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Total Synthesis of (±)-Cycloeudesmol and (±)-Epicycloeudesmol[1]

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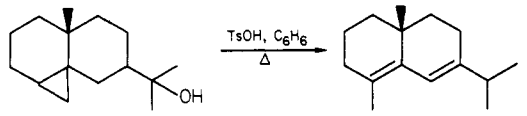
The first total synthesis of both (±)-cycloeudesmol (3) and (±)-epicycloeudesmol (4) is described. The key stereospecific construction of the bicyclo[3.1.0]hexane system was conveniently achieved by an olefin–ketocarbene cyclization reaction.

Introduction and Background

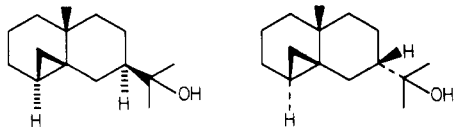
Cycloeudesmol, a member of the sesquiterpenoid class[2] of antibiotics known to possess in vitro activity against *Staphylococcus aureus*, *Salmonella cholerasins*, *Mycobacterium smegmatis*, and *Candida albicans* was first isolated from the marine alga *Chondria oppositiclada* Dawson by Fenical and Sims in 1974.[3] Structure 1 was



1 2

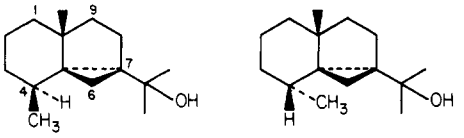
proposed based on the acid-catalyzed conversion to (+)-α-selinene (2) and on the analytical and spectral data. The depicted absolute stereochemistry about the methyl-substituted quaternary carbon was fixed in analogy to the known stereochemistry of (+)-α-selinene (2), but the available data did not permit stereochemical assignments of the cyclopropyl and 2-hydroxypropyl moieties.

However, recently the proposed structure of cycloeudesmol (1) was proven to be incorrect since the total synthesis of the four possible diastereoisomers of (1) **1a–d** has been completed.[4-7] The diastereoisomers **1a** and **1b** were first synthesized by Moss et al. in 1978.[4] In 1981 the total syntheses of **1c** and **1d** were completed by Ando et al.[5] In 1980 Kurosawa et al. isolated another sesquiterpene alcohol, **3** which was initially named isocycloeudesmol, from



1a 1b

1c 1d



3 4

the marine red alga *Laurencia nipponia* Yamada.[8] The absolute configuration of **3** was determined in 1981 by a single-crystal X-ray crystallographic study.[9] Meanwhile, the careful comparison of IR and NMR spectra and the optical rotation established that isocycloeudesmol was identical with cycloeudesmol.[10]

In this full account we report the details of the first total

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(1) Part of this work was presented at the 17th American Chemical Society Middle Atlantic Regional Meeting, White Haven, PA, April 6–8, 1983 [Chen, E. Y. Abstract 329].

(2) For examples, see: Heathcock, C. H. In "The Total Synthesis of Natural Products"; ApSimon, John, Ed.; Wiley-Interscience: New York, 1973; Vol. 2, p 197.

(3) Fenical, W., Sims, J. J. *Tetrahedron Lett.* **1974**, 1137.

(4) Moss, R. A.; Chen, E. Y.; Banger, J.; Matsuo, M. *Tetrahedron Lett.* **1978**, 4365.

(5) Ando, M.; Sayama, S.; Takase, K. *Chem. Lett.* **1979**, 191; *Ibid.* **1981**, 377.

(6) Moss, R. A.; Chen, E. Y. *J. Org. Chem.* **1981**, *46*, 1466.

(7) Caine, D.; Chen, P. C.; Frobese, A. S.; Gupton, J. T., III *J. Org. Chem.* **1979**, *44*, 4981.

(8) Suzuki, T.; Kikuchi, H.; Kurosawa, E. *Chem. Lett.* **1980**, 1267.

(9) Suzuki, T.; Furusaki, A.; Kikuchi, H.; Kurosawa, E. *Tetrahedron Lett.* **1981**, *22*, 3423.

(10) The sample isolated from *L. nipponica* showed the presence of three tertiary methyl groups and one secondary methyl group in the 100-MHz ^{1}H NMR spectrum.[3] On the other hand, the sample isolated from *C. oppositiclada* exhibited the presence of three methyl singlets, missing the recognition of the overlapping doublet methyl group at C-4 in 220-MHz ^{1}H NMR spectrum. From the above NMR spectra data, Kurosawa's sample was obviously found to be different from cycloeudesmol and previously designated as isocycloeudesmol.

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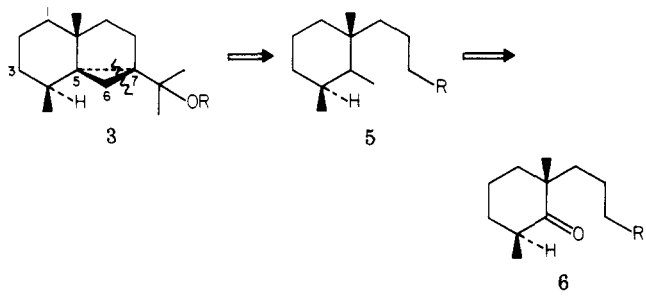
Scheme I

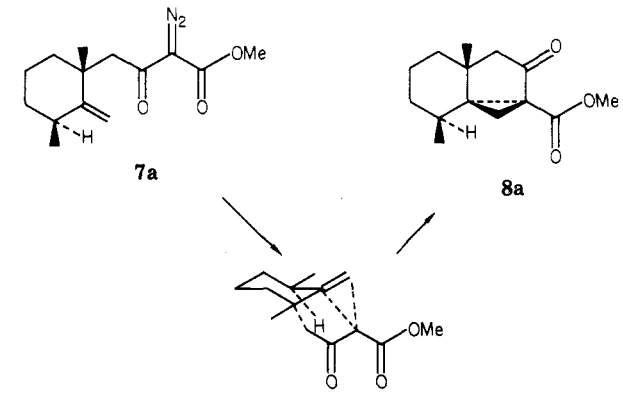


synthesis of (±)-cycloeudesmol (**3**)[11] as well as its epimer **4**. The interest in cycloeudesmol as a synthetic target stemmed from the continuing interest in carbene-related chemistry and the opportunity to establish both the structure and relative stereochemistry of cycloeudesmol via stereospecific total synthesis.

Results and Discussion

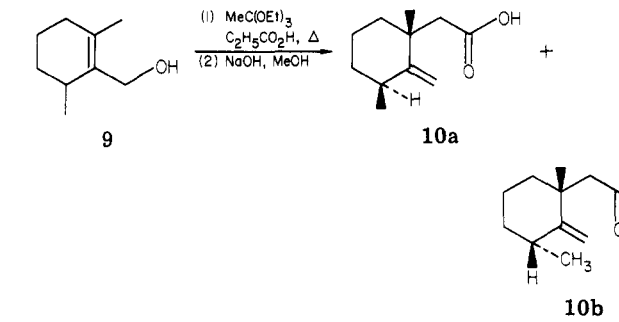
Armed with the conjecture that stereostructure **3** was the principal synthetic target, our synthetic strategy had to be sufficiently stereospecific and relatively efficient. Cycloeudesmol as well as epicycloeudesmol are good examples of compounds encompassing the unusual structure pattern of three fused carbocycles with a common carbon center. The common carbon center could be used as a starting point in the retrosynthetic analysis. Disconnection of the bonds C_7–C_6 and C_7–C_5 (Scheme I) would give one a much simpler structure (**5**), which in principle is basically a trisubstituted cyclohexanone (**6**). Therefore, the commercially available and highly symmetrical 2,6-dimethylcyclohexanone would appear to be a very attractive starting material.

It was envisaged that by an intramolecular addition process the decomposition of a diazo keto ester,[12] such as **7a**, might afford the tricyclic system such as **8a** which is

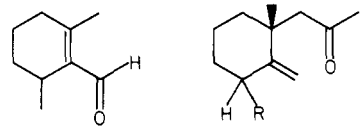


a key intermediate of this synthetic strategy to cycloeudesmol. Therefore, efforts were directed toward the acquisition of this intermediate. It was also anticipated that the stereochemistry of the resultant cyclopropyl ring in **8a** would be β. Careful examination of Dreiding models indicated that in the more favored equatorial 1,3-dimethyl conformation of the keto carbene A, generated from **7a**, the carbenic carbon could only attack the olefinic function from the α-face, leading to a β-cyclopropane product. With the correct stereochemistry of the three chiral centers in **8a** in hand the remaining problems of removing the keto function and converting the ester group to a dimethyl carbinol would be relatively simple and straightforward.

Preparation of Acid 10a by Claisen Rearrangement: The Initial Synthetic Target. The retrosynthetic analysis initially calls for a stereoselective construction of acid **10a**, in which the two methyl groups are in a 1,3-di-



axial position. It appeared that Claisen rearrangement of allylic alcohol **9** would give the required stereochemistry since there is a preference for axial bond formation in the rearrangement of allyl vinyl ethers contained within conformationally rigid cyclohexane systems.[13] Thus, Claisen rearrangement of allylic alcohol **9** in triethyl orthoacetate and a catalytic amount of propionic acid at 160–170 °C followed by hydrolysis of the ester product gave a 69% yield of 2 isomeric acids (**10**) in a ratio of 7 to 1. The minor isomer was readily removed by simple recrystallization. The stereochemical assignment of the major isomeric acid (**10a**) rests upon its 200-MHz ^{1}H NMR spectrum which revealed the equatorial methine proton as a slightly broadened singlet (δ 2.30, $w_{1/2}$ = 7 Hz), reflecting only axial–equatorial and diequatorial couplings to the adjacent methylene protons. The α-methylene protons appeared as an AB system at δ 2.34 and 2.62 (J = 13 Hz). The ^{13}C NMR spectrum did not show the presence of the corresponding epimer. The allylic alcohol **9** which was required in large quantities was conveniently prepared in 80% yield by the Bamford–Stevens reaction[14] of the tosylhydrazone of 2,6-dimethylcyclohexanone followed by trapping of the vinyl anion with excess dimethylformamide and $NaBH_4$ reduction of the conjugated aldehyde (**11**).[15]



11 **15a**, R = β-CH_3; **b**, R = α-CH_3

Preparation of Tricyclic Keto Ester 8a: The Key Intermediate. Greatly encouraged, by our ability to prepare crystalline acid **10a** in large quantities, we focused attention next on stereospecifically constructing the bicyclo[3.1.0]hexane moiety. The conversion of acid **10a** to

(11) For a preliminary account of this work see: Chen, E. Y. *Tetrahedron Lett.* **1982**, *23*, 4769.

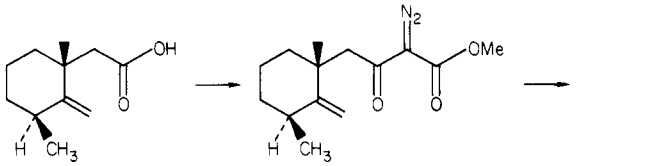
(12) For a review of keto carbene cyclization see: Kirmse, W. "Carbene Chemistry", 2nd ed.; Academic Press: New York, 1971; pp 338–342. For examples, see: Buchi, G.; White, J. D. *J. Org. Chem.* **1964**, *29*, 2884. Kondo, K.; Umemoto, T; Takahatake, Y.; Tunemoto, D. *Tetrahedron Lett.* **1977**, 113.

(13) Most applications of the Claisen rearrangement in stereoselective synthesis are based on the stereochemical consequences of a chair transition state or on chirality transfer from a C–O bond to a C–C bond. For examples of preferred axial attachment of the side chain, see: (a) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1983**, *48*, 1829. (b) Panaras, A. A. *Tetrahedron Lett.* **1983**, *24*, 3.

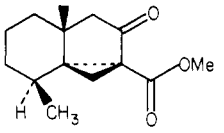
(14) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735. The best yields for **3** were obtained when 100% excess of *n*-BuLi was used as base in a solvent mixture of THF and TMEDA (4:1).

(15) All synthetic intermediates have been fully characterized; for those not discussed in detail, structure assignments rest upon spectroscopic properties and elemental composition data recorded in the Experimental Section.

α-diazo keto ester **7a** in three steps as required in the synthesis proved, as anticipated, straightforward. That is, addition of 2.5 equiv of MeLi in Et_2O, selective methoxycarbonylation[16] with dimethyl carbonate in diglyme using NaH as base, and diazotization with *p*-toluenesulfonyl azide[17] under standard conditions (Et_3N, MeCN), followed by washing with aqueous NaOH solution[18] gave the diazo compound **7a** in 79.1% yield from acid **10a**. The stage was now set for closure of the bicyclic system by thermolysis in refluxing cyclohexane using anhydrous cupric sulfate as catalyst to afford the single crystalline keto ester **8a**, mp 93–94 °C, in 53.8% yield from acid **10a**.

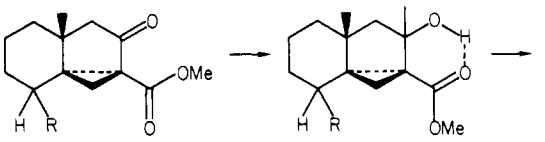


10a **7a**



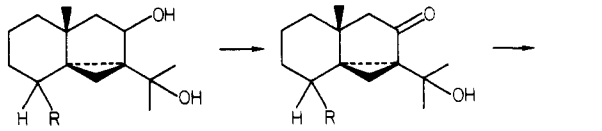
8a

Preparation of (±)-Cycloeudesmol (3). With ample quantities of tricyclic keto ester **8a** available and the stereochemistry of the three chiral centers secured, it now remained only to remove the carbonyl function and to transform the ester group to a dimethylcarbinol. Initially, several attempts at reducing the keto function directly to the corresponding methylene unit did not produce any useful results.[19] $NaBH_4$ reduction of **8a** gave only one isomer (**12a**) as evidenced by a sharp doublet at δ 4.37 (J = 7 Hz, 1 H) in its 200-MHz ^1H NMR spectrum. The IR spectrum showed intramolecular hydrogen bonding (3498, 1691 cm^{-1}). No attempt was made to assign the stereochemistry of the hydroxy group.[20] The ester group of **12a** was converted in quantitative yield with an excess of MeLi in ether to the diol **13a**, mp 83–85 °C. It should be noted that the characteristic cyclopropyl protons in **13a** are nicely resolved at δ 0.35 (d, J = 5 Hz) and 0.03 (d, J = 5 Hz) in the 200-MHz ^1H NMR spectrum. The ^{13}C NMR did not show the presence of any stereoisomers. Jones oxidation of diol **13a** followed by Wolff–Kirshner reduction gave the desired cycloeudesmol (**3**), mp 108–109 °C[21] in 90.2% yield.[22] That indeed racemic cycloeudesmol was in hand

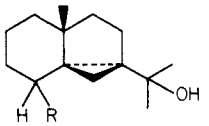


8a, R = β-CH_3
b, R = α-CH_3

12



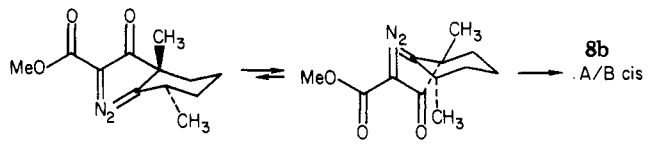
13 **14**



3, R = β-CH_3
4, R = α-CH_3

was confirmed by direct comparison of the IR, ^1H NMR, ^{13}C NMR, and MS spectra with those of the natural product.

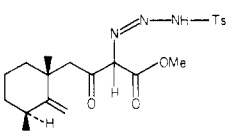
With the synthesis of cycloeudesmol (**3**) achieved and with a small amount of the isomeric mixture of acids (**10**) on hand, it was anticipated that by following the same sequence one would be able to synthesize epicycloeudesmol (**4**). However, the first problem encountered was the inability to separate the trans acid **10b** in pure form from the cis acid **10a** by fractional recrystallization. It was then decided to carry out the separation at the methyl ketone stage by flash chromatography. Thermolysis of diazo keto ester **7b** catalyzed by anhydrous $CuSO_4$ required a much higher temperature (refluxing toluene) and surprisingly gave predominately one of the two possible diastereoisomers (**8b**). The more favored conformer (ii) could only produce the cis isomer **8b**.



i ii **8b** A/B cis

The stereochemistry was determined on the basis of high-field ^1H and ^{13}C NMR data and NOE experiments. The equatorial methyl group being strongly diamagnetically shielded by the ester group gave rise in the 200-MHz ^1H NMR spectrum to a doublet (J = 7.5 Hz) at δ 0.65. The axial methine proton appeared at δ 2.23 as a multiplet which upon irradiation of the C_4 methyl resonance became a sharp doublet of doublets (J = 12.4, 3.4 Hz) reflecting the diaxial and axial–equatorial couplings to the adjacent methylene protons. In the NOE experiments, upon irradiation of the C_4 methyl group a significant enhancement of the H_5 resonance signal was observed. Furthermore, upon irradiation of the angular methyl group a positive enhancement in the resonance signals for H_1, H_3, and H_4 was also obtained, indicating they are all on the same face of the molecule. That is, the six and five membered rings are cis fused. The remaining $NaBH_4$ reduction of the keto group, MeLi conversion of the ester group, and Jones oxidation of the resulting diol (**13b**) was carried out as described before furnished the keto carbinol **14b** without complication. The final Wolff–Kishner reduction of **14b**

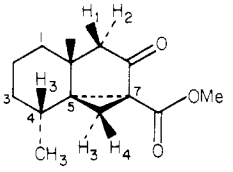
(16) Stork, G.; Guthikonda, R. N. Tetrahedron Lett. **1972**, 2755.
(17) Doering, W. von E.; DePuy, C. H. *J. Am. Chem. Soc.* **1953**, *75*, 5955.
(18) For a review on diazotization, see: Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733. Washing with aqueous NaOH solution was necessary to insure the complete removal of the tosyl group. Without washing the adduct tentatively assigned as A was isolated in 69% yield.



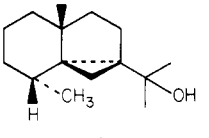
A, mp 121–123 °C

(19) Wolff–Kishner reduction of **8a** gave a complex mixture in which a minute amount of acid **14** was isolated, mass spectrum, m/e 208 (M^+), 193 (M^+ – 15). Reduction of hydrazone **8c** (mp 164–167 °C) with catecholborane according to Kabalka's procedure[22] gave less than 7% yield of **13**: mass spectrum m/e 222 (M^+), 207 ($M^+ - CH_3$), 163 ($M^+ - C_2H_3O_2$).
(20) It would be expected to give the equatorial alcohol product, due to the concave–convex nature of the tricyclic system in **8a** which provides the geometric bias for the hydride to come in a stereocontrolled fashion.
(21) Natural cycloeudesmol had mp 99.5–100.5 °C (hexane–isopropyl ether)[8] and mp 93–94 °C (hexane).[3]
(22) Kabalka, G. W.; Baker, J. D., Jr.; Neal, G. W. *J. Org. Chem.* **1977**, *42*, 512.

gave a 21.2% yield of epicycloeudesmol (4) as an oil after flash chromatography.



8b



4

Experimental Section

Materials and Equipment. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. All solvents were reagent grade and used as received. Unless otherise specified solutions were dried over anhydrous $MgSO_4$. Precoated silica gel plates (250 um) with a fluorescent indicator (Merck) were used for analytical thin-layer chromatography (TLC). Visualization was achieved via ultraviolet light or iodine or by charring with 10% aqueous sulfuric acid in methanol containing vanillin (2% w/v). Silica gel (particle sizes 0.040–0.063 mm and 0.063–0.200 mm) supplied by Merck was used for column chromatography. Proton and carbon NMR spectra were obtained for deuteriochloroform solutions on either a JEOL FX 90Q or a JEOL FX 200. Chemical shifts are reported as ppm values relative to tetramethylsilane (δ Me_4Si 0.00). All infrared spectra were recorded on an Analect Instruments FX-200 FTIR spectrometer for chloroform solutions (unless noted otherwise). Mass spectra were recorded on LKB-9000 GC-MS or VG 7070E mass spectrometer. Analytical GC was performed on a Perkin-Elmer Sigma 3B gas chromatograph, outfitted with 6 ft × $^1/_4$ in. glass columns containing 3% OV-101 or 3% OV-17 on 80/100 supelcaport.

Preparation of Unsaturated Aldehyde 11. To a solution of 2,6-dimethylcyclohexanone tosylhydrazone (147.2 g, 0.50 mol), prepared under standard procedure, in 1.3 L of THF and 250 mL of TMEDA cooled at −35 °C, under N_2 atmosphere, was added dropwise over 3 h a hexane solution of *n*-BuLi (1.25 L, 2.0 mol). The resulting dark brown solution was allowed to warm from −10 to 0 °C with stirring for 2–3 h (until the evolution of N_2 gas had subsided). DMF (120 mL) was then added slowly. The solution was allowed to warm to room temperature followed by slow addition of H_2O (1 L). The organic layer was concentrated under aspirator. The aqueous layer was partitioned between H_2O (1 L) and Et_2O/hexane (500 mL, 1:1). The organic solution was combined with the concentrated organic layer, washed with brine (3 × 300 mL), dried, and freed of solvent to give a light yellow oil (79.0 g) which contained 85% of the desired aldehyde (11) by GC analysis. The crude yellow oil was used in the next step without further purification. An analytical sample was obtained as a colorless liquid by distillation at 35–36 °C (0.10 mm): IR 2950, 2880, 1720, 1660, 1520, 1380, 1240, 1145 cm^{-1}; ^1H NMR (90 MHz) δ 1.01 (d, J = 7 Hz, 3 H), 1.35–1.85 (m, 4 H), 2.13 (s, 3 H), 2.21 (bs, 2 H), 2.76 (m, 1 H), 10.11 (s, 1 H). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.5; H, 10.5.

Preparation of Allylic Alcohol 9. To a solution containing 79.0 g of unsaturated aldehyde 11 (85% pure by GC) in 1.20 L of methanol cooled in an ice bath was added in portions powdered $NaBH_4$ (15.2 g, 0.40 mmol). The yellow solution was allowed to warm to room temperature and stirred for 2 h followed by concentration under aspirator. The residue was partitioned between brine (400 mL) and Et_2O/hexane (1:2, 300 mL). The organic layer was washed with brine and dried. Removal of solvent in vacuo and distillation at 48–52 °C (0.15 mmHg) gave allylic alcohol 9 as a colorless liquid (63.4 g, 453 mmol, 90.5%): IR 3340 (s), 2940 (s), 2880 (s), 1500 (w), 1000 (s) cm^{-1}; ^1H NMR δ 1.04 (d, J = 7 Hz, 3 H), 1.71 (s, 3 H), 4.60 (s, 2 H); mass spectrum, m/e 140 (M^+), 125 ($M - CH_3$), 122 ($M - H_2O$).

Preparation of Acid 10a. A solution containing 35 g (250.0 mmol) of allylic alcohol 9, 150 mL of triethyl orthoacetate and a catalytic amount of propionic acid (ca. 0.5 g) was heated at 110–120 °C for 3 h under conditions of distilling EtOH (21 g), and then at 140–150 °C under aspirator to remove the excess reagent. The residue was heated at 160–180 °C for 4 h and distilled at 67–72 °C (0.08 mmHg) to give a light yellow liquid (26 g). The liquid was redissolved in 400 mL of methanol and 250 mL of 2 N aqueous NaOH solution and heated at 50 °C for 4 h. The solution was cooled to room temperature and extracted with hexane (200 mL). The aqueous layer was acidified with concentrated HCl and extracted with Et_2O (2 × 200 mL) followed by the usual workup to give a light yellow solid (31.5 g, 172.9 mmol, 69.1%), which was recrystallized from Et_2O/hexane to give 27.5 g (150.9 mmol, 60.4%) of acid **10a**. Analytical samples were prepared by further recrystallization from Et_2O/hexane as colorless transparent flakes: mp 104–105 °C; IR 3514 (w), 3098 (shoulder), 2930 (s), 1712 (s), 1639 (m), 1456 (m), 1409 (m), 904 (S) cm^{-1}; ^1H NMR δ 1.05 (d, J = 7 Hz, 3 H), 1.24 (s, 3 H), 1.50–1.85 (complex m, 4 H), 2.30 (m, $w_{1/2}$ = 7 Hz, 1 H), 2.34 (d, J = 13 Hz, 1 H), 2.62 (d, J = 13 Hz, 1 H), 4.78 (s, 1 H), 4.83 (s, 1 H), 11.08 (bs, 1 H); ^{13}C NMR δ 19.2, 22.1, 26.7, 33.4, 37.1, 39.7, 40.3, 42.7, 105.2, 157.3, 178.7; mass spectrum, m/e 182 (M^+), 167 ($M^+ - CH_3$), 123 ($M^+ - C_2H_3O_2$);

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.4; H, 10.3.

Preparation of Methyl Ketone 15a. To a solution of 9.1 g (50.0 mmol) of acid **10a** in 250 mL of anhydrous ethyl ether cooled in an ice bath was added dropwise under nitrogen atmosphere 80 mL of a 1.4 M ethereal solution of methyllithium (112.0 mmol). The colorless solution was allowed to stir at room temperature for 5 h and added dropwise to a stirred mixture of ice and water (250 mL). The aqueous layer was extracted with 50 mL of ether. The combined ether solutions were washed with brine and dried. Removal of the solvent in vacuo gave 9.0 g (50.0 mmol, 100%) of methyl ketone **15a** as a colorless liquid. Analytical samples were prepared by distillation at 50–52 °C (0.08 mmHg); IR 3100 (w), 3007 (m), 2965 (s), 2931 (s), 2872 (s), 1702 (s), 1636 (w), 1456 (m), 1361 (m), 1227 (m), 904 (m) cm^{-1}; ^1H NMR (90 MHz) δ 1.08 (d, J = 7 Hz, 3 H), 1.19 (s, 3 H), 1.30–1.80 (m, 4 H), 2.05 (s, 3 H), 2.20 (d, J = 14 Hz, 1 H), 2.90 (d, J = 14 Hz, 1 H), 4.79 (s, 1 H), 4.81 (s, 1 H).

Preparation of β-Keto Ester 16a. To a mechanically stirred suspension of 1.25 g of NaH (60% dispersion in mineral oil, 31 mmol, washed with hexane) in 45 mL of diglyme was added dropwise 4.4 g (25 mmol) of methyl ketone **15a**. The mixture was stirred for 30 min or until the evolution of nitrogen gas had subsided, and 4.5 g (50 mmol) of dimethyl carbonate was added. The mixture was heated at 50 °C for 10 h. The light brown solution was diluted with 100 mL of hexane, washed with brine, dried, and freed of solvent under aspirator. Distillation of the residue at 75–80 °C (0.06 mmHg) afforded 4.8 g (20.1 mmol, 80.6%) of β-keto ester **16a** as a colorless oil: IR (neat) 2950, 2900, 1745, 1710, 1625, 1450, 1410, 1330, 1240, 1160, 1020, 905 cm^{-1}; ^1H NMR δ 1.07 (d, J = 7 Hz, 3 H), 1.18 (s, 3 H), 2.35 (d, J = 14 Hz, 1 H), 3.05 (d, J = 14 Hz, 1 H), 3.38 (s, 2 H), 3.72 (s, 3 H), 4.85 (m, 2 H).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.31. Found: C, 70.4; H, 9.4.

Preparation of Diazo Keto Ester 7a. To a magnetically stirred solution of 9.3 g (39.0 mmol) of keto ester **16a** in 45 mL of acetonitrile and 10 mL of triethylamine cooled in an ice bath was added dropwise 7.9 g (39 mmol) of *p*-toluenesulfonyl azide prepared from *p*-toluenesulfonyl chloride and sodium azide according to a published procedure.[17] The solution was allowed to warm to room temperature and stirred overnight. The concentrated solution was partitioned between 200 mL of Et_2O and 100 mL of 2 N aqueous NaOH solution. The Et_2O solution was washed consecutively twice with 2 N aqueous NaOH solution and brine and dried. Removal of solvent in vacuo gave an orange oil (**7a**) (10.1 g, 38.2 mmol, 98.1%), which was used in the next step without further purification: IR, 2960, 2925, 2133, 1723, 1652, 1437, 1308, 1208, 899 cm^{-1}; ^1H NMR δ 1.05 (d, J = 7 Hz, 3 H), 1.24 (s, 3 H), 1.40–2.00 (m, 6 H), 2.52 (bm, 1 H), 2.95 (d, J = 14 Hz, 1 H), 3.29 (d, J = 14 Hz, 1 H), 3.81 (s, 3 H), 4.75 (bs, 2 H).

Thermolysis of Diazo Keto Ester 7a. A mixture of 10.1 g (38.6 mmol) of diazo keto ester **7a** in 420 mL of cyclohexane containing 7.0 g of anhydrous cupric sulfate was heated under reflux for 10 h. The filtered solution was washed with 100 mL of water twice and dried. Removal of solvent under aspirator gave an orange oil (9.8 g) which became solid on standing. The solid was recrystallized from Et_2O to give 6.1 g (21.0 mmol, 53.8% from 5) of methyl ester **8a** as colorless needles. Analytical samples were

prepared by further recrystallization from Et_2O/hexane: mp 93–94 °C; IR (KBr) 2980, 2940, 2880, 1723, 1455, 1343, 1220 cm^{-1}; ^1H NMR (200 MHz) δ 1.19 (d, J = 7.5 Hz, 3 H), 1.20 (s, 3 H), 1.25–1.76 (complex m, 7 H), 1.62 (d, J = 5 Hz, 1 H), 1.79 (d, J = 5 Hz, 1 H), 1.83 (d, J = 14 Hz, 1 H), 2.13 (d, J = 14 Hz, 1 H), 3.79 (s, 3 H); ^{13}C NMR δ 16.8, 19.2, 22.5, 24.4, 30.0, 30.3, 37.0, 39.1, 47.9, 50.3, 52.4, 52.8, 168.0, 202; mass spectrum, m/e 236 (M^+), 221 ($M^+ - CH_3$), 205 ($M^+ - OCH_3$), 189 ($M^+ - CH_3 - CH_3OH$) 176 ($M^+ - C_2H_4O_2$).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.3; H, 8.5.

Tosylhydrazone of **8a** was prepared according to a standard procedure and recrystallized from ethanol: mp 164–167 °C dec; IR 3195 (s), 2970 (s), 2930 (s), 2850 (w), 1760 (s), 1665 (w), 1595 (w), 1440 (s), 1310 (s), 1200 (s), 1150 (s), 1070 (s), 1000 (s), 970 (s), 800 (s), 660 (s) cm^{-1}; ^1H NMR (90 MHz) δ 1.70 (d, J = 17 Hz, 1 H), 2.19 (d, J = 17 Hz, 1 H), 2.46 (s, 3 H), 3.72 (s, 3 H), 7.31 (d, J = 8 Hz, 2 H), 7.85 (d, J = 8 Hz, 2 H); mass spectrum, m/e 404 (M^+), 373 ($M^+ - 31$), 249 ($M^+ - 155$).

Preparation of Hydroxy Ester 12a. To a magnetically stirred solution of 236.3 mg (1.0 mmol) of keto ester **8a** in 10 mL of methanol cooled in an ice bath was added in portions 38.0 mg (1.0 mmol) of powdered $NaBH_4$. The resulting colorless solution was allowed to stir at room temperature for 2 h. The concentrated solution was extracted with ether, washed with brine, and dried. Removal of the solvent in vacuo gave an off-white oil which was passed through a short column of silica gel (2.0 g) with Et_2O/hexane/CH_2Cl_2 (1:3:3) as the eluent. The desired fractions (R_f 0.45) were collected and concentrated to afford 215 mg (90.2 mmol, 90.2%) of hydroxy ester **12a**: IR (neat) 3583 (s), 3498 (s), 3071 (w), 2946 (s), 2867 (s), 1720 (s), 1691 (s), 1440 (s), 1385 (s), 1300 (s), 1130 (s) cm^{-1}; ^1H NMR (200 MHz) δ 0.89 (s, 1 H), 0.91 (s, 1 H), 1.07 (s, 3 H), 1.13 (d, J = 7 Hz, 3 H), 1.60 (s, 1 H), 1.20–2.20 (complex m, 10 H), 3.73 (s, 3 H), 4.37 (d, J = 7 Hz, 1 H).

Preparation of Diol 13a. To a magnetically stirred solution of 2.2 g (9.4 mol) of hydroxy ester **12a** in 40 mL of anhydrous ethyl ether cooled in an ice bath was added dropwise 30 mL (1.4 M in ether 42.0 mmol) of MeLi solution. The colorless solution was allowed to stir at room temperature for 1 h, followed by washing with brine (2 × 30 mL), and dried. Removal of solvent in vacuo gave 2.2 g (9.4 mmol, 100%) of diol **13a** as a colorless solid. Analytical samples were prepared by recrystallization from a Et_2O/hexane mixture as transparent needles: mp 83–85 °C; IR (KBr) 3418 (s), 3360 (s), 3050 (w), 2928 (s), 2860 (m), 1406 (m), 1382 (m), 1164 (m), 917 (w) cm^{-1}; ^1H NMR (200 MHz) δ 0.35 (d, J = 5 Hz, 1 H), 0.43 (d, J = 5 Hz, 1 H), 1.01 (s, 3 H), 1.10 (d, J = 7 Hz, 3 H), 1.30 (s, 3 H), 1.50 (s, 3 H), 1.59 (s, 2 H, D_2O exchange), 1.15–2.00 (complex m, 10 H), 2.07 (m, 1 H), 4.36 (d, J = 5 Hz, 1 H); ^{13}C NMR (200 MHz) δ 16.5, 17.6, 19.0, 24.6, 28.7, 29.4, 31.3, 31.9, 38.7, 41.3, 43.3, 46.7, 47.3, 73.6, 77.2; mass spectrum, m/e 220 ($M^+ - H_2O$), 205 ($M^+ - CH_3 - H_2O$), 202 ($M^+ - 2H_2O$), 187 ($M^+ - CH_3 - 2H_2O$).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.9; H, 11.2.

Preparation of Keto Carbinol 14a. To a magnetically stirred solution of 1.30 g (5.45 mmol) of diol **13a** in 30 mL of acetone cooled in an ice bath was added dropwise 6.0 mL (6.0 mol) of Jones reagent prepared by dissolving 1.0 g (10.0 mmol) of chromium trioxide in 1.0 mL of concentrated sulfuric acid and diluting to 10 mL with water. A green black precipitate was formed during addition. The mixture was allowed to warm to room temperature in 30 min and filtered. The green-orange solution was concentrated under aspirator and then partitioned between 40 mL each of ethyl ether and saturated aqueous sodium bicarbonate. The organic layer was washed, dried, and freed of solvent to give the keto carbinol **14a** as a yellow oil (1.29 g, 5.45 mmol, 100%), which was used without further purification. An analytical sample was prepared by distillation of the crude oil at 105 °C (0.08 mmHg): IR 3460 (w), 2995 (s), 2930 (s), 1700 (s), 1450 (m), 1380 (m) cm^{-1}; ^1H NMR (200 MHz) δ 1.19 (s, 3 H), 1.20 (d, J = 7 Hz, 3 H), 1.25 (s, 3 H), 1.36 (d, J = 5 Hz, 1 H), 1.50 (s, 3 H), 1.56 (d, J = 5 Hz, 1 H), 2.01 (d, J = 1.5 Hz, 1 H), 2.10 (d, J = 1.5 Hz, 1 H), 2.16 (m, 1 H), 3.78 (s, 1 H, D_2O exchange).

Preparation of (±)-Cycloeudesmol (3). A solution containing 0.60 g (2.54 mmol) of keto carbinol **14a** and 0.50 g (15.3 mmol) of anhydrous hydrazine in 30 mL of ethylene glycol was heated at 120–130 °C for 1 h (or until the disappearance of the starting carbinol by TLC). Solid KOH (1.0 g, 87%, 15.3 mmol) was added. The mixture was then heated to reflux (190–195 °C) for 10 h. During the heating, a white solid was formed on the condenser cold finger. The solid (170 mg) was washed down with ethyl ether. The yellow solution was partitioned between 100 mL of water and 30 mL of ether. The ether solutions were combined, washed, dried, and freed of solvent in vacuo to afford a colorless solid. Recrystallization of the solid from an ether/hexane mixture gave as transparent prisms 0.51 g (2.29 mmol, 90.2%) of (±) cycloeudesmol (**3**): mp 108–109 °C; IR 3609 (m), 3053 (w), 2980 (s), 2933 (s), 2870 (s), 1462 (s), 1374 (s), 1103 (m) cm^{-1}; ^1H NMR (CCl_4, 200 MHz) δ 0.35 (d, J = 5 Hz, 1 H), 0.45 (d, J = 5 Hz, 1 H), 0.79 (s, 1 H, D_2O exchange), 1.02 (s, 3 H), 1.03 (d, J = 7.5 Hz, 3 H), 1.25 (s, 3 H), 1.35 (s, 3 H), 2.25 (m, 1 H); ^{13}c NMR ($CDCl_3$, 200 MHz) δ 12.5, 17.7, 19.2, 24.0, 27.4, 27.9, 28.4, 31.4, 32.2, 36.4, 37.4, 41.7, 41.8, 43.9, 71.6; mass spectrum, m/e 222 (M^+), 221 (M – H), 207 ($M - CH_3$), 204 ($M - H_2O$), 164 ($MH - C_3H_9O$), 149 and 59 (C_3H_7O).

Anal. Calcd for $C_{15}H_{26}O_1$: C, 81.02; H, 11.79. Found: C, 80.9; H, 12.1.

Preparation of Methyl Ketone 15b. To a magnetically stirred solution of 8.6 g (4.72 mmol) of a mixture containing both isomeric acids (**10**) (cis/trans = 5:4 by NMR) in 300 mL of anhydrous ethyl ether cooled in an ice bath, under nitrogen atmosphere, was added dropwise an etheral solution of 75 mL (120 mol) of methyllithium (1.6 M). The resulting light yellow solution was allowed to stir at room temperature for 3 h. The solution was then added dropwise to a stirred mixture of 200 mL of ice water and 50 mL of ether. The ether layer was washed with brine, dried, and freed of solvent in vacuo to give a yellow liquid (8.4 g) which was subjected to flash chromatography, eluting with 5% ether in hexane. The more mobile fractions (R_f 0.42, Et_2O/CH_2Cl_2/hexane 1:1:5) were collected to give 3.7 g (20.5 mmol, 43.4%) of the methyl ketone **15b**: ^1H NMR (200 MHz) δ 1.09 (d, J = 7 Hz, 3 H), 1.26 (s, 3 H), 2.22 (s, 3 H), 2.38 (m, 1 H), 2.66 (s, 1 H), 2.68 (s, 1 H), 4.62 (d, J = 1 Hz, 1 H), 4.72 (d, J = 1 Hz, 1 H).

The less mobile fractions (R_f 0.38) were also collected to give 4.2 g (23.3 mmol, 49.3%) of the methyl ketone **15a** whose structural assignment was further confirmed by the identity of the IR and ^1H NMR spectra with those obtained previously.

Preparation of β-Keto Ester 16b. To a suspension of 0.8 g (60% dispersion in mineral oil, 20 mmol) of sodium hydride (washed with hexane) in 35 mL of diglyme was added dropwise 3.0 g (16.6 mmol) of methyl ketone **15b**. The mixture was stirred for 30 min followed by addition of 3.0 g (33.0 mmol) of dimethyl carbonate. The resulting mixture was heated at 60 °C for 8 h. Workup as before gave 4.6 g (19.3 mmol, 96.5%) of keto ester **16b** as an orange liquid. Analytical samples were obtained as a colorless liquid by distillation at 90–95 °C (0.3 mmHg): IR (neat) 2926 (s), 2862 (s), 1747 (s), 1720 (s), 1631 (m), 1445 (m), 1240 (s), 900 (m), cm^{-1}; ^1H NMR (90 MHz) δ 1.04 (d, J = 7 Hz, 3 H), 1.23 (s, 3 H), 1.40–2.00 (complex, 7 H), 2.74 (s, 2 H), 3.49 (s, 2 H), 3.73 (s, 3 H), 4.57 (d, J = 2 Hz, 1 H), 4.69 (d, J = 2 Hz, 1 H); mass spectrum, m/e 239 (MH^+), 221, 207 ($MH^+ - CH_3OH$), 179, 165 ($M - C_3H_5O_2$), 147, 123 ($M - C_5H_7O_3$).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.31. Found: C, 70.3; H, 9.4.

Preparation of Diazo Keto Ester 7b. To a solution containing 5.0 g (21.0 mmol) of keto ester **16b** in 35 mL of acetonitrile cooled in an ice bath was added dropwise 4 mL of triethylamine followed by slow addition of 4.1 g (21.0 mmol) of *p*-toluenesulfonyl azide. The solution was stirred at room temperature for 6 h followed by partition between 100 mL of 2 N NaOH and 50 mL of ether–hexane (1:1). The organic layer was washed consecutively with 2 N NaOH, brine, and dried. Removal of solvent in vacuo gave as an orange oil 5.5 g (20.8 mmol, 99.2%) of diazo keto ester **7b**: IR (neat) 2925 (s), 2865 (m), 2142 (s), 1726 (s), 1718 (s), 1654 (s), 1448 (s), 1366 (s), 1306 (s), 1205 (s), 1119 (m), 899 (m), 749 (m) cm^{-1}; ^1H NMR (90 MHz) δ 1.04 (d, J = 7 Hz, 3 H), 1.28 (s, 3 H), 3.12 (s, 2 H), 3.84 (s, 3 H), 4.70 (bs, 2 H).

Preparation of Keto Ester 8b. A magnetically stirred mixture containing 2.8 g (10.6 mmol) of diazo keto ester **7b** and 2.4 g of anhydrous cupric sulfate in 85 mL of toluene was heated to reflux for 7 h. The filtered dark brown solution was washed with brine and concentrated under aspirator to dryness. The solid was

recrystallized from a mixture of ether and hexane to give as colorless needles 1.45 g (6.4 mmol, 58.0%) of keto ester **8b**, mp 110–114 °C. An additional 250 mg (1.05 mmol, 10%, giving a total yield of 68.0%) of the product was obtained from flash chromatography of the mother liquor with ether/methylene chloride/hexane (1:3:7) as eluent. Analytical samples were prepared by a second recrystallization of the needles from ether/hexane (3:1): mp 117–118 °C; IR (KBr) 3090 (w), 2923 (s), 2857 (m), 1728 (s), 1451 (s), 1351 (s), 1306 (m), 1203 (s), 1119 (m), 1040 (m) cm^{-1}; ^1H NMR (200 MHz) δ 0.65 (d, J = 7.5 Hz, 3 H), 1.16 (s, 3 H), 1.40 (d, J = 5 Hz, 1 H), 1.79 (d, J = 17.5 Hz, 1 H), 1.95 (d, J = 5 Hz, 1 H), 2.15 (d, J = 17.5, 1 H), 2.23 (m, 1 H), 3.76 (s, 3 H); ^{13}C NMR (200 MHz) δ 16.0, 19.0, 19.4, 22.0, 29.7, 33.2, 28.4, 29.1, 45.5, 48.4, 52.1, 76.3, 77.0, 77.6, 168.5, 202.0; mass spectrum m/e 237 (MH^+), 236 (M^+), 205 ($MH^+ - CH_3OH$), 176 ($M^+ - C_2H_4O_2$), 109, 108.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.2; H, 8.6.

Preparation of Diol 13b. To a solution containing 0.40 g (1.7 mmol) of keto ester **8b** in 30 mL of methanol cooled in an ice bath was added in partions 64 mg (1.7 mmol) of $NaBH_4$. The resulting solution was stirred at room temperature for 3 h. Most of the methanol was evaporated under aspirator and the residue was partitioned between 25 mL each of ether and water. The ether layer was washed and dried. Removal of solvent in vacuo gave 0.4 g of hydroxy ester **12b** as a light yellow oil which was redissolved in 30 mL of anhydrous ethyl ether and cooled in an ice bath. An etheral solution containing 6.2 mmol of methyllithium was added dropwise under nitrogen atmosphere. The solution became cloudy during addition. After being stirred at room temperature for 2 h, the mixture was washed with 25 mL of brine, dried, and evaporated in vacuo to dryness. Flash chromatography of the residue (0.5 g) eluting with ethyl ether/methylene chloride/hexane (1:5:5) gave 0.35 g (1.47 mmol, 86.4%) of diol **13b**. Analytical samples were prepared by recrystallization from a ether/hexane mixture as colorless transparent prisms: mp 95–96 °C; IR (KBr) 3514 (s), 3403 (s), 3063 (w), 2968 (m), 2930 (s), 2860 (m), 1462 (m), 1364 (m), 1127 (m) cm^{-1}; ^1H NMR (200 MHz) δ 0.13 (d, J = 5 Hz, 1 H), 0.72 (d, J = 5 Hz, 1 H), 0.92 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 1.45 (s, 3 H), 1.50 (s, 3 H), 1.80–2.05 (complex m, 1 H), 2.20 (m, 1 H), 2.27 (s, 1 H, tertiary OH), 2.46 (d, J = 4 Hz, 1 H, secondary OH), 4.34 (dd, J = 4, 6 Hz, 1 H); ^{13}C NMR (200 MHz) δ 12.4, 19.6, 21.5, 23.1, 30.7, 31.2, 31.8, 34.9, 38.9, 43.4, 45.0, 45.7, 47.3, 71.8, 77.9; mass spectrum, m/e 203 ($MH^+ - 2H_2O$).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.5; H, 11.0.

Preparation of Hydroxy Ketone 14b. Jones oxidation of diol **13b** (200 mg, 0.84 mmol) was carried out by following a procedure identical with that given for the isomeric **13a**. Flash chromatography of the crude oil (220 mg) eluting with ether/CH_2Cl_2/hexane (1:5:7) gave 165 mg (0.7 mmol, 83.1%) of a colorless solid **14b** (R_f 0.45, Et_2O/CH_2Cl_2/hexane 1:4:5). Analytical samples were prepared by recrystallization from an ether/hexane mixture as transparent prisms: mp 77–78 °C; IR 3260 (m), 2960 (s), 2920 (s), 2870 (m), 1700 (s), 1450 (m), 1360 (m), 1295 (m), 750 (s) cm^{-1}; ^1H NMR (90 MHz) δ 1.00 (d, J = 7 Hz, 3 H), 1.16 (s, 3 H), 1.38 (s, 3 H), 1.55 (s, 3 H), 2.03 (d, J = 4 Hz, 1 H), 2.21 (d, J = 4 Hz, 1 H), 2.27–2.58 (m, 1 H), 3.07 (s, 1 H); mass spectrum, m/e 236 (M^+), 221 ($M^+ - CH_3$), 218 ($M^+ - H_2O$).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.1; H, 10.5.

Preparation of (±)-Epicycloeudesmol (4). A magnetically stirred mixture containing 150 mg (0.63 mmol) of keto carbinol **14b** and 122 mg (3.8 mmol) of anhydrous hydrazine in 8 mL of ethylene glycol was heated at 135–140 °C for 6 h (or until the disappearance of starting material by TLC). Solid KOH (250 mg, 3.8 mmol) was added and the mixture was heated to 190–195 °C for 4 h. The dark brown solution was partitioned between 50 mL of brine and 20 mL of ether. Workup as usual gave a yellow oil (150 mg) which was passed through a short column (20 g of silica gel) eluting with Et_2O/CH_2Cl_2/hexane (1:10:10). The desired fractions (R_f 0.54, Et_2O/CH_2Cl_2/hexane 1:5:5) were collected to afford 31 mg (0.14 mmol, 22.2%) of (±)-epicycloeudesmol as a colorless oil. Analytical samples were obtained by distillation at 58–60 °C (0.12 mm Hg): IR 3615 (w), 3032 (s), 2930 (s), 1460 (m), 1374 (m), 1208 (s), cm^{-1}; ^1H NMR (200 MHz) δ 0.29 (d, J = 5 Hz, 1 H), 0.71 (d, J = 5 Hz, 1 H), 0.92 (d, J = 7 Hz, 3 H), 0.97 (s, 3 H), 1.30 (s, 3 H), 1.40 (s, 3 H), 2.15 (bm, 1 H); ^{13}C NMR (90 MHz) δ 8.8, 19.4, 21.0, 23.0, 28.2, 29.9, 30.4, 31.8, 34.8, 35.7, 37.2, 43.5, 43.8, 44.0, 70.4; mass spectrum, m/e 221 ($MH^+ - H_2$), 205 ($MH^+ - H_2O$), 164 ($MH^+ - C_3H_7O$), 163 ($MH^+ - C_3H_7OH$).

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Registry No. (±)-**3**, 85505-79-9; (±)-**4**, 90528-87-3; (±)-**7a**, 85428-15-5; (±)-**7b**, 90461-14-6; (±)-**8a**, 85428-16-6; (±)-**8b**, 90528-88-4; (±)-**9**, 85428-12-2; (±)-**10a**, 85428-13-3; (±)-**10b**, 90461-15-7; (±)-**11**, 90461-16-8; **12**, 85428-17-7; **13**, 85428-18-8; (±)-**14a**, 85428-19-9; (±)-**14b**, 90528-89-5; (±)-**15a**, 85428-20-2; (±)-**15b**, 90461-17-9; (±)-**16a**, 85428-14-4; (±)-**16b**, 90461-18-0; 2,6-dimethylcyclohexanone tosylhydrazone, 64287-34-9; dimethyl carbonate, 616-38-6.

Studies on Gibberellin Synthesis: The Total Synthesis of Gibberellic Acid from Hydrofluorenone Intermediates†

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Reductive alkylation of 2,5-dimethoxybenzoic acid with benzyl iodide **15** followed by cyclodehydration furnished fluorenone **8** which was converted into gibbane **10** by means of an acid-catalyzed intramolecular cyclization procedure based on diazo ketone **21**. Benzylic lithiation of **10**, 7-methoxymethyl ether ethylene acetal, followed by carboxylation, hydrogenation, and reductive alkylation furnished the important intermediate **11a** which possesses all the essential stereochemical and structural features necessary for the total synthesis of gibberellic acid **1**. This was achieved in a formal sense through a simple lactonization sequence leading to the advanced lactone acetal **12** which had previously been transformed into **1**.

Gibberellic acid (**1**) is the best known member of a group of sixty odd phytohormones[1] which play a central role in the regulation of plant growth.[2] The challenge posed by the construction of **1** has stimulated a wide range of creative endeavor that has added substantially to the meth-

† Dedicated to Professor C. W. Shoppee on the occasion of his 80th birthday.

(1) (a) Hedden, P. *ACS Symp. Ser.* **1979**, *No. 111*, 19. (b) Hanson, J. R. "The Tetracyclic Diterpenes"; Pergamon Press: Oxford, 1968; pp 41–59.

0022-3263/84/1949-3250$01.50/0 © 1984 American Chemical Society