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Tetrahedron: *Asymmetry* 16 (2005) 917–919
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First stereoselective total synthesis of (−)-(2*R*,10*S*)-megapodiol

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Received 22 November 2004; accepted 11 January 2005

Abstract—The first and efficient total synthesis of (−)-(2*R*,10*S*)-megapodiol **2** was accomplished stereoselectively, using a Sharpless asymmetric epoxidation of a *trans* allylic alcohol, intramolecular epoxide opening by phenolic hydroxyl and cyclization as the key reaction steps.

1. Introduction

(−)-(2*R*)-Megapodiol[1] **1** is a 2,3-dihydrobenzofuran isolated from the ground plant *Baccharis megapotamica*, Brazilian shrub of the genus Baccharis that belongs to the family of *Asteraceae*. Compound **1** showed high activity in vivo against P_{388} leukemia in mice and high cytotoxicity in vitro against KB cells.[2] The structure of **1** has not been reported earlier and the absolute chemistry at C-10 was also not known. However the configuration at C-2 was found to be *R* by degradation studies.[3] Due to its interesting antileukemic activity and our interest in the chemistry of chiral 2,3-dihydrobenzofuran antifungals,[4] we were attracted toward its total synthesis. Herein we report the first and efficient total synthesis of (−)-(2*R*,10*S*)-megapodiol **2**, thereby establishing its absolute stereochemistry (Fig. 1).

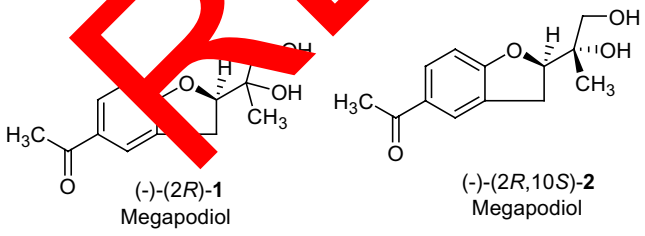

Figure 1.

2. Results and discussion

The retrosynthesis envisaged for the synthesis of (−)-(2*R*,10*S*)-megapodiol **2** is shown in Scheme 1. The key step involved in this sequence was the intramolecular epoxide opening by phenolic hydroxyl[4] with simultaneous cyclization affording the 2,3-dihydrobenzofuran moiety. The epoxide **3** was prepared by Sharpless asymmetric epoxidation[5] of *trans*-allylic alcohol[6] **4**, which was in turn prepared from 1-methyl-1-vinyloxirane[7] **6** and *p*-hydroxyacetophenone **7** in a six-step sequence involving regiospecific addition[8] through a π-allylpalladium complex, acetylation, Claisen rearrangement,[8] protection, reduction, and deprotection strategy (Scheme 1).

Accordingly, the known[6] *trans* allylic alcohol **4** was prepared from *p*-hydroxyacetophenone, by regiospecific opening[8] by the phenolic hydroxy group of *p*-hydroxyacetophenone to 1-methyl-1-vinyloxirane[7] **6** through a π-allylpalladium complex intermediate obtained from vinyloxirane and Pd(0). The crude reaction product **5** (95%) was then reacted with Ac_2O to protect the alcoholic hydroxyl as an acetoxy group and this gave **8** (98%). By using dry HCl, the latter was transformed[8] (Claisen rearrangement) into **9** (98%). Alkylation of **9** with BnBr/K_2CO_3 in acetone afforded **10** (92%). $NaBH_4$ reduction of the keto compound **10** in methanol gave alcohol **11** (90%). Reaction of **11** with TBDMSCl and imidazole, furnished **12** (90%). Further, deprotection of the acetyl group from **12** with K_2CO_3, MeOH, and H_2O afforded *trans* allylic alcohol **4** (97%). The structure of **4** was unambiguously assigned based on the spectral and NOE studies (Fig. 2). Introduction of chirality on

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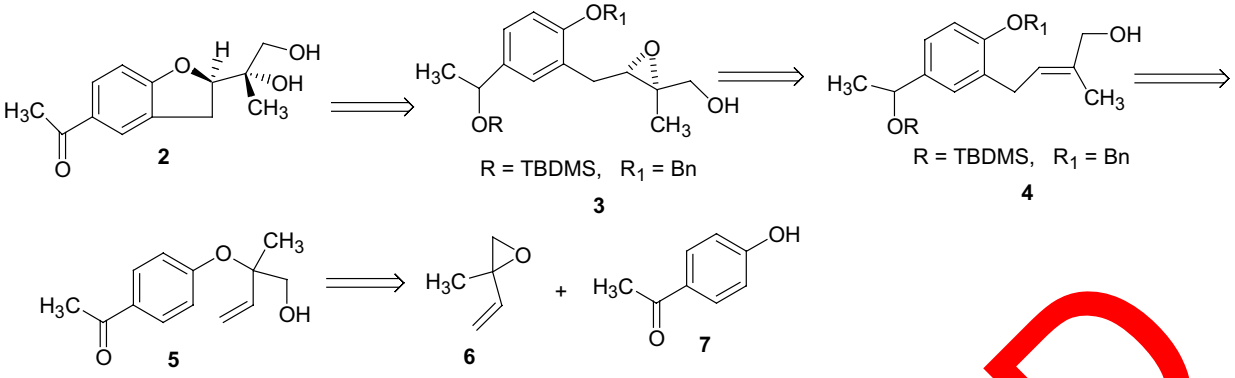
doi:10.1016/j.tetasy.2005.01.011



Scheme 1. Retrosynthetic analysis.

the *trans*-allylic double bond through Sharpless asymmetric epoxidation (SAE)[5] using L-(+)-DET as the chiral reagent afforded **3** (86%) with a (−)-(2*R*,3*S*)-configuration and 95% de (determined by NMR analysis). Debenzylation of **3** with H_2, Pd/C in MeOH, followed by cyclization with K_2CO_3, NEt_3 afforded 2,3-dihydrobenzofuran **14** (70%) rather than the isomeric 3-hydroxychroman.[4] (−)-(2*R*,10*S*)-Diol **14** on acetylation with Ac_2O, DMAP (cat) and Et_3N in CH_2Cl_2 gave

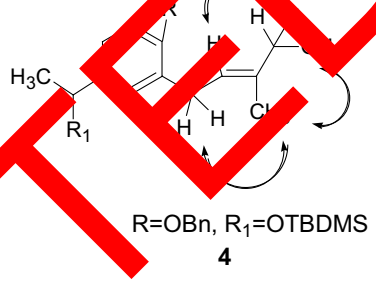
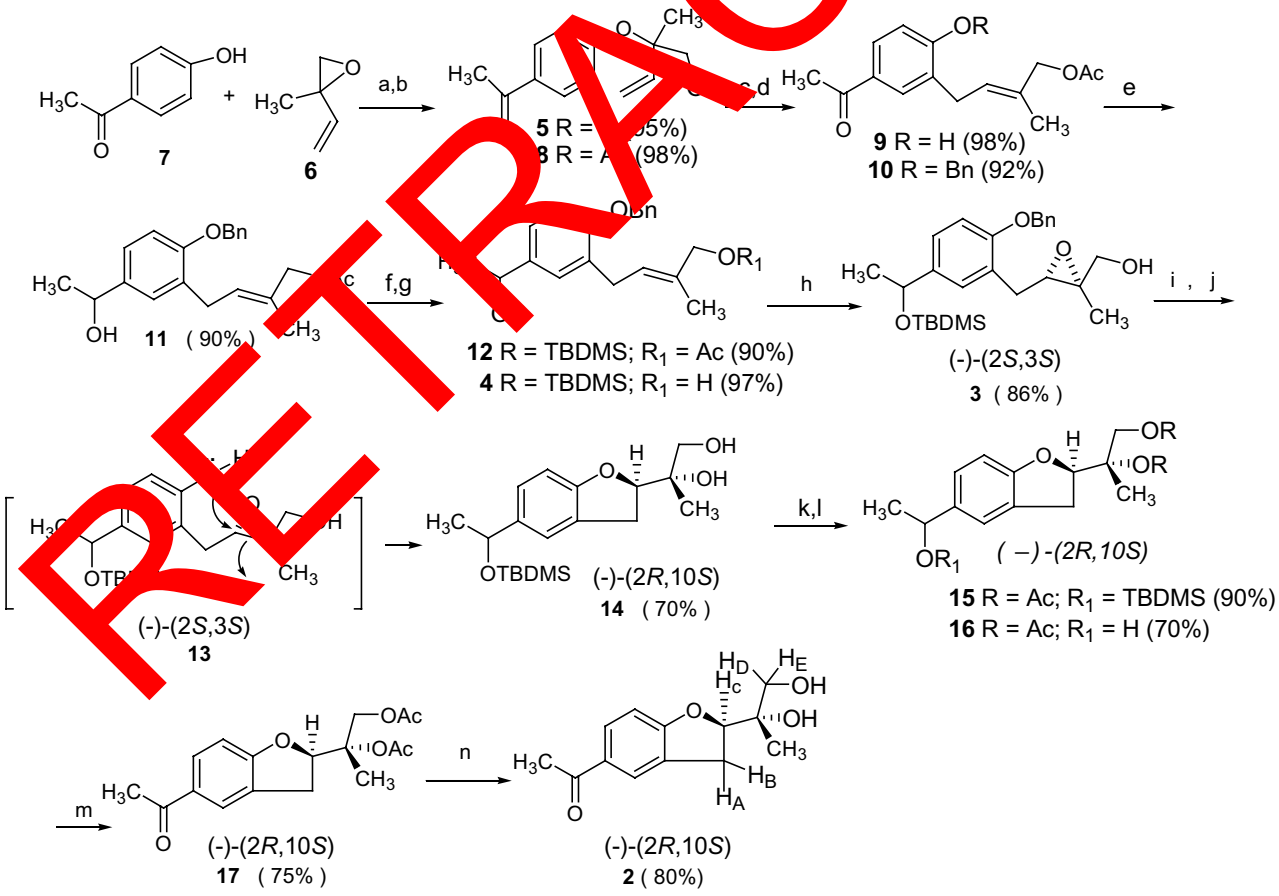


Figure 2. NOE studies on **4**.



Scheme 2. Reagents and conditions : (a) $Pd(PPh_3)_4$, CH_2Cl_2, rt, 4 h; (b) Ac_2O, Et_3N, DMAP, AcOEt, rt, 4 h; (c) HCl(g), CH_2Cl_2, rt, 2 min; (d) BnBr, K_2CO_3, acetone, reflux, 12 h; (e) $NaBH_4$, MeOH, 0 °C, 2 h; (f) TBDMS–Cl, imidazole, DMAP (cat), CH_2Cl_2, 0 °C 15 min then rt, 10 h; (g) K_2CO_3, MeOH, H_2O, rt, 2 h; (h) *t*-BuOOH, Ti(O-*i*-Pr)$_4$, L-(+)-DET, CH_2Cl_2, −24 °C, 20 h; (i) H_2, Pd/C, MeOH, rt, 4 h; (j) K_2CO_3, NEt_3, rt, 4 h; (k) Ac_2O, DMAP (cat), NEt_3, CH_2Cl_2, 0 °C, 15 min then rt, 5 h; (l) Bu_4NF, AcOH, THF, rt, 24 h; (m) PCC, NaOAc, Celite, CH_2Cl_2, 0 °C 15 min then rt, 6 h; (n) K_2CO_3, MeOH, H_2O, rt, 1 h.

(−)-(2*R*,10*S*)-**15** (90%). Deprotection of the (−)-(2*R*,10*S*)-TBDMS group of **15** with Bu_4NF and AcOH in THF afforded (−)-(2*R*,10*S*)-alcohol **16** (70%). PCC oxidation of (−)-(2*R*,10*S*)-**16** in CH_2Cl_2 and NaOAc furnished (−)-(2*R*,10*S*)-**17** (75%). Removal of the OAc protecting groups **17** with K_2CO_3, MeOH, and H_2O afforded (−)-(2*R*,10*S*)-**2** (80%) (Scheme 2), $[\alpha]_D^{25} = -64.1$ (*c* 1.25, MeOH) [lit.[1] $[\alpha]_D^{25} = -52.0$ (*c* 1.00, MeOH)] with >99.0% ee (determined by chiral HPLC analyses),[9] the spectroscopic data[10] of which were identical with those of the natural product.

3. Conclusion

In summary we have demonstrated for the first time the total synthesis of megapodiol in a highly stereoselective manner using Sharpless asymmetric epoxidation as key step. Our method involves simple and readily available reagents, which makes it useful synthetic route for the total synthesis of megapodiol.

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9. The enantiomeric excess (ee) of (−)-(2*R*,10*S*)-**15**, **-16**, **-17**, and **-2** were determined by chiral HPLC analyses using a Chiracel OD column and Chiracel OJ column (25 × 0.46 cm, Daicel, Japan) eluent: hexane–*i*-PrOH).
10. Spectroscopic data: data for compound **2**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (s, CH_3-12), 2.49 (s, 3H, CH_3-14), 3.19 (1H, dd, J = 16.0, 8.0 Hz, CH_2-3, H_A), 3.27 (1H, dd, J = 16.0, 10.0 Hz, CH_2-3, H_B), 3.48 (1H, d, J = 12.0 Hz, CH_2OH-11, H_D), 3.70 (1H, d, J = 16.0 Hz, CH_2OH-11, H_E), 4.85 (1H, m, H-2, H_C) 6.73 (1H, d, J = 10.0 Hz, H-8), 7.68 (1H, dd, J = 10.0, 2.0 Hz, H-7), 7.75 (1H, br, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$): 19.9 (CH_3-12), 26 (CH_3-14), 29.9 (C-3), 68.4 (CH_2OH-11), (C-10), 79.2 (C-2), 109.5 (C-8), 125.6 (C-5), 127.8 (C-6), (C-7), 131.6 (C-4), 163.7 (C-9), 197.8 (C=O). Anal. Calcd for $C_{13}H_{16}O_4$ (236.10): C, 66.09; H, 6.83. Found: C, 66.18; H, 6.94. MS: *m/z* (relative intensity) 236 (M^+, 18), 204 (6), 187 (9), 162 (35), 147 (19), 119 (25), 91 (25), 75 (12), 57 (20), and 43 (100). FABHRMS: Calcd $C_{13}H_{16}O_4$ (M^+) 236.105248. Found: 236.105245.