A Short Synthesis of the Tricyclic Ring System of Vinigrol

Jean-François Devaux, Issam Hanna,* and Jean-Yves Lallemand

Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, F-91128 Palaiseau, France

Thierry Prangé

Laboratoire de chimie structurale biomoléculaire associé au CNRS, 74 rue M. Cachin, F-93012 Bobigny, France

Received January 15, 1993

Summary: The first synthesis of the decahydro-1,5-butanonaphthalene skeleton of vinigrol is described which features as the key step by anionic oxy-Cope rearrangement.

Vinigrol (1), a novel diterpenoid recently isolated from a fungus,[1] is an antihypertensive and platelet aggregation inhibiting substance.[2] In addition, it was found that vinigrol is tumor necrosis factor (TNF) antagonist usable for the treatment of endotoxic shock, inflammation, infection, and cachexia and to arrest progression from AIDS-related complex (ARC) to AIDS.[3] Structurally, vinigrol possesses a unique tricyclic skeleton **2** involving an eight-membered ring.

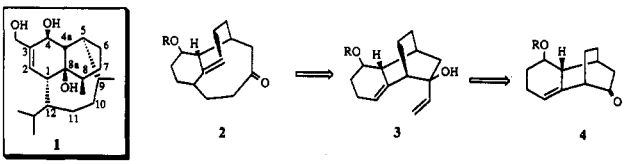
The unusual structure of vinigrol combined with its interesting biological activities make it a challenging synthetic target. We report herein the first synthesis of the decahydro-1,5-butanonaphthalene ring system of this natural product.

Construction of **2** was envisioned via a key anionic oxy-Cope rearrangement[4] of tricyclic vinyl carbinol **3** which could arise from a stereoselective alkylation of enone **4** (Scheme I).

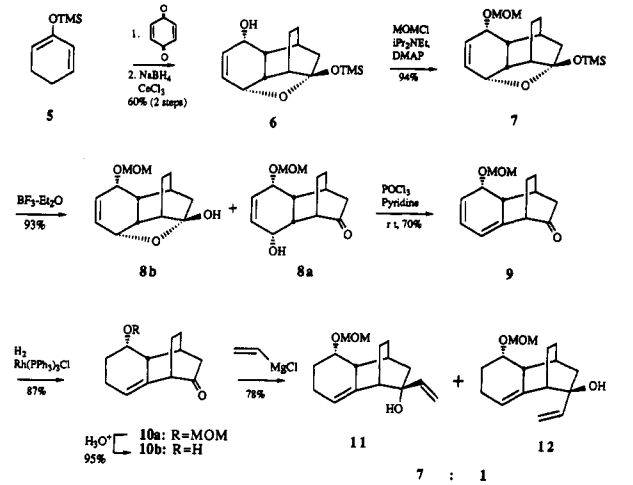
The synthesis (Scheme II) was initiated by the Diels–Alder reaction of 2-[(trimethylsilyl)oxy]-1,3-cyclohexadiene (**5**)[5] with 1,4-benzoquinone followed by Luche reduction[6] of the crude adduct to afford **6**[7] as a sole stereoisomer in 60% overall yield.[8] Protection of the hydroxyl group as its methoxymethyl ether **7** and subsequent treatment with $BF_3{\cdot}Et_2O$ in THF at −70 °C followed by hydrolysis (at −70 to 0 °C) cleanly afforded hydroxy ketone **8a** along with its hemiketal **8b** in 87.5% yield (overall from **6**). At this stage, dehydration with $POCl_3$–pyridine followed by selective hydrogenation of the less hindered double bond of conjugated diene **9** with Wilkinson's catalyst gave rise to the desired functionalized ketone **10a**[7] in good overall yield.

The addition of vinylmagnesium chloride to **10a** (THF, 0 °C to rt) gave rise to a 7:1 mixture of the diastereomeric alcohols **11** and **12** (78%) which were readily separated by flash chromatography. The stereochemical assignment

Scheme I



Scheme II



of these products is supported by the observation that the vinyl protons at the terminus of the allylic alcohol moiety of **12** appear at higher field (0.1–0.2 ppm) than the corresponding protons of **11**. This effect is presumably a consequence of diamagnetic shielding of these protons by the cyclohexenyl double bond.[9] Attempts to invert the stereochemistry of the undesirable isomer to afford **12** using the sulfoxide–sulfenate [2,3] sigmatropic rearrangement failed.[10]

In order to overcome the lack of stereoselectivity in the Grignard step, addition of vinylmagnesium chloride was attempted on hydroxy ketone **10b**, readily obtained by acid hydrolysis of **10a**. It was gratifying to find tha **10b** reacted with excess vinylmagnesium chloride affording almost exclusively the endo vinyl isomer **13** in 64% yield along with 18% of the starting material (Scheme III). The stereoselectivity of Grignard reaction with **10b** is probably the result of chelation control.[13] The Grignard reagent

(1) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292–5293.

(2) (a) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Hoshida, K. and Okuhara, M. *J. Antibiot.* **1988**, *41*, 25–30. (b) Ando, T.; Yoshida, K.; Okuhara, M. *Ibid.* 31–35.

(3) Norris, D. B.; Depledge, P.; Jakson, A. P. PCT Int. Appl. WO 91 07 953; *Chem. Abstr.* **1991**, *115*, 64776 h.

(4) For a review on the stereocontrolled construction of complex cyclic ketones via oxy-Cope rearrangements see: Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609–626.

(5) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1977**, *42*, 1051–1056.

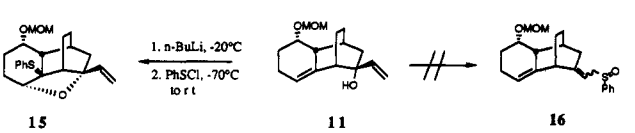
(6) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(7) All new compounds exhibit satisfactory spectroscopic and microanalytical data.

(8) For a similar transformation see: Hung, S. C.; Liao, C. C. *Tetrahedron Lett.* **1991**, *32*, 4011–4014.

(9) (a) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190–3192. (b) Paquette, L. A.; Wei, H.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, 2291–2300.

(10) In fact, treatment of **11** with phenylsulfenyl chloride according to the described procedure[11] led to tetracyclic tetrahydrofuran **15** rather than the expected sulfoxide **16**.[7,12]



0022-3263/93/1958-2349$04.00/0

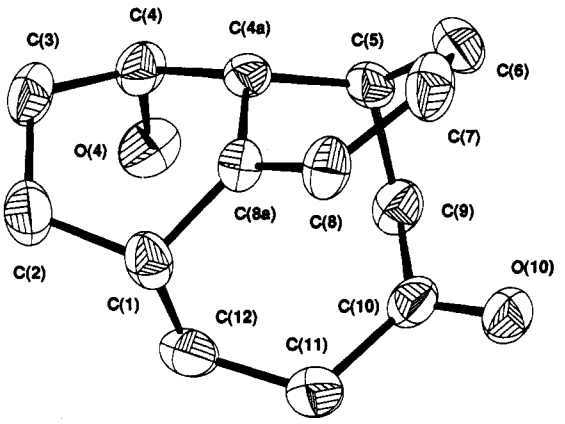
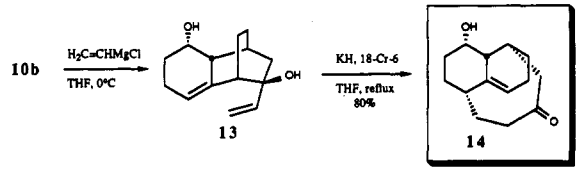


Figure 1. ORTEP drawing of 14. The numbering refers to the corresponding centers of vinigrol.

Scheme III



first deprotonates the hydroxyl group, and the intermediate Mg–alkoxy moiety then induces attack from the endo side.

Next, the anionic oxy-Cope rearrangement was effected on the diol **13**. Thus, exposure of **13** to excess KH in refluxing THF in the presence of 18-crown-6 (3 equiv) for 30 min afforded crystalline **14** in 80% yield. The structure of this compound was assigned on the basis of spectroscopic data and confirmed by X-ray crystallographic analysis[14] (Figure 1).

In conclusion, we have demonstrated the viability of the anionic oxy-Cope rearrangement to the tricyclic system of vinigrol. This approach involves few steps and yields are good. Work toward the total synthesis of this natural product is in progress.

Acknowledgment. We are grateful to Laboratoire Fournier for financial support.

Supplementary Material Available: Experimental procedures and spectral data for **6–10**, **13**, and **14** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) For example see: Morera, E.; Ortar, G. *J. Org. Chem.* **1983**, *48*, 119–121. Boeckman, R. K.; Springer, D. M.; Alessi, T. R. *J. Am. Chem. Soc.* **1989**, *111*, 8284–8286.

(12) For a related case see: Brown, W. L.; Fallis, A. G. *Can. J. Chem.* **1987**, *65*, 1828–1832.

(13) For a review on chelation-controlled reactions, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569.

(14) X-ray crystal data: the X-ray diffraction experiment was performed on a Philips PW 1100 automatic four-circle diffractometer operating with the Cu Kα radiation (λ = 1.5418 Å) monochromated by graphite. The orientation matrices of the crystals were calculated from the angular settings of 25 randomly distributed reflections found in the range $10° < \theta > 25°$ and refined by least-squares procedure. A significant decomposition was found during the data collection for **14** which was very sensitive to X-ray damage (life time was about 10 h). Two crystals were used for the complete data collection, and corrections were applied before merging and scaling. The reflections were scanned over a 1.2° angle width at a speed of $0.03°\cdot s^{-1}$, and for each reflection, the background was deduced from two stationary measurements on both sides of the reflection. The intensities, measured up to θ = 65°, were reduced to F structural factors by means of standard Lorentz and polarization corrections and considered as observed above the 2σ background level. No absorption corrections were applied. A single crystal of **14** was obtained from methanol as small plates 0.05-mm thick. The system is monoclinic, space group $P2_1/n$ with a = 6.241(4) Å; b = 14.504(5) Å; c = 13.139(4) Å; β = 102.7(1)°, and Z = 4. The structure, solved by direct methods, was refined with anisotropic factors for the non-hydrogen atoms to R = 7.4% using 1398 observed structural factors. Hydrogen atoms were all located on Fourier-difference map and introduced with an isotropic thermal factor subsequently refined as a global parameter to $\langle U_H \rangle = 0.064$. The author has deposited atomic coordinates for **14** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.