rameters one unit larger than the isotropic equivalent of that atom to which they are bound. Refinement converged at a conventional R factor of 0.042. A final difference Fourier map showed no peaks higher than 0.25 e/Å^3.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corp. for their support of this work. National Science Foundation Grants CHE 77-28505 and CHE 76-05167 aided in the purchase of the Enraf-Nonius X-ray diffractometer and Varian NMR spectrometer, respectively. We thank Professors L. Pignolet and D. Britton and Mr. M. McGuiggan for assistance in the X-ray study and Professor W. Oppolzer for providing copies of spectral data for compound **46**.

Registry No. (±)-**1**, 72055-87-9; **2**, 79449-50-6; (±)-**3a**, 79449-51-7; (±)-**3b**, 79516-65-7; (±)-**4**, 79449-52-8; (±)-**5a**, 79449-53-9; (±)-**5b**, 79516-66-8; (±)-**6**, 79449-54-0; (±)-**27**, 79449-55-1; (±)-**28**, 79449-56-2; (±)-**29**, 79449-57-3; (±)-**31**, 79449-58-4; (±)-**32**, 79449-59-5; (±)-**33**, 79449-60-8; (±)-**34**, 79449-61-9; (±)-**42**, 79449-62-0; (±)-**43c**, 79449-63-1; (±)-**45**, 56326-39-7; 6-methylhept-5-en-2-one, 110-93-0; *m*-bromoanisole, 2398-37-0; *m*-methoxyphenyllithium, 31600-88-1; 5-methylhex-4-enal, 764-32-9; *p*-bromobenzaldehyde, 1122-91-4.

Supplementary Material Available: Numbering scheme and lists of final atomic positional parameters, atomic thermal parameters, and bond distances and angles (17 pages). Ordering information is given on any current masthead page.

New Approaches to the Synthesis of Vitamin D Metabolites. 1. Stereocontrol in the Intramolecular Diels–Alder Reaction

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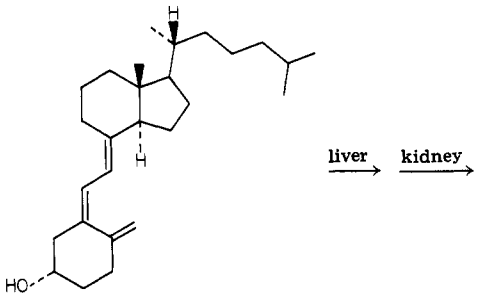
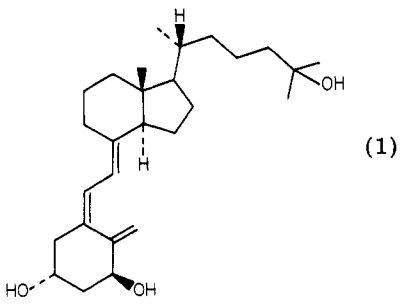
A short sequence which couples the Ireland–Claisen rearrangement with the intramolecular Diels–Alder reaction gives a 1:1 mixture of hydrindenes **3** and **13**. Hydrindenes **3** are known intermediates in the total synthesis of vitamin D derivatives.

Although cholecalciferol (vitamin D_3, **1**) was regarded as the active antirachitic hormone for many years, modern biochemical techniques have made it possible to trace the metabolism of D_3 through 25-hydroxycholecalciferol to 1α,25-dihydroxycholecalciferol (**2**, 1α,25-$(OH)_2D_3$), now believed to be the active compound[1] (eq 1). The role of



1 (D_3)



(1)

2 (1α, 25-$(OH)_2D_3$)

1α,25-$(OH)_2D_3$ as a hormone is complex and not totally understood; its main involvement appears to be in the regulation of bone formation and calcium availability. An inability to metabolize D_3 (**1**) to 1α,25-$(OH)_2D_3$ (**2**) results in the vitamin D deficiency diseases.

Because of the obvious importance of the vitamins D and their metabolites, particularly 1α,25-dihydroxyvitamin D_3 (1α,25-$(OH)_2D_3$), in the treatment and prophylaxis of bone disease, a number of groups have turned their attention to the chemical synthesis of these compounds.[2] In 1959, Inhoffen isolated vitamin D_3 from the photolysis of 5,7-cholestadienol;[3] since that time numerous syntheses of related compounds have been based on this key photochemical ring opening.[4,5]

Approaches to the total synthesis of the vitamins D from nonsteroidal precursors are rare. The extensive work of

* Alfred P. Sloan Foundation Fellow, 1977–1981, and Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1979–1984.

(1) Recent reviews on the vitamin D metabolites and their functions: (a) H. F. DeLuca, H. E. Paaren, and H. K. Schnoes, *Top. Curr. Chem.*, **83**, 3–65 (1979); (b) H. F. DeLuca, *Monogr. Endocrinol.*, **13**, (1979); (c) H. F. DeLuca, in "Trace Metals in Health and Disease", N. Kharasch, Ed., Raven Press, New York, 1979, pp 189–215.

(2) (a) P. A. Bell, in "Vitamin D", D. E. M. Lawson, Ed., Academic Press: New York, 1978; (b) P. E. Georghiou, *Chem. Soc. Rev.*, **6**, 83 (1977).

(3) H. H. Inhoffen, *Angew. Chem.*, **72**, 875 (1959).

(4) For example, the vitamin D_3 metabolite 25(*S*),26-dihydroxycholecalciferol was recently prepared from dehydroepiandrosterone; see J. J. Partridge, S.-J. Shiuey, N. K. Chadha, E. G. Baggiolini, J. F. Blount, and M. Uskokovic, *J. Am. Chem. Soc.*, **103**, 1253 (1981). For the synthesis of 24(*R*),25- and 24(*S*),25-dihydroxycholecalciferol, see J. J. Partridge, V. Toome, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **98**, 3739 (1976). See also: E. Baggiolini, J. J. Partridge, M. R. Uskokovic, U.S. Patent 4 021 423 (1977); *Chem. Abstr.*, **87**, 102541 (1977); E. Baggiolini, J. J. Partridge, and M. R. Uskokovic, U. S. Patent 4 026 882; *Chem. Abstr.*, **87**, 118020 (1977).

(5) Methods for functionalizing the steroid or hydrindane side chain[5a,b] and for attaching a side-chain synthon to the steroid nucleus with correct stereochemistry at C-20[5c-j] have appeared recently: (a) N. C. Deno and M. D. Meyer, *J. Org. Chem.*, **44**, 3383 (1979); (b) Z. Cohen, E. Berman, and Y. Mazur, *ibid.*, **44**, 3077 (1979); (c) J. S. Temple and J. Schwartz, *J. Am. Chem. Soc.*, **102**, 7382 (1980); (d) B. M. Trost and R. Verhoeven, *ibid.*, **100**, 3435 (1978); (e) A. D. Batcho, D. E. Berger, M. R. Uskokovic, and B. Snider, *ibid.*, **103**, 1293 (1981); (f) W. G. Dauben and T. Brookhart, *ibid.*, **103**, 237 (1981); (g) J. Wicha and K. Bal, *J. Chem. Soc., Perkin Trans. 1*, 1282 (1978); 1405 (1980); (h) M. Koreeda, Y. Tanaka, and A. Schwartz, *J. Org. Chem.*, **45**, 1172, (1980). (i) N. Tanabe and K. Hayashi, *J. Am. Chem. Soc.*, **102**, 862 (1980). (j) J. P. Marino and H. Abe, *ibid.*, **103**, 2907 (1981).

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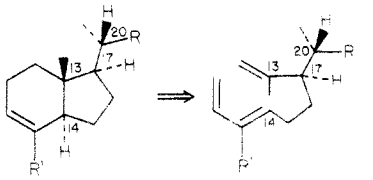
Lythgoe[6] has resulted in total syntheses of vitamins D_2 and D_3[7] and 1α-hydroxyvitamin D_3.[8] In Lythgoe's syntheses, the four chiral centers of the key *trans*-hydrindane are established by a resolution, two consecutive Claisen rearrangements, one of which employs a chiral reagent, and an equilibration.[9] Alternative preparations of key hydrindane systems by Grieco[10] and Trost[11] are based on the "bicycloheptane fragmentation" approach.[12]

Consideration of the contiguous relationship of the olefinic bond and the four chiral centers in hydrindenes **3** led us to consider a new, direct route to intermediates of this type. Our strategy is to fix the chiral centers at C-17 and C-20 (steroid numbering) in **4** by an Ireland–Claisen rearrangement and to use the C-17 center to induce the desired chiral centers at C-13 and C-14 in **3** by an intramolecular Diels–Alder reaction (eq 2). An attractive



(2)

3a, R = CH_2OH; R′ = H
b, R = CO_2Me; R′ = H

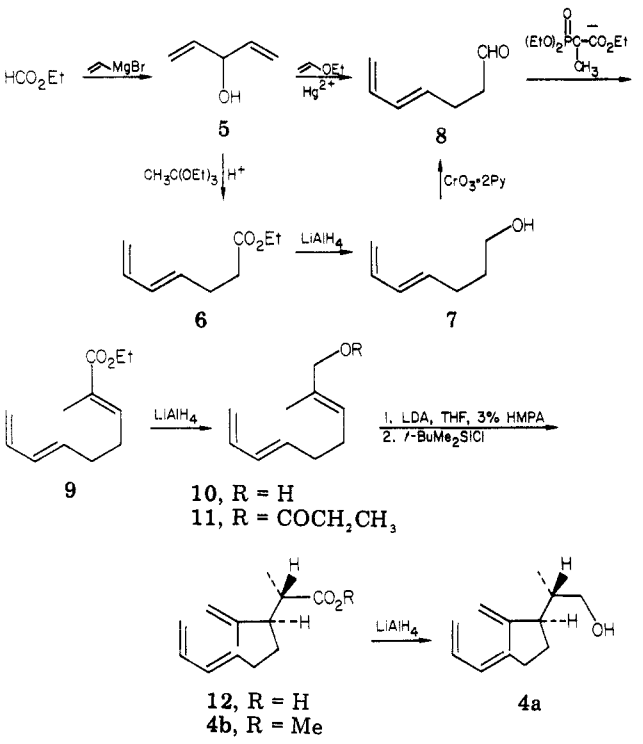
4a, R = CH_2OH; R′ = H
b, R = CO_2Me; R′ = H

feature of this approach was that the trienes **4** appeared to be readily accessible; however, the stereochemistry at the new chiral centers created in the intramolecular Diels–Alder reaction was uncertain. In this paper, we report the stereochemical outcome of the intramolecular cyclization of two of these Diels–Alder substrates, trienes **4a** and **4b**.

Results

The desired intermediate **4a** could be prepared in eight steps, or more conveniently and in better overall yield (9%) in ten steps, as shown in Scheme I. Thus, ethyl formate was converted to the known divinyl alcohol **5**[13] in 61% yield. The corresponding vinyl ether underwent thermal rearrangement to give trans dienal **8**.[14] The latter reaction was capricious, the yield of distilled material varying from 10% to 50%, and a better conversion of dienol **5** to dienal **8** was achieved by the ortho ester rearrangement (**5** → **6**),[15] reduction with lithium aluminum hydride (**6** → **7**),[15b] and oxidation with Collins reagent. Treatment of aldehyde **8** with triethyl 2-phosphonopropionate afforded the *E* olefinic ester **9** in 85% yield. Reduction of the ester moiety with lithium aluminum hydride afforded an 87% yield of

Scheme I

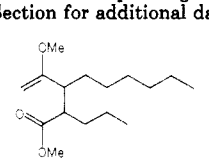


the alcohol **10**; treatment with propionyl chloride gave the ester **11** in 88% yield.

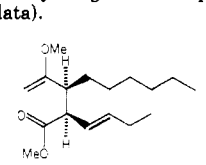
Propionate **11** was best converted to the erythro acid **12** by the following procedure.[16] Ester **11** in THF (1 mL) was added to LDA in THF/HMPA (2.6 mL/0.08 mL) at −78 °C. The resulting solution was stirred for 10 min, and *t*-$BuMe_2SiCl$ in hexane was added. After being stirred for 5 min at low temperature, the reaction mixture was warmed to 70 °C and stirred for 1 h. Hydrolysis and

(6) The most recent paper in this series is B. Lythgoe and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1405 (1980).
(7) B. Lythgoe, T. A. Morgan, M. E. N. Nambudiry, J. Tideswell, and P. W. Wright, *J. Chem. Soc., Perkin Trans. 1*, 590 (1978).
(8) (a) P. J. Kocienski and B. Lythgoe, *J. Chem. Soc., Perkin Trans. 1*, 1400 (1980); (b) P. J. Kocienski, B. Lythgoe, and J. Waterhouse, *Tetrahedron Lett.*, 4419 (1979); (c) R. G. Harrison, B. Lythgoe, and P. W. Wright, *ibid.*, 3649 (1973).
(9) (a) I. J. Bolton, R. G. Harrison, and B. Lythgoe, *J. Chem. Soc., Perkin Trans. 1*, 2950 (1971); (b) C. B. Chapleo, P. Hallett, B. Lythgoe, I. Waterhouse, and P. W. Wright, *ibid.*, 1211 (1977).
(10) P. A. Grieco, T. Takigawa, and D. R. Moore, *J. Am. Chem. Soc.*, **101**, 4380 (1979).
(11) B. M. Trost, P. R. Bernstein, and P. C. Funfschilling, *J. Am. Chem. Soc.*, **101**, 4378 (1979).
(12) R. V. Stevens and F. C. A. Gaeta, *J. Am. Chem. Soc.*, **99**, 6150 (1977).
(13) H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balint, and R. Cserr, *J. Org. Chem.*, **22**, 1602 (1957).
(14) S. F. Reed, Jr., *J. Org. Chem.*, **30**, 1663 (1965).
(15) (a) S. M. Weinreb, N. A. Khatri, and J. Shringarpure, *J. Am. Chem. Soc.*, **101**, 5073 (1979). (b) W. R. Roush, A. I. Ko, and H. R. Gillis, *J. Org. Chem.*, **45**, 4264 (1980).

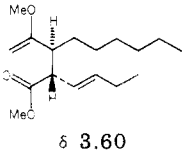
(16) In the absence of HMPA a single product was formed in low (5–15%) yield. The addition of a small amount (3% by volume) of HMPA to our reaction mixture improved the yield but also led to the production of a second, minor diastereomer. The erythro configuration was originally assigned to the major diastereomer by analogy to the behavior of similar systems under the same conditions (LDA, THF) as elucidated Ireland: R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976). Subsequent conversion of this major diastereomer to the known bicyclic **3a** confirms this assignment.
The limited NMR data available for *erythro*- and *threo*-methyl 2,3-dialkyl-4-pentenoates suggest that the absorption for the methyl ester occurs at slightly lower field for the erythro isomer than for the threo isomer. For example, in a sample of methyl 2.3-dimethyl-4-pentenoates (9.6:1 erythro–threo) prepared by us according to Ireland's procedure (LDA, THF), the methyl signal for the predominant erythro isomer occurred at 3.65 ppm; a small signal for the threo isomer was observed at 3.61 ppm.
Two other diasteriomeric pairs reported by Ireland show the same trend (see structures below).
In our own case, erythro ester **4b** has an absorption at 3.68 ppm; the threo ester has the corresponding methyl singlet at 3.61 ppm (see Experimental Section for additional data).



erythro δ 3.70
threo δ 3.63



δ 3.68

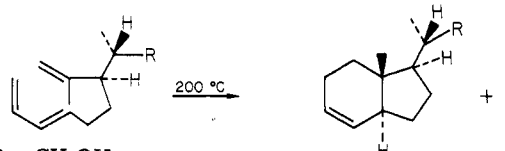


δ 3.60

extraction afforded the rearranged acid 12 and its threo isomer in a ratio of 4:1.

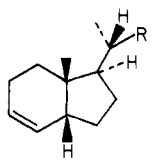
The mixture was treated with diazomethane, and the resulting mixture of esters was submitted to chromatography. In this way, a 42% yield of erythro ester **4b** was obtained from propionate 11; a 9% yield of the threo ester was also recovered. The erythro ester was converted in 84% yield to the erythro alcohol **4a** by treatment with lithium aluminum hydride.

The cyclization substrate **4a** was then heated at 200 °C for 18 h in benzene solution in a sealed tube (eq 3). The



4a, R = CH_2OH
b, R = CO_2Me

3a, R = CH_2OH
b, R = CO_2Me
c, R = $CH_2OCOC_6H_3N_2O_4$



(3)

13a, R = CH_2OH
b, R = CO_2Me
c, R = $CH_2OCOC_6H_3N_2O_4$

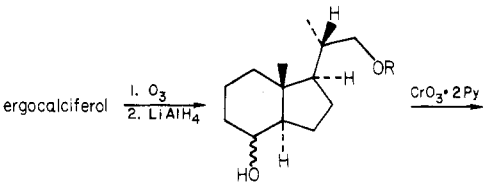
crude pyrolysis product was subjected to flash chromatography, and a 23% yield of cyclized material was isolated. The NMR spectrum of this material contained two high-field singlets (0.71 and 0.92 ppm) of approximately equal intensity. Treatment of the product mixture with 3,5-dinitrobenzoyl chloride gave a mixture of 3,5-dinitrobenzoates. Separation was accomplished by chromatography on silica gel impregnated with silver nitrate. Two components, A (R_f 0.35, benzene) and B (R_f 0.27, benzene), were isolated, each in 37% yield. Compound A had an NMR spectrum which contained a singlet at 0.77 ppm; the NMR spectrum of compound B contained a singlet at 0.97 ppm.

The spectra (IR, ^1H NMR, ^{13}C NMR) of the alcohol corresponding to compound A proved to be identical with those of our target, the known *trans*-hydrindene **3a** prepared according to Lythgoe from ergocalciferol (vitamin D_2).[9b] The isomer B appeared to be a *cis*-hydrindene. In order to compare authentic (chiral) material with our racemic compound, we prepared **13a**, the C-14 epimer of **3a**, according to Scheme II. Thus, the primary hydroxyl of diol **14**[9b] was protected as the triphenylmethyl ether; oxidation of the remaining alcohol moiety with Collins reagent gave ketone **16** (three-proton singlet at 0.59 ppm). Removal of the triphenylmethyl protecting group and epimerization of the chiral center α to the keto group were accomplished by treatment with aqueous acetic acid followed by methanolic potassium hydroxide. The resulting keto alcohol **17** (singlet, δ 1.07) was treated with tosylhydrazine to give hydrazone **18**. The Shapiro–Schechter modification of the Bamford–Stevens reaction[17] then gave olefin **13a**, which proved to have spectroscopic properties (IR, ^1H NMR, ^{13}C NMR) identical with those of the alcohol derived from the Diels–Alder product B.

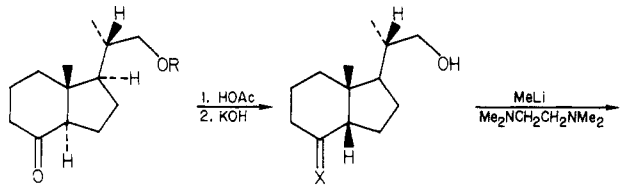
An alternative procedure resulted in an improved yield for the conversion of **4b** to **3c** and **13c**. When the ester

(17) R. H. Shapiro, *Org. React.*, **23**, 405 (1976).

Scheme II

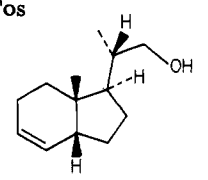


14, R = H
15, R = CPh_3



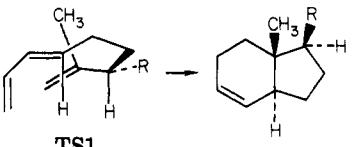
16a, R = CPh_3
b, R = H

17, X = O
18, X = NNHTos

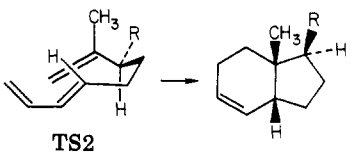


13a

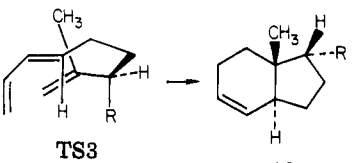
Scheme III



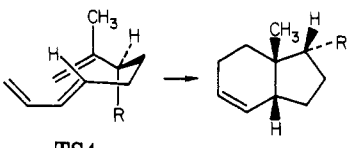
TS1 **3**



TS2 **13**



TS3 **19**



TS4 **20**

4b was heated at 200 °C for 6 h, a quantitative yield of crude cyclized esters was obtained. Lithium aluminum hydride reduction afforded a mixture of alcohols (~1:1 as indicated by the ^1H NMR spectrum); this mixture was treated with 3,5-dinitrobenzoyl chloride in pyridine, and the resulting material was subjected to column chromatography on silver nitrate impregnated silica gel (as above). The yield of **3c** was 42% (from **4b**) by this procedure; the yield of **13c** was 40%.

Discussion

The Diels–Alder reaction of trienes **4a** and **4b**, therefore, gave products in which the β configuration at C-13 had been induced; however, no control over the configuration

at C-14 was exhibited. Inspection of models of the transition states TS1 and TS2 (see Scheme III) leading to **3** and **13** and of the transition states TS3 and TS4 which would have led to the unobserved isomers **19** and **20** allows one to rationalize this result. While there is no obvious difference in energy between transition states TS1 and TS2, these appear to be of lower energy than TS3 and TS4 in which the C-17 substituent suffers some crowding with the chain linking the diene and dienophile.

Although various oxygen substituents[16b,18] and, more recently, an ethyl substituent[19] at the position adjacent to the diene moiety have been shown to influence the stereochemical outcome of Diels–Alder closure to hydrindenes,[20] the influence of a substituent adjacent to the dienophile has not been previously investigated. The examples cited here illustrate the potential of a chiral center α to the dienophile for stereochemical control in the cycloaddition.

It should also be noted that in this closure of **4** to **3** and **13**, the dienophile bears no electrophilic activating group. Therefore, presumably only steric considerations determine the outcome of the cyclization.

We are presently investigating the preparation and cyclization of trienes designed to exhibit the desired additional stereoselectivity (at C-14 as well as at C-13) in the Diels–Alder closure.

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. Dry ether, methylene choloride, glyme, pyridine, and benzene were obtained by distillation from CaH_2 and THF by distillation from lithium aluminum hydride. The chemicals used were reagent-grade and were distilled before use. E. Merck silica gel 60 (70–230 mesh) was used for column chromatography. Thin-layer chromatography was performed on precoated EM silica gel 60 F-254 plates. Infrared spectra were recorded on a Perkin-Elmer 257 grating infrared spectrometer. Nuclear magnetic resonance spectra were routinely recorded on Varian EM-360A and Bruker WP60 spectrometers and are reported in δ units relative to tetramethylsilane as an internal standard. High-field spectra were recorded on a Bruker WM-250 spectrometer at 250 (proton) and 62.9 MHz (carbon); these are specifically noted in the test. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D low-resolution instrument. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory.

4,6-Heptadienal (8).[15] The chromium trioxide–pyridine complex was prepared by adding 37.5 g (0.37 mol) of CrO_3 (dried over P_2O_5 under vacuum) in batches to a stirred solution of 61 mL (0.75 mol) of anhydrous pyridine in 800 mL of dry CH_2Cl_2 under nitrogen. The reaction mixture was stirred for 20 min, and then 7.00 g (62.5 mmol) of alcohol **7** was added. After being stirred for 0.5 h, the solution was decanted, the remaining tarry residue was extracted with ether (3 × 50 mL), and the combined organic solution was concentrated to 100 mL. Solid material was removed by filtration, and the filtrate was washed twice with water. After being dried over magnesium sulfate, the organic solution was filtered through silica gel with ether as the eluent. Most of the ether was evaporated on a rotary evaporator; distillation at 40 °C (5mm) afforded 6.00 g (87%) of a clear liquid.

Ethyl (2*E*,6*E*)-2-Methyl-2,6,8-nonatrienoate (9). A 2.85-g sample (59.4 mmol, 50% in mineral oil) of NaH was washed with pentane under nitrogen, 70 mL of glyme was added, and the suspension was cooled in an ice bath. To the suspension was added 12.9 g (56.5 mmol) of triethyl 2-phosphonopropionate. After 0.5 h at room temperature, 6.00 g (5.6 mmol) of aldehyde **8** was added dropwise, and the reaction mixture was stirred for another 2 h. At the end of that period, water was added, and the reaction mixture was extracted with ether. The ether phase was washed several times with water and dried over anhydrous $MgSO_4$. The resulting solution was concentrated and submitted to flash chromatography on silica gel (4:1 benzene/ether). Concentration of the first fractions gave 9.0 g (85%) of the unstable ester as a colorless liquid: ^{1}H NMR ($CDCl_3$) 1.28 (t, J = 7 Hz, 3 H), 1.85 (br s, 3 H) 2.26 (br t, 6 H), 4.21 (q, J = 7 Hz, 2 H), 4.85–6.9 (m, 6 H); IR (neat) 3095, 1710, 1650, 1605, 1450, 1370 cm^{-1}.

(2*E*,6*E*)-2-Methyl-2,6,8-nonatrien-1-ol (10). To a stirred solution of 1.76 g (46 mmol) of lithium aluminum hydride in 200 mL of anhydrous ether at 0 °C under nitrogen was added dropwise a solution of 9.0 g (46 mmol) of ester **9** in 10 mL of ether. The reaction mixture was stirred for 30 min and then quenched with water. The precipitate was removed, and the filtrate was washed several times with water, dried over anhydrous $MgSO_4$, and concentrated. Distillation at 100 °C (0.3 mm) afforded 6.12 g (87%) of a clear liquid: ^{1}H NMR ($CDCl_3$) 1.63 (br s, 3 H), 2.08–2.19 (m, 4 H), 2.75 (s, 1 H, exchanged with D_2O), 3.95 (br s, 2 H), 4.87–6.67 (m, 6 H); IR (neat) 3075, 3400–3200, 1645, 1600, 1000, 900 cm^{-1}.

(2*E*,6*E*)-2-Methyl-2,6,8-nonatrienyl Propionate (11). A 2.6-mL sample (39.4 mmol) of freshly distilled propionyl chloride was added dropwise to a stirred solution of 6.00 g (39.4 mmol) of allyl alcohol **10** and 3.5 mL of pyridine in 75 mL of dry methylene chloride at room temperature under nitrogen. The reaction mixture was stirred for 1 h. At the end of that period, 100 mL of water was added, and the aqueous layer was separated. The organic layer was washed twice with water, dried over anhydrous $MgSO_4$, and concentrated. Distillation at 90 °C (0.3 mm) gave 7.1 g (88%) of colorless oil: ^{1}H NMR ($CDCl_3$) 1.13 (t, J = 7.5 Hz, 3 H), 1.66 (s, 3 H), 2.13–2.23 (m, 4 H), 2.40 (q, J = 7.5 Hz, 2 H), 4.50 (br s, 2 H), 4.87–6.63 (m, 6 H); IR (neat) 3100, 1760, 1655, 1607, 1175, 1005 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_2$: C, 75.02; H, 9.61. Found: C, 75.24; H, 9.71.

Erythro Ester 4b. A 1.1-mL aliquot (1.08 mmol) of *n*-butyllithium in hexane was added to a stirred solution of 0.27 mL (1.93 mmol) of diisopropylamine in 1 mL of dry hexane at 0 °,c under nitrogen. The mixture was stirred for 10 min, and then the solvent and excess diisopropylamine were evaporated under vacuum at 0 °C. The flask was filled with argon, the residual white solid was dissolved in 2.6 mL of dry THF, and then 0.08 mL of HMPA was added. The solution was cooled to −78 °C, and 0.20 g (0.96 mmol) of propionate **11** in 1 mL of THF was slowly added. The resulting yellow solution was stirred for 10 min, and then a solution of 175 mg (1.16 mmol) of *t*-BuMe$_2$SiCl in hexane was added. The reaction mixture was stirred for 5 min, allowed to warm to room temperature, and then stirred at 70 °C (reflux) for 1 h. Then 2 mL of 13% HCl solution was added, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was made basic by the addition of 1 N NaOH solution and extracted with ether. The aqueous layer was reacidified and extracted with chloroform. The chloroform extract was dried over $MgSO_4$ and concentrated. The crude acid was esterified with excess diazomethane in ether at 0 °C. TLC (silica gel, benzene, developed twice) of the reaction mixture showed two spots; these two products were separated by medium-pressure liquid chromatography on silica gel with benzene as eluent.

Concentration of the first fractions afforded 90 mg (42%) of the erythro isomer as colorless oil: ^{1}H NMR ($CDCl_3$) 1.04 (d, J = 6.2 Hz, 3 H), 1.57 (br s, 3 H), 3.68 (s, 3 H), 4.82–6.63 (m, 7 H); IR (neat) 3080, 1740, 1647, 1605, 1165 cm^{-1}. Anal. Calcd: C, 75.70; H, 9.90. Found: C, 75.53; H, 9.85.

Further elution of the column furnished 20 mg (9%) of the threo isomer as a colorless oil: ^{1}H NMR ($CDCl_3$) 1.14 (d, J = 6.6 Hz, 3 H), 1.66 (br s, 3 H), 3.61 (s, 3 H), 6.71–6.68 (m, 7 H); IR (neat) 3080, 1740, 1645, 1605, 1165 cm^{-1}.

Alcohol 4a. To a stirred solution of 0.022 g (0.56 mmol) of lithium aluminum hydride in 5 mL of anhydrous ether at 0 °C

(18) (a) W. R. Roush, *J. Org. Chem.*, **44**, 4008 (1979); (b) W. R. Roush, *J. Am. Chem. Soc.*, **102**, 1390 (1980); (c) W. R. Roush and H. R. Gillis, *J. Org. Chem.*, **45**, 4283 (1980).

(19) (a) S. V. Levy, et al., *Tetrahedron Lett.*, 361 (1981); (b) K. C. Nicolaou and R. L. Magolda, *J. Org. Chem.*, **46**, 1507 (1981); (c) W. R. Roush, *J. Org. Chem.*, 1509 (1981).

(20) Additional examples of Diels–Alder closures to hydrindenes, particularly that of Ichihara et al.[20c] in which stereochemical control by a substituent on the diene is suggested, should be noted. (a) J. J. S. Bajorek and J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1559 (1975); (b) T. Kametani, H. Matsumoto, T. Honda, and K. Fukumoto, *Tetrahedron Lett.*, 4847 (1980); (c) A. Ichihara, R. Kimura, S. Yamada, and S. Sakamura, *J. Am. Chem. Soc.*, **102**, 6353 (1980).

was added dropwise a solution of 126 mg (0.56 mmol) of ester **4b** in 1 mL of ether. After being stirred for 30 min, the reaction mixture was carefully quenched with water and filtered. The filtrate was washed twice with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent and distillation at 105 °C (0.3 mm) furnished 91 mg (84%) of a colorless oil: ^1H NMR ($CDCl_3$) 0.90 (d, J = 6.5 Hz, 3 H), 1.65 (s, 3 H), 4.70–6.66 (m, 7 H); IR (neat) 3340 (br), 1645 (w), 1600 (w), 1450, 1375 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O$: C, 80.43; H, 11.33. Found: C, 80.26; H, 11.11.

Intramolecular Diels–Alder Reaction of Alcohol 4a. Isolation of *trans*- and *cis*-Hydrindenes 3c and 13c. A tube containing a solution of 70 mg (0.36 mmol) of trienol **4a** in 2 mL of benzene was flushed with argon before being sealed under vacuum. The sealed tube was heated at 200 °C for 18 h. After the evaporation of the solvent under reduced pressure, the semisolid residue was submitted to flash chromatography on silica gel (2:1 cyclohexane/ethyl acetate); this removed the more polar substances at the base line. The faster moving material (16 mg, 23%) proved to be a mixture: the NMR spectrum of this material exhibited signals at 5.57 (br s, ~2 H), 0.92 (s, ~1.5 H), and 0.71 ppm (s, ~1.5 H).

This crude product was treated with 40 mg of 3,5-dinitrobenzoyl chloride in 0.5 mL of pyridine. The reaction mixture was stirred overnight at room temperature. Solvent was evaporated, and the crude product was subjected to chromatography (silica gel coated with 15% w/w $AgNO_3$). Elution with benzene afforded 13.7 mg (42%) of the less strongly absorbed trans isomer **3c** (R_f 0.35), which was recrystallized from chloroform–hexane to give colorless crystals: ^1H NMR (250 MHz, $CDCl_3$) 0.77 (s, 3 H), 1.17 (d, J = 6.6, 3 H), 4.19–4.50 (m, 2 H), 5.59–5.60 (m, 2 H); IR (neat) 3100, 1730, 1630, 1550, 1285 cm^{-1}. Further elution with the same solvent gave 14.0 mg (43%) of cis isomer **13c**: R_f 0.27; ^1H NMR (250 MHz, $CDCl_3$) 0.97 (s, 3 H), 1.16 (d, J = 5.4 Hz, 3 H), 4.18–4.53 (m, 2 H), 5.51 (d, J = 9.2 Hz, 1 H), 5.65 (d, J = 9.2 Hz, 1 H), 9.17 (m, 2 H), 9.25 (m, 1 H); IR (neat) 3095, 1725, 1625, 1550, 1350, 1285 cm^{-1}.

Intramolecular Diels–Alder Reaction of Ester 4b. Isolation of *trans*- and *cis*-Hydrindenes 3c and 13c. A solution of 128 mg (0.66 mmol) of triene ester **4b** in 5 mL of dry toluene was degassed, flushed with argon, and then sealed under vacuum. The tube was heated at 200 °C for 6 h. The solvent was evaporated, and the residue [NMR ($CDCl_3$) δ 0.72 (s), 0.92 (s), 1.22 (d, J = 7 Hz), 3.70 (s), 5.56 (br s)] was dissolved in 5 mL of diethyl ether and treated with 25 mg (0.66 mmol) of lithium aluminum hydride in 10 mL of anhydrous ether at 0 °C. After being stirred for 15 min, the reaction mixture was carefully quenched with water and filtered. The filtrate was washed twice with water and then dried over anhydrous $MgSO_4$. Concentration afforded 120 mg of bicyclic alcohols: ^1H NMR 0.72 (s), 0.92 (s), 1.06 (d, J = 6 Hz), 5.63 (br s). The mixture was treated with 285 mg (1.24 mmol) of 3,5-dinitrobenzoyl chloride in 5 mL of dry pyridine and stirred overnight at room temperature. Then 15 mL of 5% $NaHCO_3$ solution was added, and the product was extracted with ether. The ether extract was dried over anhydrous $MgSO_4$ and concentrated to give 300 mg of crude product. This was chromatographed on a column of silica gel coated with 15% (w/w) silver nitrate. Elution with benzene gave 95 mg (42% from **4b**) of trans isomer **3c**: ^1H NMR (250 MHz, $CDCl_3$) 0.77 (s, 3 H), 1.17 (d, J = 6.6 Hz, 3 H), 4.15–4.50 (m, 2 H), 5.59–5.60 (m, 2 H), 9.14–9.24 (m, 3 H); IR (film) 3090, 1730, 1625, 1545, 1275, 1165 cm^{-1}.

Further elution of the column with the same solvent furnished 90 mg (40% from **4b**) of the cis isomer **13c**: ^1H NMR (250 MHz, $CDCl_3$) 0.97 (s, 3 H), 1.16 (d, J = 5.4 Hz, 3 H), 4.17–4.53 (m, 2 H), 5.50 (d, J = 9.2 Hz, 1 H), 5.64 (d, J = 9.2 Hz, 1 H), 9.17 (m, 2 H), 9.25 (m, 1 H); IR (film) 3095, 1730, 1625, 1595, 1545, 1280 cm^{-1}.

***dl* Alcohols 3a and 13a.** A solution of 38 mg (0.59 mmol) of KOH and 95 mg (0.24 mmol) of 3,5-dinitrobenzoate **3c** in 3 mL of methanol was stirred at reflux for 15 min. Then 10 mL of water was added, and the reaction mixture was extracted with ether. The organic solution was washed with water (3×) and dried over anhydrous $MgSO_4$. Concentration and distillation at 105 °C (0.3 mm) afforded 40 mg (89%) of a colorless oil: ^1H NMR ($CDCl_3$) 0.74 (s, 3 H), 1.08 (d, J = 6 Hz, 3 H), 3.20–3.80 (m, 2 H), 5.60 (br s, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) 11.0, 16.9, 24.4, 25.0, 28.0, 36.5, 39.2, 41.9, 48.3, 50.8, 68.0, 126.6, 128.2; IR (neat) 3340 (br), 1635 (w), 1370, 1220, 1035 cm^{-1}.

Hydrolysis of 90 mg of the cis isomer **13c** in the same manner afforded, after distillation, 36 mg (80%) of **13a** as a colorless viscous oil: ^1H NMR ($CDCl_3$) 0.93 (s, 3 H), 1.08 (d, J = 6 Hz, 3 H), 3.23–3.77 (m, 2 H), 5.53 (br s, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) 16.9, 22.1, 22.2, 28.8, 29.3, 33.7, 37.4, 41.3, 46.2, 48.8, 67.9, 124.8, 132.1; IR (neat) 3340 (br), 1650, 1445, 1375, 1025 cm^{-1}.

Hydrindenol 3a. An authentic sample of *trans*-hydrindenol **3a** was prepared from vitamin D_2 according to Lythgoe's procedure:[9b] ^1H NMR ($CDCl_3$) 0.75 (s, 3 H), 1.08 (d, J = 6 Hz, 3 H), 3.20–3.80 (m, 2 H), 5.60 (br s, 2 H); IR (film) 3340 (br), 1635, 1655, 1370, 1035, 1020 cm^{-1}; ^{13}C NMR (15.1 MHz, $CDCl_3$) 11.0, 16.9, 24.4, 25.0, 28.1, 36.6, 39.3, 41.9, 48.4, 51.0, 67.7, 126.6, 128.3.

Triphenylmethyl Ether 15. A solution of 200 mg (0.943 mmol) of diol **14** (from ozonolysis of ergocalciferol followed by lithium aluminum hydride workup[9b]) and 290 mg (1.04 mmol) of triphenylchloromethane in 4 mL of anhydrous pyridine was stirred under nitrogen at 100 °C for 36 h. After the reaction mixture cooled to room temperature, 50 mL of water was added, and the reaction mixture was extracted with ether. The organic phase was washed several times with water and dried over ahyydrous $MgSO_4$. Concentration and flash chromatography on silica gel (4:1 benzene/ether) gave 395 mg (92%) of a colorless semisolid: ^1H NMR ($CDCl_3$) 0.90 (s, 3 H), 1.13 (d, J = 6 Hz, 3 H), 2.67–3.32 (m, 2 H), 4.00 (br s, 1 H), 7.12–7.60 (m, 15 H); IR (film) 3500–3400, 1600, 1490, 1450, 1060 cm^{-1}.

***trans*-Hydrindanone 16.** To a stirred mixture of 6 mL of dry methylene chloride and 8.25 mg (10.4 mmol) of anhydrous pyridine was added 522 mg (5.22 mmol) of chromium trioxide (dried over P_2O_5 under vacuum). The reaction mixture was stirred for 15 min, and a solution of 395 mg (0.87 mmol) of alcohol **15** in 1 mL of methylene chloride was added. The reaction mixture was stirred for 20 min and decanted. The remaining tarry residue was extracted twice with methylene chloride, and the combined organic solution was washed (3×) with water, dried over $MgSO_4$, and concentrated. The residue was filtered through silica gel with ether as the eluent. Evaporation of the solvent gave 383 mg (97%) of a colorless mass which solidified on being stored in a refrigerator. The distilled product [Kugelrohr, 230 °C (2.5 mm)] had the following: mp 123–124 °C; ^1H NMR ($CDCl_3$) 0.59 (s, 3 H), 0.95–3.25 (m, 18 H), 7.33 (m, 15 H); IR (KBr) 1710, 1595, 1485, 1440, 1375, 1210 cm^{-1}. Anal. Calcd for $C_{32}H_{36}O_2$: C, 84.89; H, 8.03. Found: C, 84.70; H, 8.07.

***cis*-Hydrinandone 17 and *trans*-Hydrinandone 16b.** A mixture of 3.10 g (6.85 mmol) of tritylated ketone **16a** and 20 mL of 60% aqueous acetic acid was stirred at 100 °C for 1.5 h, cooled to room temperature, and quenched with 30 mL of water. The reaction mixture was extracted with ether, and the resulting organic solution was washed several times with water and dried over anhydrous $MgSO_4$. Concentration gave a mixture which was stirred with 20 mL of methanol and 1.5 g of KOH for 2 h at reflux and then at room temperature overnight. Then, 100 mL of water was added, and the reaction mixture was extracted with ether. The ether layer was washed several times with water and dried over anhydrous $MgSO_4$. Concentration and chromatography on silica gel (1:1 ethyl acetate/cyclohexane) gave 755 mg (52% yield) of cis isomer **17** as colorless crystals. An analytical sample (mp 60–61 °C) was prepared by distillation [Kugelrohr, 90–100 °C (0.1 mm)]: ^1H NMR ($CDCl_3$) 1.07 (s, 3 H), 2.72 (br s, 1 H, exchanged with D_2O), 3.18–3.77 (m, 2 H); IR (KBr) 3530, 1685, 1460, 1315, 1040 cm^{-1}; ^{13}C NMR ($CDCl_3$) 17.0, 20.7, 21.1, 23.2, 27.8, 36.4, 37.5, 40.3, 47.2, 48.6, 61.0, 67.3, 213.9; mass spectrum, m/e 210 (M^+). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.22; H, 10.56. Found: C, 74.35; H, 10.47.

Further elution of the column with the same solvent system afforded 50 mg of trans isomer **16b**: ^1H NMR ($CDCl_3$) 0.67 (s, 3 H), 1.05 (d, J = 5 Hz, 3 H), 3.23–3.77 (m, 2 H); IR (KBr) 3530 (br), 1690, 1460, 1370, 1315, 1040 cm^{-1}; ^{13}C NMR ($CDCl_3$) 12.5, 16.9, 19.2, 24.0, 27.1, 38.4, 38.9, 41.0, 50.0, 53.1, 61.7, 67.5, 212.0.

Preparation of *p*-Toluenesulfonylhydrazone 18. A solution of 210 mg (1.0 mmol) of ketone **17** and 204 mg (1.10 mmol) of *p*-toluenesulfonylhydrazine in 6 mL of absolute ethanol was stirred overnight at room temperature. The solvent was evaporated under reduced pressure, and the semisolid residue was crystallized from ether/pentane. Recrystallization from the same solvent system afforded 320 mg (85%) of a solid: mp 130–131 °C; ^1H NMR

($CDCl_3$) 0.93, 0.92 (s, overlapping d, 6 H), 2.43 (s, 3 H), 7.27, 7.87, (dd, 4 H); IR (KBr) 3540, 1600, 1405, 1320, 1150 cm^{-1}. Anal. Calcd for $C_{20}H_{30}N_2O_3S$: C, 63.50; H, 7.93; N, 7.40; S, 8.47. Found: C, 63.46; H, 7.83; N, 7.52; S, 8.61.

***cis*-Hydrindenol 13a.** To a stirred solution of 189 mg (0.5 mmol) of *p*-toluenesulfonylhydrazone **18** and 4 mL of tetramethylethylenediamine in 3 mL of anhydrous ether at 0 °C under nitrogen was added dropwise 3 mL of a 1 M solution of methyllithium in diethyl ether. The reaction mixture was stirred overnight at room temperature. Then, 20 mL of water was carefully added, and the organic layer was separated, washed several times with water, and dried over anhydrous magnesium sulfate. Concentration afforded 94 mg of crude material which was subjected to preparative TLC (silica gel, 1:1 benzene/EtOAc) to give 74 mg (76%) of colorless oil: ^1H NMR ($CDCl_3$) 0.93 (s, 3 H), 1.08 (d, J = 6 Hz, 3 H), 3.22-3.77 (m, 2 H), 5.53 (br s, 2 H); IR (neat) 3340 (br), 1655, 1440, 1370, 1025 cm^{-1}; ^{13}C NMR (62.9 MHz, $CDCl_3$) 17.0, 22.2, 22.3, 28.7, 29.5, 33.9, 37.4, 41.4, 46.8, 49.0, 68.0, 125.1, 132.3.

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Registry No. (±)-**3a**, 79980-73-7; **3a**, 64190-56-3; **3c**, 79980-74-8; **4a**, 79918-60-8; *erythro*-**4b**, 79918-61-9; *threo*-**4b**, 79918-62-0; **7**, 55048-74-3; **8**, 79280-39-0; **9**, 79918-63-1; **10**, 79918-64-2; **11**, 79918-65-3; (±)-**13a**, 79980-75-9; **13a**, 79918-66-4; **13c**, 79980-76-0; **14**, 79918-67-5; **15**, 79918-68-6; **16a**, 79918-69-7; **16b**, 79918-70-0; **17**, 79918-71-1; **18**, 79918-72-2.

Synthesis of 4-*tert*-Butyl-1,1-dimethylindan and 7-*tert*-Butyl-3,3-dimethyl-1-indanone and a Comparison of Isomers

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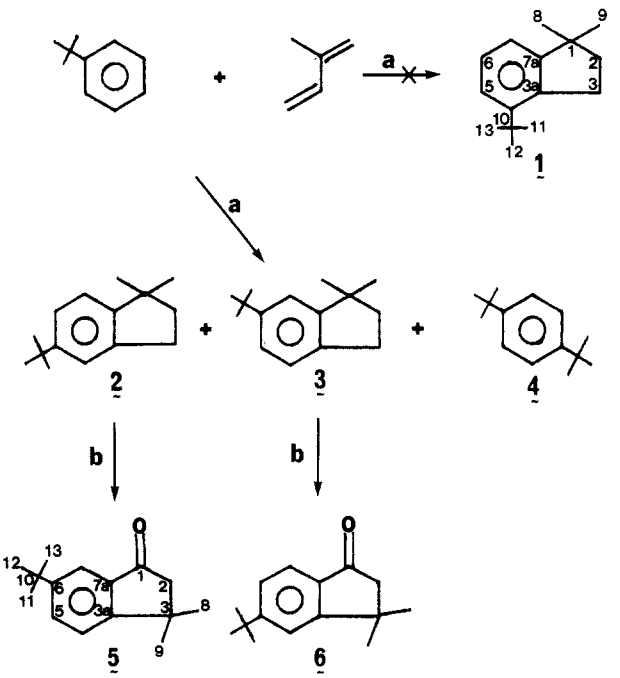
4-*tert*-Butyl-1,1-dimethylindan was synthesized to help establish the identity of products (5- and 6-*tert*-butyl-1,1-dimethylindan as minor and major products, respectively) from the sulfuric acid catalyzed condensation of *tert*-butylbenzene and isoprene. NMR (^1H and ^{13}C) studies of these hydrocarbons and their corresponding indanones, obtained through chromic acid oxidation, provided structural proof. Gated decoupling experiments were crucial to complete assignment.

It was earlier reported that the sulfuric acid catalyzed condensation of isoprene and *tert*-butylbenzene yields 6-*tert*-butyl-1,1-dimethylindan (**3**) as the major product.[2a,b,c] 1,4-Di-*tert*-butylbenzene (**4**) and what was assumed[2a] to be 4-*tert*-butyl-1,1-dimethylindan (**1**) were also reported. 5-*tert*-Butyl-1,1-dimethylidan (**2**) forms instead of **1** as shown in Scheme I. The emergence order and ratio of these cyclialkylation reaction products from a UC W-98 gas chromatography (GC) column were **4**/**3**/**2** (3:98:2). Conclusive identification of **2** as a minor reaction product of Scheme I became possible only through extensive fractional distillation[3a] and preparative GC[3b] which provided a pure sample of **2**. The infrared spectrum of **2** suggested 1,2,4 substitution rather than the 1,2,3 arrangement required for **1**.[2d,e] The evidence for the identity of **2** included chromic acid oxidation to 6-*tert*-butyl-3,3-dimethyl-1-indanone (**5**) and direct comparison with au-

Scheme I



[a] H_2SO_4. [b] CrO_3, HOAc.

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(2) (a) Eisenbraun, E. J.; Mattox, J. R.; Bansal, R. C.; Wilhelm, M. A.; Flanagan, P. W.; Carel, A. B.; Laramy, R. E.; Hamming, M. C. *J. Org. Chem.* **1968**, *33*, 2000. (b) This reaction was also carried out by Wood, T. F.; Angiolini, J. *Tetrahedron Lett.* **1963**, 1. (c) Indan **3** was synthesized and purified for the American Petroleum Institute Reference Materials program. Requests for **3** should be directed to A. J. Streiff, Carnegie-Mellon University, Schenley Park, Pittsburg, PA 15213. (d) We thank Dr. D. E. Boone for calling our attention to the incorrect assignment of structure for the minor component as **1**. Cf. Young, C. W.; DuVall, R. B.; Wright, N. (*Anal. Chem.* **1951**, *23*, 709) for use of IR spectroscopy in distinguishing 1,2,3, and 1,2,4 substitution of benzene. (e) Nakanishi, K. "Infrared Absorption Spectroscopy"; Holden Day: San Francisco, 1962; p 26.

(3) (a) We thank A. J. Streiff, API Project 58B, Carnegie-Mellon University, Pittsburgh, PA 15213, for the distillation fraction which provided **2**. (b) Preparative GC separations were made at 170 °C on a 4-in. × 10-ft column of 60-70-mesh Gas Pak W coated with 25% Carbowax 20-M. We thank R. E. Laramy, Continental Oil Co., for this purification of **2**. (c) Analytical GC studies were obtained with a 0.25-in. ×11-ft column of 80-100-mesh Chromosorb G, DMCS-treated and coated with 5% UC W-98 in a Hewlett-Packard 5750 FID GC apparatus and with a 0.25 mm × 20 m glass capillary column interior coated with SE-54 in a Vaian 3700 FID GC apparatus.

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