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Stereoselective Formal Synthesis of (+)- and (−)-Cyclophellitol and (−)-Conduritol-B and Synthesis of (−)-Conduramine-B Derivative Using a Sulfinyl Moiety for C−O Bond Formation and α-Chloro Sulfide for C−C Bond Formation

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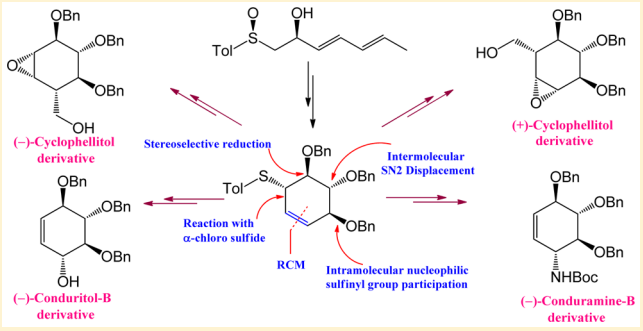
Supporting Information

ABSTRACT: The formal total synthesis of both the enantiomers of cyclophellitol and conduritol-B and synthesis of conduramine-B derivative have been achieved from a common intermediate, obtained by regio- and stereoselective vicinal functionalization of a diene utilizing an intramolecular sulfinyl group as a nucleophile, followed by stereoselective preparation of an allylic sulfide by reaction of vinylzinc bromide with an electrophilic α-chloro sulfide, and last by ring-closing metathesis reaction as the key steps. The sulfoxide, sulfilimine, and sulfur ylid prepared from this common intermediate have been transformed into derivatives of conduritol-B, conduramine-B, and (−)-cyclophellitol, respectively. The silyl sulfide was converted via sila-Pummerer rearrangement, hydrolysis, and reduction in an one-pot operation to a hydroxymethyl group. [2,3]-Wittig−Still rearrangement was employed for the synthesis of (+)-cyclophellitol. The potential utility of sulfur intermediates as nucleophilic and electrophilic partners in total synthesis is elegantly demonstrated.



INTRODUCTION

(+)-Cyclophellitol (**1**, Figure 1) was isolated[1] in 1990 from the mushroom *Phellinus sp.* and shown to possess potent β-glucosidase inhibitory activity and activity against HIV.[2] Glycosidase inhibitors, in addition to providing insight into glycoprotein processing, also find applications in immunology, diabetes, virology, and cancer. Cyclophellitol has been the target of several total syntheses due to its potent biological activity. However, most syntheses start with chiral pool starting materials, notably carbohydrates,[3] and are frequently lengthy as a consequence of manipulating functionality using protecting groups. Also these strategies provide access to one enantiomer of the natural product only, in contrast to asymmetric synthesis strategies[4] whereby both enantiomers can be synthesized and are more often efficient. Conduritols (5-cyclohexene-1,2,3,4-tetrols) are precursors for the synthesis of cyclitols,[5] pseudosugars and conduritol derivatives have interesting biological activities. Herein, we report the asymmetric synthesis of both the enantiomers of cyclophellitol taking advantage of the sulfinyl moiety as an intramolecular nucleophile for C−O bond formation and an α-chloro sulfide as an intermediate for C−C bond formation.

RESULTS/DISCUSSION

Our retrosynthesis of the targets **1**-**4** is shown in Scheme 1. As depicted, cyclophellitol, conduritol B, and conduramine B were envisaged to be obtained from a common intermediate **5** via [2,3] sigmatropic rearrangement of a sulfur ylid/sulfoxide/sulfilimine. Sulfide **5** would come from the metathesis of the diene **6** which in turn can be obtained from α-chloro sulfide derived from sulfide **7**. Compound **7** would result from the diene sulfoxide **8**, a compound prepared in the group using ethyl sorbate **10** and (*S*)-methyl *p*-tolyl sulfoxide **9** as starting materials.

The diene sulfoxide **8**, prepared as reported earlier[6] from ethyl sorbate in two steps and in 77% overall yield, was reacted with freshly recrystallized *N*-bromosuccinimide in dichloromethane in the presence of water to furnish bromodiol **11**, regio- and stereoselectively. The hydroxyl groups in **11** were protected as their TBS-ethers **12** under standard conditions and subsequent reduction of the sulfinyl moiety employing trifluoroacetic anhydride and sodium iodide[7] afforded sulfide **7** (P = TBS).[8] Treatment of **7** with *N*-chlorosuccinimide furnished the α-chloro sulfide **13**, which without isolation was reacted with vinylzinc bromide[9] to yield diene sulfide **6** (P = TBS) as the sole product.[10,11] Ring-closing metathesis of **6** using Grubbs'first-generation catalyst afforded allylic sulfide **14**. The synthetic sequence called for the nucleophilic displacement of bromide in **14** by a suitable oxygen nucleophile. Toward this end, compound **14** was subjected to oxidation with *m*-CPBA to furnish a diastereomeric mixture of sulfoxides, which without

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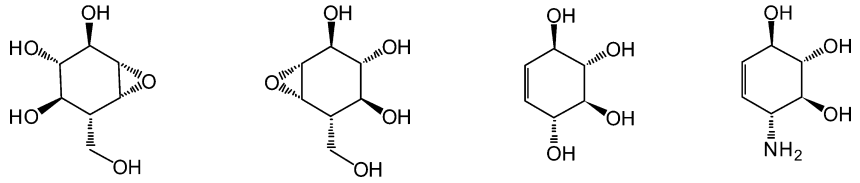
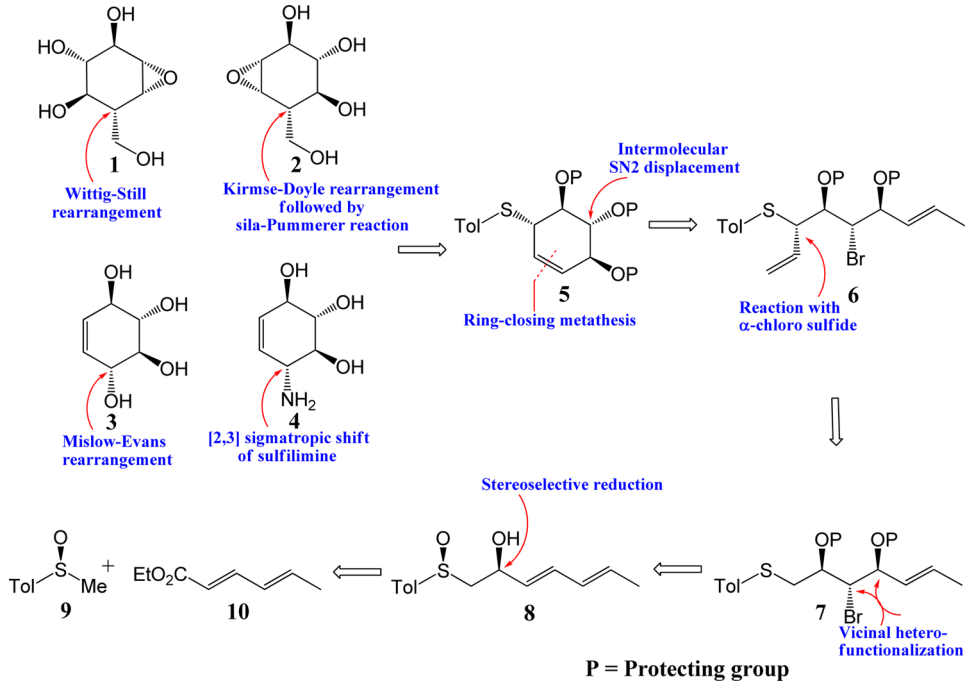
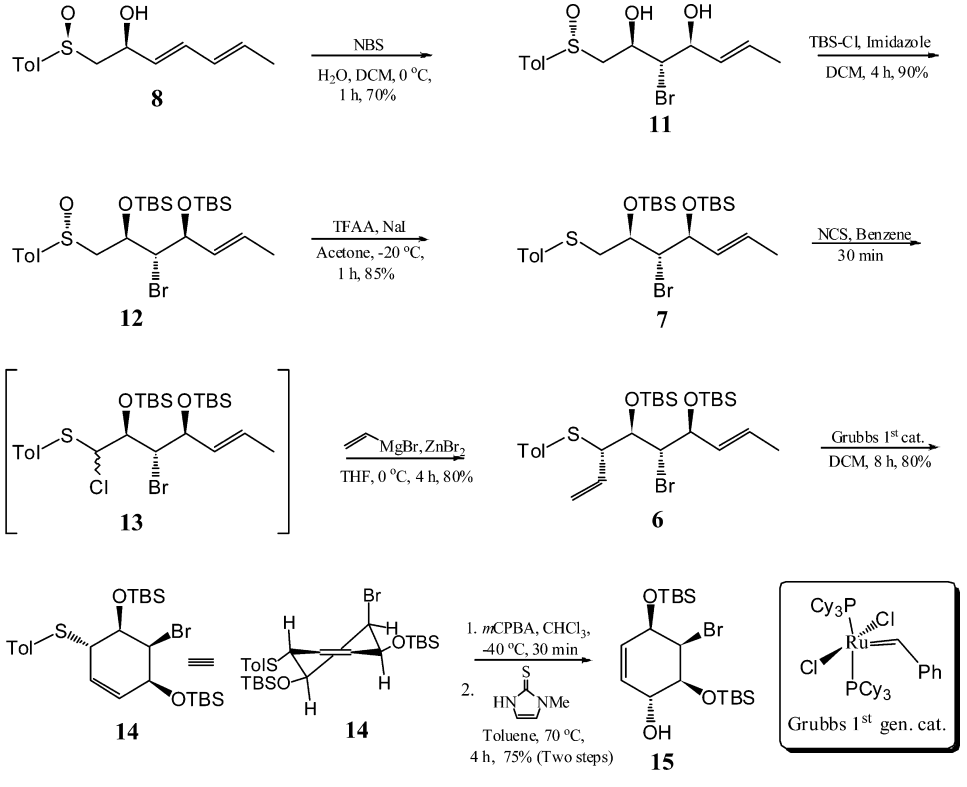


Figure 1. Cyclophellitol, conduritol-B, and conduramine-B.

Scheme 1. Retrosynthetic Disconnection of (−)-Cyclophellitol, (+)-Cyclophellitol, (−)-Conduritol B, and (−)-Conduramine B



Scheme 2. Synthesis of Bromotriol Derivative 15 From Diene Sulfoxide 8



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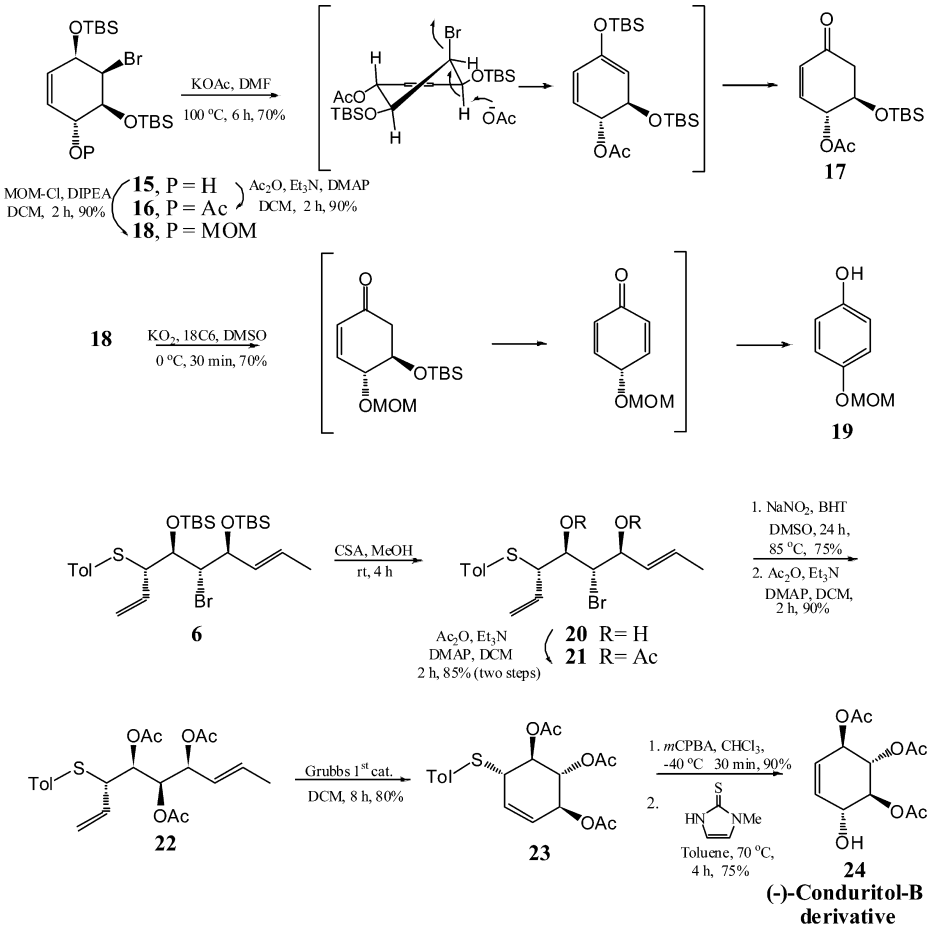
Scheme 3. Attempted Displacement of Bromide and Synthesis of (−)-Conduritol-B Derivative



isolation on warming in toluene in the presence of a thiophile underwent Mislow−Evans rearrangement[12] to furnish the bromotriol derivative **15**, Scheme 2.

S_N2 displacement of bromide in compound **15** would provide (−)-conduritol B derivative. Toward this end, the hydroxyl group in **15** was protected as its acetate **16** and was further subjected to reaction with potassium acetate as the oxygen nucleophile in DMF at 100 °C. Unfortunately, instead of the desired tetrol derivative, the unsaturated ketone **17**[13] was only obtained. E_2 elimination of HBr from **16** under the mildly basic conditions followed by hydrolysis of the silyl enol ether probably during column chromatography would account for the formation of **17**. In another trial, the MOM-ether **18**, prepared from alcohol **15**, on reaction with potassium superoxide[14] in DMSO furnished the hydroquinone derivative **19**.[15] The MOM derivative related to **17** probably suffers elimination and tautomerization to yield compound **19**.[16] Having been unsuccessful in preparing conduritol-B derivative by nucleophilic displacement on a cyclic compound, the same was attempted on the acyclic sulfide **6**. Reaction of **6** with an excess of potassium acetate/sodium nitrite[17] in DMF or DMSO at 80−120 °C for extended periods of time led to only recovered starting materials.

Assuming steric hindrance of the silyl groups to be the cause for the failure, the silyl groups were deprotected under acidic conditions to furnish the bromodiol **20**. Acetylation furnished the diacetate **21**, which on reaction with an excess of sodium nitrite in the presence of BHT[18] furnished a mixture of diacetates as a consequence of migration. The crude reaction mixture was therefore subjected to acetylation to yield the triacetate **22**. Ring-closing metathesis furnished the allylic sulfide **23**. Oxidation of sulfide to an epimeric mixture of sulfoxides followed by warming in toluene yielded (−)-conduritol-B derivative **24**, Scheme 3.

The synthesis of (−)-cyclophellitol was envisioned by a Kirmse−Doyle rearrangement of the ylid obtained by the reaction of **23** with trimethylsilyl diazomethane. Indeed, the reaction proceeded cleanly in the presence of $Rh_2(OAc)_4$[19] and excess TMS-diazomethane to yield an epimeric mixture of sulfides **25**. Oxidation of sulfide with *m*-CPBA and warming the reaction mixture resulted in the sila-Pummerer rearrangement,[20] hydrolysis followed by reduction of the ensuing aldehyde with sodium borohydride furnished a very polar compound, probably resulting from the hydrolysis of the acetate groups, which, however, could not be isolated. The strategy thus called for a protecting group that would be stable to the conditions of Pummerer followed by reduction reactions. Therefore, the acetate groups in **23** were hydrolyzed, and the resulting triol **27** protected as its benzyl ethers **28**. The structures assigned to compounds **28** and therefore compounds **22** and **23** are supported by the *J* values observed for C2*H* and C3*H* resonating at δ 3.76 (dd, J = 9.9 Hz, 7.9 Hz) and δ 3.65 (dd, J = 9.9 Hz, 8.6 Hz) in **28**. The *J* value can be rationalized only if all the methine protons are axially oriented. S_N2 displacement of the bromide in compound **21** is thus proven beyond doubt. Reaction of **28** with TMS-diazomethane and Rh(II) catalyst yielded an epimeric mixture of sulfides **29**. Oxidation of the sulfide to an epimeric mixture of sulfoxides

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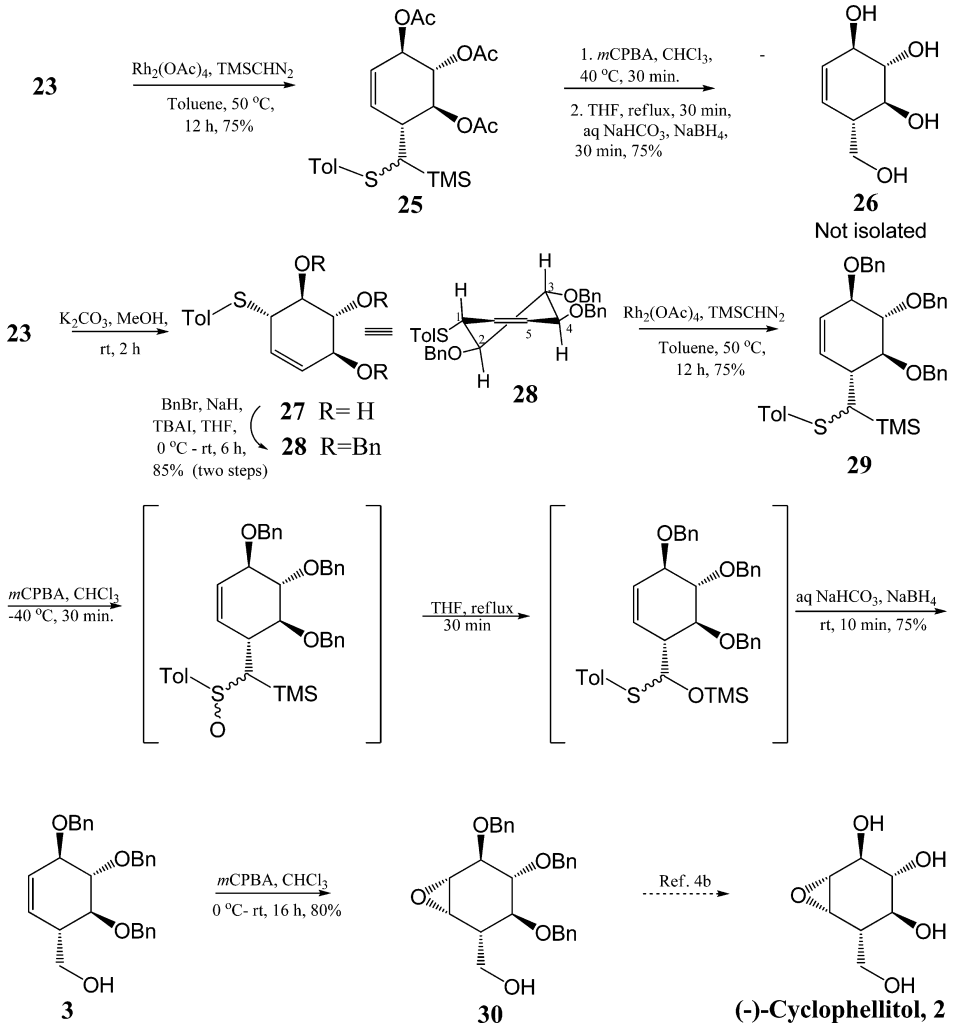
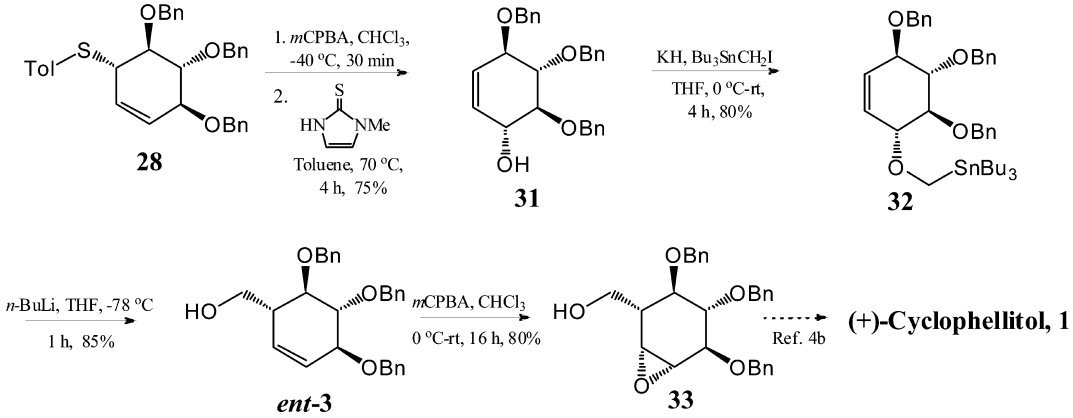
Scheme 4. Formal Synthesis of (−)-Cyclophellitol



Scheme 5. Formal Synthesis of (+)-Cyclophellitol



and warming in THF led to Pummerer rearrangement. Hydrolysis of the intermediate with aq sodium bicarbonate and reduction of the resulting aldehyde in the same pot resulted in alcohol **3** (P = Bn), Scheme 4. Stereoselective epoxidation completed the formal synthesis of (−)-cyclophellitol **2**.

The formal synthesis of (+)-cyclophellitol was completed following the sequence of reactions reported in the literature[4b] using compound **31** as the building block, as depicted in Scheme 5. Oxidation of **28** with *m*-CPBA followed by Mislow−Evans rearrangement yielded (−)-conduritol-B derivative **31**. Deprotonation of **31** with potassium hydride followed by reaction with iodomethyltributyltin[21] yielded the tin derivative **32**. Treatment of **32** with *n*-BuLi led to homoallylic alcohol *ent*-**3** via Wittig−Still rearrangement.[22] Epoxidation of the homoallylic alcohol completed the formal synthesis of (+)-cyclophellitol.

The synthesis of (−)-conduramine-B derivative was achieved by rearrangement of the sulfilimine prepared from sulfide **28**.

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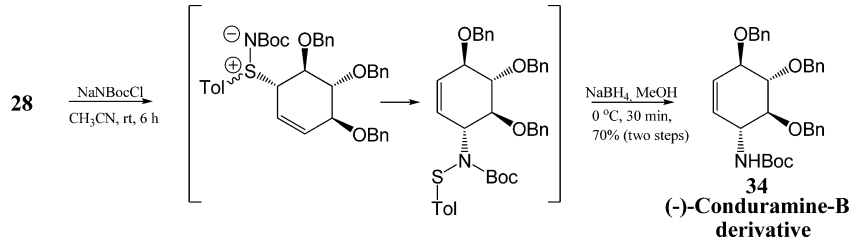
Scheme 6. Synthesis of (−)-Conduramine-B Derivative via a Sulfilimine Intermediate



Thus, treatment of **28** with *N*-chloro-*N*-*tert*-butyloxy carbamate[23] at 0 °C and warming to rt led to allylic amino derivative which, without isolation on treatment with sodium borohydride in methanol, led to the cleavage of the N−S bond to furnish carbamate **34** and thus completing the synthesis of (−)-conduramine-B derivative, Scheme 6.

In conclusion, we have disclosed an asymmetric route to (−)- and (+)-cyclophellitol. The key steps of the strategy include utilization of an intramolecular sulfinyl group as the nucleophile for vicinal heterofunctionalization of a diene, α-chloro sulfide intermediate for stereoselective C−C bond formation, ring-closing metathesis, Mislow−Evans reaction for the synthesis of conduritol derivative, Kirmse−Doyle rearrangement, and Wittig−Still rearrangement for the introduction of the hydroxymethyl substituent of cyclophellitol and preparation of conduramine derivative again by a [2,3] sigmatropic rearrangement. A characteristic feature of the synthesis is the utilization of a single allylic sulfide **28** for the synthesis of all the target molecules by C−O, C−N, and C−C bond formations. The potential utility of sulfur intermediates as nucleophilic and electrophilic partners in total synthesis is elegantly demonstrated.

EXPERIMENTAL SECTION

Dry reactions were performed under an inert atmosphere using argon or nitrogen. All glassware apparatuses used for reactions are perfectly oven-dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, toluene from CaH_2; MeOH from Mg cake; $CHCl_3$ from P_2O_5; and acetone from $KMnO_4$ and K_2CO_3. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (100−200 mesh). Analytical thin-layer chromatography (TLC) was run on silica gel 60 F254 precoated plates (250 μm thickness). Optical rotations $[\alpha]^D$ were measured on a polarimeter and given in 10−1 deg cm^2 g^{-1}. Infrared spectra were recorded in neat/KBr (as mentioned) and reported in wavenumber (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. High-resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer. ^{1}H NMR spectra were recorded at 300 or 400 or 500 MHz and ^{13}C NMR spectra at 75 or 100 or 125 MHz in $CDCl_3$ with the residual solvent signal as internal standard unless otherwise mentioned, chemical shifts are in ppm downfield from tetramethylsilane, and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(*S*,3*E*,5*E*)-1-((*S*)-*p*-Tolylsulfinyl)hepta-3,5-dien-2-ol (8). To a solution of anhydrous $ZnCl_2$ (10.88 g, 80 mmol) in anhydrous THF (150 mL) was added a solution of keto sulfoxide[6] (9.9 g, 40 mmol) in THF (50 mL) dropwise over 5 min. The reaction mixture was stirred at rt for 30 min and then cooled to −78 °C. After 5 min, Dibal-H (38 mL, 1.6 M in toluene, 60 mmol) was added dropwise over 5 min. After 30 min, MeOH (5 mL) was added slowly to the reaction mixture and allowed to warm to rt. The volatiles were evaporated under reduced pressure, and the residue was dissolved by adding aq 5% HCl (100 mL) at 0 °C. Then EtOAc (100 mL) was added, the layers were separated, and the aqueous layer extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 40% EtOAc/petroleum ether (v/v) to give pure hydroxy sulfoxide **8** (8.2 g, 32.8 mmol) in 82% yield as a gummy oil. TLC: R_f 0.25 (40% EtOAc/hexane). $[\alpha]_D^{25}$ = −194.0 (*c* 1.02, $CHCl_3$); IR (neat): 3417, 2925, 2856, 1727, 1085, 994, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.20 (dd, *J* = 15.1 Hz, 10.4 Hz, 1H), 5.98 (dd, *J* = 14.9 Hz, 10.4 Hz, 1H), 5.75−5.63 (m, 1H), 5.51 (dd, *J* = 15.1 Hz, 6.4 Hz, 1H), 4.73−4.66 (m, 1H), 3.04 (dd, *J* = 13.0 Hz, 8.9 Hz, 1H), 2.77 (dd, *J* = 13.0 Hz, 3.6 Hz, 1H), 2.41 (s, 3H), 1.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6, 140.7, 131.8, 130.8, 130.6, 130.0, 129.9, 124.1, 68.9, 63.1, 21.5, 18.2; MS (ESI): *m*/*z* 273 $[M + Na]^+$. HRMS (ESI): calcd for $C_{14}H_{18}NaO_2S$: 273.0925; found: 273.0921.

(2*R*,3*S*,4*S*,*E*)-3-Bromo-1-((*R*)-*p*-tolylsulfinyl)hept-5-ene-2,4-diol (11). To a solution of the diene **8** (7.5 g, 30 mmol) in DCM (120 mL) was added water (0.65 mL, 36 mmol), and the mixture stirred at 0 °C for 5 min. To the above solution, freshly recrystallized NBS (5.34 g, 30 mmol) was added portion wise over a period of 1 h. The reaction mixture was stirred for another 30 min when TLC examination revealed consumption of the starting material. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using 35%−50% EtOAc/petroleum ether (v/v) to give pure bromohydrin **11** (7.26 g, 21 mmol) in 70% yield as a colorless viscous oil. TLC: R_f 0.25 (50% EtOAc/hexane). $[\alpha]_D^{25}$ = +75.8 (*c* 0.5, MeOH). IR (neat): 3423, 3020, 2922, 2856, 1730, 1641, 1492, 1251, 1085, 970, 807, 761, 494 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.78−5.66 (m, 1H), 5.47 (dd, *J* = 15.7 Hz, 6.8 Hz, 1H), 5.13 (br s, OH), 4.49−4.38 (m, 1H), 4.35−4.26 (m, 1H), 4.05 (dd, *J* = 6.8 Hz, 6.1 Hz, 1H), 3.68 (br s, OH), 3.19 (dd, *J* = 12.9 Hz, 2.0 Hz, 1H), 3.08 (dd, *J* = 12.9 Hz, 9.5 Hz, 1H), 2.44 (s, 3H), 1.69 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 138.6, 130.2, 130.1, 129.5, 124.0, 73.5, 67.9, 62.1, 59.8, 21.3, 17.7; MS (ESI): *m*/*z* 347/349 $[M + H]^+$, 369/371 $[M + Na]^+$. HRMS (ESI): calcd for $C_{14}H_{19}BrO_3SNa$: 369.0130; found: 369.0149.

1-((*R*)-((2*R*,3*S*,4*S*,*E*)-3-Bromo-2,4-bis(2,3,3-trimethylbutan-2-yloxy)hept-5-enyl)sulfinyl)-4-methylbenzene (12). To a solution of the bromohydrin **11** (7.26 g, 21 mmol) in DCM (84 mL) cooled at 0 °C were added imidazole (5.7 g, 84 mmol) and then TBS-Cl (7.0 g, 46.2 mmol). The reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction mixture was quenched by the addition of water and diluted with DCM (100 mL). The layers were separated, and the organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 10% EtOAc/petroleum ether (v/v) to give pure TBS ether **12** (10.8 g, 18.7 mmol) in 90% yield as a gummy oil. TLC: R_f 0.5 (20% EtOAc/hexane). $[\alpha]_D^{25}$ = +35.2 (*c* 0.5, $CHCl_3$). IR (neat): 3019, 2973, 2924, 1709, 1492, 1211, 1094, 806, 756, 495 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.5 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 5.70−5.52 (m, 1H), 5.46 (dd, *J* = 15.8 Hz, 7.5 Hz, 1H), 4.60 (dt, *J* = 9.8 Hz, 2.3 Hz, 1H), 4.19 (t, *J* = 6.7 Hz, 1H), 4.12−4.03 (dd, *J* = 6.7 Hz, 2.3 Hz, 1H), 3.13 (dd, *J* = 12.8 Hz, 2.3 Hz, 1H), 2.89 (dd, *J* = 12.8 Hz, 9.8 Hz, 1H), 2.38 (s, 3H), 1.70 (d, *J* = 5.3 Hz, 3H), 0.95 (s, 9H), 0.77 (s, 9H), 0.24 (s, 3H), 0.14 (s, 3H), 0.02 (s, 3H), −0.05 (s, 3H);

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^{13}C NMR (75 MHz, $CDCl_3$): δ 141.7, 140.8, 131.5, 129.7, 129.4, 123.6, 75.8, 65.6, 65.3, 64.5, 25.7, 25.6, 21.3, 18.0, 17.8, 17.4, −4.1, −4.73, −4.75, −4.9; MS (ESI): *m*/*z* 597/599 [M + Na]$^+$. HRMS (ESI): calcd for $C_{26}H_{47}O_3BrSSi_2Na$: 599.1834; found: 599.1835.

((2*R*,3*S*,4*S*,*E*)-3-Bromo-2,4-dimethoxyhept-5-enyl)(*p*-tolyl)-sulfane (7). To a stirred solution of a mixture of TBS ether **12** (10.3 g, 18 mmol) and NaI (10.8 g, 72 mmol) in acetone (72 mL) cooled at −20 °C was added TFAA (5 mL, 36 mmol) dropwise. The reaction mixture was stirred for 1 h at −20 °C and then quenched by adding an aq saturated Na_2SO_3 solution (20 mL). Acetone was evaporated under reduced pressure and the aq phase was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were successively washed with aq saturated $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure furnished the crude compound which was purified by column chromatography using 5−10% EtOAc/petroleum ether (v/v) to give pure sulfide **7** (8.55 g, 15.3 mmol) in 85% yield as a gummy oil. TLC: R_f 0.5 (10% EtOAc/hexane). $[\alpha]_D^{20}$ = +85.8 (*c* 1.0, $CHCl_3$). IR (neat): 3015, 2960, 2924, 1729, 1452, 1211, 1094, 806, 756, 495 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 5.72−5.57 (m, 1H), 5.39 (dd, *J* = 15.8 Hz, 7.5 Hz, 1H), 4.36 (t, *J* = 6.0 Hz, 1H), 4.17−4.09 (m, 2H), 3.35 (dd, *J* = 13.5 Hz, 3.0 Hz, 1H), 3.20 (dd, *J* = 13.5 Hz, 7.54 Hz, 1H), 2.32 (s, 3H), 1.7 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 133.5, 131.5, 129.8, 129.5, 128.9, 75.0, 71.1, 64.5, 39.9, 25.9, 25.8, 20.9, 18.2, 18.1, 17.5, −4.0, −4.2, −4.8; MS (ESI): *m*/*z* 581/583 [M + Na]$^+$. HRMS (ESI): calcd for $C_{26}H_{47}$ $BrNaO_2SSi_2$: 581.1911; found: 581.1906.

(5*S*,6*S*,7*R*)-6-Bromo-2,2,3,3,9,9,10,10-octamethyl-5-((*E*)-prop-1-enyl)-7-((*R*)-*p*-tolylsulfinylmethyl)-4,8-dioxa-3,9-disilaundecane (6). To a solution of vinylmagnesium bromide (30 mL, 30 mmol, 1 M in THF) cooled at 0 °C was added $ZnBr_2$ (24 mL, 36 mmol, 1.5 M in THF) and stirred for 30 min. To the resulting vinylzinc bromide maintained at 0 °C was added the solution of chloro sulfide (10 mmol) in benzene (100 mL) prepared by the dropwise addition of a solution of the sulfide **7** (5.6 g, 10 mmol) in anhydrous benzene (50 mL) to the solution of *N*-chlorosuccinimide (1.4 g, 10.5 mmol) in benzene (50 mL) at ambient temperature and stirring for a period of 30 min. The reaction mixture was stirred and gradually allowed to warm to rt, and stirred for a period of 4 h when TLC examination indicated complete consumption of the chloro sulfide. The reaction mixture was cooled to 0 °C and quenched by the addition of an aq saturated NH_4Cl solution. It was allowed to warm to rt and diluted with Et_2O (25 mL), the layers were separated and aq layer extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using hexanes as the eluent to afford the pure product **6** (4.68 g, 8 mmol) in 80% yield as a colorless viscous liquid. TLC: R_f 0.55 (10% EtOAc/hexane). $[\alpha]_D^{20}$ = −55.1 (*c* 0.72, $CHCl_3$). IR (neat): 2954, 2929, 2857, 1466, 1363, 1254, 1095, 838, 776, 684 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 7.5 Hz, 2H), 5.97−5.82 (m, 1H), 5.78−5.62 (m, 1H), 5.42 (dd, *J* = 15.1 Hz, 6.0 Hz, 1H), 4.99 (dd, *J* = 10.5 Hz, 1.5 Hz, 1H), 4.93 (dd, *J* = 16.6 Hz, 1.5 Hz, 1H), 4.54 (dd, *J* = 6.0 Hz, 5.3 Hz, 1H), 4.38 (t, *J* = 5.3 Hz, 1H), 4.20−4.12 (m, 2H), 2.31 (s, 3H), 1.73 (d, *J* = 6.7 Hz, 3H), 0.97 (s, 9H), 0.92 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9, 136.5, 133.1, 130.7, 129.4, 128.8, 116.8, 75.3, 72.1, 63.8, 59.4, 26.1, 25.9, 21.0, 18.6, 18.2, 17.7, −3.71, −3.89, −3.97, −4.56; MS (ESI): *m*/*z* 607/609 [M + Na]$^+$. HRMS (ESI): calcd for $C_{28}H_{49}O_2BrNaSSi_2$: 607.20674; found: 607.20673.

((1*R*,2*S*,3*S*,6*S*)-2-Bromo-6-(*p*-tolylthio)cyclohex-4-ene-1,3-diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (14). To a solution of the compound **6** (275 mg, 0.47 mmol) in dry DCM (1 mL) maintained under an atmosphere of N_2 at ambient temperature was added Grubbs first generation catalyst (20 mg, 0.02 mmol). The reaction was heated at 40 °C for 8 h. The solution was concentrated under vacuum to afford a crude compound which was purified by column chromatography using 5−15% EtOAc/petroleum ether (v/v) to afford the pure product **14** (205 mg, 0.38 mmol) in 80% yield as a colorless oil. TLC: R_f 0.3 (10% EtOAc/hexane). $[\alpha]_D^{20}$ = +33.7 (*c* 0.72, $CHCl_3$). IR (neat): 2960, 2924, 1729, 1452, 1211, 1094, 806, 756, 495 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 5.72 (dt, *J* = 10.3 Hz, 2.4 Hz, 1H), 5.40 (dq, *J* = 10.2 Hz, 1.8 Hz, 1H), 4.43−4.33 (m, 2H), 3.89−3.82 (m, 1H), 3.75 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 2.33 (s, 3H), 0.94 (s, 9H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 132.3, 130.8, 129.6, 129.5, 127.9, 72.2, 68.2, 63.1, 51.7, 25.8, 25.7, 21.0, 18.2, 18.1, −4.4, −4.6, −4.7; MS (ESI): *m*/*z* 565/567 [M + Na]$^+$. HRMS (ESI): calcd for $C_{25}H_{43}O_2BrNaSSi_2$: 565.1597/567.1578; found: 565.1599/567.1577.

(1*R*,4*R*,5*R*,6*S*)-5-Bromo-4,6-bis(*tert*-butyldimethylsilyloxy)-cyclohex-2-enol (15). To a solution of sulfide **14** (90 mg, 0.16 mmol) in anhydrous $CHCl_3$ (1 mL) cooled at −40 °C was added *m*CPBA (26 mg, 0.16 mmol). The reaction mixture was stirred for 30 min at the same temperature when TLC examination revealed complete transformation of sulfide to sulfoxide. A solution of 2-mercapto-1-methyl imidazole (38 mg, 0.33 mmol) in toluene (2 mL) was added and the reaction mixture was gradually allowed to warm to rt and then heated at 70 °C for 4 h. The reaction mixture was cooled to rt and quenched by the addition of saturated sodium sulfite solution (5 mL). The layers were separated and the aq layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with aq saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash chromatography on silica gel using 8−15% EtOAc/hexane (v/v) as the eluent afforded **15** as a colorless oil (52 mg, 0.12 mmol) in 75% overall yield. TLC: R_f 0.15 (10% EtOAc/hexane). $[\alpha]_D^{20}$ = −15.1 (*c* 0.1, $CHCl_3$). IR (neat): 3446, 3015, 2960, 2924, 1728, 1452, 1211, 1054, 806, 756, 495 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.69 (dt, *J* = 10.5 Hz, 2.2 Hz, 1H), 5.49 (dd, *J* = 10.5 Hz, 1.5 Hz, 1H), 4.55−4.46 (m, 2H), 4.33−4.28 (m, 1H), 3.62 (dd, *J* = 7.5 Hz, 3.0 Hz, 1H), 0.95 (s, 9H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.8, 128.0, 74.6, 71.8, 68.6, 62.3, 25.7, 25.6, 18.2, 18.0, 1.01, −4.5, −4.71, −4.7; MS (ESI): *m*/*z* 459/461 [M + Na]$^+$. HRMS (ESI): calcd for $C_{18}H_{37}$ $BrNaO_3Si_2$: 459.1357; found: 459.1330.

(1*R*,4*R*,5*R*,6*S*)-5-Bromo-4,6-bis(*tert*-butyldimethylsilyloxy)-cyclohex-2-enyl acetate (16). To a stirred solution of compound **15** (50 mg, 0.11 mmol) in anhydrous DCM (1 mL) cooled at 0 °C, DMAP (2 mg, 0.01 mmol), Et_3N (0.05 mL, 0.33 mmol), and Ac_2O (0.02 mL, 0.17 mmol) were sequentially added. After stirring this mixture for 2 h at rt it was quenched by addition of aq saturated $NaHCO_3$ solution and extracted with DCM (2 × 10 mL). The organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated to furnish the crude acetate which was purified by column chromatography using 5−10% EtOAc/petroleum ether (v/v) to afford the pure product **16** (49.3 mg, 0.1 mmol) in 90% yield as a viscous oil. TLC: R_f 0.25 (10% EtOAc/hexane). $[\alpha]_D^{20}$ = −29.9 (*c* 0.1, $CHCl_3$). IR (neat): 2960, 2924, 1725, 1452, 1094, 856, 715, 495 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.61 (dt, *J* = 10.5 Hz, 2.1 Hz, 1H), 5.58−5.53 (m, 2H), 4.52−4.48 (m, 1H), 4.30−4.28 (m, 1H), 3.87 (dd, *J* = 7.5 Hz, 2.6 Hz, 1H), 2.07 (s, 3H), 0.93 (s, 9H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 132.3, 125.0, 74.9, 71.4, 68.3, 62.4, 25.7, 25.5, 21.1, 18.2, 17.9, −4.6, −4.7, −4.8; MS (ESI): *m*/*z* 501/503 [M + Na]$^+$. HRMS (ESI): calcd for $C_{20}H_{39}BrNaO_4Si_2$: 501.1463; found: 501.1459.

(1*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-4-oxocyclohex-2-enyl acetate (17). To a stirred solution of bromo acetate **16**(35 mg, 0.07 mmol) in dry DMF (0.7 mL) was added KOAc (68 mg, 0.7 mmol) and the mixture heated at 100 °C for 6 h when TLC examination revealed complete consumption of starting material. The reaction mixture was cooled to rt, quenched by the addition of water and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to furnish the crude compound which was purified by column chromatography using 10−20% EtOAc/petroleum ether (v/v) to afford the pure product **17** (16 mg, 0.05

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mmol) in 70% yield as a viscous oil. TLC: R_f 0.25 (20% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.7 (dd, J = 9.6 Hz, 1H), 6.05 (dd, J = 9.6 Hz, 1H), 5.5 (m, 1H), 4.21−4.10 (m, 1H), 2.75 (dd, J = 16.4 Hz, 6.0 Hz, 1H), 2.51 (dd, J = 16.4 Hz, 3.2 Hz, 1H), 2.12 (s, 3H), 0.89 (s, 9H), 0.01 (s, 6H).

((1*S*,2*R*,3*R*,6*R*)-2-Bromo-6-(methoxymethoxy)cyclohex-4-ene-1,3-diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (18). To a stirred solution of compound **15** (50 mg, 0.11 mmol) in anhydrous DCM (1 mL) cooled at 0 °C, DIPEA (0.06 mL, 0.34 mmol), and MOM-Cl (0.014 mL, 0.165 mmol) were sequentially added. After stirring this mixture for 2 h at rt the reaction was quenched by addition of aq saturated $NaHCO_3$ solution and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to furnish the MOM ether which was purified by column chromatography using 5−10% EtOAc/petroleum ether (v/v) to afford the pure product **18** (49 mg, 0.1 mmol) in 90% yield as a gummy liquid. TLC: R_f 0.45 (10% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): 5.6 (dt, J = 10.2 Hz, 2.2 Hz, 1H), 5.39 (dd, J = 10.2 Hz, 2.6 Hz, 1H), 4.71 (d, J = 6.7 Hz, 1 H), 4.58 (d, J = 6.7 Hz, 1H), 4.40−4.32 (m, 1H), 4.27−4.20 (m, 1H), 4.20−4.15 (m, 1H), 3.61 (dd, J = 7.5 Hz, 2.6 Hz, 1H), 3.30 (s, 3H), 0.82 (s, 18H), 0.01 (s, 6H), −0.01 (s, 6H).

4-(Methoxymethoxy)phenol (19). 18-crown-6 (26 mg, 0.1 mmol) and potassium superoxide (30 mg, 0.4 mmol) were added to a solution of the compound **18** (50 mg, 0.10 mmol) in anhydrous dimethyl sulfoxide (1 mL) cooled at 0 °C. After 30 min the reaction mixture was diluted with diethyl ether (5 mL) and poured into brine. The organic phase was separated, and the aq phase was extracted with diethyl ether (2 × 5 mL). The organic layers were washed with aq 1 N HCl, water, dried with Na_2SO_4 and evaporated. The resulting crude compound was purified by column chromatography using 10−20% EtOAc/petroleum ether (v/v) to afford the pure product **19** (10 mg, 0.07 mmol) in 70% yield as a liquid. TLC: R_f 0.15 (20% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 5.10 (s, 2H), 3.48 (s, 3H).

(3*S*,4*R*,5*S*,6*S*,*E*)-5-Bromo-3-(*p*-tolylthio)nona-1,7-diene-4,6-diyl Diacetate (21). To a stirred solution of bromo compound **5** (4.1 g, 7 mmol) in MeOH (25 mL) was added (±)-camphorsulfonic acid (90 mg, 0.4 mmol) at rt, and the mixture stirred for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue diluted with DCM (25 mL). DMAP (35 mg, 0.28 mmol), Et_3N (4 mL, 28 mmol), and Ac_2O (1.4 mL, 14 mmol) were sequentially added at 0 °C. After stirring this mixture for 2 h at rt, it was quenched by the addition of aq saturated $NaHCO_3$ solution and extracted with DCM (2 × 50 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to furnish the crude diacetate which was purified by column chromatography using 5−15% EtOAc/petroleum ether (v/v) to afford the pure product **21** (2.66 g, 5.95 mmol) in 85% yield as a gummy oil. TLC: R_f 0.3 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = −20.2 (c 0.56, $CHCl_3$). IR (neat): 2977, 1748, 1492, 1371, 1224, 1021, 966, 810, 606, 499 cm^{-1}..^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 5.85−5.63 (m, 1H), 5.62−5.51 (m, 1H), 5.41 (dd, J = 7.5 Hz, 3.7 Hz, 1H), 5.35 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 5.08 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 2.2 Hz, 1H), 4.77 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 4.14 (dd, J = 8.3 Hz, 3.0 Hz, 1H), 2.32 (s, 3H), 2.10 (s, 6H), 1.73 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 169.2, 137.7, 134.7, 133.6, 133.5, 129.9, 129.6, 124.8, 117.4, 74.2, 72.9, 56.7, 54.9, 21.1, 21.0, 20.7, 17.9; MS (ESI): m/z 458/460 $[M + NH_4]^+$. HRMS (ESI): calcd for $C_{20}H_{29}BrNO_4S$: 458.0995; found: 458.0986.

(3*S*,4*S*,5*R*,6*S*,*E*)-3-(*p*-Tolylthio)nona-1,7-diene-4,5,6-triyl Triacetate (22). To a stirred solution of bromo compound **21** (872 mg, 2 mmol) in dry DMSO (8 mL) were added BHT (45 mg, 0.2 mmol) and $NaNO_2$ (1.38 g, 20 mmol), and the mixture heated at 85 °C for 24 h in the dark. The reaction mixture was cooled to rt, quenched by the addition of water, and extracted with $CHCl_3$ (2 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to furnish the crude compound which was purified by column chromatography using10−20% EtOAc/petroleum ether (v/v) to afford the triol derivative as a mixture of diacetates (567 mg, 1.5 mmol) in 75% yield as a viscous liquid. To the purified mixture of diacetates (567 mg, 1.5 mmol) in dry DCM (6 mL) cooled at 0 °C, DMAP (6 mg, 0.05 mmol), Et_3N (0.43 mL, 3 mmol), and Ac_2O (0.14 mL, 1.5 mmol) were sequentially added. After stirring the mixture for 2 h at rt, it was quenched by the addition of aq saturated $NaHCO_3$ solution and extracted with DCM (2 × 20 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to furnish the crude triacetate which was purified by column chromatography using 10−15% EtOAc/petroleum ether (v/v) to afford the pure product **22** (567 mg, 1.35 mmol) in 90% yield as a viscous liquid. TLC: R_f 0.5 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = +61.3 (c 0.5, $CHCl_3$). IR (neat): 2924, 1748, 1372, 1217, 1027, 962, 810, 601, 500 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.3 (d, J = 7.9 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 5.82−5.71 (m, 1H), 5.70−5.60 (m, 1H), 5.40 (dd, J = 6.2 Hz, 2.7 Hz, 1H), 5.36 (dd J = 10.5 Hz, 3.2 Hz, 1H), 5.31 (dd, J = 7.1 Hz, 2.7 Hz, 1H), 5.23 (dd J = 7.1 Hz, 3.3 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 4.89 (d, J = 16.3 Hz, 1H), 3.71 (dd, J = 8.4 Hz, 7.7 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.68 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.7, 169.4, 137.6, 133.6, 133.1, 133.0, 129.7, 129.5, 124.2, 118.0, 73.1, 72.2, 71.7, 54.3, 21.0, 20.8, 20.6, 20.6, 17.7; MS (ESI): m/z 438 $[M + NH_4]^+$. HRMS (ESI): calcd for $C_{22}H_{32}O_6SN$: 438.1929; found: 438.1945.

(1*S*,2*R*,3*S*,6*S*)-6-(*p*-Tolylthio)cyclohex-4-ene-1,2,3-triyl Triacetate (23). To a solution of the compound **22** (210 mg, 0.5 mmol) in dry DCM (1 mL) maintained under an atmosphere of N_2 at ambient temperature was added Grubbs first-generation catalyst (45 mg, 0.05 mmol). The reaction was heated at 40 °C for 8 h. The solution was concentrated under vacuum to afford a crude compound which was purified by column chromatography using 10−15% EtOAc/petroleum ether (v/v) to afford the pure product **23** (150 mg, 0.4 mmol) in 80% yield as a viscous liquid. TLC: R_f 0.3 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = +146.8 (c 1.0, $CHCl_3$). IR (neat): 2926, 1751, 1371, 1222, 1045, 964, 811, 769, 601 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.83 (dt, J = 10.2 Hz, 2.2 Hz, 1H), 5.48 (dt, J = 10.2, Hz, 2.4 Hz, 1H), 5.38−5.32 (m, 1H), 5.24−5.19 (m, 2H), 3.77−3.72 (m, 1H), 2.3 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 170.0, 169.7, 138.9, 135.0, 129.8, 129.7, 126.9, 126.0, 72.4, 71.3, 71.2, 49.3, 21.1, 20.8, 20.5; MS (ESI): m/z 396 $[M + NH_4]^+$. HRMS (ESI): calcd for $C_{19}H_{26}O_6SN$: 396.1475; found: 396.1470.

(1*S*,2*S*,3*R*,6*R*)-6-Hydroxycyclohex-4-ene-1,2,3-triyl Triacetate (24). To a solution of sulfide **23** (50 mg, 0.13 mmol) in anhydrous $CHCl_3$ (1 mL) cooled at −40 °C was added *m*CPBA (22 mg, 0.13 mmol). The reaction mixture was stirred for 30 min at same temperature when TLC examination revealed complete transformation of sulfide to sulfoxide. A solution of 2-mercapto-1-methyl imidazole (23 mg, 0.2 mmol) in toluene (2 mL) was added, and the reaction mixture was gradually allowed to warm to rt and then heated at 70 °C for 4 h. The reaction mixture was cooled to rt and quenched by the addition of saturated sodium sulfite solution (5 mL). The layers were separated, and the aq layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash chromatography on silica gel using 8−15% EtOAc/hexane (v/v) as the eluent afforded **24** as a colorless oil (26.3 mg, 0.097 mmol) in an overall 75% yield. TLC: R_f 0.25 (30% EtOAc/hexane). $[\alpha]_D^{20}$ = −116.3 (c 0.5, $CHCl_3$). {Lit.:[4c] −111.8 (c 0.1, $CHCl_3$)}. IR (neat): 3448, 2922, 2852, 1633, 1021, 763 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (dt, J = 10.3 Hz, 2.13 Hz, 1H), 5.62 (dt, J = 10.3 Hz, 2.6 Hz, 1H), 5.57 (dq, J = 8.0 Hz, 2.6 Hz, 1H), 5.29 (dd, J = 11.1 Hz, 8.0 Hz, 1H), 5.04 (dd, J = 10.9 Hz, 7.7 Hz, 1H), 4.45−4.41 (m, 1H), 2.11 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 170.2, 170.0, 131.0, 125.4, 75.5, 71.8, 71.1, 70.6, 20.8, 20.7, 20.6; MS (ESI): m/z 290 $[M + NH_4]^+$. HRMS (ESI): calcd for $C_{12}H_{20}O_7N$: 290.1234; found: 290.1228.

(1*S*,2*S*,3*R*,6*R*)-6-(*p*-Tolylthio(trimethylsilyl)methyl)cyclohex-4-ene-1,2,3-triyl Triacetate (25). Trimethylsilyl diazomethane (0.2 mL, 2 M in hexanes, 0.4 mmol) was added to a solution of allyl sulfide **23** (30 mg, 0.08 mmol) and rhodium(II) acetate dimer (3 mg, 0.006

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mmol) in toluene (1.5 mL). After stirring for 12 h at 50 °C, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 2% EtOAc/petroleum ether (v/v) to give as a mixture of epimeric sulfide **25** (27 mg, 75%) as a colorless liquid. TLC: R_f 0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = −69.1 (*c* 0.5, $CHCl_3$). IR (neat): 2963, 2954, 1723, 1456, 1211, 1094, 806, 756, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.2 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.02 (dt, *J* = 10.2 Hz, 2.2 Hz, 1H), 5.65−5.61 (m, 3H), 5.60−5.50 (m, 4H), 5.23−5.11 (m, 2H), 3.05−3.0 (m, 1H), 2.85−2.79 (m, 1H), 2.53 (d, *J* = 2.2 Hz, 1H), 2.51 (d, *J* = 1.8 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H), 0.22 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 170.2, 170.0, 169.2, 136.7, 136.6, 133.2, 132.5, 131.3, 130.2, 129.8, 129.77, 129.70, 129.0, 126.0, 124.2, 73.4, 72.7, 72.16, 72.11, 71.8, 71.6, 45.4, 43.4, 36.1, 35.4, 21.0, 20.9, 20.8, 20.6, 20.5, −0.8, −1.7; MS (ESI): *m*/*z* 482 $[M + NH_4]^+$. HRMS (ESI): calcd for $C_{23}H_{36}O_6NSSi$: 482.2027; found: 482.2009.

***p*-Tolyl((1*S*,4*S*,5*R*,6*S*)-4,5,6-tris(benzyloxy)cyclohex-2-enyl)-sulfane (28).** To a stirred solution of triacetate compound **23** (200 mg, 0.52 mmol) in MeOH (3 mL) was added K_2CO_3 (20 mg, 0.14 mmol) at rt, and the mixture stirred for 2 h. The mixture was filtered, and the filtrate evaporated to furnish the crude triol **27** which was used in the next step without further purification.

The suspension of the sodium hydride (70 mg, 1.75 mmol, 60% dispersion in Nujol was washed twice with dry petroleum ether) in anhydrous THF (2.5 mL), cooled at 0 °C, was added to *n*-tetrabutylammonium iodide (20 mg, 0.05 mmol) followed by dropwise addition of a solution of the triol **27** (l30 mg, 0.5 mmol) in anhydrous THF (2.5 mL) under nitrogen atmosphere. After stirring at room temperature for l h, benzyl bromide (0.21 mL, 1.75 mmol) was added dropwise, and the resulting mixture stirred for 6 h. The reaction was then quenched by the addition of ice pieces, and the mixture extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed successively with water and brine. The organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography using 3−8% EtOAc/petroleum ether (v/v) to give compound **28** (234 mg, 0.44 mmol, 85%) as a colorless oil. TLC: R_f 0.35 (10% EtOAc/hexane). $[\alpha]_D^{20}$ = +196.8 (*c* 1.0, $CHCl_3$). IR (neat): 2923, 2856, 1493, 1454, 1355, 1138, 1070, 1026, 807, 739, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.27 (m, 15H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.75 (dt, *J* = 10.1 Hz, 2.2 Hz, 1H), 5.66 (dt, *J* = 10.1 Hz, 2.0 Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 4.91 (d, *J* = 10.3 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.13−4.08 (m, 1H), 3.85−3.79 (m, 1H), 3.76 (dd, *J* = 9.9 Hz, 7.9 Hz, 1H), 3.65 (dd, *J* = 9.9 Hz, 8.6 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 138.4, 138.2, 137.7, 133.5, 129.7, 129.6, 128.8, 128.34, 128.33, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.2, 84.6, 81.7, 79.8, 75.9, 75.5, 72.3, 52.5, 21.0; MS (ESI): *m*/*z* 545 $[M + Na]^+$. HRMS (ESI): calcd for $C_{34}H_{34}NaO_3S$: 545.2121; found: 545.2109.

Trimethyl(*p*-tolylthio((1*R*,4*R*,5*S*,6*S*)-4,5,6-tris(benzyloxy)-cyclohex-2-enyl)methyl)silane (29). Trimethylsilyl diazomethane (0.15 mL, 2 M in hexanes, 0.3 mmol) was added to a solution of allyl sulfide **28** (30 mg, 0.057 mmol) and rhodium(II) acetate dimer (3 mg, 0.005 mmol) in toluene (1.5 mL). After stirring for 12 h at 50 °C, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 2% EtOAc/petroleum ether (v/v) to give as a mixture of epimeric sulfide **29** (26 mg, 75%) as a colorless liquid. TLC: R_f 0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$ = −87.1 (*c* 0.25, $CHCl_3$). IR (neat): 2923, 2855, 1733, 1638, 1459, 1257, 1079, 757, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40−7.24 (m, 30H),7.23 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 5.90 (dt, *J* = 10.2 Hz, 2.1 Hz, 1H), 5.81 (dt, *J* = 10.2 Hz, 2.1 Hz, 1H), 5.70 (dt, *J* = 10.2 Hz, 2.1 Hz, 1H), 5.56 (dt, *J* = 10.2 Hz, 2.1 Hz, 1H), 5.02 (d, *J* = 11.4 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 2H), 4.84 (d, *J* = 11.7 Hz, 1H), 4.79 (d, *J* = 11.9 Hz, 1H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 2H), 4.68 (d, *J* = 11.7 Hz, 2H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 10.8 Hz, 1H), 4.26−4.18 (m, 2H), 3.74 (dd, *J* = 9.7 Hz, 8.2 Hz, 1H), 3.68 (dd, *J* = 9.7 Hz, 8.2 Hz, 1H), 3.58 (dd, *J* = 9.6 Hz, 5.7 Hz, 1H), 3.54 (dd, *J* = 9.7 Hz, 5.1 Hz, 1H), 2.94 (d, *J* = 2.2 Hz, 1H), 2.9−2.85 (m, 1H), 2.85 (d, *J* = 2.2 Hz, 1H), 2.83−2.78 (m, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 0.19 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.4, 136.4, 135.5, 135.4, 133.2, 132.4, 131.3, 130.8, 129.7, 129.6, 129.0, 128.9, 128.7, 128.36, 128.33, 128.3, 128.0, 127.7, 127.6, 127.5, 127.4, 127.0, 126.5, 125.7, 124.4, 123.9, 85.7, 85.4, 81.0, 80.9, 80.5, 79.9, 75.4, 75.3, 74.7, 73.8, 72.1, 71.9, 47.4, 46.0, 38.7, 36.6, 23.7, 22.9, −0.3, −1.5; MS (ESI): *m*/*z* 631 $[M + Na]^+$. HRMS (ESI): calcd for $C_{38}H_{44}NaO_3SSi$: 631.2673; found: 631.2703.

((1*S*,4*R*,5*S*,6*S*)-4,5,6-Tris(benzyloxy)cyclohex-2-enyl)-methanol (3). To a solution of sulfide **29** (25 mg, 0.04 mmol) in anhydrous $CHCl_3$ (1 mL), cooled at −40 °C, was added *m*CPBA (7 mg, 0.04 mmol). The reaction mixture was stirred for 30 min at same temperature. After complete transformation of sulfide to sulfoxide, dry THF (2 mL) was added, and the reaction mixture was refluxed for 30 min. After the reaction mixture was cooled to rt, aq $NaHCO_3$ (33 mg, 1 mL) and $NaBH_4$ (15.5 mg, 0.4 mmol) were added, and the mixture stirred for 10 min. The reaction mixture was quenched by the addition of water and extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel using 10−25% EtOAc/petroleum ether (v/v) as the eluent provided the homoallylic alcohol **3** (15 mg, 0.03 mmol) in 75% yield as a colorless oil. TLC: R_f 0.2 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = −106.1 (*c* 1.0, $CHCl_3$). {Lit.:[4b] For the enantiomer +104.5 (*c* 1.92, $CHCl_3$)}. IR (neat): 3442, 3030, 2878, 1454, 1359 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.4−7.25 (m, 15H), 5.76 (dt, *J* = 10.0 Hz, 2.4 Hz, 1H), 5.55 (dt, *J* = 10.0 Hz, 1.9 Hz, 1H), 5.0 (d, *J* = 11.1 Hz, 1H), 4.95 (d, *J* = 11.1 Hz, 1H), 4.92 (d, *J* = 10.9 Hz, 1H), 4.70 (s, 2H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.26−4.21 (m, 1H), 3.85 (dd, *J* = 9.9 Hz, 7.6 Hz, 1H), 3.68−3.63 (m, 3H), 2.52−2.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.3, 138.2, 128.4, 128.37, 128.34, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 85.0, 80.7, 78.5, 75.1, 75.0, 72.0, 63.2, 45.7; MS (ESI) *m*/*z* 453 $[M + Na]^+$. HRMS (ESI): calcd for $C_{28}H_{30}NaO_4$: 453.2036; found: 453.2041.

((1*S*,2*S*,3*S*,4*R*,5*S*,6*S*)-3,4,5-Tris(benzyloxy)-7-oxabicyclo-[4.1.0]heptan-2-yl)methanol (30). *m*CPBA (10 mg, 0.052 mmol) was added to a solution of the alkene **3** (15 mg, 0.034 mmol) in $CHCl_3$ (1 mL) cooled at 0 °C. The mixture was warmed to rt and stirred for overnight. The mixture was diluted with $CHCl_3$ (10 mL) and washed with 1 N NaOH (2 × 10 mL) and brine. The aqueous layer was back extracted with $CHCl_3$ (10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel using 25−45% EtOAc/petroleum ether (v/v) as the eluent provided epoxy alcohol **30** (12 mg, 0.02 mmol, 80%) as a crystalline white solid. TLC: R_f 0.2 (40% EtOAc/hexane). Mp 93−95 °C, $[\alpha]_D^{20}$ = −69.3 (*c* 1.0, $CHCl_3$). {Lit.:[4b] for the enantiomer +71.0 (*c* 0.9, $CHCl_3$)}. IR (neat): 3314, 3030, 2891, 1454, 1359, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.4−7.27 (m, 15H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 11.1 Hz, 1H), 4.80 (d, *J* = 11.4 Hz, 1H), 4.73 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 3.96 (dd, *J* = 10.7 Hz, 4.4 Hz, 1H), 3.89−3.83 (m, 2H), 3.59 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 3.46 (t, *J* = 10.0 Hz, 1H), 3.34 (d, *J* = 3.6 Hz, 1H), 3.16 (d, *J* = 3.7 Hz, 1H), 2.20−2.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 138.0, 137.5, 128.53, 128.51, 128.3, 128.1, 127.9, 127.8, 127.7, 127.5, 84.9, 79.8, 75.5, 75.3, 73.1, 62.7, 55.8, 52.9, 43.9; MS (ESI): *m*/*z* 469 $[M + Na]^+$. HRMS (ESI): calcd for $C_{28}H_{30}NaO_5$: 469.1985; found: 469.1992.

(1*R*,4*R*,5*S*,6*S*)-4,5,6-Tris(benzyloxy)cyclohex-2-enol (31). Compound **31** was prepared following the procedure detailed for the preparation of allylic alcohol 24 from **23** (50 mg, 0.13 mmol). TLC: R_f 0.2 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = −103.8 (*c* 1.0, $CHCl_3$). {Lit.:[4b] −116.0 (*c* 1.87, $CHCl_3$)}. IR (neat): 3448, 3087, 3062, 3030, 2864, 1469, 1453, 1202, 1088, 1073, 1027, 952, 910, 735, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.4−7.27 (m, 15H), 5.72 (dt, *J* = 10.3 Hz, 2.1 Hz, 1H), 5.67 (dt, *J* = 10.3 Hz, 1.8 Hz, 1H), 5.02 (d, *J* = 11.4 Hz, 1H), 4.91 (s, 2H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.70 (s, 2H), 4.34−4.29 (m, 1H), 4.28−4.23 (m, 1H), 3.78 (dd, *J* = 10.3 Hz, 7.6 Hz, 1H), 3.53 (dd, *J* = 10.2 Hz, 7.9 Hz, 1H), 2.17 (d, *J* = 3.3 Hz, 1H); ^{13}C NMR

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(75 MHz, $CDCl_3$): δ 138.5, 138.1, 129.3, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 126.9, 84.2, 83.2, 80.5, 75.2, 72.2, 71.8; MS (ESI): *m*/*z* 439 $[M + Na]^+$. HRMS (ESI): calcd for $C_{27}H_{28}NaO_4$: 439.188; found: 439.1902.

Tributyl(((1*R*,4*R*,5*S*,6*S*)-4,5,6-tris(benzyloxy)cyclohex-2-enyloxy)methyl)stannane (32). Potassium hydride (10 mg, 0.24 mmol, 30% suspension in mineral oil) was washed with anhydrous hexane (2 × 1 mL) and suspended in THF (2.5 mL) at 0 °C. The alcohol **31** (50 mg, 0.12 mmol) was added slowly as a solution in THF (1 mL), and the mixture was warmed to rt. After 30 min, the mixture was cooled to 0 °C, and iodomethyltributyltin (80 mg, 0.18 mmol) was added. The mixture was warmed to rt. After 4 h, aq ammonium chloride (3 mL) was added, and the mixture was extracted with diethyl ether (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel using 2−5% EtOAc/petroleum ether (v/v) provided the tributylstannylmethyl ether **32** (70 mg, 80%) as a colorless oil. TLC: R_f 0.4 (5% EtOAc/hexane). $[\alpha]_D^{20}$ = −86.8 (*c* 1.0, $CHCl_3$). {Lit.:[4b] −83.9 (*c* 1.32, $CHCl_3$)}. IR (neat): 2924, 1454, 1368, 1221, 1067, 952, 910, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.4−7.25 (m, 15H), 5.79 (dt, *J* = 10.3 Hz, 1.9 Hz, 1H), 5.72 (dt, *J* = 10.2 Hz, 1.8 Hz, 1H), 4.94 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 11 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 2H), 4.73 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.23−4.17 (m, 1H), 3.97−3.91 (m, 1H), 3.93 (d, *J* = 9.6 Hz, 1H), 3.77 (d, *J* = 9.6 Hz, 1H), 3.72 (dd, *J* = 10.3 Hz, 7.7 Hz, 1H), 3.64 (dd, *J* = 10.3 Hz, 7.4 Hz, 1H), 1.56−1.46 (m, 6H), 1.36−1.23 (m, 6H), 0.95−0.90 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 138.8, 138.4, 128.3, 128.25, 128.22, 127.9, 127.79, 127.78, 127.6, 127.45, 127.41, 127.3, 85.1, 83.4, 83.0, 80.0, 75.5, 75.2, 72.4, 59.9, 29.1, 27.2, 13.6, 8.9; MS (ESI): *m*/*z* 743 $[M + Na]^+$. HRMS (ESI): calcd for $C_{40}H_{56}NaO_4Sn$: 743.3093; found: 743.3109.

((1*R*,4*S*,5*R*,6*R*)-4,5,6-Tris(benzyloxy)cyclohex-2-enyl)-methanol (*ent*-3). *n*-Butyl lithium (0.10 mL, 2.0 M in hexanes, 0.2 mmol) was added to a solution of the stannylmethyl ether **32** (50 mg, 0.07 mmol) in THF (1.5 mL) cooled to −78 °C. After 1 h, the reaction was quenched with aq saturated ammonium chloride (3 mL), warmed to rt, and extracted with diethyl ether (3 × 10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel 10−25% EtOAc/petroleum ether (v/v) provided the homoallylic alcohol ***ent*-3** (25 mg, 85%) as a colorless oil. TLC: R_f 0.2 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = +106.3 (*c* 1.0, $CHCl_3$). {Lit.:[4b] +104.5 (*c* 1.92, $CHCl_3$)}. IR (neat): 3442, 3030, 2878, 1454, 1359 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.4−7.25 (m, 15H), 5.76 (dt, *J* = 10 Hz, 2.4 Hz, 1H), 5.55 (dt, *J* = 10 Hz, 1.9 Hz, 1H), 5.0 (d, *J* = 11.1 Hz, 1H), 4.95 (d, *J* = 11.1 Hz, 1H), 4.92 (d, *J* = 10.9 Hz, 1H), 4.70 (s, 2H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.26−4.21 (m, 1H), 3.85 (dd, *J* = 9.9 Hz, 7.6 Hz, 1H), 3.68−3.63 (m, 3H), 2.52−2.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.3, 138.2, 128.4, 128.37, 128.34, 128.2, 128.1, 127.86, 127.82, 127.6, 127.5, 85.0, 80.7, 78.5, 75.1, 75.0, 72.0, 63.2, 45.7; MS (ESI): *m*/*z* 453 $[M + Na]^+$. HRMS (ESI): calcd for $C_{28}H_{30}NaO_4$: 453.2036; found: 453.2041.

((1*R*,2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-7-oxabicyclo-[4.1.0]heptan-2-yl)methanol (33). Compound **33** was prepared following the procedure detailed for the preparation of compound 30 from **3** (15 mg, 0.034 mmol). TLC: R_f 0.2 (40% EtOAc/hexane). Mp 93−95 °C, $[\alpha]_D^{20}$ = +69.3 (*c* 1.0, $CHCl_3$). {Lit.:[4b] +71.0 (*c* 0.9, $CHCl_3$)}.

***tert*-Butyl (1*R*,4*R*,5*S*,6*S*)-4,5,6-Tris(benzyloxy)cyclohex-2-enylcarbamate (34).** To a stirred suspension of NaNBocCl (35 mg, 0.19 mmol) in dry acetonitrile (0.5 mL) was added a solution of the sulfide **28** (20 mg, 0.038 mmol) in dry acetonitrile (0.5 mL) at rt, and the mixture stirred at rt for 6 h. The reaction mixture was diluted with EtOAc (10 mL), washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was used for the next step without purification.

To a stirred solution of the above crude compound (20 mg, 0.03 mmol) in MeOH (1 mL) was added $NaBH_4$ (10 mg, 0.3 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 30 min, the reaction mixture was quenched with water and extracted with EtOAc (2 × 10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel using 5−15% EtOAc/petroleum ether (v/v) as the eluent provided the compound **34.** TLC: R_f 0.33 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = −30.1 (*c* 0.62, $CHCl_3$). IR (neat): 3448, 3029, 2924, 2855, 1685, 1526, 1251, 755, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.27 (m, 15H), 5.70 (dt, *J* = 10.2 Hz, 2.3 Hz, 1H), 5.60 (dt, *J* = 10.2 Hz, 1.8 Hz, 1H), 4.89 (d, *J* = 10.6 Hz, 1H), 4.88 (d, *J* = 10.6 Hz, 1H), 4.83 (d, *J* = 11.1 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.69 (d, *J* = 10.2 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 8.5 Hz, -NH), 4.34−4.25 (m, 1H), 4.2−4.16 (m, 1H), 3.81 (dd, *J* = 9.5 Hz, 7.3 Hz, 1H), 3.53 (t, *J* = 9.2 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 138.5, 138.2, 129.2, 128.39, 128.36, 128.1, 127.9, 127.8, 127.7, 127.6, 126.9, 83.4, 81.1, 81.0, 79.4, 75.1, 74.8, 72.1, 28.3; MS (ESI): *m*/*z* 538 $[M + Na]^+$. HRMS (ESI): calcd for $C_{32}H_{37}NNaO_5$: 538.2564; found: 538.2556.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00616.

Copies of ^1H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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