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Stereoselective Synthesis of Both Tetrahydropyran Rings of the Antitumor Macrolide, (–)-Lasonolide A

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Abstract

Stereoselective syntheses of both functionalized tetrahydropyran subunits of (–)-lasonolide A are described. These tetrahydropyran rings were constructed using catalytic asymmetric hetero Diels-Alder reactions as the key steps. The C22 quaternary stereocenter present in the upper tetrahydropyran ring was constructed by a stereoselective alkylation and the C9 hydroxy stereochemistry of bottom tetrahydropyran was constructed by a stereoselective epoxidation followed by a regioselective epoxide opening reaction.

Lasonolide A was isolated from Caribbean marine sponge, *Forcepia* sp, by McConnell and co-workers in 1994.¹ Lasonolide A exhibited potent antitumor activity against a range of cancer cell lines in the low nanomolar level. It has shown IC₅₀ values of 8.6 nM and 89 nM against A-549 human lung carcinoma and Panc-1 human pancreatic carcinoma, respectively.¹ Furthermore, it showed cell adhesion in the EL-4.IL-2 cell line, which detects signal-transduction agents. Interestingly, the mechanism of action of lasonolide A is still unknown. The natural abundance of lasonolide is very limited. The scarce supply and important biological properties of lasonolide A has attracted much interest in the chemistry and biology of lasonolide A. The structure of lasonolide A was initially determined by extensive NMR studies. Subsequently, its structure was revised through total synthesis² and biological studies were reported by Lee and co-workers.³ Since then, two more total syntheses and numerous synthetic studies on both tetrahydropyran rings have been reported.^{4–6} We recently reported an asymmetric total synthesis of lasonolide A.⁵ Utilizing this synthetic lasonolide A, we have investigated the biological mechanism of action in collaboration with the National Cancer Institute.⁷ Our studies revealed that lasonolide A uniquely induces premature chromosome condensation which may lead to a new treatment of many disorders. In an effort to further elucidate lasonolide A's structure-activity relationships as well as to identify its biological target, we sought to improve the synthesis of both tetrahydropyran subunits of lasonolide A. Herein, we report our studies leading to a stereoselective synthesis of both highly-substituted tetrahydropyran rings using asymmetric hetero Diels-Alder reactions as key steps.

Our previous route⁵ to the upper tetrahydropyran ring utilized a diastereoselective intramolecular 1,3-dipolar cycloaddition. The bicyclic isoxazoline led to the tetrahydropyran ring as well as the C22 quaternary stereocenter. However, the route was long with over 20 steps including a number of steps with low yields. The bottom tetrahydropyran ring was constructed using an asymmetric catalytic hetero Diels-Alder reaction developed by Jacobsen and co-workers.⁸ However, elaboration of the C9 hydroxy stereochemistry

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required ketone reduction producing a mixture of diastereoisomers (1:2 minor isomer being the desired isomer), separation, and then recycling of the major isomer through an oxidation/reduction sequence.⁵ Our retrosynthesis of lasonolide A is summarized in Figure 1. Key macrolactone **2** will be prepared from acyclic precursor **3**, which we had previously constructed by a Julia-Kocienski reaction,^{5,9} using sulfone **4** and aldehyde **5**.⁵ We further envisioned that both sulfone **4** and the aldehyde **5** could be stereoselectively constructed using Jacobsen's chromium-catalyzed hetero Diels-Alder reactions as key steps.⁸

As shown in Scheme 1, the synthesis of silyloxy dienes for the hetero Diels-Alder reaction commenced with the known aldehyde **8**.¹⁰ Methyl or ethylmagnesium bromide was added to aldehyde **8** to afford the respective alcohol in 97% and 95% yields, respectively. Parikh-Doering oxidation¹¹ of the resulting alcohols provided the corresponding ketones. Reaction of these ketones with TMSOTf or TESOTf in the presence of triethylamine provided silyl enol ethers **9**¹² and **10** in 99% and 91% yields, respectively. Asymmetric hetero Diels-Alder reactions of the silyl enol ethers **9** and **10** with benzyloxyacetaldehyde **12**¹³ in the presence of chiral Cr(III) catalyst **11**⁸ (7.5 to 10 mol%) afforded cycloadducts **6** and **7**. The enantiomeric excess of the cycloadducts **6** (91% ee) and **7** (93% ee) was determined by Chiral HPLC. These silyl enol ethers were then used as the key intermediates in the construction of the two tetrahydropyran rings.

As shown in Scheme 2, for the construction of the top tetrahydropyran ring, silyl ether **6** was treated with MeLi at $-78\text{ }^{\circ}\text{C}$ for 1 h. The resulting lithium enolate was reacted with ethyl cyanofornate to provide the corresponding β -keto ester as a mixture in 82% yield. The mixture was subjected to alkylation with NaH and MeI to provide the desired methylation product **13** in 92% total yield (*dr* 6.6:1 by ¹H NMR analysis). Exposure of β -keto ester **13** to L-selectride in THF provided the corresponding axial alcohol, which was subjected to LiAlH₄ reduction in the same pot to afford diol **14** diastereoselectively (ratio 10:1) and diastereomers were separated to provide **14** in 82% yield. Protection of the diol as an acetonide followed by removal of the benzyl group using catalytic hydrogenation afforded the alcohol **15** in 84% yield over 2 steps. Parikh-Doering oxidation¹¹ of **15** gave the precursor aldehyde which, was subjected to a Julia-Kocienski reaction.⁹ The requisite sulfone **17** was readily prepared by a Mitsunobu reaction with known alcohol **16**,¹⁴ triphenyl phosphine, diisopropylazodicarboxylate (DIAD) and phenyl tetrazole thiol. Reaction of the sulfone **17** with KHMDS in a mixture (5:1) of DME and HMPA followed by addition of an aldehyde provided the corresponding *trans*-olefin as a major isomer (*trans/cis* = 10:1 by ¹H NMR analysis) in 90% yield. Interestingly, *trans/cis* selectivity was reduced when THF was used as the solvent (75% yield, *trans/cis* = 5:1 by ¹H NMR analysis). The resulting *trans* sulfide was oxidized to the corresponding sulfone using ammonium heptamolybdate¹⁵ as the catalyst in the presence of hydrogen peroxide. Subsequent protecting-group manipulation afforded the sulfone **4** in 10 steps from the hetero Diels-Alder product **6**.⁵

The synthesis of the bottom tetrahydropyran ring is shown in Scheme 3. Hetero Diels-Alder product **7** was treated with TBAF in the presence of acetic acid in THF to provide ketone **19** in 72% yield over 2 steps. As described previously, selective reduction⁵ of this ketone to the desired axial alcohol **21** was very challenging. Direct reduction with a variety of hydride reagents provided undesired alcohol **20** as the major isomer (*dr* \geq 2:1). Conversion of the undesired alcohol **20** back to alcohol **21** using Swern oxidation followed by reduction did improve the yield of **21**. However, it required tedious separation, which was not very convenient even during large scale preparation. We therefore devised an alternative strategy to circumvent the poor diastereoselectivity issue. Thus, ketone **19** was converted to the corresponding enol triflate with NaHMDS and phenyl triflimide.¹⁶ Palladium-catalyzed reduction¹⁷ of the resulting enol triflate afforded alkene **22** in 75% yield over two steps. Epoxidation of the resulting olefin with dimethyldioxirane (DMDO) afforded the desired

epoxide in 69% yield as a major isomer (5.3:1 ratio). Epoxidation presumably proceeded from the top-side as shown in the stereochemical model **23**. The isomers were separated by silica gel chromatography. DIBAL-H reduction of the major epoxide provided alcohol **21** as a single isomer in excellent yield. The observed epoxide ring opening selectivity is consistent with the expected diaxial epoxide opening, in accordance with the Fürst-Plattner rule.¹⁸ Protection of the alcohol as a TBS ether followed by selective deprotection of the primary TBS group with CSA in MeOH provided the primary alcohol **24** in 89% yield. Parikh-Doering oxidation of alcohol **24** followed by Horner-Wadsworth-Emmons olefination of the resulting aldehyde furnished the α,β -unsaturated ester **25** in 91% yield. This was converted to alcohol **26** in a three step sequence involving, (1) DIBAL-H reduction; (2) protection of the resulting alcohol as a TBS ether, and (3) selective removal of the benzyl group¹⁹ with Li in liquid ammonia in 70% yield, over three steps. Alcohol **26** was converted to aldehyde **5** as described by us previously.⁵ Deprotonation of sulfone **4** using KHMDS in THF at -78 °C followed by addition of aldehyde **5** afforded *trans*-olefin **3** as a single isomer in 70% yield. This coupling product **3** was the key intermediate of our previous synthesis of lasonolide A.⁵

In summary, we have accomplished a stereoselective synthesis of both tetrahydropyran subunits of lasonolide A using catalytic asymmetric hetero Diels-Alder reactions as key steps. The C22 quaternary carbon stereocenter present in the upper tetrahydropyran ring was installed using diastereoselective alkylation followed by diastereoselective reduction steps. The C9 hydroxy group in the bottom tetrahydropyran ring was introduced stereoselectively using selective epoxidation with DMDO and reduction with DIBAL-H. Julia-Kocienski reaction of the two subunits provided an advanced intermediate **3** of our previous synthesis of lasonolide A. The synthesis of **3** has been carried out in 12 linear steps (13.5% overall yield from **8**), and 25 overall steps. In comparison, our previous synthesis of **3** was accomplished in 23 linear steps (2.78% overall yield) and 38 overall steps.⁵ The overall routes are amenable to the synthesis of structural analogs of lasonolide A.

EXPERIMENTAL SECTION

General experimental details are provided as Supporting Information.

(2-((2S,6S)-6-(benzyloxymethyl)-4-(trimethylsilyloxy)-5,6-dihydro-2H-pyran-2-yl)ethoxy) (tert-butyl)dimethylsilane (6)

A mixture of enol ether **9**¹² (1.05 g, 3.51 mmol), **12** (1.58 g, 10.5 mmol), 4Å molecular sieves (1.2 g) was treated with the Jacobsen's catalyst **11** (123 mg, 0.26 mmol) at 23 °C for 24 h. The reaction was diluted with EtOAc and filtered through a short pad of Celite, eluted with EtOAc. The filtrate was collected and concentrated in vacuo. The residue was purified quickly by a short pad of silica gel (1% NEt₃/5% EtOAc/Hexanes) to afford enol ether **6** (1.12 g, 71%) as a yellow oil. $[\alpha]_D^{25} -23.2$ (c 0.6, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.26 (m, 5H), 4.80 (s, 1H), 4.59 (ABq, $J_{AB} = 12.3$ Hz, 2H), 4.32-4.27 (m, 1H), 3.82-3.71 (m, 3H), 3.55 (dd, $J = 10.3, 6.2$ Hz, 1H), 3.49 (dd, $J = 10.3, 4.2$ Hz, 1H), 2.15-2.06 (m, 1H), 1.91 (m, 1H), 1.80-1.68 (m, 2H), 0.89 (s, 9H), 0.20 (s, 2H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 148.0, 138.3, 128.3, 127.6, 127.5, 106.6, 73.6, 73.3, 72.7, 71.2, 59.6, 39.4, 32.8, 25.9, 18.3, 0.2, -5.4; FT-IR (film) 2955, 2928, 1668, 1098 cm⁻¹. ESI-MS m/z 451.2 ([M+H]⁺), 473.4 ([M+Na]⁺). ESI-HRMS calcd for C₂₄H₄₃O₄Si₂ ([M+H]⁺) 451.2694; found: 451.2708.

(2S,3S,6S)-Ethyl-6-((benzyloxy)methyl)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyl-4-oxotetrahydro-2H-pyran-3-carboxylate (13)

To a solution of **6** (1.12 g, 2.49 mmol) in dry THF (10 mL) was added MeLi (1.6 M in diethyl ether, 4.7 mL) at $-78\text{ }^{\circ}\text{C}$. The reaction was then kept at $-20\text{ }^{\circ}\text{C}$ for 1 h and then cooled down to $-78\text{ }^{\circ}\text{C}$. NCCO₂Et (0.74 mL, 7.46 mmol) was added. The mixture was warmed to $23\text{ }^{\circ}\text{C}$ and quenched with water. The aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (10% EtOAc/Hexanes) of the residue provided alkylated product (922 mg, 82%) as a yellow oil.

To a solution of the former oil (392 mg, 0.87 mmol) in dry THF (5 mL) was added NaH (42 mg, 60% in oil, 1.04 mmol) at $0\text{ }^{\circ}\text{C}$. After 30 min, MeI (494 mg, 3.48 mmol) was added. The reaction was kept at $0\text{ }^{\circ}\text{C}$ for 1 h and then at $23\text{ }^{\circ}\text{C}$ overnight. The reaction was quenched with aq. NH₄Cl. The aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (10% EtOAc/Hexanes) of the residue afforded the desired isomer **13** (324 mg, 80%) as a colorless oil. $[\alpha]_{\text{D}}^{25}$ 45.2 (*c* 1.1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.26 (m, 5H), 4.60 (ABq, $J_{\text{AB}} = 12.3\text{ Hz}$, 2H), 4.27-4.23 (m, 1H), 4.20 (q, $J = 6.8\text{ Hz}$, 2H), 3.97-3.90 (m, 1H), 3.81-3.70 (m, 2H), 3.64-3.55 (m, 2H), 2.63 (dd, $J = 12.1, 5.5\text{ Hz}$, 1H), 2.32 (dd, $J = 15.2, 2.8\text{ Hz}$, 1H), 1.81-1.70 (m, 1H), 1.45-1.41 (m, 1H), 1.37 (s, 3H), 1.26 (t, $J = 6.9\text{ Hz}$, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 206.4, 170.6, 137.9, 128.4, 127.7, 127.5, 76.6, 76.1, 73.4, 71.9, 61.8, 61.2, 59.1, 39.8, 33.7, 25.8, 18.2, 14.3, 14.0, $-5.4, -5.6$; FT-IR (film) 2955, 2930, 2858, 1738, 1715, 1254 1103 cm⁻¹. ESI-MS *m/z* 465.1 ([M+H]⁺), 487.1 ([M+Na]⁺). ESI-HRMS calcd for C₂₅H₄₀O₆SiNa ([M+Na]⁺) 487.2486; found: 487.2496.

(2S,3R,4R,6S)-6-((Benzyloxy)methyl)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(hydroxymethyl)-3-methyltetrahydro-2H-pyran-4-ol (14)

To a solution of **13** (320 mg, 0.69 mmol) in dry THF (5 mL) was added L-selectride (1 M in THF, 2.07 mL) at $-78\text{ }^{\circ}\text{C}$. The reaction was kept at $-78\text{ }^{\circ}\text{C}$ for 3 h. LiAlH₄ (26 mg, 0.69 mmol) was then added and the reaction was allowed to stir at $0\text{ }^{\circ}\text{C}$ for 2 h. The reaction was quenched slowly with aq. NaOH (1 M, 2 mL) and aq. 30% H₂O₂ (1 mL). The mixture was stirred at $0\text{ }^{\circ}\text{C}$ for another 1 h. The aqueous layers were extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (40% EtOAc/Hexanes to 50% EtOAc/Hexanes) of the residue afforded diol **14** (240 mg, 82%) as a colorless oil. $[\alpha]_{\text{D}}^{25}$ 34.6 (*c* 0.70, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.25 (m, 5H), 4.57 (s, 2H), 4.11 (d, $J = 6.8\text{ Hz}$, 1H), 4.03 (m, 1H), 3.90 (s, 1H), 3.82-3.78 (m, 2H), 3.67 (d, $J = 11.6\text{ Hz}$, 1H), 3.55-3.46 (m, 3H), 1.80-1.63 (m, 2H), 1.61-1.42 (m, 2H), 0.90 (s, 9H), 0.76 (s, 3H), 0.07 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 138.4, 128.3, 127.5, 127.4, 74.6, 73.21, 73.16, 71.6, 71.5, 69.7, 61.3, 39.9, 32.5, 26.0, 18.4, 15.1, -5.4 ; FT-IR (film) 3376, 2955, 2928, 1089 cm⁻¹. ESI-MS *m/z* 425.2 ([M+H]⁺), 447.1 ([M+Na]⁺). ESI-HRMS calcd for C₂₃H₄₀O₅SiNa ([M+Na]⁺) 447.2543; found: 447.2539.

((4aS,5S,7S,8aR)-5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2,2,4a-trimethylhexahydropyrano[4,3-*d*][1,3]dioxin-7-yl)meth anol (15)

To a solution of **14** (276 mg, 0.651 mmol) in dry CH₂Cl₂ (5 mL) was added 2,2-dimethoxypropane (2 mL) followed by PPTS (16.4 mg, 0.065 mmol). The reaction was kept at $23\text{ }^{\circ}\text{C}$ for 10 h. The reaction was quenched with aq. NaHCO₃. The aqueous layers were extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (10% EtOAc/Hexanes) of the residue provided the acetone derivative as a colorless oil (278 mg, 92%).

A mixture of the former colorless oil (295 mg, 0.64 mmol), Pd(OH)₂-C (20% wt, 50% wet, 60 mg) in EtOAc (6 mL) was stirred at 23 °C under H₂ atmosphere for 10 h. The solid was filtered off and washed with EtOAc twice. The combined organic phase was concentrated in vacuo and purified by flash chromatography to afford alcohol **15** (217 mg, 91%) as a colorless oil. $[\alpha]_D^{25}$ 36.0 (*c* 1.05, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 4.26 (d, *J* = 10.3 Hz, 1H), 3.89-3.80 (m, 2H), 3.77-3.70 (m, 2H), 3.65-3.54 (m, 1H), 3.54-3.45 (m, 2H), 3.46-3.37 (m, 1H), 2.10-2.01 (br, 1H), 1.84-1.72 (m, 1H), 1.70-1.64 (m, 1H), 1.52-1.32 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.73 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 98.4, 72.3, 71.7, 71.3, 66.0, 65.9, 60.1, 34.5, 32.3, 29.24, 29.17, 25.9, 18.8, 18.2, 14.7, -5.36, -5.42; FT-IR (film) 3460, 2955, 1089 cm⁻¹. ESI-MS *m/z* 397.2 ([M+Na]⁺). ESI-HRMS calcd for C₁₉H₃₈O₅SiNa ([M+Na]⁺) 397.2381; found: 397.2387.

1-Phenyl-5-((3-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)prop yl)thio)-1*H*-tetrazole (**17**)

To a solution of **16** (4.34 g, 16.19 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (3.33 g, 19 mmol) and Ph₃P (7.86g, 30mmol) in dry CH₂Cl₂ (150 mL) was added DIAD (4.44 g, 22 mmol) dropwise. The reaction was kept at 23 °C overnight. The solvent was removed and the residue was purified by silica gel chromatography to give the desired sulfide **17** as a white solid (5.26 g, 76%). ¹H NMR (400 MHz, CDCl₃) δ 7.71-7.26 (m, 10H), 3.95 (t, *J* = 7.0 Hz, 2H), 3.60 (t, *J* = 6.9 Hz, 2H), 2.61 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 153.2, 153.1, 133.3, 132.8, 131.5, 130.3, 129.8, 129.7, 125.0, 123.8, 54.2, 31.0, 22.3; FT-IR (film) 1730, 1498, 1340 cm⁻¹. ESI-MS *m/z* 429.1 ([M+H]⁺). ESI-HRMS calcd for C₁₇H₁₇O₂N₈S₂ ([M+H]⁺) 429.0910; found: 429.0925.

2-((4*aS*,5*S*,7*S*,8*aR*)-2,2,4*a*-Trimethyl-7-((*E*)-4-((1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl)but-1-en-1-yl)hexahydropyrano[4,3-*d*] [1,3]dioxin-5-yl)ethanol (**18**)

To a solution of **15** (210 mg, 0.56 mmol) in CH₂Cl₂ (5 mL) and DMSO (2 mL) was added NEt₃ (0.63 mL, 4.49 mmol) followed by SO₃.Py (358 mg, 2.25 mmol) at 0 °C. The reaction was kept at 0 °C for 2 h. The reaction was quenched with aq. NaHCO₃. The aqueous layers were extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated. Purification of the residue by flash chromatography (30% EtOAc/Hexanes) afforded the desired aldehyde (206 mg, 99%) as a colorless oil.

To a solution of **17** (960 mg, 2.25 mmol) in DME/HMPA (v/v, 10 mL/2 mL) was added KHMDS (0.5 M in toluene, 4.5 mL, 2.25 mmol) at -78 °C. After 30 min, a solution of above aldehyde (206 mg, 0.56 mmol) in dry DME (1 mL) was added. The reaction was kept at -78 °C for 2 h and then quenched with aq. NH₄Cl. The layers were separated and the aqueous layers were extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated. Purification of the residue by flash chromatography (15% EtOAc/Hexanes) afforded the corresponding olefin (290 mg, 91%) as a colorless oil. $[\alpha]_D^{25}$ 24.9 (*c* 0.95, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.51 (m, 5H), 5.70-5.61 (m, 1H), 5.59-5.48 (m, 1H), 4.27-4.12 (m, 2H), 3.85-3.80 (m, 1H), 3.76-3.63 (m, 2H), 3.53-3.44 (m, 2H), 3.43-3.36 (m, 2H), 2.58-2.49 (m, 2H), 1.73-1.62 (m, 2H), 1.52-1.46 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 0.90 (s, 9H), 0.72 (s, 3H), 0.06 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 154.2, 133.9, 133.6, 130.0, 129.7, 127.4, 123.8, 98.4, 77.2, 71.9, 71.1, 66.0, 59.9, 34.2, 33.5, 32.8, 32.2, 31.8, 29.2, 25.9, 18.8, 18.2, 14.8, -5.35, -5.42; FT-IR (film) 2928, 1384, 836 cm⁻¹. ESI-MS *m/z* 575.2 ([M+H]⁺), 597.2 ([M+Na]⁺). ESI-HRMS calcd for C₂₉H₄₆N₄O₄SSiNa ([M+Na]⁺) 597.2907; found: 597.2904.

To a solution of above olefin (245 mg, 0.43 mmol) in EtOH (5 mL) and THF (2 mL) was added buffer (pH = 7.5, Na₂HPO₄-NaH₂PO₄, 0.5 mL) followed by (NH₄)₆Mo₇O₂₄·7H₂O

(132 mg, 0.107 mmol), aq. H₂O₂ (30%, 0.5 mL) at 0 °C. The reaction was allowed to stir at 23 °C for 2 h until another portion of (NH₄)₆Mo₇O₂₄·7H₂O (132 mg, 0.11 mmol), aq. H₂O₂ (30%, 0.5 mL) was added. The mixture was stirred for 12 h and then carefully quenched with aq. Na₂SO₃. The mixture was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated.

Above residue was dissolved in THF (5 mL). HF.Py (0.16 mL, 4.27 mmol) was added. The reaction was allowed to stir at 23 °C for 4 h and then it was quenched with aq. NaHCO₃. The mixture was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (50% EtOAc/Hexanes) of the residue afforded the desired alcohol **18**⁵ (160 mg, 76% for 2 steps) as a colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ 7.65-7.54 (m, 5H), 5.68-5.48 (m, 2H), 4.35 (t, *J* = 7.6 Hz, 1H), 4.27-4.24 (m, 1H), 3.84-3.69 (m, 5H), 3.50 (ABq, *J*_{AB} = 12.5 Hz, 2H), 2.95 (br, 1H), 2.68-2.60 (m, 2H), 1.71-1.64 (m, 3H), 1.50 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 0.75 (s, 3H).

TES-enol ether (10)

To a solution of **8** (1.9 g, 8.88 mmol) in dry THF (40 mL) was added ethylmagnesium bromide (3 M in ether, 3.85 mL) at -20 °C. The reaction was kept at -20 °C for 2 h and then quenched with aq. NH₄Cl. The mixture was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (20% EtOAc/Hexanes) of the residue gave the desired alcohol (2.05 g, 95%) as a colorless oil.

To a solution of above alcohol (1.71 g, 7 mmol) in CH₂Cl₂/DMSO (2:1, 45 mL) was added Et₃N (9.75 mL, 70 mmol) followed by SO₃.Py (2.79 g, 17.5 mmol) at 0 °C. When the reaction was complete as shown by TLC, it was quenched with aq. NaHCO₃. The mixture was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (10% EtOAc/Hexanes) of the residue gave the desired ketone (1.61 g, 95%) as a yellow oil.

To a solution of the former ketone (2.63 g, 10.9 mmol) in diethyl ether (15 mL) was added NEt₃ (3.8 mL, 27.2 mmol) followed by TESOTf (4.3 g, 16.3 mmol) at -78 °C. The reaction was kept at -78 °C for 30 min and at 0 °C for 1 h. The reaction was quenched with aq. NaHCO₃. The mixture was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated. Purification by flash chromatography (1% NEt₃/5% EtOAc/Hexane) afforded TES-enol ether **10** (3.53 g, 91%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.90 (d, *J* = 15.4 Hz, 1H), 5.82-5.70 (m, 1H), 4.73 (q, *J* = 7.0 Hz, 1H), 3.64 (t, *J* = 6.8 Hz, 2H), 2.29 (q, *J* = 6.9 Hz, 2H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.03-0.91 (m, 12H), 0.89 (s, 9H), 0.70 (q, *J* = 8.1, 5.9 Hz, 6H), 0.05 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 149.5, 130.4, 124.3, 107.4, 62.9, 35.8, 25.8, 18.2, 11.3, 6.7, 6.3, 5.4, -5.4; FT-IR (film) 2954, 1657, 1627, 1097 cm⁻¹. MS *m/z* 357.3 ([M+H]⁺). ESI-HRMS calcd for C₁₉H₄₁O₂Si₂ ([M+H]⁺) 357.2640; found: 357.2648.

(2-((2S,5S,6S)-6-(benzyloxymethyl)-5-methyl-4-(triethylsilyloxy)-5,6-dihydro-2H-pyran-2-yl)ethoxy)(tert-butyl)dimethylsilane (7)

A mixture of the TES-enol ether **10** (3.4 g, 9.55 mmol), **12** (4.3 g, 28.7 mmol), 4 Å molecular sieves (3.2 g) was treated with the Jacobsen's catalyst **11** (278 mg, 0.57 mmol) at 23 °C for 48 h. The reaction was diluted with EtOAc and filtered through a short pad of Celite, eluted with EtOAc. The combined filtrate was concentrated in vacuo. The residue was purified with flash chromatography (1% NEt₃/5% EtOAc/Hexane) to afford the desired cycloadduct **7** as a colorless oil. [α]_D²⁵ + 46.3 (*c* 0.8, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.21

(m, 5H), 4.69 (m, 1H), 4.58 (ABq, $J_{AB} = 12.0$ Hz, 2H), 3.23 (t, $J = 5.1$ Hz, 1H), 3.90-3.63 (m, 3H), 3.58 (dd, $J = 9.8, 6.9$ Hz, 1H), 3.47 (dd, $J = 9.8, 6.1$ Hz, 1H), 2.10-1.98 (m, 1H), 1.80-1.68 (m, 2H), 0.99 (t, $J = 3.8$ Hz, 9H), 0.98 (d, $J = 7.5$ Hz, 3H), 0.91 (s, 9H), 0.68 (q, $J = 7.9$ Hz, 6H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.4, 138.2, 128.2, 127.6, 127.4, 104.1, 75.5, 73.3, 71.4, 70.4, 59.6, 39.4, 36.1, 25.9, 18.3, 11.9, 6.6, 4.9, -5.4; FT-IR (film) 2935, 2955, 1664, 1089 cm^{-1} . MS m/z 507.25 ($[\text{M}+\text{H}]^+$). ESI-HRMS calcd for $\text{C}_{28}\text{H}_{51}\text{O}_4\text{Si}_2$ ($[\text{M}+\text{H}]^+$) 507.3320; found: 507.3335.

(2S,3S,6S)-2-((Benzyloxy)methyl)-6-(2-((tert-butyl dimethylsilyl)oxy)ethyl)-3-methyl dihydro-2H-pyran-4(3H)-one (19)

To a solution of the former silyl enol ether **7** in dry THF (100 mL) was added HOAc (1.1 mL, 19.1 mmol) followed by TBAF (1 M in THF, 9.55 mL, 9.55 mmol) dropwise at 0 °C. The reaction was allowed to stir at 0 °C for 2 h. The reaction was quenched with aq. NaHCO_3 . The mixture was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (10% EtOAc/Hexanes) gave ketone **19** (2.69 g, 72% over 2 steps) as a colorless oil. $[\alpha]_{\text{D}}^{25} + 14.6$ (c 1.07, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.27 (m, 5H), 4.59 and 4.50 (ABq, $J_{AB} = 11.7$ Hz, 2H), 3.90-3.85 (m, 1H), 3.85-3.70 (m, 3H), 3.65 (dd, $J = 9.6, 6.9$ Hz, 1H), 3.49 (dd, $J = 9.6, 6.2$ Hz, 1H), 2.58-2.52 (m, 1H), 2.46 (dd, $J = 13.0, 11.6$ Hz, 1H), 2.28 (d, $J = 15.1$ Hz, 1H), 1.90-1.82 (m, 1H), 1.78-1.68 (m, 1H), 1.09 (d, $J = 7.5$ Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 210.8, 137.9, 128.3, 127.7, 127.6, 74.1, 73.3, 69.4, 58.8, 46.8, 44.5, 39.2, 25.9, 18.2, 10.8, -5.4, -5.5; FT-IR (film) 2928, 1717, 1093 cm^{-1} . ESI-MS m/z 393.2 ($[\text{M}+\text{H}]^+$), 415.1 ($[\text{M}+\text{Na}]^+$). ESI-HRMS calcd for $\text{C}_{22}\text{H}_{36}\text{O}_4\text{SiNa}$ ($[\text{M}+\text{Na}]^+$) 415.2275; found: 415.2282.

(2S,3R,4R,6S)-2-((Benzyloxy)methyl)-6-(2-((tert-butyl dimethylsilyl)oxy)ethyl)-3-methyl tetrahydro-2H-pyran-4-ol (18) and (2S,3R,4S,6S)-2-((Benzyloxy)methyl)-6-(2-((tert-butyl dimethylsilyl)oxy)ethyl)-3-methyl tetrahydro-2H-pyran-4-ol (20)

To a solution of **19** (2.7 g, 6.89 mmol) in dry CH_2Cl_2 (50 mL) was added DIBAL-H (1 M in CH_2Cl_2 , 10.3 mL) dropwise at -78 °C. The reaction was kept at -78 °C for 2 h before it was quenched with MeOH (1 mL). EtOAc and aq. Rochelle salt were added. The reaction was stirred for 2 h and then extracted with ethyl acetate. The combined extracts was wash with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (20% EtOAc/Hexanes to 30% EtOAc/Hexanes) afforded alcohol **21** (810 mg, 30%) as a colorless oil. $[\alpha]_{\text{D}}^{25} - 12.6$ (c 1.10, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.26 (m, 5H), 4.60 and 4.49 (ABq, $J_{AB} = 12.3$ Hz, 2H), 4.13 (dt, $J = 2.8, 6.9$ Hz, 1H), 3.95-3.86 (m, 2H), 3.75-3.68 (m, 2H), 3.53 (dd, $J = 9.6, 6.8$ Hz, 1H), 3.39 (dd, $J = 9.7, 6.1$ Hz, 1H), 1.78-1.65 (m, 2H), 1.65-1.48 (m, 3H), 0.89 (s, 9H), 0.88 (d, $J = 7.2$ Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.4, 128.3, 127.6, 127.5, 73.2, 72.7, 71.0, 70.5, 69.0, 59.5, 39.2, 36.5, 34.4, 25.9, 18.3, 10.9, -5.4; FT-IR (film) 3443, 2927, 1096 cm^{-1} . MS m/z 395.2 ($[\text{M}+\text{H}]^+$), 417.2 ($[\text{M}+\text{Na}]^+$). ESI-HRMS calcd for $\text{C}_{22}\text{H}_{38}\text{O}_4\text{SiNa}$ ($[\text{M}+\text{Na}]^+$) 417.2437; found: 417.2440.

Undesired alcohol **20** (1.76 g, 65%) was obtained as a colorless oil. $[\alpha]_{\text{D}}^{25} - 6.7$ (c 1.04, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.26 (m, 5H), 4.59 and 4.48 (ABq, $J_{AB} = 12.0$ Hz, 2H), 3.90 (m, 1H), 3.89-3.61 (m, 2H), 3.60-3.45 (m, 3H), 3.45 (m, 1H), 2.02-1.99 (m, 1H), 1.80-1.71 (m, 1H), 1.70-1.60 (m, 2H), 1.56 (br, 1H), 1.43-1.33 (m, 1H), 0.88 (s, 9H), 0.83 (d, $J = 6.9$ Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.2, 128.3, 127.6, 127.5, 77.4, 73.3, 72.9, 70.8, 70.7, 59.4, 38.9, 36.1, 35.4, 25.9, 18.3, 4.8, -5.4; FT-IR (film) 3411, 2927, 1093 cm^{-1} . MS m/z 417.3 ($[\text{M}+\text{Na}]^+$). ESI-HRMS calcd for $\text{C}_{22}\text{H}_{38}\text{O}_4\text{SiNa}$ ($[\text{M}+\text{Na}]^+$) 417.2437; found: 417.2437.

(2-((2S,5R,6S)-6-((Benzyloxy)methyl)-5-methyl-5,6-dihydro-2H-pyran-2-yl)ethoxy)(tert-butyl)dimethylsilane (22)

To a solution of **19** (245 mg, 0.63 mmol) in dry THF (6.3 mL) was added NaHMDS (1 M in THF, 0.94 mL) at $-78\text{ }^{\circ}\text{C}$. The reaction was kept at $-78\text{ }^{\circ}\text{C}$ for 1 h before a solution of PhNTf₂ (290 mg, 0.81 mmol) in THF (1 mL) was added. The reaction was stirred at that temperature for 30 min and then at $23\text{ }^{\circ}\text{C}$ overnight. The reaction was quenched with aq. NH₄Cl. The mixture was extracted with ethyl acetate and the combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated. Purification of the residue by passing through a short pad of silica gel (20% EtOAc/Hexanes) gave the crude enol triflate as a colorless oil.

To a solution of the former enol triflate, Pd(OAc)₂ (7 mg, 0.03 mmol), PPh₃ (16.4 mg, 0.06 mmol) and DIPEA (404 mg, 3.13 mmol) in dry DMF (5 mL) was added HCO₂H (86.3 mg, 1.88 mmol) at $23\text{ }^{\circ}\text{C}$. After addition, the reaction was allowed to stir at $65\text{ }^{\circ}\text{C}$ for 1 h. Then cooled to $23\text{ }^{\circ}\text{C}$, diluted with ether and washed with water and brine and dried over Na₂SO₄. Evaporation of solvent gave a residue which was chromatographed (20% EtOAc/Hexanes) to afford alkene **22** (176 mg, 75% over 2 steps) as a colorless oil. $[\alpha]_{\text{D}}^{25} -46.7$ (*c* 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.26 (m, 5H), 5.82-5.77 (m, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 4.62 and 4.52 (ABq, *J*_{AB} = 11.6 Hz, 2H), 4.29 (m, 1H), 3.89-3.82 (m, 1H), 3.80-3.71 (m, 2H), 3.55 (dd, *J* = 10.4, 6.8 Hz, 1H), 3.44 (dd, *J* = 10.1, 6.0 Hz, 1H), 2.12 (m, 1H), 1.80-1.69 (m, 2H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 138.4, 131.0, 129.3, 128.3, 127.6, 127.5, 75.1, 73.3, 72.4, 70.9, 59.5, 38.6, 30.8, 25.9, 18.3, 13.9, -5.4 ; FT-IR (film) 2928, 1255, 1089 cm⁻¹. MS *m/z* 377.3 ([M+H]⁺). ESI-HRMS calcd for C₂₂H₃₇O₃Si ([M+H]⁺) 377.2512; found: 377.2509.

(2S,3R,4S,6S)-2-((Benzyloxy)methyl)-6-(2-((tert-butyl)dimethylsilyloxy)ethyl)-3-methyltetrahydro-2H-pyran-4-ol (21)

To a solution of **22** (40 mg, 0.11 mmol) in MeCN (1 mL) and buffer (pH = 7.5, Na₂HPO₄-NaH₂PO₄, 1 mL) was added a solution of DMDO in acetone (1.5 mL) at $-15\text{ }^{\circ}\text{C}$ slowly. The reaction was allowed to stir at $-15\text{ }^{\circ}\text{C}$ for 20 min and then at $23\text{ }^{\circ}\text{C}$ for 4 h. The reaction was quenched with aq. Na₂SO₃. The mixture was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (10% EtOAc/Hexanes) of the residue gave the epoxide (29 mg, 69%) as a colorless oil.

To a solution of the epoxide (26 mg 0.07 mmol) in dry THF (1 mL) was added DIBAL-H (1 M in CH₂Cl₂, 0.2 mL) slowly at $-15\text{ }^{\circ}\text{C}$. The reaction was allowed to stir at $0\text{ }^{\circ}\text{C}$ to $23\text{ }^{\circ}\text{C}$ for 2 h before it was quenched with aq. Rochelle salt. EtOAc was added and the reaction was allowed to stir vigorously at $23\text{ }^{\circ}\text{C}$ for another 2 h. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel afforded the desired alcohol **21** (26 mg, 99%) as a colorless oil.

2-((2S,4S,5S,6S)-6-((Benzyloxy)methyl)-4-((tert-butyl)dimethylsilyloxy)-5-methyltetrahydro-2H-pyran-2-yl)ethanol (24)

To a solution of **21** (1.38 g, 3.49 mmol) in dry CH₂Cl₂ (20 mL) was added 2,6-lutidine (747 mg, 6.98 mmol) followed by TBSOTf (1.2 g, 4.53 mmol) at $0\text{ }^{\circ}\text{C}$. The reaction was kept at $0\text{ }^{\circ}\text{C}$ for 1 h before it was quenched with aq. NaHCO₃. The layers were separated and the aqueous phase was extracted with CH₂Cl₂. The combined extracts was dried over Na₂SO₄ and concentrated. Purification of the residue by flash chromatography (5% EtOAc/Hexanes) afforded di-TBS-protected diol (1.72 g, 97%) as a colorless oil.

To a solution of the former di-TBS ether (1.72 g, 3.39 mmol) in MeOH (15 mL) and CH₂Cl₂ (15 mL) was added CSA (78.6 mg, 0.34 mmol) at 23 °C. After 2 h, the reaction was quenched with aq. NaHCO₃. The aqueous phase was extracted with ethyl acetate. The combined organic layers was washed with water and brine, dried over Na₂SO₄ and concentrated. Purification of the residue by flash chromatography (20% EtOAc/Hexanes) gave the primary alcohol **24** (1.18 g, 89%) as a colorless oil. [α]_D²⁵ + 9.9 (c 1.05, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.26 (m, 5H), 4.57 and 4.48 (ABq, J_{AB} = 12.3 Hz, 2H), 4.21 (m, 1H), 4.06 (m, 1H), 3.88-3.75 (m, 3H), 3.47 (dd, J = 9.6, 8.2 Hz, 1H), 3.36 (dd, J = 9.9, 3.5 Hz, 1H), 1.81-1.53 (m, 4H), 1.38-1.29 (m, 1H), 0.89 (s, 9H), 0.83 (d, J = 6.8 Hz, 3H), 0.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 138.2, 128.4, 127.7, 127.5, 73.8, 73.3, 73.1, 70.6, 62.2, 37.4, 36.8, 34.7, 25.7, 18.0, 11.0, -5.0; FT-IR (film) 3443, 2928, 1254, 1098 cm⁻¹. ESI-MS m/z 395.1 ([M+H]⁺), 417.2 ([M+Na]⁺). ESI-HRMS calcd for C₂₂H₃₉O₄Si ([M+H]⁺) 395.2612; found: 395.2620.

(E)-Ethyl-4-((2S,4S,5S,6S)-6-((benzyloxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-5-methyltetrahydro-2H-pyran-2-yl) but-2-enoate (25)

To a solution **24** (1.15 g, 2.92 mmol) in CH₂Cl₂/DMSO (2:1, 20 mL) was added Et₃N (4 mL, 29.2 mmol) followed by SO₃.Py (1.16 g, 7.31 mmol) at 0 °C. When the reaction was complete as shown by TLC, it was quenched with aq. NaHCO₃. The aqueous phase was extracted with ethyl acetate. The combined organic layers was washed with water and brine, dried over Na₂SO₄ and concentrated. Purification of the residue by silica gel chromatography (10% EtOAc/Hexanes) gave the desired aldehyde (1.14 g, 99%) as a colorless oil.

To a solution of triethyl phosphonoacetate (1.3 g, 5.82 mmol) in dry THF (15 mL) was added NaH (60% in oil, 209 mg, 5.23 mmol) portionwise at 0 °C. A solution of the aldehyde (1.14 g, 2.91 mmol) in dry THF (5 mL) was then added slowly. The reaction was then stirred at 0 °C for 2 h before it was quenched with aq. NH₄Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined extracts was washed with water and brine, dried over Na₂SO₄ and concentrated. Silica gel chromatography (5% EtOAc/Hexanes) afforded ester **25** (1.22 g, 91%) as a colorless oil. [α]_D²⁵ + 2.3 (c 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.26 (m, 5H), 7.01 (dt, J = 15.8, 6.9 Hz, 1H), 5.88 (d, J = 15.7 Hz, 1H), 4.63 and 4.51 (ABq, J_{AB} = 12.0 Hz, 2H), 4.21-4.14 (m, 1H), 4.16 (q, J = 6.8 Hz, 2H), 3.94 (m, 1H), 3.78 (m, 1H), 3.50 (dd, J = 10.3, 7.5 Hz, 1H), 3.38 (dd, J = 10.3, 4.1 Hz, 1H), 2.47-2.36 (m, 1H), 2.35-2.27 (m, 1H), 1.65-1.50 (m, 2H), 1.38-1.32 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.03 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 145.4, 138.5, 128.3, 127.5, 127.4, 123.1, 73.3, 73.2, 71.5, 70.78, 70.75, 60.0, 38.6, 36.8, 34.4, 25.7, 18.0, 14.2, 10.9, -4.9; FT-IR (film) 2929, 1722, 1257, 1073 cm⁻¹. ESI-MS m/z 485.2 ([M+Na]⁺). ESI-HRMS calcd for C₂₆H₄₂O₅SiNa ([M+Na]⁺) 485.2699; found: 485.2709.

((2S,3S,4S,6S)-4-((tert-Butyldimethylsilyl)oxy)-6-((E)-4-((tert-butyldimethylsilyl)oxy)but-2-en-1-yl)-3-methyltetrahydro-2H-pyran-2-yl)methanol (26)

To a solution of **25** (1.22 g, 2.64 mmol) in dry CH₂Cl₂ (10 mL) was added DIBAL-H (1 M in CH₂Cl₂, 7.93 mL) dropwise at -78 °C. The reaction was kept at -78 °C for 2 h before it was quenched with MeOH (1 mL). EtOAc and aq. Rochelle salt were added. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers was washed with water and brine, dried over Na₂SO₄ and concentrated. Purification of the residue by flash chromatography (5% EtOAc/Hexanes) gave the desired alcohol (1 g, 90%) as a colorless oil.

To a solution of the former oil (1 g, 2.39 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (1 mL, 7.16 mmol), DMAP (29.3 mg, 0.24 mmol) followed by TBSCl (540 mg, 3.58 mmol). The reaction was kept at 23 °C overnight. The reaction was quenched with aq. NaHCO_3 . The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (25% EtOAc/Hexanes) to afford the di-TBS ether (1.22 g, 96%) as a colorless oil.

A solution of Li (120 mg, 17.1 mmol) in liquid NH_3 (60 mL) was transferred dropwise to a solution of the di-TBS ether (400 mg, 0.75 mmol), allyl ethylether (645 mg, 7.49 mmol) in dry THF (7 mL) at -78 °C. The reaction was quenched with solid NH_4Cl (1 g) at -78 °C and then gradually raised to 23 °C. Water and EtOAc were added. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. Silica gel chromatography (25% EtOAc/Hexanes) of the residue gave alcohol **26**⁵ (283 mg, 81%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 5.54-5.66 (m, 2H), 4.12 (d, J = 4.4 Hz, 2H), 4.01 (dt, J = 9.0, 3.0 Hz, 1H), 3.74-3.82 (m, 2H), 3.64 and 3.41 (ABq, J_{AB} = 11.0 Hz, 2H), 2.25 (m, 1H), 2.14 (m, 1H), 2.09 (br, 1H), 1.47-1.52 (m, 2H), 1.38 (m, 1H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.83 (d, J = 7.5 Hz, 3H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (125MHz, CDCl_3) δ 135.2, 117.1, 75.4, 72.1, 71.4, 64.9, 40.8, 37.4, 34.7, 26.2, 18.4, 11.8, -4.5.

Supplementary Material

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Acknowledgments

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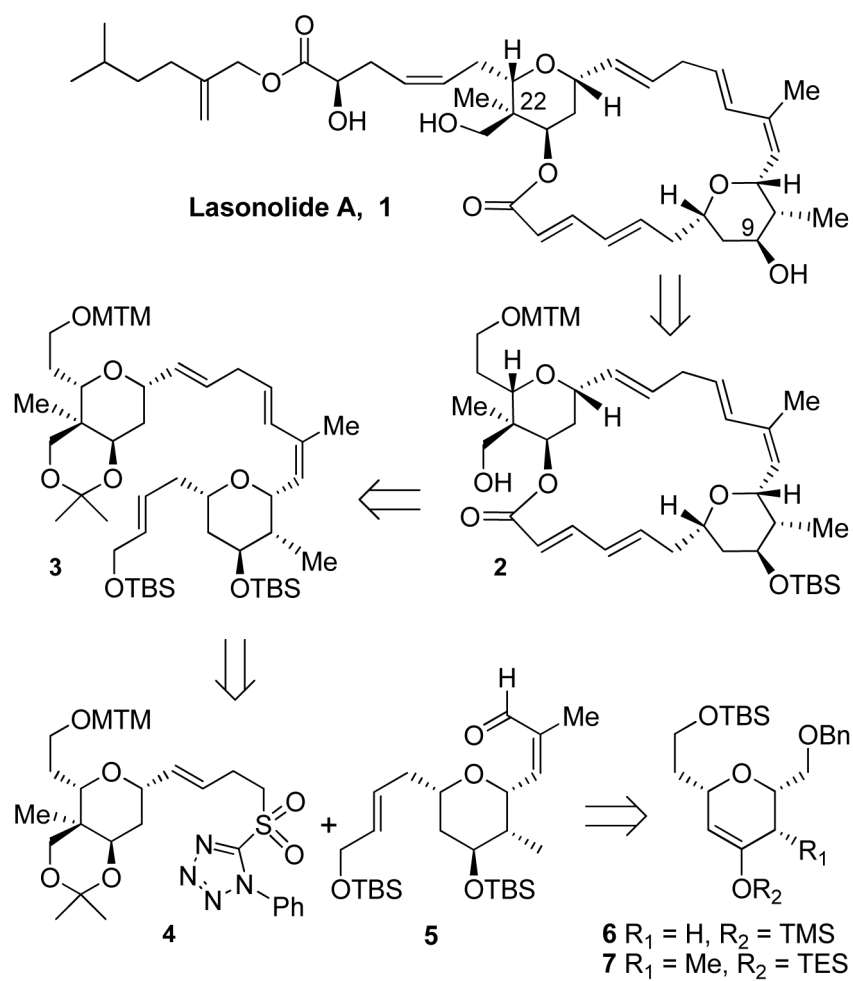
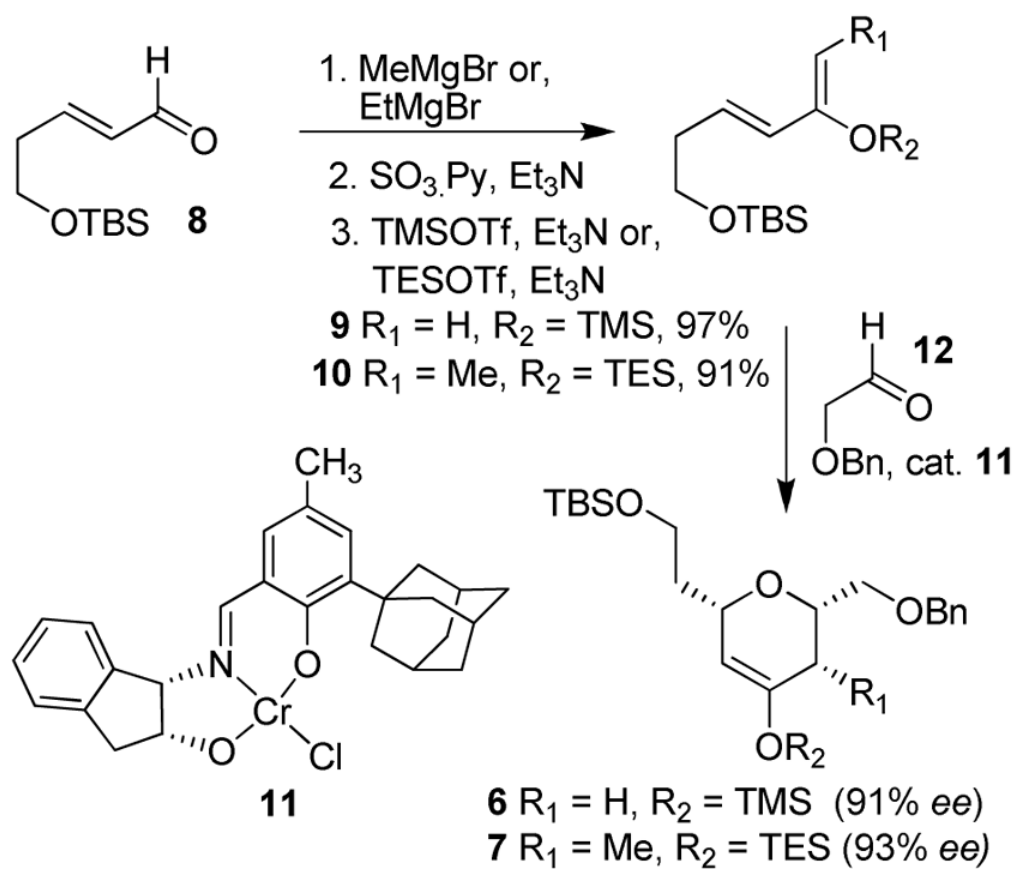
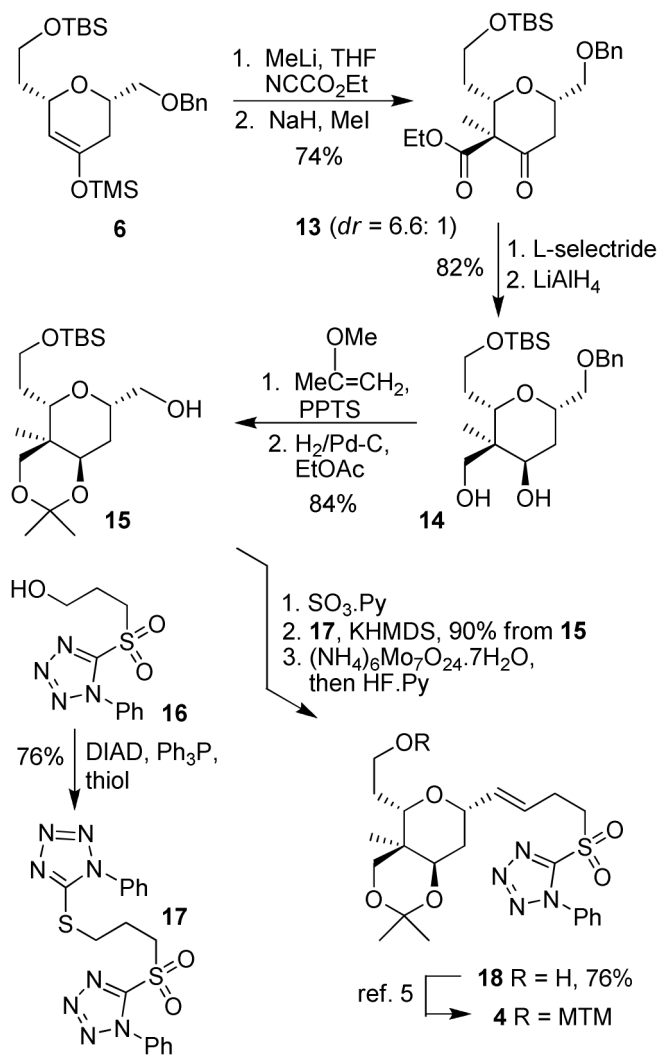


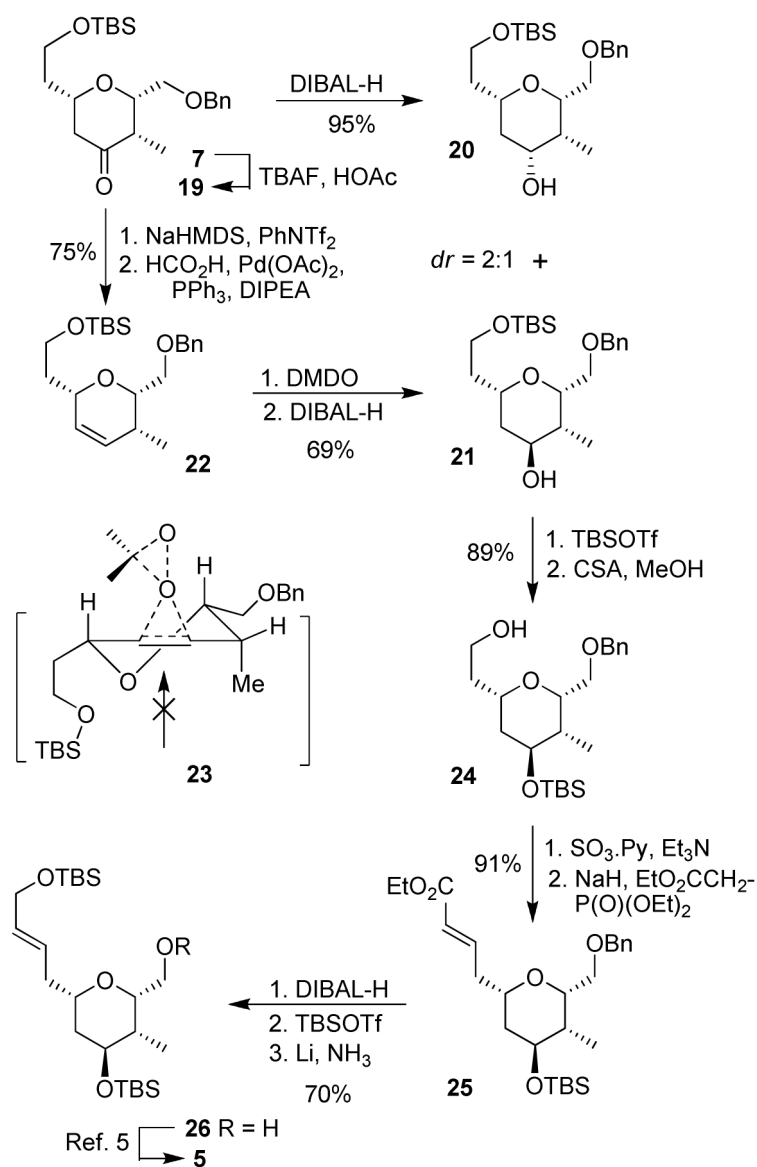
Figure 1.
Retrosynthetic analysis of lasonolide A



Scheme 1.
Synthesis of dihydropyrans **6** and **7**



Scheme 2.
 Synthesis of the upper tetrahydropyran ring



Scheme 3.
Synthesis of the bottom tetrahydropyran ring