Facile Enantiospecific Synthesis of Dihydroconduritols E and F

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Received 15 May 2008

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. 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. Considerable effort from a number of synthetic groups has been directed towards the asymmetric synthesis of conduritols including constrained analogues (Figure 1). While racemic synthesis of these compounds is reported either by oxidation of cyclohexadienes, or by the reduction of the epoxy peroxides derived from cyclohexadienes, 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, ring opening of chiral oxabicycles, stereoselective oxyxyleneolation of cyclohexenyl ethers, and the chemoenzymatic synthesis reported by Hudlicky et al. 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 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, resulting in the γ-oxobutyramide 10 in 90% yield. Stereoselective reduction of the keto group in 10 with K-Selectride furnished alcohol 8.

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 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 (Scheme 3).

SYNTHESIS 2008, No. 19, pp 3155–3159
Advanced online publication: 05.09.2008
DOI: 10.1055/s-2008-1067261; Art ID: C03308SS
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After successfully accomplishing the synthesis of dihydroconduritol F (1), synthesis of dihydroconduritol E (2), was undertaken. Thus, the reaction of 6 under Mitsunobu conditions 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). 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.

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 I2 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.

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

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 solution was cooled to −15 °C and 1 M but-3-enylmagnesium bromide in THF (3 mL, 0.5 mmol) was added dropwise under argon. The mixture was stirred for 30 min, quenched with sat. NH4Cl (3 mL) and extracted with EtOAc (2 × 15 mL). The combined ethereal layers were washed with brine, dried (Na2SO4), 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. 

$\delta_{D}=+4.4$ (c 3.6, CHCl3).

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

$\delta_{H}$ NMR (300 MHz, CDCl3): $\delta = 5.82$ (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).

$\delta_{C}$ NMR (75 MHz, CDCl3): $\delta = 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.

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 H₂O (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, PE–EtOAc, 7:3) to give 1 (0.6 g, 86%) 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 CHCl₃ (15 mL) at 0 °C were added DPEA (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 H₂O (15 mL), and extracted with Et₂O (3 × 25 mL). The combined ethereal extracts were washed with brine (30 mL), dried (Na₂SO₄), 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.

IR (neat): 3488, 2931, 1641, 1442, 1379, 1250, 1034, 916, 883, 740 cm⁻¹.


SPECIAL TOPIC

Facile Synthesis of Dihydroconudoriluts E and F: 3157
(3R,4R)-3-(tert-Butyldimethylsiloxy)-4-(methoxymethoxy)cyclohex-1-ene (14)

To a solution of 13 (0.13 g, 0.43 mmol) in anhyd CH₂Cl₂ (10 mL) was added Grubbs 1st generation catalyst (36 mg, 0.043 mmol) under argon. The mixture was stirred at rt for 6 h until completion (TLC). The mixture was passed through a short pad of silica gel. The silica gel pad was washed with Et₂O (2 × 15 mL) and the solvent was evaporated. The crude residue was subjected to column chromatography (silica gel, PE–Et₂O, 9:1) to afford 14 (0.1 g, 84%) as a colorless oil.

\[ \delta_{\mathrm{H}} = \begin{cases} 5.76–5.67 (m, 1 H), 5.56–5.47 (m, 1 H), 4.76, 4.70 (2 d, J = 6.7 H z, 2 H), 4.18–4.08 (m, 2 H), 3.59 (dd, J = 9.6, 6.1, 3.2 H z, 1 H), 3.37 (s, 3 H), 2.16–2.04 (m, 2 H), 2.00–1.90 (m, 1 H), 1.72–1.58 (m, 1 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H). \end{cases} \]

IR (KBr): 3437, 2950, 1472, 1452, 1102, 1041, 963, 872 cm⁻¹.

HRMS: \[ m/z + 295 (c 0.4, \text{CHCl}_3). \]

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

To a solution of 14 (0.08 g, 0.3 mmol) in THF (1.6 mL) and H₂O (0.4 mL) was added a 50% solution of NMO in H₂O (0.2 mL, 0.9 mmol) and OsO₄ (0.01 mmol) at 0 °C. The mixture was gradually warmed up to rt and stirred for 24 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 15 (0.18 g, 1.08 mmol) as a colorless solid; mp 155–157 °C.

\[ \delta_{\mathrm{H}} = \begin{cases} 5.68 (dt, J = 9.0, 3.5 H z, 2 H), 6.06 (dt, J = 9.8, 3.5 H z, 1 H), 5.88–5.78 (m, 1 H), 5.68 (t, J = 4.4 H z, 1 H), 4.74, 4.66 (2 d, J = 6.9 H z, 2 H), 4.02 (dt, J = 10.8, 3.5 H z, 1 H), 3.33 (s, 3 H), 2.48–2.30 (m, 1 H), 2.29–2.14 (m, 1 H), 2.10–2.00 (m, 1 H), 1.96–1.80 (m, 1 H). \end{cases} \]

IR (neat): 2939, 1721, 1607, 1528, 1472, 1272, 1105, 1032, 719 cm⁻¹.

HRMS: \[ m/z + 295 (c 0.4, \text{CHCl}_3). \]

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

To a stirred solution of 16 (90 mg, 0.26 mmol) in anhyd CH₂Cl₂ (5 mL) was added Grubbs 1st generation catalyst (22 mg, 10 mol%, 0.03 mmol) at rt and the mixture was stirred at rt for 2 h (TLC monitoring). The resulting mixture was vigorously stirred at rt for 30 min and further extracted with EtOAc (3 × 10 mL). Combined organic layers were washed with brine (20 mL), dried (anhyd Na₂SO₄), and the solvent was evaporated. Column chromatography of the residue (silica gel, PE–EtOAc, 2:8) afforded 17 (77 mg, 94%) as a colorless oil.

\[ \delta_{\mathrm{H}} = \begin{cases} 5.82 (d, J = 8.8 H z, 2 H), 6.02–5.88 (m, 1 H), 5.82 (ddt, J = 16.8, 10.2, 6.6 H z, 1 H), 5.68 (dt, J = 6.4, 1.3 H z, 1 H), 5.45–5.30 (m, 2 H), 5.12–4.95 (m, 2 H), 4.80, 4.67 (2 d, J = 6.9 H z, 2 H), 3.85 (dt, J = 7.2, 3.8 H z, 1 H), 3.37 (s, 3 H), 2.34–2.10 (m, 2 H), 1.81–1.65 (m, 2 H). \end{cases} \]

IR (KBr): 3547, 3457, 2935, 2621, 1713, 1521, 1350, 1290, 1093, 963, 872 cm⁻¹.

HRMS: \[ m/z + 295 (c 0.4, \text{CHCl}_3). \]
References


(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.