Facile Enantiospecific Synthesis of Dihydroconduritols E and F

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Abstract: An enantiospecific synthesis of cyclohexane-1,2,3,4-tetrols was accomplished from L-(+)-tartaric acid. Pivotal steps in the synthetic sequence include zinc-mediated Boord-type fragmentation of an acetonide, ring-closing metathesis (RCM), and osmium-mediated dihydroxylation.

Key words: cyclitols, ring-closing metathesis, tartaric acid, Boord fragmentation

Owing to their diverse biological activity and importance as synthetic intermediates in organic synthesis, cyclitols have been a topic of interest in recent years.[1] Naturally occurring cyclohex-5-ene-1,2,3,4-tetrols (conduritols) are inhibitors of glycosidases and a number of derivatives of conduritols have been found to possess biological activity.[2] Considerable effort from a number of synthetic groups has been directed towards the asymmetric synthesis of conduritols including constrained analogues (Figure 1).[3] While racemic synthesis of these compounds is reported either by oxidation of cyclohexadienes,[4] or by the reduction of the epoxy peroxides derived from cyclohexadienes,[5] very few approaches are reported in the literature for the enantioselective synthesis of dihydroconduritols. Methods for the asymmetric synthesis of cyclohexanetetrols include the direct reduction of conduritols,[6] ring opening of chiral oxabicycles,[7] stereoselective oxyselenylation of cyclohexenyl ethers,[8] and the chemoenzymatic synthesis reported by Hudlicky et al.[9] Herein, we disclose our efforts towards the enantiospecific synthesis of dihydroconduritols.

Our approach to the synthesis of dihydroconduritols **1** and **2** was based on the dihydroxylation of the cyclohexene derivative **5**. The synthesis of **5** was anticipated from ring-closing metathesis (RCM) of diene **6**. Formation of the diene **6** was envisioned by Boord-type fragmentation[10] of the acetonide iodide **7**. γ-Hydroxybutyramide **8**, derived from the bis-Weinreb amide of tartaric acid **9**, was identified as the precursor for the synthesis of iodide **7** (Scheme 1).

Accordingly, the synthetic sequence commenced with the controlled addition of but-3-enylmagnesium bromide to the bis-Weinreb amide **9**,[11] resulting in the γ-oxobutyramide **10** in 90% yield. Stereoselective reduction of the keto group in **10** with K-Selectride furnished alcohol **8**.

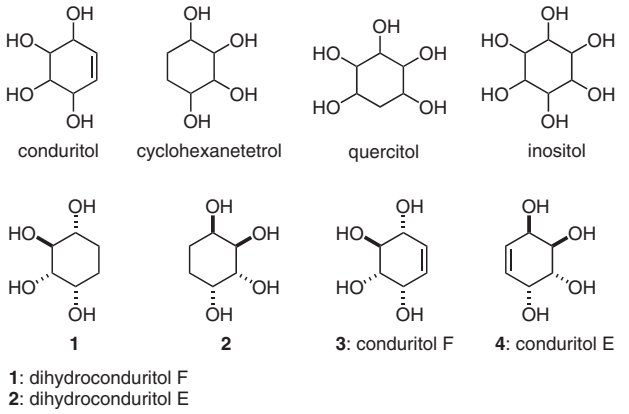
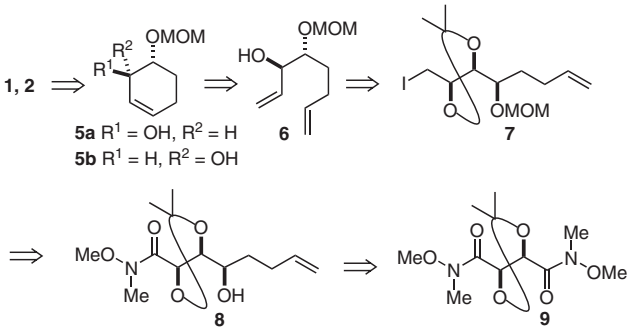


Figure 1 Conduritols and dihydroconduritols



Scheme 1 Retrosynthesis of cyclitols **1** and **2**

Protection of the hydroxy group as the methoxymethyl ether **11**, followed by reduction of the Weinreb amide in **11** with sodium borohydride furnished the alcohol **12** in 94% yield. Treatment of **12** with triphenylphosphine/imidazole and iodine afforded the iodide **7** in 86% yield. Reaction of **7** with zinc in refluxing ethanol cleanly produced the diene **6** in 94% yield (Scheme 2).

Protection of the free hydroxy group in **6** as the corresponding silyl ether **13** was affected with *tert*-butyldimethylsilyl triflate in presence of pyridine. Ring-closing metathesis[12] of **13** with the Grubbs 1st generation catalyst furnished the cyclohexene **14** in 84% yield. Osmium-mediated dihydroxylation of **14** afforded the corresponding diol **15** in good yield. Deprotection of the silyl group as well as the methoxymethyl group in **15** with trifluoroacetic acid resulted in the cyclitol **1** (dihydroconduritol F) in 93% yield. Spectral and physical data of the compound is in agreement with that reported in literature[7] (Scheme 3).

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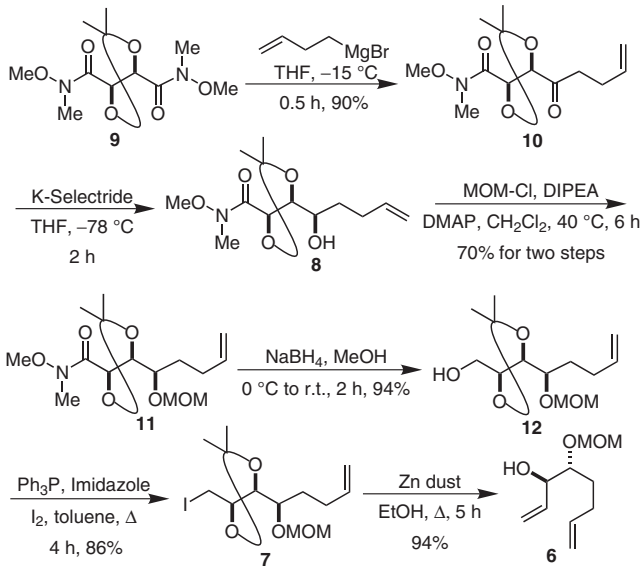
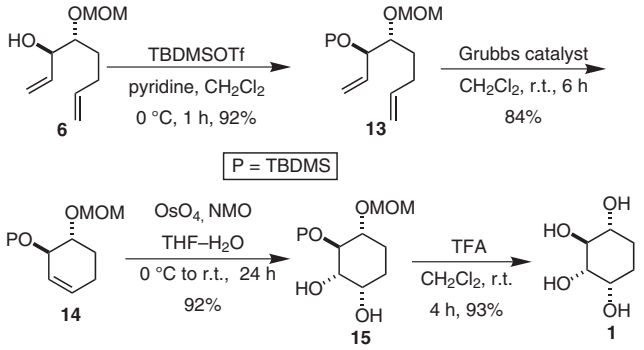


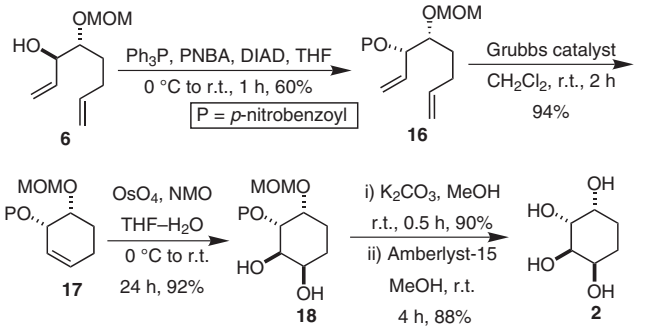
Scheme 2 Synthesis of 3-hydroxy-4-(methoxymethoxy)octa-1,7-diene **6**



Scheme 3 Synthesis of dihydroconduritol F (**1**)

After successfully accomplishing the synthesis of dihydroconduritol F (**1**), synthesis of dihydroconduritol E (**2**), was undertaken. Thus, the reaction of **6** under Mitsunobu conditions[13] proceeded smoothly to afford the 4-nitrobenzoyl ester **16** in 60% yield. Ring-closing metathesis of **16** with the Grubbs 1st generation catalyst furnished the cyclohexene **17** in excellent yield. Osmium-mediated dihydroxylation of the diene gave the diol **18** in 92% yield; the stereochemistry of **18** was further proved by X-ray crystal structure analysis (Figure 2).[14] Deprotection of the 4-nitrobenzoyl ester and the methoxymethyl ether provided dihydroconduritol E (**2**) in 79% yield for two steps (Scheme 4).

In conclusion, facile synthesis of dihydroconduritol F and dihydroconduritol E was accomplished from tartaric acid. Pivotal reactions include Boord-type fragmentation of an iodo acetonide to afford a 3,4-dihydroxyocta-1,7-diene and subsequent ring-closing metathesis of the diene. The approach described is amenable for the synthesis of higher analogues such as cycloheptane- and cyclooctanetetrols.



Scheme 4 Synthesis of dihydroconduritol E (**2**)

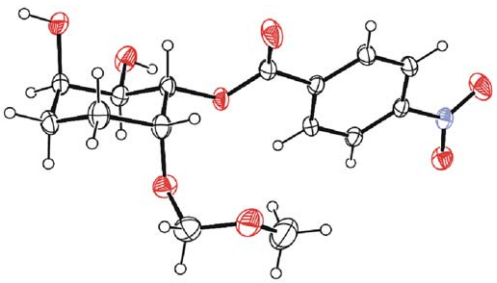


Figure 2

Column chromatography was performed on silica gel (Acme grade 100–200 mesh), petroleum ether = PE. TLC plates were visualized either with UV, or in an I_2 chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na/benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, all the reactions were performed under an inert atmosphere.

(4*R*,5*R*)-*N*-Methoxy-*N*,2,2-trimethyl-5-(pent-4-enoyl)-1,3-dioxolane-4-carboxamide (10)

In an oven-dried, two-neck, 50-mL round-bottom flask equipped with magnetic stirrer bar and argon inlet was placed the bis-Weinreb amide **9** (0.5 g, 1.8 mmol) dissolved in THF (6 mL). The soln was cooled to –15 °C and 1 M but-3-enylmagnesium bromide in THF (3 mL, 3 mmol) was added dropwise under argon. The mixture was stirred for 30 min, quenched with sat. NH_4Cl (3 mL) and extracted with Et_2O (2 × 15 mL). The combined ethereal layers were washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (PE–EtOAc, 7:3) to afford **10** (0.44 g, 90%) as a colorless oil.

$[\alpha]_D$ +4.4 (*c* 3.6, $CHCl_3$).

IR (neat): 3079, 2987, 1720, 1670, 1457, 1442, 1382, 1157, 1081, 995 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.82 (ddt, *J* = 16.8, 10.5, 6.3 Hz, 1 H), 5.10–4.95 (m, 3 H), 4.83 (d, *J* = 4.5 Hz, 1 H), 3.71 (s, 3 H), 3.24 (s, 3 H), 2.83 (dt, *J* = 18.0, 7.2 Hz, 1 H), 2.70 (dt, *J* = 18.0, 7.2 Hz, 1 H), 2.42–2.29 (m, 2 H), 1.49 (s, 3 H), 1.44 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.4, 169.6, 136.6, 115.3, 112.7, 82.1, 73.8, 61.6, 38.3, 32.4, 26.9, 26.6, 26.1.

HRMS: *m/z* $[M + Na]^+$ calcd for $C_{13}H_{21}NNaO_5$: 294.1317; found: 294.1309.

(4*R*,5*S*)-*N*-Methoxy-5-[(*R*)-1-(methoxymethoxy)pent-4-enyl]-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (11)

To a soln of **10** (0.8 g, 2.9 mmol) in anhyd THF (8 mL) at –78 °C was added 1 M K-Selectride in THF (4.4 mL, 4.4 mmol) dropwise over 10 min under argon and the mixture was stirred at –78 °C for 2 h. When the reaction was complete (TLC), it was cautiously quenched by addition of MeOH and then poured into H_2O (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, PE–EtOAc, 6:4) afforded the alcohol **8** (0.65 g, 80%) as a colorless oil. The alcohol was isolated with traces of K-Selectride impurity and was used as such in the next step.

To a soln of alcohol **8** (0.6 g, 2.2 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C were added DIPEA (1.14 mL, 6.6 mmol), DMAP (54 mg, 0.44 mmol), and MOMCl (0.32 mL, 4.4 mmol). The mixture was stirred at 0 °C for 15 min and then heated to 40 °C and stirred for 6 h. When the reaction was complete (TLC), it was cooled to r.t., poured into H_2O (15 mL), and extracted with Et_2O (3 × 25 mL). The combined ethereal extracts were washed with brine (30 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was subjected to column chromatography (silica gel, PE–EtOAc, 7:3) to give **11** (0.6 g, 86%) as a colorless oil.

$[\alpha]_D$ –4.8 (*c* 1.1, $CHCl_3$).

IR (neat): 2986, 2938, 1668, 1455, 1371, 1256, 1216, 1032, 917 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H), 5.07–4.95 (m, 2 H), 4.80–4.72 (m, 1 H), 4.75, 4.65 (2 d, *J* = 6.8 Hz, 2 H), 4.61–4.52 (m, 1 H), 3.75 (s, 3 H), 3.75–3.67 (m, 1 H), 3.39 (s, 3 H), 3.22 (s, 3 H), 2.26–2.08 (m, 2 H), 1.71–1.60 (m, 2 H), 1.47 (s, 3 H), 1.44 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 138.1, 115.0, 111.2, 96.7, 79.4, 76.6, 73.2, 61.8, 55.9, 32.3, 30.4, 29.6, 27.0, 26.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{27}NNaO_6$: 340.1736; found: 340.1750.

(4*S*,5*S*)-4-(Hydroxymethyl)-5-[(*R*)-1-(methoxymethoxy)pent-4-enyl]-2,2-dimethyl-1,3-dioxolane (12)

To a soln of **11** (0.55 g, 1.73 mmol) in MeOH (5 mL) cooled to 0 °C was added $NaBH_4$ (0.13 g, 3.5 mmol) portionwise over a period of 15 min and the mixture was stirred at r.t. for 2 h. It was quenched by cautious addition of H_2O (5 mL), poured into H_2O (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and the solvent was evaporated. Column chromatography of the residue (silica gel, PE–EtOAc, 7:3) afforded **12** (0.43 g, 94%) as a colorless oil.

$[\alpha]_D$ +4.7 (*c* 1, $CHCl_3$).

IR (neat): 3488, 2931, 1641, 1442, 1379, 1250, 1034, 916, 883, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.83 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1 H), 5.10–4.98 (m, 2 H), 4.77, 4.70 (2 d, *J* = 6.8 Hz, 2 H), 4.05 (dt, *J* = 8.3, 4.1 Hz, 1 H), 3.98 (dd, *J* = 8.3, 4.5 Hz, 1 H), 3.84–3.65 (m, 3 H), 3.43 (s, 3 H), 2.57 (br s, 1 H), 2.32–2.11 (m, 2 H), 1.80–1.59 (m, 2 H), 1.44 (s, 3 H), 1.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 115.1, 108.9, 97.0, 78.7, 77.3, 76.6, 62.6, 56.0, 29.9, 29.8, 27.1, 27.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{24}NaO_5$: 283.1521; found: 283.1518.

(4*R*,5*S*)-4-(Iodomethyl)-5-[(*R*)-1-(methoxymethoxy)pent-4-enyl]-2,2-dimethyl-1,3-dioxolane (7)

To a soln of **12** (0.4 g, 1.53 mmol) in anhyd toluene (20 mL) was added Ph_3P (1.2 g, 4.6 mmol), imidazole (0.31 g, 4.6 mmol), and I_2 (0.78 g, 3.1 mmol) at r.t. and the mixture was stirred under reflux for 4 h. When the reaction was complete (TLC), the mixture was cooled to r.t., poured into H_2O (10 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and sat. $Na_2S_2O_3$ (10 mL), dried (Na_2SO_4), and the solvent was evaporated. Column chromatography of the residue (silica gel, PE–Et_2O, 96:4) gave the iodide **7** (0.49 g, 86%) as a colorless oil.

$[\alpha]_D$ –14.2 (*c* 1, $CHCl_3$).

IR (neat): 2933, 1641, 1452, 1371, 1218, 1033, 917, 887, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddt, *J* = 16.7, 10.5, 6.7 Hz, 1 H), 5.14–5.00 (m, 2 H), 4.77, 4.72 (2 d, *J* = 6.8 Hz, 2 H), 4.01–3.85 (m, 2 H), 3.81–3.70 (m, 1 H), 3.47–3.40 (m, 1 H), 3.45 (s, 3 H), 3.32 (dd, *J* = 10.4, 4.9 Hz, 1 H), 2.30–2.14 (m, 2 H), 1.83–1.64 (m, 2 H), 1.50 (s, 3 H), 1.47 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 115.3, 109.4, 96.7, 82.0, 76.0, 75.7, 56.2, 30.1, 29.9, 27.5, 27.2, 7.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{23}INaO_4$: 393.0539; found: 393.0538.

(3*R*,4*R*)-4-(Methoxymethoxy)octa-1,7-dien-3-ol (6)

To a soln of iodide **7** (0.45 g, 1.21 mmol) in abs EtOH (20 mL) was added Zn dust (0.63 g, 9.7 mmol) at r.t. and the mixture was stirred at 80 °C for 5 h (TLC monitoring). When the reaction was complete, the mixture was filtered through a short pad of Celite and the Celite pad was washed with Et_2O (2 × 15 mL) and the solvent was evaporated. Column chromatography of the residue (silica gel, PE–EtOAc, 7:3) furnished **6** (0.21 g, 94%) as a colorless oil.

$[\alpha]_D$ –10.7 (*c* 1, $CHCl_3$).

IR (neat): 3460, 2931, 1641, 1443, 1215, 1033, 995, 918, 837 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.92–5.72 (m, 2 H), 5.40–5.19 (m, 2 H), 5.06–4.95 (m, 2 H), 4.74, 4.68 (2 d, *J* = 6.8 Hz, 2 H), 4.04 (t, *J* = 6.2 Hz, 1 H), 3.42 (s, 3 H), 3.25 (br s, 1 H), 2.26–2.05 (m, 2 H), 1.74–1.50 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.2, 116.9, 114.9, 97.4, 83.0, 74.7, 55.8, 30.4, 29.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{18}NaO_3$: 209.1154; found: 209.1155.

(3*R*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-4-(methoxymethoxy)octa-1,7-diene (13)

To a precooled (0 °C) soln of alcohol **6** (0.1 g, 0.53 mmol) in anhyd CH_2Cl_2 (2 mL) was added pyridine (0.11 mL, 1.3 mmol) and TBDMSOTf (0.15 mL, 0.63 mmol) and the mixture was stirred at 0 °C for 1 h. The mixture was then poured into H_2O (10 mL) and extracted with Et_2O (3 × 15 mL). Combined ethereal extracts were washed with brine (20 mL), dried (anhyd Na_2SO_4) and the solvent was evaporated. Column chromatography of the residue (silica gel, PE–EtOAc, 95:5) afforded **13** (0.15 g, 92%) as a colorless oil.

$[\alpha]_D$ +58.7 (*c* 1.1, $CHCl_3$).

IR (neat): 2954, 2932, 1641, 1472, 1254, 1136, 1034, 920, 862 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.93–5.85 (m, 1 H), 5.81 (ddt, *J* = 16.9, 10.4, 6.9 Hz, 1 H), 5.29–5.13 (m, 2 H), 5.05–4.92 (m, 2 H), 4.80, 4.65 (2 d, *J* = 6.7 Hz, 2 H), 4.24 (t, *J* = 5.2 Hz, 1 H), 3.51–3.40 (m, 1 H), 3.40 (s, 3 H), 2.24–2.17 (m, 1 H), 2.14–2.02 (m, 1 H), 1.73–1.60 (m, 1 H), 1.46–1.34 (m, 1 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 137.3, 115.7, 114.6, 97.4, 81.0, 74.7, 55.7, 30.0, 29.1, 25.8, 18.2, –4.7, –4.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{32}NaO_3Si$: 323.2018; found: 323.2022.

(3*R*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-4-(methoxymethoxy)cyclohex-1-ene (14)

To a soln of **13** (0.13 g, 0.43 mmol) in anhyd CH_2Cl_2 (10 mL) was added Grubbs 1st generation catalyst (36 mg, 0.043 mmol) under argon. The mixture was stirred at r.t. for 6 h until completion (TLC). The mixture was passed through a short pad of silica gel. The silica gel pad was washed with Et_2O (2 × 15 mL) and the solvent was evaporated. The crude residue was subjected to column chromatography (silica gel, PE–Et_2O, 9:1) to afford **14** (0.1 g, 84%) as a colorless oil.

$[\alpha]_D$ –51.0 (*c* 1, $CHCl_3$).

IR (neat): 2954, 2930, 1472, 1150, 1050, 921, 835 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.76–5.67 (m, 1 H), 5.56–5.47 (m, 1 H), 4.76, 4.70 (2 d, *J* = 6.7 Hz, 2 H), 4.18–4.08 (m, 1 H), 3.59 (ddd, *J* = 9.6, 6.1, 3.2 Hz, 1 H), 3.37 (s, 3 H), 2.16–2.04 (m, 2 H), 2.00–1.90 (m, 1 H), 1.72–1.58 (m, 1 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.0, 128.6, 96.2, 78.2, 71.2, 55.2, 25.9, 25.8, 23.8, 18.1, –4.6, –4.7.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{28}NaO_3Si$: 295.1705; found: 297.1700.

(1*S*,2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-4-(methoxymethoxy)cyclohexane-1,2-diol (15)

To a soln of **14** (0.08 g, 0.3 mmol) in THF (1.6 mL) and H_2O (0.4 mL) was added a 50% soln of NMO in H_2O (0.2 mL, 0.9 mmol) and OsO_4 (3 mg, 0.01 mmol) at 0 °C. The mixture was gradually warmed up to r.t. and stirred for 24 h. It was then quenched with sat. Na_2SO_3 soln (2 mL). EtOAc (2 mL) was then introduced and the resulting mixture was vigorously stirred at r.t. for 30 min and further extracted with EtOAc (3 × 10 mL). Combined organic layers were washed with brine (20 mL), dried (anhyd Na_2SO_4), and the solvent was evaporated. Column chromatography of the residue (silica gel, PE–EtOAc, 2:8) afforded **15** (0.084 g, 92%) as a colorless solid; mp 74–76 °C.

$[\alpha]_D$ +19.0 (*c* 1, $CHCl_3$).

IR (KBr): 3437, 2950, 1472, 1254, 1102, 1041, 963, 836, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.64 (s, 2 H), 3.93–3.78 (m, 2 H), 3.57–3.53 (br m, 1 H), 3.50–3.45 (br m, 1 H), 3.36 (s, 3 H), 1.90–1.65 (m, 3 H), 1.61–1.48 (m, 1 H), 0.86 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.0, 77.5, 74.8, 72.9, 68.1, 55.5, 25.7, 24.8, 24.3, 17.9, –4.7, –5.0.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{28}NaO_3Si$: 329.1760; found: 329.1758.

(1*S*,2*S*,3*S*,4*R*)-Cyclohexane-1,2,3,4-tetrol (Dihydroconduritol F, 1)

To a soln of **15** (50 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) at r.t. was added TFA (1 mL) and the mixture was stirred at r.t. for 2 h. When the reaction was complete (TLC), the volatiles were removed under reduced pressure. The residue thus obtained was triturated with Et_2O and the Et_2O was evaporated to furnish **1** (22 mg, 93%) as a thick viscous mass.

$[\alpha]_D$ +31.6 (*c* 0.6, H_2O) {Lit.[7] $[\alpha]_D$ +31 (*c* 0.7, H_2O)}.

IR (KBr): 3400, 2946, 2891, 1535, 1343, 1277, 1051, 985 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 3.94–3.89 (m, 1 H), 3.51 (t, *J* = 8.9 Hz, 1 H), 3.40–3.24 (m, 2 H), 1.83–1.60 (m, 3 H), 1.54–1.42 (m, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 75.1, 74.7, 72.8, 69.2, 26.8, 26.4.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_6H_{12}NaO_4$: 171.0633; found: 171.0627.

(3*S*,4*R*)-4-(Methoxymethoxy)-3-(4-nitrobenzoyl)octa-1,7-diene (16)

To a precooled (0 °C) soln of **6** (0.1 g, 0.53 mmol) in anhyd THF (5 mL) was added Ph_3P (0.28 g, 1.08 mmol) and 4-nitrobenzoic acid (0.18 g, 1.08 mmol) under argon and the mixture was stirred for 10 min. DIAD (0.16 mL, 0.8 mmol) was added over a period of 15 min at 0 °C and then the mixture was warmed up to r.t. and stirred for 1 h. When the reaction was complete (TLC), the volatiles were removed under reduced pressure and the crude residue obtained was purified by column chromatography (silica gel, PE–EtOAc, 9:1) to afford **16** (0.11 g, 60%) as a colorless oil.

$[\alpha]_D$ –14.0 (*c* 1, $CHCl_3$).

IR (neat): 2939, 1726, 1529, 1350, 1269, 1102, 916 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.8 Hz, 2 H), 8.23 (d, *J* = 8.8 Hz, 2 H), 6.02–5.88 (m, 1 H), 5.82 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1 H), 5.68 (dt, *J* = 6.4, 1.3 Hz, 1 H), 5.45–5.30 (m, 2 H), 5.12–4.95 (m, 2 H), 4.80, 4.67 (2 d, *J* = 6.9 Hz, 2 H), 3.85 (dt, *J* = 7.2, 3.8 Hz, 1 H), 3.37 (s, 3 H), 2.34–2.10 (m, 2 H), 1.81–1.65(m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 150.6, 137.8, 135.7, 132.0, 130.8, 123.6, 119.4, 115.4, 96.4, 77.9, 77.7, 56.0, 29.9, 29.8.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{21}NNaO_6$: 358.1267; found: 358.1275.

(3*S*,4*R*)-4-(Methoxymethoxy)-3-(4-nitrobenzoyl)cyclohex-1-ene (17)

To a stirred soln of **16** (90 mg, 0.26 mmol) in anhyd CH_2Cl_2 (5 mL) was added Grubbs 1st generation catalyst (22 mg, 10 mol%, 0.03 mmol) at r.t. and the mixture was stirred at r.t. for 2 h (TLC monitoring). It was then filtered through a short pad of silica gel and the silica gel pad washed with Et_2O (2 × 15 mL) and the solvent was evaporated. The residue was subjected to column chromatography (silica gel, PE–EtOAc, 8:2) to yield **17** (77 mg, 94%) as a colorless oil.

$[\alpha]_D$ +295 (*c* 0.4, $CHCl_3$).

IR (neat): 2939, 1721, 1607, 1528, 1347, 1272, 1105, 1032, 719 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 9.0 Hz, 2 H), 8.24 (d, *J* = 9.0 Hz, 2 H), 6.06 (dt, *J* = 9.8, 3.5 Hz, 1 H), 5.88–5.78 (m, 1 H), 5.68 (t, *J* = 4.4 Hz, 1 H), 4.74, 4.66 (2 d, *J* = 6.9 Hz, 2 H), 4.02 (dt, *J* = 10.8, 3.5 Hz, 1 H), 3.33 (s, 3 H), 2.44–2.30 (m, 1 H), 2.29–2.14 (m, 1 H), 2.10–2.00 (m, 1 H), 1.96–1.80 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 150.4, 135.9, 134.0, 130.7, 123.4, 122.9, 94.9, 72.3, 68.8, 55.5, 24.4, 23.9.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{17}NNaO_6$: 330.0954; found: 330.0949.

(1*R*,2*R*,1*S*,2*R*)-4-(Methoxymethoxy)-3-(4-nitrobenzoyl)cyclohexane-1,2-diol (18)

To a soln of **17** (65 mg, 0.21 mmol) in THF (1.6 mL) and H_2O (0.4 mL) was added a 50% soln of NMO in H_2O (0.15 mL, 0.63 mmol) and OsO_4 (3 mg, 0.01 mmol) at 0 °C. The mixture was gradually warmed up to r.t. and stirred for 24 h. When the reaction was complete (TLC), it was quenched by addition of sat. Na_2SO_3 (2 mL). The resulting mixture was vigorously stirred at r.t. with EtOAc (2 mL) for 30 min and further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anhyd Na_2SO_4), and the solvent was evaporated. Column chromatography of the residue (silica gel, PE–EtOAc, 3:7) afforded **18** (66 mg, 92%) as a colorless solid; mp 155–157 °C.

$[\alpha]_D$ –54.0 (*c* 0.5, EtOH).

IR (KBr): 3547, 3457, 2935, 2621, 1713, 1521, 1350, 1290, 1093, 1042, 872 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD): δ = 8.30 (d, *J* = 9.0 Hz, 2 H), 8.26 (d, *J* = 9.0 Hz, 2 H), 5.34 (dd, *J* = 8.0, 2.5 Hz, 1 H), 4.67, 4.63 (2 d, *J* = 6.8 Hz, 2 H), 4.23–4.15 (m, 1 H), 4.17–4.03 (m, 2 H), 3.30 (s, 3 H), 2.02–1.73 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD): δ = 164.5, 150.4, 135.5, 130.6, 123.4, 95.3, 75.3, 73.1, 69.7, 69.1, 55.3, 25.2, 23.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NNaO_8$: 364.1008; found: 364.1006.

(1*R*,2*R*,3*S*,4*R*)-4-(Methoxymethoxy)cyclohexane-1,2,3-triol

To a MeOH (20 mL) soln of **18** (50 mg, 0.14 mmol) was added K_2CO_3 (40 mg, 0.3 mmol) and the mixture was stirred at r.t. for 30 min. When the reaction was complete (TLC), the solvent was removed under reduced pressure and the residue obtained was purified by column chromatography (silica gel, EtOAc) to afford the product (25 mg, 90%) as a viscous mass.

$[\alpha]_D$ –16.0 (*c* 1, MeOH).

IR (KBr): 3423, 2925, 2853, 1452, 1150, 1076, 1033, 916 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD): δ = 4.53 (s, 2 H), 3.85 (br s, 1 H), 3.75 (br s, 1 H), 3.59 (dd, *J* = 8.6, 2.2 Hz, 1 H), 3.55 (dd, *J* = 8.6, 2.2 Hz, 1 H), 3.23 (s, 3 H), 1.68–1.45 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD): δ = 96.1, 76.7, 72.1, 71.1, 68.9, 55.2, 25.2, 23.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_8H_{16}NaO_5$: 215.0895; found: 215.0900.

(1*R*,2*R*,3*R*,4*R*)-Cyclohexane-1,2,3,4-tetrol (Dihydroconduritol E, 2)

To a soln of triol obtained above (22 mg, 0.11 mmol) in MeOH at r.t. was added Amberlyst-15 (100 mg) and the mixture was stirred for 4 h (TLC monitoring). When the reaction was complete, it was filtered and concentrated under reduced pressure to afford **2** (15 mg, 88%) as a viscous mass.

$[\alpha]_D$ –35.5 (*c* 0.9, MeOH).

IR (KBr): 3410, 2909, 1455, 1211, 1080, 898, 847 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD, $CDCl_3$): δ = 3.95 (br s, 4 H), 3.70 (br s, 4 H), 1.82–1.70 (m, 2 H), 1.69–1.55 (m, 2 H).

^{13}C NMR (125 MHz, CD_3OD, $CDCl_3$): δ = 71.4, 68.6, 24.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_6H_{12}NaO_4$: 171.0633; found: 171.0639.

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(14) Stereochemistry of **18** was further proved by X-ray crystal structure analysis. (The crystallographic data has been deposited with The Cambridge Crystallographic Data Centre, CCDC687686). This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data request/cif.