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A carbohydrate approach for the formal total synthesis of the prostacyclin analogue (16*S*)-iloprost

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ABSTRACT

The formal total synthesis of the synthetic and stable analogue of prostacyclin, (16*S*)- iloprost is described via a convergent synthesis starting from readily available D-glucose. Julia olefination and the aldol reaction are the key steps involved in the synthesis.

1. Introduction

Prostacyclins play a major role in vascular, central nervous system, and inflammatory disorders.[1] However, since the activities of prostacyclins are hampered by their low metabolic half-lives,[2] research is more focussed on designing new synthetic analogues as alternatives to the natural prostacyclins.[3] Iloprost (Fig. 1), a highly potent and stable compound is an example of a synthetic analogue for prostacyclin which is used in treatment of thrombo-angiitis obliterans, ischemia, Raynaud's disease, and pulmonary arterial hypertension.[4] Even though, iloprost suffers from low oral activity, its potent biological activity has lead it to be utilized as a drug which is administered either by inhalation or through infusion. So far there are very few synthetic contributions[5] for this compound and majority of them rely on stereoselective keto reduction (C15) resulting in the mixture of diastereomers.

Our group has taken up a program to design facile strategies toward the total synthesis of potent prostaglandins and prostacyclins. As a part of this program, we have recently published our initial results on the formal total synthesis of anti-platelet drug beraprost[6] (Fig. 1) wherein the tricyclic ring with an α-side chain has been accomplished. Herein we report the synthesis of the ω-side chain [which happens to be a common core for both beraprost and (16*S*)-iloprost] and its utility toward formal total synthesis of (16*S*)-iloprost following a chiron pool approach starting from the inexpensive and readily available D-glucose.

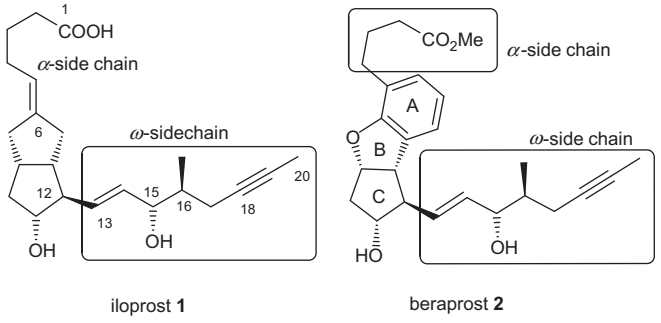

Figure 1. Structures of (16*S*)-iloprost **1** and beraprost **2.**

2. Results and discussion

Retrosynthetically, (16*S*)-iloprost can be obtained from the known intermediate **3**. The key intermediate **3** can be obtained via a Julia olefination reaction between aldehyde **4** and sulfone **5** followed by MOM and ketal deprotection. Aldehyde **4** in turn can be obtained from bicyclic ketone **6** via an aldol reaction followed by further manipulations in a five step sequence. Further, sulfone **5** can be obtained from the commercially available D-glucose **7** (Scheme 1).

Our synthesis began with the preparation of bicyclic ketal **6** through a condensation reaction of the readily available glyoxal and dimethyl-1,3-acetone dicarboxylate[7] followed by selective protection of the keto functionality as the corresponding ketal with neopentyl glycol following the known literature procedures.[8] Ketone **6** was converted into the chiral TES enolate with LiCl-complexed lithium amide[9] and TESCl, and then subjected to a Mukaiyama aldol reaction with benzyl glyoxaldehyde **9** using $BF_3{\cdot}OEt_2$ to afford a diastereomeric mixture **10** in a 4:1 ratio.[10] Compound **11**, when subjected to $NaBH_4$ reduction in MeOH at −45 °C, afforded diol **12** which was further treated with Pd/C to afford triol **12**. Triol **12** when treated with $NaIO_4$, underwent oxidative cleavage to yield the desired key fragment **4** (Scheme 2).

We next carried out the synthesis of the sulfone intermediate starting from commercially available D-glucose **7**. Thus D-glucose

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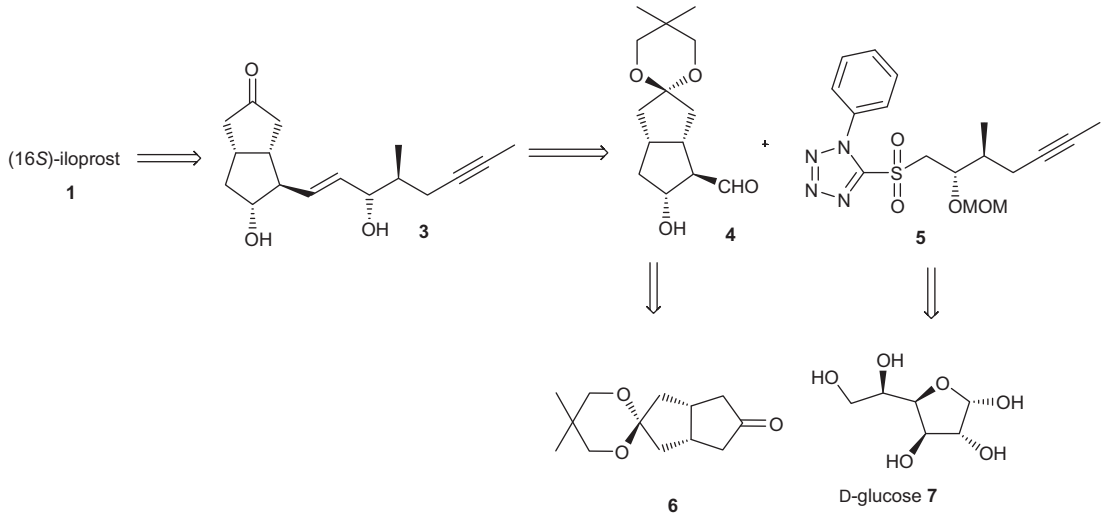
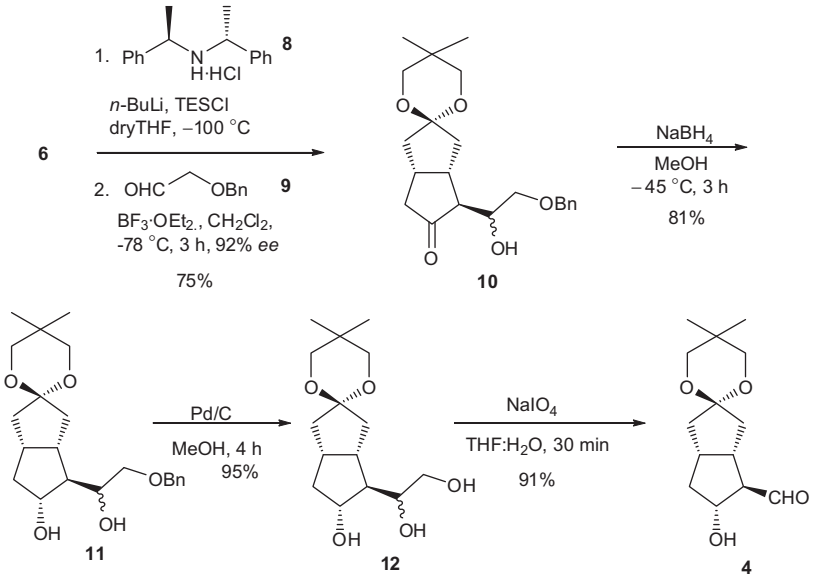


Scheme 1. Retrosynthetic analysis for (16*S*)-iloprost.



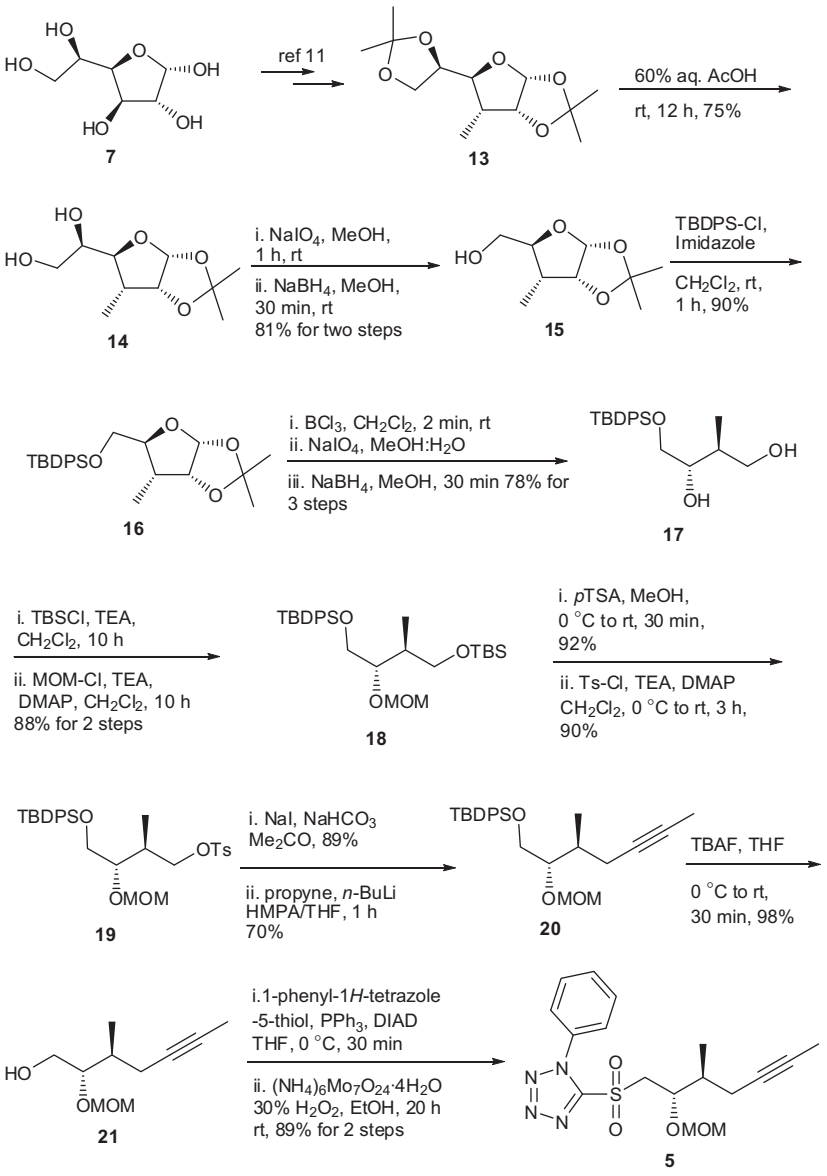
Scheme 2. Synthesis of bicyclic aldehyde **4.**

was converted into product **13** in four steps as reported earlier.[11] Selective primary acetonide deprotection was achieved with 60% AcOH to give diol **14**, which upon oxidative cleavage by $NaIO_4$ followed by reduction with $NaBH_4$ yielded alcohol **15**. Alcohol **15** was protected as the corresponding silyl ether **16** with TBDPSCl in the presence of imidazole. Deprotection of the acetonide moiety[12] with BCl_3 followed by oxidative cleavage of the acetal afforded the aldehyde which was reduced to 1,3-diol **17** with $NaBH_4$ (Scheme 3). The primary alcohol in **17** was selectively protected as the corresponding silyl ether with TBSCl in the presence of TEA and then to MOM ether with MOMCl to give the fully masked compound **1**8. Compound **18**, when treated with *p*TSA in methanol, gave the TBS-deprotected compound, which was converted into tosylate **19** with tosyl chloride in the presence of TEA and DMAP. Tosylate **19** was converted into the corresponding iodide and then coupled with metallated propyne (generated in situ by treatment of propyne with *n*-BuLi) to give **20**.[13] The coupled product **20** upon desilylation with TBAF afforded alcohol **21**, which was converted into thioether upon treatment with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions and then subjected to oxidation with ammonium molybdate to give sulfone **5**[14] (Scheme 3).

With the two key fragments, aldehyde **4** and sulfone **5**, in hand, we were ready to couple them under Julia olefination conditions to obtain the core structure of iloprost. Thus, sulfone **5** was treated with LiHMDS and to this was added aldehyde **4** to give olefin **22**.[15] Global deprotection was achieved with 6 M HCl to provide the key intermediate **3** (Scheme 4). Compound **3** can be converted into the target molecule in a few further manipulations.[5d] Thus, we have accomplished the formal synthesis of (16*S*)-iloprost.

3. Conclusions

In conclusion, we have achieved a highly stereoselective formal synthesis of (16*S*)-iloprost starting from commercially available D-glucose following a chiron approach. The key steps involved are the



Scheme 3. Synthesis of **5.**

Mukaiyama aldol reaction and the Julia–Kocienski olefination. The strategy adopted paves the way for the synthesis of a key ω-branch starting from a readily available inexpensive sugar which can also be utilized for the total synthesis of beraprost. The application of this strategy to the total synthesis of other prostacyclin analogues is currently being investigated.

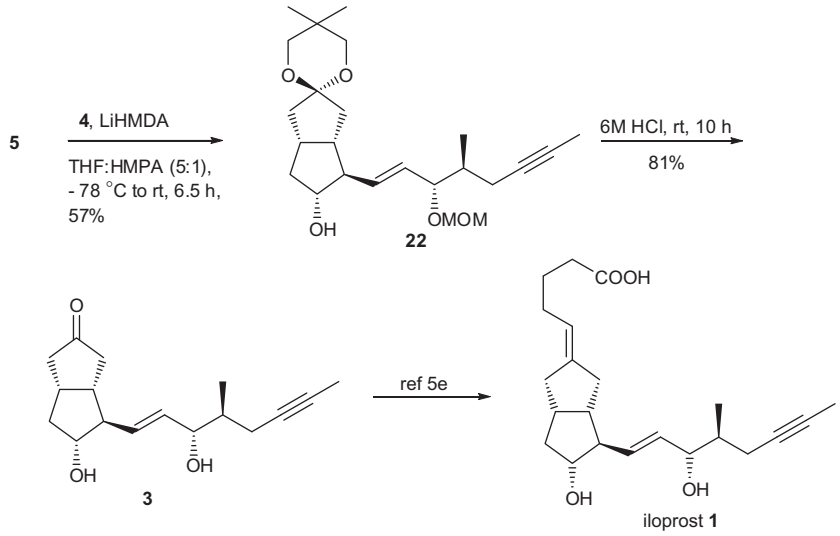
4. Experimental section

4.1. General

All reagents were of reagent grade and used without further purification unless specified otherwise. Solvents for the reactions were distilled prior to use: THF, toluene, and diethyl ether were distilled from Na and benzophenone ketyl; MeOH from Mg and I_2; CH_2Cl_2 from CaH_2. All air or moisture sensitive reactions were conducted under a nitrogen atmosphere in flame-dried or oven-dried glassware with magnetic stirring. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent on a 200 or 300 MHz spectrometer at ambient temperature. The coupling constant J is given in Hz. The chemical shifts are reported in ppm on a scale downfield from TMS as the internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sex = sextet, m = multiplet, br = broad. FTIR spectra were recorded on KBr pellets $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). Optical rotations were measured on digital polarimeter using a 1 mL cell with a 1 dm path length. For low (MS) and high (HRMS) resolution, m/z ratios are reported as values in atomic mass units. Mass analysis was done in ESI mode. Column chromatography was carried out using silica gel (60–120 or 100–200 mesh) packed in glass columns. Technical grade ethyl acetate, and petroleum ether used for column chromatography were distilled prior to use.

4.1.1. (3a′*S*,4′*S*,6a′*R*)-4′-(2-(Benzyloxy)-1-hydroxyethyl)-5,5-dimethyltetrahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-5′(3′*H*)-one 10

A suspension of (*R*,*R*)-bis(phenylethyl)ammonium chloride **8** (4.6 g, 17.6 mmol) in THF (50 mL) was cooled to −78 °C and *n*-BuLi (1.6 M in hexane, 22.5 mL, 35.26 mmol) was added dropwise. The



Scheme 4. Synthesis of key intermediate **3**.

mixture was warmed to 0 °C, re-cooled to −105 °C and treated dropwise with a solution of the ketone **6** (2.5 g, 11.15 mmol) in THF (25 mL). After stirring the mixture for 30 min at −105 °C, it was warmed to −78 °C and treated with $ClSiEt_3$ (3.3 mL, 22.32 mmol). After stirring the mixture for 15 min, a saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was warmed to ambient temperature and extracted with ether (80 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (hexanes/EtOAc, 9:1) of the residue gave the silyl enol ether (3.7 g, 94%). A solution of aldehyde **9** (1.8 g, 12.0 mmol) in CH_2Cl_2 (40 mL) was treated at room temperature with $BF_3{\cdot}Et_2O$ (1.7 ml, 12.0 mmol), and the resulting mixture was cooled immediately to −95 °C. After the addition of a solution of the above silyl enol ether (3.7 g, 10.9 mmol) (92% ee) in CH_2Cl_2 (50 mL), the resultant orange mixture was stirred for 1 h. The mixture was treated with a saturated aqueous $NaHCO_3$ solution (60 mL), warmed to ambient temperature and extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (hexanes/EtOAc, 1:1) of the residue provided a mixture of **10a** and **10b** (3.07 g, 75%, ratio 4:1) as colorless oils. R_f = 0.33 (SiO_2, 30% EtOAc in petroleum ether) ^{1}H NMR of compound **10a** (300 MHz, $CDCl_3$): δ 7.31–7.36 (m, 5H), 4.52–4.60 (m, 2H), 3.43–3.62 (m, 7H), 1.64–2.35 (m, 9H), 0.94 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220, 137.7, 128.3, 127.8, 127.6, 109.6, 73.2, 72.4, 72.0, 69.5, 56.7, 44.9, 41.2, 41.0, 37.7, 35.1, 29.9, 22.3; IR (Neat) ν_{max} 3454, 2952, 2864, 1733, 1453, 1328, 1114, 1012, 739, 699 cm^{-1}; ESI/HRMS calcd for $C_{22}H_{30}O_5$ [M+Na]$^+$ 397.1994, found 397.1983.

4.1.2. (3a′*S*,4′*R*,5′*R*,6a′*R*)-4′-(2-(Benzyloxy)-1-hydroxyethyl)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-5′-ol 11

A solution of **10** (3.0 g, 8.02 mmol) in EtOH (60 mL) was cooled to −45 °C and treated with $NaBH_4$ (0.603 g, 16.04 mmol). After stirring the mixture for 3 h, the reaction mixture was concentrated and to this was added a saturated aqueous NH_4Cl solution (20 mL). The mixture was warmed to ambient temperature and extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Silica gel column chromatography (hexanes/EtOAc, 1:1) of the residue afforded **11** (2.4 g, 81%) as a colorless solid. Mp 99–105 °C; R_f = 0.27 (SiO_2, 30% EtOAc in petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.40 (m, 5H), 4.56 (s, 2H), 3.91–4.02 (m, 2H), 3.58–3.64 (m, 1H), 3.48–3.52 (m, 1H), 3.46 (d, 4H, J = 6.5 Hz), 2.58 (br s, 2H), 2.33–2.44 (m, 2H), 2.13–2.24 (m, 3H), 1.68–1.80 (m, 3H), 1.40–1.51 (m, 1H), 0.95 (d, 6H, J = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 128.4, 127.8, 127.7, 110.2, 75.0, 73.5, 73.3, 72.1, 71.8, 70.6, 56.6, 41.6, 40.7, 39.7, 38.7, 35.8, 30.0, 22.4; IR (Neat) ν_{max} 3414, 2951, 2864, 1454, 1327, 1110, 1015, 746, 699 cm^{-1}; ESI/HRMS calcd for $C_{22}H_{32}O_5$ [M+Na]$^+$ 399.2152, found 399.2139.

4.1.3. ((3a′*S*,4′*R*,5′*R*,6a′*R*)-5′-Hydroxy-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalene]-4′-yl)ethane-1,2-diol 12

To a stirred solution of benzyl ether **11** (2.4 g, 6.3 mmol) in EtOAc (25 mL) was added 10% Pd/C (0.2 g) at room temperature The flask was evacuated and pressurized with H_2 (balloon) and the mixture was then stirred for 4 h. The mixture was then filtered through a pad of Celite. After washing thoroughly with EtOAc, the filtrate was concentrated, and purified by column chromatography using EtOAc:hexane (3:1) to afford triol **12** as a colorless solid (1.7 g, 95%). Mp 84–90 °C; R_f = 0.24 (SiO_2, 50% EtOAc in petroleum ether) ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (br s, 2H), 3.86–4.05 (m, 2H), 3.58–3.68 (m, 2H), 3.35–3.45 (m, 4H), 2.79 (br s, 1H), 2.27–2.42 (m, 1H), 2.00–2.21 (m, 4H), 1.59–1.81 (m, 3H), 1.48 (q, 1H, J = 10.7 Hz and 21.5 Hz), 0.95 (d, 6H, J = 13.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.1, 75.5, 74.9, 74.3, 65.3, 56.3, 44.5, 44.0, 41.2, 39.7, 35.4, 30.0, 29.6, 22.5; IR (Neat) ν_{max} 3385, 2951, 2868, 1729, 1467, 1329, 1108, 1014, 757 cm^{-1}; ESIMS: m/z 287 [M+H]$^+$.

4.1.4. (3a′*S*,4′*R*,5′*R*,6a′*R*)-5′-Hydroxy-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalene]-4′-carbaldehyde 4

A solution of triol **12** (1.7 g, 5.9 mmol) in THF: H_2O (3:1) (30 mL) was treated with $NaIO_4$ (3.8 g, 17.8 mmol) portion wise at 0 °C and stirred at room temperature for 2 h. The reaction mixture was filtered, the filtrate evaporated, and the residue obtained was dissolved in water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography using EtOAc:hexane (1:1) as an eluent to afford aldehyde **4** (1.4 g, 96%) as a light yellow oil. R_f = 0.72 (SiO_2, 50% EtOAc in petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (s, 1H), 4.30 (q, 1H, J = 7.3 Hz and 14.7 Hz), 3.51 (s, 2H), 3.46 (s, 2H), 2.50–2.64 (m, 2H), 1.92–2.29 (m, 7H), 1.55–1.66 (m, 1H), 0.96 (d, 6H, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1, 128.2, 74.4, 72.3, 71.8, 66.3, 41.4, 40.0, 39.0, 38.7, 36.7, 30.0, 22.4; IR (Neat) ν_{max} 3414, 2951, 2865, 1717, 1468, 1328, 1110, 1014, 770 cm^{-1}; $[\alpha]_D^{25} = +15.0$ (c 3.5, MeOH); ESIMS: m/z 255 [M+H]$^+$.

4.1.5. (3a*R*,5*S*,6*R*,6a*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2,6-trimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole 13

To a well stirred solution of D-glucose **7** (100.0 g) in dry acetone (2 L), anhydrous copper sulfate (100.0 g) was added, followed by concentrated sulfuric acid (4 mL). The reaction mixture was then stirred at room temperature for 16 h. The solvent was decanted and the residue was washed with acetone (3 × 200 mL) and the combined acetone layers were neutralized with solid sodium bicarbonate (neutral to pH paper), and stirred for 2 h, then filtered and the filtrate was concentrated. The residue was taken in chloroform (200 mL), washed with a saturated aqueous $NaHCO_3$ solution (150 mL), water (150 mL), brine (150 mL), and dried over anhydrous Na_2SO_4, concentrated in vacuo and recrystallized from distilled petroleum ether to give glucose diacetonide (75 g, 65%) as a crystalline solid (m.p.: 109 °C). A mixture of diacetone glucose (20.28 g, 78 mmol), pyridinium dichromate (35.20 g, 94 mmol), and acetic anhydride (22 mL, 234 mmol) in CH_2Cl_2 (150 mL) was heated at reflux for 1 h. The solvent was evaporated and the residue was taken in ether and filtered through a small pad of silica gel. The combined ether layers were washed with aqueous sodium bicarbonate (60 mL), water (60 mL), dried over anhydrous Na_2SO_4, and concentrated to give the ketone (16.10 g, 80%) as a white solid, which was utilized as such without further purification. A suspension of methyltriphenylphosphonium iodide (50.10 g, 124 mmol) in dry THF (100 mL) at −78 °C, *n*-BuLi (85.3 mL, 136 mmol) was added slowly under a nitrogen atmosphere. The reaction mixture became yellowish and it was stirred for 30 min at the same temperature. The above ketone (16.0 g, 62 mmol) in THF (50 mL) was added slowly to the yellow phosphorane solution. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was then quenched with aqueous saturated NH_4Cl solution (100 mL), and extracted with EtOAc (2 × 120 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using petroleum ether/EtOAc (98:2) to afford the *exo*-methylene compound (13.02 g, 82% yield) as a colorless oil. To a stirred solution of the above compound (11.78 g, 46 mmol) in EtOH (100 mL) was added 10% Pd/C (2 g) at room temperature. The flask was evacuated and pressurized with H_2 (balloons) and the mixture was then stirred for 2 h. The mixture was then filtered through a pad of Celite, washed thoroughly with EtOAc (30 mL), and the filtrate was concentrated in vacuo and the residue was purified by column chromatography (eluent: EtOAc:petroleum ether = 98:2) to afford 3-*C*-methyl-3-deoxy derivative **13** (11.27 g, 95% yield) as a colorless oil. R_f = 0.52 (SiO_2, 20% EtOAc in petroleum ether) ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (d, J = 3.5 Hz, 1H), 4.41 (t, J = 4.1 Hz, 1H), 4.03–3.91 (m, 1H), 3.90–3.75 (m, 2H), 3.60–3.48 (m, 1H), 1.88–1.73 (m, 1H), 1.41 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 1.09 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.4, 109.3, 104.8, 83.4, 82.7, 77.8, 67.4, 42.7, 26.8, 26.6, 26.4, 25.3, 10.0; IR (KBr): ν_{max} 3033, 2860, 1603, 1495, 1258, 1100, 1013, 911 cm^{-1}; ESIMS: m/z 259.1 [M+H]$^+$. $[\alpha]_D^{20}$ = +36 (c 1.0, $CHCl_3$).

4.1.6. (*R*)-1-((3a*R*,5*S*,6*R*,6a*R*)-2,2,6-Trimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethane-1,2-diol 14

Deoxy glucose diacetonide **13** (9.80 g, 38 mmol) was treated with 60% aqueous acetic acid (50 mL) and stirred at room temperature for 12 h. After completion of the reaction, chloroform was added and stirred for a further 30 min and the mixture was extracted with chloroform (3 × 100 mL). The combined organic layers were neutralized with solid $NaHCO_3$ and stirring was continued for 1 h. Next, it was filtered and concentrated to afford a residue, which was purified by column chromatography using petroleum ether/EtOAc (40:60) to give pure diol **14** (6.21 g, 75% yield). R_f = 0.15 (SiO_2, 50% EtOAc in petroleum ether) ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.71 (d, J = 3.6 Hz, 1H), 4.55 (m, 1H), 3.84–3.80 (m, 2H), 3.72–3.62 (m, 2H), 3.41 (br.s, 2H), 2.12–1.90 (m, 1H), 1.50 (s, 3H), 1.32 (s, 3H), 1.14 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.5, 104.5, 83.3 (2C), 73.0, 63.4, 40.3, 26.6, 26.2, 10.0; IR (KBr): ν_{max} 3435, 2985, 2860, 1240, 1127, 1050 cm^{-1}; ESIMS: m/z 219 [M+H]$^+$; $[\alpha]_D^{28}$ = +22.0 (c 2, $CHCl_3$).

4.1.7. ((3a*R*,5*S*,6*R*,6a*R*)-2,2,6-Trimethyltetrahydrofuro[3,2-*d*]-[1,3]dioxol-5-yl)methanol 15

A solution of diol **14** (6.10 g, 28 mmol) in methanol (60 mL) was treated with $NaIO_4$ (23.97 g, 112 mmol) portionwise at 0 °C and stirred at room temperature for 2 h. The reaction mixture was filtered, the filtrate evaporated, and the residue was dissolved in water (50 mL) and extracted with EtOAc (3 × 80 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the aldehyde, which was used immediately for further reaction without purification. A solution of the aldehyde (4.8 g, 2.61 mmol) in MeOH (60 mL) was cooled to 0 °C and treated with $NaBH_4$ (1.98 g, 5.22 mmol). After stirring the mixture for 30 min, the reaction mixture was concentrated to remove methanol and to this was added a saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with diethyl ether and the organic phase was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (hexanes/EtOAc, 1:1) of the residue afforded alcohol **15** (3.9 g, 81%) as a colorless solid. R_f = 0.22 (SiO_2, 30% EtOAc in petroleum ether) ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.74 (d, 1H, J = 3.5 Hz), 4.52 (t, 1H, J = 4.1 Hz and 8.1 Hz), 3.74–3.87 (m, 2H), 3.44–3.54 (m, 1H), 2.53 (br s, 1H), 1.95–2.08 (m, 1H), 1.45 (s, 3H), 1.28 (s, 3H), 1.01 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.3, 104.6, 83.0, 82.8, 61.1, 37.9, 26.5, 26.1; IR (Neat) ν_{max} 3439, 2935, 1377, 1216, 1112, 1017, 874 cm^{-1}; $[\alpha]_D^{25}$ = +29.2 (c 2.5, MeOH); ESI/HRMS calcd for $C_9H_{16}O_4$ [M+Na]$^+$ 211.0945, found 211.0926.

4.1.8. *tert*-Butyldiphenyl(((3a*R*,5*S*,6*R*,6a*R*)-2,2,6-trimethyl-tetrahydrofuro[3,2-*d*][1,3]dioxol-5-yl)methoxy)silane 16

To a stirred solution of alcohol **15** (3.9 g, 20.7 mmol) in dry CH_2Cl_2 (45 mL) was added imidazole (4.23 g, 62.23 mmol) at 0 °C and stirred for 15 min at the same temperature. Then TBDPSCl (6.4 mL, 24.8 mmol) was added at 0 °C and the reaction mixture was stirred for an additional 15 min at the same temperature. The reaction was quenched with a saturated NH_4Cl (aq.) (60 mL) solution at 0 °C, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fraction was dried over anhydrous Na_2SO_4. The solvent was removed through a rotary evaporator under reduced pressure and the residue was purified through silica gel column chromatography using 8% EtOAc/petroleum ether to yield TBDPS ether **16** as a colorless oil (7.45 g, 90%). R_f = 0.9 (SiO_2, 30% EtOAc in petroleum ether) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.78 (m, 4H), 7.36–7.48 (m, 6H), 5.84 (d, 1H, J = 3.3 Hz), 4.58 (t, 1H, J = 3.9 Hz and 7.9 Hz), 3.71–3.95 (m, 3H), 2.13–2.24 (m, 1H), 1.53 (s, 3H), 1.36 (s, 3H), 1.07–1.11 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 135.5, 134.7, 129.5, 127.6, 104.9, 83.1, 83.0, 63.1, 39.0, 26.7, 26.5, 26.3, 9.3; IR (Neat) ν_{max} 2933, 1377, 1111, 1024, 704, 505 cm^{-1}; $[\alpha]_D^{25}$ = +7.8 (c 2.9, MeOH); ESI/HRMS calcd for $C_{25}H_{34}O_4Si$ [M+Na]$^+$ 449.2116, found 449.2102.

4.1.9. (2*S*,3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methylbutane-1,3-diol 17

To a stirred solution of TBDPS protected compound **16** in CH_2Cl_2 was added a BCl_3 solution (20 mL) at 0 °C. After 2 min, the reaction was quenched with water (75 ml). The compound was extracted twice with CH_2Cl_2 (2 × 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and then concentrated using a rotary

evaporator to afford the diol. The diol so obtained without further purification was dissolved in MeOH:H_2O (8:2) 40 mL and cooled to 0 °C. To this was added $NaIO_4$ (11.2 g, 52.5 mmol) and the mixture was stirred for 30 min The reaction mixture was then filtered, the filtrate was evaporated, and the residue was dissolved in water (50 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the di-aldehyde, which was taken in MeOH (60 mL) and cooled to 0 °C and then treated with $NaBH_4$ (2.6 g, 70.0 mmol). After stirring the mixture for 30 min, the methanol was evaporated and a saturated aqueous NH_4Cl (20 mL) was added. The mixture was extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (hexanes/EtOAc, 1:1) of the residue afforded **17** (4.8 g, overall yield 78%) as a colorless oil. R_f = 0.19 (SiO_2, 30% EtOAc in petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64–7.75 (m, 4H), 7.32–7.48 (m, 6H), 3.55–4.0 (m, 5H), 2.09–2.25 (m, 1H), 1.07 (d, 12H, J = 4.9 Hz), 0.88 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 129.6, 127.6, 78.4, 67.4, 65.1, 31.5, 26.7, 19.2, 12.8; IR (Neat) ν_{max} 3450, 2932, 1425, 1340, 1111, 703, 504 cm^{-1}; $[\alpha]_D^{25} = +10.9$ (c 2.4, MeOH); ESIMS: m/z 381 [M+Na]$^+$.

4.1.10. (6*S*,7*S*)-6-(methoxymethoxy)-2,2,7,10,10,11,11-heptamethyl-3,3-diphenyl-4,9-dioxa-3,10-disiladodecane 18

To an ice-bath cooled solution of diol **17** (4 g, 11 mmol), and TEA (3.5 ml, 24 mmol) in anhydrous CH_2Cl_2 (50 mL) were added a solution of TBDMSCl (1.8 g, 12.2 mmol) in anhydrous CH_2Cl_2 (15 mL) and a catalytic amount of DMAP. The mixture was stirred at room temperature for 3 h, then diluted with water (50 mL) and extracted with $CHCl_3$ (3 × 60 mL). The combined organic phases were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration *in vacuo*, the product was purified by flash chromatography (eluent; EtOAc: petroleum ether = 1:4) to give primary TBS ether as a colorless oil in 85% yield. To a stirred solution of the above alcohol (4.4 g, 9.3 mmol) and diisopropylethyl amine (4.86 mL, 27.9 mmol) in dry CH_2Cl_2 (30 mL) were added MOMCl (0.97 g, 12 mmol) under a nitrogen atmosphere over 5 min, and a catalytic amount of DMAP at 0 °C after which the mixture was allowed to warm to room temperature for 5 h. After cooling to 0 °C, the reaction mixture was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with water (3 × 40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) gave MOM protected alcohol **18** (4.8 g, 95% yield) as a colorless syrupy liquid. R_f = 0.74 (SiO_2, 50% EtOAc in petroleum ether) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.81 (m, 4H), 7.37–7.49 (m, 6H), 4.75 (dd, 2H, J = 6.7 Hz and 31.7 Hz), 3.76–3.85 (m, 2H), 3.64–3.71 (dd, 2H, J = 4.53 Hz and 9.8 Hz), 3.54–3.62 (m, 1H), 3.37 (s, 3H), 1.96 – 2.11 (m, 1H), 1.09 (s, 9H), 0.89–0.95 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.5, 129.5, 127.6, 96.6, 79.7, 64.8, 64.7, 55.6, 37.7, 26.8, 25.9, 19.2, 18.2, 13.4, -5.4; IR (Neat) ν_{max} 3015, 1469, 1172, 1254, 1059, 703, 504 cm^{-1}; ESIMS: m/z 539 [M+Na]$^+$. $[\alpha]_D^{20} = -12.9$ (c 1, $CHCl_3$).

4.1.11. (2*S*,3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-(methoxymethoxy)-2-methylbutyl 4-methylbenzenesulfonate 19

To an ice-bath cooled solution of the TBS ether **18** (4.5 g, 8.7 mmol) in MeOH (40 mL) was added *p*-TsOH (300 mg). The reaction mixture was stirred at 15 °C for 30 min The reaction mixture was then quenched with solid $NaHCO_3$ (2 g) and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (3:1 hexanes:EtOAc → 2:1 hexanes:EtOAc) to afford 3.04 g (87%) of the primary alcohol as a colorless oil. To an ice-bath cooled solution of primary alcohol (3 g, 7.4 mmol) in anhydrous CH_2Cl_2 (30 mL) were added successively TEA (1.6 mL, 11.1 mmol), a solution of *p*-TsCl (1.56 g, 8.2 mmol) in anhydrous CH_2Cl_2 (15 mL), and a catalytic amount of DMAP. After being stirred at room temperature for 3 h, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and water, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed successively with a saturated solution of $NaHCO_3$ (50 mL), brine (50 mL) and dried over Na_2SO_4. After purification by flash chromatography (eluent: EtOAc:petroleum ether = 10:90), product tosylate **19** (3.7 g, 90%) was obtained as a colorless oil. R_f = 0.65 (SiO_2, 20% EtOAc in petroleum ether) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.81 (m, 6H), 7.26–7.46 (m, 8H), 4.58 (d, 1H, J = 6.6 Hz), 4.48 (d, 1H, J = 6.7 Hz), 4.00–4.18 (m, 2H), 3.58–3.73 (m, 2H), 3.42–3.51 (m, 1H), 3.23 (s, 3H), 2.42 (s, 3H), 2.16–2.28 (m, 1H), 1.02 (s, 9H), 0.93 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 135.4, 129.6, 127.8, 127.6, 96.2, 78.7, 72.4, 63.6, 55.6, 34.6, 26.7, 21.5, 19.1, 13.5; IR (Neat) ν_{max} 3430, 2930, 2856, 1360, 1176, 1111, 817, 703, 505 cm^{-1}; $[\alpha]_D^{25} = +3.4$ (c 2.5, MeOH); ESI/HRMS calcd for $C_{30}H_{40}O_6SSi$[M+Na]$^+$ 579.2198, found 579.2215.

4.1.12. (*S*)-5-((*S*)-Hex-4-yn-2-yl)-9,9-dimethyl-8,8-diphenyl-2,4,7-trioxa-8-siladecane 20

Sodium hydrogen carbonate (0.79 g, 9.4 mmol) and sodium iodide (1.1 g, 7.5 mmol) were added to a solution of tosylate **19** (3.5 g, 6.2 mmol) in dry acetone (25 mL). The mixture was stirred and heated at reflux for 3 h and extracted with pentane. The extracts were washed with water, a 10% sodium thiosulfate solution, saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate and concentrated in vacuo to give the crude iodide. Propyne gas (2.2 g, 54.6 mmol) was dissolved in dry THF (10 ml) below −40 °C under Ar. It was then stirred for 10 min below −50 °C and then *n*BuLi in hexane (1.60 M, 3.8 ml, 6.0 mmol) was added slowly to the solution in a dropwise manner. The mixture was then stirred for 10 min below −50 °C, after which HMPA (1.5 ml) was added dropwise, and the mixture was stirred for a further 30 min below −50 °C. Next, a second portion of *n*BuLi in hexane (1.60 M, 3.8 ml, 6.0 mmol) was slowly added to the solution, after which it was stirred for 10 min below −50 °C. A solution of crude iodide (2.8 g, 5.4 mmol) in dry THF (50 ml) was added dropwise to this solution at −50 °C to −40 °C and the temperature was gradually allowed to return to room temperature. After stirring for 3 h at room temperature, the mixture was poured into an ice-cooled satd. ammonium chloride solution and extracted with diethyl ether. The ether extracts were washed with a saturated aqueous ammonium chloride solution, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo after filtration. The residue was chromatographed on silica gel (30 g). Elution with pentane diethyl ether (25:l) gave 1.62 g of alkyne **20** (70%) as a viscous liquid. R_f = 0.64 (SiO_2, 10% EtOAc in petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.64 (m, 4H), 7.26–7.36 (m, 6H), 4.53–4.69 (m, 2H), 3.61–3.70 (m, 2H), 3.42–3.51 (m, 1H), 3.27 (s, 3H), 1.86–2.33 (m, 3H), 1.68 (s, 3H), 0.92–1.01 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 135.5, 129.6, 129.6, 127.6, 96.4, 80.8, 64.2, 55.7, 34.5, 26.8, 22.0, 19.1, 15.9, 3.4; IR (Neat) ν_{max} 2931, 1428, 1109, 1035, 703, 504 cm^{-1}; $[\alpha]_D^{25} = -12.8$ (c 1.0, MeOH); ESIMS: m/z 425 [M+H]$^+$.

4.1.13. (2*S*,3*S*)-2-(Methoxymethoxy)-3-methylhept-5-yn-1-ol 21

A solution of TBDPS ether **20** (1.5 g, 3.5 mmol) in THF (30 mL) was treated with TBAF (1 M in THF) (8 mL, 7.1 mmol) at 0 °C and stirred for 30 min at room temperature. After completion of the reaction, the reaction mixture was washed with an aq. saturated $NaHCO_3$ solution (20 mL). The organic layer was separated, dried

over anhydrous Na_2SO_4, concentrated in vacuo, and then purified by silica gel chromatography using petroleum ether/EtOAc (80:20) to give pure product **21** (0.65 g, 98% yield) as a colorless oil. $R_f = 0.13$ (SiO_2, 10% EtOAc in petroleum ether). ^1H NMR (300 MHz, $CDCl_3$): δ 4.66–4.80 (m, 2H), 3.66–3.78 (m, 1H), 3.39–3.60 (m, 5H), 1.80–2.04 (m, 3H), 1.77 (s, 3H), 0.96–1.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.3, 78.7, 72.4, 63.6, 55.6, 34.6, 26.7, 21.5, 19.1, 13.5; IR (Neat) ν_{max} 3448, 2929, 2172, 1429, 1106, 1034, 701 cm^{-1}; $[\alpha]_D^{25} = -15.2$ (*c* 1.2, MeOH); ESIMS: *m*/*z* 187 $[M+H]^+$.

4.1.14. (3a′*S*,4′*R*,5′*R*,6a′*R*)-4′-((3*S*,4*S*,*E*)-3-(Methoxymethoxy)-4-methyloct-1-en-6-ynyl)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-5′-ol 22

To a solution of alcohol **21** (200 mg, 1.07 mmol) in THF (10 mL) cooled to 0 °C were added 1-phenyl-1*H*-tetrazole-5-thiol (287 mg, 1.6 mmol), Ph_3P (422 mg, 1.6 mmol), and DIAD (0.25 mL, 1.6 mmol), and the resultant solution was stirred at room temperature for 30 min The reaction was quenched with a sat. aq. $NaHCO_3$ (15 ml) solution at 0 °C, and the resultant mixture was extracted with EtOAc (3 × 20 ml). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10–15% EtOAc/hexanes) gave a sulfide (407.0 mg), which contained some impurities but was used in the next reaction without further purification.

To a solution of the above material (sulfide) in EtOH (10 mL) was added a portion (3 mL) of a stock solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (330.0 mg) and 30% H_2O_2 (5 mL). The reaction mixture was then stirred at room temperature for 20 h. The resultant mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10–15% EtOAc/hexanes) gave sulfone **5** (360 mg, 89% for two steps) as a colorless oil. The crude sulfone without further purification was directly utilized for the Julia olefination reaction.

To a solution of sulfone **5** (100 mg, 0.27 mmol) in THF/HMPA (5:1, v/v, 1.0 mL) cooled to −78 °C was added LHMDS (1.0 M solution in THF, 0.24 mL, 0.238 mmol), and the resultant solution was stirred at same temperature for 20 minutes. To this solution was added a solution of aldehyde **4** (30 mg, 0.119 mmol) in THF/HMPA (5:1, v/v, 0.350 mL), and the resultant solution was allowed to warm to room temperature over a period of 6.5 h. The reaction was quenched with a sat. aq. NH_4Cl (10 mL) solution at 0 °C, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5–15% EtOAc/hexanes) gave the major isomer 95% *de* (*E*)-olefin **22** (65 mg, 57%) as a light yellow oil. $R_f = 0.53$ (SiO_2, 20% EtOAc in petroleum ether). ^1H NMR (300 MHz, $CDCl_3$): δ 5.32–5.81 (m, 2H), 4.65–4.76 (m, 1H), 4.50–4.64 (m, 1H), 3.65–4.30 (m, 2H), 3.42–3.52 (m, 4H), 3.33–3.41 (m, 3H), 1.98–2.50 (m, 8H), 1.76–1.82 (m, 3H), 1.51–1.69 (m, 4H), 0.90–1.01 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.4, 130.7, 127.8, 110.1, 94.3, 81.6, 81.4, 78.1, 72.0, 72.0, 71.9, 58.3, 57.3, 55.3, 40.2, 37.0, 35.6, 30.0, 29.6, 22.4, 15.5, 3.4; IR (Neat) ν_{max} 3424, 2925, 2854, 1732, 1456, 1375, 1152, 1099, 1032, 766 cm^{-1}; $[\alpha]_D^{25} = +2.8$ (*c* 0.49, MeOH); ESIMS: *m*/*z* 429 $[M+Na]^+$.

4.1.15. (3a*S*,4*R*,5*R*,6a*R*)-5-hydroxy-4-((3*S*,4*S*,*E*)-3-hydroxy-4-methyloct-1-en-6-ynyl)hexahydropentalen-2(1*H*)-one 3

A solution of MOM ether **22** and **6** M HCl(10 ml) was stirred for 20 h at room temperature. After completion of the reaction, the mixture was extracted using EtOAc (3 × 10 mL). The combined organic layer was washed with a sat. aq. $NaHCO_3$ solution (2 × 20 mL), then with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography using EtOAc:Hex (4:1) as eluent gave keto diol **3** (42 mg, 81%) as a colorless oil. $R_f = 0.23$ (SiO_2, 30% EtOAc in petroleum ether). ^1H NMR (300 MHz, $CDCl_3$): δ 5.54–5.62 (m, 2H), 3.91–4.07 (m, 2H), 2.03–2.78 (m, 10H), 1.53–1.83 (m, 5H), 0.94 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.1, 134.0, 132.5, 77.8, 77.4, 77.2, 76.0, 57.8, 45.9, 43.1, 42.3, 41.2, 38.2, 34.8, 22.1, 15.8, 3.5; IR (Neat) ν_{max} 3446, 2925, 2855, 1737, 1640, 1461, 1260, 1093, 1022, 799 cm^{-1}; $[\alpha]_D^{25} = +9$ (*c* 1.0, MeOH); ESIMS: *m*/*z* 299 $[M+Na]^+$.

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