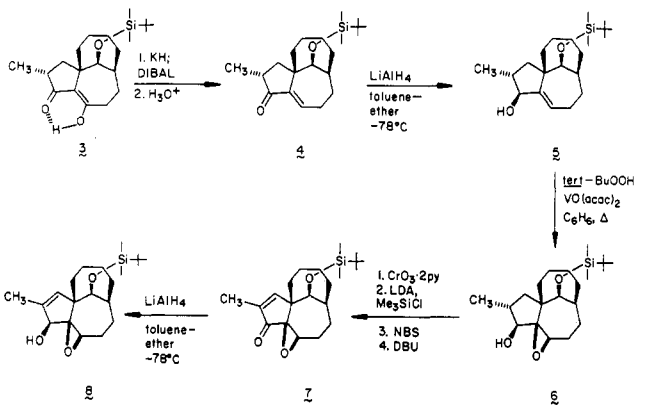
of natural *d*-α-tocopherol (**15**)[8] (Scheme III). The alkylation of trimethylhydroquinone 4-acetate[9] with sulfide **13** derived from (2*E*,7*R*,11*R*)-phytol (**10**)[10] via (2*R*,3*R*)-2,3-epoxyphytol (**11**)[11,12] afforded tetrasubstituted hydroquinone derivative **14**, $[\alpha]_D^{20}$ −2.22° (*c* 2.21, EtOH), in 75% yield. Reductive desulfurization of **14** with Raney nickel W4 in ethanol, followed by reductive elimination of the two acetyl groups with lithium aluminum hydride, afforded a tocopherol hydroquinone which was directly cyclized with an acid catalyst[8g] to give (2*R*,4′*R*,8′*R*)-α-tocopherol (**15**), $[\alpha]_D^{23}$ −1.1° (*c* 0.85, benzene), in 81% overall yield with an optical purity of 96% ee.[13] In a comparison of its spectral and chromatographic properties, the synthetic material proved identical in all respects with an anthentic sample of natural α-tocopherol.

Scheme I



3 4 5 6 7 8

(8) For a synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol and its precursor, see: (a) Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 650. (b) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Ibid.* **1976**, *59*, 290. (c) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (d) Chan, K.-K.; Specian, A. C., Jr.; Saucy, G. *Ibid.* **1978**, *43*, 3435. (e) Barner, R.; Schmid, M. *Helv. Chim. Acta* **1979**, *62*, 2384. (f) Cohen, N.; Lopresti, R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, *101*, 6710. (g) Cohen, N.; Lopresti, R. J.; Neukom, C. *J. Org. Chem.* **1981**, *46*, 2445. (h) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1982**, 205. (i) Cohen, N.; Banner, B. L.; Neukom, C. *Synth. Commun.* **1982**, *12*, 57. (j) Sakito, Y.; Suzukamo, G. *Tetrahedron Lett.* **1982**, 23, 4953. (k) Solladie, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097. (l) Takabe, K.; Okisaka, K.; Uchiyama, Y.; Katagiri, T.; Yoda, H. *Chem. Lett.* **1985**, 561.

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(12) $[\alpha]_D^{20}$ 4.39° (*c* 2.78, EtOH), lit.[11] $[\alpha]_D^{25}$ 4.3° (*c* 2.8, EtOH). The enantiomeric excess was determined by ^{1}H NMR on the corresponding epoxy acetate in the presence of Eu(hfbc)$_3$ to be 95% ee.

(13) The enantiomeric excess was determined by optical rotation of chromatographed $K_3Fe(CN)_6$ oxidation product of synthetic α-tocopherol, $[\alpha]_D^{17}$ +32.4° (*c* 0.17, isooctane), compared with that of natural α-tocopherol, $[\alpha]_D^{19}$ +33.9° (*c* 0.40, isooctane); see ref 8g.

Seiichi Inoue, Hiroshi Ikeda, Shuichi Sato
Kiyohiro Horie, Tomomi Ota
Osamu Miyamoto, Kikumasa Sato*
Department of Applied Chemistry
Faculty of Engineering
Yokohama National University
Tokiwadai, Hodogaya-ku
Yokohama 240, Japan
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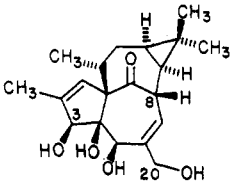
Ingenane Synthetic Studies. Stereocontrolled Introduction of All Oxygenated and Unsaturated Centers in an Ingenol Prototype

Summary: The keto tetrol **2**, a close prototype of ingenol, has been synthesized in highly stereoselective fashion.

Sir: In the period 1960–1985, during the course of extensive systematic phytochemical studies of the genus *Euphorbia* (ca. 1600 species), many esters of ingenol (**1**) were isolated and identified as the irritant principles of these plants. Of foremost importance, select 3-acylated derivatives of **1** were shown to possess potent tumor-promoting activity.[2] Kupchan's disclosure that ingenol 3,20-dibenzoate is an antileukemic agent[3] further heightened interest in this class of molecules.

X-ray crystallographic analysis of the triacetate of **1**[4,5] revealed its parent tetracyclic diterpenoid nucleus to feature inside–outside stereochemistry about the central bicyclo[4.4.1]undecanone core and to be characterized by an unusually dense all-cis array of contiguous hydroxyl functional groups along the outer periphery of rings A and B. To date, four approaches to construction of the ABC subunit of ingenol have been described.[5-8] Although that devised by Winkler actually leads to the correct intrabridgehead stereochemistry,[8] all products happen to be seriously underfunctionalized.



1

Herein, we describe experiments which for the first time properly set in place the second novel structural feature of ingenol, viz. its highly oxidized A/B ring functionality. The protocol, based on the readily available β-diketone **3**,[5] was predetermined to give **2** and ultimately permit bioassay of select fatty acid esters. Noteworthily, no analogues of **1** having inverted stereochemistry at C-8 have previously been available for biological evaluation.

Reductive deoxygenation of **3** was best effected (85%) by Dibal reduction of the potassium enolate at −45 °C with subsequent acidic workup (Scheme I). Enone **4** proved

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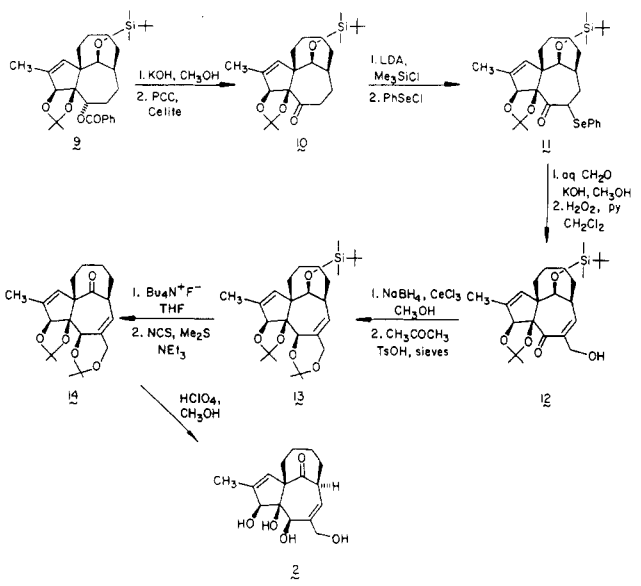
Scheme II



to be more prone to 1,4-reduction than expected. However, recourse to $LiAlH_4$ in toluene at −78 °C[9,10] did provide **5** in 65% yield alongside 4% of the epimer and 22% of the saturated ketone. The stereochemistry of the hydroxyl group in **5**, established by a comparative lanthanide shift ^1H NMR study of the two alcohols,[11] provided an additional clue[5] that delivery of reagents from the α surface might be generally favored kinetically.

To arrive at **6**, it was necessary to override this tendency and advantage was taken of the Sharpless epoxidation.[12,13] Introduction of the double bond in ring A was most expeditiously accomplished at this juncture. Subsequent to Cr(VI) oxidation of **6**, the ketone was converted into its silyl enol ether.[14] Of the several oxidation schemes applied to this intermediate, the combination of NBS[15] and DBU[16] was most accommodating, leading to **7** in 70% overall yield from **6**. Low-temperature hydride reduction of **7** then gave **8**.

Heightened functionalization of ring B was next initiated by titanium isopropoxide induced opening of the epoxy alcohol in the presence of ammonium benzoate.[17] Ensuing acetonide formation delivered **9** (91% for the two steps) and made possible chemospecific manipulation of the benzoyloxy group. To this end, saponification and oxidation of **9** with PCC on Celite[18] led to **10** (95%, Scheme II). For the purpose of introducing an oxygenated carbon α to its carbonyl group, the enolate of **10** was prepared and condensed with benzyl chloromethyl ether. However, complex mixtures and low yields were invariably seen. Recourse to SEMCl fared better at this stage, but the blocking group could not subsequently be disengaged. Accordingly, the enol silyl ether of **10** was reacted with benzeneselenenyl chloride[19] to give **11** (90%). Although the ^1H and ^{13}C NMR spectra of **11** revealed it to be a single stereoisomer, the relative orientation of the C–Se bond was not determined. Activation of the system in this manner permitted direct base-promoted condensation with aqueous formaldehyde[20] and caused oxidative elimination[21] within the single carbinol so produced to proceed more efficaciously than when alkylation preceded selenation. Noteworthy here is that no protection of the primary hydroxyl proved necessary during introduction of the final carbon center.

With **12** in hand, it remained to adjust the oxidation level at two key sites. As expected, reduction with $CeCl_3$-doped $NaBH_4$[22] proceeded exclusively to afford the 5-β-ol, nicely setting the stage for the subsequent elaboration of **13** (99% overall). Cleavage of the silyl ether with n-$Bu_4N^+F^-$ followed by Corey–Kim oxidation[23] resulted in smooth conversion to **14** (75%). Unmasking of the four hydroxyl groups merely required stirring **14** at 20 °C with 7% perchloric acid in methanol.[24,25]

As in the case of **1**, it has proven possible to acylate **2** regiospecifically at C-3 and to prepare 3,5-diesters. The 3-palmitate, in particular, carries all of the functional groups presently known to be required for cocarcinogenic activity.[26] However, a major distinction with 3-*O*-palmitoylingenol is the level of inherent strain energy. What is the relationship between ring strain and the potential to serve as tumor promoter? How necessary are the additional four carbons attached to ring C for hydrophilicity? We plan to respond to these questions and to report on a total synthesis of **1** at a future date.[27]

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(25) All new compounds exhibited compatible infrared, proton/carbon magnetic resonance, and mass spectrometric or combustion analysis data. Yields refer to isolated chromatographically homogeneous materials. For **2**: mp 173–176 °C; IR (thin film, cm^{-1}) 3700–3100 (br), 2940, 2860, 1675, 1455, 1435, 1380, 1370, 1330, 1280, 1220, 1115, 1055, 1025, 1005, 970, 925, 875, 845; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (s, 1 H), 5.26 (s, 1 H), 4.61 (s, 1 H), 4.58 (s, 1 H), 4.56 (br s, 1 H, OH), 4.47 (br d, J = 11 Hz, 1 H), 4.12 (d, J = 11 Hz, 1 H), 3.79 (br s, 1 H, OH), 3.53 (s, 1 H), 3.41 (br s, 1 H, OH), 3.17 (br s, 1 H, OH), 2.23 (dd, J = 14.9, 11.7 Hz, 1 H), 2.00–1.92 (m, 1 H), 1.81 (s, 3 H), 1.80–1.50 (m, 5 H), 1.07 (qt, J = 12 Hz, 1 H); MS, m/z (M^+) calcd 294.1467, obsd 294.1449.
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(27) This work was supported by the National Cancer Institute through Grant CA-12115.

Robert J. Ross,[1] Leo A. Paquette*
Evans Chemical Laboratories
The Ohio State University
Columbus, Ohio 43210
Received August 4, 1987

Thermal and Photochemical Reactions of Bicyclic Azoalkanes in Concentrated Sulfuric Acid

Summary: Thermolysis of bicyclic azo compounds **1a–d** in concentrated sulfuric acid affords ethylene (trapped as ethyl sulfate) and pyrazoles **3** in marked contrast to thermolysis of the nonprotonated azoalkanes, for which only loss of nitrogen (N_2) is observed.

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