Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 8101-8104, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10119-8

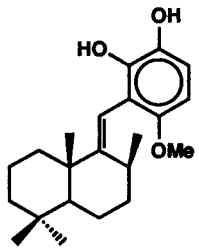
Enantiospecific Synthesis of Wiedendiol-B from (-)-Sclareol and (+)-*cis*-Abienol

Alejandro F. Barrero,* Enrique J. Alvarez-Manzaneda and Rachid Chahboun

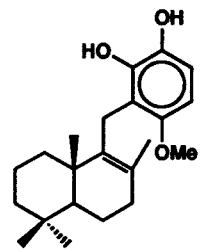
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada (Spain)

Abstract: The first enantiospecific synthesis of the cholesteryl ester transfer protein (CETP) inhibitor wiedendiol-B (**1**) is described. The drimanic synthon was prepared from (-)-sclareol (**4**) and (+)-cis-abienol (**13**) by two alternative routes. The key steps of the reaction sequences are the chemo- and diastereoselective hydrogenation of the C_8-C_9 double bond of enal **6** and the stereoselective cationic hydrogenation of the hydroxyl group of **13**, respectively, and the selective reduction of benzyl groups of **15**. © 1997 Elsevier Science Ltd.

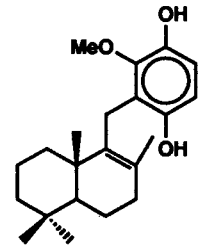
Merosesquiterpenes wiedendiol-A (**2**) and wiedendiol-B (**1**), isolated from the marine sponge *Xestospongia wiedenmayeri*,[1] inhibit the cholesteryl ester transfer protein (CETP)[2] and may find utility as antiatherosclerosis therapy. The synthesis of **2** from (+)-sclareolide has been reported recently. **2** was obtained along a high proportion of the isomeric compound **3**.[3]



1



2

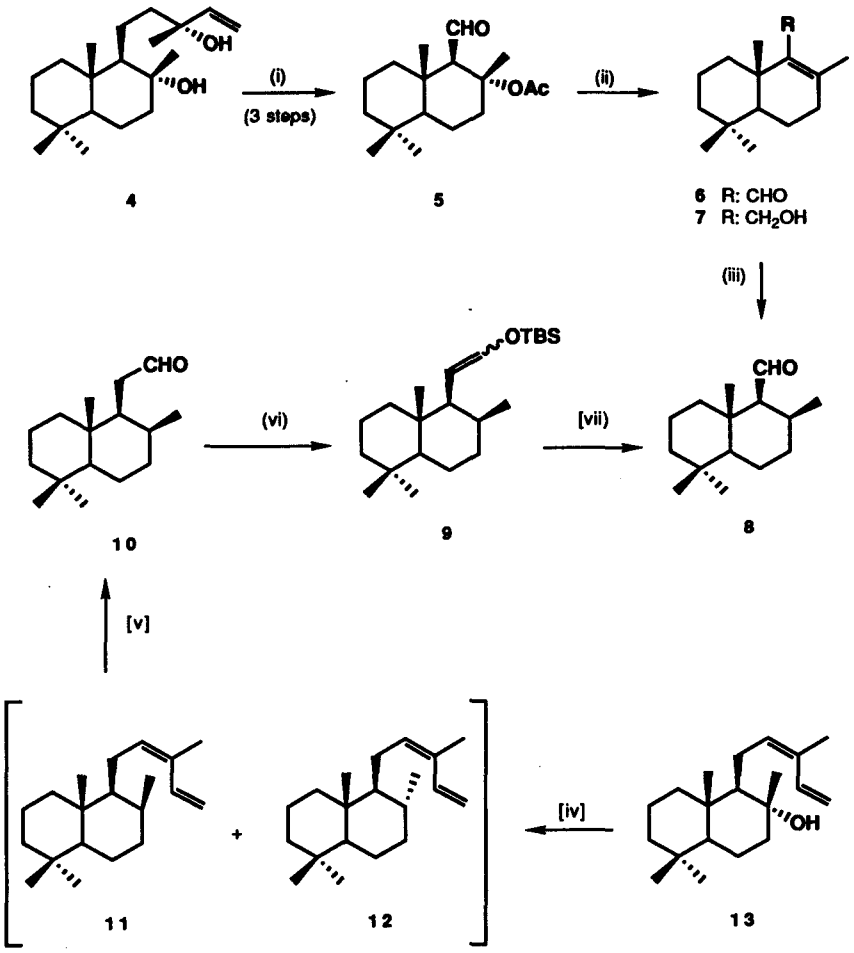


3

Following the authors' research on the synthesis of marine metabolites[4] two efficient routes to wiedendiol -B (**1**) from (-)-sclareol (**4**) and (+)-*cis*-abienol (**13**) are reported. The synthetic strategy is based on the condensation of the drimanic aldehyde **8**[5] with the aryllithium derived from **16**.

In the first route the drimanic synthon **8** was efficiently prepared from the acetoxyaldehyde **5**, whose preparation from (-)-sclareol (**4**) has been previously reported by the present authors[6] (Scheme 1). Treatment of **5** with collidine at 200°C yielded regioselectively the enal **6**, which catalytic hydrogenation at room temperature gave a mixture of **8** (50%) and the allylic alcohol **7** (35%).[7] The saturated aldehyde **8** and the alcohol **7** were obtained in 70 and 10% yield, respectively, when the reduction was carried out at 0°C. The configuration at C-8 of **8** was established by nOe experiments and by comparison of the ^{1}H NMR and ^{13}C NMR data of this compound with those of its C-8 epimer, whose obtention as a racemate by electrophilic cyclization had been previously reported.[8]

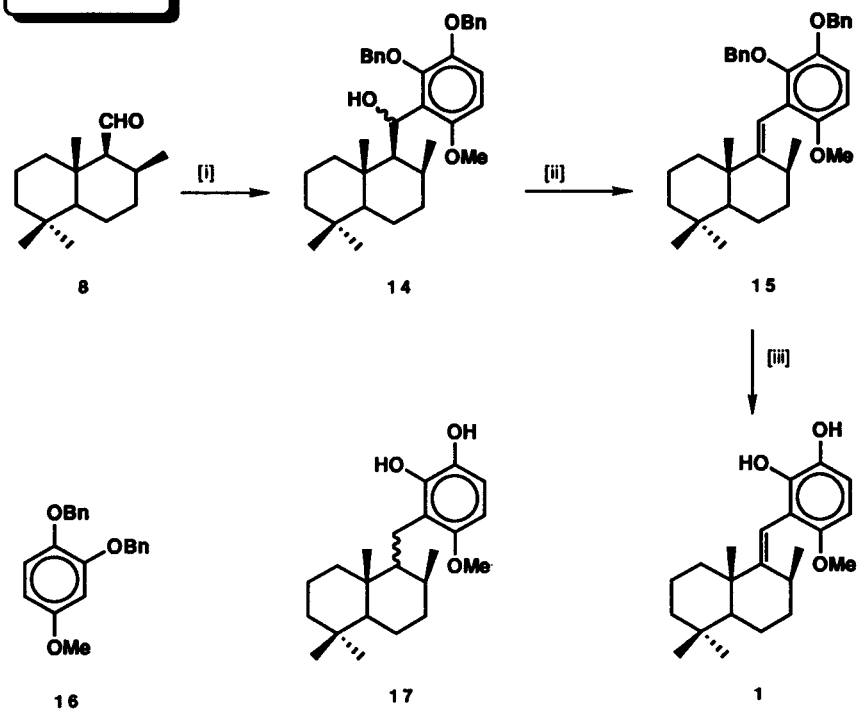
Scheme 1



(i) Ref. 6. (ii) Collidine, 200°C, 3h, 78%. (iii) H_2, Pd-C, MeOH-EtOAc (1:1), 0°C, 1h, 70%. (iv) Et_3SiH-CF_3COOH, -78°C- -15°C, 2h 30min, 80%; or ZnI_2-$NaBH_3CN$ (1.8 : 3 equiv), 0°C-- rt, 2h 15 min, 96%. (v) O_3, CH_2Cl_2, -78°C, 1h 15min; Me_2S, r t, 18h, 83%. (vi) NaH, THF; TBSCl, r t, 4h, 92%. (vii) O_3, CH_2Cl_2, -78°C, 45min; Me_2S, r t, 4h, 95%.

8 was prepared from (+)-*cis*-abienol (**13**) in an alternative route. The treatment of **13** with Et_3SiH-CF_3COOH yields a 1:1 mixture of epimers **11**[5] and **12**. However the use of ZnI_2-$NaBH_3CN$ allows the diastereoselective cationic reduction of **13**, affording **11** as the main product (ratio **11/12** 4:1). The ozonolysis of **11** and **12**, with Me_2S as reducing agent, gives a resolvable mixture of epimeric aldehydes. The treatment of **10**[5] with *tert*-butyldimethylsilyl chloride yields the corresponding silyl enol ethers **9** (E/Z 3:1), which after ozonolysis lead to the aldehyde **8** (Scheme 1).

Scheme 2



(i) **16**, *n*-BuLi, Et_2O - TMEDA (4:1), -40°C-- 0°C, 1h 30min, 55%. (ii) TsOH, Benzene, 35°C, 13h, 82%. (iii) H_2, Pd-C, MeOH-EtOAc (1:1), 0°C, 2h, 93%.

The aromatic synthon **16**[5] was obtained in quantitative yield by treating 3,4-dibenzyloxyphenol[4] with methyl iodide and sodium hidride. Addition of the anion derived from **16** to the aldehyde **8** yielded the alcohol **14**[5] as a mixture of two diastereomers. p-Toluenesulphonic acid-mediated dehydration at room temperature provided **15**[5] in 82% yield. When the dehydration temperature was increased debenzylation took place and significative amounts of cyclic ethers, formed through the phenolic hydroxyl attack on the olefinic system, were found. In order to prepare **1** different debenzylation methods were studied.The treatment of **15** with Raney Ni[4] caused simultaneous debenzylation and double bond reduction to give **17**. However catalytic hydrogenation of **15** at 0°C gave wiedendiol-B (**1**) in 93% yield. **1** showed physical properties which are identical to those of the natural product.

REFERENCES AND NOTES

1. Coval, S.J.; Conover,M.A.; Mierzwa, R.; King, A.; Puar, M.S.; Phife, D.W.; Pai, J.-K.; Burrier, R.E.; Ahn, M.-S.; Boykow, G.C.; Patel, M.; Pomponi, S.A., *Bio med. Chem. Lett.* **1995**, *5*, 605.

2. Tall, A.R., *J. Lipid Res.* **1993**, *34*, 1255.
3. Chackalamannil, S.; Wang, Y.; Xia, Y.; Czarniecki, M., *Tetrahedron Lett.* **1995**, *36*, 5315.
4. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R., *Tetrahedron Lett.* **1997**, *38*, 2325.
5. Representative physical data are given below:
8 ^{1}H RMN ($CDCl_3$, 400 MHz) δ 9.86 (d, J= 1.7 Hz, 1H), 2.37 (m, 1H), 1.94 (m, 1H), 1.16 (s, 3H), 1.02 (d, J= 7.4 Hz, 3H), 0.85 (s, 3H), 0.83 (s, 3H).
^{13}C RMN ($CDCl_3$, 100 MHz) : δ 39.7 (C_1), 17.3 (C_2), 42.0 (C_3), 33.2 (C_4), 55.7 (C_5), 18.1 (C_6), 34.2 (C_7), 29.9 (C_8), 65.6 (C_9), 37.1 (C_{10}), 33.5 (C_{11}), 21.6 (C_{12}), 18.0 (C_{13} or C_{14}), 17.2 (C_{14} or C_{13}), 206.7 (C_{15}).
10 ^{1}H RMN ($CDCl_3$, 300 MHz) δ 9.72 (dd, J= 3.3, 1.6 Hz, 1H), 2.50 (ddd, J= 15.9, 4.6, 1.6 Hz, 1H), 2.30 (ddd, J= 15.9, 8.9, 3.3 Hz, 1H), 1.90 (dt, J= 8.9, 4.6 Hz, 1H), 0.94 (d, J= 7.5 Hz, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.82 (s, 3H).
^{13}C RMN ($CDCl_3$, 75 MHz) : δ 39.9 (C_1), 17.5 (C_2), 42.7 (C_3), 33.5 (C_4), 56.6 (C_5), 18.4 (C_6), 34.6 (C_7), 32.6 (C_8), 48.2 (C_9), 39.4 (C_{10}), 33.4 (C_{11}), 21.6 (C_{12}), 16.6 (C_{13} or C_{14}), 15.8 (C_{14} or C_{13}), 39.8 (C_{15}), 203.7 (C_{16}).
11 ^{1}H RMN ($CDCl_3$, 300 MHz) δ 6.83 (dd, J= 17.2, 10.7 Hz, 1H), 5.37 (t, J= 7.4 Hz, 1H), 5.19 (d, J= 17.2 Hz, 1H), 5.08 (d, J= 10.7 Hz, 1H), 1.82 (sa, 3H), 0.91 (d, J= 7.8 Hz, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H).
14 ^{1}H RMN ($CDCl_3$, 300 MHz) δ 7.38-7.47 (m, 20H), 6.88 (d, J= 8.9 Hz, 1H), 6.87 (d, J= 8.9 Hz, 1H), 6.59 (d, J= 8.9 Hz, 2H), 5.37-4.97 (m, 10H), 3.86 (s, 3H), 3.85 (s, 3H), 3.40 (da, J= 10.7 Hz, 1H), 2.90 (da, J= 11.1 Hz, 1H), 2.28 (m, 1H), 2.08 (m, 1H), 1.90 (m, 1H), 1.79 (m, 1H), 1.18 (d, J= 7.3 Hz, 3H), 1.13 (s, 3H), 1.03 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.69 (d, J= 7.2 Hz, 3H).
15 ^{1}H RMN ($CDCl_3$, 400 MHz) δ 7.28-7.45 (m, 10H), 6.83 (d, J= 8.9 Hz, 1H), 6.55 (d, J= 8.9 Hz, 1H), 5.89 (s, 1H), 5.08 (s, 2H), 4.95 (d, J= 10.6 Hz, 1H), 4.90 (d, J= 10.6 Hz, 1H), 3.72 (s, 3H), 2.66 (m, 1H), 1.84 (d, J= 11.9 Hz, 1H), 1.70 (dt, J= 13.7, 3.5 Hz, 1H), 1.20 (s, 3H), 1.05 (d, J= 7.5 Hz, 3H), 0.89 (s, 3H), 0.86 (s, 3H).
^{13}C RMN ($CDCl_3$, 100 MHz) : δ 38.7 (C_1), 19.0 (C_2), 42.3 (C_3), 34.0 (C_4), 54.6 (C_5), 17.9 (C_6), 33.9 (C_7), 32.3 (C_8), 158.0 (C_9), 40.9 (C_{10}), 33.5 (C_{11}), 22.5 (C_{12}), 21.5 (C_{13} or C_{14}), 21.9 (C_{14} or C_{13}), 113.1 (C_{15}), 124.5 ($C_{1'}$), 146.5 ($C_{2'}$ or $C_{3'}$), 147.4 ($C_{3'}$ or $C_{2'}$), 110.9 ($C_{4'}$), 106.1 ($C_{5'}$), 152.2 ($C_{6'}$).
16 ^{1}H RMN ($CDCl_3$, 300 MHz) δ 7.31-7.44 (m, 10H), 6.86 (d, J= 8.8 Hz, 1H), 6.56 (d, J= 2.9 Hz, 1H), 6.37 (dd, J= 8.8, 2.9 Hz, 1H), 5.13 (s, 2H), 5.08 (s, 2H), 3.72 (s, 3H).
6. Barrero, A. F.; Alvarez-Manzaneda, E. ; Altarejos, J.; Salido, S.; Ramos, J. M.; Simmonds, M.S.J.; Blaney, W.M. . *Tetrahedron* **1995**, *51*, 7435-7450.
7. Hueso-Rodriguez, J.A.; Rodriguez, B., *Tetrahedron* **1989**, *45*, 1567.
8. Simmons, D.P.; Reichlin, D.; Skuy, D., *Helv. Chim Acta* **1988**, *71*, 1000.

(*Received in UK* 5 *August* 1997; *revised* 11 *September* 1997; *accepted* 12 *September* 1997)