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

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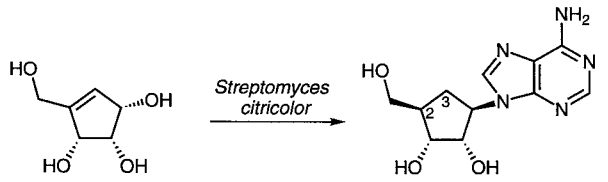
Dedicated to Professor Gilbert Stork in recognition of his significant contributions to the art of organic synthesis.

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 citricolor* to support production of both aristeromycin (**2a**) and neplanocin A[3] (**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 nucleosides, tetraol **1** was chosen as a synthetic target.



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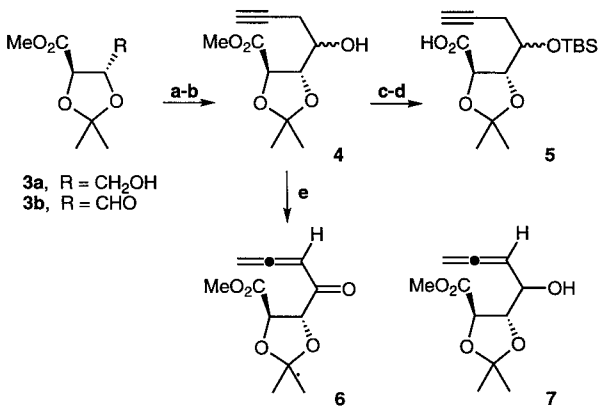
2a, Aristeromycin
2b, 2,3-dehydro; Neplanocin A

Swern oxidation[5] of threonate **3a** provided the corresponding aldehydo ester **3b**.[6] This substance failed to exhibit the expected aldehyde proton resonance in its ^{1}H 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 bromide[7] 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**.

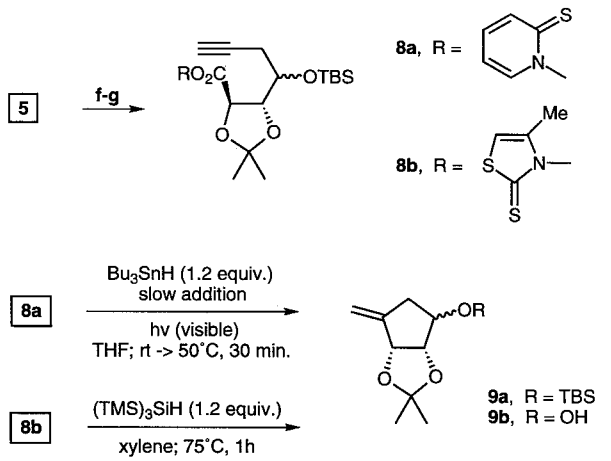
Attempts to prepare the allenic analog of **4** were unsuccessful because isomerization to the acetylene was unavoidable. For example, zinc bromide-mediated condensation of **3b** with propargyl triphenylstannane[8] gave a mixture of allenyl alcohols **7** and propargyl alcohols **4** which, when chromatographed on Florisil, afforded **4** exclusively. Conversely, the oxidation of **4** with Dess-Martin periodinane[9] 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



Reagents and Conditions: **a**) $(COCl)_2$, DMSO, Et_3N; -78°C. **b**) propargyl bromide, Zn/Hg, THF; rt. **c**) TBSOTf, pyr., CH_2Cl_2; 0°C (74% from **3a**). **d**) LiOH, aq. THF; rt (quant.) **e**) Dess-Martin periodinane, CH_2Cl_2; rt (90%).

SCHEME I

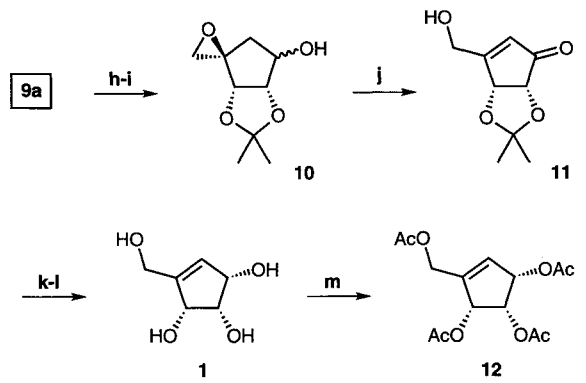


Reagents and Conditions: For **8a**: **f**) 2,2'-dithiobis(pyridine N-oxide), Bu_3P, THF; 0°C -> rt, 30 min. For **8b**: **g**) i. $ClCO_2Bu^i$, N-methylmorpholine, THF; -23°C. ii. N-hydroxy-4-methylthiazole-2(3H)-thione, pyr.; -23°C -> rt, 40 min.

SCHEME II

earlier observations of Giese[12,13] and consistent with a higher homolytic bond dissociation energy (79 kcal mol^{-1}) and decreased second order rate constant for hydrogen abstraction by $RCH_2^\bullet$ (3.8 x 10^5 M^{-1} s^{-1} at 25°C) for $(TMS)_3SiH$ vs. 74 kcal mol^{-1} and 2.3 x 10^6 M^{-1} s^{-1}, respectively, for n-Bu_3SnH.[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 solution[16] provided epoxy alcohols **10** in high yield. Each of these epoxides, which were prepared independently from



Reagents and Conditions: **h)** TBAF, THF; 0°C (90-92%). **i)** dimethyldioxirane (3-4 equiv.) aq. acetone; rt (88%). **j)** Dess-Martin periodinane (1.3 equiv.), CH_2Cl_2; rt (89%). **k)** $NaBH_4$, $CeCl_3.6H_2O$, MeOH; rt (86%). **l)** aq. HCl / THF; rt (83%). **m)** Ac_2O, pyr., CH_2Cl_2 (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[9] provided the expected epoxy ketone, which was efficiently rearranged to enone **11** upon silica gel chromatography. Luche reduction[17] 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 tetra-acetate **12** displayed ^1H NMR, ^{13}C NMR, and mass spectral data in agreement with that reported.[4,18]

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(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 N_2 and the suspension was cooled in an ice bath. Bu_3P (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 nBu_3SnH (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 cyclopentenes **9a** (321 mg). Subsequent chromatography (30:63:7 $CHCl_3$/cyclohexane/Et_2O) 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, $CDCl_3$) δ 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, $R_2CHOTBS$), 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), 0.08 (3H, s), 0.07 (3H, s) ; ^{13}C NMR (75 MHz, $CDCl_3$) 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 ($CHCl_3$) 2955, 2931, 2857, 1374, 1257 cm^{-1}; LRMS (EI, M+ -CH_3 = 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. 71°C (pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.21 (1H, s, vinyl), 5.14 (1H, s, vinyl), 4.72 (1H, d, J = 5.7 Hz, ROC*H*-CR=CH_2), 4.56 (1H, app. t, J = 5.6 Hz), 3.96-3.88 (1H, m), 2.55-2.41 (3H, m, -CH_2- + OH), 1.52 (3H, s), 1.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 144.3, 114.3, 111.6, 81.4, 79.2, 71.0, 38.1, 26.1, 24.4 ppm.; IR ($CHCl_3$) 3570, 3015, 2993, 2938 cm^{-1}; LRMS(EI) (M+ -CH_3 = 155); Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found : C, 63.77; H, 8.32.
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