Studies toward the Synthesis of Vinigrol. First Construction of the Tricyclic Ring System

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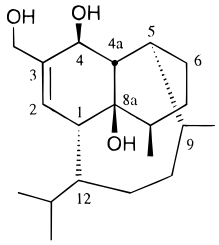
The first synthesis of a functionalized tricyclic skeleton of vinigrol is described. The key step involved an anionic oxy-Cope rearrangement of bicyclic allylic alcohol **18**, readily prepared by highly stereoselective addition of vinyl magnesium chloride to the hydroxy enone **15b**. Introduction of the tertiary hydroxy group at carbon 8a was achieved by an unexpected hydration of **30** with aqueous trifluoroacetic acid.

Vinigrol (**1**), a diterpene isolated in 1987 from a culture of the fungal strain identified as *Virgaria nigra*,[1] is an antihypertensive and platelet aggregation-inhibiting substance.[2] In addition, it was found that **1** and its salts are tumor necrosis factor (TNF) antagonists. Therefore, vinigrol may be used for the treatment of endotoxic shock inflammation, infections, and cachexia and to arrest progression from AIDS-related complex to AIDS.[3] Structurally, vinigrol possesses a unique tricyclic skeleton **2**, involving a bridged eight-membered ring. The unusual structure of this natural product combined with its interesting biological activities provide a challenging synthetic target. Herein, we report the first successful entry into the functionalized decahydro-1,5-butanonaphthalene ring system of this natural product.[5]



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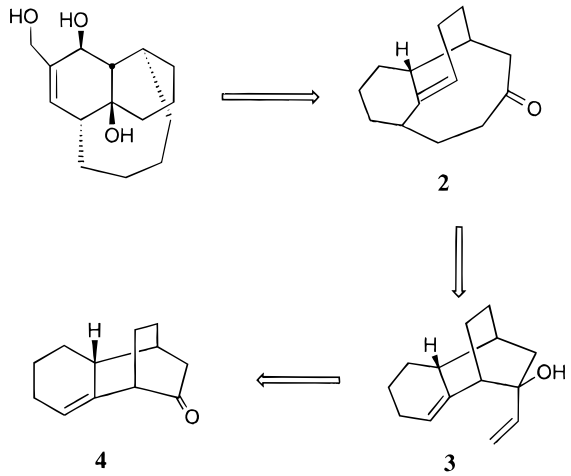
As for cyclooctanoid substances, the most critical issue in the synthesis of vinigrol is the construction of the eight-membered ring. Our strategy is based on the recognition that the oxygenated tricyclic skeleton **2** of vinigrol can be quickly elaborated via anionic oxy-Cope rearrangement[4] of a tricyclic vinyl carbinol such as **3**, which could arise from stereoselective alkylation of enone **4** (Scheme 1).

In a first approach, the preparation of **4** was achieved starting from the known dione **5**[6] (Scheme 2). Treatment of **5** with lithium bis(trimethylsilyl)amide LiN(TMS)$_2$ (1.2 equiv) in tetrahydrofuran containing HMPA at −30 °C followed by the addition of *N*-phenyltrifluoromethanesulfonimide led to the enol triflate **6** in 81% yield. Palladium-catalyzed coupling[7] of vinyltributyltin with **6** using tetrakis(triphenylphosphine)palladium in the presence of LiCl in refluxing THF cleanly afforded diene **7** in 88% yield. Diels−Alder cycloaddition of **7** with phenyl vinyl sulfone[8] has been found to be neither regio- nor stereoselective. Thus, heating **7** with phenyl vinyl sulfone in benzene at 120 °C in a sealed tube gave a mixture of four stereoisomers (90%) that was directly desulfonated with excess 6% sodium amalgam, affording tricyclic ketone **4** as an unseparable 3:1 mixture of isomers in 69% yield. Since spectroscopic data were found to be impractical for the determination of the stereochemistry at C-4a,[9] the mixture was submitted to epoxidation (*m*-CPBA) leading to readily separable epoxides **8** in 2.5:1 ratio[10] in 85% combined yield (eq 1). The major isomer, which is crystalline, was submitted to X-ray crystallographic analysis, giving structure **8a**.[30] We therefore

Scheme 1



2 **4** **3**

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(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.; Ushida, I.; Hoshida, K.; 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 stereocontrolled construction of complex cyclic ketones via oxy-Cope rearrangements, see: Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609−626.

(5) For our preliminary report see: Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y.; Prangé, T. *J. Org. Chem.* **1993**, *58*, 2349−2350.

(6) Gerlach, H.; Müller, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1030−1031. Almqvist, F.; Eklund, L.; Frejd, T. *Synth. Commun.* **1993**, *23*, 1499−1505.

(7) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630−4632; *Org. Synth.* **1990**, *68*, 116−129.

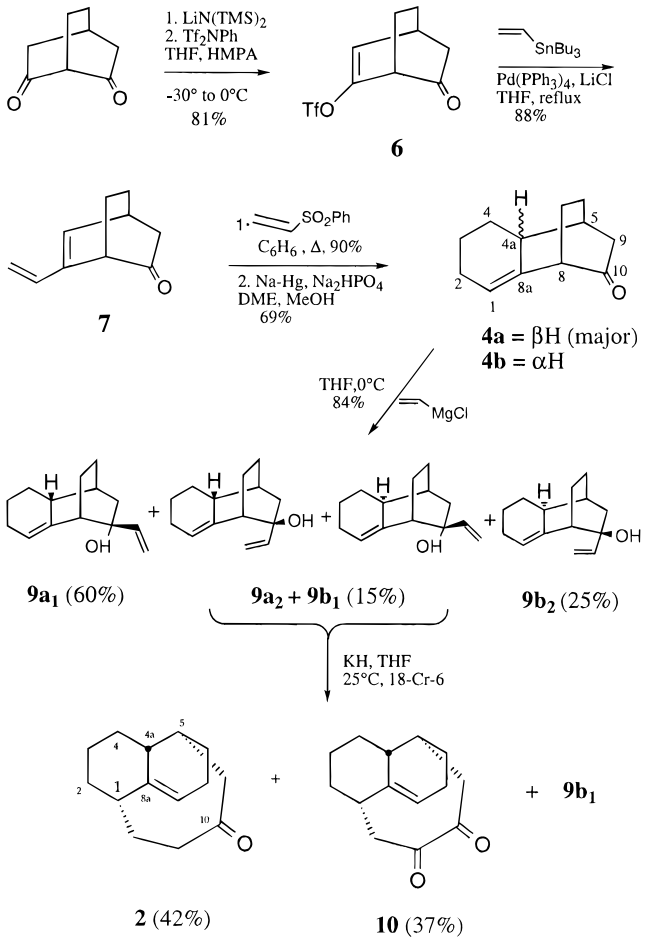
(8) For a review on the chemistry of vinyl sulfones, see: Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951−6984.

(9) The numbering used in this paper refers to the corresponding centers of vinigrol.

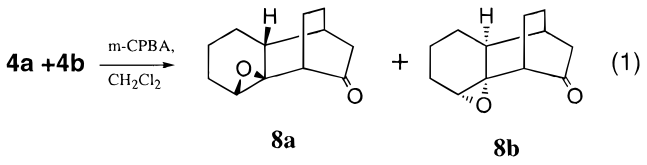
(10) This ratio (2.5:1 instead 3:1 for **8**) is due to further Baeyer−Villiger oxidation of **8a** leading to an epoxy lactone.

S0022-3263(97)00343-5 CCC: $14.00

Scheme 2



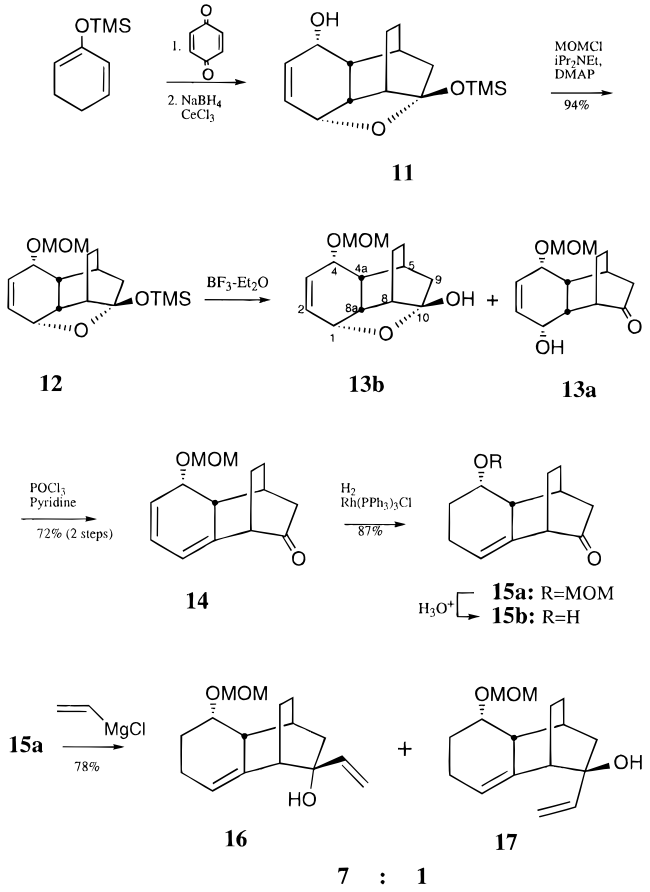
deduced that isomer **4a** has the same stereochemistry (4aβ) at the cyclohexane−bicyclo[2.2.2]octane ring junction.



Addition of vinylmagnesium chloride to **4** in THF at 0 °C gave rise to a mixture of four alcohols **9** in 84% combined yield. Separation by flash chromatography provided two isomers in a pure form, $\mathbf{9a_1}$ and $\mathbf{9b_2}$ in 60% and 25% yield, respectively, along with alcohols $\mathbf{9a_2}$ and $\mathbf{9b_1}$ as a 2:1 unseparable mixture in 15% combined yield. Obviously, isomers $\mathbf{9a_1}$ and $\mathbf{9a_2}$ must arise from the major ketone **4a**. The two products $\mathbf{9a_2}$ and $\mathbf{9b_2}$ were easily recognized to be those diastereoisomers resulting from endo addition. The stereochemical assignment of these products is supported by the observation that their vinyl protons at the terminus of the allylic alcohol moiety appear at higher field (0.1−0.2 ppm) than the corresponding protons of $\mathbf{9a_1}$ and $\mathbf{9b_1}$. This effect is presumably a consequence of diamagnetic shielding of these protons by the cyclohexenyl double bond.[11]

As we were unable to separate these isomers, the anionic oxy-Cope rearrangement was effected on the mixture ($\mathbf{9a_2}$ + $\mathbf{9b_1}$). Treatment with KH (3 equiv) in the presence of 18-crown-6 in THF at room temperature gave rise to a mixture readily separated by flash chromatography of the desired rearranged product **2** (42% with respect to $\mathbf{9a_2}$), the α-diketone **10**[12] (37%), and $\mathbf{9b_1}$ recovered unchanged. The structure of **2** and **10** was assigned on the basis of their spectroscopic data. As expected, the epimeric vinylcarbinol $\mathbf{9a_1}$ was recovered unchanged when subjected to the same conditions (even in diglyme at 145 °C). However, $\mathbf{9b_2}$ likewise failed to undergo the rearrangement despite the apparent proper stereochemistry of the allylic alcohol moiety.

Scheme 3



Having thus ascertained that $\mathbf{9a_2}$ underwent a facile alkoxide-accelerated [3,3]sigmatropic rearrangement to give the tricyclic ring system of vinigrol, we then turned to the synthesis of the more elaborate ketone **15**. Furthermore, this approach in Scheme 2 suffered from several drawbacks, in particular the lack of selectivity in both the Diels−Alder and Grignard steps.

The preparation of **15** (Scheme 3) was initiated by the Diels−Alder reaction of 2-[(trimethylsilyl)oxy]-1,3-cyclohexadiene[13] with 1,4-benzoquinone followed by Luche reduction[14] of the crude adduct to afford **11** as a sole stereoisomer in 60% overall yield.[15] Protection of the

(11) (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.

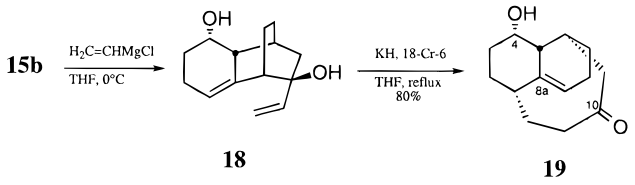
(12) The formation of diketone **10** resulted from in situ overoxidation of the enolate formed as a result of the oxy-Cope process. See, for example: Paquette, L. A.; De Russy, N. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576−4581 and references cited therein.

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

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

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

Scheme 4



18 **19**

hydroxy group as its methoxymethyl ether **12** 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 **13a** along with its hemiacetal **13b**. At this stage, dehydration was effected by slow addition of phosphorus oxychloride to a solution of **13** in dichloromethane in the presence of pyridine. During this addition, the temperature must be kept at 22−24 °C.[16] Purification of the crude product was accomplished by careful chromatography on silica gel−silver nitrate (1.5%), in order to eliminate chlorinated byproducts. Under these conditions, pure diene **14** was obtained in 72% overall yield from **12**.[17] Selective hydrogenation of the less hindered double bond of conjugated diene **14** with Wilkinson's catalyst gave rise to the desired functionalized ketone **15a** in almost quantitative yield.

Exposure of **15a** to vinylmagnesium chloride in ether at 0 °C gave rise to a 7:1 mixture of the diastereomeric alcohols **16** and **17** (78%), which were readily separated by flash chromatography. As was observed previously in the case of ketone **4**, the attack that prevailed was from the sterically less hindered exo face. Attempts to invert the stereochemistry of the undesirable isomer to afford **17** using the sulfoxide−sulfenate [2,3] sigmatropic rearrangement failed.[18]

In order to overcome the lack of stereoselectivity in the Grignard step, addition of vinylmagnesium chloride was attempted on hydroxy ketone **15b**, readily obtained by acid hydrolysis of **15a**. It was gratifying to find that **15b** reacted with excess vinylmagnesium chloride, affording almost exclusively the endo vinyl isomer **18** in 75% yield (Scheme 4). Reprotection of the hydroxy group gave the corresponding methoxymethyl ether, which has analytical and spectoscopic data identical with those of previously prepared **17**. The stereoselectivity of the Grignard reaction with **15b** is probably the result of chelation control:[21] the Grignard reagent first deprotonates the hydroxy group and then the intermediate Mg−alkoxy moiety and then induces the attack from the α-side (Figure 1). This unprecedented remote effect of the hydroxy group on π-facial selectivity was observed in the addition of various Grignard reagents (MeMgBr, CH_2=CHMgBr, (*E*)-i$PrCH_2$=CHMgBr, etc....) to ketone **15b**.[22]

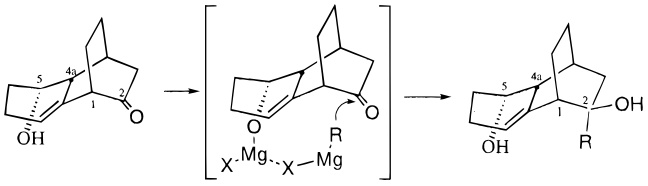


Figure 1. Remote effect of the hydroxyl group.

Next, the anionic oxy-Cope rearrangement was effected on diol **18**. Exposure of **18** to excess KH in refluxing THF under argon in the presence of 18-crown-6 (3 equiv) for 30 min cleanly afforded **19** in 83% yield. The structure of this compound was assigned on the basis of spectroscopic data and confirmed by X-ray crystallographic analysis.[5,30] Consequently, a short route from easily available raw materials to a tricyclic cyclooctanoid substance related to vinigrol had been successfully implemented.

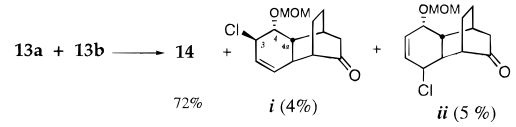
Our attention was next turned to functional group modification in **19**. Specifically, completion of a route to functionalize squeleton of vinigrol required (1) reductive removal of the carbonyl group at carbon 10, (2) introduction of a tertiary alcohol at 8a, and (3) functionalization of ring A.

To this end, the hydroxyl group at carbon 4 was first protected as its methoxymethyl (MOM) **22** or triethylsilyl (TES) ether **23**. A large number of methods have been reported for the reductive removal of the carbonyl group (Huang-Minlon reduction, conversion to the tosylhydrazone, the diethyl phosphate or the dithioacetal, and subsequent reduction, etc....).[23] When these conditions were applied to **19** and **22**, none resulted in isolation of the desired compound (Scheme 5). Accordingly, removal of the carbonyl group was then attempted *via* alcohols **24** and **25**[24] using the Barton deoxygenation procedure[25] or Ireland technology.[26] However, **24** remained unchanged upon treatment with bis(dimethylamino)phosphorochloridate. On the other hand, when the thiocarbonate derived from **25** was reduced with tributyltin hydride, only tetracyclic compound **26** was formed.

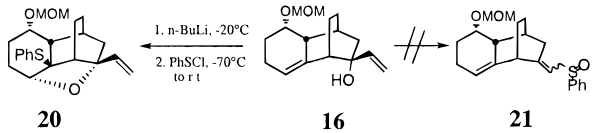
Subsequently, more detailed investigations revealed that these observations were due to the proclivity of this tricyclic system for transannular cyclization under acidic or radical conditions.

(16) When the reaction was effected at 0 °C or below, aromatization occurred, leading to a great amount (30−35%) of undesirable aromatic ketone.

(17) Diene **14** must be freed completely of chlorinated byproducts **i** and **ii** prior hydrogenation in order to realize reproducibility complete conversion to **15a**.



(18) In fact, treatment of **16** with phenylsulfenyl chloride according to the described procedure[19] led to tetracyclic tetrahydrofuran **20** rather than the expected sulfoxide **21**.[20]



20 **16** **21**

(19) 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.

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

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

(22) Devaux, J.-F.; Fraisse, P.; Hanna, I.; Lallemand, J.-Y. *Tetrahedron Lett.* **1995**, *36*, 9471−9474.

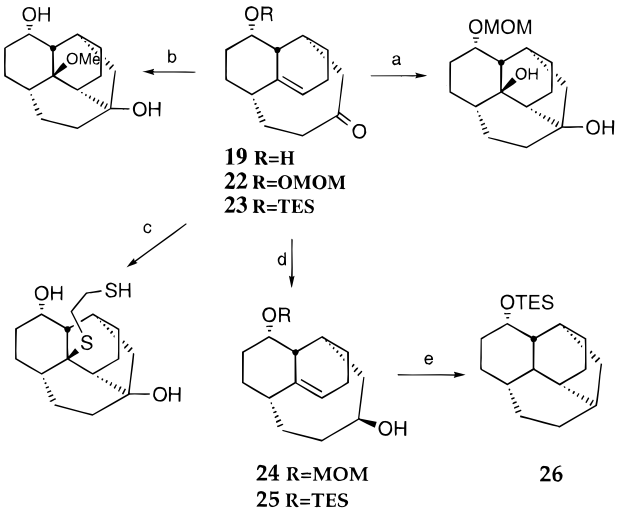
(23) For a review, see: Hutchins, O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 327−362.

(24) Treatment of **22** with lithium aluminum hydride in THF at 0 °C was found to give **24** (98%) as the only detectable stereoisomer. Assignment of configuration to this alcohol was deduced from X-ray crystallographic analysis of the acid-catalyzed rearrangement product of its methyl ether, see: Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y.; Prangé, T. *J. Chem. Res., Synop.* **1996**, 32. Under the same conditions, ketones **23** and **19** afforded **25** and **30**, respectively.

(25) Barton, D. H. R.; McCombie, S. W. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

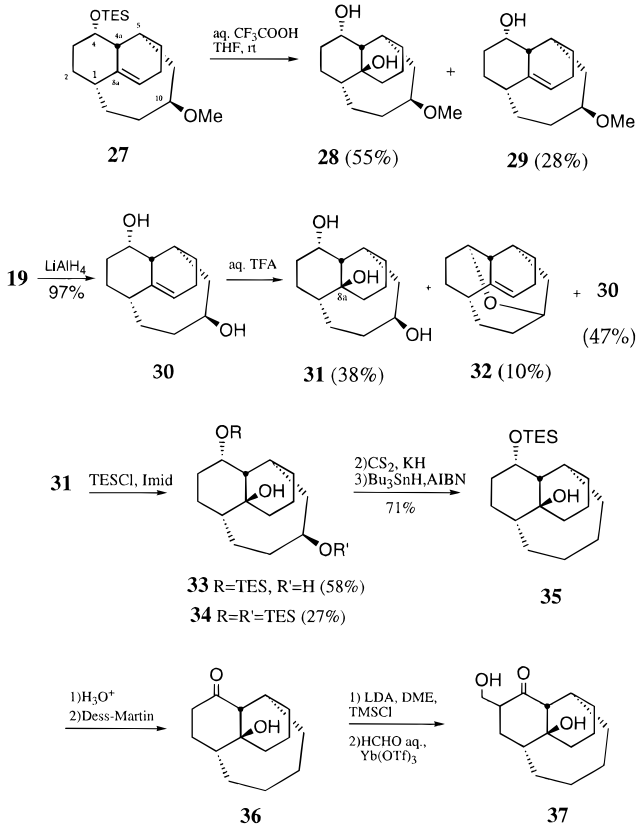
(26) Ireland, R. E.; Giger, R.; Kamata, S. *J. Org. Chem.* **1977**, *42*, 1271−1283.

Scheme 5[a]



[a] Key: (a) LDA THF, −70 to −10 °C, then $ClP(O)(OEt)_2$, −70 to +25 °C; (b) $TsNHNH_2$, MeOH, reflux, 84%; (c) $HS(CH_2)_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 20 °C, 70%; (d) $LiAlH_4$, THF, 0 °C, 98%; (e) (1) KH, THF, CS_2, MeI; (2) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 60%.

Scheme 6



Finally, the solution came from an unexpected observation. Exposure of triethylsilyl ether **27**, readily prepared from **25** (KH, MeI, THF, rt, 99% yield), to 25% aqueous trifluoroacetic acid in THF at room temperature led to diol **28** (55% yield) along with **29** (28% yield), which can be converted to **28**. The formation of **28** obviously resulted from the regio- and stereoselective hydration of the double bond in **27**. Under the same conditions, diol **30**[24] furnished triol **31** (38% yield) together with cyclic ether **32** (10% yield) and recovered starting material (47% yield) (Scheme 6). In this way, the hydroxy group at carbon 8a with the right stereochemistry was set up. We then considered the removal of the oxygenated function on the eight-membered ring, and a selective protection of the hydroxyl function at carbon 4 was attempted. Fortunately, treatment of **31** with triethylsilyl chloride in the presence of imidazole in DMF gave rise to a mixture of monosilylated ether **33** and the doubly protected diol **34** in 58% and 27% yield, respectively. The latter could be desilylated to give back the starting diol **31** in good yield. Reductive removal of the secondary hydroxyl group was achieved in a straightforward manner using the Barton deoxygenation procedure to afford **35** in 71% yield.

Following this successful effort to arrive at **35**, attention was directed to the functionalization of ring A. Thus, **35** was desilylated and then subjected to Dess−Martin oxidation[27] to furnish hydroxy ketone **36** in 73% overall yield. Our plan initially involved three crucial steps: (a) carboxymethylation of **36** at C-3, (b) introduction of the A-ring double bond, and (c) stereoselective reduction of the β-keto ester moiety. Unfortunately, all attempts to prepare β-keto ester from **36** failed. For example, treatment of **36** with lithium diisopropylamide followed by quenching with methyl cyanoformate either in THF or ether[28] produced mostly O-acylation. This failure is probably due to the higher steric demand of ketone **36**.

Consequently, introduction of the hydroxymethyl unit at C-3 was next considered via the silyl enol ether according to Kobayashi's procedure.[29] Thus, reaction of **36** with LDA in dimethoxyethane at −78 °C followed by quenching with chlorotrimethylsilane gave a mixture of mono- and disilylated enol ethers in 75−95% combined yield. Subsequent exposure of these compounds to 37% aqueous formaldehyde in the presence of a catalytic amount of ytterbium triflate [$Yb(OTf)_3$] in THF and water led to a separable mixture of hydroxymethyl ketone **37** (45−55% yield) and starting ketone **36** (32−37% yield). However, all attempts to introduce the double bond by selenylation of **37** (LDA, DME, then PhSeCl) and subsequent selenoxide oxidation failed to give the desired α,β-unsaturated ketone. Instead, a mixture of intractable compounds was obtained.

Despite the failure in the final steps, at this point in this model study, we know a great deal about the functionalized tricyclic system of vinigrol. At present, our efforts are focused on the total synthesis of vinigrol by setting up the missing alkyl groups (two methyl groups at C-8 and C-9 and isopropyl at C-12).

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

Experimental Section

Melting points were determined on a Reichert hot stage apparatus. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer as solutions in CCl_4. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 or AM 400 NMR spectrometers as solutions in $CDCl_3$, using residual protic

(27) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(28) Crabtree, S. R.; Alex Chu, W. L.; Mander, L. N. *Synlett* **1990**, 169−170.

(29) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590−3596.

(30) The author has deposited atomic coordinates for **8a** and **19** 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.

solvent $C\underline{H}Cl_3$ (δ_H = 7.27 ppm) or $\underline{C}DCl_3$ (δ_C = 77.1 ppm) as internal reference. Mass spectra were determined on a Hewlett-Packard HP 5970B/5890A at 70 eV. All reactions were monitored by TLC carried out on 0.2 mm Merck aluminum silica gel (60 F_{254}) precoated plates using UV light and 5% ethanolic phosphomolybdic acid and heat as developing agent. Flash chromatography was performed on 40−63 μm (400−230 mesh) silica gel 60 with ethyl acetate (AcOEt)−petroleum ether (bp 40−60 °C) (PE) as eluent. Commercially available reagents and solvents were purified and dried when necessary by usual methods.

(2α,2aα,5*β*,5aα,8aα,8bα)-2a,3,4,5,5a,6,8a,8b-Octahydro-2-[(trimethylsilyl)oxy]-2,5-methanonaphth[1,8-*bc*]-6-ol (11). A magnetically stirred solution of 1,4-benzoquinone (2.04 g, 18.9 mmol) and 2-[(trimethylsilyl)oxy]-1,3-cyclohexadiene (4.0 g, 23.8 mmol) in dry benzene (20 mL) was refluxed under argon for 5 h. Evaporation of the solvent afforded a greenish solid (5.04 g) that was used in the next reaction without further purification: ^{1}H NMR (200 MHz) δ 6.67 (2 H, s), 4.95 (1 H, dd, J = 7.0, 2.0 Hz), 3.18 (1 H, m), 3.0−2.9 (3 H, m), 1.7−1.3 (4 H, m), 0.13 (9 H, s) ppm: ^{13}C NMR (50 MHz) δ 199.7, 198.6 (2 C), 155.7 (C), 142.3, 142.0 (2 CH), 102.4 (CH), 50.2, 49.7 (2 CH), 41.2, 36.4 (2 CH), 26.2, 25.5 (2 CH_2), 0.2 (CH_3) ppm.

To a mixture of the above crude adduct and $CeCl_3\cdot 7H_2O$ (7.74 g, 20.8 mmol) in MeOH (90 mL) stirred at 0 °C was added $NaBH_4$ (0.79 g, 20.8 mmol) in small portions. Stirring was continued for 5 min before neutralization of the reaction mixture by addition of 0.1 N HCl (10 mL). After evaporation of the solvent under reduced pressure, the residue was taken up with AcOEt and water, and the layers were separated. The aqueous phase was extracted with AcOEt (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt/PE 1:2) to afford 3.20 g (61%) of **11** as a white solid: mp 70−72 °C (ether); IR 3623, 3032 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.77 (2H), 4.38 (1H, d, J = 7.2 Hz), 4.20 (1H, dd, J = 6.7, 2.9 Hz), 2.56 (1H, dd, J = 6.7, 2.9 Hz), 2.2−1.4 (9H, m), 0.15 (9H, s) ppm; ^{13}C NMR (50 MHz) δ 131.6 and 128.5 (CH), 105.1 (C), 66.5 and 66.1 (CH), 44.7 (CH_2), 44.6 (CH), 38.6 (CH), 37.2 (CH), 29.8 (CH_2), 23.8 (CH), 15.4 (CH_2), 2.0 (CH_3) ppm. Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63. Found: C, 64.48; H, 8.58.

The (Methoxymethyl)oxy Ether 12. To a stirred solution of **11** (15.60 g, 55.6 mmol) in dry CH_2Cl_2 (185 mL) were added iPr_2NEt (68 mL, 390 mmol) and DMAP (0.34 g). To this mixture, cooled in an ice−water bath, was added MOMCl (21 mL, 280 mmol) dropwise, and the resulting mixture was allowed to warm to room temperature overnight. The excess MOMCl was carefully hydrolyzed with water (20 mL), and the mixture was diluted with CH_2Cl_2. The organic phase was washed with aqueous 0.5 N HCl (3 × 100 mL) and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/PE 1:9) to give 16.52 g (91%) of **12** as a colorless, viscous oil that crystallized on cooling: mp 41−45 °C (petroleum ether); IR 3036 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.73 (2H, s), 4.65 (2H, s), 4.20 (2H, m), 3.35 (3H, s), 2.50 (1H, dd, J = 13.7, 6.8 Hz), 2.1 (2H, m), 1.93 (2H, m), 1.8−1.3 (5H, m), 0.10 (9H, s) ppm; ^{13}C NMR (50 MHz) δ 129.9 and 128.4 (CH), 104.9 (C), 95.4 (CH_2), 71.6 (CH), 66.0 (CH), 55.3 (CH_3), 44.5 (CH_2), 44.5 (CH), 36.8 (CH), 36.3 (CH), 29.6 (CH_2), 24.3 (CH), 15.2 (CH_2), 1.8 (CH_3) ppm. Anal. Calcd for $C_{17}H_{28}O_4Si$: C, 62.93; H, 8.70. Found: C, 63.17; H, 8.88.

Cleavage of the Acetal 12, 13a, and 13b. To a stirred solution of **12** (16.51 g, 50.9 mmol) in anhydrous THF (127 mL) cooled in dry ice−acetone bath was added dropwise $BF_3\cdot Et_2O$ (25.0 mL, 204 mmol) under argon. After the solution was stirred for 15 min at −78 °C, water (50 mL) was carefully added and the mixture allowed to warm to 0 °C prior to dilution with ethyl acetate (240 mL). The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL). The aqueous layer was extracted with AcOEt, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to afford 4.88 g of the mixture **13a** and **13b** as a white solid, mp 70.5−79 °C (from ether), which was used without further purification in the next step: IR 3588, 3353, 1723 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.58; H, 8.09.

Ketone 13a: ^{13}C NMR (50 MHz) δ 218.7 (C), 132.6 and 132.0 (CH), 95.3 (CH_2), 71.2 (CH), 67.0 (CH), 55.4 (CH_3), 43.2 (CH), 42.0 (CH), 41.8 (CH_2, C-*9*), 38.0 (CH), 28.4 (CH), 25.2 and 23.4 (CH_2) ppm.

Hemiketal 13b: ^{13}C NMR (50 MHz) δ 130.4 and 127.9 (CH), 104.0 (C), 95.3 (CH_2), 71.5 (CH), 67.0 (CH), 55.4 (Me), 43.7 (CH), 42.1 (CH_2), 37.0 and 36.1 (CH), 24.0 (CH), 29.3 and 15.2 (CH_2) ppm.

(1α,4α,4aα,5*β*)-3,4,4a,5-Tetrahydro-5-(methoxymethoxy)-1,4-ethanonaphthalen-2(1*H*)-one (14). To a stirred solution of **13** (6.41 g, 25.44 mmol) in dry pyridine (68 mL) was added dropwise freshly distilled $POCl_3$ (9.48 mL, 102 mmol), *while the temperature was kept between 22 and 24 °C* by cooling with a cold water bath. The reaction mixture was stirred for 20 min, cooled to 0° C, and then diluted with ether (140 mL), and the excess $POCl_3$ was hydrolyzed by careful addition of water (75 mL). The organic phase was separated and the aqueous layer extracted with ether (3 × 500 mL). The combined organic phases were washed with aqueous saturated $CuSO_4$ solution (4 × 65 mL) and brine and dried ($MgSO_4$). Concentration in vacuo afforded diene **14**, which was carefully purified by chromatography on silica gel−$AgNO_3$(AcOEt/PE 1:4), yielding 4.29 g (72% from **12**): mp 48.5−50 °C; IR 3043, 1728 cm^{-1}; ^{1}H NMR (200 MHz) δ 6.20 (1H, dd, J = 9.7, 5.2 Hz), 6.05 (1H, ddt, J = 9.7, 5.4 Hz), 5.90 (1H, dd, J = 5.2, 3.4 Hz), 4.70 (1H, d J = 6.8 Hz), 4.50 (1H, d J = 6.8 Hz), 4.06 (1H, dd, J = 6.5, 5 Hz), 3.32 (3H, s), 3.06 (1H, t, J = 2 Hz), 2.84 (1H, dt, J = 18.8, 2 Hz), 2.59 (1H, m), 2.40 (1H, br s), 2.22 (1H, ddd, J = 18.8, 3.2, 1 Hz), 2.1−1.6 (4H, m) ppm; ^{13}C NMR (50 MHz) δ 211.4 (C), 137.4 (C), 127.5, 123.9 and 117.8 (CH), 94.7 (CH_2), 68.9 (CH), 55.5 (CH_3), 53.4 (CH), 43.4 (CH_2), 42.7 (CH), 30.0 (CH, C-*5*), 27.7 and 23.5 (CH_2) ppm. Anal. Calcd for $C_{10}H_{12}O$: C, 71.77; H, 7.74. Found: C, 72.04; H, 7.78.

(1α,4α,4aα,5*β*)-3,4,4a,5,6,7-Hexahydro-5-(methoxymethoxy)-1,4-ethanonaphthalen-2(1*H*)-one (15a). To a solution of diene **14** (4.52 g, 19.3 mmol) in benzene (45 mL) was added tris(triphenylphosphine)rhodium chloride (0.54 g, 0.58 mmol), and the mixture was stirred under a hydrogen atmosphere for 3 h at room temperature. The solvent was removed under reduced pressure, affording a residue that was purified by flash chromatography (AcOEt/PE 1:3) to give 4.45 g of **15a** (94%) as a colorless viscous oil that crystallized on cooling: mp 51−53 °C; IR 1712 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.45 (1H, m), 4.64 (1H, d, J = 6.8 Hz), 4.50 (1H, d, J = 6 Hz), 4.03 (1H, m), 3.27 (3H, s), 2.94 (1H, dt, J = 18.5, 2 Hz), 2.77 (1H, t, J = 2 Hz), 2.40 (1H, m), 2.2−1.4 (10H, m) ppm; ^{13}C NMR (50 MHz) δ 212.5 (C), 131.9 (C), 122.3 (CH), 94.6 (CH_2), 72.6 (CH), 55.5 (CH_3), 53.2 (CH), 42.6 (CH_2), 42.1 (CH), 31.6 (CH, C-*5*), 28.1 (CH_2), 25.7 (CH_2), 22.3 (CH_2), 21.5 (CH_2) ppm; MS CI(NH_3) *m*/*z* 254 (100, M + NH_4^+), 357 (60, M + H^+), 222 (33), 205 (53).

Addition of Vinylmagnesium Chloride to 15a. A solution of vinylmagnesium chloride in THF (4.1 mL of 1.69 M, 6.9 mmol) was added dropwise to a solution of ketone **15a** (364 mg, 1.54 mmol) in dry THF (6 mL) at 0 °C and the mixture stirred for 1 h at this temperature. After quenching with water (5 mL) and dilution with ether (10 mL), the pH was adjusted to neutrality with 1 N HCl. The layers were separated, the aqueous phase was extracted with ether (2 × 10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (AcOEt/PE 1:4) to give 42 mg (10%) of **17**, 277 mg (68%) of its epimer **16**, and 22 mg (6%) of the starting ketone **15a**.

Minor isomer: (1α,2α,4α,4aα,5*β*)-2-ethenyl-1,2,3,4,4a,-5,6,7-octahydro-5-(methoxymethoxy)-1,4-ethanonaphthalen-2-ol (17): ^{1}H NMR (200 MHz) δ 6.22 (1 H, dd, J = 17.5, 10.7 Hz), 5.32 (1 H, m), 5.17 (1 H, dd, J = 17.5, 1.2 Hz), 4.94 (1 H, dd, J = 10.7, 1.2 Hz), 4.72 (1 H, d, ^2J = 6.7 Hz), 4.58 (1 H, d, ^2J = 6.7 Hz), 4.02 (1 H, br s), 3.36 (3 H, s), 2.43 (1 H, d, J = 14 Hz), 2.3−1.2 (12 H, m) ppm; ^{13}C NMR (50 MHz) δ 146.7 (CH), 136.9 (C), 119.9 (CH), 109.2 (CH_2), 94.9 (CH_2), 74.8 (C), 73.4 (CH), 55.5 (Me), 46.3 (CH), 42.0 (CH), 39.7 (CH_2), 31.1 (CH), 27.3, 26.5, 21.6, 19.7 (4 CH_2) ppm.

Major isomer: (1α,2*β*,4α,4aα,5*β*)-2-ethenyl-1,2,3,4,4a,-5,6,7-octahydro-5-(methoxymethoxy)-1,4-ethanonaphthalen-2-ol (16): ^{1}H NMR (200 MHz) δ 5.94 (1 H, dd, J =17.2, 10.7 Hz), 5.50 (1 H, m), 5.32 (1 H, dd, J = 17.2, 1.5 Hz), 5.11 (1 H, dd, J = 10.7, 1.5 Hz), 4.74 (1 H, d, ^2J = 6.8 Hz), 4.62 (1 H, d, ^2J = 6.8 Hz), 4.06 (1 H, m), 3.36 (3 H, s), 3.20 (1 H, br s), 2.3−1.4 (13 H, m) ppm; ^{13}C NMR (50 MHz) δ 142.9 (CH), 135.7 (C), 121.7 (CH), 112.5 (CH_2), 94.8 (CH_2), 73.9 (CH), 72.7 (C), 55.8 (Me), 47.4 (CH), 43.7 (CH), 39.6 (CH_2), 30.6 (CH), 28.0, 26.3, 21.8, 20.0 (4 CH_2) ppm.

(1α,4α,4aα,5*β*)-3,4,4a,5,6,7-Hexahydro-5-hydroxy-1,4-ethanonaphthalen-2(1*H*)-one (15b). To a solution of the (methoxymethyl)oxy ether **15a** (8.75 g, 37 mmol) in THF (90 mL) was added 4 N aqueous HCl (110 mL), and the mixture was heated at 65 °C for 15 min. After cooling, ether (250 mL) was added, and the layers were separated. The aqueous phase was extracted with ether, and the combined organic layers were washed with aqueous saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was removed on a rotary evaporator and the residue purified by flash chromatography (AcOEt/PE 3:2) to afford 6.49 g (91%) of **15b** as a colorless solid: mp 74.5−76 °C (petroleum ether); IR 3625, 3454 (broad), 1721 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.51 (1H, dd, J = 6.5, 3.2 Hz), 4.15 (1H, dd, J = 5.9, 3.0 Hz), 2.95 (1H, dt, J = 19.7, 2.4 Hz), 2.82 (1H, t), 2.36 (1H, br s), 2.2−1.2 (10H, m) ppm; ^{13}C NMR (50 MHz) δ 213.1 (C), 132.1 (C), 122.1 (CH), 68.0 (CH), 53.4 (CH), 42.8 (CH), 42.5 (CH_2), 31.5 (CH), 29.5 (CH_2), 28.1 (CH_2), 22.2 (CH_2), 20.7 (CH_2) ppm. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.62; H, 8.11.

Addition of Vinylmagnesium Chloride to 15b. A solution of vinylmagnesium chloride in THF (83 mL of 1.69 M, 141 mmol) was added dropwise to a solution of ketone **15b** (6.76 g, 35.2 mmol) in dry ether (235 mL) at 0 °C and the mixture was stirred for 3 h at this temperature. The reaction mixture was diluted with ether and carefully quenched with water (30 mL), and the pH was adjusted to neutrality with 1 N HCl (140 mL). The layers were separated, the aqueous phase was extracted with ether (3 × 100 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (AcOEt/petroleum ether 1:2) to give 5.80 g (75%) of **18**, 0.62 g (8%) of its epimer, and 0.74 g (11%) of the starting ketone **15b**.

(1α,2α,4α,4aα,5*β*)-2-Ethenyl-1,2,3,4,4a,5,6,7-octahydro-1,4-ethanonaphthalene-2,5-diol (18): mp 96−98 °C (AcOEt/petroleum ether); IR 3605, 3085 cm^{-1}; ^{1}H NMR (200 MHz) δ 6.09 (1H, dd, J = 17.4, 10.7 Hz), 5.31 (1H, m), 5.15 (1H, dd, J = 17.4, 1.3 Hz), 4.92 (1H, dd, J = 10.7, 1.3 Hz), 4.08 (1H, m), 2.35 (1H, dt, J = 14.4 Hz), 2.2−1.2 (12H, m) ppm; ^{13}C NMR (50 MHz) δ 146.2 (CH), 137.1 (C), 119.6 (CH), 110.4 (CH_2) 74.3 (C), 68.9 (CH), 46.2 (CH), 42.7 (CH), 39.2 (CH_2), 31.0 (CH), 30.2 (CH_2), 27.3 (CH_2), 20.7 (CH_2), 19.5 (CH_2) ppm. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.46; H, 9.08.

Oxy-Cope Rearrangement of 18. To a suspension of KH (3.73 g, 93 mmol) [obtained from excess KH in mineral oi1 washed with dry pentane (3 × 20 mL) under argon] in anhydrous THF (25 mL) cooled to 0 °C was added dropwise a solution of allylic alcohol **18** (6.26 g, 28.41 mmol) and 18-crown-6 (15.67 g, 59 mmol) in THF (110 mL). The reaction mixture was then heated at reflux for 1.5 h, cooled, quenched by careful addition of water (30 mL), diluted with ether (200 mL), and washed with aqueous NH_4Cl (2 × 80 mL). The layers were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The combined organic layers were washed with brine and dried. Evaporation of the solvent under reduced pressure afforded 6.92 g of a white solid that was recrystallized from AcOEt to give 5.19 g (83%) of pure **20**: mp 160−162 °C (AcOEt); IR 3626 (sharp), 3425 (broad), 1683 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.29 (1H, d, J = 6.8 Hz), 4.35 (1H, brs), 3.33 (1H, dd, J = 10.7, 3.1 Hz), 2.8−2.6 (2H, m), 2.5−2.4 (2H, m), 2.30 (1H, s), 2.2−2.0 (3H, m), 2.0−1.8 (7H, m), 1.7−1.5 (2H, m); ^{13}C NMR (50 MHz) δ 216.7 (C, C-*10*), 140.7 (C, C-*8a*), 127.8 (CH, C-*8*), 68.5 (CH, C-*4*), 45.3 (CH_2), 43.3 (CH), 43.2 (CH_2), 38.5 (CH), 36.0 (CH), 34.1 (CH_2), 29.9 (CH_2), 26.2 (CH_2), 23.1 (CH_2), 21.4 (CH_2) ppm. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 75.81; H, 9.35.

(1*R,4*S**,4a*R**,5*S**,10*S**)-1,2,3,4,4a,5,6,7-Octahydro-1,5-butanonaphthalene-4,10-diol (30).** To a stirred suspension of $LiAlH_4$ (1.14 g) in THF (25 mL) under nitrogen at 0 °C was added dropwise a solution of **19** (2.20 g, 10.0 mmol) in THF (60 mL). After the mixture was stirred for 10 min, ethyl acetate (70 mL) was slowly added followed by water (25 mL) and 1 N HCl solution (15 mL). Usual workup and flash chromatography (AcOEt−PE 2:1) of the residue led to 2.18 g of **30** (97%) as a colorless solid: mp 99−101 °C; IR 3623, 3537 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.93 (1 H, de, J = 7.6 Hz), 4.25−4.08 (2 H, m), 2.7 (2 H, m), 2.3−1.5 (15 H, m) ppm; ^{13}C NMR (100 MHz) δ 150.4 (C), 123.0 (CH), 69.9, 69.7 (2 CH), 41.7 (CH), 41.2 (CH_2), 35.9 (CH_2), 34.7 (CH), 33.4 (CH), 31.8 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 25.6 (CH_2), 22.7 (CH_2) ppm.

(1*R,4*S**,4a*S**,5*S**,8a*S**,10*S**)-2,3,4,4a,5,6,7,8-Octahydro-1,5-butanonaphthalene-4,8a,10(1*H*)-triol (31).** To a solution of **30** (184 mg, 0.83 mmol) in THF (8 mL) cooled to 0 °C was added 25% aqueous TFA (7.6 mL). After being stirred at room temperature for 5 h, the mixture was neutralized with sodium bicarbonate (2.5 g) and extracted with AcOEt (6 × 10 mL). The combined organic layers were dried, the solvent was removed, and the residue was chromatographed (AcOET−PE 4:1) to give 17 mg (10%) of ether **32**, followed by 86 mg (47%) of the starting diol and 75 mg (38%) of **31** as a colorless solid that sublimed at 200 °C, (from MeOH−AcOEt 1:10): ^{1}H NMR (CD_3OD, 200 MHz) δ 4.30 (1 H, m), 4.00 (1 H, m), 2.7−1.4 (19 H, m) ppm; ^{13}C NMR (CD_3OD, 50 MHz) δ 75.6 (C), 70.3, 69.3 (2 CH), 49.5 (CH), 42.3 (CH_2), 41.4 (CH), 39.2 (CH_2), 33.4 (CH), 32.4 (2 CH_2), 30.2 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 22.9 (CH_2) ppm. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.98; H, 10.25.

Monoprotection of the Triol 31. To a solution of **31** (152 mg, 0.65 mmol) in freshly distilled DMF (4 mL) at 0 °C was added imidazole (215 mg, 5 equiv) followed by chlorotriethylsilane (265 μL, 2.5 equiv), and the mixture was stirred at 10 °C for 8 h. After dilution with ether, the mixture was washed with aqueous $CuSO_4$ solution. Usual workup gave a residue that was purified by flash chromatography (AcOEt−PE 1:9 then 1:2), affording 81 mg (27%) of **34** followed by 130 mg (58%) of **33**.

(1*R,4*S**,4a*S**,5*S**,8a*S**,10*S**)-2,3,4,4a,5,6,7,8-Octahydro-4-[(triethylsilyl)oxy]-1,5-butanonaphthalene-8a,10(1*H*)-diol (33):** colorless solid; mp 146−147 °C (from AcOEt/EP 1:9); IR 3623 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.40 (1 H, dt, J = 10.9, 7.0 H), 4.13 (1 H, m), 2.6−1.2 (19 H, m), 0.96 (9 H, t, J = 7.9 Hz), 0.58 (6 H, q, J = 7.9 Hz) ppm; ^{13}C NMR (50 MHz) δ 75.0 (C), 69.9, 69.0 (2 CH), 49.7 (CH), 42.1 (CH_2), 40.8 (CH), 38.7 (CH_2), 32.4 (CH), 31.8 (2 CH_2), 30.5 (CH_2), 24.8 (2 CH_2), 22.1 (CH_2), 7.1 (3 Me), 5.2 (3 CH_2) ppm. Anal. Calcd for $C_{20}H_{38}O_3Si$: C, 67.74; H, 10.80. Found: C, 67.77; H, 11.01.

(1*R,4*S**,4a*S**,5*S**,8a*S**,10*S**)-2,3,4,4a,5,6,7,8-Octahydro-4,10-bis[(triethylsilyl)oxy]-1,5-butanonaphthalen-8a(1*H*)-ol (34):** colorless oil; IR 3604 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.40 (1 H, dt, J = 11.1, 6.8 Hz), 4.05 (1 H, m), 2.8−1.2 (19 H, m), 0.96 (18 H, t, J = 7.9 Hz), 0.57 (12 H, q, J = 7.9 Hz) ppm; ^{13}C NMR (50 MHz) δ 75.1 (C), 70.1, 69.2 (2 CH), 50.0 (CH), 42.3 (CH_2), 41.1 (CH), 39.1 (CH_2), 32.8 (CH_2), 32.6 (CH), 31.4 (CH_2), 30.6 (CH_2), 24.9 (2 CH_2), 22.1 (CH_2), 6.9 (6 Me), 5.3 (3 CH_2), 5.1 (3 CH_2) ppm.

(1α,4α,4a*β*,5α,8a*β*)-4-[(Triethylsilyl)oxy]-2,3,4,4a,5,6,7,8-octahydro-1,5-butanonaphthalen-8a(1*H*)-ol (35). To a suspension of potassium hydride (46 mg) (obtained from excess KH in mineral oil washed with dry pentane) in THF (1.5 mL) under nitrogen at 0 °C was added a solution of **33** (130 mg, 0.37 mmol) in THF (5 mL). After the mixture was stirred at room temperature for 3 h, carbon sulfide (110 μL) was added followed, after 30 min, by neat iodomethane (225 μL). The reaction mixture was stirred for an additional 30 min, cooled to 0 °C, and then poured into saturated NH_4Cl solution. Extraction with ether and usual workup gave a residue that was purified by flash chromatography (AcOEt−PE 1:9) to give 132 mg (82%) of pure xanthate as a colorless oil: IR 3604 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.98 (1 H, m), 4.43 (1 H, qe, J = 9.1 Hz), 2.59 (3 H, s), 2.4−2.1 (7 H, m), 1.99 (1 H, dd, J = 11.0,

4.0 Hz), 1.88 (1 H, t, $J = 6.4$ Hz), 1.8−1.4 (10 H, m), 0.95 (9 H, t, $J = 7.9$ Hz), 0.57 (6 H, q, $J = 7.9$ Hz) ppm.

To the stirred solution of the above xanthate and AIBN (2.5 mg) in dry benzene (4 mL) was added tributyltin hydride (316 μL, 5 equiv), and the mixture was heated to reflux under nitrogen for 15 min. Evaporation of the solvent at reduced pressure left a residue that was purified by flash chromatography (AcOEt−PE 1:19), furnishing 87 mg (87%) of **35** as a colorless oil: ^{1}H NMR (200 MHz) δ 4.39 (1 H, dt, $J = 11.4$, 6.3 Hz), 2.47 (1 H, m), 2.20−1.20 (20 H, m), 0.96 (9 H, t, $J = 7.9$ Hz), 0.56 (6 H, q, $J = 7.9$ Hz) ppm; ^{13}C NMR (50 MHz) δ 75.2 (C), 69.5 (CH), 49.7 (CH), 41.8 (CH_2), 41.6 (CH), 32.7 (CH_2), 32.1 (CH_2), 31.7 (CH), 31.1 (CH_2), 30.8 (CH_2), 25.8 (2 CH_2), 25.1 (CH_2), 23.8 (CH_2), 7.1 (3 Me), 5.2 (3 CH_2) ppm.

(1α,4a*β*,5α,8a*β*)-2,4a,5,6,7,8-Hexahydro-8a(1*H*)-hydroxy-1,5-butanonaphthalen-4(3*H*)-one (36). To the solution of **35** (676 mg, 2.0 mmol) in THF (10 mL) cooled to 0 °C was added 10% aqueous TFA solution (7.5 mL) and the mixture stirred for 15 min at room temperature. Dilution with ether followed by neutralization with saturated Na_2CO_3 and usual workup afforded a residue that was purified by flash chromatography (AcOEt−PE 1:3) to give 570 mg (95%) of the corresponding diol as a colorless solid: IR 3625, 3605, 3435 (brOH) cm^{-1}; ^{1}H NMR (200 MHz) δ 4.42 (1 H, dt, $J = 12.0$, 6.1 Hz), 2.43 (1 H, m), 2.2−1.2 (20 H, m) ppm; ^{13}C NMR (50 MHz) δ 75.0 (C), 69.4 (CH), 48.7 (CH), 41.6 (CH), 41.6 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 31.4 (CH), 31.0 (CH_2), 30.1 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 25.0 (CH_2), 23.6 (CH_2) ppm.

To a solution of the above diol in dichloromethane (10 mL) cooled to 0 °C and stirred under nitrogen was added pyridine (0.5 mL) followed by Dess−Martin periodinane (1.37 g). After being stirred for 45 min at room temperature, the mixture was cooled to 0 °C, diluted with ether, and treated with 1:1 saturated $NaHCO_3$−$Na_2S_2O_3$ solution (15 mL) for 5 min. Extraction with dichloromethane and usual workup gave a residue that was purified by flash chromatography (AcOEt−PE 1:2) to give 326 mg (73%, two steps) of hydroxy ketone **36** as a colorless solid that sublimated at 109 °C (from ether): IR 3600, 3420, 1702 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.55−2.35 (1 H, m), 2.10−1.75 (5 H, m), 1.75−1.50 (20 H, m), 1.50−1.35 (2 H, m) ppm; ^{13}C NMR (50 MHz) δ 215.9 (C), 74.6 (C), 59.4 (CH), 40.9 (CH), 39.8 (CH_2), 38.9 (CH_2), 35.3 (CH), 32.7 (CH_2), 32.0 (CH_2), 39.2 (CH_2), 25.8 (CH_2), 24.8 (CH_2), 24.6 (CH_2), 23.0 (CH_2) ppm. Anal. Calcd for $C_{14}H_{22}O_3$: C, 75.63; H, 9.97. Found: C, 75.16; H, 9.93.

Hydroxymethylation of 36. A solution of 2.5 M *n*-butyllithium in hexanes (0.9 mL, 2.25 mmol) was added to a solution of diisopropylamine (330 μL, 2.52 mmol) in DME (1.5 mL) at −20° C. After 15 min, the solution of LDA was cooled to −70 °C and a solution of **36** (111 mg, 0.5 mmol) in DME (1.5 mL) was added dropwise. The resulting mixture was allowed to warm to −15 °C prior to addition of chlorotrimethylsilane (250 μL, 1.96 mmol). The mixture was allowed to warm to 10 °C and then quenched with a saturated solution of sodium bicarbonate. The product was extracted with ether (3 × 30 mL), and the combined organic layers were washed with brine (30 mL) before drying. The solvent was removed under reduced pressure to provide a slightly yellow oil that was chromatographed on silica gel (elution with petroleum ether) to give 132 mg (78%) of the disilylated enol ether, followed by 15 mg (10%) of monosilyl enol ether.

To a 37% aqueous formaldehyde solution (1 mL) and THF (3 mL) were successively added $Yb(OTf)_3$ (40 mg, 60 μmol) and the above disilyl enol ether (132 mg, 0.39 mmol) in THF (1 mL). The mixture was stirred at room temperature for 36 h, and then THF was removed under reduced pressure. Water was added, and the product was extracted with dichloromethane. After the usual workup, the crude product was chromatographed on silica gel (AcOEt−PE 1:2 and 1:1) to give 27 mg (32%) of the starting ketone **36**, followed by 44 mg (45%) of **37**: IR 3600, 3471, 1691 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.27 (1H, br s), 3.74−3.79 (1H, m), 3.58−3.61 (1H, m), 3.35 (1H, br s), 2.77−2.80 (1H, m), 2.40−2.44 (2H, m), 2.16−2.19 (1H, m), 1.87−2.10 (6H, m), 1.61−1.80 (8H, m), 1.42−1.58 (2H, m) ppm; ^{13}C NMR δ 23.3 (CH_2), 24.9 (CH_2), 26.0 (CH_2), 28.2 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 32.7 (CH_2), 35.9 (CH), 39.8 (CH_2), 41.5 (CH), 49.4 (CH), 60.5 (CH), 64.2 (CH_2), 74.8 (C), 220 (C); MS (IE) *m*/*z* 252, M^+), 234 (M − 18), 216 (M − 36).

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Supporting Information Available: Experimental procedures including synthesis and characterization of compounds **2**−**10** and the X-ray crystal data for compounds **8a** and **19** (6 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.

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