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

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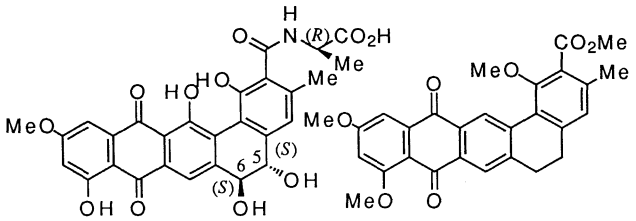
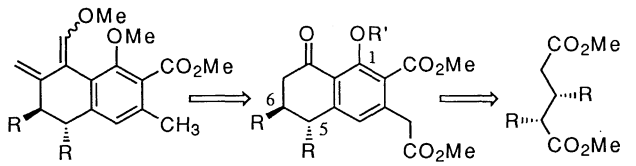
An optically active dihydroxy-α-tetralone was synthesized from methyl α-D-xylopyranoside *via* dimethyl (2*R*,3*S*)-dihydroxyglutarate. This α-tetralone is a key intermediate to construct the natural benanomicinone.

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



Benanomicinone **1**

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 benanomicinone. 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**).



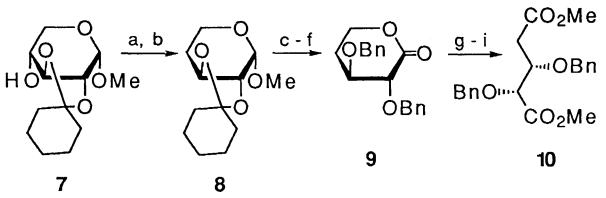
2 R = H
3 R = OH

4 R = H R' = Me
5 R = OH R' = H

R = H
6 R = OH

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 dibenzyloxy-δ-lactone (**9**). $[\alpha]_D^{22}$ +85.0° (*c* 0.8, CH_2Cl_2). Sequential treatment of **9** with *p*-toluenesulfonic acid in MeOH and PDC in CH_2Cl_2 followed by PDC-MeOH in DMF provided dimethyl (2*R*,3*S*)-2,3-dibenzyloxyglutarate (**10**).[4] $[\alpha]_D^{22}$ +24.5° (*c* 0.8, CH_2Cl_2) (Scheme 2).

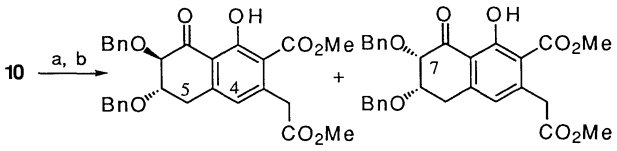


7 **8** **9** **10**

a) SO_2Cl_2, pyridine (50%); b) Bu_3SnH, 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, CH_2Cl_2 (58% in two steps); g) *p*-TSA, MeOH (83%); h) PDC, CH_2Cl_2 (73%); i) PDC, MeOH, DMF (66%).

Scheme 2.

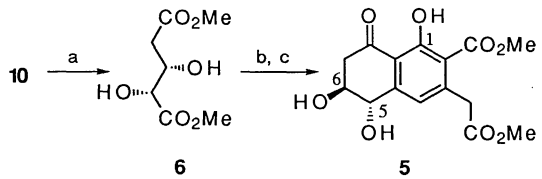
The dual Claisen condensation was employed to yield **5**. The dibenzyloxyglutarate **10** was condensed with methyl acetoacetate by Yamaguchi's method[5] to provide an undesired α-tetralone (**11**, 20%)[4] along with a 7-epimer (**12**, 8%)[6] (Scheme 3). The clear observation of NOE between 4-H and 5-H_2 confirmed the structure of **11**.



11 **12**

a) Methyl acetoacetate, NaH, BuLi, THF; b) $Ca(OAc)_2$, MeOH, reflux.

Scheme 3.



6 **5**

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] $[\alpha]_D^{25}$ -17.5° (*c* 1, $CHCl_3$), 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° (*c* 1, $CHCl_3$), 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 benanomicinone 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

1 T. Takeuchi, T. Hara, H. Naganawa, M. Okada, M. Hamada, H. Umezawa, S. Gomi, M. Sezaki, and S. Kondo, *J. Antibiotics*, **41**, 807 (1988).

2 S. Hirosawa, 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 ($CDCl_3$) 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, CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 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 ($CDCl_3$) 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, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.15 (1H, broad dd, 2-H), and 4.40 (1H, m, 3-H). **11**: FABMS *m/z* 505 (MH^+). ^1H NMR ($CDCl_3$) 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, CO_2-CH_3), 3.71 (2H, s, CH_2CO_2), 3.91 (3H, s, CO_2CH_3), 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 ($CDCl_3$ and a drop of CD_3OD) 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, CO_2CH_3), 3.77 (2H, s, CH_2CO_2), 3.92 (3H, s, CO_2CH_3), 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). ^{13}C NMR ($CDCl_3$ and a drop of CD_3OD) δ 39.8 (CH_2CO_2), 44.2 (C-7), 52.3 (ester CH_3 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 (CO_2), 170.8 (CH_2CO_2), 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 Ag_2O in benzene. ^1H NMR ($CDCl_3$) 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, CH_2CO_2), 3.69 (3H, s, CO_2CH_3), 3.89 and 3.90 (each 3H, OCH_3), 4.19 (1H, m, 6-H), 4.26 (1H, d, *J*=2.2 Hz, 7-H), and 6.94 (1H, s, 4-H).