, 2H), 5.95-5.74 (m, 2H), 5.23-5.01 (m, 4H), 4.55-4.24 (m, 4H), 3.82 (s, 3H), 3.63-3.44 (m, 2H), 2.02-1.76 (m, 2H), 1.35-1.23 (m, 7H), 1.05-1.04 (m, 12H), 0.97-0.93 (m, 3H).

**¹³C NMR** (100 MHz, CDCl₃): δ 159.0, 141.4, 141.1, 129.4, 129.2, 113.9, 113.7, 113.7, 73.6, 72.6, 70.9, 66.4, 55.3, 38.0, 37.7, 22.8, 22.6, 17.4, 17.2, 14.3.

**HRMS** (ESI⁺) m/z calcd for C₂₆H₄₄O₄Si [M + Na]⁺ 471.2907, found 471.2907.
(5R, 9S, 11R, 12S)-11-(Benzyloxy)-7,7-diisopropyl-1-(4-methoxyphenyl)-12,14,14,15,15-pentamethyl-5,9-divinyl-2,6,8,13-tetraoxa-7,14-disilahexadecane (64): Dichlorodiisopropylsilane (0.028 ml, 0.15 mmol) was added to imidazole (0.029 g, 1.31 mmol) in DCM (0.13 ml) at 0 °C. The solution was stirred for 5 minutes, then the fragment 67 (0.05 g, 0.142 mmol) in DCM (0.1 ml) was added dropwise over 1 h period at 0 °C. After the mixture was stirred for 15 minutes at 0 °C, a solution of the fragment 66 (0.031 g, 0.142 mmol) in DCM (0.1 ml) was added at 0 °C. The reaction mixture was warmed to the room temperature and stirred for 14 h. The reaction mixture was filtered and washed with hexane, then concentrated in vacuo to afford the crude oil, which was purified by flash chromatography on silica gel (pet ether:ethyl acetate = 95:5) to afford bis-alkoxysilane 64 as a colorless oil.

Yield: 0.084 g, 87%

**Mol. Formula:** C_{39}H_{64}O_{6}Si_{2}

$[\alpha]_{D}^{25}$: +26.86 (c 0.2, CHCl₃).

**IR (CHCl₃, cm⁻¹):** $\nu_{\text{max}}$ 2935, 2856, 1713, 1600, 1504, 1265, 1065, 1071, 920, 885.

**¹H NMR (400 MHz, CDCl₃):** δ 7.27-7.15 (m, 7H), 6.82-6.77 (m, 2H), 5.84-5.62 (m, 2H), 5.12-4.91 (m, 4H), 4.48-4.19 (m, 6H), 4.03-3.79 (m, 1H), 3.73 (s, 3H), 3.66-3.26 (m, 3H), 1.68-1.66 (m, 4H), 1.53-1.33 (m, 2H), 1.07 (d, $J$=6.31 Hz, 3H), 0.95-0.94 (m, 12H), 0.83 (s, 9H), -0.02 (s, 6H).

**¹³C NMR (100 MHz, CDCl₃):** δ 159.0, 140.9, 139.3, 139.1, 130.8, 129.1, 128.2, 127.6, 127.3, 127.2, 114.6, 113.7, 81.6, 72.9, 72.7, 71.6, 71.2, 70.6, 55.2, 39.9, 26.0, 25.8, 18.0, 17.4, 17.3, -4.6, -4.7.

**HRMS (ESI⁻) m/z calcd for C_{39}H_{64}O_{6}Si_{2} [M + Na]⁻: 707.4139, found 707.4139.**
(4S, 7R)-4-Butyl-2,2-diisopropyl-7-(2-(4-methoxybenzylxy)ethyl)-4,7-dihydro-1,3,2-dioxasilepine (79): A solution of 0.1 g (0.22 mmol) 63 in 50 mL toluene was degassed (for 5 minutes using argon), then 0.006 g (0.006 mmol) Grubbs-II catalyst A were added and the solution was degassed again. It was stirred at 80 °C for 18 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (pet ether:ethyl acetate = 95:5) to give cyclized product 79.

Yield: 0.082 g, 88%

Mol. Formula: C_{24}H_{40}O_{4}Si

[α]_D^{25}: + 3.00 (c 0.65, CHCl₃).

IR (CHCl₃, cm⁻¹): ν_max 2929, 2865, 1612, 1513, 1465, 1248, 1092, 884.

¹H NMR (400 MHz, CDCl₃): δ 7.23-7.21 (m, 2H), 6.91-6.88 (m, 2H), 5.86-5.39 (m, 2H), 4.88-4.48 (m, 2H), 3.79 (s, 3H) 3.75-3.43 (m, 4H), 1.40-1.29 (m, 10H), 1.03 (s, 12 H), 0.89-0.87 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 159.1, 135.5, 134.8, 133.9, 129.32, 113.7, 72.8, 71.0, 67.9, 66.7, 55.3, 38.6, 38.3, 22.6, 22.5, 17.6, 17.2, 14.1.

HRMS (ESI⁺) m/z calcd for C_{24}H_{44}O_{4}Si [M + H]⁺ 421.2774, found 421.2775.

(4S, 7R)-4-((2R, 3S)-2-(Benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-2,2-diisopropyl-7-((2-(4-methoxybenzylxy)oxy)ethyl)-4,7-dihydro-1,3,2-dioxasilepine (82): A solution of 0.075 g (0.109 mmol) 64 in 18 mL toluene was degassed (for 5 minutes using argon), then 2 mg (3.28 µmol) Hoveyda–Grubbs second-generation catalyst B were added and the solution was degassed again. It was stirred at 80 °C for
18 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (pet ether:ethyl acetate = 90:10) to give cyclized product 80.

**Yield:** 0.054 g, 75%

**Mol. Formula:** C_{37}H_{59}O_{6}Si_{2}

[α]_D^{25}: 27.98 (c 0.8, CHCl_3).

**IR (CHCl_3, cm⁻¹):** ν_{max} 2931, 2901, 2301, 1800, 1654, 1466, 885, 847, 770, 681.

**¹H NMR (400 MHz, CDCl_3):** δ 7.27-7.18 (m, 7H), 6.83-6.78 (m, 2H), 5.60-4.63 (m, 2H), 4.61-4.36 (m, 4H), 4.16-3.97 (m, 1H), 3.87-3.78 (m, 1H), 3.73 (s, 3H), 3.65-3.35 (m, 3H), 2.36-1.46 (m, 7H), 1.11 (d, J=6.19 Hz, 3H), 0.98-0.94 (m, 12H), 0.83 (s, 9H), -0.01 (s, 6H).

**¹³C NMR (100 MHz, CDCl_3):** δ 159.2, 138.7, 129.4, 128.2, 128.0, 127.8, 127.5, 113.7, 80.9, 72.9, 72.7, 71.0, 68.5, 67.9, 64.9, 55.2, 39.1, 39.0, 30.2, 25.8, 18.0, 17.2, 16.9, -4.5, -4.6.

**HRMS (ESI⁻) m/z calcd for C_{37}H_{60}O_{6}Si_{2} [M + H]⁻ 657.4007, found 657.4007.**

2-((4R, 7S)-7-Butyl-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)ethanol (81): To a stirring solution of PMB ether 79 (0.070 g, 0.164 mmol) in DCM/H_2O (0.5:0.03) was added DDQ (0.046 g, 0.199 mmol). The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous NaHCO₃ and further diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (80:20) as eluent gave 81.

**Yield:** 0.046 g, 93%
Mol. Formula: C\textsubscript{16}H\textsubscript{32}O\textsubscript{3}Si

[α]\textsubscript{D}\textsuperscript{25}—6.18 (c 1.0, CHCl\textsubscript{3}).

IR (CHCl\textsubscript{3}, cm\textsuperscript{-1}): ν\textsubscript{max} 3456, 2929, 2865, 1665, 1465, 1248, 1092, 884.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 5.68-5.45 (m, 2H), 3.89-3.83 (m, 2H), 3.66-3.62 (m, 2H), 1.35-1.29 (m, 10H), 0.92-0.80 (m, 15H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 135.2, 132.8, 71.8, 71.0, 61.3, 39.1, 37.7, 22.7, 22.6, 19.8, 17.2, 14.1.

HRMS (ESI\textsuperscript{+}) m/z calcd for C\textsubscript{16}H\textsubscript{32}O\textsubscript{3}Si [M + Na]\textsuperscript{+} 323.2018, found 323.2018.

2-((4\textsubscript{R}, 7S)-7-((2\textsubscript{R}, 3S)-2-(Benzyl oxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)ethanol (82): To a stirring solution of PMB ether 80 (0.050 g, 0.076 mmol) in DCM/H\textsubscript{2}O (0.2:0.012) was added DDQ (0.020 g, 0.091 mmol). The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous NaHCO\textsubscript{3} and further diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (80:20) as eluent gave 82.

Yield: 0.037 g, 92%

Mol. Formula: C\textsubscript{29}H\textsubscript{52}O\textsubscript{5}Si\textsubscript{2}

[α]\textsubscript{D}\textsuperscript{25} 12.43 (c 0.8, CHCl\textsubscript{3}).

IR (CHCl\textsubscript{3}, cm\textsuperscript{-1}): ν\textsubscript{max} 3440, 2967, 2861, 1609, 1582, 1513, 1445, 1348, 1092, 889.
\( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): δ 7.33-7.25 (m, 5H), 5.70-5.46 (m, 2H), 5.00-4.82 (m, 2H), 4.78-4.63 (m, 1H), 4.60-4.45 (m, 1H), 3.94-3.83 (m, 3H), 3.76-3.40 (m, 1H), 1.96-1.58 (m, 6H), 1.18-1.15 (m, 3H), 1.06-0.99 (m, 12H), 0.89 (s, 9H), 0.07-0.01 (m, 6H).

\( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): δ 138.9, 135.7, 135.4, 134.9, 128.2, 127.8, 80.5, 73.3, 72.5, 69.3, 68.4, 61.3, 39.2, 29.7, 25.8, 18.5, 17.4, 17.1, -4.5, -4.7.

HRMS (ESI\(^+\)) m/z calcd for C\(_{29}\)H\(_{52}\)O\(_5\)Si\(_2\) [M + Na]\(^+\) 559.3251, found 559.3252.

(Z)-Ethyl 4-([4\(R\), 7\(S\)]-7-buty1-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-y1)but-2-enoate (83): Dess–Martin periodinane (0.046 g, 0.109 mmol) was added to a solution of compound 81 (0.030 g, 0.099 mmol) and pyridine (0.04 ml, 0.49 mmol) in DCM (0.8 ml) at 0 °C. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous Na\(_2\)S\(_2\)O\(_3\) and saturated aqueous NaHCO\(_3\). The organic layer was washed with satd NaCl solution and dried over Na\(_2\)SO\(_4\) and concentrated to afford an aldehyde that was used immediately in the next step without further purification.

To a solution of (PhO)\(_2\)P(O)CH\(_2\)COOEt (0.043 g, 0.108 mmol) in THF (0.6 mL) at 0°C was added NaI (0.012 g, 0.084 mmol). After 5 min NaH (60% dispersion, 0.002 g, 0.108 mmol) was added, and the resulting solution was cooled to −78 °C. The aldehyde (0.026 g, 0.084 mmol) dissolved in 0.6 mL of THF was then added drop wise. After 2 h at −78 °C, saturated NH\(_4\)Cl (0.7 mL) was added and the reaction mixture was extracted with Et\(_2\)O (3×5 mL). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. The crude product was purified by flash chromatography using pet ether:ethyl acetate (85:15) as eluent to give 83.

Yield: 0.033 g, 90%

Mol. Formula: C\(_{20}\)H\(_{36}\)O\(_4\)Si

\([\alpha]_0^{25}\) : −7.60 (c 0.3, CHCl\(_3\)).
IR (CHCl₃, cm⁻¹): νmax 2930, 2861, 1723, 1650, 1610, 1512, 1460, 1241, 1092, 885.

¹H NMR (400 MHz, CDCl₃): δ 6.46-6.39 (m, 1H) 5.87-5.84 (m, 1H), 5.66-5.58 (m, 1H), 5.51-5.44 (m, 1H), 4.82-4.54 (m, 2H), 4.18-4.14 (m, 2H), 3.08-2.99 (m, 1H), 2.90-2.80 (m, 1H), 1.32-1.26 (m, 1H), 1.03-0.98 (m, 12H), 0.90-0.88 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 166.5, 146.5, 135.1, 132.9, 120.9, 71.1, 70.2, 59.9, 38.3, 37.3, 22.7, 22.5, 17.6, 17.1, 14.3, 14.1.

HRMS (ESI⁺) m/z calcd for C₂₀H₃₇O₅Si [M + H]⁺ 369.2461, found 369.2464.

(Z)-Ethyl 4-((4R, 7S)-7-((2R, 3S)-2-(benzylloxy)-3-((tert-butylidemethylsilyloxy)butyl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)but-2-enolate (84): Dess–Martin periodinane (0.026 g, 0.061 mmol) was added to a solution of compound 82 (0.030 g, 0.055 mmol) and pyridine (22 µl, 0.3 mmol) in DCM (0.5 ml) at 0 °C. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃. The organic layer was washed with satd NaCl solution and dried over Na₂SO₄ and concentrated to afford an aldehyde that was used immediately in the next step without further purification.

To a solution of (PhO)₂P(O)CH₂COOEt (0.026 g, 0.07 mmol) in THF (0.3 mL) at 0°C was added NaI (8 mg, 0.054 mmol). After 5 min NaH (60% dispersion, 0.003 g, 0.07 mmol) was added, and the resulting solution was cooled to −78 °C. The aldehyde (0.029 g, 0.054 mmol) dissolved in 0.3 mL of THF was then added drop wise. After 2 h at −78 °C, saturated NH₄Cl (0.7 mL) was added and the reaction mixture was extracted with Et₂O (3×5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated. The crude product was purified by flash chromatography using pet ether:ethyl acetate (85:15) as eluent to give 84.

Yield: 0.030 g, 93%
**Mol. Formula**: C_{20}H_{36}O_{4}Si

[α]D<sup>25</sup>: 18.06 (c 0.6, CHCl₃).

**IR** (CHCl₃, cm⁻¹): ν<sub>max</sub> 2932, 2867, 1742, 1705, 1670, 1620, 1422, 1302, 1274, 1101, 965, 889, 773.

**¹H NMR** (400 MHz, CDCl₃): δ 7.33-7.27 (m, 5H), 6.46-6.36 (m, 1H), 5.86 (d, J=11.7 Hz, 1H), 5.67-5.48 (m, 2H), 4.92-4.46 (m, 5H), 4.16 (q, J=7.15 Hz, 2H), 3.94-3.83 (m, 1H), 1.79-1.57 (m, 4H), 1.27-1.24 (m, 5H), 1.18-1.15 (m, 3H), 1.02-0.98 (m, 12H), 0.88 (s, 9H), 0.06 (m, 6H).

**¹³C NMR** (100 MHz, CDCl₃): δ 166.4, 146.3, 139.0, 128.2, 127.8, 127.7, 127.4, 121.0, 80.5, 72.5, 70.2, 68.4, 59.8, 40.8, 37.5, 29.7, 25.8, 19.1, 17.4, 17.2, 14.3, -4.5, -4.7.

**HRMS** (ESI⁺) m/z calcd for C_{33}H_{56}O_{6}Si₂ [M + H]⁺ 605.3694, found 605.3696.

**Desacetyllumuravumbolide (8a)**: To a stirred solution of compound 83 (25 mg, 67.8 µmol) in THF (0.6 mL) was added TBAF (40 µL, 0.13 mmol) at room temperature and the yellow solution was stirred overnight at the same temperature. Water was added and the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated to give crude triol, which was used for the next step without purification.

The diol was dissolved in benzene (0.4 mL) and Ti(OiPr)₄ (2 µL, 6 µmol) was added. The yellow solution was refluxed for 1 h. The solution was cooled to RT and the solvent was removed in vacuo. The residue was purified by flash chromatography (100 g silica gel, DCM/MeOH, 98:2) to yield lactone 8a as a colorless oil.

**Yield**: 16 mg, 92%

**Mol. Formula**: C_{12}H_{18}O_{3}
IR (CHCl₃, cm⁻¹): νmax 3456, 1720, 1685, 1644, 1390, 1060.

¹H NMR (400 MHz, CDCl₃): δ 6.89-6.87 (m, 1H), 6.00-5.97 (m, 1H), 5.78-5.65 (m, 1H), 4.62-4.34 (m, 1H), 2.41-2.19 (m, 2H), 1.56-1.47 (m, 2H), 1.45-1.26 (m, 4H), 0.93 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 164.1, 146.6, 135.8, 127.4, 123.1, 72.8, 67.2, 37.0, 29.9, 27.0, 23.1, 14.0.

HRMS (ESI⁺) m/z calcd for C₁₂H₁₅O₃ [M + Na]⁺ 233.1154, found 233.1155.

Umuravumbolide (8b): To a stirred solution of compound 8a (15 mg, 0.071 mmol) in dry CH₂Cl₂ (1.5 mL) was added Et₃N (0.023 mL, 0.171 mmol), acetic anhydride (0.008 mL, 0.085 mmol), DMAP (1.75 mg, 0.009 mmol) and the resulting mixture was stirred at room temperature for 1 h. After completion of the reaction, water was added, the organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (3x5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane, 2:8) afforded 8b as a yellow oil.

Yield: 16.5 mg, 92%

Mol. Formula: C₁₄H₂₀O₄

[α]D²⁵: [α]D²⁵ = −2.3 (c 0.5, CHCl₃), lit.²⁹ [α]D²⁵ = −5.3 (c 1.3, CHCl₃).

IR (CHCl₃, cm⁻¹): νmax 1745, 1730, 1685, 1256.

¹H NMR (400 MHz, CDCl₃): δ 6.88-6.86 (m, 1H), 6.03-5.99 (m, 1H), 5.93-5.66 (m, 1H), 5.42-5.08 (m, 3H), 2.31-2.29 (m, 2H), 2.02 (s, 3H), 1.41-1.35 (m, 6H), 0.87 (m, 3H).
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 169.7, 163.5, 146.4, 130.9, 130.5, 123.7, 72.8, 69.9, 34.5, 30.2, 28.9, 22.2, 21.9, 14.0.

HRMS (ESI\(^{+}\)) m/z calcd for C\(_{14}\)H\(_{20}\)O\(_4\) [M + Na]\(^+\) 275.1259, found 275.1258.

\((R)-6\)-((3\(S\), 5\(R\), 6\(S\), Z)-5-(Benzyloxy)-3,6-dihydroxyhept-1-en-1-yl)-5,6-dihydro-2H-pyran-2-one (85): To a stirred solution of compound 84 (25 mg, 40 \(\mu\)mol) in THF (0.6 mL) was added TBAF (85 \(\mu\)L, 0.293 mmol) at room temperature and the yellow solution was stirred overnight at the same temperature. Water was added and the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with Na\(_2\)SO\(_4\) and concentrated to give crude triol, which was used for the next step without purification.

The diol was dissolved in benzene (0.2 mL) and Ti(OiPr)\(_4\) (1.2 \(\mu\)L, 4 \(\mu\)mol) was added. The yellow solution was refluxed for 1 h. The solution was cooled to RT and the solvent was removed in vacuo. The residue was purified by flash chromatography (100 g silica gel, DCM/MeOH, 98:2) to yield lactone 85 as a colorless oil.

**Yield:** 12.6 mg, 96%

**Mol. Formula:** C\(_{19}\)H\(_{24}\)O\(_5\)

\([\alpha]_D^{25}\) \(\approx\) 1.7 (c 0.7, CHCl\(_3\)).

**IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 3330, 2937, 1823, 1654, 1470, 1320, 1245, 1076, 872.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.30-7.23 (m, 5H), 6.40-6.31 (m, 1H), 5.80 (d, \(J\)=11.87 Hz, 1H), 5.62-5.43 (m, 2H), 4.87-4.54 (m, 3H), 3.88-3.79 (m, 1H), 1.74-1.52 (m, 4H), 1.13-1.10 (m, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 172.6, 144.2, 139.0, 130.7, 129.8, 128.5, 127.9, 127.7, 127.6, 126.7, 84.0, 70.3, 67.1, 66.6, 64.7, 41.6, 31.6, 22.4.

HRMS (ESI\(^{+}\)) m/z calcd for C\(_{19}\)H\(_{24}\)O\(_5\) [M + Na]\(^+\) 355.1521, found 355.1521.
**Hyptolide (9):** To a solution of 85 (10 mg, 30 µmol) in anhydrous DCM (0.35 mL) under nitrogen at 0 °C was added TiCl$_4$ (28 mg, 16 µL, 0.15 mmol). After 20 min, excess of reagent was quenched with water, extracted with DCM, washed with water, dried (Na$_2$SO$_4$) and evaporated to afford the triol that was used immediately in the next step without further purification.

The triol was then dissolved in dry CH$_2$Cl$_2$ (0.12 mL) and treated with Et$_3$N (33 µL, 0.24 mmol), acetic anhydride (20 µL, 0.2 mmol) and DMAP (1.4 mg, 12 µmol). After stirring overnight, the reaction mixture was worked up (extraction with DCM) and chromatographed on a silica gel column (pet ether:ethyl acetate = 70:30) to give hyptolide 9 as a colorless solid.

**Yield:** 7 mg, 90%

**Mol. Formula:** C$_{18}$H$_{24}$O$_8$

**MP** 83–86 °C, lit.$^{43}$ mp 87–88 °C

[α]$_D^{25}$: +12.3 (c 0.7, CHCl$_3$), lit.$^{43}$ [α]$_D^{25}$ +11.2 (c 0.6, CHCl$_3$).

**IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 1737, 1645, 1280.

**$^1$H NMR** (400 MHz, CDCl$_3$): δ 6.86-6.84 (m, 1H), 6.09-6.03 (m, 1H), 5.73-5.71 (m, 1H), 5.52-5.50 (m, 2H), 5.11-5.07 (m, 1H), 5.03-4.80 (m, 2H), 2.36-2.33 (m, 2H), 2.04-2.02 (m, 10H), 1.81 (s, 1H), 1.15-1.11 (m, 3H).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): δ 169.7, 169.0, 164.8, 139.2, 129.5, 126.5, 124.0, 72.8, 70.5, 69.9, 67.2, 61.5, 33.7, 22.6, 14.0.

**HRMS** (ESI$^+$) m/z calcd for C$_{18}$H$_{24}$O$_8$ [M + Na]$^+$ 511.2492, found 511.2495.
### 3.1.7. Spectra

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<td>12</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
<td>78</td>
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<tr>
<td>13</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
<td>63</td>
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<td>14</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
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<td>$^1$H and $^{13}$C spectra of compound</td>
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<td>$^1$H and $^{13}$C spectra of compound</td>
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<td>19</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
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<tr>
<td>20</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
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<td>21</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
<td>8a</td>
</tr>
<tr>
<td>22</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
<td>85</td>
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<td>23</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
<td>8b</td>
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<td>24</td>
<td>$^1$H and $^{13}$C spectra of compound</td>
<td>9</td>
</tr>
<tr>
<td>25</td>
<td>$^{19}$F spectra of compound</td>
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</tr>
</tbody>
</table>
Chapter 3: Section A
Chapter 3: Section A
$^{19}$F spectrum of Möscher ester of 58
3.1.8. References

10 Olliaro, P.; Bryceson, A. Parasitol. Today 1993, 9, 323.
19 Pereda, R.; Fragoso, M.; Cerda, C. Tetrahedron 2001, 57, 47.
168


31 The reagent used was of 84% *ee*. Midland reported 92% *ee* with optically pure reagent for a similar alcohol on the basis of *¹H NMR* analysis in the presence of Eu(dcm)3.

32 To confirm the efficacy of this upgradation procedure, we prepared 1-buty-3-ol and 1-octyn-3-ol of 72% and 76% *ee*, respectively, by Alpine-Borane (84% *ee*) reduction of the corresponding ketone and upgraded them to 99% *ee* via the 3,5-dinitrobenzoate.


34 We did not observe any of the diastereomers by *¹H NMR* spectroscopy. The configuration is based on analogy for allylboration with 15. This was confirmed by the rotation of the target molecule.


In anticipation of unsatisfactory diastereoselectivities in reactions of aldehyde 43 with standard ethynylating reagents such as ethynylmagnesium bromide (as turned out to be the case), we envisaged the oxidation of the resulting alcohols (46+epimer) to a conjugated ynone, followed by stereoselective reduction. Since a free β-hydroxy carbonyl group might be convenient for that purpose, we placed an easily cleavable silyl group (TES) at this position.

Frantz, D. E.; Fa’ëssler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. In addition to trimethylsilylacetylene, we also used 2-methyl-3-butyn-2-ol: Boyall,
However, whereas the addition step was successful, all attempts to cleave the acetone fragment only led to decomposition.


For examples of silicon-tethered ring-closing metathesis cross-coupling reactions, see: Hoye, T. R.; Promo, M. A. Tetrahedron Lett. 1999, 40, 1429; Van de

68 The enantiomeric excess of diol 72 was determined by converting its derivative allylic alcohol 66 into the Möscher ester and analyzing the $^{19}$F spectrum (see the spectrum).
3.2 Section B

ATTEMPTED TOTAL SYNTHESIS OF HYPURTICIN VIA TEMORARY SILICON TETHERED-RING CLOSING METATHESIS

3.2.1. Introduction

Currently, chemical and pharmacological research are largely directed toward the discovery of new cytotoxic agents from natural sources.\(^1\) Configurational and conformational behaviour of bioactive principles requires an accurate description of their three-dimensional properties, thus permitting visualization and understanding of the possible interactions with target biomolecules.\(^2\) For example, a relevant group of cytotoxic compounds, occurring in several members of the mint family (Lamiaceae), comprises polyacylated-6-heptenyl-5,6-dihydro-2H-pyran-2-ones\(^3\) (e.g., 1-8, Figure 1) containing an \(\alpha,\beta\)-unsaturated \(\delta\)-lactone known to bind protein thiol groups. This class of bioactive chemicals is structurally related to pironetin, an anticancer natural product, which selectively targets Lys-352 of R-tubulin.\(^4\) Compounds such as hyptolide (2),\(^5\) spicigerolide (3),\(^6\) pectinolides A-C (4-6),\(^7\) and 10-epi-olguine (7)\(^8\) exhibit activity against specific tumor cell lines. However, the mechanism of action, the specific molecular target, the pharmacophore conformational requirements, and, in some cases, the absolute configuration of the stereogenic centers in the flexible side chain are not yet established, as in the case of the polyacylated chain of hypurticin (1), a natural 6-heptenyl-5,6-dihydro-2H-pyran-2-one. During the isolation of 1 from *Hyptis urticoides* by Romo de Vivar’s group,\(^9\) the C-6 absolute configuration was established as \(S\) by chiroptical measurements, the CD curve showing a positive Cotton effect similar to that of previously known 6-substituted-5,6-dihydro-R-pyrone,\(^10\) such as hyptolide (2)\(^5\) and olguine (8).\(^11\) The C-5 stereogenic center was assigned the \(S\) configuration due to the \(J_{5,6}\) coupling constant, which evidenced the \(cis\) relationship between these hydrogens.\(^9\) However, the absolute configuration of the stereogenic centers located at the heptenyl side chain could not be determined. The variety of configurational possibilities and the high number of conformational arrangements...
arising from the flexibility of this molecular moiety precluded its full structural
determination at that time. However recently Pereda-Miranda and co-workers\textsuperscript{12a}
determined the configuration of polyacylated chain of hypurticin and the revised
structure was found to correspond to that of pectinolide E, recently isolated from
\textit{Hyptis pectinata}.\textsuperscript{12b}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{6-Heptenyl-5,6-dihydro-2\textit{H}-pyran-2-ones from Lamiaceae.}
\end{figure}
3.3.2. PRESENT WORK

Objective

As discussed in foregoing section, with the development of an efficient approach to the synthesis of polyacylated-6-heptenyl-5,6-dihydro-2H-pyran-2-ones such as umuravumbolide, hyptolide through a silicon tethered ring-closing metathesis reaction sequence, our attention was further focused to extrapolate this protocol for the synthesis of hypurticin (1). Synthetic studies toward the aforementioned molecules (2-6) have been reported by Marco,13 Chakraborty,13b and Yadav et al.13c To the best of our knowledge, all attempts have been in linear fashion involving semi-hydrogenation of the alkyne part using Lindlar’s catalyst to generate the side chain olefin and ring closing metathesis reaction for the construction of lactone ring. However, no total synthesis of hypurticin 1 has yet been reported.

As a part of our current interest in naturally occurring, pharmacologically active α, β-unsaturated δ-lactone,14 we have attempted at the first total synthesis of hypurticin 1 by a highly convergent strategy to confirm its structure, including the absolute stereochemistry. We note in advance that our approach is both concise and versatile exploiting temporary silicon tethered ring-closing metathesis (TST-RCM)15 and reaction of β-acetoxy aldehydes with the lithium enolate of methyl acetate16 to construct the olefins. The strategy provides convergent synthetic access to all members of the Lamiaceae family. The general synthetic analysis is depicted in Scheme 1.

Scheme 1. Retro-synthetic analysis of hypurticin 1.

We aimed to construct the side chain Z-olefin through ring closing metathesis of bis-siloxane intermediate 9. The intermediate 9 would originate by the coupling of two
allylic alcohols 10 and 11 which in turn could be derived from TBS protected L-lactaldehyde and diethyl L-tartrate 12 respectively.

3.2.3. Results and Discussion

Synthesis of fragment 10

The synthesis of fragment 10 is already mentioned in section B of chapter 3 (Scheme 9. Synthesis of fragment 67, page no. 114).

Synthesis of fragment 11

The preparation of fragment 11 is summarized in scheme 2. The introduction of benzyl group on the secondary alcohol moiety of the known epoxy alcohol 13,\textsuperscript{17} derived from diethyl L-tartrate 12 according to Tatsuta’s procedure afforded 14 in 90% yield. Appearance of multiplet in the range of $\delta$ 3.08-3.01, 2.72-2.68, 2.53-2.49 in $^1$H NMR and disappearance of OH peak in IR spectrum confirmed the formation of the product 14. The epoxide 14 was subsequently exposed to Corey–Chaykovsky’s\textsuperscript{18} condition (dimethylsulfonium methilide mediated opening of epoxide) to produce the one carbon homologated allylic alcohol fragment 11 in 85% yield and was confirmed by IR spectrum and $^1$H NMR. The IR spectrum of 11 gave broad hydroxyl absorption at 3414 cm\textsuperscript{-1} and the $^1$H NMR spectrum of 11 gave olefin peaks at $\delta$ 6.00-5.83 (multiplet, one proton) and 5.43-5.20 (multiplet, two protons) which confirmed the structure.

![Scheme 2. Preparation of fragment 11](image)

Coupling of Fragments 10 and 11: Synthesis of Hypurticin
With substantial amount of both the fragments in hand the coupling of allylic alcohol 10 and 11 was achieved by using the modified condition for tethering, used for the synthesis of umuravumbolide in the foregoing section, to afford the disiloxane intermediate 15 in 89% yield. The structure of 15 was proven by the $^1$H NMR and $^{13}$C NMR spectra. We next examined the ring closing metathesis (RCM) of disiloxane 15 using Grubbs catalyst (figure 2) under variety of reaction conditions to get exclusively the cis-product in appreciable yield (Table 1).

**Table 1.** Optimization of RCM condition for disiloxane 15

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst</th>
<th>solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs II A</td>
<td>DCM</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs II A</td>
<td>DCE</td>
<td>84</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Grubbs II A</td>
<td>Toluene</td>
<td>110</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs-Hoveyda II B</td>
<td>Toluene</td>
<td>110</td>
<td>65</td>
</tr>
</tbody>
</table>

**Scheme 3.** Synthetic strategy for hypurticin 1.
Initial few experiments using Grubbs second–generation catalyst A in different solvents such as DCM, DCE and toluene gave the required product albeit in low yield (Table 1; entry 1-3). However the best result was obtained when we employed Grubbs-Hoveyda second generation catalyst B in toluene at 110 °C providing the cyclized product 16 in 65% yield (Table 1; entry 4). The appearance of internal olefin at δ 5.98-5.70 and disappearance of four protons at δ 5.33-4.99 in 1H NMR confirmed the product.

Figure 2: Metal-alkylidene metathesis catalysts.

Our next objective toward the completion of the synthesis was to form the requisite lactone ring with unsaturation. Toward this end, we first deprotected the silyl groups using TBAF in THF and the crude triol thus obtained was eventually acetylated to give 17 in 92% yield. Appearance of singlet at δ 2.06, 2.02, 1.99 in 1H NMR and appearance of characteristic carbonyl group absorption of acetate at 1740 cm⁻¹ in IR spectrum confirmed the formation of the product 17. This was followed by removal of the PMB protecting group, to give the desired primary alcohol 18 in 92% yield. The IR spectra of 18 showed hydroxyl absorption at 3449 cm⁻¹. In the 1H NMR spectra, the peaks owing to PMB group disappeared. Dess Martin periodinane oxidation led to the formation of aldehyde, now properly functionalized to effect incorporation of the lactone ring in a single step using the lactone annulation process. Lactone annulation was effected by reaction of this material with the lithium enolate of methyl acetate (initially at –78 °C for 15 min with warming to 0 °C and reaction at that temperature for 30 min). After quenching and normal workup, the desired lactone 19 was obtained in 74% yield. The IR spectrum of 19 showed characteristic carbonyl group absorption of α,β-unsaturated δ-lactone at 1650 cm⁻¹.
Mechanism of the Cyclization Reaction

It was proposed that these reactions proceed via initial addition of the lithium enolate to the aldehyde carbonyl, followed by acetate migration and subsequent lactonization and β-elimination (Scheme 4). An alternative possibility involving an intramolecular condensation of an acetate enolate generated by a proton transfer-equilibration process is considered extremely unlikely on the basis of the following evidence (Table 2). First of all, with substrate 24, conversion to 21a was found to occur (albeit in lower yield) when the benzoate derivative was used in place of the acetate (Table 1, entries 2 and 3). This is consistent with the suggested pathway, and also with the expectation that the benzoate would undergo the critical migration step less readily than the acetate. Second, when the propionate 24 rather than the acetate derivative of substrate 23 was employed in a reaction with the enolate of methyl acetate, 23a was again obtained in essentially the same yield, demonstrating that the propionate group was lost in the reaction (Scheme 5). This result is compatible with the proposed overall pathway.

Table 2. Preparation of Lactone Products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>%Yield</th>
</tr>
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<tr>
<td>1</td>
<td><img src="" alt="Substrate 20" /></td>
<td><img src="" alt="Product 20a" /></td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td><img src="" alt="Substrate 21" /></td>
<td><img src="" alt="Product 21a" /></td>
<td>73</td>
</tr>
</tbody>
</table>
Scheme 4. Proposed mechanism

Scheme 5. Preparation of lactone

Unfortunately final debenzylation followed by the acetylation of secondary alcohols proved to be unsuccessful and could not give the target molecule hypurticin 1 (Scheme 3).

3.2.4. Conclusion

In conclusion, an attempt has been made to synthesize the polyacylated-6-heptenyl-5,6-dihydro-2H-pyran-2-one, hypurticin 1 by using temporary silicon tetherd ring closing metathesis (TST-RCM). The side chain Z-olefin and the α,β-unsaturated
lactone were synthesized successfully by the reaction of \( \beta \)-acetoxy aldehydes and the lithium enolate of methyl acetate as the key step.

### 3.2.5. Experimental Section

General Methods: All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. \(^1\)H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (\( \delta \)) downfield relative to CDCl\(_3\) as internal standard and \(^{13}\)C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (\( \delta \)) relative to CDCl\(_3\). Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.

\[
\text{(S)-2-((S)-1-(Benzyloxy)-2-((4-methoxybenzyl)oxy)ethyl)oxirane (14):} \quad \text{To the epoxy alcohol 13 (0.5 g, 2.23 mmol) in DMF (1.2 mL) at 0 \degree C was added NaH (60 \% dispersion in mineral oil, 0.10 g, 2.45 mmol). After 15 min, benzyl bromide (0.42g, 0.3 mL, 2.45 mmol) was introduced and the reaction mixture further stirred for 4 h at room temperature. Water was carefully added to the reaction mixture, extracted with diethyl ether, washed with water and dried (Na\(_2\)SO\(_4\)). Silica gel column chromatography of the crude product using petroleum ether/EtOAc (90:10) as eluent afforded benzyl compound 14.}
\]

**Yield:** 0.63 g, 90%

**Mol. Formula:** C\(_{19}\)H\(_{22}\)O\(_4\)Na

\([\alpha]_D^{25} \approx -9.02 \ (c 3, \text{CHCl}_3)\).

**IR (CHCl\(_3\), cm\(^{-1}\)):** \( v_{\max} 2970, 2858, 1457, 1460, 1370, 1256, 1110, 1001, 785.\)
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.32-7.26 (m, 5H), 7.23-7.13 (m, 2H), 6.81-6.76 (m, 2H), 4.76-4.54 (m, 2H), 4.40 (s, 2H), 3.72 (s, 3H), 3.54-3.51 (m, 2H), 3.27 (m, 1H), 3.08-3.01 (m, 1H), 2.72-2.68 (m, 1H), 2.53-2.49 (m, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 159.2, 138.2, 129.2, 128.2, 127.9, 127.7, 113.7, 79.1, 73.1, 71.9, 70.0, 55.2, 53.1, 43.3.

HRMS (ESI\(^+\)) m/z calcd for C\(_{19}\)H\(_{22}\)O\(_4\)Na [M + Na]\(^+\) 337.1416, found 337.1417.

(3S, 4S)-4-(Benzyloxy)-5-((4-methoxybenzyl)oxy)pent-1-en-3-ol (11): To a suspension of trimethylsulfonium iodide (1.18 g, 5.82 mmol) in dry THF (2.5 mL) at \(-20^\circ\)C was added \(n\)-BuLi (3.88 mL, 1.6 M solution in hexane, 6.2 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide 14 (0.3 g, 0.95 mmol) in dry THF (1.5 mL) was added to the above reaction mixture and stirred for 3 h. After consumption of the starting material the reaction mixture was quenched with H\(_2\)O (10 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (85:15) gave 11 as a colorless liquid.

**Yield:** 0.26 g, 85%

**Mol. Formula:** C\(_{20}\)H\(_{24}\)O\(_4\)Na

\([\alpha]_D^{25}\): +1.52 (c 3.4, CHCl\(_3\)).

**IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 3414, 1613, 1586, 1248, 1089, 1039.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.40-7.35 (m, 5H), 7.29-7.24 (m, 2H), 6.92-6.88 (m, 2H), 6.00-5.83 (m, 1H), 5.43-5.20 (m, 2H), 4.79-4.48 (m, 5H), 4.29-4.24 (m, 1H), 3.82 (s, 3H), 3.73-3.55 (m, 3H), 2.42 (s, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 159.2, 138.0, 137.2, 129.9, 129.3, 128.3, 127.8, 127.7, 116.6, 113.7, 80.2, 73.1, 72.9, 72.5, 69.4, 55.2.

HRMS (ESI\(^+\)) m/z calcd for C\(_{20}\)H\(_{24}\)O\(_4\)Na [M + Na]\(^+\) 351.1572, found 351.1568.
(4S, 5S, 9S, 11R, 12S)-4,11-Bis(benzyloxy)-7,7-diisopropyl-1-(4-methoxyphenyl)-12,14,14,15,15-pentamethyl-5,9-divinyl-2,6,8,13-tetraoxa-7,14-disilahexadecane (15): Dichlorodiisopropylsilane (0.029 ml, 0.16 mmol) was added to imidazole (0.029 g, 0.43 mmol) in DCM (0.04 ml) at 0 ºC. The solution was stirred for 5 minutes, then the fragment 10 (0.05 g, 0.143 mmol) in DCM 0.035 ml) was added dropwise over a period of 1 h at 0 ºC. After the mixture was stirred for 15 minutes at 0 ºC, a solution of the fragment 11 (0.046 g, 0.143 mmol) in DCM (0.035 mL) was added at 0 ºC. The reaction mixture was warmed to the room temperature and stirred for 14 h. The reaction mixture was filtered and washed with hexane, then concentrated in vacuo to afford the crude oil, which was purified by flash chromatography on silica gel (pet ether:ethyl acetate = 98:2) to afford bis-alkoxysilane 15 as a colorless oil.

**Yield:** 0.094 g, 85%

**Mol. Formula:** C_{46}H_{70}O_{15}Si_{2}Na

[α]_D^{25} = −1.86 (c 1.1, CHCl₃).

**IR** (CHCl₃, cm⁻¹): ν max 2935, 2856, 1713, 1504, 1265, 1065, 1071, 920, 885.

**¹H NMR** (400 MHz, CDCl₃): δ 7.40-7.25 (m, 12H), 6.88 (d, J=8.37 Hz, 2H), 6.00-5.72 (m, 2H), 5.33-4.99 (m, 4H), 4.91-4.77 (m, 2H), 4.72-4.43 (m, 6H), 3.94-3.87 (m, 1H), 3.83 (s, 3H), 3.77-3.72 (m, 2H), 3.53-3.37 (m, 2H), 1.18-1.14 (m, 3H), 1.10-1.08 (m, 4H), 1.04-1.02 (m, 12H), 0.92 (s, 9H), 0.10-0.05 (m, 6H).

**¹³C NMR** (100 MHz, CDCl₃): δ 159.0, 140.9, 139.3, 139.1, 136.7, 134.8, 130.9, 129.1, 128.2, 127.6, 127.3, 127.2, 115.3, 114.6, 113.7, 81.6, 80.4, 72.9, 72.7, 72.4, 72.0, 71.6, 71.2, 70.63, 59.25, 39.9, 26.6, 26.0, 25.8, 18.7, 18.0, 17.4, 17.3, -4.6, -4.7.

**HRMS** (ESI⁺) m/z calcd for C_{46}H_{70}O_{15}Si_{2}Na [M + Na]⁺ 813.4558, found 813.4552.
(4S, 7S)-4-((S)-1-(Benzyloxy)-2-((4-methoxybenzyl)oxy)ethyl)-7-((2R, 3S)-2-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)butyl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepine (16): A solution of 0.07 g (0.088 mmol) 15 in 16 mL toluene was degassed (for 5 minutes using argon), then 1 mg (0.003 mmol) Hoveyda–Grubbs second-generation catalyst B was added and the solution degassed again. It was stirred at 80 °C for 18 h, before the solvent was removed in vacuo and the residue was purified by flash chromatography (pet ether:ethyl acetate = 98:2) to give cyclized product 16.

Yield: 0.043 g, 65%

Mol. Formula: C_{46}H_{70}O_{7}Si_{2}

\[ \alpha \]_D ^{25} = -1.73 \, (c \, 0.8, \, CHCl_3).

IR (CHCl_3, cm\(^{-1}\)): \( \nu_{\text{max}} \) 2931, 2901, 2301, 1800, 1654, 1466, 885, 847, 770, 681.

\(^{1}\)H NMR (400 MHz, CDCl_3): \( \delta \) 7.38-7.26 (m, 12H), 6.86 (d, \( J\) =8.60 Hz, 2H), 5.98-5.70 (m, 2H), 4.90-4.75 (m, 2H), 4.56-4.41 (m, 6H), 3.92-3.86 (m, 1H), 3.81 (s, 3H), 3.75-3.71(m,2H), 3.52-3.34 (m, 2H), 1.16-1.31 (m, 3H), 1.09-1.06 (m,4H), 1.02-1.00 (m, 12H), 0.90 (s,9H), 0.07-0.04 (m, 6H).

\(^{13}\)C NMR (100 MHz, CDCl_3): \( \delta \) 159.1, 139.2, 130.9, 130.4, 129.2, 128.8, 128.2, 127.9, 127.7, 127.4, 113.7, 81.2, 81.0, 73.8, 73.5, 72.9, 71.0, 69.9, 65.6, 55.3, 39.5, 30.6, 30.2, 29.6, 25.8, 19.2, 18.9, 17.3, 17.0, -4.5, -4.7.

HRMS (ESI\(^{+}\)) m/z calcd for C_{46}H_{71}O_{8}Si_{2} [M + H]\(^{+}\) 763.4425, found 763.4423.
(2S,3R,5S,8S,9S,Z)-3,9-Bis(benzyloxy)-10-((4-methoxybenzyl)oxy)dec-6-ene-2,5,8-triyl triacetate (17): To a stirred solution of compound 16 (40 mg, 52 µmol) in THF (0.5 mL) was added TBAF (0.1 mL, 0.37 mmol) at room temperature and the yellow solution was stirred overnight at the same temperature. Water was added and the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated to give crude triol, which was used for the next step without purification.

The triol was then dissolved in dry CH₂Cl₂ (0.25 mL) and treated with Et₃N (30 µL, 0.22 mmol), acetic anhydride (19 µL, 0.2 mmol) and DMAP (0.38 mg, 3 µmol). After stirring overnight, the reaction mixture was subjected to usual work up (extraction with CH₂Cl₂) and purification by silica gel column chromatography (pet ether:ethyl acetate = 80:20) to give triacetate 17.

Yield: 0.03 mg, 98%

Mol. Formula: C₃₈H₄₆O₁₀

[α]D²⁵: –20.45 (c 0.5, CHCl₃).

IR (CHCl₃, cm⁻¹): νmax 2900, 2301, 1800, 1740, 1654, 1513, 1445, 1348, 1092, 889.

¹H NMR (400 MHz, CDCl₃): δ 7.37-7.27 (m, 10H), 7.25-7.23 (m, 2H), 6.89-6.87 (m, 2H), 5.78-5.67 (m, 2H), 5.53-5.45 (m, 1H), 5.42-5.35 (m, 1H), 5.16-5.09 (m, 1H), 4.72-4.60 (m, 3H), 4.45-4.34 (m, 3H), 3.82 (s, 3H), 3.69-3.64 (m, 1H), 3.55-3.43 (m, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.71-1.69 (m, 2H), 1.23 (d, J=6.66 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 170.4, 169.9, 159.2, 138.2, 138.1, 131.8, 130.9, 131.2, 129.2, 128.9, 128.4, 128.3, 127.8, 127.7, 113.7, 79.0, 78.9, 73.1, 73.0, 71.8, 71.6, 70.9, 69.1, 55.2, 35.1, 21.3, 21.2, 21.1, 15.1.

HRMS (ESI⁺) m/z calcd for C₃₈H₄₇O₁₀ [M + H]⁺ 663.3169, found 663.3169.
To a stirring solution of PMB ether 17 (0.03 g, 0.052 mmol) in DCM/H$_2$O (0.15:0.008) was added DDQ (0.014 g, 0.063 mmol). The resulting mixture was stirred for 10 min at r.t. The mixture was poured into saturated aqueous NaHCO$_3$ and further diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (70:30) as eluent gave 18.

**Yield:** 0.026 g, 95%

**Mol. Formula:** C$_{30}$H$_{38}$O$_9$

[α]$_D^{25}$ – 17.61 (c 0.5, CHCl$_3$).

**IR (CHCl$_3$, cm$^{-1}$):** $\nu_{max}$ 3456, 2967, 2861, 2350, 1730, 1498, 1409, 1100, 905.

**$^1$H NMR (400 MHz, CDCl$_3$):** δ 7.37-7.29 (m, 10H), 5.71-5.59 (m, 2H), 5.44-5.42 (m, 1H), 5.36-5.32 (m, 1H), 5.10-5.09 (m, 1H), 4.70-4.45 (m, 4H), 3.56-3.42 (m, 5H), 2.04 (m, 6H), 1.98 (s, 3H), 1.74-1.69 (m, 2H), 1.21 (d, $J=6.7$Hz, 3H).

**$^{13}$C NMR (100 MHz, CDCl$_3$):** δ 170.4, 170.2, 170.1, 139.3, 137.9, 137.9, 132.3, 128.6, 128.5, 128.4, 127.9, 80.1, 73.4, 73.2, 71.8, 71.7, 70.0, 61.1, 35.1, 21.2, 21.1, 14.1.

**HRMS (ESI$^+$) m/z calcd for C$_{30}$H$_{39}$O$_9$ [M + H]$^+$ 543.2594, found 543.2596.

(2S,3R,5S,Z)-3-(benzyloxy)-7-((2S,3S)-3-(benzyloxy)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-6-ene-2,5-diyl diacetate (19): Dess–Martin periodinane (0.02 g, 0.05 mmol) was added to a solution of compound 18 (0.025 g, 0.046 mmol) in DCM (0.4 ml) at 0 ºC. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous Na$_2$S$_2$O$_3$ and saturated aqueous NaHCO$_3$. The
organic layer was washed with satd NaCl solution and dried over Na$_2$SO$_4$ and concentrated to afford an aldehyde that was used immediately in the next step without further purification.

To a 0 °C solution of diisopropylamine (6.8 µL, 48 µmol) in THF (0.6 mL), was added $n$-BuLi (27 µL, 44 µmol). After 20 min at 0 °C the solution was cooled to −78 °C and methyl acetate (3.8 µL, 48 µmol) was added by syringe and stirring continued for 15 min. The aldehyde (24 mg, 44 µmol) in 0.2 mL THF was cooled to −78 °C and transferred to the enolate solution via cannula. Stirring was continued for 15 min at which time TLC analysis indicated the starting material was consumed. The reaction mixture was warmed to 0 °C, stirred an additional 30 min and finally warmed to rt for 15 min. The solution was transferred via cannula into an Erlenmeyer flask containing pH=7 buffer (3 mL) and CH$_2$Cl$_2$ (3 mL). The resulting solution was extracted with CH$_2$Cl$_2$ (2 × 5 mL) and ethyl acetate (1 × 5 mL). The combined organics were dried over Na$_2$SO$_4$, filtered through a pad of Celite, and concentrated by rotary evaporation. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (80:20) as eluent gave 19 as a colorless oil.

**Yield:** 0.017 g, 75%

**Mol. Formula:** C$_{30}$H$_{34}$O$_8$

$[\alpha]_D^{25}$: $-$3.1 (c 0.5, CHCl$_3$).

**IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 1823, 1732, 1650, 1470, 1320, 1245, 1076, 872.

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.20-7.17 (m, 10H), 6.98-6.94 (m, 1H), 6.67-6.63 (m, 1H), 6.03-5.99 (m, 1H), 5.85-5.80 (m, 1H), 5.13-5.06 (m, 1H), 4.40-4.31 (m, 4H), 3.95-3.90 (m, 1H), 3.68-3.52 (m, 3H), 2.10 (s, 3H), 1.97 (s, 3H), 1.72-1.56 (m, 2H), 1.15 (d, $J$= 6.67 Hz, 3H).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 174.4, 165.5, 146.5, 138.9, 133.4, 133.3, 130.4, 130.1, 129.7, 128.1, 127.6, 125.6, 74.3, 72.1, 70.6, 70.0, 69.2, 66.4, 65.5, 31.9, 22.7, 14.1.

**HRMS** (ESI$^+$) m/z calcd for C$_{30}$H$_{35}$O$_8$[M + H]$^+$ 523.2332, found 523.2330.
### 3.2.6. Spectra

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Chloroform-d

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Chloroform-d
3.2.7. References


10 Davis-Coleman, M. T.; Rivett, D. E. A. In *Naturally Occurring 6-Substituted 5,6-Dihydro-R-Pyrones*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Tamm, Ch.,


