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Stereoselective synthesis of the C1–C8 subunit of peloruside A

Sadagopan Raghavan *, V. Vinoth Kumar

Division of Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

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ABSTRACT

Two routes to the C1–C8 subunit of peloruside A are disclosed. The first route involving 14 steps exploits Krische's allylation, substrate controlled 1,3-asymmetric induction during bromohydrin formation from an alkene utilizing an intramolecular sulfinyl group as a nucleophile and Pummerer reaction as key steps. The second, shorter, scalable route (seven steps) exploits catalytic asymmetric reactions including Jacobsen's hydrolytic kinetic resolution of an epoxide and Sharpless' asymmetric dihydroxylation reaction as the key steps.

1. Introduction

Peloruside A **1**, is a marine metabolite isolated from *Mycale hentscheli* by Northcote and co-workers.[1] Peloruside A is an architecturally complex 16-membered macrolide. It possesses potent taxol-like microtubule stabilizing activity,[2] although binding to tubulin at a site different from taxol.[3] NMR studies helped in establishing the relative stereochemistry of the ten stereogenic centers and the absolute stereochemistry became known with De Brabander's synthesis.[4] The structural complexity, interesting biological activity, and scarcity in nature have led to a considerable interest in peloruside from the synthesis community.[5–10]

We envisioned the synthesis of (+)-peloruside A **1**, Scheme 1, by coupling C1–C8 alkyne subunit **2** with the C9–C19 aldehyde subunit **3**,[11] followed sequentially by, the oxidation of the ensuing epimeric propargylic alcohols to a ketone, partial reduction of the alkyne to a *cis*-alkene, diastereoselective dihydroxylation, ketal formation, and lastly macrolactonization. The alkyne **2** was envisaged to be obtained from triflate **4** and TMS-acetylene. Triflate **4** was proposed to be obtained by stereoselective oxidative heterofunctionalization of alkene **5** by taking advantage of its C5 stereocenter. Compound **5** in turn can be traced to terminal alkene **6** and *cis*-1,4-butene diol **7**, Scheme 1.

2. Results/discussion

The synthesis began with the oxidation of phenylthio ethanol **8** with IBX[12] to phenylthio acetaldehyde **9** that on exposure to allyltributyl tin following Keck's protocol[13] afforded homoallyl alcohol **6** (89.5% ee, 63% yield).[14] Subsequently, alcohol **6** was obtained directly from phenylthio ethanol **8** and allyl acetate in a single step by adopting Krische's protocol[15] in the presence catalyst **10**, prepared in situ using 5 mol % of (*S*)-BINAP, 3-nitrobenzoic acid, and 2.5 mol % of $[Ir(cod)Cl]_2$, in good yield, and selectivity (93.5% ee, 82% yield).[16] Cross metathesis of **6** with an excess of *cis*-butene diol **7** using Grubbs' catalyst **11**, furnished diol **12**.[17] Protection of diol **12** with TBDPS–Cl in the presence of imidazole furnished silyl ether **13** (P=TBBPS). Selective oxidation of the sulfanyl group in **13** using *m*CPBA at low temperature yielded an equimolar, inseparable, epimeric mixture of sulfoxide **5**. Oxidative heterofunctionalization of the alkene in **5** using *N*-bromosuccinimide as the electrophile and the sulfinyl group as the intramolecular nucleophile furnished bromohydrin **14** via substrate controlled asymmetric induction involving putative transition states **I** and **II**, Scheme 2.[18]

It was intended to introduce the oxygen functionality at C2 by intermolecular displacement of bromide by an oxygen nucleophile. Toward this end, the carbinol in **14** was protected as its MOM-ether **15** employing standard conditions. Attempted displacement[19] of the bromide in **15** by an acetate using excess KOAc in DMF at 90 °C for 48 h furnished unreacted starting material while, treatment with an excess of $NaNO_2$ in DMSO at 100 °C for 24 h afforded a complex mixture of products. In parallel, the MOM-ether **15** was subjected to Pummerer rearrangement[20] by treatment with TFAA

* Corresponding author. E-mail addresses: sraghavan@iict.res.in, purush101@yahoo.com (S. Raghavan).

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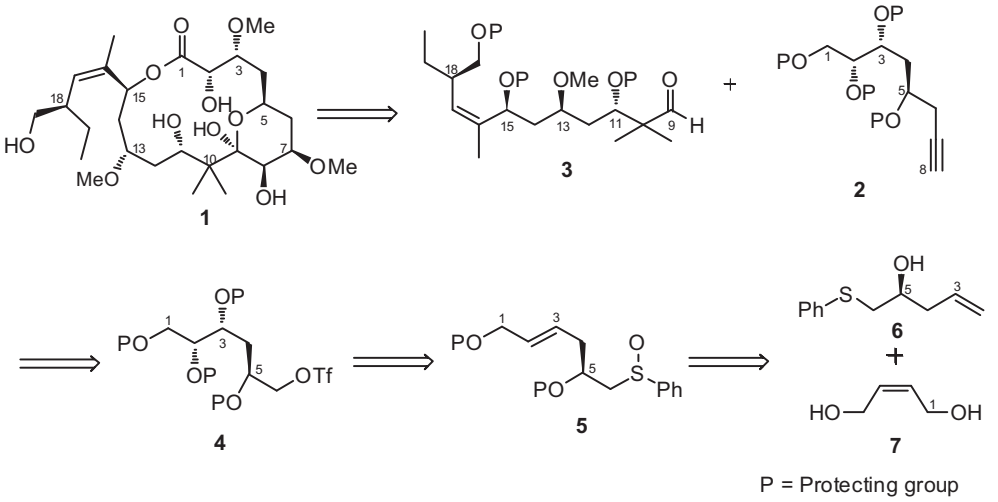
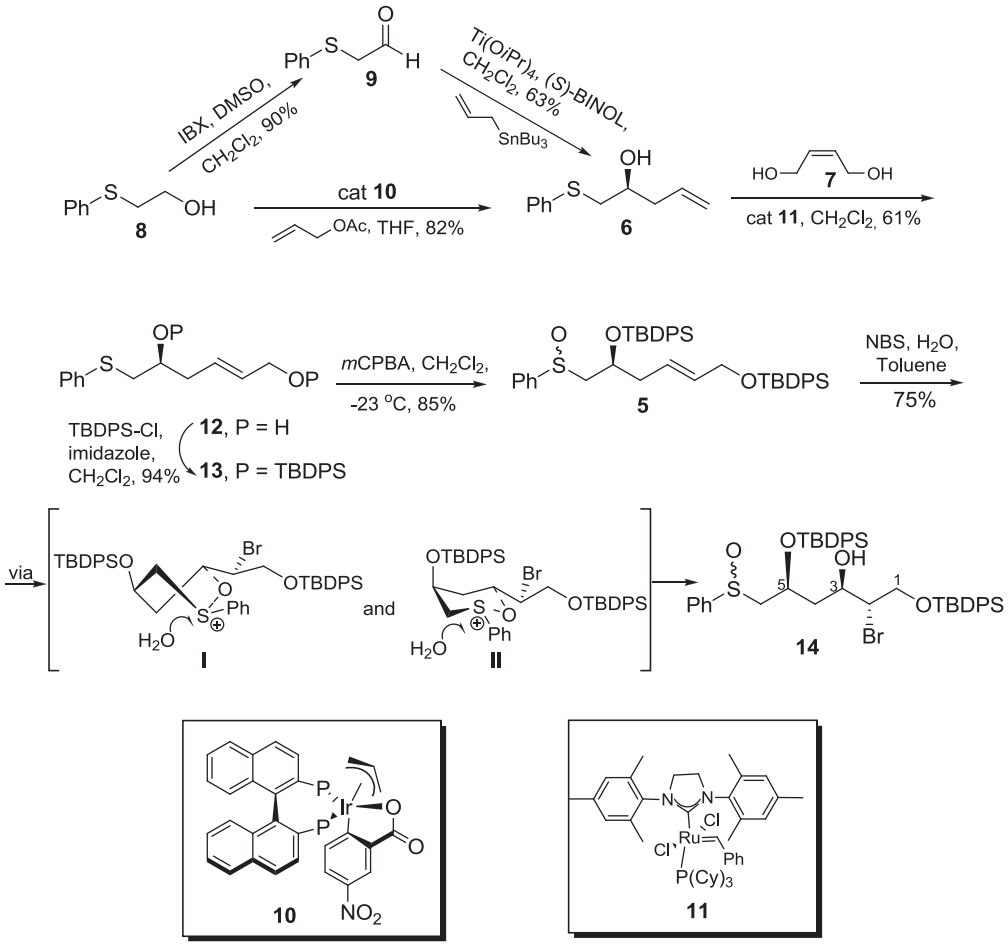


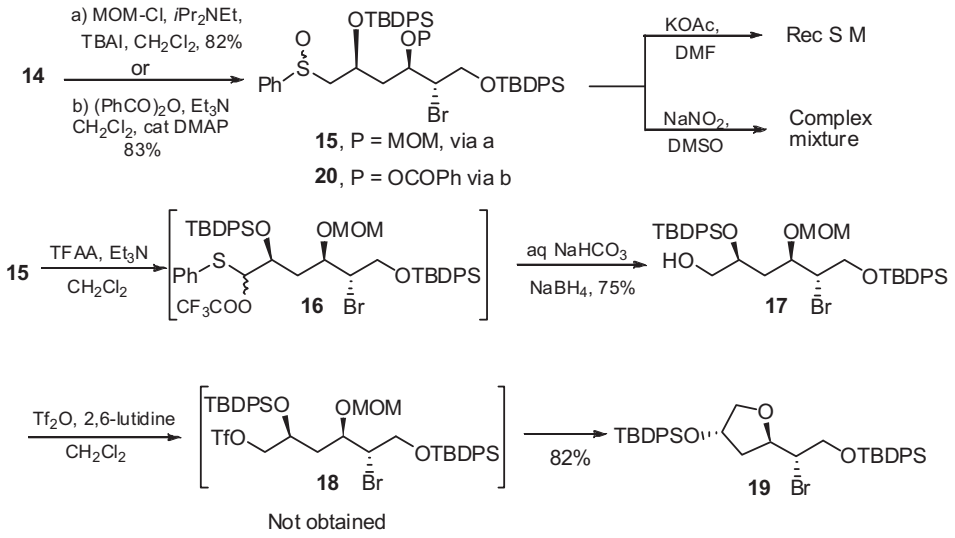
Scheme 1. Retrosynthetic disconnection of peloruside A.



Scheme 2. Stereoselective synthesis of bromohydrin **14**.

in the presence of triethylamine and the resulting intermediate **16** without isolation was hydrolyzed to yield an aldehyde that was reduced in the same pot with $NaBH_4$ to yield alcohol **17**. Treatment with triflic anhydride and 2,6-lutidine expecting to obtain triflate **18**, instead yielded tetrahydrofuran **19** as the sole product by intramolecular etherification, Scheme 3.

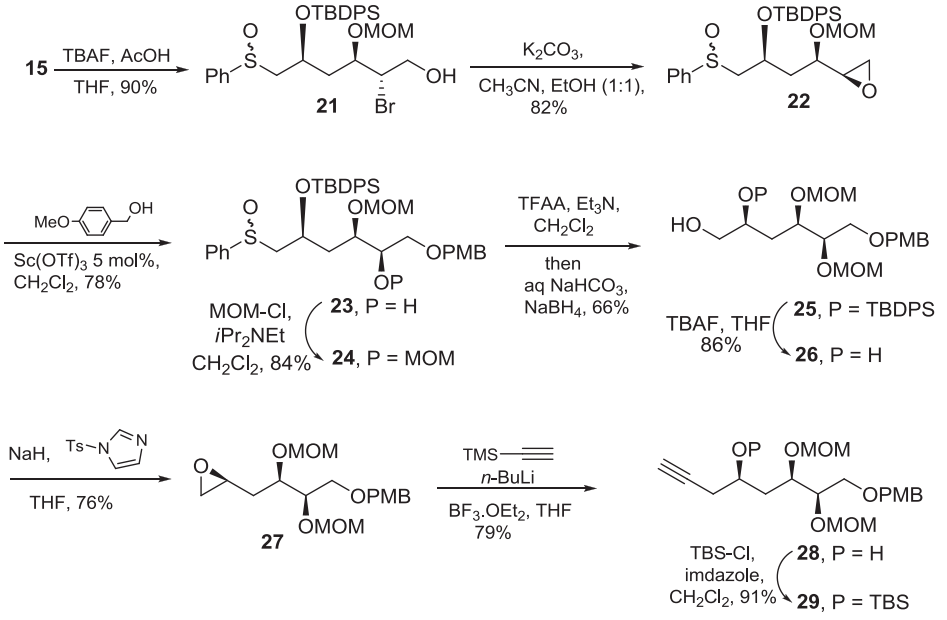
It was apparent from the formation of **19** that a nucleophilic ether type protecting group at C3 was not suitable for the eventual introduction of the alkyne moiety. The bromohydrin **14** was therefore reacted with benzoic anhydride to afford benzoate **20**, Scheme 3. Again, attempted displacement of bromide in **20** with KOAc in DMF at 90 °C afforded unreacted starting material while,



Scheme 3. Attempted intermolecular displacement of bromide by an oxygen nucleophile.

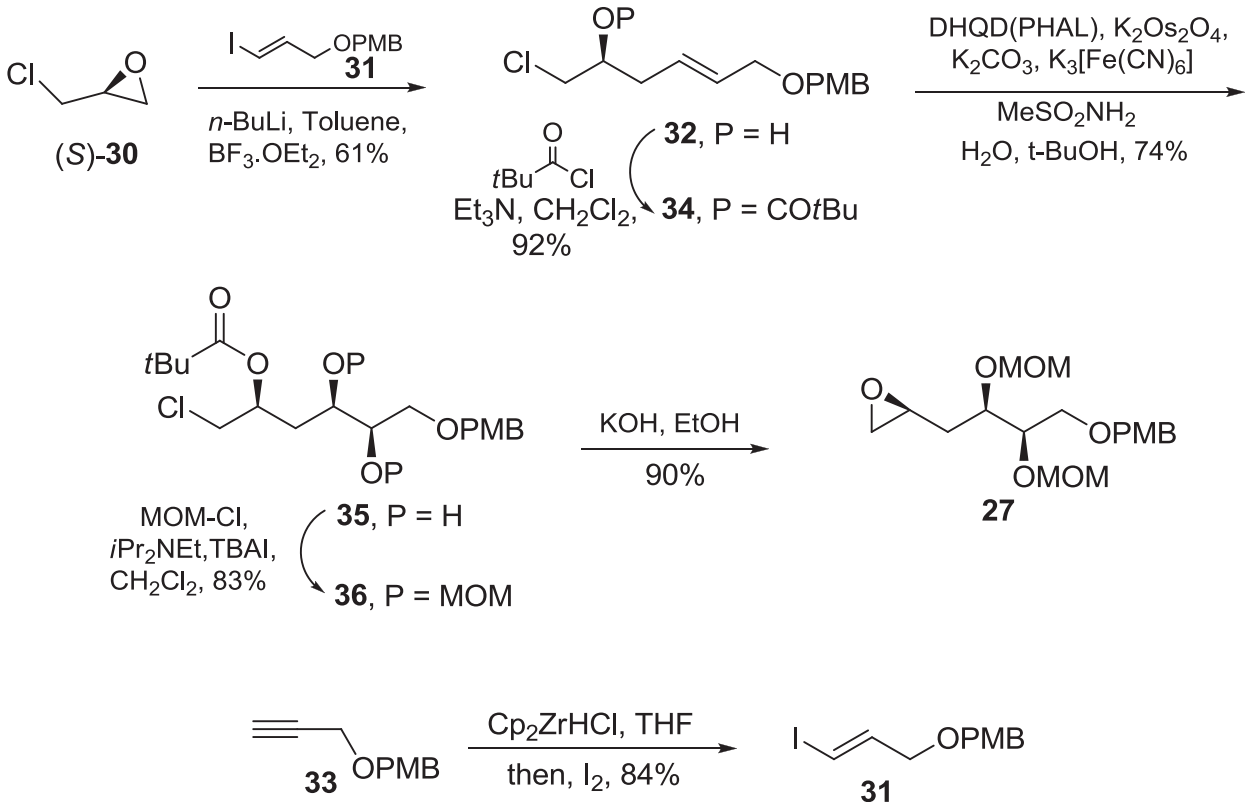
attempted reaction with $NaNO_2$ in DMSO at 100 °C furnished a complex mixture of products. Having failed to introduce an oxygen functionality at C2 via an intermolecular reaction it was thought fit to attempt an intramolecular displacement.

Proceeding, the MOM-ether **15** was subjected to selective deprotection of the primary silyl ether using TBAF under buffered conditions to afford bromohydrin **21**. Epoxide formation proceeded cleanly on treatment of **21** with anhydrous K_2CO_3 in a mixture of acetonitrile and ethanol to yield **22**. Treatment of **22** with 4-methoxybenzyl alcohol in the presence of catalytic amounts of $Sc(OTf)_3$[21] furnished tetrol derivative **23** via regioselective epoxide opening. The hydroxy group in **23** was protected following the standard protocol, to yield the MOM-ether **24**. It only remained to introduce the alkynyl residue. Toward this end, the compound **24** was subjected to Pummerer rearrangement followed by one-pot hydrolysis of the intermediate and in situ reduction of the resulting aldehyde to afford alcohol **25**. TBAF promoted deprotection of the silyl ether yielded diol **26** that on treatment with an excess of NaH and an equivalent of *N*-tosyl imidazole[22] yielded epoxide **27**. Subjecting epoxide **27** to reaction with TMS-acetylide following Yamaguchi's protocol[23] furnished alcohol **28** by a concomitant desilylation, probably during work up. Protection of the alcohol as its TBS ether using standard conditions yielded silyl ether **29**, Scheme 4, corresponding to the C1–C8 subunit of peloruside A.



Scheme 4. Synthesis of the C1–C8 subunit of peloruside A.

The C1–C8 subunit was thus synthesized in 14 steps beginning from phenylthio ethanol in 3.7% overall yield. Although the subunit was successfully synthesized the route was not suitable for bringing more material due to its length. We therefore sought an alternate route to the C1–C8 fragment and we describe below its synthesis by a shorter seven-step sequence, Scheme 5. (*S*)-Epichlorohydrin



Scheme 5. Alternate, short synthesis of the C1–C8 subunit.

30, obtained by hydrolytic kinetic resolution,[24] was subjected to $BF_3 \cdot OEt_2$ promoted opening by the lithio alkene, prepared from iodo alkene **31**, to furnish chlorohydrin **32**.[25] The iodo alkene **31** was prepared by hydrozirconation[26] of propargyl ether **33** followed by iodine quench. Protection of the carbinol as its pivalate **34** followed by asymmetric dihydroxylation[27] yielded diol **35** (>95% de, 74% yield). The hydroxy groups were protected employing usual conditions as their MOM-ethers to afford compound **36**. Exposure of **36** to ethanolic KOH yielded epoxide **27** identical in all respects to that obtained from diol **26**. The epoxide **27** was elaborated to alkyne **29** as detailed earlier. The overall yield of **29** by the second route was 22%.

3. Conclusion

In summary, we have disclosed two routes, one exploiting the nucleophilic potential of the sulfinyl group for oxidative functionalization of an alkene and the other utilizing the Sharpless asymmetric dihydroxylation as key steps for introduction of the C2 and C3 stereogenic centers in the C1–C8 subunit of peloruside A. The second route is shorter, scalable, and is desirable.

4. Experimental section

4.1. General information

All materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame dried glassware, which was then cooled under nitrogen gas. Tetrahydrofuran (THF), toluene was distilled over Na/Ph_2CO under nitrogen atmosphere. Dichloromethane (CH_2Cl_2), hexane, acetonitrile, dimethylsulfoxide, dimethylformamide, triethylamine (TEA), 2,6-lutidine, and diethyl ether (Et_2O) were dried over CaH_2 and distilled prior to use. 4 Å molecular sieves were flame dried and then cooled under high vacuum prior to use. All reactions were monitored by E. Merck analytical thin-layer chromatography (TLC) plates and analyzed with 254 nm UV light and/or anisaldehyde–sulfuric acid or potassium permanganate or PMA treatment. Silica gel for column chromatography was purchased from Acme (Silica Gel 60–120, 100–200 mesh). All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Gemini 200, Avance 300, Inova 400, Inova 500, Bruker 600 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ as an internal reference (^1H: δ 7.26 ppm, ^{13}C: δ 77.00 ppm). Coupling constants (J) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Enantiomeric excess were recorded by Waters HPLC instrument. Mass spectra were recorded using Waters Mass spectrometers. High resolution spectroscopies (HRMS) were recorded using Applied Bio-Sciences HRMS spectrometer. All IR-spectra were recorded using Nexus 870-FT-IR Thermo Nicolet spectrometer. The optical rotations were measured on JASCO DIP-360 digital polarimeter.

4.2. Compound 6 using Keck's protocol

To a solution of 2-iodoxy benzoic acid (3.7 g, 14.4 mmol) in DMSO (14 mL) was added a solution of phenylthio ethanol **8** (1.85 g, 12 mmol) in CH_2Cl_2 (60 mL) at rt and the mixture was stirred for 4 h. The precipitated solid was filtered, washed with CH_2Cl_2, and the combined filtrates were washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue via flash chromatography on silica gel using 10% EtOAc/hexane (v/v) as the eluent afforded aldehyde **9** (1.64 g, 10.8 mmol) in 90% yield as a light yellow oil. TLC R_f=0.40 (10% EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 9.49 (t, J=3.2 Hz,

1H), 7.47–7.15 (m, 5H), 3.53 (d, J=3.2 Hz, 2H). A mixture of (*S*)-BINOL (286 mg, 1 mmol), Ti(^{i}OPr)$_4$ (0.15 mL, 0.5 mmol), and 2 g of activated 4 Å molecular sieves in anhydrous CH_2Cl_2 (20 mL) was stirred at rt for 3 h. The red-brown reaction mixture was cooled to −10 °C and a solution of the above aldehyde **9** (1.52 g, 10 mmol) in anhydrous CH_2Cl_2 (10 mL) was added followed by allyl tri-*n*-butyltin (3.72 mL, 12 mmol). After 16 h of stirring at the same temperature the reaction mixture was quenched with aq saturated $NaHCO_3$ and stirred for further 1 h. The mixture was filtered through a pad of Celite and washed with dichloromethane. The layers were separated and the aq layer was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to provide the crude material, which was purified by column chromatography using hexanes/EtOAc (9:1, v/v) to afford **6** (1.22 g, 6.3 mmol) in 63% yield as a colorless oil. TLC R_f=0.25 (15% EtOAc/hexanes). $[\alpha]_D^{35}$=+18.5 (*c* 1, $CHCl_3$). IR (KBr): 3471, 3072, 2923, 1438, 1026, 917, 740, 691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.12 (m, 5H), 5.88–5.72 (m, 1H), 5.13–5.06 (m, 2H), 3.74–3.66 (m, 1H), 3.09 (dd, J=13.5, 4.5 Hz, 1H), 2.85 (dd, J=13.5, 8.3 Hz, 1H), 2.39–2.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 129.7, 128.9, 126.3, 118.0, 68.7, 41.0, 40.2. MS (ESI) 233 $[M+Na]^+$. HRMS (ESI) m/z calcd for $C_{11}H_{14}O_2NaS$ 233.06067; found 233.06098.

4.3. Compound 6 via Krische's protocol

To a sealed tube charged with phenylthio ethanol **8** (760 mg, 5 mmol), $[Ir(cod)Cl]_2$ (85 mg, 0.125 mmol), (*S*)-BINAP (155 mg, 0.25 mmol), Cs_2CO_3 (325.0 mg, 1 mmol), *m*-nitrobenzoic acid (82.5 mg, 0.5 mmol) was added anhydrous THF (25.0 mL) followed by allyl acetate (5.5 mL, 50 mmol). The reaction mixture was stirred at 110 °C for 30 h. The reaction mixture was allowed to cool to rt and filtered through a small pad of silica gel. The organic layer was evaporated under reduced pressure. The crude residue was purified via column chromatography using hexanes/EtOAc (9:1, v/v) to furnish **6** (800 mg, 4.1 mmol) in 82% yield as a colorless oil.

4.4. Compound 12

To a solution of **6** (1.55 g, 8 mmol) and *cis*-butene diol **7** (2.1 g, 24 mmol) in anhydrous CH_2Cl_2 (24 mL) was added Grubbs' II generation catalyst **11** (680 mg, 0.8 mmol) and stirred at reflux temperature. After 24 h, a second portion of catalyst **11** (680 mg, 0.8 mmol) was added and stirring continued for a further 24 h. The volatiles were evaporated and the crude product was purified by column chromatography using hexanes/EtOAc (6:4, v/v) to afford **12** (1.1 g, 4.9 mmol) in 61% yield as a solid. Mp: 79 °C. TLC R_f=0.10 (50% EtOAc/hexanes). $[\alpha]_D^{35}$=+25.0 (*c* 1, $CHCl_3$). IR (KBr): 3471, 3072, 2923, 1438, 1026, 917, 740, 691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.20 (m, 5H), 5.68–5.58 (m, 2H), 4.10–4.02 (m, 2H), 3.84–3.60 (m, 1H), 3.25 (dd, J=13.6, 4.5 Hz, 1H), 2.82 (dd, J=13.6, 8.3 Hz, 1H), 2.34–2.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.3, 132.6, 129.9, 129.0, 127.7, 126.5, 68.9, 63.1, 41.1, 38.7. MS (ESI) 247 $[M+Na]^+$. HRMS (ESI) m/z calcd for $C_{12}H_{16}O_2NaS$ 247.0768; found 247.0775.

4.5. Compound 13

To a solution of **12** (1.01 g, 4.5 mmol) and imidazole (1.28 g, 19.8 mmol) in anhydrous CH_2Cl_2 (22.5 mL) cooled at 0 °C was added TBDPS–Cl (2.58 mL, 9.9 mmol). After 6 h the solvent was evaporated to provide the crude compound, which was purified by column chromatography using hexanes/EtOAc (9:1, v/v) to provide pure **13** (2.96 g, 4.24 mmol) in 94% yield as a viscous oil. TLC R_f=0.26 (20% EtOAc/hexanes). $[\alpha]_D^{35}$=−4.7 (*c* 1, $CHCl_3$). IR (KBr): 3072, 2923, 1438, 1026, 917, 740, 691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64–7.62 (m, 8H), 7.44–7.28 (m, 12H), 7.12–6.96 (m, 5H), 5.70 (dt, J=15.3, 6.8 Hz, 1H), 5.51 (dt, J=15.3, 4.7 Hz, 1H), 4.12 (d, J=4.7 Hz, 2H), 4.02–3.92 (m, 1H), 2.95 (d, J=6.8 Hz, 2H), 2.48–2.31 (m, 2H), 1.10 (s, 9H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5, 135.8, 135.5, 133.9, 133.7, 132.3, 129.6, 129.5, 128.6, 127.6, 125.4, 125.3, 71.5, 64.2, 38.7, 37.9, 26.9, 26.8, 19.3, 19.2. MS (ESI) 723 $[M+Na]^+$. HRMS (ESI) m/z calcd for $C_{44}H_{52}O_2Si_2SNa$ 723.31188; found 723.31262.

4.6. Compound 5

To a solution of **13** (2.8 g, 4 mmol) in anhydrous CH_2Cl_2 (20 mL) cooled at −23 °C was added *m*CPBA (920 mg, 4 mmol) portionwise over a 2 h period. After 1 h of further stirring, the reaction was quenched with aq saturated sodium sulfite solution. The layers were separated and aq layer was extracted with DCM (3×50 mL). The combined organic layers were washed with water, aq saturated $NaHCO_3$, water, brine, dried over Na_2SO_4, and the solvent evaporated. The crude product was purified by column chromatography using hexanes/EtOAc (8:2, v/v) to provide **5** (2.44 g, 3.4 mmol) in 85% yield as an inseparable mixture of epimers in equimolar amount. TLC R_f=0.18 (20% EtOAc/hexanes). $[\alpha]_D^{35}$=+10.7 (*c* 1, $CHCl_3$). IR (KBr): 3072, 2923, 1438, 1026, 917, 740, 691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.26 (m, 50H), 5.75–5.32 (m, 4H), 4.46–4.02 (m, 6H), 3.00–2.73 (m, 4H), 2.26–2.18 (m, 4H), 1.18–1.00 (m, 36H). MS (ESI) 717 $[M+H]^+$. HRMS (ESI) m/z calcd for $C_{44}H_{53}O_3Si_2S$ 717.3257; found 717.3230.

4.7. Compound 14

To a solution of sulfoxide **5** (2.15 g, 3 mmol) in anhydrous toluene (12 mL) was added water (81 μL, 4.5 mmol) followed by freshly recrystallized *N*-bromosuccinimide (0.64 g, 3.6 mmol) portionwise over 30 min and the reaction mixture was stirred further for 1 h at rt. The reaction was quenched by the addition of an aq saturated $NaHCO_3$ solution. The layers were separated and the aq layer was extracted with ethylacetate (4×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product that was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to afford bromohydrin **14** (1.8 g, 2.25 mmol) in 75% yield as a viscous oil. The bulk sample was carried ahead to the next step without separating epimeric sulfoxides. However, for characterization purposes a small sample was separated into individual epimeric sulfoxides. *Less polar isomer*: TLC R_f=0.10 (20% EtOAc/hexanes). $[\alpha]_D^{36}$=−8.2 (*c* 1, $CHCl_3$). IR (KBr): 3389, 3068, 2931, 2890, 2857, 1427, 1109, 1024, 821, 743, 702, 609, 504 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76–7.58 (m, 8H), 7.52–7.2 (m, 17H), 4.36–4.20 (m, 2H), 4.05–3.82 (m, 3H), 3.19 (dd, J=13.4, 7.9 Hz, 1H), 2.93 (dd, J=13.4, 3.2 Hz, 1H), 2.38–2.20 (m, 1H), 2.12–1.96 (m, 1H), 1.10 (s, 9H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 135.7, 135.6, 135.4, 133.2, 132.8, 130.5, 129.8, 129.7, 128.9, 127.6, 123.6, 68.6, 66.6, 65.1, 60.9, 59.7, 39.4, 26.8, 26.7, 19.1. MS (ESI) 813 $[M+H]^+$. HRMS (ESI) m/z calcd for $C_{44}H_{54}O_4Si_2SBr$ 813.2464; found 813.2452. *More polar isomer*: TLC R_f=0.09 (20% EtOAc/hexanes). $[\alpha]_D^{35}$=+27.2 (*c* 1, $CHCl_3$). IR (KBr): 3384, 3068, 2932, 2890, 2857, 1427, 1387, 1109, 821, 743, 702, 609, 503 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78–7.62 (m, 8H), 7.46–7.28 (m, 17H), 4.67–4.57 (m, 1H), 4.20–4.10 (m, 1H), 3.98–3.76 (m, 3H), 3.23 (dd, J=13.2, 5.8 Hz, 1H), 2.71 (dd, J=13.2, 7.1 Hz, 1H), 2.05–1.80 (m, 2H), 1.10 (s, 9H), 1.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 135.9, 135.7, 135.4, 133.1, 132.7, 130.8, 129.9, 129.7, 129.1, 127.7, 123.6, 68.0, 66.8, 64.8, 64.6, 60.0, 40.4, 26.9, 26.6, 19.3, 19.1. MS (ESI) 813 $[M+H]^+$. HRMS (ESI) m/z calcd for $C_{44}H_{54}O_4Si_2SBr$ 813.2464; found 813.2473.

4.8. Compound 15

To a solution of bromohydrin **14** (1.25 g, 1.5 mmol) in anhydrous CH_2Cl_2 (6 mL) cooled at 0 °C was added diisopropylethylamine (0.52 mL, 3 mmol), TBAI (58 mg, 0.15 mmol) followed by Mom-Cl (0.17 mL, 2.25 mmol). After 16 h of stirring, the reaction mixture was quenched by adding aq saturated $NaHCO_3$. The layers were separated and the aq layer was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting crude product was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to furnish pure **15** (1.06 g, 1.22 mmol) in 82% yield as a viscous oil. While the bulk sample was taken ahead without separating the individual sulfoxides for characterization purposes a small sample was separated. *Less polar isomer*: TLC R_f=0.16 (20% EtOAc/hexanes). $[\alpha]_D^{35}$=−24.3 (*c* 1, $CHCl_3$). IR (KBr): 3066, 2932, 2891, 2857, 1108, 1039, 821, 744, 701, 611, 503 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.73–7.60 (m, 8H), 7.48–7.25 (m, 17H), 4.37 (d, *J*=7.2 Hz, 1H), 4.22–4.20 (m, 2H), 4.15–4.13 (m, 1H), 3.85–3.77 (m, 3H), 3.10 (s, 3H), 3.04 (dd, *J*=13.2, 4.9 Hz, 1H), 2.84 (dd, *J*=13.2, 5.2 Hz, 1H), 2.18–2.13 (m, 1H), 2.07–2.03 (m, 1H), 1.11 (s, 9H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 135.8, 135.5, 133.2, 132.8, 130.6, 129.8, 128.9, 127.7, 123.9, 96.5, 75.2, 66.7, 64.7, 64.6, 58.0, 55.8, 38.1, 26.9, 26.7, 19.2, 19.1. MS (ESI) 857 $[M+H]^+$. HRMS (ESI) *m*/*z* calcd for $C_{46}H_{58}O_5Si_2SBr$ 857.2726; found 857.2762. *More polar isomer*: TLC R_f=0.15 (20% EtOAc/hexanes). $[\alpha]_D^{34}$=+19.2 (*c* 1, $CHCl_3$). IR (KBr): 3067, 2931, 2892, 2857, 1108, 1041, 821, 744, 702, 611, 504 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.65–7.53 (m, 8H), 7.38–7.12 (m, 17H), 4.31 (d, *J*=6.9 Hz, 1H), 4.15–4.06 (m, 3H), 3.78–3.69 (m, 3H), 3.02 (s, 3H), 2.95 (dd, *J*=12.7, 5.0 Hz, 1H), 2.81 (dd, *J*=12.7, 4.1 Hz, 1H), 2.09–2.05 (m, 1H), 2.01–1.96 (m, 1H), 1.04 (s, 9H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 135.5, 135.4, 133.4, 132.9, 130.6, 129.1, 127.7, 123.6, 96.3, 73.9, 66.6, 65.9, 64.7, 57.1, 56.2, 39.1, 27.0, 26.7, 19.5, 19.1. MS (ESI) 857 $[M+H]^+$. HRMS (ESI) *m*/*z* calcd for $C_{46}H_{58}O_5Si_2SBr$ 857.2726; found 857.2732.

4.9. Compound 17

To a solution of sulfoxide **15** (171 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (1 mL) cooled at 0 °C was added Et_3N (56 μL, 0.4 mmol) followed by TFAA (57 μL, 0.4 mmol). After 30 min of stirring, when TLC examination revealed consumption of starting material, aq saturated $NaHCO_3$ (1 mL) was added followed by solid $NaBH_4$ (37 mg, 1.0 mmol) portionwise. After 30 min the reaction mixture was diluted with dichloromethane (5 mL) and filtered through a pad of Celite. The Celite pad was washed with dichloromethane. The layers were separated and the aq layer was extracted with dichloromethane (2×20 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, and evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to afford pure **17** (115 mg, 0.15 mmol) in 75% yield as a viscous oil. TLC R_f=0.15 (20% EtOAc/hexanes). $[\alpha]_D^{35}$=−9.2 (*c* 1, $CHCl_3$). IR (KBr) 3541, 3302, 3030, 2964, 2930, 1455, 1361, 1097, 1024, 740, 698, 636, 509 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76–7.64 (m, 8H), 7.48–7.32 (m, 12H), 4.61 (d, *J*=7.0 Hz, 1H), 4.52 (d, *J*=7.0 Hz, 1H), 4.22–4.18 (m, 1H), 4.08–3.96 (m, 2H), 3.85 (d, *J*=6.0 Hz, 2H), 3.58 (dd, *J*=11.9, 4.9 Hz, 1H), 3.52 (dd, *J*=11.9, 3.9 Hz, 1H), 3.20 (s, 3H), 2.02–1.92 (m, 1H), 1.88–1.82 (m, 1H), 1.09 (s, 9H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 132.8, 129.8, 127.7, 96.6, 74.9, 70.9, 65.3, 64.8, 57.8, 56.0, 35.5, 27.0, 26.7, 19.2, 19.1. MS (ESI) 771 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{40}H_{53}NaO_5Si_2Br$ 771.2512; found 771.2519.

4.10. Compound 19

To a solution of **17** (75 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (1 mL) cooled at −40 °C was added anhydrous 2,6-lutidine (17 μL, 0.14 mmol) followed by triflic anhydride (20 μL, 0.12 mmol) and the mixture stirred at the same temperature for 30 min. To the reaction mixture anhydrous hexane (5 mL) was added and the precipitated solid was filtered, washed with hexane, and the combined filtrated were concentrated under reduced pressure. The triflate was dissolved in anhydrous THF (1 mL). In another rb flask containing a solution of TMS-acetylene (28 μL, 0.2 mmol) in anhydrous THF (2 mL) cooled at 0 °C was added *n*-BuLi (0.08 mL, 0.2 mmol) and the mixture stirred for 30 min at the same temperature. The resulting TMS-acetylide was added to the triflate prepared above at −40 °C dropwise and stirred further for 1 h at same temperature. The reaction mixture was quenched by adding aq NH_4Cl solution at 0 °C. The reaction mixture was diluted with DCM and the layers were separated. The aq layer was extracted with DCM (2×5 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. Purification by column chromatography using hexanes/EtOAc (9:1, v/v) as the eluent provided pure product **19** (57 mg, 0.082 mmol) in 82% yield as a viscous oil. TLC R_f=0.20 (15% EtOAc/hexanes). $[\alpha]_D^{34}$=−2.2 (*c* 1, $CHCl_3$). IR (KBr) 3069, 2933, 2858, 1428, 1262, 1108, 1005, 822, 704, 613, 505 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.73–7.62 (m, 8H), 7.47–7.36 (m, 12H), 4.61–4.55 (m, 1H), 4.47–4.43 (m, 1H), 4.18–4.12 (m, 1H), 3.95 (dd, *J*=10.9, 4.9 Hz, 1H), 3.88 (dd, *J*=10.9, 5.9 Hz, 1H), 3.80–3.74 (m, 2H), 2.11–2.04 (m, 1H), 1.88–1.80 (m, 1H), 1.08 (s, 9H), 1.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.0, 129.7, 127.7, 77.9, 76.1, 73.6, 65.5, 58.3, 39.3, 26.8, 26.7, 19.3, 19.0. MS (ESI) 711 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{47}O_3BrNaSi_2$ 709.21393; found 709.21568.

4.11. Compound 20

To a solution of **14** (203 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (1 mL) cooled at 0 °C was added triethylamine (70 μL, 0.5 mmol), catalytic amount of DMAP followed by benzoic anhydride (68 mg, 0.3 mmol), and the mixture stirred for 16 h at ambient temperature. The reaction mixture was diluted with dichloromethane (5 mL), successively washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography using hexanes/EtOAc (9:1, v/v) as the eluent to afford product **20** (192 mg, 0.21 mmol) in 83% yield as a viscous oil. *Less polar isomer*: TLC R_f=0.13 (20% EtOAc/hexanes). $[\alpha]_D^{35}$=−20.8 (*c* 1, $CHCl_3$). IR (KBr) 2933, 2858, 1719, 1467, 1384, 1254, 1106, 1003, 833, 704, 613, 435 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76–7.53 (m, 11H), 7.49–7.13 (m, 19H), 5.45 (td, *J*=10.6, 3.0 Hz, 1H), 4.23–4.16 (m, 1H), 4.09–4.01 (m, 1H), 3.91–3.80 (m, 2H), 3.10 (dd, *J*=13.6, 5.3 Hz, 1H), 2.81 (dd, *J*=13.6, 4.5, 1H), 2.44–2.26 (m, 2H), 1.10 (s, 9H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 135.9, 135.8, 135.6, 133.1, 129.9, 129.8, 128.9, 128.2, 127.7, 123.9, 70.1, 66.6, 64.5, 63.7, 55.9, 37.6, 26.9, 26.7, 19.2, 19.1. MS (ESI) 939 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{51}H_{58}O_5BrSSi_2$ 917.27214; found 917.27496. *More polar isomer*: TLC R_f=0.12 (20% EtOAc/hexanes). $[\alpha]_D^{35}$=+15.7 (*c* 1, $CHCl_3$). IR (KBr) 3063, 2935, 2859, 1720, 1463, 1426, 1269, 1108, 703, 502 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76–7.23 (m, 30H), 5.46–5.39 (m, 1H), 4.55–4.42 (m, 2H), 3.76–3.63 (m, 2H), 3.03 (dd, *J*=12.8, 3.0 Hz, 1H), 2.81 (dd, *J*=12.8, 9.0 Hz, 1H), 2.41–2.04 (m, 2H), 1.11 (s, 9H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 136.0, 135.8, 135.4, 133.6, 132.6, 129.7, 129.1, 128.2, 127.7, 123.6, 69.6, 66.0, 65.5, 64.5, 55.3, 38.1, 26.9, 26.6, 19.5, 19.1. MS (ESI) 939 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{51}H_{58}O_5BrSSi_2$ 917.27214; found 917.27475.

4.12. Compound 21

To a solution of **15** (856 mg, 1 mmol) in anhydrous THF (3 mL) cooled at 0 °C was added acetic acid (136 μL, 2.4 mmol) and TBAF (2.4 mL, 1 M in THF, 2.4 mmol). The reaction mixture was stirred gradually allowing it to warm to rt over 3 h. The solvent was evaporated to provide the crude product, which was purified by column chromatography using hexanes/EtOAc (7:3, v/v) as the eluent to afford **21** (550 mg, 0.9 mmol) in 90% yield as a viscous oil. *Less polar isomer*: TLC R_f=0.12 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=−29.8 (*c* 1, $CHCl_3$). IR (KBr) 3390, 3067, 2932, 2891, 2857, 1428, 1106, 1033, 916, 821, 744, 702, 610, 503 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78–7.65 (m, 4H), 7.48–7.36 (m, 11H), 4.58 (d, *J*=7.5 Hz, 1H), 4.50–4.42 (m, 1H), 4.38 (d, *J*=7.5 Hz, 1H), 4.32 (dt, *J*=9.8, 3.0 Hz, 1H), 3.95 (dd, *J*=11.3, 2.2 Hz, 1H), 3.90–3.84 (m, 2H), 3.13 (dd, *J*=14.3, 1.5 Hz, 1H), 2.99 (s, 3H), 2.58 (dd, *J*=14.3, 4.5 Hz, 1H), 2.49–2.45 (m, 1H), 2.28–2.16 (m, 1H), 1.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 135.6, 133.3, 132.7, 130.8, 129.8, 129.2, 127.7, 127.6, 123.4, 95.3, 73.3, 67.4, 63.7, 63.4, 57.1, 55.5, 35.7, 26.8, 19.1. MS (ESI) 641 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{40}O_5SiSBr$ 619.1549; found 619.1551. *More polar isomer*: TLC R_f=0.11 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=+14.9 (*c* 1, $CHCl_3$). IR (KBr) 3392, 3068, 2931, 1452, 1428, 1387, 1147, 1107, 1033, 916, 744, 702, 610, 503 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78–7.64 (m, 4H), 7.52–7.28 (m, 11H), 4.54–4.28 (m, 3H), 4.07–4.02 (m, 1H), 3.84–3.54 (m, 3H), 3.26 (s, 3H), 3.01 (dd, *J*=12.8, 4.5 Hz, 1H), 2.83 (dd, *J*=12.8, 7.5 Hz, 1H), 2.04–1.91 (m, 2H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0, 135.9, 135.8, 133.7, 132.8, 129.8, 129.7, 129.1, 127.6, 123.6, 96.5, 74.9, 66.1, 66.0, 63.2, 58.4, 56.1, 39.8, 26.9, 19.3. MS (ESI) 641 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{40}O_5SiSBr$ 619.1549; found 619.1523.

4.13. Compound 22

To a solution of **22** (495 mg, 0.8 mmol) in the mixture of ethanol (1.2 mL) and acetonitrile (1.2 mL) cooled at 0 °C was added K_2CO_3 (130 mg, 0.96 mmol). After 6 h, water was added and the mixture extracted with ether (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated to provide the crude product, purification by column chromatography using hexanes/EtOAc (7:3, v/v) as the eluent afforded **22** (355 mg, 0.66 mmol) in 82% yield as a viscous oil. *Less polar isomer*: TLC R_f=0.11 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=−16.4 (*c* 1, $CHCl_3$). IR (KBr) 3065, 2932, 2893, 1470, 1394, 1148, 1105, 1029, 921, 821, 744, 702, 505 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72–7.61 (m, 4H), 7.44–7.36 (m, 11H), 4.74 (d, *J*=6.6 Hz, 1H), 4.47 (d, *J*=6.6 Hz, 1H), 4.42–4.36 (m, 1H), 3.42–3.38 (m, 1H), 3.10 (s, 3H), 3.06 (dd, *J*=13.2, 3.3 Hz, 1H), 2.88–2.82 (m, 1H), 2.80 (dd, *J*=13.2, 5.5 Hz, 1H), 2.64 (t, *J*=4.4 Hz, 1H), 2.46–2.45 (m, 1H), 2.31–2.26 (m, 1H), 2.10–2.04 (m, 1H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 135.8, 135.5, 133.4, 133.2, 130.7, 129.9, 129.1, 127.8, 127.7, 123.8, 95.5, 75.6, 67.0, 63.7, 55.6, 54.6, 43.5, 37.8, 26.9, 19.2. MS (ESI) 539 $[M+H]^+$. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{39}O_5SiS$ 539.2287; found 539.2308. *More polar isomer*: TLC R_f=0.10 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=+29.2 (*c* 1, $CHCl_3$). IR (KBr) 3066, 2932, 2857, 1638, 1428, 1396, 1105, 1029, 859, 744, 702, 505 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81–7.70 (m, 4H), 7.56–7.37 (m, 11H), 4.68 (d, *J*=6.6 Hz, 1H), 4.60–4.55 (m, 1H), 4.48 (d, *J*=6.6 Hz, 1H), 3.30–3.25 (m, 1H), 3.22 (s, 3H), 3.07 (dd, *J*=12.1, 3.3 Hz, 1H), 2.94 (dd, *J*=12.1, 8.8 Hz, 1H), 2.72–2.68 (m, 1H), 2.46 (t, *J*=4.4 Hz, 1H), 2.08–2.07 (m, 1H), 1.85–1.80 (m, 1H), 1.73–1.68 (m, 1H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 135.8, 135.1, 133.4, 132.5, 130.7, 129.9, 129.5, 129.0, 127.7, 127.4, 123.8, 95.5, 75.6, 66.9, 63.7, 55.6, 54.6, 43.5, 37.8, 26.9, 19.2. MS (ESI) 539 $[M+H]^+$. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{39}O_5SiS$ 539.2287; found 539.2286.

4.14. Compound 23

To a solution of **22** (215 mg, 0.4 mmol) and *p*-methoxybenzyl alcohol (116 mg, 0.48 mmol) in anhydrous CH_2Cl_2 cooled at 0 °C was added scandium triflate (10 mg, 0.02 mmol, 5 mol %) and the mixture gradually allowed to equilibrate to rt over a 3 h period. The volatiles were evaporated and the crude product was purified by column chromatography using hexanes/EtOAc (7:3, v/v) as the eluent to afford pure **23** (410 mg, 0.31 mmol) in 78% yield as a viscous oil. *Less polar isomer*: TLC R_f=0.11 (40% EtOAc/hexanes). $[\alpha]_D^{35}$=−46.5 (*c* 1, $CHCl_3$). IR (KBr) 3424, 3066, 2932, 1521, 1429, 1389, 1247, 1106, 1032, 913, 745, 702, 504 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–7.60 (m, 4H), 7.47–7.31 (m, 11H), 7.21 (d, *J*=9.1 Hz, 2H), 6.82 (d, *J*=9.1 Hz, 2H), 4.44 (s, 2H), 4.40 (d, *J*=6.8 Hz, 1H), 4.28 (d, *J*=6.8 Hz, 1H), 4.25–4.06 (m, 1H), 3.78 (s, 3H), 3.63–3.51 (m, 2H), 3.43–3.30 (m, 2H), 3.08 (s, 3H), 3.03 (dd, *J*=13.6, 3.7 Hz, 1H), 2.74 (d, *J*=13.6, 5.2 Hz, 1H), 2.31 (ddd, *J*=13.6, 9.0, 3.7 Hz, 1H), 1.90 (ddd, *J*=13.6, 9.0, 5.2 Hz, 1H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 144.6, 135.8, 133.7, 132.8, 130.7, 129.8, 129.3, 127.6, 123.7, 113.6, 96.7, 76.5, 72.9, 71.5, 70.3, 66.1, 64.2, 55.7, 55.1, 38.3, 26.9, 19.4. MS (ESI) 677 $[M+H]^+$. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{49}O_7SiS$ 677.2968; found 677.2968. *More polar isomer*: TLC R_f=0.10 (40% EtOAc/hexanes). $[\alpha]_D^{35}$=+37.1 (*c* 1, $CHCl_3$). IR (KBr) 3429, 3067, 2858, 1613, 1467, 1389, 1247, 1107, 1032, 821, 702, 611, 504 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78–7.66 (m, 4H), 7.53–7.32 (m, 11H), 7.12 (d, *J*=8.3 Hz, 2H), 6.79 (d, *J*=8.3 Hz, 2H), 4.62–4.24 (m, 5H), 3.78 (s, 3H), 3.50–3.37 (m, 2H), 3.26–3.16 (m, 5H), 3.00 (d, *J*=12.8, 3.0 Hz, 1H), 2.76 (dd, *J*=12.8, 9.0 Hz, 1H), 1.78–1.71 (m, 2H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 144.4, 136.0, 135.9, 133.5, 133.3, 130.9, 129.5, 129.5, 127.9, 127.8, 124.1, 113.8, 96.8, 77.0, 73.1, 72.0, 70.7, 67.1, 64.2, 55.7, 55.3, 37.6, 27.1, 19.3. MS (ESI) 677 $[M+H]^+$. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{49}O_7SiS$ 677.2968; found 677.2950.

4.15. Compound 24

To a solution of **23** (170 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (2 mL) cooled at 0 °C was added $^iPr_2NEt$ (90 μL, 0.5 mmol) TBAI (9 mg, 0.025 mmol) followed by Mom-Cl (25 μL, 0.38 mmol). After 7 h of stirring gradually allowing the mixture to warm to rt, the reaction was quenched by adding saturated aq $NaHCO_3$. The layers were separated and the aq layer was extracted with dichloromethane (3×10 mL). The combined organic layers were successively washed with water, brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to afford pure **24** (150 mg, 0.21 mmol) in 84% yield as a viscous oil. *Less polar isomer*: TLC R_f=0.25 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=−37.4 (*c* 1, $CHCl_3$). IR (KBr): 2927, 2856, 2100, 1727, 1617, 1465, 1368, 1254, 1217, 1102, 1032, 918, 803, 764, 506 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–7.60 (m, 4H), 7.47–7.31 (m, 11H), 7.23 (d, *J*=9.1 Hz, 2H), 6.85 (d, *J*=9.1 Hz, 2H), 4.69–4.59 (m, 2H), 4.44–4.40 (m, 2H), 4.29–4.22 (m, 2H), 3.83–3.67 (m, 4H), 3.57–3.30 (m, 7H), 3.10 (dd, *J*=12.8, 4.5 Hz, 1H), 3.01 (s, 3H), 2.87–2.80 (m, 1H), 2.26–1.91 (m, 2H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 144.8, 136.0, 135.9, 133.4, 130.7, 129.9, 129.6, 129.2, 127.7, 127.6, 124.0, 113.6, 97.1, 96.9, 77.7, 75.0, 72.8, 69.4, 67.1, 64.5, 55.7, 55.6, 55.2, 37.4, 26.9, 19.2. MS (ESI) 721 $[M+H]^+$. HRMS (ESI) *m*/*z* calcd for $C_{40}H_{53}O_8SiS$ 721.3230; found 721.3197. *More polar isomer*: TLC R_f=0.24 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=+34.2 (*c* 1, $CHCl_3$). IR (KBr): 2930, 2857, 1727, 1521, 1466, 1369, 1102, 1032, 702, 611, 407 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.81–7.61 (m, 4H), 7.53–7.34 (m, 11H), 7.12 (d, *J*=9.1 Hz, 2H), 6.79 (d, *J*=9.1 Hz, 2H), 4.65–4.27 (m, 6H), 3.80–3.74 (m, 4H), 3.58–3.45 (m, 2H), 3.37–3.25 (m, 3H), 3.18 (s, 3H), 3.14 (s, 3H), 2.83–2.71 (m, 1H), 1.77–1.64 (m, 2H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 145.0, 136.0, 135.8, 134.0, 132.9, 130.5, 129.7, 129.1, 127.6, 127.4, 123.6, 113.6, 96.6, 77.6, 74.1, 72.8, 69.1, 66.2, 66.0, 55.9, 55.5,

55.1, 38.2, 26.9, 19.4. MS (ESI) 721 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{40}H_{53}O_8SiS$ 721.3230; found 721.3216.

4.16. Compound 25

To an ice cooled solution of sulfoxide **24** (144 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (1 mL) was added Et_3N (56 μL, 0.4 mmol) followed by TFAA (57 μL, 0.4 mmol). After complete consumption of starting sulfoxide (30 min), the reaction was quenched using aq saturated $NaHCO_3$ (1 mL). Then solid $NaBH_4$ (37 mg, 1.0 mmol) was added portionwise. After 30 min the reaction mixture was diluted with dichloromethane (5 mL) and filtered through a pad of Celite. The filter pad was washed with dichloromethane. The layers were separated and the aq layer was extracted with dichloromethane (2×20 mL). The combined organic layers were washed successively with water, brine, dried over anhydrous Na_2SO_4, and evaporated to provide the crude product, which was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to afford pure **25** (80 mg, 0.13 mmol) in 66% yield as a viscous oil. TLC R_f=0.26 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=−5.2 (*c* 0.5, $CHCl_3$). IR (KBr) 3459, 3063, 2935, 2859, 1463, 1426, 1269, 1108, 818, 703, 611, 502 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68–7.65 (m, 4H), 7.41–7.34 (m, 6H), 7.24 (d, *J*=9.0 Hz, 2H), 6.82 (d, *J*=9.0 Hz, 2H), 4.55–4.49 (m, 4H), 4.43–4.41 (m, 2H), 4.27–4.24 (m, 1H), 4.11–4.06 (m, 1H), 4.02–3.98 (m, 1H), 3.83 (dd, *J*=10.0, 5.1 Hz, 1H), 3.78 (s, 3H), 3.69–3.59 (m, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.20 (ddd, *J*=13.8, 7.8, 1.9 Hz, 1H), 1.99 (ddd, *J*=13.8, 8.4, 2.8 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 135.8, 135.6, 133.8, 133.5, 129.7, 129.2, 127.7, 113.6, 96.8, 77.6, 74.7, 72.9, 71.1, 69.5, 65.4, 55.7, 55.6, 55.2, 34.4, 26.9, 19.2. MS (ESI) 635 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{34}H_{48}O_8NaSi$ 635.3016; found 635.3026.

4.17. Compound 26

To a solution of **25** (85 mg, 0.14 mmol) in anhydrous THF (0.75 mL) cooled at 0 °C was added TBAF (0.2 mL, 1 M in THF, 0.2 mmol) and stirred at ambient temperature for 3 h. The solvent was evaporated to afford the crude product, which was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to afford pure **26** (45 mg, 0.12 mmol) in 86% yield as a viscous oil. TLC R_f=0.08 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=−8.9 (*c* 0.5, $CHCl_3$). IR (KBr) 3645, 3443, 3069, 2960, 1590, 1369, 1107, 822, 703, 615, 505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J*=8.3 Hz, 2H), 6.87 (d, *J*=8.3 Hz, 2H), 4.83–4.63 (m, 4H), 4.46 (s, 2H), 4.01–3.82 (m, 2H), 3.80 (s, 3H), 3.67–3.45 (m, 3H), 3.42–3.30 (m, 8H), 1.96–1.85 (m, 1H), 1.79–1.69 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 129.9, 129.3, 113.7, 96.9, 77.6, 76.9, 73.0, 70.3, 69.4, 66.6, 55.9, 55.7, 55.2, 33.7. MS (ESI) 397 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{18}H_{30}O_8Na$ 397.18329; found 397.18417.

4.18. Compound 27

To a suspension of NaH (12 mg, 60% in Nujol, 0.3 mmol) in anhydrous THF (1 mL) cooled at 0 °C was added a solution of **26** (45 mg, 0.12 mmol) in THF (0.5 mL) dropwise. The reaction was stirred for 1 h and freshly prepared tosyl imidazole (29 mg, 0.13 mmol) was added at the same temperature. The reaction was stirred for 1 h and quenched with saturated aq NH_4Cl at 0 °C. The reaction mixture was diluted with ether, the layers were separated, and the aq layer was extracted with ether (2×5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded the crude product, which was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to afford pure **27** (45 mg, 0.09 mmol) in 76% yield as a viscous oil. TLC R_f=0.20 (30% EtOAc/hexanes). $[\alpha]_D^{33}$=−26.4 (*c* 1, $CHCl_3$). IR (KBr): 2934, 1513, 1249, 1100, 1032, 918, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.9 Hz, 2H), 6.80 (d, *J*=8.9 Hz, 2H), 4.76–4.63 (m, 4H), 4.46–4.42 (m, 2H), 3.90–3.79 (m, 4H), 3.62 (dd, *J*=9.9, 3.9 Hz, 1H), 3.53 (dd, *J*=9.9, 3.9 Hz, 1H), 3.31–3.28 (m, 7H), 3.03–3.01 (m, 1H), 2.72–2.69 (m, 1H), 2.43–2.40 (m, 1H), 1.88–1.84 (m, 1H), 1.64–1.60 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 130.0, 129.2, 113.6, 96.8, 96.7, 77.7, 75.7, 72.9, 69.3, 55.7, 55.6, 55.1, 49.5, 46.6, 33.9. MS (ESI) 379 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{18}H_{28}O_7Na$ 379.1732; found 379.1748.

4.19. Compound 28

To a solution of TMS-acetylene (20 μL, 0.14 mmol) in anhydrous THF (1.4 mL) cooled at 0 °C was added *n*-BuLi (59 μL, 2.4 M in hexane, 0.14 mmol) and stirred for 1 h at the same temperature. The reaction mixture was cooled to −78 °C and a solution of epoxide **27** (45 mg, 0.09 mmol) in anhydrous THF (1 mL) was added slowly followed by $BF_3 \cdot OEt_2$ (15 μL, 0.14 mmol). Stirring was continued for 3 h at the same temperature before quenching with saturated aq NH_4Cl. The reaction mixture was diluted with ether and the layers were separated. The aq layer was extracted with ether (2×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure to afford the crude product. The crude mixture was purified by column chromatography using hexanes/EtOAc (85:15, v/v) as the eluent to afford pure **28** (26.7 mg, 0.07 mmol) in 79% yield as a viscous oil. TLC R_f=0.28 (30% EtOAc/hexanes). $[\alpha]_D^{35}$=−17.3 (*c* 1, $CHCl_3$). IR (KBr): 3421, 2895, 2860, 2172, 1613, 1465, 1585, 1216, 1033, 916, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J*=8.3 Hz, 2H), 6.83 (d, *J*=8.3 Hz, 2H), 4.77 (d, *J*=6.6 Hz, 1H), 4.71–4.64 (m, 3H), 4.44 (s, 2H), 3.94–3.83 (m, 2H), 3.80 (s, 3H), 3.61 (dd, *J*=10.0, 3.4 Hz, 1H), 3.53 (dd, *J*=10.0, 6.2 Hz, 1H), 3.41–3.35 (m, 7H), 2.39–2.37 (m, 2H), 2.03–1.92 (m, 2H), 1.66–1.56 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 129.7, 129.0, 113.4, 96.9, 96.7, 80.5, 77.1, 76.7, 72.8, 70.2, 69.1, 68.3, 55.7, 55.5, 54.9, 36.2, 27.0. MS (ESI) 405 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{20}H_{30}O_7Na$ 405.1889; found 405.1869.

4.20. Compound 29

To solution of **28** (26.7 mg, 0.07 mmol) in anhydrous CH_2Cl_2 (1 mL) cooled at 0 °C was added imidazole (11 mg, 0.17 mmol) followed by TBS-Cl (13 mg, 0.086 mmol). After 3 h of stirring at rt the volatiles were evaporated and the crude product was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to afford pure **29** (45 mg, 0.064 mmol) in 91% yield as a viscous oil. TLC R_f=0.20 (30% EtOAc/hexanes). $[\alpha]_D^{33}$=−15.8 (*c* 1.2, $CHCl_3$). IR (KBr): 2933, 2858, 2175, 1513, 1465, 1429, 1248, 1105, 1033, 844, 762, 702, 610, 507 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J*=8.3 Hz, 2H), 6.86 (d, *J*=8.3 Hz, 2H), 4.81 (d, *J*=6.8 Hz, 1H), 4.69 (d, *J*=6.8 Hz, 1H), 4.66–4.65 (m, 2H), 4.46 (s, 2H), 4.00–3.92 (m, 1H), 3.89–3.78 (m, 5H), 3.63–3.60 (m, 2H), 3.38 (s, 3H), 3.36 (s, 3H), 2.42–2.37 (m, 2H), 2.07–1.98 (m, 1H), 1.97 (t, *J*=2.3 Hz, 1H), 1.80–1.70 (m, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 130.3, 129.3, 113.7, 96.9, 96.6, 81.4, 77.3, 74.6, 73.0, 70.1, 69.9, 67.9, 55.9, 55.8, 55.2, 37.6, 27.3, 25.8, 18.0, −4.4, −4.6. MS (ESI) 519 $[M+Na]^+$. HRMS (ESI) *m/z* calcd for $C_{26}H_{44}O_7NaSi$ 519.27485; found 519.27477.

4.21. Compound 31

To a solution of Cp_2ZrCl_2 (8.02 g, 27.5 mmol) in anhydrous THF (75 mL) cooled at 0 °C was added $^iBu_2AlH$ (18.2 mL, 1.5 M in toluene, 27.5 mmol) dropwise over 10 min. The resultant suspension was stirred for 30 min at same temperature, followed by addition of a solution of propargyl ether **33** (4.4 g, 25.0 mmol) in anhydrous

THF (15 mL). The mixture was warmed to rt, stirred for 1 h, and then cooled to −78 °C, followed by the addition of a solution of I_2 (8.25 g, 32.5 mmol) in THF (37 mL). After 30 min the reaction mixture was quenched with aq 1 N HCl. The layers were separated and the aq layer extracted with ether (3×100 mL). The combined organic layers were washed successively with aq saturated sodium thiosulfate, $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography using hexanes/EtOAc (9:1, v/v) as the eluent to afford (*E*)-iodo alkene **31** (6.3 g, 21 mmol) in 84% yield as a colorless oil. TLC R_f=0.18 (10% EtOAc/hexanes). IR (KBr): 2956, 2929, 2857, 1465, 1253, 1105, 1059, 835, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, *J*=7.9 Hz, 2H), 6.81 (d, *J*=7.9 Hz, 2H), 6.59 (dt, *J*=14.8, 5.9 Hz, 1H), 6.34 (d, *J*=14.8 Hz, 1H), 4.40 (s, 2H), 3.87 (d, *J*=5.9 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 142.3, 129.6, 129.3, 113.7, 78.7, 71.8, 71.3, 55.1. Anal. Calcd for $C_{11}H_{13}IO_2$: C, 43.44; H, 4.31. Found: C, 43.74; H, 3.85.

4.22. Compound 32

To a solution of vinyl iodide **31** (6.02 g, 20 mmol) (azeotropically dried once with toluene (10 mL)) dissolved in anhydrous toluene (80 mL) and cooled at −78 °C was added *n*-BuLi (8 mL, 2.5 M in hexane, 20 mmol) dropwise over 5 min. The colorless solution was stirred for 30 min and a solution of **30** (2.05 mL, 26 mmol) in anhydrous toluene (5 mL) was added followed by $BF_3\cdot OEt_2$ (2.7 mL, 22 mmol) giving a yellow solution. Stirring was continued at −78 °C for 1 h; then the reaction mixture was quenched by adding saturated aq $NaHCO_3$. After the mixture had attained rt, it was diluted with ether (100 mL). The phases were separated and the aq phase was extracted with ether (3×50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the residue was purified by column chromatography using hexanes/EtOAc (85:15, v/v) to afford **32** (3.3 g, 12.2 mmol) in 61% yield as a colorless oil. TLC R_f=0.20 (20% EtOAc/hexanes). $[\alpha]_D^{33}$=−6.8 (*c* 1, $CHCl_3$). IR (KBr): 3421, 2933, 2861, 1611, 1512, 1247, 1033, 819, 572 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J*=9.7 Hz, 2H), 6.83 (d, *J*=9.7 Hz, 2H), 5.71–5.68 (m, 2H), 4.42 (s, 2H), 3.92–3.82 (m, 2H), 3.84–3.80 (m, 4H), 3.58 (dd, *J*=10.8, 3.9 Hz, 1H), 3.48 (dd, *J*=10.8, 6.9 Hz, 1H), 2.36–2.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 133.0, 129.7, 128.8, 128.3, 113.5, 71.5, 70.3, 69.9, 54.9, 48.7, 36.9. MS (ESI) 293 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}O_3ClNa$ 293.09149; found 293.09125.

4.23. Compound 34

To a cooled solution of **32** (2.7 g, 10 mmol) in anhydrous CH_2Cl_2 (30 mL) was added Et_3N (2.1 mL, 15 mmol) followed by pivaloyl chloride (1.47 mL, 12 mmol) and stirred for 4 h. Water was added to destroy excess acid chloride. The layers were separated, the aq layer was extracted with dichloromethane (2×40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated to provide crude product, which was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to afford pure **34** (3.25 g, 9.2 mmol) in 92% yield as an oil. TLC R_f=0.27 (20% EtOAc/hexanes). $[\alpha]_D^{33}$=−6.2 (*c* 1, $CHCl_3$). IR (KBr): 2967, 2838, 1728, 1613, 1514, 1281, 1249, 1150, 1034, 822 cm^{-1}. ^1H NMR δ 7.19 (d, *J*=8.3 Hz, 2H), 6.81 (d, *J*=8.3 Hz, 2H), 5.74–5.45 (m, 2H), 5.02–4.93 (m, 1H), 4.43 (d, *J*=7.5 Hz, 1H), 4.37 (d, *J*=7.5 Hz, 1H), 4.01 (d, *J*=6.0 Hz, 1H), 3.90 (d, *J*=6.0 Hz, 1H), 3.79 (s, 3H), 3.64–3.48 (m, 2H), 2.47–2.38 (m, 2H), 1.20 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.5, 159.3, 131.9, 129.7, 129.4, 129.2, 113.8, 78.8, 71.1, 70.4, 57.0, 55.2, 44.4, 38.9, 27.0. MS (ESI) 377 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{27}O_4ClNa$ 377.14901; found 377.15029.

4.24. Compound 35

To the mixture of K_2CO_3 (3.26 g, 24 mmol), potassium ferricyanide (7.87 g, 24 mmol) in a mixture of distilled water (20 mL) and *tert*-butanol (20 mL) was added potassium osmate (15 mg, 0.04 mmol) and DHQD(PHAL) (32 mg, 0.04 mmol) and stirred for 30 min resulting in an orange suspension. The reaction mixture was cooled at 0 °C and a solution of **33** (2.83 g, 8 mmol) in toluene (4 mL) was added followed by the addition of methane sulfonamide (800 mg, 8 mmol). Stirring was continued for 20 h at the same temperature. The reaction was quenched by addition of solid sodium sulfite and stirred further for 1 h at rt. The layers were separated and the aq layer was diluted with water to dissolve the salts and reextracted with dichloromethane (5×60 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to provide a crude product that was purified by column chromatography using hexanes/EtOAc (6:4, v/v) as the eluent to afford pure **35** (2.3 g, 5.9 mmol) in 74% yield as a viscous oil. TLC R_f=0.12 (40% EtOAc/hexanes). $[\alpha]_D^{33}$=−15.2 (*c* 1, $CHCl_3$). IR (KBr): 3426, 2959, 2871, 1725, 1512, 1248, 1170, 1034, 820 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J*=7.9 Hz, 2H), 6.80 (d, *J*=7.9 Hz, 2H), 5.17–5.12 (m, 1H), 4.45 (d, *J*=10.8, 1H), 4.41 (d, *J*=10.8 Hz, 1H), 3.79 (s, 3H), 3.73–3.64 (m, 3H), 3.58–3.48 (m, 3H), 1.89–1.86 (m, 2H), 1.20 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 159.2, 129.4, 129.3, 113.6, 72.9, 71.9, 71.5, 70.2, 68.6, 55.0, 45.6, 38.6, 34.6, 26.8. MS (ESI) 411 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{29}O_6ClNa$ 411.1550; found 411.1568.

4.25. Compound 36

To a solution of diol **35** (1.94 g, 5 mmol) in anhydrous CH_2Cl_2 (20 mL) cooled at 0 °C was added $^iPr_2NEt$ (1.95 mL, 14 mmol), TBAI (184.5 mg, 0.5 mmol) followed by Mom-Cl (0.9 mL, 12 mmol). After 12 h the reaction was quenched by adding aq $NaHCO_3$. The layers were separated and the aq layer was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to furnish crude product, which was purified by column chromatography using hexanes/EtOAc (8:2, v/v) as the eluent to provide pure **36** (1.97 g, 4.15 mmol) in 83% yield as a viscous oil. TLC R_f=0.20 (30% EtOAc/hexanes). $[\alpha]_D^{33}$=−8.5 (*c* 1, $CHCl_3$). IR (KBr): 2958, 1727, 1513, 1250, 1154, 1103, 1033, 918, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.5 Hz, 2H), 6.80 (d, *J*=8.5 Hz, 2H), 5.20–5.12 (m, 1H), 4.73 (d, *J*=6.9 Hz, 1H), 4.64–4.61 (m, 2H), 4.57 (d, *J*=6.9 Hz, 1H), 4.43 (s, 2H), 3.78–3.68 (m, 5H), 3.63–3.49 (m, 3H), 3.36–3.31 (m, 7H), 2.12–2.04 (m, 1H), 1.85–1.76 (m, 1H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.4, 158.9, 129.8, 129.1, 113.5, 96.7, 96.6, 77.0, 74.0, 72.8, 69.5, 68.8, 55.7, 55.5, 54.9, 45.4, 38.6, 32.3, 26.8. MS (ESI) 499 $[M+Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{37}O_8ClNa$ 499.20692; found 499.20674.

4.26. Compound 27

To a solution of compound **36** (1.9 g, 4 mmol) in ethanol (12 mL) was added crushed KOH (269 mg, 4.8 mmol) at 0 °C. After 2 h, water was added and the mixture extracted with ether (4×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to provide the crude product that was purified by column chromatography using hexanes/EtOAc (7:3, v/v) as the eluent to afford epoxide **27** (1.58 g, 3.6 mmol) in 90% yield as a viscous oil. All the physical data were identical to the sample obtained from **26**.

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Supplementary data

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