

Enantioselective Synthesis of (-)-Boschnialactone

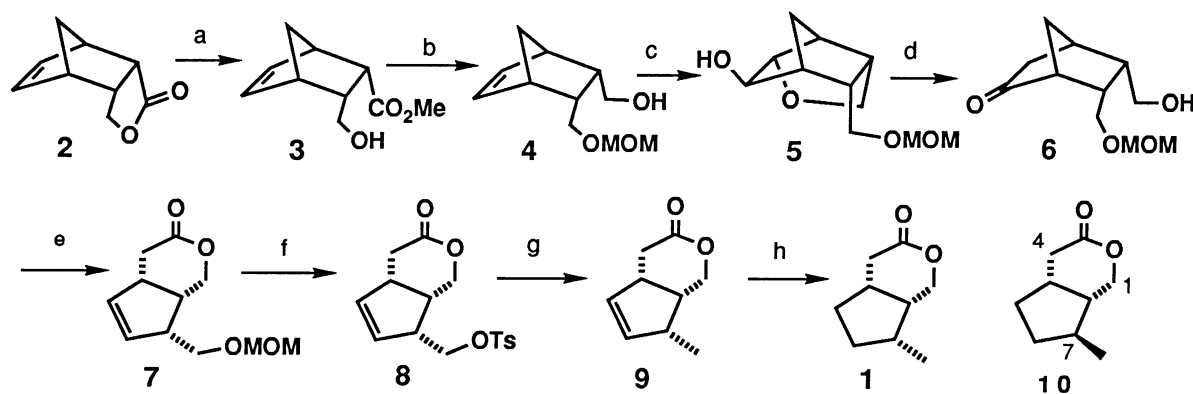
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An enantioselective synthesis of (-)-boschnialactone was accomplished starting from a chiral fused bicyclo[2.2.1]heptane lactone readily available *via* an asymmetric Diels-Alder reaction.

Boschnialactone (**1**), one of the iridoids, was isolated from *Boschniakia rossica* Hult. and the absolute stereostructure was determined by Sakan and collaborators.¹⁾ Because of its unique biological properties such as cat-attracting effect and insect-repellent, several syntheses of ($\pm$)-**1** have been reported to date.^{1,2)} However, there have been no enantioselective syntheses of (-)-**1**. Recently we reported a facile, enantiodivergent preparation of a chiral bicyclo[2.2.1]heptane lactone **2** available in a short step from the adduct obtained by an asymmetric Diels-Alder reaction.³⁾ The lactone **2** is suitable as a synthetic tool for the chiral synthesis of both of the enantiomers of **1**, with natural and unnatural configuration. Herein, we disclose the first enantioselective synthesis of (-)-**1** with natural configuration starting from the (+)-lactone **2**.

The construction of the cyclopentapyranone ring is based upon a ring fission of a bicyclo[2.2.1]heptanone framework. According to the literature method,⁴⁾ saponification of **2** and the subsequent esterification afforded the ester alcohol **3**, which was protected as the methoxymethyl ether (87% yield). Careful reduction of the ester



a) Ref. 4 b) MOMCl, i Pr₂NEt, CH₂Cl₂, r.t., 12 h, 87%; LiAlH₄, THF, -3 °C, 10 min, 73% c) mcpba, CH₂Cl₂, 0 °C, 2.5 h, 59% d) PCC, molecular sieves 4A, CH₂Cl₂, r.t., 5 h, 72%; Al-Hg, THF, EtOH, 0 °C, 3 h, 91% e) $h\nu$ (200 W, low-pressure Hg lamp, quartz filter), CH₃CN, r.t., 4 h, then conc. HCl (cat.), r.t., 1 h; PCC, molecular sieves 4A, CH₂Cl₂, r.t., 7 h, 64% f) PPTS, ^tBuOH, reflux, 8 h, 86%; TsCl, pyridine, DMAP (cat.), r.t., 12 h, 93% g) Zn, NaI, dimethoxyethane, reflux, 1 h, q.y. h) H₂ (1 atm), 5% Pt on alumina, ^tBuOH, r.t., 5 h, 85%

yielded the alcohol **4** (73% yield). Exposure of **4** to 3-chloroperoxybenzoic acid (mcpba) gave the tricyclic ether **5** in 59% yield. PCC oxidation⁵⁾ of **5** followed by reduction with Al-Hg produced the keto alcohol **6** (66% yield). Photolysis of **6**⁶⁾ and treatment of a 1:1 mixture of the resulting hemiacetal with PCC gave the lactone **7** in 64% yield. Removal⁷⁾ of the methoxymethyl group in **7**, tosylation, and reduction⁸⁾ afforded dehydroboschnialactone (**9**)^{2a)} in 80% yield. Hydrogenation of **9** over Pd-C gave **1** which was contaminated by a certain amount of its epimer. The epimer was inseparable from **1** by chromatography, and the stereochemistry would be assigned to be **10**^{2b)} on the basis of the NMR spectrum of the crude product. It was assumed that the isomerization of the double bond in **9** should occur during the hydrogenation.⁹⁾ Finally, platinumium-catalyzed hydrogenation furnished boschnialactone (**1**)¹⁰⁾ without contamination by any stereoisomers in 85% yield.

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References

- 1) T. Sakan, F. Murai, Y. Hayashi, Y. Honda, T. Shono, M. Nakajima, and M. Kato, *Tetrahedron*, **23**, 4635 (1967).
- 2) a) P. Callant, P. Storme, E. Van der Eycken, and M. Vandewalle, *Tetrahedron Lett.*, **24**, 5797 (1983); b) T.-F. Wang and C.-F. Yang, *J. Chem. Soc., Chem. Commun.*, **1989**, 1876; c) M. Demuth and K. Schaffner, *Angew. Chem., Int. Ed. Engl.*, **21**, 820 (1982); K. Sisido, T. Kageyama, H. Mera, K. Utimoto, *Tetrahedron Lett.*, **1967**, 1553; J.-C. Caille, B. Tabyaoui, and R. Guillard, *Synth. Commun.*, **15**, 669 (1985); B. Hanquet, B. Tabyaoui, J.-C. Caille, M. Farnier, and R. Guillard, *Can. J. Chem.*, **68**, 620 (1990).
- 3) Y. Arai, M. Matsui, and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1233.
- 4) A. Ichihara, N. Nio, Y. Terayama, R. Kimura, and S. Sakamura, *Tetrahedron Lett.*, **1979**, 3731; K.P. Lok, I.J. Jakovac, and J.B. Jones, *J. Am. Chem. Soc.*, **107**, 2521 (1985).
- 5) J. Herscovici, M.-J. Egron, and K. Antonakis, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 1967.
- 6) Transformation of a bicyclo[2.2.1]heptane system into a cyclopentapyrane derivative by Norrish type I cleavage was well-documented; see: J. Meinwald and R.A. Chapman, *J. Am. Chem. Soc.*, **90**, 3218 (1968); K. Furuichi, K. Abe, and T. Miwa, *Tetrahedron Lett.*, **1974**, 3685; ref. 2a.
- 7) H. Monti, G. Léandri, M. Klos-Ringuet, and C. Corriol, *Synth. Commun.*, **13**, 1021 (1983).
- 8) Y. Fujimoto and T. Tatsuno, *Tetrahedron Lett.*, **1976**, 3325.
- 9) B.P. Mundy and J.J. Theodore, *J. Am. Chem. Soc.*, **102**, 2005 (1980).
- 10) Selected physical data: **5**: mp 82-84 °C; $[\alpha]_D^{26}$ -30.2° (c 1.69, CHCl₃). **6**: bp 121-125 °C / 0.15 mmHg (1 mmHg= 133.322 Pa); $[\alpha]_D^{25}$ -5.0° (c 1.90, CHCl₃). **7**: mp 42-44 °C; $[\alpha]_D^{25}$ -17.3° (c 2.10, CHCl₃). **8**: mp 127 °C; $[\alpha]_D^{25}$ +19.9° (c 2.73, CHCl₃). **9**: mp 90-91 °C; $[\alpha]_D^{25}$ -19.8° (c 0.77, CHCl₃). **1**: bp 109-115 °C / 13 mmHg (lit.¹⁾ 105-112 °C / 6 mmHg); $[\alpha]_D^{26}$ -21.3° (c 0.34, CHCl₃) {lit.¹⁾ $[\alpha]_D^{21}$ -18.2° (c 2.10, CHCl₃)}.

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