A Synthesis of Naturally Occurring (1S,2S,3R)-4-Hydroxymethylcyclopent-4-ene-1,2,3-triol Utilizing the Cyclization of a Dioxolanyl Radical

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Dedicated to Professor Gilbert Stork in recognition of his significant contributions to the art of organic synthesis.

Abstract: A radical cyclization is employed in the synthesis of a biosynthetic precursor of aristeromycin and neplanocin A. A derivative of L-tartaric acid is used as both the source of chirality and the carbon radical.

We recently described the cyclization of a dioxolanyl radical into the indole nucleus as a novel method for the synthesis of chiral, oxygenated perhydro-3H-pyrrolo[1,2a]indoles.1 Central to this methodology was the utilization of methyl 2,3-O-isopropylidene-L-threonate (3a)2 as the asymmetric template that also contained the latent radical center. This strategy was considered directly amenable to the preparation of a number of naturally occurring hydroxylated cyclopentanoids. In this Letter, we describe the synthesis of one of these substances by the dioxolanyl radical method.

Turner, et al. have demonstrated the ability of a non-aristeromycin producing mutant strain of Streptomyces cattlicolor to support production of both aristeromycin (2a) and neplanocin A3 (2b) when provided with metabolite 1, itself isolated from a related mutant of the same organism.4 Owing to its central role in the production of these nuclosides, tetraol 1 was chosen as a synthetic target.

Swern oxidation5 of threonate 3a provided the corresponding aldehyde ester 3b.6 This substance failed to exhibit the expected aldehyde proton resonance in its 1H NMR spectrum although GC/MS analysis (EI) was consistent with the desired product 3b. Working upon the assumption that the substance was present as a carbonyl oligomer, treatment of the material with an excess of propargyl zinc bromide7 provided a 2:3:1 diastereomeric mixture of acetylenes 4 (Scheme I). Silylation of the hydroxyl group with TBSOTf and subsequent saponification of the ester group gave rise to the carboxylic acids 5 in 74% overall yield from hydroxy ester 3a.

Attempts to prepare the allenic analog of 4 were unsuccessful because isomerization to the acetylene was unavoidable. For example, zinc bromide-mediated condensation of 3b with propargyl triphenylstannane8 gave a mixture of allenyl alcohols 7 and propargyl alcohols 4 which, when chromatographed on Florisil, afforded 4 exclusively. Conversely, the oxidation of 4 with Dess-Martin periodinane9 provided only allenic ketone 6, whose instability to alkali precluded its use in subsequent radical cyclizations.

Transformation of carboxylic acids 5 to the thiohydroxamate esters 8a or 8b was accomplished as described by Barton (Scheme II).10 Both derivatives proved suitable for the formation of methylene cyclopentane 9a; however, the conversion 5 → 9a via 8a was conveniently performed in a one-flask operation; it is the method of choice for larger scale reactions. Formation of 9a from thiohydroxamate 8a was achieved by visible light photolysis as tributyltin hydride was introduced slowly during the early phase of the photolysis. Alternatively, thiohydroxamate 8b was conveniently converted to 9a in refluxing xylene in the presence of tris(trimethylsilyl)silane.11 That tris(trimethylsilyl)silane proved superior to tributyltin hydride in the thermal reaction is in accord with

Earlier observations of Giese12,13 and consistent with a higher homolytic bond dissociation energy (79 kcal mol⁻¹) and decreased second order rate constant for hydrogen abstraction by RCH2⁺ (3.8 × 10⁵ M⁻¹ s⁻¹ at 25°C) for (TMS)3SiH versus 74 kcal mol⁻¹ and 2.3 × 10⁶ M⁻¹ s⁻¹, respectively, for n-Bu3SnH.14 The overall, isolated yield of methylene cyclopentane 9a from carboxylic acids 5 ranged from 55-65% following chromatography on silica gel.15

The mixture of silyl ethers 9a was converted to tetraol 1 in a straightforward manner (Scheme III). Although the diastereomers of 9a were separated for characterization and independently converted to tetraol 1, this exercise was not necessary from the synthetic perspective. Desilylation of 9a with TBAF/THF and subsequent epoxidation of the exocyclic olefin with freshly prepared dimethyldioxirane solution16 provided epoxy alcohols 10 in high yield. Each of these epoxides, which were prepared independently from

![Chemical Structure](image-url)
Reagents and Conditions: h) TBAF, THF; 0°C (90-92%). i) dimethylformamide (3:4 equiv.) aq. acetic acid; rt (88%). j) Dess-Martin periodinane (1.3 equiv.), CH₂Cl₂, rt (88%). k) NaBH₄, CeCl₃, H₂O, MeOH, rt (80%). l) aq. HCl/THF; rt (83%). m) AAO, pyr., CH₂Cl₂ (79%).

SCHEME III

The separated olefins 9b, was presumed to have undergone selective epoxidation from the convex face. Oxidation of epoxy alcohol 10 with Dess-Martin periodinane provided the expected epoxy ketone, which was efficiently rearranged to enone 11 upon silica gel chromatography. Luche reduction from the convex face of enone 11 and hydrolysis of the isopropylidene ketal afforded a single diastereomer of (1S,2S,3R)-4-hydroxymethylcyclopent-4-ene-1,2,3-triol (1). The derived tetraacetate 12 displayed 1H NMR, 13C NMR, and mass spectral data in agreement with that reported.4,18

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References and Notes

(13) For a review on hydroxilanes as radical reducing agents, see Chatgilialoglu, C. Acc. Chem. Res. 1992, 25, 188.
(15) A representative procedure for the conversion of 5 to 9a and 9b is as follows: Carboxylic acid 5 (547 mg, 1.67 mmol) and 2,2'-dithiobis(pyridine N-oxide) (463 mg, 1.84 mmol) were dissolved in 9.3 mL dry THF under N₂ and the suspension was cooled in an ice bath. Bu₂SnH (0.46 mL, 1.84 mmol) was added dropwise and the mixture was stirred in the dark at room temperature for 40 min. The solution was diluted with THF (7.7 mL) and irradiation was begun (500 W tungsten filament and 300 W flood lamp) as nBu₂SnH (0.54 mL, 2.0 mmol) in THF (15.3 mL) was added over 15 min via a syringe pump. The resulting solution was photolyzed another 10 min, cooled to room temperature, and the solvent removed in vacuo. Flash chromatography (15% EtOAc/hexanes) provides an impure mixture of cyclopenenesa (321 mg). Subsequent chromatography (30:67:3 CHCl₃/cyclohexane/Et₂O) provides pure 9a (minor diastereomer, 84 mg, 18%) and a mixture containing (1H NMR integration) 9a (major diastereomer, 202 mg, 42%) along with reduced, uncyclized material, (24 mg, 5%). 9a (minor): 1H NMR (300 MHz, CDCl₃) 5 5.26 (1H, d, J = 1.9 Hz, vinyl), 5.13 (1H, d, J = 1.3 Hz, vinyl), 4.83 (1H, d, J = 5.7 Hz), 4.37 (1H, d, J = 5.7 Hz), 4.16 (1H, d, J = 4.5 Hz, R₂CHOTBS), 2.80-2.74 (1H, m), 2.14 (1H, d, J = 15.5 Hz), 1.45 (3H, s), 1.33 (3H, s), 0.87 (9H, s); 13C NMR (75 MHz, CDCl₃) 148.5, 113.1, 110.8, 86.8, 81.5, 75.2, 39.0, 26.6, 26.0, 24.4, 18.1, -4.7 ppm.; IR (CHCl₃) 2955, 2951, 2857, 1374, 1257 cm⁻¹; LRMS (EI, M⁺-CH₃ = 269). Following removal of the TBS group, the major diastereomer 9a could be obtained in pure form as the free alcohol. 9b (major): m.p. 171°C (pentane); 1H NMR (300 MHz, CDCl₃) δ 5.21 (1H, s, vinyl), 5.14 (1H, s, vinyl), 4.72 (1H, d, J = 5.7 Hz, ROCH-C=CH₂), 4.56 (1H, t, J = 5.6 Hz), 3.96-3.88 (1H, m), 2.55-2.41 (3H, m, -CH₂- + OH), 1.52 (3H, s), 1.39 (3H, s); 13C NMR (75 MHz, CDCl₃) 144.3, 114.3, 111.6, 81.4, 79.2, 71.0, 38.1, 26.1, 24.4 ppm.; IR (CHCl₃) 3570, 3015, 2993, 2938 cm⁻¹; LRMS(EI) (M⁺-CH₃ = 155); Anal. Calcd. for C₉H₁₆O₂: C, 53.51; H, 8.29. Found: C, 63.77; H, 8.32.
(20) A discrepancy between the optical rotation we observed, [α]D¹⁹ = +47.5° (c=1.2, CHCl₃), and that reported for tetra-acetate 12, [α]D²⁴ = +89.8° (c=0.84, CHCl₃), is ref. 4 exists. Professor Turner has informed us that their value may be too large.