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 ($MH^+ - C_3H_7OH$).

Acknowledgment. I thank Prof. R. A. Moss of Rutgers University for encouragement and many helpful discussions, and Drs. M. Shapiro and E. Fu of Sandoz, Inc., for aid in recording and interpreting the high-field NMR and mass spectra, respectively.

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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Received April 2, 1984

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.

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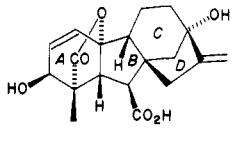
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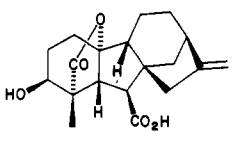
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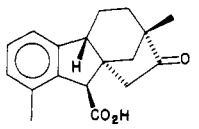
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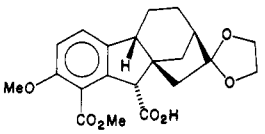
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odology of organic synthesis.[3] Much of this effort has been addressed to the respective problems of elaborating the chemically sensitive A-ring and D-ring regions. A successful strategy for the complete synthesis, however, must ensure that solutions to these two problems are coordinated effectively, as well as deal with the obvious logistical and stereochemical difficulties.[3-5] The prospect of utilizing intermediates that incorporate a benzenoid A ring is an attractive one and many early studies were based on this kind of approach.[6-7] Indeed, the first reported synthesis of a natural gibberellin, GA_4 (2), was achieved in this way, utilizing epigibberic acid (3) (a degradation product of 1) as a relay, although the complete sequence traversed approximately 55 steps.[8] The pioneering studies of Loewenthal et al. on the reductive alkylation of 1-naphthoic acid derivatives (Chart I) have provided a very much more efficient and elegant solution to the elaboration of the A ring.[6a] Additional research by this group has established methodology for the introduction of the B-ring carboxyl substituent as illustrated by the preparation of the tetracyclic ester 4,[6b,c] a potential intermediate for the synthesis of GA_4 (2). Baker[7c] and House[7a,b] have also reported valuable insights into this type of approach to gibberellin synthesis, but further progress has not yet been reported by any of these three groups.

Some years ago we described the conversion of fluorene 7 into ketol 9 by means of a novel acid-catalyzed diazo ketone cyclization which was developed especially for the purpose.[9] More recently we have achieved an efficient,

Chart I

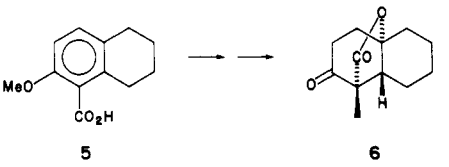
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Chart II

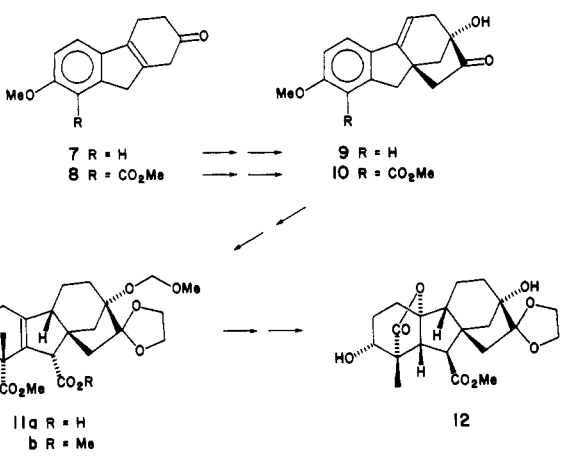
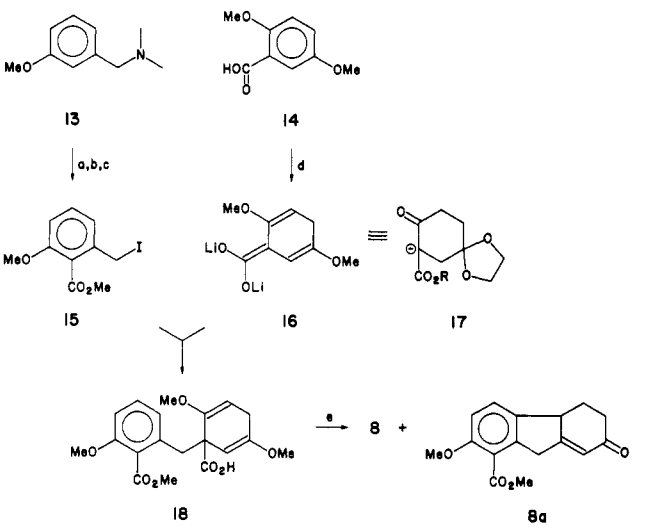

7 R = H, 8 R = CO_2Me → 9 R = H, 10 R = CO_2Me; 11a R = H, b R = Me; 12

Chart III[a]


13 14 15 16 17 18 8a

[a] Reagents: (a) *n*-BuLi, $MeOCO_2Me$; (b) $ClCO_2Me$; (c) NaI; (d) Li, NH_3; (e) PPA.

convergent synthesis of the fluorenone 8[10] which, in combination with our diazo ketone based procedures[9] and methodology derived from the Loewenthal studies,[6] has led to a formal total synthesis of gibberellic acid (1).[5b] In this paper we describe those endeavors, which may be conveniently divided into four stages (Chart II): i.e., the elaboration of tricyclic ketone 8, its transformation into the gibbane 10, thence 11a, and finally 12, which we have prepared by a completely independent route and converted into 1.[5a]

The preparation of the fluorenone 8, which has been outlined in a preliminary communication,[10] is delineated in Chart III. The precursor of the A ring was prepared from a sequence beginning with metalation of amine 13 by *n*-BuLi in diethyl ether followed by acylation with dimethyl carbonate.[11] The isolated product was then

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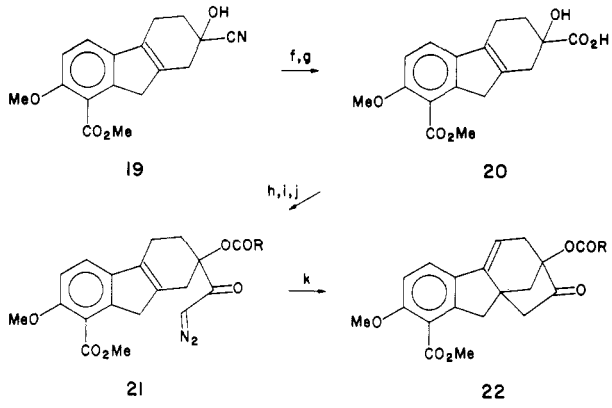
(10) Hook, J. M.; Mander, L. N. *J. Org. Chem.* **1980**, *45*, 1722–1724.

Chart IV[a]

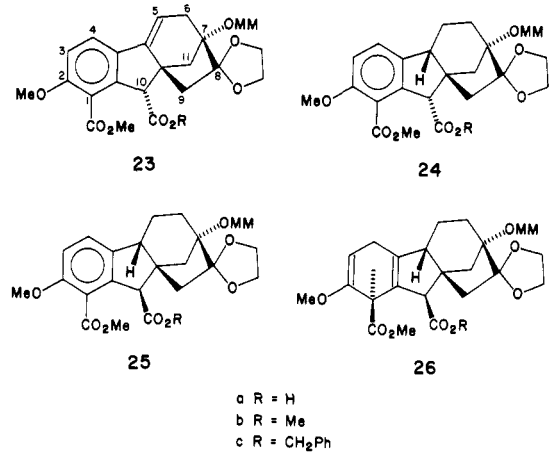


[a] Reagents: (f) HCl, MeOH; (g) NaOH, MeOH; (h) $ClCH_2COCl$; (i) $(COCl)_2$, DMF; (j) CH_2N_2; (k) CF_3CO_2H.

treated with methyl chloroformate to give the benzyl chloride, the derived iodide **15** from which was used to alkylate enediolate **16**.[12] This intermediate serves as a synthetic equivalent to the traditional anion derived from the β-keto ester **17**,[13] but is more simply prepared and very much more nucleophilic. This latter aspect is crucial since **15** and its analogues are prone to form the corresponding phthalides. Cyclization of the resulting adduct **18** proceeded smoothly to furnish fluorene **8** as a 4:1 mixture with the isomeric α,β-unsaturated ketone **8a**. Both products were readily autooxidized and chromatographic separation was accompanied by significant losses. Fortunately it was possible to use the mixture directly in the next step of the synthesis, i.e., hydrocyanation to give **19**, since the α,β-unsaturated **8a** isomer did not react with hydrogen cyanide, but was isomerized under the reaction conditions (excess of NaCN) to **8**.

The conversion of cyanohydrin **19** into the tetracyclic ketone **22** (Chart IV) was modelled on the preparation of **9**,[9] but with some important changes. Acid **20** was most efficiently prepared from cyanohydrin **19** in two steps: methanolysis[14] followed by selective hydrolysis, which is assisted by the α-hydroxyl group. The tetracyclic ketone **22** (R = $CHCl_2$) was then prepared from acid-catalyzed cyclization of diazo ketone **21** (R = $CHCl_2$). In order to prevent the bridgehead oxygen from attacking the protonated diazoacetyl group, we had resorted earlier to the use of a trifluoroacetyl ester,[9] but this function is too easily removed by adventitious nucleophiles. It was hoped, therefore, that a dichloracetate function in **21** would provide a better compromise between stability and nucleophilicity.[15,16] In the event, an unacceptably low overall yield of the tetracyclic ketone **22** (R = $CHCl_2$) was ultimately obtained, due mainly to difficulties in the preparation of the acyl chloride precursor to diazo ketone **21** (R = $CHCl_2$). The overall yield was improved considerably by switching to the chloroacetate **21** (R = CH_2Cl) and by modifying the procedure for the preparation of the acyl chloride (see Experimental Section), however. In this way **22** (R = CH_2Cl) was obtained in 64% overall yield from hydroxy acid **20**.

The next stage of the synthesis (**10** → **11a**) involved the introduction of the B-ring carboxyl and the elaboration of the quaternary center at C(1). To this end, **10** was masked as an ethylene acetal, and following the procedures established by Loewenthal,[6c] attempts were made to carboxylate the benzylic C(10) position after deprotonation with lithium *N*-*tert*-butyl-*N*-cyclohexylamide, but without success. The derived 7-(methoxymethyl)oxy ether, however, afforded acid **23a** in excellent yield. It is not clear



a R = H
b R = Me
c R = CH_2Ph

why the relatively remote 7-hydroxy substituent (apart from consuming 1 equiv of base) should inhibit deprotonation at C(10), but it became apparent[15] that it would be also necessary to mask this function during the subsequent reductive alkylation step.

The stereochemistry at C(10) in **23** was assigned on the basis of stereoelectronic considerations, i.e., the expectation of more effective overlap between an axially oriented carbanion and the aromatic π-orbitals. Although epimerization would be ultimately required to achieve the correct gibberellin configuration, the 10α-carboxyl is essential for the control of stereochemistry at C(4b) and C(1). On the basis of very early studies on degradation products of GA_3 (**1**) it was expected that hydrogen would be delivered to the opposite side of the molecule to the carboxy function.[6c,17] It was also apparent from these studies that the 10α-isomer, **24a**, would be thermodynamically less stable than the 10β-isomer and so the assignment of structure **24a** was confirmed when the derived methyl ester **24b** was converted by base into a 1:2 mixture of **24b** and its 10β-epimer **25b**. A good match was also obtained between the ^1H NMR chemical shifts observed for H(10) and H(4b) in **24b** and **25b** respectively with those reported for the corresponding 7-deoxy compounds.[6c]

The original synthesis plan had involved the reductive alkylation of the dicarboxylic acid derived from **24a**. Reports of partial hydrogenolysis of *o*-methoxy groups during metal–ammonia reductions of anisoic acid derivatives,[7a,b,18] as well as a facile oxidative decarboxylation which had occurred with one such product,[7c] led us to

(11) This procedure was adapted from a literature procedure (Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115–2122), which described metalation of *N*,*N*-dimethyl-3,4-dimethoxybenzylamine in tetrahydrofuran as solvent and treatment of the resulting anion with 2 equiv of methyl chloroformate, thereby achieving acylation and replacement of the amine group by chloride in one pot. To achieve regiospecific metalation of **13**, however, it was necessary to employ a diethyl ether solution. Since this solvent was unsatisfactory for the amine metathesis (the *N*-acylammonium intermediate precipitated from this medium) the sequence was carried out in a stepwise manner.

(12) Hook, J. M.; Mander, L. N.; Urech, R. *Synthesis* **1979**, 374–376.

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(14) Birch, A. J.; Macdonald, P. L.; Powell, V. H. *J. Chem. Soc. C* **1970**, *1469*–1476.

(15) Mander, L. N.; Urech, R. *Aust. J. Chem.* **1983**, *36*, 1177–1185.

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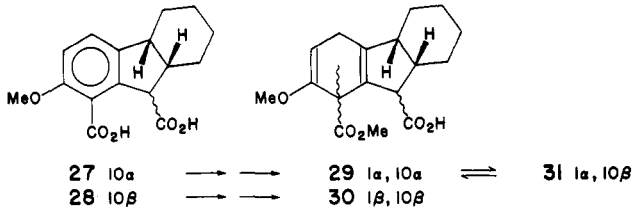
(17) (a) Grove, J. F.; Mulholland, T. P. C. *J. Chem. Soc.* **1960**, 3007–3022. (b) Grove, J. F.; MacMillan, J.; Mulholland, T. P. C.; Turner, W. B. *Ibid.* **1969**, 3049–3057. (c) Stork, G.; Newmann, H. *J. Am. Chem. Soc.* **1959**, *81*, 3168.

(18) Birch, A. J.; Slobbe, J. *Aust. J. Chem.* **1977**, *30*, 1045–1049.

Chart V[a]



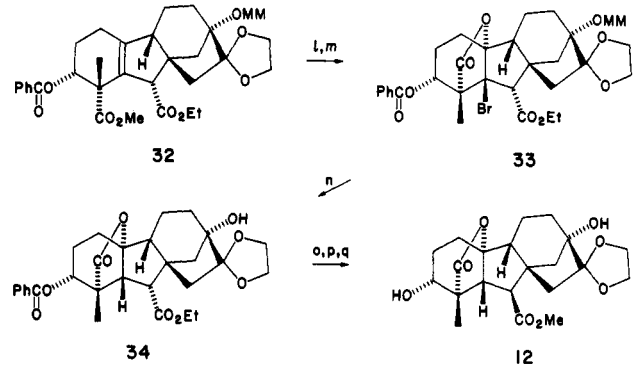
[a] Numbering based on gibbane skeleton.

consider the reductive methylation of the half ester **24a** instead, however. At the time, ring reduction of aromatic esters was very much a speculative exercise,[19] but with the benefit of experience gained in the reductive alkylation of ketones,[20] hydrophenanthrene analogues[15] of **24**, and simple esters,[21] it was possible to obtain a high yield of **11a**. This was achieved by pretreating a solution of **24a** in liquid ammonia with 1 equiv of potassium *tert*-butoxide—this serves the dual purpose of neutralizing the ammonium ions generated by addition of the carboxylic acid to the ammonia and providing 1 equiv of an acid stronger than ammonia for protonation of the intermediate radical–anions (or dianions)—then effecting reduction at −70 °C with potassium, followed by alkylation with methyl iodide. It should be noted that with reductive alkylations of esters in general, metathesis to the lithium enolate is necessary with most other alkyl halides.[21]

Only one diastereomer was obtained from reductive methylation and although the results obtained by House et al. for the model substrates **27** and **28** (Chart V)[7a] lead to the expectation that **24a** should afford the desired 1β-methyl derivative **11a**, ^{1}H NMR spectra were ambiguous: the chemical shift of the methyl resonance from the presumed **11b**, for example, was observed at δ 1.36, i.e., intermediate between the values of δ 1.39 and 1.32 reported for **29** and **31**, respectively.

In the hope that reductive methylation of the 10β-epimer of **24a**, i.e., **25a**, might shed light on the problem, the partial hydrolysis of **25b** was attempted, but all attempts furnished the dicarboxylic acid instead. The benzyl ester **24c** was therefore prepared, isomerization to **25c** effected with diazabicyclononene (DBN), and the desired acid **25a** obtained through subsequent hydrogenolysis. Reductive methylation followed by esterification with diazomethane again gave a single product, but with δ (1-CH_3) 1.46, an excellent match with the value reported for **30** (δ 1.47)[7a] and therefore strongly indicative of structure **26b**. It appeared to be almost certain, therefore, that reductive alkylation of **24a** had also occurred anti to the 10-carboxyl function and that the desired **11a** had been produced. This conclusion was substantiated when methoxide-catalyzed equilibration (under conditions which led to isotopic exchange of H(10) in methanol-d_1) of either **11b** or **26b** returned the parent compound. If **24a** had afforded the C(4) epimer of **11a** then the treatment of **11b** and **26b**, respectively, by base should have led to the same equilibrium mixture. The elaboration of the A-ring functionality (Chart VI) was conceptually straightforward, but the range of reagents and methodology used in simpler substrates[6a,7b] was proscribed by the presence of the acetal groups. Weak acids which might have been expected to catalyze hydrolysis of the enol ether function were ineffectual,[22] while stronger reagents[19] led to the destruction of the methoxymethyl and ketal substituents. In a search for a better π-electrophile, the use of mercury(II) salts was also examined, and although mercury(II) acetate[23] was not useful, treatment with mercury(II) nitrate in aqueous acetonitrile[24] furnished the corresponding ketone. This was reduced and benzoylated to give the 2α-benzoate which was converted into the 10-ethyl ester **32** in order to facilitate the selective liberation of the 1α-carboxyl group by thiolate-induced demethylation[25] as a prelude to lactonization. A range of procedures was examined in relation to this last important step, but only a traditional bromo lactonization at 0 °C with $KBr_3/KHCO_3$[7b] was effective. The very unstable bromo lactone **33** (ν_{max} 1792 cm^{-1}) was immediately reduced to **34** with chromous(II) acetate in the presence of propanethiol as a hydrogen donor[26]. ^{1}H NMR spectra of this last series of compounds showed a significant deshielding of H(2) in **33** relative to **32** (0.65 ppm) and **34** (0.57 ppm), revealing a syn relationship between H(2) and the 10aβ-bromo substituent, and thereby confirming the assignment of C(2) stereochemistry to **32**.

Chart VI[a]



[a] Reagents: (l) *n*-PrSLi; (m) KBr_3, K_2CO_3; (n) Cr(II)-$(OAc)_2$, *n*-PrSH; (o) DBU; (p) NaOH; (q) CH_2N_2

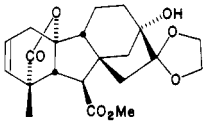
The more important chirality at C(10a) in **34** was not so readily determined, however. Precedents for Cr(II) dehalogenation reactions appear to allow no definitive prediction of the stereochemical outcome, but were consistent with the expectation of the thermodynamically more stable product,[6a,7b] which in the present case should be the desired 10aβ-epimer. Tentative support was provided by the ^{1}H NMR spectrum of **34** which showed doublets at δ 3.05 (H10) and δ 2.44 (H10a) with J = 11 Hz, a coupling constant which was consistent with the expected dihedral angle of ca. 170° between H(10aβ) and H(10β). The correctness of the assignment was rigorously established by eventual correlation with (+)-**12** which had been obtained by degradation of gibberellic acid **1**.[27] To this end **34** was treated with sodium methoxide in boiling methanol, with a view to achieving concomitant epimeri-

(19) We are grateful to Professor Loewenthal for alerting us to this possibility. Cf. Loewenthal, H. J. E. "Guide for the Perplexed Organic Experimentalist"; Heyden: London, 1978; pp 133–138.
(20) Brown, J. M.; Cresp, T. M.; Mander, L. N. *J. Org. Chem.* **1977**, *42*, 3984–3986.
(21) Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095–1098.
(22) Hydrolysis of **11a** was unsuccessful with acetic, formic, and chloroacetic acid as well as sodium hydrogen sulfate. Cf. Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803–806.
(23) Dauben, W. G.; Bastin, C. P.; van Riel, H. C. H. A. *J. Org. Chem.* **1979**, *44*, 1567–1569.
(24) de Oliveira Baptista, M. J. V.; Barrett, A. G. M.; Barton, D. H. R.; Girijavallabhan, M.; Jennings, R. C.; Kelly, J.; Papadimitriou, V. J.; Turner, J. V.; Usher, N. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1477–1550.
(25) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459–4462.
(26) Barton, D. H. R.; Basu, N. K.; Hesse, R. H.; Morehouse, F. S.; Pechet, M. M. *J. Am. Chem. Soc.* **1966**, *88*, 3016–3021.
(27) Lombardo, L.; Mander, L. N.; Turner, J. V. *Aust. J. Chem.* **1981**, *34*, 745–753.

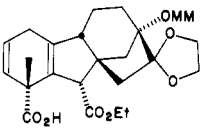
zation, transesterification, and benzoate removal. During the prolonged treatment that was necessary to effect these changes, however, extensive decomposition occurred, presumably as a consequence of the retroaldol reaction which is a feature of the chemistry of 2-hydroxy gibberellins.[5a] It was preferable to proceed in a stepwise fashion, i.e., epimerization at C(10) with diazabicycloundecene (DBU), hydrolysis, and then reesterification with diazomethane.

The product obtained thus was identical in all respects (melting point, mixture melting point, ^{1}H NMR, IR, and mass spectra) with a sample of **12** prepared by an alternative route in our laboratories[5a]. Since **12** has been transformed into gibberellic acid (**1**), the present work constitutes a formal total synthesis of this compound in ~34 steps from 2,5-dimethoxybenzoic acid.

The route from **12** to **1** proceeds via the olefinic lactone **35**, so it appeared that a more efficient approach to **1** might be based on **36**, since the 2-oxy substituent in **11** is not only



35



36

redundant, but also complicates a number of the subsequent transformations. If **36** could be prepared and utilized, there would be a potential saving of seven steps involved in the manipulation of the A-ring functionality and the B-ring carboxylate.

In order to test the feasibility of the alternative sequence, the 2α-phenylsulfonate analogue of **32** was prepared and treated with tetrabutylammonium bromide—diazabicyclononene in dimethyl formamide followed by thiolate induced demethylation, thereby furnishing **36**. The results of several lactonization experiments with this substrate, however, indicated that only the C-2 double bond was participating—presumably as a consequence of steric factors. Thus a 2-methoxy substituent, which had originally been envisaged as a precursor to the 2β-hydroxy function of **1**, serves instead to allow discrimination between the two olefinic bonds in **11**. It is also important as an activating group in the cyclization of **18** to **8**.[10] One further attempt was made to shorten the sequence from **11a** to **36** by eliminating the minor redundancy 2α-OH → 2α-OCOPh → 2α-OH → 2α-OSO_2Ar, but neither the 2α-phenylsulfonate nor 2α-tosylate corresponding to 2α-benzoate **32** could be demethylated cleanly. Concomitant elimination of arylsulfonic acid occured with lithium propanethiolate in HMPA and acid **36** was the only identifiable product.

Conclusion

This route for the total synthesis of gibberellic acid (**1**) is, within the limits of analysis, completely diastereoselective. It arrives in only ~13 steps at an intermediate (**11a**) in which the major structural and stereochemical problems have been solved, and therefore has the potential of an unusually direct approach to **1**. Although it has subsequently been overshadowed by more direct sequences developed in our own laboratories[5a] and those of Corey,[28] it brings to a very satisfactory conclusion the very considerable international effort which has been centered on the aromatic A-ring based strategy for C_{19} gibberellin synthesis. It has also led to two especially useful developments in synthetic methodology with broad potential, i.e., the intramolecular alkylation of π-systems by protonated diazomethyl ketones,[29] and the reductive alkylation of aromatic substrates.[10,12,20,21,30]

Experimental Section[31]

Methyl 6-[(*N*,*N*-Dimethylamino)methyl]-2-methoxybenzoate. A solution of amine **13** (prepared from *m*-methoxybenzyl bromide in 91% yield,[33] 115.5 g, 0.7 mol) in dry ether (1000 mL) under argon was treated with *n*-butyllithium (675 mL, 1.6 M in hexane) at room temperature. After 20 h, dry dimethyl carbonate (163 mL, 1.80 mol) was added to the deep orange solution at such a rate to maintain a gentle reflux. When the addition was complete, the reaction mixture was stirred for an additional 4 h, before water (2000 mL) was added. The layers were separated, and the organic layer was extracted with 5 N hydrochloric acid (2 × 500 mL). The acidic extracts were combined and made alkaline (pH 13) by cautiously adding potassium hydroxide pellets. The alkaline solution was then extracted with ether (3 × 1000 mL), and the extracts were washed with brine (1 × 1000 mL) and dried. Removal of the solvent gave a pale yellow oil, which upon distillation gave the amino ester (125 g, 80%): bp 100–104 °C (0.3 mmHg); mp ~30 °C; ^{1}H NMR δ 7.20 (t, J = 8 Hz, 1 H, H-4), 6.84 (d, J = 8 Hz, 1 H, ArH), 6.78 (d, J = 8 Hz, 1 H, ArH), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.34 (s, 2 H, $ArCH_2$), 2.10 (s, 6 H, 2 × NCH_3); IR (film) 1740, 1585 cm^{-1}; m/z 223 (35%, M^+), 222 (5), 208 (78), 192 (93), 179 (12),176 (100), 163 (46), 149 (22), 148 (24); mass calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1205.

Methyl 6-(Chloromethyl)-2-methoxybenzoate. A solution of the above amino ester (30 g, 0.135 mol) in dry THF (150 mL) was added dropwise over 45 min, to a stirred solution of freshly distilled methyl chloroformate (32 mL, 0.415 mol) in dry THF (150 mL) at 25 °C under nitrogen. After stirring for 18 h, the volatiles were removed and the residue partitioned between ether (200 mL) and water (pH 5, 100 mL). The layers were separated, and the organic phase was washed with water (2 × 100 mL) and brine (1 × 100 mL) and dried. Removal of the solvent, gave the chloro ester (27 g, 95%) homogeneous by TLC (R_f 0.7 dichloromethane): ^{1}H NMR δ 7.32 (t, J = 8 Hz, 1 H, H-4), 6.98 (d, J = 8 Hz, 1 H, ArH), 6.88 (d, J = 8 Hz, 1 H, ArH), 4.56 (s, 2 H, $ArCH_2$), 3.86 (s, 3 H), 3.73 (s, 3 H); IR (film) 1740 cm^{-1}; m/z 217 (10), 214 (32%, M^+), 185 (17), 184 (37), 183 (50), 182 (100); mass calcd for

(28) Corey, E. J.; Munroe, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 6129–6130.

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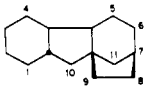
(31) Melting points were determined on a Reichert hotstage apparatus. Melting points and boiling points are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) were recorded by using a Jeol Minimar 100 spectrometer operating at 100 MHz. The spectra were measured in $CDCl_3$, unless otherwise stated, with Me_4Si as internal standard. Infrared spectra (IR) were determined on a JASCO IRA-1 or a Perkin Elmer 457 spectrometer. Nujol mulls were used unless otherwise indicated. The mass spectra were recorded on an AEI MS 902 double-focussing mass spectrometer. Microanalysis were performed by the Australian National University Analytical Services Unit, Canberra. "Dry" solvents were distilled shortly before use from an appropriate drying agent and/or stored over molecular sieves. In particular, tetrahydrofuran (THF) and ether were distilled from the ketyl formed by the reaction of sodium and benzophenone. Petroleum ether refers to the fraction which boils between 40 and 60 °C. Reactions were run under an atmosphere of nitrogen. Organic extracts were dried with $MgSO_4$. Compounds have been named, where appropriate, as derivatives of gibbane **i**.[32]



i

(32) *Chem. Abstr. 10th Collect. Index* **1977–1981**, *86–95*, CS 23191.

(33) Eliel, E. L.; Ferdinand, T. N.; Hermann, M. C. *J. Org. Chem.* **1954**, *19*, 1693–1698.

$C_{10}H_{11}ClO_3$ 214.0399, found 214.0397.

An attempt to purify the chloro ester by distillation gave 7-methoxyphthalide in virtually quantitative yield: mp 107–109 °C (lit.[34] 107–109 °C).

Methyl 6-(Iodomethyl)-2-methoxybenzoate (15). A solution of the chloro ester (15.5g, 86 mmol) in acetone (100 mL) was added dropwise over 20 min to a stirred solution of sodium iodide (32 g, 213 mmol) in acetone (140 mL). After 1.5 h, the filtered solution was concentrated in vacuo, and the dark orange residue (***Caution***! potent lachrymator) partitioned between ether (200 mL) and water (100 mL). The layers were separated and the organic phase was washed with water (1 × 100 mL), aqueous 5% sodium thiosulfate solution (1 × 100 mL), and brine (1 × 200 mL) and dried. Evaporation of the solvent gave the unstable iodo ester **15** (25.5 g, 96%) was a pale yellow oil, homogeneous by TLC (R_f ~0.8, dichloromethane). This alkylating agent was used without purification: ^{1}H NMR δ 7.26 (t, J = 8 Hz, 1 H, H-4), 6.94 (d, J = 8 Hz, 1 H, ArH), 6.80 (d, J = 8 Hz, 1 H, ArH), 4.40 (s, 2 H, $ArCH_2$), 3.86 (s, 3 H), 3.72 (s, 3 H); IR (film) 1720–1740 cm^{-1}; m/z 306 (5), 275 (6), 179 (100), 149 (24), 148 (29), 105 (23).

2,5-Dimethoxy-1-[(3′-methoxy-2′-(methoxycarbonyl)-phenyl)methyl]-2,5-cyclohexadiene-1-carboxylic Acid (18). Lithium metal (ca. 1.1 g, 160 mmol) was added piecewise to a stirred suspension of 2,5-dimethoxybenzoic acid (12 g, 66 mmol) in liquid ammonia (1000 mL) and dry THF (100 mL) at −33 °C until a deep blue color persisted. After 20 min the ammonia was removed under a stream of nitrogen, ensuring that the internal temperature did not rise above 0 °C. To the resultant yellow suspension was added iodide **15** (25 g, 81 mmol) in THF (150 mL) at 0 °C. After removing the ice bath the reaction was stirred for an additional 16 h, then concentrated in vacuo. The residue was dissolved in ethyl acetate (300 mL) and extracted with dilute ammonium hydroxide solution. The basic aqueous phase was cooled to 0 °C, layered with fresh ethyl acetate (500 mL), and acidified (5 N hydrochloric acid) to pH 5.5. The layers were separated, and the aqueous phase was extracted further with ethyl acetate (2 × 200 mL). The extracts were washed with water (200 mL) and brine (200 mL) and dried. Removal of the solvent gave the cream-colored crystalline acid **18** (21 g, 88%): mp 138–140 °C (acetone–hexane); ^{1}H NMR δ 11.40 (broad, 1 H, CO_2H), 7.28 (t, J = 8 Hz, 1 H, H-4′), 6.70 (m, 2 H, H3′ and H-5′), 4.72 (t, J = 4 Hz, 1 H, H-3), 4.48 (s, 1 H, H-6), 3.88 (s, 3 H), 3.76 (s, 3 H), 3.58 (s, 3 H, C=$COCH_3$), 3.52 (s, 3 H, C=$COCH_3$), 3.37 and 3.12 (ABq, J_{AB} = 14 Hz, $ArCH_2$), 2.70 (dd, J_1 = 21 Hz, J_2 = 4 Hz, 1 H, H-4), 2.34 (dd, J_1 = 21 Hz, J_2 = 4 Hz, 1 H, H-4); IR 2600, 1740, 1705, 1660 cm^{-1}; m/z 362 (2%, M$^+$), 331 (16), 318 (69), 285 (18), 271 (28), 255 (23), 180 (100), 165 (34), 148 (90), 139 (77). Anal. Calcd for $C_{19}H_{22}O_7$: C, 63.0; H, 6.1. Found: C, 63.2; H, 6.0.

Methyl 2-Methoxy-7-oxo-5,6,7,8-tetrahydrofluorene-1-carboxylate (8) and Methyl 2-Methoxy-7-oxo-4b,5,6,7-tetrahydrofluorene-1-carboxylate (8a). Finely powdered acid **18** (18.1 g, 50 mmol) was added to mechanically stirred PPA (500 g, predegassed with a stream of nitrogen 30 min) at 60 °C as quickly as possible (foams). The solution was stirred rapidly for another 30 min at this temperature, cooled, and poured onto ice (1000 g) in five portions with vigorous stirring. The yellow precipitate was extracted into ethyl acetate (3 × 500 mL), and the extracts were washed with water (500 mL), 1 N aqueous sodium bicarbonate (500 mL), and brine (500 mL) and dried. Removal of the solvent gave a yellow solid (13.0 g) which was a 4:1 mixture of fluorenones **8** and **8a** (^{1}H NMR analysis). The major component **8** could be isolated by PLC (5% methanol–dichloromethane) as a colorless crystalline solid (36%) which oxidized rapidly in air: mp 162–165 °C (benzene); ^{1}H NMR δ 7.30 (d, J = 8 Hz, 1 H, H-4), 6.94 (d, J = 8 Hz, 1 H, H-3), 3.94 (s, 3 H), 3.90 (s, 3 H), 3.45 (broad s, 2 H, H-9), 3.26 (broad s, 2 H, H-8) 2.72 (m, 4 H, H-5, H-6); IR 1715, 1580 cm^{-1}; UV 208 (ϵ 16 800), 268 (14 400), 277 (sh) (11 000) nm; m/z 272 (100% M$^+$), 244 (7), 241 (24), 240 (22), 230 (16), 212 (41), 198 (44); mass calcd for $C_{16}H_{16}O_4$ 272.1049, found 272.1048.

Dimethyl 2-Hydroxy-7-methoxy-1,2,3,4-tetrahydrofluorene-2,8-dicarboxylate. The crude mixture of **8** and **8a** (13.0 g, 47.8 mmol) was dissolved in THF (400 mL), water (250 mL) was added, and the system purged of oxygen with a stream of nitrogen for 1 h. Sodium cyanide (14.0 g, 287 mmol) was added, followed by the dropwise addition of 4 N hydrochloric acid (72 mL) over 2 h (***Caution***! HCN evolution). After the addition was completed (TLC showed a single spot), the excess of hydrogen cyanide was driven off with a nitrogen stream (14 h, aqueous permanganate trap). Ethyl acetate (200 mL) was added and the layers separated. The organic phase was washed with water (3 × 100 mL) and brine (200 mL) and dried. Removal of the solvent gave the cyanohydrin **19** (14.0 g) as a brown foam.

A sample crystallized from ethyl acetate–light peroleum as pale pink crystals: mp 165–169 °C; ^{1}H NMR δ 7.26 (d, J = 8 Hz, 1 H, H-5), 6.92 (d, J = 8 Hz, 1 H, H-6), 3.94 (s, 3 H), 3.90 (s, 3 H), 3.50 (s, 1 H, OH), 3.42 (broad s, 2 H, H-9), 2.90 (m, 2 H, H-1), 2.66 (e, 2 H, H-4), 2.22 (e, 2 H, H-3); IR 3500, 2240, 1715, 1585 cm^{-1}; m/z 299 (1%, M$^+$), 272 (100), 241 (25) 240 (20), 239 (15), 212 (42), 198 (45). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.0; H, 5.9; N, 4.4.

A stirred suspension of the cyanohydrin **19** (14.0 g, 46.8 mmol) in absolute methanol (250 mL) was cooled to 0 °C and then treated with hydrogen chloride gas until the methanol was saturated. The flask was then stoppered securely and the solution allowed to warm to room temperature overnight. The resultant dark solution was concentrated to about half the volume and then poured onto ice (250 g) with stirring. After 1 h, the precipitate that had formed was extracted into ethyl acetate (3 × 200 mL). The ethyl acetate extracts were washed with water (100 mL), 1 N aqueous bicarbonate solution (100 mL), and brine (200 mL) and dried. Removal of the solvent gave a dark brown oil (12.1 g) which was chromatographed on silica gel (360 g, chloroform) to give the corresponding methyl ester (8.3 g, 50% from acid **18**): mp 118–120 °C (ether); ^{1}H NMR 7.22 (d, J = 8 Hz, 1 H, H-5), 6.86 (d, J = 8 Hz, 1 H, H-6), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.39 (broad s, 2 H, H-9), 3.26 (s, 1 H, OH), 2.90 (e, 1 H), 2.62 (e, 3 H), 2.00 (e, 2 H); IR 3450, 1740, 1720, 1590 cm^{-1}; m/z 332 (56%, M$^+$), 314 (52), 301 (17), 282 (6), 273 (12), 272 (9), 230 (27), 198 (100). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.1; H, 6.1. Found: C, 64.8; H, 6.4.

2-Hydroxy-7-methoxy-8-(methoxycarbonyl)-1,2,3,4-tetrahydrofluorene-2-carboxylic Acid (20). The hydroxy ester (7.5 g, 22.6 mmol) was dissolved in THF (100 mL), methanol (100 mL), and water (10 mL) and the solution purged of oxygen with a stream of nitrogen for 1 h. Potassium hydroxide pellets (2.53 g, 45 mmol) were added and the reaction was stirred at 25 °C for 2 h. The solution was concentrated in vacuo at 20 °C, the residue dissolved in water (60 mL) and extracted with ethyl acetate (3 × 50 mL). The basic aqueous phase was then cooled to 0 °C and acidified to pH 1 with 10 N hydrochloric acid, and the precipitate collected by filtration and dried to give the hydroxy acid **20** (6.7 g, 93%) as a white solid, mp 225–230 °C, homogeneous by TLC (R_f ~0.4, 10% methanol–dichloromethane): mp 230–232 °C (THF–petroleum ether); ^{1}H NMR δ ($CDCl_3$/Me_2SO-d_6) 7.26 (d, J = 8 Hz, 1 H, H-5), 6.94 (d, J = 8 Hz, 1 H, H-6), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.30 (e, 2 H, H-9), 2.90 (m, 1 H), 2.50 (e, 3 H), 2.00 (e, 2 H); IR 3440, 1739–1710, 1590 cm^{-1}; m/z 318 (51%, M$^+$), 300 (21), 287 (15), 230 (37), 198 (100). Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.1; H, 5.7. Found: C, 64.4, H, 5.7.

2-(Dichloroacetoxy)-7-methoxy-1,2,3,4-tetrahydro-8-(methoxycarbonyl)fluorene-2-carboxylic Acid. A suspension of hydroxy acid (**20**) (5 g, 15.7 mmol) in a mixture of dichloroacetyl chloride (5 g, 15.7 mmol) and 1,2-dichloroethane (200 mL) was heated under reflux for 3 h. The resulting solution was concentrated, water (30 mL) was added, and then acetone (70 mL) was added. After stirring for 2 h the solution was concentrated, the resulting dark green precipitate collected, washed, dried, and recrystallized from acetone–hexane to give a colorless solid (6.23 g, 93%): mp 182–186 °C; ^{1}H NMR δ ($CDCl_3$/Me_2SO-d_6) 7.25 (d, J = 8 Hz, 1 H, H-5), 6.93 (d, J = 8 Hz, 1 H, H-6), 5.96 (s, 1 H, $COCHCl_2$), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.30 (bs, 2 H, H-9), 2.90 (m, 1 H), 2.50 (e, 2 H); IR 1760, 1730–1710 1585 cm^{-1}; m/z 393 (1%, M$^+$ − Cl), 358 (5), 300 (100), 298 (15), 269 (18), 268 (30), 267 (24), 266 (26). Anal. Calcd for $C_{19}H_{18}Cl_2O_7$: C, 53.2; H, 4.2; Cl, 16.5. Found: C, 53.1; H, 4.4; Cl, 16.2.

2-(Chloroacetoxy)-7-methoxy-8-(methoxycarbonyl)-1,2,3,4-tetrahydrofluorene-2-carboxylic Acid. A suspension of hydroxy acid **20** (7.95 g, 25 mmol) and chloroacetic anhydride (12.83 g, 75 mmol) in 1,2-dichloroethane (250 mL) was heated at

(34) Blair, J.; Brown, J. J.; Newbold, G. T. *J. Chem. Soc.* **1955**, 708–712.

reflux for 3 h, resulting in a homogeneous solution. The cold solution was washed with water (2 × 100 mL) and brine (15 mL) and dried. Removal of the solvent gave a crystalline residue, which was washed with cold ether (3 × 20 mL) to leave the chloroacetate (8.86 g, 90%) as colorless crystals: mp 183–185 °C; ^{1}H NMR δ ($CDCl_3$/Me_2SO-d_6) 8.45 (b, 1 H), 7.17 (d, J = 8 Hz, 1 H, H-5), 6.87 (d, J = Hz, 1 H, H-6), 4.05 (s, 2 H, $COCH_2Cl$), 2.91 (s, 3 H, CO_2CH_3), 3.87 (s, 3 H, $ArOCH_3$), 3.41 (bs, 2 H, H-9), 3.03 (m, 2 H, H-1), 2.65–2.14 (m, 4 H, H-3, H-4); IR 1745, 1720, 1700, 1580 cm^{-1}; M/z 396 (1%), 394 (3, M$^+$), 378 (1.5), 376 (4), 358 (31), 300 (100), 272 (22), 268 (29); mass calcd for $C_{19}H_{19}ClO_7$ 394.0819, found 394.0823.

(±)-Methyl 7-(Dichloroacetoxy)-2-methoxy-8-oxogibba-1,3,4a(10a),4b-tetraene-1-carboxylate (22) (R = Cl_2CH). Dry DMF (0.1 mL) was added to a stirred suspension of dichloroacetoxy acid (6 g, 14 mmol) in oxalyl chloride (4 mL) and dry dichloromethane (50 mL) at 0 °C (drying tube). There was a vigorous evolution of gas, and after 45 min the suspension had dissolved. After 16 h at 25 °C, the volatiles were removed in vacuo, the residue was treated with cold dry benzene (20 mL) and filtered, and the precipitate was washed with fresh portions of dry benzene (3 × 20 mL). The filtrate was concentrated, and treatment of the residue with dry benzene repeated. The benzene was then evaporated, and the last traces of hydrogen chloride were removed under high vacuum (20 h) to give the acid chloride as a pale orange-colored glass (6.2 g): IR (CH_2Cl_2) 1790 (COCl), 1760 ($COCHCl_2$), 1740 (CO_2CH_3) cm^{-1}. A solution of the acid chloride (6.2 g) in dry dichloromethane (60 mL) was added to diazomethane (~140 mmol) in ether (250 mL) at −20 °C under nitrogen. The yellow solution was allowed to warm to room temperature overnight and then concentrated in vacuo to give the crude diazo ketone **21** (R = Cl_2CH) as an orange gum (6 g): ^{1}H NMR δ 6.00 (s, 1 H, $COCHCl_2$), 5.6 (s, 0.6 H, CHN_2); IR ($CHCl_3$), 2120 (CHN_2), 1765 ($COCHCl_2$), 1720 (CO_2CH_3), 1645 ($COCHN_2$), 1590 cm^{-1}.

A solution of the crude diazo ketone (6 g) in dry dichloromethane (60 mL) was added dropwise over 10 min to a slurry of trifluoroacetic acid (120 mL) and dry dichloromethane (60 mL) stirred vigorously at −20 °C under nitrogen. After 10 min, ice (100 g) was added, and the layers were separated. The organic phase was washed with water (2 × 100 mL) and brine (1 × 100 mL) and dried. Evaporation of the solvent left a dark red gum which was chromatographed on silica gel (100 g, 10% benzene–chloroform) to give the dichloroacetoxy ketone **22** (R = $CHCl_2$) (2.1 g, 35%) as a pale yellow crystalline solid. A sample for analysis crystallized as colorless cubes from acetone–petroleum ether: mp 162–165 °C; ^{1}H NMR δ 7.30 (d, J = 8 Hz, 1 H, H-4), 6.72 (d, J = 8 Hz, 1 H, H-3), 5.88 (s, 1 H, $COCHCl_2$), 5.60 (t, J = 4 Hz, 1 H, H-5), 3.82 (s, 3 H), 3.78 (s, 3 H); m/z 426 (34%), 424 (51, M$^+$), 395 (13), 393 (17), 314 (70), 396 (65), 264 (100), 211 (73); IR 1765, 1750, 1720, 1600, 1590 cm^{-1}. Anal. Calcd for $C_{20}H_{18}Cl_2O_6$: C, 56.5; H, 4.3; Cl, 16.7. Found: C, 56.4; H, 4.3; Cl, 16.6.

Methyl 2-(Chloroacetoxy)-2-(diazoacetyl)-7-methoxy-1,2,3,4-tetrahydrofluorene-8-carboxylate (21) (R = CH_2Cl). Dry DMF (0.03 mL, 0.4 mmol) was added to a stirred suspension of the above acid (7.88 g, 20 mmol) and oxalyl chloride (5.15 mL, 60 mmol) in dichloromethane (100 mL) at 0 °C. When the gas evolution has ceased, DMF (0.03 mL) was added again and the homogeneous mixture was allowed to reach room temperature. The addition of DMF was repeated in 1 h intervals until TLC analysis (4% methanol–dichloromethane) indicated complete conversion. The volatiles were removed in vacuo and the resulting precipitate, the corresponding acid chloride (8.1 g), was freed from residual hydrogen chloride at an oil pump: IR (CH_2Cl_2) 1790, 1755, 1720, 1580 cm^{-1}.

A solution of the acid chloride (8.1 g) of dichloromethane (100 mL) was added to diazomethane (~120 mmol) in ether (250 mL) at −20 °C and allowed to warm to room temperature. Filtration and removal of the solvent gave diazo ketone **21** (R = CH_2Cl) (8.0 g) as a yellow solid. A small sample was purified by chromatography (PLC, 4% methanol–dichloromethane): mp 147–150 °C; ^{1}H NMR δ 7.24 (d, J = 8 Hz, 1 H, H-5), 6.92 (d, J = 8 Hz, 1 H, H-6), 5.57 (s, 1 H, $COCHN_2$), 4.05 (s, 2 H, $COCH_2Cl$), 3.93 (s, 3 H, CO_2CH_3), 3.87 (s, 3 H, $ArOCH_3$), 3.44 (bs, 2 H, H-9), 3.14 and 2.88 (ABq, J_{AB} = 18 Hz, 2 H, H-1), 2.52 (e, 2 H, H-4), 2.46–2.00 (m, 2 H, H-3); IR 2100, 1745, 1715, 1635, 1580 cm^{-1}; M/z 429 (1.5), 418 (4, M$^+$), 392 (12), 390 (34), 324 (100), 314 (26), 262 (82), 272 (40), 236 (59), 225 (51), 178 (41), 165 (43).

(±)-Methyl 7-(Chloroacetoxy)-2-methoxy-8-oxogibba-1,3,4a(10a),4b-tetraene-1-carboxylate (22) (R = CH_2Cl). A solution of the crude diazo ketone (8.0 g) in dichloromethane (100 mL) was added over 15 min to a stirred mixture of trifluoroacetic acid (200 mL) and dichloromethane (100 mL) at −20 °C. After a further 10 min ice and water (total 300 g) were added, and the layers separated. Reextraction of the aqueous layers (dichloromethane 2 × 100 mL) and washing of the organic phase (water 2 × 100 mL, brine 100 mL) gave after drying and solvent removal a brown oil (7.3 g). Chromatography on silica gel (140 g, chloroform) afforded gibbane **22** (R = CH_2Cl) (5.54 g, 71%) as yellowish crystals: mp 133–135 °C (plates from dichloromethane–petroleum ether); ^{1}H NMR δ 7.34 (d, J = 8 Hz, 1 H, H-4), 6.82 (d, J = 8 Hz, 1 H, H-3), 5.68 (t, J = 3.5 Hz, 1 H, H-5), 4.07 (s, 2 H, $COCH_2Cl$), 3.87 (s, 3 H, CO_2CH_3), 3.83 (s, 3 H, $ArOCH_3$), 3.40–2.08 (m, 8 H); IR 1755, 1730, 1720, 1600, 1590 cm^{-1}; m/z 390 (13%), 388 (35, M$^+$), 361 (5), 359 (16), 296 (74), 264 (100), 211 (35). Anal. Calcd for $C_{20}H_{19}ClO_6$: C, 61.5; H, 4.9; Cl, 9.1. Found: C, 61.3; H, 4.9; Cl, 9.2.

(±)-Methyl 7-Hydroxy-2-methoxy-8-oxogibba-1,3,4a-(10a),4b-tetraene-1-carboxylate (10). Gibbane **22** (5.46 g, 14 mmol) in THF (40 mL), methanol (90 mL), and water (10 mL) was heated at reflux for 1 h in a nitrogen atmosphere. The solution was cooled to 0 °C, potassium carbonate (7.73 g, 56 mmol) and potassium bicarbonate (0.56 g, 5.6 mmol) were added, and stirring continued for 1.5 h at 20 °C. The solvents were removed in vacuo at 20 °C and dichloromethane (100 mL) and water (50 mL) were added. The organic layer was washed with water (50 mL), 1 N acetic acid (50 mL), water (50 mL), and brine (50 mL). After drying, solvent removal, and recrystallization from dichloromethane–ether ketol **10** (3.91 g, 89%) was obtained as colorless crystals: mp 150–152 °C (acetone–hexane); ^{1}H NMR δ 7.38 (d, J = 8 Hz, 1 H, H-4), 6.78 (d, J = 8 Hz, 1 H, H-3), 5.72 (t, J = 4 Hz, 1 H, H-5), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.25 and 3.05 (ABq, J_{AB} = 16 Hz, H-10), 2.78–2.14 (complex, 6 H); IR 3420, 1740–1715, 1600, 1585 cm^{-1}; m/z 314 (100%, M$^+$), 286 (4), 283 (20), 282 (18), 243 (16), 211 (70). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.8; H, 5.8. Found: C, 68.7; H, 5.6.

(±)-Methyl 8,8-(Ethylenedioxy)-7-hydroxy-2-methoxy-gibba-1,3,4a(10a),4b-tetraene-1-carboxylate. The α-hydroxy ketone **10** (3.77 g, 12 mmol), ethylene glycol (6.7 mL, 120 mmol), p-toluenesulfonic acid (1 mg), and 1,2-dichloroethane (150 mL) were combined and heated at reflux with azeotropic removal of water (reverse Dean–Stark apparatus containing 4-Å molecular sieves). After 16 h the cooled mixture was washed with water (2 × 75 mL) and brine (75 mL). Reextraction of the aqueous layers (dichloromethane, 2 × 100 mL), drying of the combined organic extracts, and solvent removal afforded the corresponding hydroxy acetal (4.08 g, 95%) as a white solid: mp 162–165 °C (acetone–light petroleum); ^{1}H NMR δ 7.34 (d, J = 8 Hz, 1 H, H-4), 6.74 (d, J = 8 Hz, 1 H), 5.78 (t, J = 4 Hz, 1 H, H-5), 3.92 (s, 4 H, OCH_2CH_2O), 3.84 (s, 3 H), 3.80 (s, 3 H) 3.10 and 2.80 (ABq, J_{AB} = 18 Hz, H-10), 2.84 (s, 1 H, exchangeable, OH), 2.60 (m, 2 H, H-6), 2.00 (m, 4 H, H-9 and H-11); IR 3500, 1730, 1600, 1595 cm^{-1}; m/z 358 (100%, M$^+$), 340 (7), 327 (23), 301 (7), 296 (42), 272 (30), 264 (37). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.0; H, 6.2. Found: C, 67.2; H, 6.1.

(±)-Methyl 8,8-(Ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a),4b-tetraene-1-carboxylate. A stirred solution of the above hydroxy acetal (3.58 g, 10 mmol) in dry dichloromethane (25 mL) and N-diisopropyl-N-ethylamine (70 mL) under nitrogen was cooled to 0 °C and treated dropwise with methoxymethyl chloride (15 mL, 200 mmol). After stirring for 16 h at 25 °C, ice (250 g) and dichloromethane (500 mL) were added and the layers separated. The organic phase was washed with water (1 × 500 mL) and aqueous 50% acetic acid (1 × 250 mL) and dried. Removal of the solvent and trituration of the residue with 50% ether–light petroleum gave the methoxymethyl ether as a pale yellow crystalline solid (3.94 g, 98%): mp 122–125 °C; ^{1}H NMR δ 7.34 (d, J = 8 Hz, 1 H, H-4), 6.74 (d, J = 8 Hz, 1 H, H-3), 5.74 (t, J = 4 Hz, 1 H, H-5), 4.97 and 4.67 (ABq, J_{AB} = 7 Hz, OCH_2OCH_3), 3.90 (m, 4 H, OCH_2CH_2O), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.56 (s, 3 H, OCH_2OCH_3e, 2.12 and 2.84 (ABq, J_{AB} = 17 Hz, H-10), 2.64 (m, 2 H, H-6), 2.41 and 1.95 (ABq, J_{AB} = 11 Hz, H-11), 2.04 (s, 2 H, H-9); IR 1730, 1590 cm^{-1}; m/z 402 (31%,

M^+), 371 (44), 370 (55), 358 (8), 357 (34), 341 (13), 340 (12), 316 (12), 315 (52), 296 (21), 284 (18), 271 (24), 270 (28), 254 (28), 230 (100), 211 (99). Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.7; H, 6.5. Found: C, 65.8; H, 6.4.

(±)-(10α)-8,8-(Ethylenedioxy)-2-methoxy-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a),4b-tetraene-10-carboxylic Acid (23a). To the above ester (3.22 g, 8 mmol) and HMPA (1.54 mL, 8.8 mmol) in THF (40 mL) at −20 °C was added dropwise lithium *tert*-butylcyclohexylamide in benzene–hexane (0.5 M, 24 mL) over 10 min.[6b] The purple solution was stirred for an additional 10 min at −20 °C and siphoned onto a suspension of carbon dioxide (large excess) in ether at −78 °C. After room temperature had been reached, the solvents were evaporated and the residue was dissolved in water (100 mL). The aqueous layer was extracted with chloroform (3 × 20 mL) which in turn was backwashed with 1 N potassium carbonate (2 × 20 mL). The combined aqueous layers were acidified to pH 1 with 6 N hydrochloric acid in a two-phase system (ethyl acetate, 100 mL) at 0 °C. The saturated aqueous layer (sodium chloride) was reextracted (ethyl acetate, 2 × 50 mL) and the organic layer washed with water (50 mL) and brine (100 mL) and dried. Removal of the solvent gave after crystallization from dichloromethane–ether acid **23a** (3.17 g, 89%) as colorless crystals: mp 173–175 °C; ^{1}H NMR δ 9.10 (b, 1 H, CO_2H), 7.41 (d, J = 8 Hz, 1 H, H-4), 6.87 (d, J = 8 Hz, 1 H, H-3), 5.84 (t, J = 3.5 Hz, 1 H, H-5), 4.95 and 4.68 (ABq, J = 7 Hz, 2 H, OCH_2O), 2.92 (m, 5 H, OCH_2CH_2O, H-10), 3.79 (s, 3 H, $ArOCH_3$), 3.76 (s, 3 H, CO_2CH_3), 3.31 (s, 3 H, CH_2OCH_3), 2.65 (m, 2 H, H-6), 2.59 and 2.00 (ABq, J = 11 Hz, 2 H, H-11), 2.14 (e, 2 H, H-9); IR 1730, 1695, 1585 cm^{-1}; m/z 446 (23%, M^+), 414 (42), 401 (20), 239 (61), 211 (40), 87 (100), 45 (95). Anal. Calcd for $C_{23}H_{26}O_9$: C, 61.9; H, 5.9. Found: C, 61.5; H, 6.2.

(±)-(10α)-Dimethyl 8,8-(Ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a),4b-tetraene-1,10-dicarboxylate (23b). Acid **23a** (223 mg, 0.5 mmol) in dichloromethane (10 mL) at 0 °C was treated with diazomethane (~0.75 mmol) in ether (3 mL). The solution was allowed to warm to room temperature and the volatiles were removed to give diester **23b** (223 mg, 97%) as a colorless oil: ^{1}H NMR δ 7.43 (d, J = 8 Hz, 1 H, H-4), 6.90 (d, J = 8 Hz, 1 H, H-3), 5.85 (t, J = 4 Hz, 1 H, H-5), 4.96 and 4.68 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 3.95 (m, 5 H, OCH_2CH_2O, H-10), 3.83 (s, 3 H, $ArOCH_3$), 3.81 (s, 3 H, $ArCO_2CH_3$) 3.64 (s, 3 H, CO_2CH_3), 3.35 (s, 3 H, CH_2OCH_3), 2.67 (m, 2 H, H-6), 2.42 and 1.90 (ABq, J = 11 Hz, 2 H, H-11), 2.14 (e, 2 H, H-9); IR (film) 1730–1710, 1600, 1590 cm^{-1}; m/z 460 (25%, M^+), 428 (51), 415 (18), 401 (13), 341 (30), 313 (33), 297 (39), 296 (22), 269 (59), 87 (100), 45 (57); mass calcd for $C_{24}H_{28}O_9$ 460.1733, found 460.1733.

(±)-(4bβ,10α)-8,8-(Ethylenedioxy)-2-methoxy-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a)-triene-10-carboxylic Acid (24a). The acid **23a** (2.68 g, 6 mmol) in methanol (13 mL) and ethyl acetate (13 mL) was hydrogenated at atmospheric pressure over palladium on charcoal (10%, 25 mg). After 16 h at room temperature the mixture was filtered through Celite and the solvents removed. Acid **24a** (2.44 g, 91%) was obtained as a white powder: mp 215 °C (extensive sweating); ^{1}H NMR δ 8.68 (bs, 1 H, CO_2H), 7.15 (d, J = 8 Hz, 1 H, H-4), 6.85 (d, J = 8 Hz, 1 H, H-3), 4.79 and 4.61 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.16 (s, 1 H, H-10), 4.00 (s, 4 H, OCH_2CH_2O), 3.82 (s, 3 H, $ArOCH_3$), 3.80 (s, 3 H, $ArCO_2CH_3$), 3.27 (s, 3 H, CH_2OCH_3), 2.96 (m, 1 H, H-4b), 2.68 (d, J = 14 Hz, 1 H, H-11), 2.53–1.65 (m, 7 H); IR 1715–1690, 1580 cm^{-1}; m/z 448 (3%, M^+), 447 (4), 417 (8), 416 (6), 404 (12), 403 (58), 87 (43), 73 (33), 45 (100). Anal. Calcd for $C_{23}H_{28}O_9$: C, 61.6; H, 6.3. Found: C, 61.5; H, 6.2.

(±)-(4bβ,10α)-Dimethyl 8,8-(Ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a)-triene-1,10-dicarboxylate (24b). (i) Ester **23b** (200 mg, 0.43 mmol) was hydrogenated under the same conditions as acid **23a** to afford ester **24b** (199 mg, 99%) as a colorless oil: ^{1}H NMR δ 7.08 (d, J = 8 Hz, 1 H, H-4), 6.80 (d, J = Hz, 1 H, H-3), 4.70 and 4.56 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.10 (s, 1 H, H-6), 3.96 (s, 4 H, OCH_2CH_2O), 3.81 (s, 3 H, $ArOCH_3$), 3.72 (s, 3 H, $ArCO_2CH_3$), 3.67 (s, 3 H, CO_2CH_3), 3.25 (s, 3 H, CH_2OCH_3), 2.94 (m, 1 H, H-4b), 2.58 (d, J = 14 Hz, 1 H, H-11), 2.36–1.30 (m, 7 H); IR (film) 1730–1710, 1590 cm^{-1}; m/z 462 (13%, M^+), 417 (100), 357 (49), 87 (33), 45 (58); mass calcd for $C_{24}H_{30}O_9$ 462.1889, found 462.1884.

(ii) To acid **24a** (20 mg) in dichloromethane (3 mL) was added diazomethane (excess) in ether. Evaporation of the solvent gave diester **24b** in quantitative yield (TLC and ^{1}H NMR analysis).

(±)-(4bβ,10β)-Dimethyl 8,8-(Ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a)-triene-1,10-dicarboxylate (25b). Diester **24b** (116 mg, 0.25 mmol) in methanol (2 mL) was added to a solution of sodium methoxide (from 100 mg sodium) in methanol (3 mL) and the resulting mixture was heated at reflux for 16 h. The solvent was removed, saturated aqueous sodium dihydrogen phosphate (10 mL) and dichloromethane (30 mL) were added, and the layers were separated. The organic portion was washed with brine (20 mL), dried, and treated with an excess of ethereal diazomethane. Removal of the solvent gave an oil (103 mg) which was a ~2:1 mixture of diesters **25b** and **24b** (^{1}H NMR analysis). Chromatography (PLC 2% methanol–dichloromethane) afforded starting material **24b** (26 mg, 22%) and the epimer **25b** (47 mg, 41%) as a colorless oil: ^{1}H NMR δ 7.16 (d, J = 9 Hz, 1 H, H-4), 6.82 (d, J = 9 Hz, 1 H, H-3), 4.82 and 4.56 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 3.98 (bs, 4 H, OCH_2CH_2O), 3.85 (s, 6 H, $ArCO_2CH_3$, $ArOCH_3$), 3.78 (s, 1 H, H-6), 3.64 (s, 3 H, CO_2CH_3), 3.37 (m, 1 H, H-4b), 3.29 (s, 3 H, CH_2OCH_3), 2.56–1.36 (m, 8 H); IR (CH_2Cl_2) 1730–1710, 1580 cm^{-1}; m/z 462 (13%, M^+), 417 (100), 357 (15); mass calcd for $C_{24}H_{30}O_9$ 462.1889, found 462.1884.

(±)-(1α,4bβ,10α)-8,8-(Ethylenedioxy)-2-methoxy-1-(methoxycarbonyl)-1,7-[(methoxymethyl)oxy]-1-methylgibba-2,4a(10a)-diene-10-carboxylic Acid (11a). To the acid **24a** (896 mg, 2 mmol) in THF (40 mL) at 20 °C was added potassium *tert*-butoxide (224 mg, 2 mmol). After 30 min ammonia (distilled off sodium amide, 400 mL) was condensed into the reaction flask. To the resulting solution at −78 °C was added potassium (~195 mg, 5 mmol) in small pieces until a persistent blue color was obtained (20 min). Methyl iodide (1.25 mL, 20 mmol) was introduced over 30 min and the mixture was allowed to reach −33 °C. After addition of ammonium chloride (~1 g) the ammonia was evaporated with a stream of nitrogen. Water (50 mL) was added, and the solution was extracted with ether (2 × 50 mL) and saturated with sodium dihydrogen phosphate (pH 5). Extraction with dichloromethane (3 × 50 mL), drying of the organic portion, and solvent removal afforded the acid **11a** (780 mg, 84%) as white crystals: mp 170–172 °C (dichloromethane–ether); ^{1}H NMR δ 8.69 (b, 1 H, CO_2H), 4.80 and 4.50 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.76 (t, J = 4 Hz, 1 H, H-3), 3.97 (bs, 4 H, OCH_2CH_2O), 3.66 (s, 1 H, H-10), 3.64 (s, 3 H, CO_2CH_3), 3.52 (s, 3 H, $C{=}COCH_3$), 3.33 (s, 3 H, CH_2OCH_3), 2.91 and 2.62 (ABq, J_{AB} = 16 Hz, 2 H, H-4), 2.56–1.28 (m, 9 H), 1.39 (s, 3 H, CH_3); IR 1725, 1710, 1685, 1650 cm^{-1}; m/z 464 (18%, M^+), 463 (4), 433 (7), 432 (8), 419 (40), 405 (19), 402 (17), 373 (45), 360 (28), 343 (69), 315 (43), 87 (60), 73 (41), 45 (100). Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.1; H, 6.9. Found: C, 62.0; H, 6.9.

(±)-(4bβ,10α)-Benzyl 8,8-(Ethylenedioxy)-2-methoxy-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]gibba-1,3,4a-(10a)-triene-10-carboxylate (24c). Benzyl bromide (0.18 mL, 1.5 mmol) was added to a mixture of acid **24a** (224 mg, 0.5 mmol) and potassium carbonate (207 mg, 1.5 mmol) in DMF (0.5 mL). Stirring at room temperature was continued for 16 h, triethylamine (0.21 mL, 1.5 mmol) was added (to destroy the excess benzyl bromide), and the mixture was stirred for another 2 h. Water (20 mL) and ether (30 mL) were added and the layers separated. The aqueous phase was reextracted (ether, 2 × 20 mL) and the organic portions were washed with cold 0.5 N hydrochloric acid (2 × 20 mL), water (2 × 10 mL), and brine (20 mL). The solvent was evaporated and the crude product crystallized (from dichloromethane–petroleum ether) to leave benzyl ester **24c** (227 mg, 86%) as colorless crystals: mp 127–129 °C; δ 7.35 (m, 5 H, ArH), 7.14 (d, J = 8 Hz, 1 H, H-4), 6.86 (d, J = 8 Hz, 1 H, H-3), 5.19 and 5.12 (ABq, J_{AB} = 12 Hz, 2 H, CO_2CH_2Ph), 4.63 and 4.55 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.18 (s, 1 H, H-10) 3.96 (m, 4 H, OCH_2CH_2O), 3.83 (s, 3 H, $ArOCH_3$), 3.68 (s, 3 H, CO_2CH_3), 3.23 (s, 3 H, CH_2OCH_3), 2.89 (m, 1 H, 4-Hb), 2.63 (d, J = 14 Hz, 1 H, H-11), 2.46–1.28 (m, 7 H); IR 1725, 1700, 1595, 1589 cm^{-1}; m/z (base peak 91, >91 relative 493) 538 (12%, M^+), 494 (30), 493 (100), 357 (32). Anal. Calcd for $C_{30}H_{34}O_9$: C, 66.9; H, 6.4. Found: C, 67.0; H, 6.3.

(±)-(4bβ,10β)-8,8-(Ethylenedioxy)-2-methoxy-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a)-triene-

10-carboxylic Acid (25a). Ester **24c** (200 mg, 0.37 mmol) was dissolved in 1,5-diazabicyclo[4.3.0]non-5-ene (1 mL). After standing at room temperature for 16 h a 2:1 equilibrium mixture of β-ester **25c** and ester **24c** was reached (same ratio after additional 24 h). Water (10 mL) and dichloromethane (10 mL) were added, the layers were separated, and the aqueous portion was reextracted 'dichloromethane 2 × 10 mL). The organic layers were washed with cold 0.5 N hydrochloric acid (10 mL), water (10 mL), and brine (10 mL) and dried. Evaporation of the solvent left a yellowish oil (14 mg, 87%) which was homogeneous by TLC (2% methanol–dichloromethane, 50% ethyl acetate–ether). The ^{1}H NMR spectrum of the mixture had the following peaks in addition to those from **24c**: δ 7.30 (s, ArH), 7.19 (d, J = 8 Hz, H-1), 5.08 (s, CO_2CH_2Ph), 4.84 and 4.53 (ABq, J_{AB} = 7 Hz, OCH_2O), 3.66 (s, CO_2CH_3), 3.35 (m, H-4b), 3.26 (s, CH_2OCH_3). The mixture of esters **24c** and **25c** (174 mg, 0.32 mmol) in methyl acetate (4 mL) and methanol (4 mL) was hydrogenated over palladium on charcoal (10%, 5 mg) at atmospheric pressure. After 16 h at room temperature the mixture was filtered (Celite) and the solvents were removed. Chromatography (PLC, 7% methanol–dichloromethane) of the resulting mixture (160 mg) gave acid **24a** (30 mg, 21%) and β-acid **25a** (67 mg, 47%) as colorless crystals: mp 138–141 °C; ^{1}H NMR δ 8.85 (b, 1 H, CO_2H), 7.14 (d, J = 8 Hz, 1 H, H-4), 6.87 (d, J = 8 Hz, 1 H, H-3), 4.85 and 4.57 (AB_q, J_{AB} = 7 Hz, 2 H, OCH_2O), 3.98 (bs, 4 H, OCH_2CH_2O), 3.85 (s, 6 H, $ArCO_2CH_3$, $ArOCH_3$), 3.73 (s, 1 H, H-10), 3.35 (m, 1 H, H-4b), 3.29 (s, 3 H, CH_2OCH_3), 2.46 (d, J = 14 Hz, 1 H, H-11), 2.40–1.45 (m, 7 H); IR 1725, 1590 cm^{-1}; m/z 448 (15%, M$^+$), 447 (16), 417 (8(, 403 (67), 372 (28), 371 (100), 343 (37), 241 (60); mass calcd for $C_{23}H_{28}O_9$ 448.1733, found 448.1726.

(±)-(1β,4bβ,10β)-8,8-(Ethylenedioxy)-2-methoxy-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methylgibba-2,4a-(10a)-diene-10-carboxylic Acid (26a). Acid **25a** (45 mg, 0.1 mmol) was reduced and methylated as described for acid **24a** to give acid **26a** (35 mg, 75%) after crystallization from dichloromethane–petroleum ether: mp 142–144 °C; ^{1}H NMR δ 9.30 (b, 1 H, CO_2H), 4.78 and 4.61 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.76 (t, J = 4 Hz, 1 H, H-3), 3.97 (bs, 4 H, OCH_2CH_2O), 3.54 (s, 6 H, CO_2CH_3, C=$COCH_3$), 3.34 (s, 3 H, CH_2OCH_3), 3.28 (s, 1 H, H-10), 2.79 (e, 2 H, H-4), 2.58.1.10 (m, 9 H), 1.46 (s, 3 H, CH_3); IR 1730, 1700, 1690, 1650 cm^{-1}; m/z 464 (65%, M$^+$), 434 (11), 419 (35), 405 (42), 373 (34), 359 (81), 343 (100), 331 (88), 301 (96), 227 (81); mass calcd for $C_{24}H_{32}O_9$ 464.2046, found 464.2035.

(±)-(1α,4bβ,10α)-Dimethyl 8,8-(Ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]-1-methylgibba-2,4a(10a)-diene-1,10-dicarboxylate (11b). To acid **11a** (100 mg, 0.24 mmol) in dichloromethane (5 mL) at 0 °C was added diazomethane (~9,5 mmol) in ether (3 mL). After standing 1 h at room temperature the solvents were removed to leave the ester **11b** (100 mg, 97%) as a colorless oil: ^{1}H NMR δ 4.80 and 4.67 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.76 (t, J = 4 Hz, 1 H, H-3), 3.98 (bs, 4 H, OCH_2CH_2O), 3.66 (s, 4 H, H-10, CO_2CH_3), 3.64 (s, 3 H, CO_2CH_3), 3.51 (s, 3 H, C=$COCH_3$), 3.34 (s, 3 H, CH_2OCH_3), 2.92 and 2.62 (ABq, J_{AB} = 16 Hz, 2 H, H-4), 2.53–1.23 (m, 9 H), 1.36 (s, 3 H, CH_3); IR (CH_2Cl_2) 1740, 1695, 1660 cm^{-1}; m/z 478 (24%, M$^+$), 447 (19), 434 (28), 433 (100), 419 (46), 387 (64), 373 (60), 357 (82); mass calcd for $C_{25}H_{34}O_9$ 478.2202, found 478.2202.

(±)-(1β,4bβ,10β)-Dimethyl 8,8-(Ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]-1-methylgibba-2,4a(10a)-diene-1,10-dicarboxylate (26b). Acid **26a** (30 mg, 0.065 mmol) was treated with diazomethane as described above to give ester **26b** (31 mg, 100%) as an oil: ^{1}H NMR δ 4.83 and 4.65 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.81 (t, J = 4 Hz, 1 H, H-3), 3.99 (bs, 4 H, OCH_2CH_2O), 3.63 (s, 3 H, CO_2CH_3), 3.59 (s, 3 H, CO_2CH_3), 3.55 (s, 3 H, C=$COCH_3$), 3.35 (s, 4 H, H-10, CH_2OCH_3), 2.78 (e, 2 H, H-4), 2.65–1.40 (m, 9 H), 1.46 (s, 3 H, CH_3); IR (CH_2Cl_2) 1740–1720, 1690, 1655 cm^{-1}; m/z 478 (21%, M$^+$), 447((13), 433 (89), 419 (84), 374 (35), 373 (100), 357 (33); mass calcd for $C_{25}H_{34}O_9$ 478.2202, found 478.2202.

(±)-(1β,4bβ,10β)-Dimethyl 8,8-(Ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]-1-methylgibba-2,4a(10a)-diene-1,10-dicarboxylate (26b). Acid **26a** (30 mg, 0.065 mmol) was treated with diazomethane as described above to give ester **26b** (31 mg, 100%) as an oil: ^{1}H NMR δ 4.83 and 4.65 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.81 (t, J = 4 Hz, 1 H, H-3), 3.99 (bs, 4 H, OCH_2CH_2O), 3.63 (s, 3 H, CO_2CH_3), 3.59 (s, 3 H, CO_2 CH_3), 3.55 (s, 3 H, C=$COCH_3$), 3.35 (s, 4 H, H-10, CH_2OCH_3), 2.78 (e, 2 H, H-4), 2.65–1.40 (m, 9 H), 1.46 (s, 3 H, CH_3); IR (CH_2Cl_2) 1740–1720, 1699, 1655 cm^{-1}; m/z 478 (21%, M$^+$), 447 (13), 433 (89), 419 (84), 374 (35), 373 (100), 357 (33); mass calcd for $C_{25}H_{34}O_9$ 478.2202, found 478.2204.

Attempted C(10) Epimerization of Esters 11b and 26b. Both esters **11b** and **26b** (24 mg, 0.05 mmol) were recovered unchanged after heating under reflux (40 h) in methanol containing sodium methoxide [from sodium (11.5 mg, 0.5 mmol)]. When methanol-^2H was used as the solvent, ester **11b** gave the corresponding **11b**-*10*-^2H (92%): ^{1}H NMR as **11b**, but 3.66 (s, 3 H); m/z 479 (20%, M$^+$), 448 (15), 435 (30), 434 (100), 420 (42), 288 (55), 374 (52), 358 (32); mass calcd for $C_{25}H_{30}DO_9$ 479.2265, found 479.2252. Ester **26b** afforded under the same conditions a mixture of **26b** and **26b**-*10*-^2H: m/z 479 (15%, M$^+$ **26b**-*10*-^2H, 478 (16, M$^+$ **26b**), 434 (91), 433 (69), 420 (40), 419 (67), 375 (43), 374 (100), 373 (22), 358 (40), 357 (31).

(±)-(1α,4bβ,10α)-8,8-(Ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methyl-2-oxogibb-4a-(10a)-ene-10-carboxylic Acid. To acid **11a** (650 mg, 1.4 mmol) in acetonitrile (20 mL) and water (4 mL) was added mercury(II) nitrate (137 mg, 0.42 mmol) and the reaction mixture stirred for 18 h at 22 °C. Water (20 mL) and dichloromethane (30 mL) were added, the layers were separated, and the aqueous portion was reextracted with dichloromethane (2 × 20 mL). After the organic portion was dried, the solvent was evaporated and the residue crystallized from dichloromethane–petroleum ether to give the corresponding ketone (485 mg, 77%) as colorless crystals: mp 139–140.5 °C; ^{1}H NMR δ 7.32 (b, 1 H, CO_2H), 4.81 and 4.65 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 3.98 (s, 4 H, OCH_2CH_2O), 3.66 (s, 3 H, CO_2CH_3), 3.50 (s, 1 H, H-10), 3.34 (s, 3 H, CH_2OCH_3), 3.06–1.28 (m, 13 H), 1.33 (s, 3 H, CH_3); IR 1720, 1705 cm^{-1}; m/z 450 (12%, M$^+$), 449 (12), 419 (20), 418 (34), 405 (100), 389 (35), 388 (82), 359 (40), 344 (55). Anal. Calcd for $C_{23}H_{30}O_9$: C, 61.3; H, 7.0. Found: C, 61.2; H, 6.9.

(±)-(1α,2α,4bβ,10α)-8,8-(Ethylenedioxy)-2-hydroxy-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methylgibb-4a(10a)-ene-10-carboxylic Acid. Sodium borohydride (38 mg, 1 mmol) was added portionwise over 20 min to a stirred solution of the above keto ester (450 mg, 1 mmol) in ethanol (10 mL) at 0 °C. After a further 40 min at 0 °C saturated aqueous sodium dihydrogen phosphate (5 mL) and ethyl acetate (50 mL) were added. The organic layer was dried and the solvent removed to give after crystallization from dichloromethane–petroleum ether the 2α-alcohol (407 mg, 90%) as white crystals: mp 129–132 °C; ^{1}H NMR δ 5.34 (b, 2 H), 4.81 and 4.63 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 3.96 (bs, 4 H, OCH_2CH_2O), 3.66 (s, 3 H, CO_2CH_3), 3.48 (m, 2 H, H-2, H-10), 3.35 (s, 3 H, CH_2OCH_3), 2.60–1.26 (m, 13 H), 1.30 (s, 3 H, CH_3); IR 3400, 3200, 1730–1705 cm^{-1}; m/z 452 (7%, M$^+$), 434 (9), 421 (14), 420 (28), 407 (58), 390 (100); mass calcd for $C_{23}H_{32}O_9$ 452.2046, found 452.2035.

(±)-(1α,2α,4bβ,10α)-Ethyl 2-(Benzoyloxy)-8,8-(ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methylgibb-4a(10a)-ene-10-carboxylate (32). To the above acid (100 mg, 0.22 mmol) in dichloromethane (3 mL) was added diazoethane[35] (~0.4 mmol) in ether (2 mL). After 30 min the excessive diazoethane was blown off with a stream of nitrogen and the volatiles were removed. To a solution of the resulting ethyl ester in pyridine (0.5 mL) at 0 °C was added benzoyl chloride (0.13 mL, 1.1 mmol). After 2 h at 0 °C, stirring was continued at 25 °C for 16 h. The reaction mixture was cooled to 0 °C, THF (1 mL) and water (0.4 mL) were added, and stirring was continued for 2 h at 25 °C. Water (20 mL) was added and the solution was extracted with dichloromethane (3 × 20 mL). The organic extracts were washed with water (20 mL), 2 N acetic acid (20 mL), 1 N sodium bicarbonate (2 × 10 mL), and brine (20 mL) and dried. Evaporation of the solvent and purification by chromatography (PLC, 4% methanol–dichloromethane) gave benzoylated diester **32** (101 mg, 79%) as slightly yellowish crystals: mp 133–135 °C (ether–petroleum ether); ^{1}H NMR δ 7.96 (m, 2 H, ArH), 7.44 (m, 3 H, ArH), 4.94 (m, 1 H, H-2), 4.80 and 4.68 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.18 (bq, J = 7 Hz, $CO_2CH_2CH_3$), 4.00 (m, 4 H,

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OCH_2CH_2O), 3.84 (s, 3 H, CO_2CH_3), 3.33 (s, 4 H, H-10, CH_2OCH_3), 2.71–1.20 (m, 13 H), 1.29 (t, J = 7 Hz, $CO_2CH_2CH_3$), 1.23 (s, 3 H, CH_3); IR 1735, 1720, 1600 cm^{-1}; m/z (base peak 105, >105 relative 539), 584 (15%, M^+), 552 (10), 539 (100), 523 (125), 496 (20), 357 (40), 344 (75). Anal. Calcd for $C_{32}H_{40}O_{10}$: C, 65.7; H, 6.9. Found: C, 65.6; H, 6.9.

(±)-(1α,2α,4bβ,10α)-2-(Benzoyloxy)-10-(ethoxycarbonyl)-8,8-(ethylenedioxy)-7-[(methoxymethyl)oxy]-1-methylgibb-4a(10a)-ene-1-carboxylic Acid. Finely powdered diester **32** (93 mg, 0.16 mmol) was added to a solution of lithium propanethiolate in HMPA (0.5 M, 2 mL) and the solution stirred for 2 h. Ether (20 mL) and water (10 mL) were added and the stirred two-phase system acidified to pH 2 with 2 N HCl at 0 °C. The layers were separated and the aqueous portion was reextracted with ether (2 × 20 mL). The organic layers were sequentially washed with water (3 × 10 mL) and brine (10 mL) and dried. Removal of the solvent and crystallization from dichloromethane–ether gave the corresponding acid (70.2 mg, 77%) as a white powder: mp 178–182 °C (dichloromethane–ether); ^1H NMR δ 8.60 (b, 1 H), 7.96 (m, 2 H, ArH), 7.40 (m, 3 H, ArH), 4.96 (m, 1 H, H-2), 4.80 and 4.68 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.16 (m, 2 H, $CO_2CH_2CH_3$), 4.00 (m, 4 H, OCH_2CH_2O), 3.33 (s, 4 H, C10, CH_2OCH_3), 2.78–1.20 (m, 13 H), 1.29 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.26 (s, 3 H, CH_3): IR 1725–1690, 1595, 1575 cm^{-1}; m/z (base peak 105, > 105 relative 525) 570 (5%, M^+), 539 (7), 525 (100), 508 (71). Anal. Calcd for $C_{31}H_{38}O_{10}$: C, 65.3; H, 6.7. Found: C, 65.4; H, 6.8.

(±)-(1α,2α,4aα,4bβ,10α)-2-(Benzoyloxy)-10a-bromo-10-(ethoxycarbonyl)-8,8-(ethylenedioxy)-7-[(methoxymethyl)-oxy]-1-methylgibbane-1,4a-carbolactone (33). To a suspension of the above acid (57 mg, 0.1 mmol) in THF (1 mL) and 1 N aqueous potassium bicarbonate (1.2 mL) at 0 °C was added 0.8 N aqueous potassium tribromide (1 mL) over 3 min. The mixture was stirred at 0 °C for 1 h resulting in a red solution, which contained no starting material (TLC, 2% methanol–dichloromethane). Ether (20 mL) and 1 N aqueous sodium metabisulfite solution were added, the layers were separated, and the aqueous phase was reextracted with ether (2 × 10 mL). The organic portion was washed with water (10 mL) and brine (10 mL) and dried. Removal of solvent gave the unstable bromo lactone **33** (65 mg) as a yellowish oil: ^1H NMR δ 8.12 (m, 2 H, ArH), 7.51 (m, 3 H, ArH), 5.61 (m, 1 H, H-2), 4.79 and 4.71 (ABq, J_{AB} = 7 Hz, 2 H, OCH_2O), 4.20 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 4.00 (m, 4 H, OCH_2CH_2O), 3.88 (s, 1 H, H-10), 3.33 (s, 3 H, CH_2OCH_3), 2.61–1.23 (m, 12 H), 1.31 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.25 (s, 3 H, CH_3); IR (CH_2Cl_2) 1792, 1740, 1720, 1600, 1580 cm^{-1}; m/z (base peak 105, >105 relative 525) 605/603 (2%, M^+ – 45), 569 (3), 525 (100), 403 (19), 357 (30).

(±)-(1α,2α,4aα,4bβ,10α)-2-(Benzoyloxy)-10-(ethoxycarbonyl)-8,8-(ethylenedioxy)-7-hydroxy-1-methylgibbane-1,4a-carbolactone (34). The solution of the crude bromo lactone **33** (65 mg, 0.1 mmol) in Me_2SO (2 mL) was purged of oxygen with a stream of nitrogen (1 h). 1-Propanethiol (0.072 mL, 0.8 mmol) was added to the stirred solution, followed by chromium(II) acetate (~250 mg, 1.47 mmol) in 6 portions over 2 h at 25 °C (the red color obtained upon addition of chromium(II) acetate regularly disappeared slowly). The reaction mixture was poured onto ice (15 g) and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with water (3 × 10 mL) and brine (15 mL) and dried. The solvent was evaporated and the residue chromatographically purified (PLC, 2% methanol–dichlormethane) to give lactone **34** (26 mg, 50% from acid) as colorless crystals: mp 208–210 °C (dichloromethane–ether), 218–220 °C (needles reformed above 210 °C); ^1H NMR δ 8.09 (m, 2 H, ArH), 7.44 (m, 3 H, ArH), 5.04 (m, 1 H, H-2), 4.11 (m, 2 H, $CO_2CH_2CH_3$), 3.96 (s, 4 H, OCH_2CH_2O), 3.05 (d, J = 11 Hz, 1 H, H-10), 2.44 (d, J = 11 Hz, 1 H, H-10a), 2.60–1.28 (m, 14 H), 1.29 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.17 (s, 3 H, CH_3); IR 3440, 1775, 1737, 1715, 1600, 1585 cm^{-1}, m/z (base peak 105, >105 relative 480) 526 (44%, M^+), 508 (21), 480 (100), 360 (68), 272 (82); mass calcd for $C_{29}H_{34}O_9$ 526.2203, found 526.2213.

(±)-(1α,2α,4aα,4bβ,10β)-2-(Benzoyloxy)-10-(ethoxycarbonyl)-8,8-(ethylenedioxy)-7-hydroxy-1-methylgibbane-1,4a-carbolactone. Lactone **34** (15 mg, 0.028 mmol) in DMF (0.3 mL) containing 1,5-diazabicyclo[5.4.0]undec-5-ene (0.021 mL, 0.14 mmol) was heated to 90 °C for 17 h. To the cooled solution was added dichloromethane (10 mL) which was washed with cold 0.5 N hydrochloric acid (2 × 5 mL), water (5 mL), and brine (10 mL). The aqueous layer was reextracted with dichloromethane (2 × 10 mL), and the organic portions were washed, combined, and dried. Removal of solvent and crystallization from dichloromethane–ether–petroleum ether gave the epimeric 10β-ether (13 mg, 86%) as colorless crystals: mp 217–219 °C (dichloromethane–ether); ^1H NMR δ 8.02 (m, 2 H, ArH), 7.47 (m, 3 H, ArH), 5.18 (m, 1 H, H-2), 4.19 (q, J = 4 Hz, 2 H, $CO_2CH_2CH_3$), 3.95 (bs, 4 H, OCH_2CH_2O), 2.68 (s, 2 H, H-10, H-10a), 2.46 (bs, 1 H, OH), 2.50–1.32 (m, 13 H), 1.28 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.12 (s, 3 H, CH_3); IR 3520, 1772, 1735, 1715, 1600, 1585 cm^{-1}; m/z (100%, M^+), 481 (18), 453 (24), 438 (36), 405 (66), 492 (15), 316 (16), 272 (24), 270 (22), 105 (95). Anal. Calcd for $C_{29}H_{34}O_9$: C, 66.1; H, 6.5. Found: C, 65.9; H, 6.8.

(±)-(1α,2α,4aα,4bβ,10β)-8,8-(Ethylenedioxy)-2,7-dihydroxy-10-(methoxycarbonyl)-1-methylgibbane-1,4a-carbolactone (12). The above lactone (10 mg, 0.019 mmol) was dissolved in methanol (1 mL), 5% aqueous sodium hydroxide (0.25 mL) was added, and the resulting solution was kept at 25 °C for 40 h. Ethyl acetate (5 mL) and water (8 mL) were added and the layers separated. The aqueous portion was acidified in a two-phase system (ethyl acetate, 10 mL) to pH 1 with 6 N hydrochloric acid at 0 °C. Reextraction with ethyl acetate (2 × 10 mL), washing of the organic layers (water 2 × 10 mL, brine 10 mL), drying, and solvent removal afforded the acidic extract (4.0 mg) which was treated with ethereal diazomethane. Evaporation of the solvent gave after crystallization from dichloromethane–ether gibbane **12** (3 mg, 40%) as colorless crystals: mp 272–274 °C (lit.[5a] 275–277 °C); ^1H NMR δ ($CDCl_3/CD_3OD$) 3.94 (bs, 4 H, OCH_2CH_2O), 3.73 (s, 3 H, CO_2CH_3), 2.66 (d, J = 10 Hz, 1 H, H-10), 2.48 (d, J = 10 Hz, 1 H, H-10a), 2.20–1.40 (m, 16 H), 1.13 (s, 3 H, CH_3); IR 3525, 3475, 1752, 1728 cm^{-1}; m/z 408 (100%, M^+), 291 (13), 390 (18), 377 (21), 349 (32), 320 (60), 87 (70); mass calcd for $C_{21}H_{28}O_8$ 408.1784, found 408.1785.

(±)-(1α,4bβ,10α)-Ethyl 8,8-(Ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methylgibb-4a(10a)-ene-10-carboxylate (36). Benzenesulfonyl chloride (0.23 μL, 1.38 mmol) was added to a stirred solution of the 2α-alcohol precursor to benzoate **32** (160 mg, 0.33 mmol) in pyridine (0.85 mL) at 0 °C and then stirring continued for 18 h at 5 °C and a further 6 h at 25 °C. Water (1 mL) was added slowly followed by dichloromethane (50 mL). After washing with 0.5 N HCl (2×), 1 N $NaHCO_3$, and brine the dried solution was concentrated and the residue chromatographed (PLC, dichloromethane–ether, 3:1). The 2α-benzenesulfonate was obtained as a colorless oil (170 mg): ^1H NMR δ 7.80 (m, 2 H, ArH), 7.44 (m, 3 H ArH), 4.70, 4.58 (ABq, J = 7 Hz, 2 H, OCH_2O), 4.44 (dd, J = 4,12 Hz, 1 H, H-2), 4.08 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.92 (e, 4 H, OCH_2CH_2O), 3.60 (s, 3 H, CO_2CH_3), 3.26 (s, 3 H, OCH_3), 1.22 (t, J = 7 Hz 3 H, CH_2CH_3), 1.03 (s, 3 H, CH_3); IR 1730–1700 cm^{-1}; m/z 620 (13%, M^+), 575 (100), 532 (16), 501 (19), 417 (25), 357 (19); mass calcd for $C_{31}H_{40}O_{11}S$ 620.2291, found 620.2284.

A mixture of 2α-benzenesulfonate (30 mg, 0.062 mmol), DBN (0.040 mg), tetra-*n*-butylammonium bromide (100 mg), and dimethyl formamide (0.63 mL) was heated and stirred under nitrogen for 21 h at 85 °C. The cooled mixture was worked up as above and then the crude product was purified by filtering a solution in dichloromethane–ether (10:1) through a short column of silica gel. The product diene was obtained as a colorless oil (25 mg): ^1H NMR 5.84 (dt, J = 10, 3.5 Hz, 1 H, H-3), 5.60 (d, J = 10 Hz, 1 H, H-2), 4.82, 4.60 (ABq, J = 7 Hz, 2 H, OCH_2O), 4.10 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.58 (m, 4 H, OCH_2CH_2O), 3.64 (s, 3 H, CO_2CH_3), 3.27 (s, 3 H, OCH_3), 3.18 (s, 1 H, H-10), 2.88 (m, 1 H, H-4b), 2.70 (m, 2 H, H-4), 1.27 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.2 (s, 3 H, CH_3); IR 1730–1710, 1625 cm^{-1}; m/z 462 (14%, M^+), 430 (29), 417 (90), 358 (38), 344 (100), 312 (47); mass calcd for $C_{25}H_{34}O_8$ 462.2253, found 462.2257.

Demethylation as described for **32** afforded acid **36** (14 mg) as colorless crystals from ether–petroleum ether: mp 136–138 °C; ^1H NMR 6.66 (e, 1 H, CO_2H), 5.84 (dt, J = 10, 3 Hz, 1 H, H-3), 5.63 (d, J = 10 Hz, 1 H, H-2), 4.81, 4.64 (ABq, J = 7 Hz, 2 H, OCH_2O), 4.10 (q, J = 4 Hz, 2 H, $CO_2CH_2CH_3$), 3.98 (m, 4 H, OCH_2CH_2O), 3.32 (s, 3 H, OMe), 1.23 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.21 (s, 3 H, CH_3); IR 1730–1700 cm^{-1}; m/z 448 (22%, M^+), 447 (32), 403 (100), 341 (42). Anal. Calcd for $C_{24}H_{22}O_8$: C, 64.27; H,

7.19. Found: C, 64.14; H, 7.41.

(±)-(1α,2α,4bβ,10α)-Ethyl 8,8-(Ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methyl-2-(4-tolylsulfonyloxy)gibb-4a(10a)-ene-10-carboxylate. This compound was prepared in 74% yield as described for the corresponding 2α-benzenesulfonate and crystallized from ether: mp 157–159 °C; ^{1}H NMR 7.70 (d, J = 8 Hz, 2 H, ArH), 7.25 (d, J = 8 Hz, 2 H, ArH), 4.70, 4.58 (ABq, J = 7 Hz, 2 H, OCH_2O), 4.40 (dd, J = 4, 12 Hz, 1 H, H-2), 4.09 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.93 (m, 4 H, OCH_2CH_2O), 3.65 (s, 3 H, CO_2CH_3), 3.24 (s, 3 H, OCH_3), 2.42 (s, 3 H, $ArCH_3$), 1.24 (t, J = 7 Hz, CH_2CH_3), 1.04 (s, 3 H, CH_3); IR 1725, 1320 cm^{-1}; m/z 634 (2%, M$^+$), 589 (25), 515 (22), 486 (10), 462 (15), 430 (14), 417 (100). Anal. Calcd for $C_{32}H_{42}O_{11}S$: C, 60.55; H, 6.67. Found: C, 60.48; H, 6.59.

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Registry No. 8, 73177-45-4; (±)-8a, 91127-18-3; (±)-10, 54099-85-3; (±)-11a, 75758-96-2; (±)-11b, 91156-85-3; (±)-12, 75758-88-2; 13, 15184-99-3; 15, 73177-51-2; 18, 91127-19-4; (±)-19, 91127-20-7; (±)-20, 75758-89-3; (±)-20 methyl ester, 75758-84-8; (±)-21 (R = CH_2Cl), 75758-92-8; (±)-21 (R = Cl_2CH), 91127-21-8; (±)-22 (R = Cl_2CH), 91156-86-4; (±)-22 (R = CH_2Cl), 75758-93-9; (±)-23a, 75758-95-1; (±)-23b, 91156-78-4; (±)-24a, 91127-22-9; (±)-24b, 91127-23-0; (±)-24c, 91127-24-1; (±)-25a, 91127-25-2; (±)-25b, 91127-26-3; (±)-26a, 91156-87-5; (±)-26b, 91127-27-4; (±)-32, 75758-97-3; (±)-33, 75758-99-5; (±)-34, 75759-00-1; (±)-36, 91127-28-5; methyl 6-[(*N*,*N*-dimethylamino)methyl]-2-methoxybenzoate, 91127-29-6; methyl 6-(chloromethyl)-2-methoxybenzoate, 91127-30-9; (±)-2-(dichloroacetoxy)-7-methoxy-1,2,3,4-tetrahydro-8-(methoxycarbonyl)fluorene-2-carboxylate, 91127-31-0; (±)-2-(chloroacetoxy)-7-methoxy-8-(methoxycarbonyl)-1,2,3,4-tetrahydrofluorene-2-carboxylic acid, 75758-90-6; (±)-methyl 8,8-(ethylenedioxy)-7-hydroxy-2-methoxygibba-1,3,4a(10a),4b-tetraene-1-carboxylate, 75758-94-0; (±)-methyl 8,8-(ethylenedioxy)-2-methoxy-7-[(methoxymethyl)oxy]gibba-1,3,4a(10a),4b-tetraene-1-carboxylate, 75758-85-9; (±)-(1α,4bβ,10α)-8,8-(ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methyl-2-oxogibb-4a(10a)-ene-10-carboxylic acid, 91156-88-6; (±)-(1α,2α,4bβ,10α)-8,8-(ethylenedioxy)-2-hydroxy-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methylgibb-4a(10a)-ene-10-carboxylic acid, 91156-89-7; (±)-(1α,2α,4bβ,10α)-2-(benzoyloxy)-10-(ethoxycarbonyl)-8,8-(ethylenedioxy)-7-[(methoxymethyl)oxy]-1-methylgibb-4a(10a)-ene-1-carboxylic acid, 75758-98-4; (±)-(1α,2α,4aα,4bβ,10β)-2-(benzoyloxy)-10-(ethoxycarbonyl)-8,8-(ethylenedioxy)-7-hydroxy-1-methylgibbane-1,4a-carbolactone, 75759-01-2; (±)-(1α,2α,4bβ,10α)-ethyl 8,8-(ethylenedioxy)-1-(methoxycarbonyl)-7-[(methoxymethyl)oxy]-1-methyl-2-(4-tolylsulfonyloxy)gibb-4a(10a)-ene-10-carboxylate, 91156-90-0; (±)-(1α,2α,4bβ,10α)-ethyl 8,8-(ethylenedioxy)-1-(methoxycarbonyl)-2-(phenylsulfonyl)-7-[(methoxymethyl)-oxy]-1-methylgibb-4a(10a)-ene-10-carboxylate, 91127-32-1; *m*-methoxybenzyl bromide, 874-98-6; 2,5-dimethoxybenzoic acid, 2785-98-0.

Phospholipid Studies of Marine Organisms. 7.[1] Stereospecific Synthesis of (5*Z*,9*Z*)-, (5*Z*,9*E*)-, (5*E*,9*Z*)-, and (5*E*,9*E*)-5,9-Hexacosadienoic Acid

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(5*Z*,9*Z*)-5,9-Hexacosadienoic acid (**5a**) and its stereoisomers **9a**, **15a**, and **21a** were synthesized stereospecifically. The difunctionalized (4*Z*)-1,1-dimethoxy-8-tosyl-4-octene (**2b**) prepared by selective ozonolysis of (1*Z*,5*Z*)-1,5-cyclooctadiene (**1**) was coupled with tridecylmagnesium bromide to afford the cis acetal **3**. The corresponding trans acetal **7** was obtained by olefin inversion in 98% stereoisomeric purity. The aldehydes **4** and **8** obtained by hydrolysis of the acetals **3** and **7** were coupled with the Wittig salt of 5-bromovaleric acid to give the 5*Z*,9*Z* (**5a**) and 5*Z*,9*E* (**9a**) acids, respectively. Reaction of **4** and **8** with vinylmagnesium bromide gave the appropriate allylic alcohols **10** and **16** which upon Claisen rearrangement led stereospecifically to (4*E*,8*Z*)- and (4*E*,8*E*)-4,8-pentacosadienoic acid methyl esters **11** and **17**. The stereoisomeric pair 5*E*,9*Z* (**15a**) and 5*E*,9*E* (**21a**) were prepared by standard one-carbon chain extension: lithium aluminum hydride reduction, mesylation, displacement by cyanide, and hydrolysis. Differentiation of these four isomers among themselves is possible by reversed-phase HPLC with silver nitrate in the mobile phase as well as on the basis of ^{13}C NMR measurements.

Recent phospholipid studies from our laboratory[3-8] have revealed the presence of high levels of unusual fatty acids in certain marine invertebrates. Litchfield et al.[9] reported the occurrence of a new class of C_{24-30} "demospongic" acids in marine sponges; in addition to unusual chain length, many of these acids possess the uncommon *cis*,*cis*-$\Delta_{5,9}$-diene systems. In order to understand the stereochemical effect of such double bonds in fatty acyl moieties of phospholipids, we have undertaken a stereospecific synthesis of the four geometrical isomers of the naturally occurring (5*Z*,9*Z*)-5,9-hexacosadienoic acid (**5a**) for eventual incorporation into phospholipids needed for model membrane studies.

Results and Discussion

Since stereochemical purity is of great importance in nature, we selected a synthetic approach by taking advantage of the cis configuration in the readily available (1*Z*,5*Z*)-1,5-cyclooctadiene (**1**) to introduce the C-9 double bond. Selective ozonolysis of this diene has already been used in pheromone synthesis[10] although no experimental

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