Construction of 8-Membered Ring Skeleton of Vinigrol *via* SmI_2-Promoted Barbier Coupling

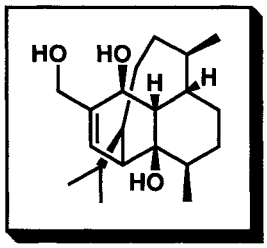
M. Kito, T. Sakai, H. Shirahama, M. Miyashita, and F. Matsuda*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan

Received 12 November 1996

Abstract: The 8-membered ring framework of vinigrol, a unique tricyclic diterpene isolated as a novel antihypertensive compound from a culture of *Virgaria nigra*, was efficiently synthesized employing an SmI_2-induced intramolecular Barbier coupling.

Vinigrol (**1**), an unusual tricyclic diterpenoid, was isolated from a culture broth of the fungal strain identified as *Virgaria nigra* by Ando *et al.*, who also described the antihypertensive and platelet aggregation inhibitory properties of **1**.[1] Furthermore, it was found that **1** is a tumor necrosis factor (TNF) antagonist.[2] Therefore, **1** may be used to control conditions attributable to TNF such as endotoxic shock, inflammation, infection, cachexia, and the progression from the AIDS-related complex to AIDS. It features a complicated fused ring system involving an 8-membered ring. Its interesting physiological activity and unique structure distinguish the molecule as a very interesting target for total synthesis.[3] In conjunction with our program directed toward the total synthesis of **1**, we synthesized the 8-6 fused ring system of this diterpene through the efficient cyclization of the 8-membered ring using an SmI_2-induced Barbier coupling.[4-6] Natural products possessing 8-membered ring substructural units have attracted much attention because of their potent biological activity and the synthetic challenge posed by the required formation of the carbocycle or heterocycle.

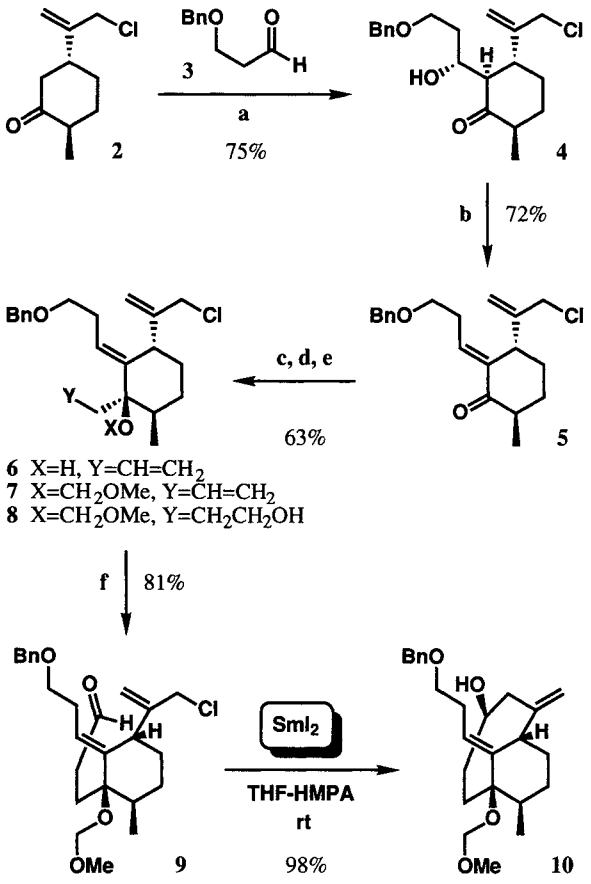


The stereoselective cross aldol reaction of 3-benzyloxypropionaldehyde (**3**)[7] with the Li-enolate generated from (+)-chlorodihydrocarvone (**2**)[8] provided the hydroxy ketone **4**, which upon treatment with 2-fluoropyridinium tosylate gave the (*E*)-α-enone **5** (Scheme I). The 1,2-addition of CH_2=$CHCH_2MgBr$ to **5** occurred in a stereoselective manner and the β-alcohol **6** was obtained along with a small amount of its α-epimer (α:β = 5:1). The β-alcohol **6** was converted into the aldehyde **9** in the following sequence, (1) protection of the hydroxyl group of **6** as its MOM ether, (2) regioselective hydroboration-oxidation of the terminal olefin of the MOM ether **7** by thexylborane, and (3) Dess-Martin oxidation of the resulting alcohol **8**.

Treatment of **9** with SmI_2 in the presence of HMPA cleanly allowed the 8-membered ring closing reaction to furnish the cyclooctanol **10**[9] relevant to the 8-6 fused ring system of vinigrol (**1**) as the only detectable product. The *quantitative yield* of **10** is remarkable in view of the difficulties normally encountered during the cyclization of 8-membered rings. The addition of HMPA was essential for this SmI_2-promoted intramolecular Barbier coupling.[10] The reaction in the absence of HMPA produced a substantial decrease in product yield (15%). The major isolated product was the reduced alcohol **8**.

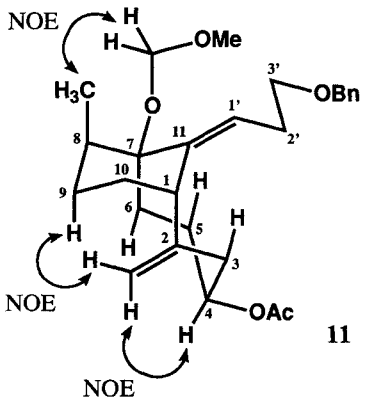
The structure of **10** was confirmed by 2D-COSY and 2D-NOESY experiments on the acetate **11**[9] prepared from **10** through acetylation (Ac_2O, Py, rt, 100%). The stereochemical assignment to **11** definitely follows from inspection of the selected key coupling constants and NOE's as illustrated in Figure I.

The synthesis of the 8-6 fused ring skeleton of vinigrol (**1**) described here is noteworthy for the high efficiency with which the 8-membered ring is assembled. The protocol should be applicable to the construction of various 8-membered rings.



(a) (1) LDA, THF, –78 °C. (2) **3**, –78 °C. (b) FC_5H_5NMe•OTs, Et_3N, CH_2Cl_2, reflux. (c) CH_2=$CHCH_2MgBr$, ether, –78 °C. (d) $MeOCH_2Cl$, $^iPr_2NEt$, CH_2Cl_2, rt. (e) (1) $ThexylBH_2$, THF, 0 °C. (2) 30% H_2O_2, rt. (f) Dess-Martin Periodinane, Py, CH_2Cl_2, rt.

Scheme I



J_{3ax-4} = 11.0 Hz
J_{4-5ax} = 11.0 Hz
$J_{5ax-6ax}$ = 11.0 Hz

Figure I

Acknowledgment. The present work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "New Development of Rare Earth Complexes" No. 06241201 from The Ministry of Education, Science and Culture of Japan. Financial support was also provided by Ono Pharmaceutical Co., Ltd.

References and Notes

(1) (a) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Toda, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292. (b) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 25. (c) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 31.

(2) Norris, D.B.; Depledge, P.; Jackson, A.P. PCT Int. Appl. *WO 91/07953*, Jun 13, 1991; *Chem. Abstr.* **1991**, *115*, 64776h.

(3) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1993**, *58*, 2349.

(4) Samarium(II) iodide (SmI_2) has become an exceedingly useful reagent for promoting reductive coupling reactions in the last decade. For reviews, see: (a) Kagan, H.B. *New J. Chem.* **1990**, *14*, 453. (b) Molander, G.A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G.A.; Harris, R.H. *Chem. Rev.* **1996**, *96*, 307.

(5) Recently, we described the new types of highly stereoselective reductive couplings mediated by SmI_2. See: (a) Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett* **1991**, 391. (b) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158. (c) Kan, T.; Nara, S.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5111. (d) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532. (e) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (f) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729. (g) Matsuda, F. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 987. (h) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (i) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett*, **1996**, 1057. (j) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, T.; Shirahama, H.; Matsuda, F. *Synlett*, **1997,** in press.

(6) In this laboratory, the *cis*-decalin ring of vinigrol (**1**) was prepared with complete stereocontrol using the SmI_2-promoted ketyl-olefin coupling (ref 5i).

(7) Martinelli, M.J. *J. Org. Chem.* **1990**, *55*, 5065.

(8) (+)-Chlorodihydrocarvone (**2**) was prepared by treatment of (+)-dihydrocarvone with HOCl. See: Hegde, S.G.; Bechwith, D.; Doti, R.; Wolinsky, J. *J. Org. Chem.* **1985**, *50*, 894.

(9) Physical and ^{1}H-NMR spectral data for **10** and **11** are as follows. **10**: $[\alpha]_D^{25}$ –80.9° (*c* 0.915, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.81 (3H, d, J = 6.9 Hz, C_8-Me), 1.31 (1H, brd, J = 12.3 Hz, C_{9eq}-H), 1.44 (1H, brdq, J = 6.5, 11.1 Hz, C_{5ax}-H), 1.74 (1H, brdd, J = 11.1, 14.5 Hz, C_{6ax}-H), 2.45 (1H, dq, J = 14.2, 7.1 Hz, $C_{2'}$-H), 2.47 (1H, dd, J = 4.0, 11.1 Hz, C_{3eq}-H), 2.51 (1H, dq, J = 14.2, 7.1 Hz, $C_{2'}$-H), 3.37 (3H, s, OMe), 3.42 (1H, brs, C_1-H), 3.59 (3H, m, C_4-H, $C_{3'}$-H_2), 4.49 (1H, d, J = 7.5 Hz, C*H*OMe), 4.53 (2H, s, PhCH_2), 4.77 (1H, d, J = 7.5 Hz, C*H*OMe), 4.97, 4.99 (each 1H, brs, C_2=CH_2), 5.98 (1H, t, J = 7.3 Hz, $C_{1'}$-H), 7.25 – 7.38 (5H, m, Ph). **11**: $[\alpha]_D^{25}$ –60.6° (*c* 0.930, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.81 (3H, d, J = 6.9 Hz, C_8-Me), 1.31 (1H, brd, J = 12.5 Hz, C_{9eq}-H), 1.52 (1H, brdq, J = 6.5, 11.0 Hz, C_{5ax}-H), 1.58 – 1.72 (3H, m, C_{5eq}-H, C_{9ex}-H, C_{10}-H), 1.76 (1H, brdd, J = 11.0, 15.1 Hz, C_{6ax}-H), 1.90 (1H, brdd, J = 6.5, 15.1 Hz, C_{6eq}-H), 1.95 (1H, t, J = 11.0 Hz, C_{3ax}-H), 1.97 (3H, s, Ac), 2.02 (1H, m, C_8-H), 2.44 (1H, dq, J = 14.2, 7.1 Hz, $C_{2'}$-H), 2.48 (1H, dd, J = 4.2, 11.0 Hz, C_{3eq}-H), 2.54 (1H, dq, J = 14.2, 7.1 Hz, $C_{2'}$-H), 3.36 (3H, s, OMe), 3.43 (1H, brs, C_1-H), 3.58 (2H, m, $C_{3'}$-H_2), 4.47 (1H, d, J = 7.5 Hz, C*H*OMe), 4.55 (2H, s, PhCH_2), 4.71 (1H, tt, J = 4.2, 11.0 Hz, C_4-H), 4.76 (1H, d, J = 7.5 Hz, C*H*OMe), 5.05, 5.10 (each 1H, brs, C_2=CH_2), 5.96 (1H, t, J = 7.1 Hz, $C_{1'}$-H), 7.25 – 7.38 (5H, m, Ph).

(10) Many SmI_2-induced reactions benefit from the presence of HMPA. See: (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (b) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (c) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487. (d) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437. (a) (1) LDA, THF, –78 °C. (2) **3**, –78 °C. (b) FC_5H_5NMe•OTs, Et_3N, CH_2Cl_2, reflux. (c) CH_2=$CHCH_2MgBr$, ether, –78 °C. (d) $MeOCH_2Cl$, $^iPr_2NEt$, CH_2Cl_2, rt. (e) (1) $ThexylBH_2$, THF, 0 °C. (2) 30% H_2O_2, rt. (f) Dess-Martin Periodinane, Py, CH_2Cl_2, rt.