

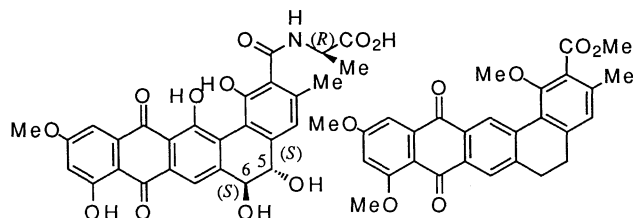
Synthesis of an Optically Active α -Tetralone: A Key Intermediate to Natural Benanomycinone

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An optically active dihydroxy- α -tetralone was synthesized from methyl α -D-xylopyranoside *via* dimethyl (2*R*,3*S*)-dihydroxyglutarate. This α -tetralone is a key intermediate to construct the natural benanomycinone.

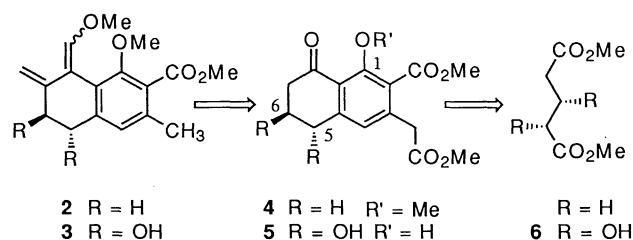
In our synthetic approach toward benanomycin A,¹ we reported the general synthesis of the substituted 5,6-dihydrobenzo[*a*]naphthacenequinone (**1**), an analog of benanomycinone,



Benanomycinone

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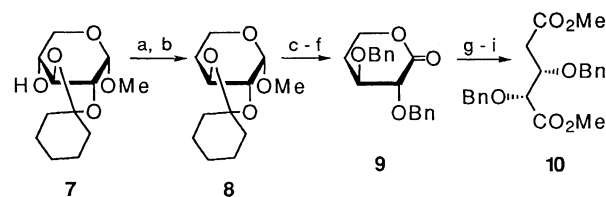
using Diels-Alder reaction of **2** derived from **4** with 2-chloro-5,7-dimethoxynaphthoquinone in a good yield.² This strategy promises to provide an optically active 5,6-dihydroxy-5,6-dihydrobenzo[*a*]naphthacenequinone by the use of **3** instead of **2** (Scheme 1). Introduction of the two chiral centers on C-5 and C-6 positions is the critical step in the synthesis of the natural benanomycinone. We report here the regio- and stereoselective synthesis of the optically active dihydroxy- α -tetralone (**5**), which is a precursor of **3**, from methyl α -D-xylopyranoside *via* dimethyl (2*R*,3*S*)-dihydroxyglutarate (**6**).



Scheme 1.

The starting methyl 2,3-*O*-cyclohexylidene- α -D-xylopyranoside (**7**),³ derived from methyl α -D-xylopyranoside by selective acetal exchange reaction with 1,1-dimethoxycyclohexane, was treated with sulfuryl chloride in pyridine and tributylstannane in the presence of AIBN to afford the 4-deoxy glycoside (**8**). Removal of acetal of **8** with 1 M HCl in dioxane followed by benzylation with benzyl bromide and sodium hydride gave di-*O*-benzyl ether, which was hydrolyzed with 1 M

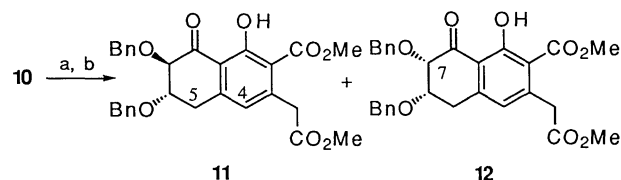
HCl at 100 °C and oxidized with PDC to give the dibenzoyloxy- δ -lactone (**9**). [α]_D²⁵ +85.0° (*c* 0.8, CH₂Cl₂). Sequential treatment of **9** with *p*-toluenesulfonic acid in MeOH and PDC in CH₂Cl₂ followed by PDC-MeOH in DMF provided dimethyl (2*R*,3*S*)-2,3-dibenzoyloxyglutarate (**10**).⁴ [α]_D²⁵ +24.5° (*c* 0.8, CH₂Cl₂) (Scheme 2).



a) SO₂Cl₂, pyridine (50%); b) Bu₃SnH, AIBN, toluene (99%); c) 1 M HCl, dioxane, r. t. (100%); d) BnBr, NaH, DMF (83%); e) 1 M HCl, dioxane, 100 °C; f) PDC, CH₂Cl₂ (58% in two steps); g) *p*-TSA, MeOH (83%); h) PDC, CH₂Cl₂ (73%); i) PDC, MeOH, DMF (66%).

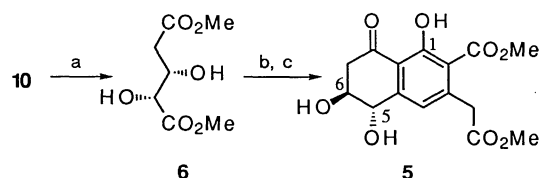
Scheme 2.

The dual Claisen condensation was employed to yield **5**. The dibenzoyloxyglutarate **10** was condensed with methyl acetoacetate by Yamaguchi's method⁵ to provide an undesired α -tetralone (**11**, 20%)⁴ along with a 7-epimer (**12**, 8%)⁶ (Scheme 3). The clear observation of NOE between 4-H and 5-H₂ confirmed the structure of **11**.



a) Methyl acetoacetate, NaH, BuLi, THF; b) Ca(OAc)₂, MeOH, reflux.

Scheme 3.



a) 1,4-Cyclohexadiene, Pd(OH)₂, EtOH; b) Methyl acetoacetate, NaH, BuLi, THF; c) Ca(OAc)₂, MeOH, reflux.

Scheme 4.

When dimethyl (2*R*,3*S*)-2,3-dihydroxyglutarate (**6**),⁴ [α]_D²⁵ -17.5° (*c* 1, CHCl₃), derived from **10** by de-*O*-benzylation with Pd(OH)₂ and 1,4-cyclohexadiene in EtOH was treated with

methyl acetoacetate in the same manner as **10**, the desired α -tetralone **5**,⁴ $[\alpha]_D^{25} +8.9^\circ$ (c 1, CHCl₃), was obtained as a sole product even in 11% yield (Scheme 4). The structure of **5** was fully assigned by NMR experiments. The cross peak between 4-H (δ 7.16) and C-5 (δ 72.8) was observed in HMBC spectrum of **5**. The coupling constant between 5- and 6-H ($J_{5,6} = 8.9$ Hz) revealed that the stereochemistry of **6** has been retained in **5**. The regioselectivity of the condensation has been explained in the literature.⁶ We have had a key intermediate for the synthesis of benanomycinone in hand.

In order to obtain a large quantity of **5**, improvement of the yield of the dual Claisen condensation is under investigation.

References and Notes

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- 2 S. Hirose, T. Nishizuka, S. Kondo, and D. Ikeda, *Chem. Lett.*, **1997**, 305.
- 3 F. H. Bissett, M. E. Evans, and F. W. Parrish, *Carbohydr. Res.*, **5**, 184 (1967).
- 4 **10**: FABMS m/z 373 (MH⁺). ¹H NMR (CDCl₃) δ 2.67 (1H, dd, $J=16.1$ and 7.3 Hz, 4-H), 2.74 (1H, dd, $J=16.6$ and 6.4 Hz, 4-H), 3.59 (3H, s, CO₂CH₃), 3.76 (3H, s, CO₂CH₃), 4.15 (1H, d, $J=3.9$ Hz, 2-H), and 4.30 (1H, m, 3-H). **6**: FAB-MS m/z 193 (MH⁺). ¹H NMR (CDCl₃) δ 2.63 (1H, dd, $J=16.6$ and 4.4 Hz, 4-H), 2.75 (1H, dd, $J=16.1$ and 8.3 Hz, 4-H), 3.02 (1H, d, $J=4.4$ Hz, 3-OH), 3.09 (1H, d, $J=5.9$ Hz, 2-OH), 3.72 (3H, s, CO₂CH₃), 3.85 (3H, s, CO₂CH₃), 4.15 (1H, broad dd, 2-H), and 4.40 (1H, m, 3-H). **11**: FABMS m/z 505 (MH⁺). ¹H NMR (CDCl₃) δ 2.99 (1H, dd, $J=17.1$ and 8.3 Hz, 5-H), 3.31 (1H, dd, $J=17.1$ and 3.9 Hz, 5-H), 3.69 (3H, s, CO₂-CH₃), 3.71 (2H, s, CH₂CO₂), 3.91 (3H, s, CO₂CH₃), 4.05 (1H, m, 6-H), 4.15 (1H, d, $J=7.8$ Hz, 7-H), 6.94 (1H, s, 4-H), and 12.59 (1H, s, hydrogen-bonded 1-OH). **5**: FABMS m/z 325 (MH⁺) and 347 (MNa⁺). ¹H NMR (CDCl₃ and a drop of CD₃OD) δ 2.72 (1H, dd, $J=17.8$ and 11.1 Hz, 7-H), 3.11 (1H, dd, $J=17.8$ and 4.4 Hz, 7-H), 3.71 (3H, s, CO₂CH₃), 3.77 (2H, s, CH₂CO₂), 3.92 (3H, s, CO₂CH₃), 4.01 (1H, ddd, $J=11.1$, 8.9 , and 4.4 Hz, 6-H), 4.60 (1H, d, $J=8.9$ Hz, 5-H), and 7.16 (1H, s, 4-H). ¹³C NMR (CDCl₃ and a drop of CD₃OD) δ 39.8 (CH₂CO₂), 44.2 (C-7), 52.3 (ester CH₃ x 2), 70.5 (C-6), 72.8 (C-5), 114.8 (C-8a), 119.7 (C-4), 121.5 (C-2), 141.7 (C-3), 146.4 (C-4a), 160.0 (C-1), 166.6 (CO₂), 170.8 (CH₂CO₂), and 201.8 (C-8).
- 5 M. Yamaguchi, K. Hasebe, H. Higashi, M. Uchida, A. Irie, and T. Minami, *J. Org. Chem.*, **55**, 1611 (1990).
- 6 Compound **12** was characterized after 1-*O*-methylation with MeI and Ag₂O in benzene. ¹H NMR (CDCl₃) δ 3.14 (1H, dd, $J=18.2$ and 3.6 Hz, 5-H), 3.32 (1H, dd, $J=18.2$ and 5.4 Hz, 5-H), 3.64 (2H, ABq, $J=12$ Hz, CH₂CO₂), 3.69 (3H, s, CO₂CH₃), 3.89 and 3.90 (each 3H, OCH₃), 4.19 (1H, m, 6-H), 4.26 (1H, d, $J=2.2$ Hz, 7-H), and 6.94 (1H, s, 4-H).