TABLE I

Proton donor (25 mmol)	Acidic fraction, mg	Neutral fraction, mg	% Hydrolapachol in acidic fraction
MeOH	75.55	149.1	31.4
MeOH	73.30	152.0	27.1
EtOH	86.80	94.60	32.2
EtOH	87.80	122.8	33.8
t-BuOH	108.0[a]	116.5[a]	42.8
t-BuOH	108.2[a]	93.91[a]	43.9

[a] Acidic and neutral weights are corrected. Originally, each acidic fraction amounted to ~150 mg, which, however, contained ~28% of **11** from oxidative ring opening of **9**.

proved by ir and nmr to be pure **2**. Reduction in the presence of ethanol (1 ml) gave an acidic fraction comprised of 71.6% of **2** and 28.4% of **5**.

Lapachol.—Attempted reductions (procedures A and B) of **1** resulted in recovery of pure **1** (recoveries: 89 and 92%, respectively).

α-Lapachone.—A reduction was carried out using procedure B [360 mg (1.5 mmol) of **9** and 25 mmol of ethanol in 10 ml of THF] and it showed that **9** is a nonparticipant in the production of **5**. The recovery of **9** was 70% (containing a small amount of **3**); the acidic material (32 mg), which was isolated as an orange-red oil, was identified (by tlc, two solvent systems) as γ-hydroxyhydrolapachol (**11**).

α-Lapachone is converted into γ-hydroxyhydrolapachol (**11**) (of excellent quality, 45% yield) by sodium–ammonia reduction of **9** (absence of alcohol donor) and then permitting exposure of the reduced solution of **9** to air during evaporation of ammonia. Thus a solution of **9** (500 mg, 2.06 mmol) in 10 ml of THF was added dropwise to a solution of 280 mg (13.4 mmol) of sodium dissolved in ~40 ml of ammonia (under nitrogen). After addition was complete, nitrogen purging was ceased, the bluish green solution was stirred for 15 min, and the system was opened to the atmosphere to permit evaporation (without the aid of nitrogen, ~1 hr). Ethanol (2 ml) was added to the residual liquor, followed by 50 ml of water, and the clear solution was carefully acidified with drops of 6 *N* hydrochloric acid (an excess must be avoided[20]) and let stand for 15 min. Total product was isolated with ether and partitioning with dilute alkali gave a neutral fraction (38 mg, comprised of **3** and **9**) and a salt solution which was carefully acidified; the acidic product was reisolated with ether and partitioned once again with dilute alkali. Careful acidification (6 *N* HCl) of the alkaline solution gave a bright yellow turbid solution which was induced by *immediate* scratching to give bright yellow microcrystalline prisms of γ-hydroxyhydrolapachol (**11**) (201 mg), mp 124.7–125.0°. An additional 42 mg of **11** (chromatographically uniform) was obtained from the filtrate as an orange oil by isolation with ether, drying (Na_2SO_4), and evaporation; 15.25 mg of this oil was converted by concentrated sulfuric acid to 13.0 mg of chromatographically pure β-lapachone (**10**), which was recrystallized from ethanol to give orange-red needles (5.7 mg): mp 154–159°; total yield of **11**, 243 mg, 45%. The crystalline product, mp 124.7–125.0°, was identical (by mixture melting point, ir, tlc, and nmr) with a sample of γ-hydroxyhydrolapachol, mp 125.0–125.5°, prepared from α-lapachone (**9**) (alkaline hydrolysis) using essentially the same manipulations described by Hooker for the conversion of β-lapachone (**10**) into **11**.[20]

The nmr spectrum of **11** contained a sharp singlet at δ 1.33 (6 H), two four-line multiplets centered at 1.77 (2 H) and 2.80 (2 H), and aromatic proton multiplets at 7.75 (2 H) and 8.12 (2 H).

γ-Hydroxyhydrolapachol.—The reduction was conducted as described in the first paragraph for α-lapachone, using 384 mg (1.5 mmol) of **11** and 1.46 ml (25 mmol) of ethanol. Work-up followed the procedure described in the second paragraph under α-lapachone, except that nitrogen was used during the evaporation of ammonia. The recovery of γ-hydroxyhydrolapachol was 83%, and its purity was indicated by microscopic examination, its sharp mp of 124.5–125°, tlc, and its ir spectrum.

Equilibration Experiments.—Using essentially procedure A, where a solution of either **1** or **2** (360 mg) in THF was added dropwise to a solution of sodium amide in ammonia (prepared from 8.7 mmol of sodium, and then reaction vessel purged with nitrogen), the recovery of **1**, mp 140.5–142°, was 80% and the recovery of **2**, mp 116–123°, was 70%; purities were verified by nmr.

Registry No.—**1**, 84-79-7; **2**, 4042-39-1; **3**, 15297-92-4; **4**, 15297-93-5.

Acknowledgment.—We wish to thank Dr. Thomas C. Butler for his encouragement and support of this work. We gratefully acknowledge the able technical assistance of Mrs. Irma Jean Davis, who carried out multiple preparations of isolapachol and aided R. W. C. with the spectroanalytical work. We are indebted to Dr. C. G. Moreland (North Carolina State University) and Mr. C. Fenske and Mr. J. Younger (Research Triangle Institute), who kindly provided us liberal time on their nmr instruments.

Synthesis of Compounds Related to Gibberellic Acid. III. Analogs of Ring A of the Gibberellins

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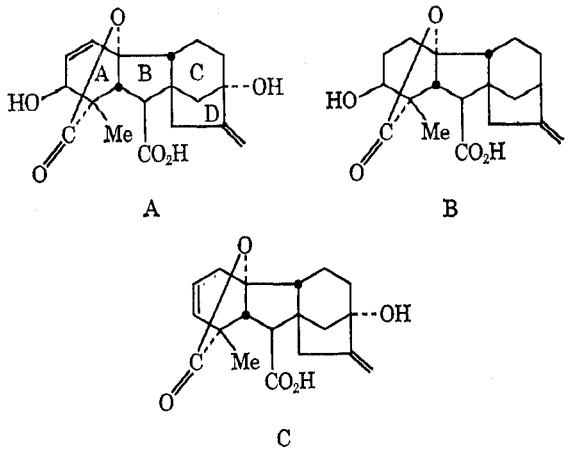
Reductive alkylation of tetrahydronaphthoic acids **1** and **8** gave the alkylated hexahydro acids **3** and **9a**, respectively. These were lactonized under acidic conditions to the *trans* lactones **4** and **10**, and the latter was elaborated to hydroxy lactones representing the elements of ring A of most of the gibberellins. The hydroxy acid **20** was converted into an iodo lactone **21** whose deiodination led stereospecifically to a *cis*-decalin lactone. Similar reactions were used for the synthesis and elaboration of compounds containing an additional double bond or a ketone group in the second naphthalene ring. Attempted acid-catalyzed lactonization of most of these led to decarboxylation or aromatization, and the deiodination of the ketal iodo lactone **44** was not stereospecific.

In previous work in this field,[1,2] we described a synthetic path to the bicyclo[3.2.1]octane system represented by rings C and D of the gibberellins. We now turned our attention[3] to the construction of the ring A system of some of the gibberellins[4] which consists of a cyclohexane ring containing a methyl group, a γ-lactone bridge and in addition a hydroxyl group and/or a double bond, as exemplified in gibberellic acid (A), gibberellin A_4 (B), and gibberellin A_5 (C).

(1) Y. Kos and H. J. E. Loewenthal, *J. Chem. Soc.*, 605 (1963).
(2) H. J. E. Loewenthal and S. K. Malhotra, *ibid.*, 990 (1965).
(3) Preliminary communication: M. D. Bachi, J. W. Epstein, and H. J. E. Loewenthal, *Tetrahedron Lett.*, **43**, 5333 (1966).
(4) For reviews see: J. F. Grove, *Quart. Rev.* (London), **15**, 56 (1961); P. W. Brian, J. F. Grove, and J. MacMillan, *Fortschr. Chem. Org. Naturstoffe*, **18**, 350 (1960).

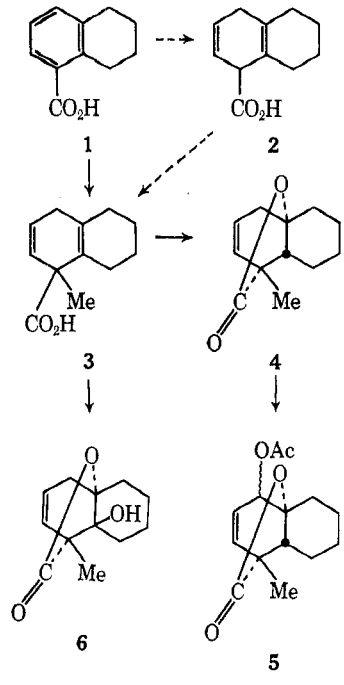


Some previous approaches to this problem have been described by Moffatt[5] and by Mori and his coworkers,[6] who prepared some simple monocyclic lactones of this type starting from suitable cyclohexanecarboxylic acid derivatives. More recently a different approach based on the internal aldol cyclization of a lactone aldehyde[7] has been described.

At first we studied the lactonization and subsequent transformation of 1,4,5,6,7,8-hexahydro-1-methyl-1-naphthoic acid (**3**). This compound was initially prepared analogously to the corresponding benzoic acid: 1,4 reduction of 5,6,7,8-tetrahydro-1-naphthoic acid (**1**)[8] using sodium in liquid ammonia with ethanol as a proton donor,[9] followed by treatment of the resulting dihydro acid **2** with sodamide or potassium amide in liquid ammonia and alkylation of the resulting carbanion with methyl iodide.[10] We found later that for the reduction of acid **1** to the dihydro stage no hydroxylic proton donor is necessary. The 1,4-dicarbanion which is initially formed is presumably protonated immediately by the ammonia solvent at the 4 position, thus enabling alkylation *in situ* of the anion at C-1. The situation here appears to be similar to the case of the reductive alkylation of α,β-unsaturated ketones studied and applied by Stork and his coworkers.[11] Eventually we have found that this type of reaction is specific to other aromatic rings containing carboxyl groups as will be shown later.

The acid **3** could be lactonized in good yield, either with trifluoroacetic acid or with sulfuric acid in chloroform, to the unsaturated lactone **4** (Scheme I). By analogy with lactonizations in similar systems[12,13] we had assumed this to be a *trans*-fused octalin derivative, and this was confirmed later by a study of hydroxy lactones mentioned below. The second question was that of the position of the double bond in this lactone. Again, this was shown later to be between C-2 and C-3 which in any case would appear to be its

SCHEME I



stable position in a *trans*-fused octalin system.[14] Thus the lactone **4** is formally an analog of ring A in gibberellin A_5.

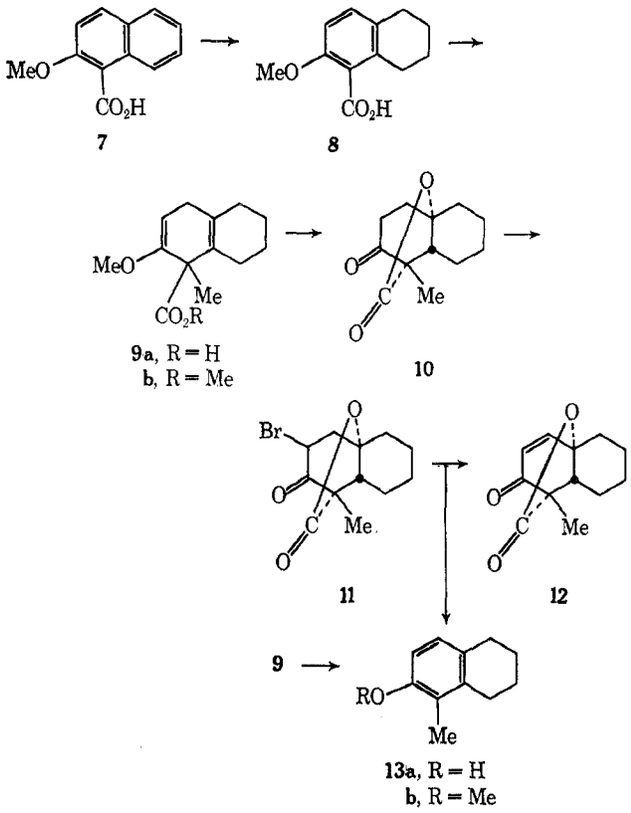
Attempts to introduce an allylic oxygen function into the lactone were at first abortive. The compound could not be subjected to allylic photooxidation,[15] and no useful product could be obtained by the action of a large variety of reagents such as *t*-butyl chromate, sodium dichromate in acetic acid–acetic anhydride, selenium dioxide in various solvents, active manganese dioxide or mercuric acetate. Finally, bromination with N-bromosuccinimide, followed by solvolysis with silver acetate in acetic acid, did give an allylic acetoxy compound (probably **5**) but this was useless for our synthetic aim. Peroxy lactonization of the acid **3**, using trifluoroacetic acid containing *m*-chloroperbenzoic acid, did give a hydroxy lactone, but it became clear that the hydroxyl group was tertiary and that this product should be formulated as **6**.

In a different approach, 5,6,7,8-tetrahydro-2-methoxy-1-naphthoic acid[16] (**8**) was reductively methylated by the above procedure to give in good yield the unstable methoxy acid **9** (Scheme II). Short treatment of this with sulfuric acid in chloroform gave in surprisingly good yield, *via* simultaneous lactonization and enol ether cleavage, the keto lactone **10**. Its reduction with sodium borohydride led to a mixture of the epimeric hydroxy lactones **14a** and **15a** in which the α epimer **14a** predominated (Scheme III); Meerwein–Ponndorf reduction, on the other hand, gave approximately equal amounts of the epimers.

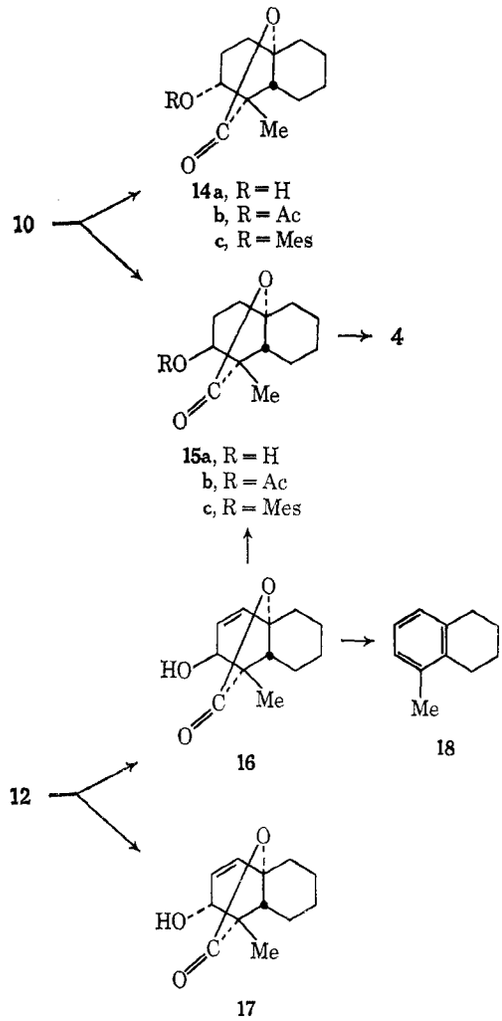
The configurational assignment of these hydroxy lactones follows from their spectral data and those of their acetates. Compound **14a** showed evidence of hydrogen bonding in the infrared and hence a *cis* relationship between the hydroxyl and lactone carbonyl (shift to lower wave numbers as compared with **15a**[5]). The acetate **14b** showed a sharp band at 1240 cm^{-1}

(5) J. S. Moffatt, *J. Chem. Soc.*, 2595 (1963).
(6) K. Mori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem.* (Tokyo), **25**, 205 (1961).
(7) L. J. Dolby and R. J. Milligan, *J. Amer. Chem. Soc.*, **88**, 4536 (1966).
(8) W. G. Dauben, C. F. Hiskey, and A. H. Markhart, *ibid.*, **73**, 1393 (1951).
(9) M. E. Kuehne and B. F. Lambert, *Org. Syn.*, **43**, 22 (1963).
(10) N. A. Nelson, J. H. Fassnacht, and J. U. Piper, *J. Amer. Chem. Soc.*, **83**, 206 (1961).
(11) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965).
(12) M. F. Ansell and M. H. Palmer, *Quart. Rev.* (London), **18**, 211 (1964).
(13) W. Herz and H. J. Wahlborg, *J. Org. Chem.*, **30**, 1881 (1965).
(14) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955).
(15) A. Nickon and J. F. Bagli, *ibid.*, **83**, 1498 (1961).
(16) R. T. Arnold, H. E. Zaugg, and J. Sprung, *ibid.*, **63**, 1314 (1941).

SCHEME II



SCHEME III



indicating an equatorial acetate group;[17,18] furthermore it showed a broad multiplet at 4.75–5.1 ppm in its nmr spectrum indicative of an axial hydrogen next to the acetoxy group.[19] The acetate **15b**, on the other hand, showed a more complex band in the infrared 1210–1240 cm^{-1}, and its nmr spectrum contained a well-defined triplet centered at 4.92 ppm indicating an equatorial hydrogen. These data, *inter alia*, support the assumption of a *trans*-fused decalin system in these compounds (assuming a chair conformation for the six-membered ring). Finally, treatment of the mesylate **15c** with collidine produced the unsaturated lactone **4** thus unequivocally establishing the position of its double bond. Compound **15a** is of course an analog of ring A of gibberellin A_4.

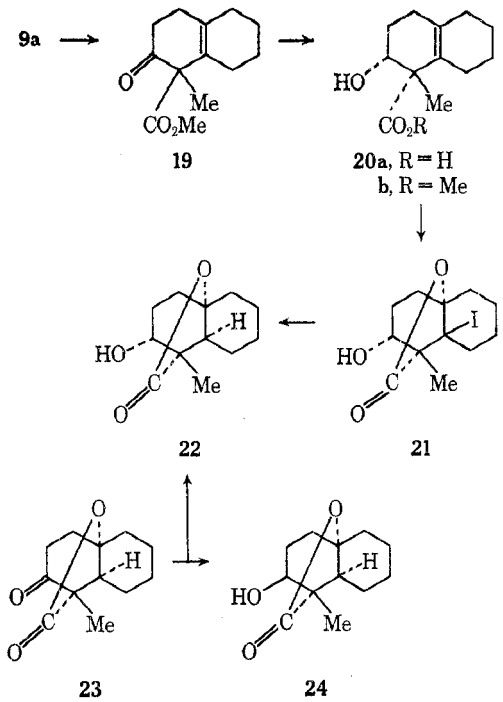
Careful bromination of the keto lactone **10** gave a bromo ketone **11** which could be dehydrobrominated by prolonged treatment with lithium chloride in N,N-dimethylformamide[20] to give the enone **12**, accompanied by the phenol **13a**. Our results of attempted selective reduction of the keto group in the enone closely paralleled those found in a similar system in the santonin series.[21] Thus, hydride ion reduction, even using lithium tri-*t*-butoxy hydride, appeared to affect primarily the double bond, and Meerwein–Ponndorf reduction was eventually successful without giving rise to decarboxylation products to any extent. Of the two unsaturated hydroxy lactones **16** and **17** thus produced the former is analogous to ring A of the gibberellic acid. Indeed, treatment of **16** with acid under conditions similar to those causing the aromatization of ring A of gibberellic acid (to give allogibberic acid)[22] led to a product which on spectroscopic evidence was 5,6,7,8-tetrahydro-1-methylnaphthalene (**18**). Finally, the configurational assignment of **16** and **17** was secured by catalytic hydrogenation of **16** under especially mild conditions (to prevent hydrogenolysis[23]) to the hydroxy lactone **15a**.

We then investigated the possibility of forming the lactone bridge under nonacidic condition. Attempted iodo lactonization of the acid **9a** was unsuccessful; immediate decarboxylation occurred under the usual experimental conditions, and the only product obtained was the phenol ether **13b**. The acid was therefore transformed *via* its methyl ester to the keto ester **19** by mild cleavage of the enol ether group, and the keto ester was reduced with sodium borohydride and hydrolyzed, to give the hydroxy acid **20a** (Scheme IV). The hydride reduction appeared to be stereospecific to give the *cis* product as was shown later.

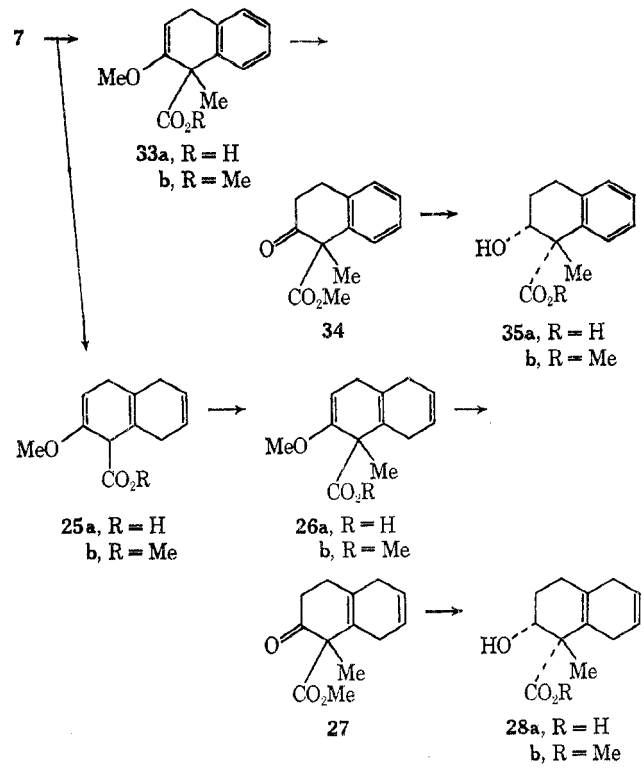
Iodo lactonization[24] of acid **20a** now gave in good yield iodo lactone **21**. A variety of conditions (irradiation in cyclohexene, catalytic reduction over palladium or Raney nickel in the presence of acetate or bicarbonate) did not lead to simple deiodination of this

(17) A. R. H. Cole, *J. Chem. Soc.*, 4969 (1952).
(18) W. G. Dauben, E. Hoerger, and N. K. Freeman, *J. Amer. Chem. Soc.*, **74**, 5206 (1952).
(19) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., Amsterdam, 1964, p 79.
(20) R. P. Holysz, *J. Amer. Chem. Soc.*, **75**, 4432 (1953).
(21) E. J. Corey and A. G. Hortmann, *ibid.*, **87**, 5736 (1965).
(22) B. E. Cross, *J. Chem. Soc.*, 4670 (1954).
(23) S. Masamune, *J. Amer. Chem. Soc.*, **83**, 1515 (1961).
(24) *Cf.* R. Grewe, A. Heinke, and C. Sommer, *Ber.*, **89**, 1978 (1956).

SCHEME IV



SCHEME V



compound. Eventually the method developed by Barton and his coworkers,[25] using chromous ion in dimethyl sulfoxide in the presence of ethanethiol, proved successful. This led in good yield to a single hydroxy lactone **22**, which was not identical with either of the *trans*-hydroxy lactones **14a** or **15a**; nor was the derived keto lactone **23** identical with the *trans* compound **10**. It appeared that the deiodination (presumably through a radical mechanism[25]) proceeded with inversion to give a *cis*-fused decalin system. Barton and his coworkers[25] have indicated that the radical debromination of steroid 9α,11β-bromohydrins leads exclusively to 9α compounds without inversion, and the stereochemistry of such reaction therefore seems to depend mainly on the over-all geometry of the substrate (see below).

Meerwein–Ponndorf reduction of the ketone **23** gave in approximately equal amounts the epimeric *cis*-hydroxy lactones **22** and **24**. Here again the configuration of the hydroxyl groups, and hence in that of the starting acid **20a**, was apparent from their ir spectra which indicated hydrogen bonding and hence a *cis* relationship in the hydroxy lactone **22**.

We now sought to extend the results obtained so far to hydronaphthoic acids containing some function in the second ring, which could be eventually transformed (*e.g.*, by ring contraction) to the cyclopentanecarboxylic acid unit present in ring B of all the gibberellins.

It has been shown[26,27] that Birch reduction (with an alkali metal in liquid ammonia in the presence of ethanol) of the acid **7** leads to reduction of both aromatic rings to the tetrahydro stage, giving the acid **25** (Scheme V). Under such conditions isolation of an intermediate 1,4-dicarbanion and its *in situ* alkylation at C-1 is not feasible; and hence acid **25** was reconverted into its C-1 carbanion using sodamide in liquid ammonia. Methylation of this now gave the methylated acid **26** in good yield. Attempted direct acid-catalyzed lactonization of this led to extensive decarboxylation and aromatization, and only a very low yield of a lactone could be obtained; this was later shown to be the rearranged product **32** (see below).

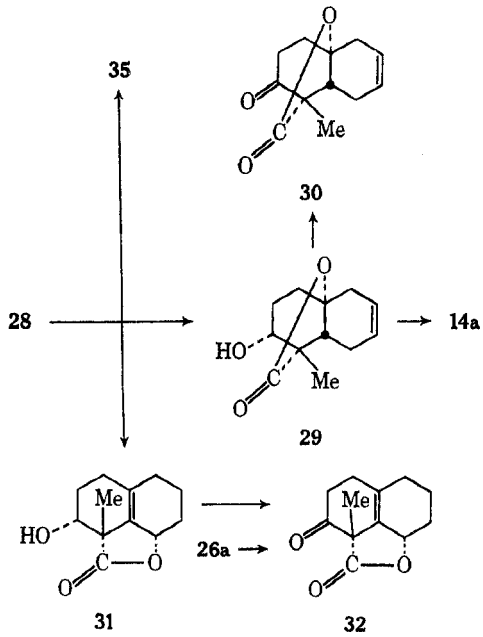
Compound **26** was therefore transformed into the hydroxy acid **28** *via* keto ester **27**, a sequence first tried out on the partially aromatic analog **33** (sequence **33** → **35**). Acid treatment of **28** now led to lactonization in somewhat better yield, but a mixture of products was formed. One was the hoped-for unsaturated lactone **29**, whose catalytic hydrogenation gave the saturated lactone **14a** obtained previously. The second product was also a γ-lactone, but this contained a tetrasubstituted double bond as shown by spectroscopic evidence. It should therefore be formulated as **31**, in whose formation isomerization of the 6,7 double bond to the 7,8 position had preceded lactonization. Its oxidation gave the keto lactone **32** (Scheme VI), which was mentioned above.

These results, and the tendency of intermediates **25**–**28** to undergo aromatization, appeared to rule out the use of a double bond as a gibberellin ring B starting point, and we therefore tried an alternative sequence wherein this point of departure would be a keto group.

Vigorous Birch reduction of 2,7-dimethoxy-1-naphthoic acid[28] (**36**) also proceeded to the tetrahydro stage to give acid **37**; however, this could not be transformed into a C-1 carbanion under a variety of conditions. Hence **36** was subjected to the reductive alkylation procedure described for its analogs **7** and **8**. This proved once again to be quite specific to the carboxyl-containing aromatic ring, notwithstanding the presence of the activating 7-methoxyl group, and gave acid **38**. The latter was transformed into the hydroxy acid **40**

(25) D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse, and M. M. Pechet, *J. Amer. Chem. Soc.*, **88**, 3016 (1966).
(26) E. L. Eliel and T. E. Hoover, *J. Org. Chem.*, **24**, 938 (1959).
(27) *Cf.* B. Weinstein and A. H. Fenselau, *ibid.*, **30**, 3209 (1965).
(28) R. Adams, M. W. Miller, F. C. McGrew, and A. W. Anderson, *J. Amer. Chem. Soc.*, **64**, 1795 (1942).

SCHEME VI



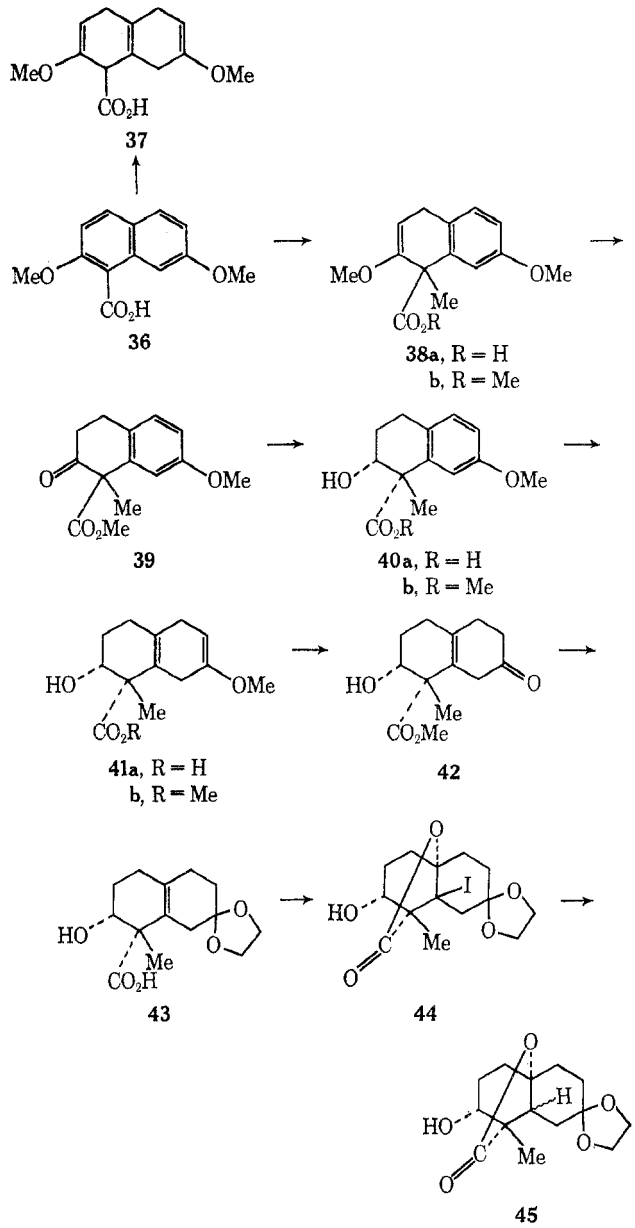
in which a *cis* relationship between hydroxyl and carboxyl was assumed by analogy with previous examples (see above). Birch reduction of the latter now gave the enol ether **41** whose attempted direct lactonization once again led to extensive decarboxylation, probably *via* the vinylogous β-ketocarboxylic acid which might be expected as an intermediate.

With the aim of ultimately forming the lactone bridge by iodo lactonization the ester **41a** was now converted into the hydroxy keto ester **42** by mild acid hydrolysis. The tetrasubstituted double bond in this compound was expected and confirmed by spectroscopic data. Ketalization followed by alkaline hydrolysis now gave ketal acid **43**, which was converted in moderate yield into the iodo lactone **44** (Scheme VII).

Its deiodination was now studied using two different methods: treatment with chromous ion in dimethyl sulfoxide in the presence of ethanethiol as tried successfully on its analog **21**; and treatment with tri-*n*-butyltin hydride,[29] which was conveniently prepared by lithium aluminum hydride reduction of the chloride, followed by destruction of excess reducing reagent with ethanol. Both methods led to deiodination, but this time, contrary to our experience with compound **21**, the reaction was not stereospecific in either case. The crude product showed two C-methyl peaks in its nmr spectrum with similar intensities, indicating that it was a mixture of C-9 epimers. It could not be resolved by column or thin layer chromatography, but gave the correct molecular peak in its mass spectrum and correct elementary analysis. Extensive recrystallization appeared to lead to enrichment in the epimer showing the C-methyl peak at lower field, to which, by analogy with the epimer pair **22** and **24**, a *cis*-decalin stereochemistry should be allocated, but complete separation could not be effected. This also applied to the mixture of derived O-acetates.

(29) H. O. House, S. E. Boots, and V. K. Jones, *J. Org. Chem.*, **30**, 2519 (1965).

SCHEME VII



Experimental Section[30]

1,4,5,6,7,8-Hexahydro-1-methyl-1-naphthoic Acid (3).—Onto a suspension of 5,6,7,8-tetrahydro-1-naphthoic acid[8] (4.37 g) in absolute ether (30 ml) was condensed liquid ammonia (*ca.* 100 ml) with stirring. The suspension was cooled in a Dry Ice–acetone bath under nitrogen. Sodium (1.37 g) was added in small pieces until a blue color persisted. Methyl iodide (*ca.* 7.1 g) was then added over a period of 10 min, whereupon the color turned to bright orange. After addition of ammonium chloride (4 g), the ammonia was removed in a slow stream of nitrogen and finally *in vacuo*. The remaining material was dissolved in water (50 ml), and the solution washed with ether. The aqueous layer was cooled to −5° and acidified to pH 5 with concentrated hydrochloric acid. The product was immediately extracted with ether. Drying (Na_2SO_4) and removal of solvent left 3.27 g of the crude acid, which after recrystallization from

(30) Melting points are uncorrected. Ultraviolet spectra (Perkin–Elmer Model 137) were determined in 95% ethanol. Infrared spectra are quoted in cm^{-1} (Perkin-Elmer Model 237) and were taken in chloroform unless contraindicated. Nuclear magnetic resonance spectra are for deuteriochloroform solutions unless otherwise mentioned (Varian Model A-60) and are quoted in parts per million downfield from tetramethylsilane. Only significant peaks or absorption areas are quoted. Thin layer chromatography examination was usually done on silica gel G plates developed with hexane–acetone mixtures.

pentane had mp 76–76.5°; ir (CCl_4) 1700 (acid C=O); nmr 1.32 (s, 3, C—CH_3), 5.32–6.05 (m, 2, =C—H). The analytical specimen was obtained by sublimation at 60–70° (0.01 mm).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.95; H, 8.4. Found: C, 74.85; H, 8.35.

1,4,5,6,7,8,9β,10-Octahydro-10α-hydroxy-1β-methyl-1α-naphthoic Acid 1→10α-Lactone (4). A.—The above acid (100 mg) in chloroform (7 ml) was cooled to −5° and the solution was added to a mixture of concentrated sulfuric acid (2 ml), and chloroform (2 ml) at −5°. The mixture was swirled in an ice bath for 5 min and then poured on ice. The product was extracted with dichloromethane; the extract was washed with potassium bicarbonate solution and dried; and the solvent was removed. The residue (93 mg) was recrystallized from pentane below 0° to give the **lactone**: mp 38–39°; ir 1770 (lactone C=O), 1165, 1120, 985, 940, and 910; nmr 1.20 (s, 3, C—CH_3), 1.20–2.30 (9, —CH_2— and —CH<), 2.40 (broad split s, 2, allylic —CH_2—) and 5.77 (broad split s, 2, —HC=CH—). The analytical specimen was obtained by evaporative distillation at 80° (0.01 mm).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.95; H, 8.4. Found: C, 74.75; H, 8.4.

B.—The acid **3** (8.85 g) was dissolved in trifluoroacetic acid (120 ml) whilst cooling in ice. The solution was allowed to reach room temperature overnight after which it was concentrated *in vacuo;* ice was added; and the product was isolated as under A. The neutral fraction (8.29 g) was distilled at 100° (0.1 mm) to give the lactone (7.96 g) which crystallized on cooling but had a lower melting point than that obtained under A.

1,4,5,6,7,8,9,10-Octahydro-9β,10α-dihydroxy-1β-methyl-1α-naphthoic Acid 1→10-Lactone (6).—The acid **3** (4.065 g) was dissolved in ice-cold trifluoroacetic acid (60 ml) containing *m*-chloroperbenzoic acid (85%, 4.75 g), and the solution was kept at room temperature overnight. It was then concentrated *in vacuo,* and the residue taken up in ether. The extract was washed with potassium carbonate solution, and the washings were back-extracted with ether. The combined ether extracts, after drying and removal of solvent, left a residue (3.17 g), crystallization of which from isopropyl ether gave the **hydroxy lactone** (0.60 g), mp 117.5–118.5°; chromatography of the mother liquors on Florisil gave another 0.90 g with the same melting point; ir 3555 (OH), 1770 (lactone C=O); nmr 1.20 (s, 3, C—CH_3), 1.25–2.25 (8, —CH_2—), 2.25—3.0 (3, OH and allylic —CH_2—), 5.40 (broad d, 1), 5.9 (m, 1, =C—H); the analytical specimen had mp 119–119.5°.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.75. Found: C, 69.05; H, 7.8.

This compound was recovered unchanged on attempted acetylation (acetic anhydride–pyridine at room temperature) or oxidation (active manganese dioxide in chloroform or chromic oxide–pyridine).

1,4,5,6,7,8,9β,10-Octahydro-4-acetoxy-10α-hydroxy-1β-methyl-1α-naphthoic Acid 1→10-Lactone (5).—The lactone **4** (0.288 g) was refluxed with N-bromosuccinimide (0.335 g) in dry carbon tetrachloride (10 ml) over a 150-W GEC Photoflood lamp. After 15–20 min, the reaction was complete; and after cooling, the mixture was filtered, and the filtrate was concentrated *in vacuo.* The residue (0.5 g) was stirred with silver acetate (0.5 g) in acetic acid (*ca.* 3 ml) at 90–100° overnight. The mixture was cooled and filtered; water was added to the filtrate; and the product was isolated with ether. The neutral crude product (0.336 g) was chromatographed over Florisil, and the total crystalline eluates (0.205 g) were combined and recrystallized from hexane to give the **acetoxy lactone**: mp 163.5–164°; ir 1650, 1740 (acetate C=O), 1775 (lactone C=O); nmr 1.22 (s, 3, C—CH_3), 2.15 (s, 3, —OCOCH_3).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.2; H, 7.25. Found: C, 67.4; H, 7.45.

Catalytic hydrogenation of this compound (25 mg) in ethyl acetate with palladium on carbon led to absorption of 1 mol/equiv of hydrogen. The tlc of the product (an acetoxy lactone according to the ir spectrum) showed that it was not identical with the acetates of either of the hydroxy lactones **14** or **15** (see below).

2-Methoxy-1-naphthoic acid (7) was prepared according to the literature[31] from the corresponding aldehyde; the yield was improved by vigorous stirring and use of an excess of potassium permanganate: yield 81%; mp 181° (lit.[32] mp 175–177°).

5,6,7,8-Tetrahydro-2-methoxy-1-naphthoic Acid (8).—The acid **7** (15.0 g) in acetic acid (200 ml) was hydrogenated at 35° in the presence of platinum oxide (50 mg) initially at 50 psi. Two further portions of platinum oxide (total 100 mg) were added at 3-hr intervals. After 24 hr when absorption had ceased, the solution was filtered, and the solvent removed *in vacuo* from the filtrate. A portion of the residue was esterified with diazomethane; tlc of the resulting ester showed the presence of only one product. The acid was recrystallized from acetic acid, mp 148–149° (lit.[16] mp 148–150°).

1,4,5,6,7,8-Hexahydro-2-methoxy-1-methyl-naphthoic Acid (9a).—The acid **8** (20.2 g) was reduced with sodium in ether–liquid ammonia, and the resulting carbanion was alkylated with methyl iodide exactly as described for the preparation of **3**. The alkaline solution of the product was acidified cautiously at −5° under a dichloromethane layer, and the aqueous phase was immediately extracted with further portions of solvent after saturation with sodium chloride. The combined extracts were dried (Na_2SO_4), and the solvent was removed giving 18.9 g of the crude **acid**, mp 139–141°, which after recrystallization from isopropyl ether had mp 149–150° dec; ir 1700, 1715, and 1750 (carboxyl C=O), 1670 (C=C), 1115; nmr 1.41 (s, 3, C—CH_3), 3.55 (s, 3, OCH_3), 4.75 (t, 1, J = 4 cps, =C—H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.15. Found: C, 70.3; H, 8.1.

9β-Decahydro-10α-hydroxy-1β-methyl-2-oxo-1α-naphthoic Acid 1→10-Lactone (10).—A solution of the above acid (5.00 g) in chloroform (100 ml), cooled to −5°, was added to a mixture of sulfuric acid (50 ml) and chloroform (70 ml), also at −5°, and the mixture was swirled for 5 min in an ice bath. The neutral residue (4.60 g), obtained after adding ice and isolation with dichloromethane, was recrystallized from isopropyl ether–pentane to give the **keto lactone**: mp 58–59°, ir 1775 (lactone C=O), 1721 (ketone C=O), 1165, 1120, 940.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.75. Found: C, 69.1; H, 7.65.

9β-Decahydro-3β-bromo-10α-hydroxy-1β-methyl-2-oxo-1α-naphthoic Acid 1→10-Lactone (11).—Bromine–ether complex was prepared by dropwise addition of absolute ether to bromine (0.766 g) with ice cooling until a second liquid phase appeared. The complex was added dropwise to a rapidly stirred solution of the above keto lactone (1.01 g) in absolute ether (175 ml) during 0.5 hr. After stirring for another 15 min, the ether layer was washed with water and with 10% potassium bicarbonate solution and dried (Na_2SO_4). Removal of solvent and recrystallization from methanol gave the **bromoketo lactone**: mp 128–129°; ir 1745 (ketone C=O), 1790 (lactone C=O), 1165, 1119, 960 (the shift of 15 cm^{-1} in the ketone band as compared to the starting material indicates the bromine to be equatorial). The analytical sample had mp 131.5–132°.

Anal. Calcd for $C_{12}H_{15}BrO_3$: C, 50.2; H, 5.25. Found: C, 50.35; H, 5.5.

1,2,5,6,7,8,9β,10-Octahydro-10α-hydroxy-1β-methyl-2-oxo-1-α naphthoic Acid 1→10-Lactone (12).—A solution of the above bromo ketone (5.00 g) and lithium chloride (3 g) in N,N-dimethylformamide (90 ml) was stirred under nitrogen for 24 hr at 125°, after which the mixture was poured into water, and the product was extracted with dichloromethane. The extracts were washed with water and dried, and the solvent was removed. The residue was chromatographed on Florisil in hexane. The first fraction, eluted with hexane–dichloromethane (1:1) (1.3 g), was identified as **5,6,7,8-tetrahydro-1-methyl-2-naphthol (13a)**, mp 113–114° (lit.[32] mp 113.5–114.5°). Further elution with the same solvent mixture gave some unchanged material; elution with hexane–ether (1:1) gave the **unsaturated keto lactone** (1.31 g) which after recrystallization from hexane–isopropyl ether had mp 70–71°; ir 1780 (lactone C=O), 1695 (enone C=O), 1618 (C=C). The analytical specimen had mp 72–73°.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.6; H, 6.85. Found: C, 69.9; H, 6.7.

Exposure of this compound to light led to the formation of a highly insoluble product (*m/e* 412.5), presumably a photodimer.

When the above dehydrobromination was conducted for shorter periods or at lower temperatures only starting material was recovered. Dehydrobromination was also unsuccessful using boiling pyridine or 2,4,6-trimethylpyridine or through attempted formation of a 2,4-dinitrophenylhydrazone.

9β-Decahydro-2,10α-dihydroxy-1β-methyl-1α-naphthoic Acid 1→10-Lactone, 2α (14) and 2β (15) Epimers. A.—A solution of the keto lactone **10** (200 mg) in ethanol (20 ml) was treated

(31) F. L. Warren, M. Gindy, and F. G. Baddar, *J. Chem. Soc.*, 687 (1941).
(32) R. H. Martin and R. Robinson, *ibid.*, 491 (1943).

at 0° with sodium borohydride (0.8 g) added in portions with stirring. After 3 hr at room temperature, dilute hydrochloric acid was added, and the ethanol was removed *in vacuo*. The oily neutral residue (0.185 g) isolated with dichloromethane was chromatographed on Florisil in hexane–ether (1:1). First fractions gave the **2β epimer** (45 mg): mp 110.5–111° (from hexane); ir (CCl_4) 3490, 3630 (both OH), 1780 (lactone C=O).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.95; H, 8.6.

Later fractions from the above chromatogram gave the **2α epimer** (127 mg): mp 88.5–89° (from hexane); ir (CCl_4) 3580, 3460 (both OH), 1775 (lactone C=O).

Anal. Found: C, 68.25; H, 8.2.

The **acetates**, prepared with acetic anhydride–pyridine at room temperature, showed the following data: **2α epimer (14b)**: mp 129–130° (from hexane); ir (CCl_4) 1785 (lactone C=O), 1745 (ester C=O), 1240 (sharp, equatorial OAc); nmr 1.08 (s, 3, C—Me), 2.10 (s, 3, $OCOCH_3$), 4.75–5.1 (m, 1, axial CHOAc).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.6; H, 8.0. Found: C, 66.7; H, 7.85.

The **2β epimer (15b)** had mp 95–96° (from hexane); ir (CCl_4) 1770 (lactone C=O), 1750 (ester C=O), 1210–1240 (split, axial OAc); nmr 1.08 (s, 3, C—Me), 2.12 (s, 3, $OCOCH_3$), 4.92 (t, 1, J = 3 cps, equatorial CHOAc).

Anal. Found: C, 66.6; H, 8.0.

B.—A solution of the keto lactone **10** (1.52 g) in 2-propanol (40 ml) containing aluminum isopropoxide (2.6 g) was refluxed under a Vigreux column for 4 hr with slow removal of the acetone formed. The mixture was cooled and acidified with concentrated hydrochloric acid, and the product was isolated by extraction with several portions of dichloromethane. The crude neutral product (1.30 g) was chromatographed as under A to yield 0.48 g of the 2β epimer and 0.46 of the 2α epimer.

Dehydration of the Hydroxy Lactone 15a.—This compound (1.20 g) was allowed to stand in pyridine (100 ml) with methanesulfonyl chloride (4 ml) at room temperature for 24 hr. The pyridine was removed *in vacuo*, and the residue taken up in ether. The extract was washed with 10% hydrochloric acid and dried, and the ether was removed. The residue (0.91 g) after recrystallization from acetone–hexane, gave the **mesylate (15c)**: mp 161–161.5°; ir 1780 (lactone C=O), 1170 and 1340 (sulfonate).

Anal. Calcd for $C_{13}H_{20}O_5S$: C, 54.15; H, 7.0; S, 11.1. Found: C, 53.95; H, 6.75; S, 11.5.

A solution of this mesylate (0.91 g) in 2,4,6-trimethylpyridine (4.0 ml) was refluxed for 5 hr. After cooling, ether was added, and the collidine was removed by repeated washing with dilute acid. The aqueous washings were back-extracted several times with ether. Drying and removal of ether gave a residue (0.70 g) which was chromatographed on Florisil in hexane. Total crystalline eluted material was recrystallized from pentane to give the unsaturated lactone **4**, mp 39.5–40°, identical by mixture melting point and ir spectrum.

1,2,5,6,7,8,9β,10-Octahydro-2,10α-dihydroxy-1β-methyl-1α-naphthoic Acid 1→10-Lactone, 2β (16) and 2α (17) Epimers.—A solution of the unsaturated keto lactone **12** (0.50 g) and aluminum isopropoxide (0.8 g) in 2-propanol (10 ml) was refluxed under a Vigreux column for 2 hr with slow removal of acetone. Working up as for the preparation of **14** and **15** gave an oil (0.42 g) which upon chromatography on Florisil gave, in order of elution, the **2β epimer**: mp 95–95.5° (from hexane); ir (CCl_4) 3620 and 3470 (OH), 1780 (lactone C=O), 1650 (C=C).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.75. Found: C, 69.45; H, 7.8.

This was followed by the **2α epimer**: mp 116.5–119° (from hexane); ir (CCl_4) 3570 and 3455 (both OH), 1770 (lactone C=O), 1645 (C=C).

Anal. Found: C, 69.0; H, 7.9.

Catalytic hydrogenation of the **2β epimer** (0.137 g) in tetrahydrofuran–pyridine (25:1, 15 ml) over prereduced palladium on calcium carbonate (5%, 0.10 g) at atmospheric pressure ceased after absorption of 1 mol/equiv of hydrogen. The usual working up gave 8 mg of acidic and 120 mg of neutral material. The latter, upon crystallization from benzene–hexane, gave the saturated 2β-hydroxy lactone **15a**, mp 110–111°, identified by mixture melting point and ir spectrum.

Acid Treatment of the Unsaturated Hydroxy Lactone 16.—This compound (0.20 g) in 1 N hydrochloric acid (5 ml) was heated for 2 hr at 80°. The evolved gas precipitated barium carbonate from a baryta solution. After cooling the neutral product was isolated with dichloromethane. After removal of solvent, the residue was chromatographed in hexane on Florisil, and the first-eluted fraction was examined. Its ir spectrum (liquid film) showed absorption of a 1,2,3-trisubstituted benzene (709 and 765); the nmr spectrum showed a complex pattern at 1.65–1.9 (4, $-CH_2-$), 2.2 (s, 3, aromatic Me), 2.4–2.9 (m, 4, benzylic $-CH_2-$), 6.95 (broad s, 3, aromatic **H**), thus indicating that this product was 5,6,7,8-tetrahydro-1-methylnaphthalene (**18**).

Attempted Iodo Lactonization of 9a.—The methoxy acid (0.955 g) was dissolved in sodium bicarbonate solution (0.5 M, 40 ml), and a solution of iodine (3.3 g) and of potassium iodide (7 g) in water (20 ml) was added. There was an immediate uptake of iodine and a precipitate formed. The product was extracted with dichloromethane and, after drying and removal of solvent, was recrystallized from pentane to give 5,6,7,8-tetrahydro-2-methoxy-1-methylnaphthalene (**13b**), mp 51–52° (lit.[26] mp 51.5–52°).

1,2,3,4,5,6,7,8-Octahydro-2α-hydroxy-1β-methyl-1α-naphthoic Acid (20a).—The acid **9a** was converted into its methyl ester **9b** using diazomethane in ether. The crude ester (2.0 g) in methanol (10 ml), tetrahydrofuran (5 ml), water (2 ml), and concentrated hydrochloric acid (0.9 ml) was allowed to stand at room temperature for 1 hr, after which an excess of potassium bicarbonate was added and the solvents were removed *in vacuo*. The resulting keto ester (1.83 g) **19**, isolated with dichloromethane, was dissolved in ethanol (50 ml), and the solution was treated at 0° in portions with sodium borohydride (0.3 g) while stirring. After 5 hr at room temperature, the excess of hydride was destroyed by addition of acid, and the ethanol was removed *in vacuo*. The product (1.65 g), isolated with dichloromethane, was refluxed with ethanolic potassium hydroxide (10%, 50 ml) for 5 hr under nitrogen, after which water was added and the ethanol was removed *in vacuo*. After washing with ether, the aqueous solution was acidified, and the product was extracted ten times with ether. Drying of the extracts and removal of solvent gave the crystalline **hydroxy acid** (1.26 g): mp 116–117° (from isopropyl ether); ir 3600, 3500, 1710 (carboxyl).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.65; H, 8.5.

Decahydro-2α,10α-dihydroxy-9β-iodo-1β-methyl-1α-naphthoic Acid 1→10-Lactone (21).—The above hydroxy acid (0.50 g) was dissolved in sodium bicarbonate solution (0.5 M 20 ml) and a solution of iodine (1.7 g) and potassium iodide (3.5 g) in water (10 ml) was added at room temperature. A brown precipitate formed immediately, and the mixture was kept in the dark for 1.5 hr, after which ether (20 ml) and an excess of sodium thiosulfate solution were added. The ether layer was dried, and the solvent was removed to give a yellow residue of the **iodo lactone** (0.65 g), mp 164–165° dec (unchanged by further recrystallization from benzene–hexane).

Anal. Calcd for $C_{12}H_{17}IO_3$: C, 42.9; H, 5.1; I, 37.8. Found: C, 43.1; H, 5.1; I, 38.1.

9α-Decahydro-2α,10α-dihydroxy-1β-methyl-1α-naphthoic Acid 1→10-Lactone (22).—To a stirred solution of chromous acetate (3.4 g) in dimethyl sulfoxide (80 ml) and ethanethiol (2 ml) was added under nitrogen with stirring a solution of the above iodo lactone (1.20 g) in dimethyl sulfoxide (40 ml). After stirring for 1 hr at room temperature, the mercaptan was removed at the water pump and the dimethyl sulfoxide by distillation at 0.3 mm. The residue was taken up in chloroform–benzene, and the remaining dimethyl sulfoxide and chromium salts were removed by repeated washings with water, which were back-extracted with chloroform–benzene. Drying of the organic extracts and removal of solvents left a crystalline residue of the **hydroxy lactone** (0.66 g): mp 181.5–182° after recrystallization from benzene; ir 3580 (OH), 1775 (lactone C=O).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.85; H, 8.6.

9α-Decahydro-10α-hydroxy-2-oxo-1β-methyl-1α-naphthoic Acid 1→10-Lactone (23).—The above hydroxy lactone (0.10 g) in acetone (10 ml) was oxidized by dropwise addition of 8 N chromic acid in dilute sulfuric acid to a permanent orange color at 0°. After neutralization with potassium bicarbonate, the neutral product was isolated with dichloromethane to give the **keto lactone** (87 mg): mp 121–122° (from benzene–hexane); ir 1785 (lactone C=O), 1725 (ketone C=O), 1125, 1035, 960.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.75. Found: C, 69.1; H, 7.65.

Meerwein–Ponndorf reduction of this ketone (1.20 g) exactly

as described for reduction of the ketone **10**, followed by chromatography of the product, gave in order of elution **9α-decahydro-2β,10α-dihydroxy-1β-methyl-1α-naphthoic acid 1→10-lactone (24)**: mp 140–141° (from benzene–hexane); ir 3620 (OH), 1780 (lactone C=O).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.65. Found: C, 68.35; H, 8.85.

This was followed by the above epimeric hydroxy lactone **22**. The two epimers were present in approximately equal amounts.

The nmr spectra of hydroxy lactone **22** and **24** both showed C-methyl peaks at 1.25; in the *trans*-hydroxy lactones **14** and **15** these appeared at 1.18 and 1.20, respectively.

1,4,5,8-Tetrahydro-2-methoxy-1-naphthoic acid (25a) was prepared as reported[27] to yield 73%: mp 138° (lit.[27] mp 133.5–134.5°); λ_{max} 206 mμ (log ε 3.65). Its methyl ester (**25b**), prepared with diazomethane, had mp 64.5–65° (from pentane).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.95; H, 7.6.

1,4,5,8-Tetrahydro-2-methoxy-1-methyl-1-naphthoic Acid (26a).—The finely powdered acid **25a** (10.5 g) was added in portions to a suspension of sodamide (from 3.5 g of sodium) in liquid ammonia (400 ml) cooled in a Dry Ice–acetone bath. While stirring, the cooling bath was removed to allow the temperature to reach *ca.* −35°, and a red-brown suspension was obtained. Cooling was resumed and, after 7.5 hr, an excess of methyl iodide was added dropwise during 20 min until the color was discharged. After addition of ammonium chloride (16 g), the ammonia was allowed to evaporate; water was added to dissolve the residue; and the solution was washed with ether. The aqueous layer was cautiously acidified with 1 *N* sodium dihydrogen phosphate solution to pH 4 under a layer of ether–dichloromethane. The layers were separated, and the aqueous phase was extracted four times with dichloromethane. The combined extracts were washed with water and dried, and the solvents were removed. The residue (10.0 g, mp 146–150°) was recrystallized (charcoal) from ether–benzene to give the **acid** (6.5 g), mp 162–163° dec.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.85; H, 7.5.

Its **methyl ester 26b**, prepared with ethereal diazomethane in quantitative yield, had mp 85–86° (from hexane); ir 1730 (ester C=O), 1710, 1680, 1660 (C=C); nmr 1.45 (s, 3, C—Me), 3.55 (s, 3, OMe), 3.70 (s, 3, OMe), 4.80 (t, 1, J = 3 cps, =C—**H**), 5.7–5.85 (m, 2, =C—**H**).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.75; H, 7.75. Found: C, 71.75; H, 7.75.

1,2,3,4,5,8-Hexahydro-1-methyl-2α-hydroxy-1β-methyl-1α-naphthoic Acid (28a).—Crude methyl ester obtained from acid **26a** (10.61 g) was dissolved in a mixture of tetrahydrofuran (15 ml), methanol (50 ml), water (13 ml), and concentrated hydrochloric acid (6 ml), and the solution was allowed to stand at room temperature. After 1 hr, sodium acetate (6 g) was added, and the organic solvents were removed *in vacuo*. The product was taken up in ether, and the extract was washed with water, potassium carbonate solution, again with water, dried, and the solvent was removed. The residue (10.0 g, homogeneous by tlc, ir 1715, 1740) was dissolved in methanol (120 ml), and the solution was treated at 0° with potassium borohydride (4 g) and then left overnight at room temperature. Water was added, and the product was isolated with ether giving an oil (homogeneous by tlc, 10.0 g). This product (7.2 g) was refluxed in ethanolic potassium hydroxide (10%, 110 ml) under nitrogen overnight. The ethanol was removed *in vacuo*, and the residue was dissolved in water. The solution was washed with ether and acidified, and the product was extracted with ether. The extract was dried, treated with charcoal, and filtered, and the solvent was removed. The residue (5.4 g) was recrystallized from isopropyl ether to give two crops: 3.80 g, mp 118–123°, and 0.62 g, mp 104–110. Repeated recrystallization from isopropyl ether and from tetrahydrofuran–cyclohexane gave the pure **acid**: mp 125–125.5°; ir (KBr) 1695 broad, 1040; nmr (acetone-d_6) 1.36 (s, 3, C—Me), 3.5–3.8 (m, 1, C**H**OH), 5.0–5.25 (broad s, 2, disappears on addition of trifluoroacetic acid, O**H** and CO_2**H**), 5.68 (broad s, 2, =C—**H**).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.75. Found: C, 69.45; H, 7.6.

Fractions of lower melting point showed in the nmr additional peaks at 7.0–7.3; and the uv spectrum showed a shoulder at 265 mμ, indicating an aromatic impurity; the pure acid showed λ_{max} 207 mμ (log ε 3.45).

Lactonization of Acid 28a.—The acid (5.19 g, mp 118–123°) was refluxed in trifluoroacetic acid (100 ml) under nitrogen for 6 hr after which the solvent was removed *in vacuo*. The residue was dissolved in benzene and separated into acidic (extracted with 5% potassium carbonate, 1.29 g) and neutral (3.44 g) fractions. The latter showed strong ir absorption at 1790 indicating the presence of trifluoroacetate ester. It was refluxed in dry methanol (170 ml) for 3 hr after which the solution was concentrated *in vacuo* to leave an oily residue (2.79 g). This (2.66 g) was chromatographed in dichloromethane–hexane (1:1) over Florisil (50 g), eluting with ascending proportions of dichloromethane and then with chloroform. i and ii were obtained in order of elution. (i) **1,2,3,4,5,6,7,8-Octahydro-2,8-dihydroxy-1-methyl-1-naphthoic acid 1→8-lactone (31**, 580 mg) had mp 101–101.5° (from hexane); ir 3545 (OH), 1760 (lactone C=O), 1310, 1100, 1070, 1045, 1010, 975, 940; nmr 1.28 (s, 3, C—Me), 4.10 (t, 1, J = 2 cps, CHOH), 4.7–5.2 (m, CHOCO—), no vinyl proton.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.75. Found: C, 69.4; H, 7.75.

(ii) **1,2,3,4,5,8,9β,10-Octahydro-2α,10α-dihydroxy-1β-methyl-1α-naphthoic acid 1→10-lactone (29**, 1.23 g) had mp 115–115.5°; ir 3575 (OH), 1770 (lactone C=O), 1145, 1085, 1050, 1030, 960, 900; nmr 1.22 (s, 3, C—CH_3), 3.4–3.85 (m, 1, —C**H**OH), 5.70 (broad split s, 2, =C**H**—).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.75. Found: C, 69.3; H, 7.9.

Catalytic hydrogenation of the hydroxy lactone **29** (250 mg) in methanol (12.5 ml) over palladium on carbon (10%, 60 mg) at atmospheric pressure led to absorption of 1 mol/equiv of hydrogen. Filtration, removal of methanol, and chromatography on Florisil gave in high yield **9β-decahydro-2α,4α-dihydroxy-1β-methyl-1α-naphthoic acid 1→10-lactone (14)**, mp 87.5–88.5°, identical (mixture melting point ir and nmr spectra) with the compound described above.

Oxidation of the hydroxy lactone **29** (100 mg) in acetone (10 ml) with 8 *N* chromic acid in dilute sulfuric acid (0.3 ml), followed by the usual work-up and crystallization from hexane, gave **1,2,3,4,5,8,9β,10-octahydro-10α-hydroxy-2-oxo-1β-methyl-1α-naphthoic acid 1→10-lactone (30)**: mp 85.5–86°; ir 1780 (lactone C=O), 1730 (ketone C=O), 1140.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.85: C, 69.75; H, 6.95.

Oxidation of the hydroxy lactone **31** (140 mg) in the same manner gave, after crystallization from hexane, **1,2,3,4,5,6,7,8-octahydro-8-hydroxy-2-oxo-1β-methyl-1α-naphthoic acid 1→8-lactone (32)**: mp 82–83.5°; ir 1780 (lactone C=O), 1730 (ketone C=O, abnormally weak), 1015; nmr 1.55 (s, 3, C—Me), 4.75–5.1 (m, 1, —C**H**OH—), no vinyl protons.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.85. Found: C, 69.4; H, 6.75.

The acidic fraction from the above lactonization, after repeated crystallization from isopropyl ether, had mp 143–148°, raised to 145–148° upon admixture with the aromatic hydroxy acid **35a**, mentioned below.

Attempted Lactonization of Acid 26a.—Treatment of this acid with trifluoroacetic acid resulted in immediate decarboxylation, and no useful product could be isolated. However, some lactonization occurred when it was treated with sulfuric acid in chloroform below 0° for between 30 and 60 sec. About 50% by weight of neutral material (not extracted by bicarbonate) could be obtained. Extensive chromatography on Florisil gave in *ca.* 5% over-all yield the keto lactone **32**, identified by mixture melting point and ir and nmr spectra.

1,4-Dihydro-2-methoxy-1-methyl-1-naphthoic Acid (33a).—Onto a suspension of the acid **1** (15.0 g) in dry ether (120 ml) was condensed liquid ammonia to a total volume of *ca.* 550 ml while cooling in Dry Ice–acetone. Sodium (total of *ca.* 4.3 g, 2.5 mol/equiv) was added in small pieces until the color turned through orange and green to blue until the latter color persisted for 0.5 hr. An excess of methyl iodide was then added during 10 min until the color was completely discharged. After addition of ammonium chloride, the ammonia was allowed to evaporate, finally *in vacuo*. The residue was dissolved in water, and the solution was washed with dichloromethane, cooled to 0°, and cautiously acidified to pH 4 (1:1 hydrochloric acid) under a layer of ether–dichloromethane (1:1). The aqueous phase was extracted again with ether–dichloromethane, and the combined extracts were washed with saturated sodium chloride solution. Drying and removal of solvents gave a residue of the **acid** (15.4 g): mp 143° dec (unchanged by further crystallization from

tetrahydrofuran–cyclohexane); ir 1715–1690 (carboxyl C=O), 1115, 1040; nmr 1.62 (s, 3, C—Me), 3.52 and 3.60 (s, total 5, OMe and benzylic —CH_2—), 4.95 (t, 1, J = 3 cps, =CH—), 7.1–7.4 (m, 4, aromatic **H**), 11.2 (s, 1, CO_2H).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.55; H, 6.45. Found: C, 71.85; H, 6.8.

The **methyl ester** (**33b**), prepared with ethereal diazomethane, had mp 60–60.5° (from pentane); ir 1740 (ester C=O), 1695 (C=C), 1120; nmr 1.63 (s, 3, C—Me), 3.59 (s, 8, OMe and benzylic —CH_2—), 4.93 (t, 1, J = 3 cps, =CH—), 7.16 (s, 4, aromatic **H**).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.4; H, 6.95. Found: C, 71.9; H, 7.15.

Methyl 1,2,3,4-Tetrahydro-1-methyl-2-oxonaphthalene-1-carboxylate (**34**).—The above methyl ester (8.6 g) was cleaved with hydrochloric acid in methanol–tetrahydrofuran–water, exactly as described for the methyl ester **26b** (see above). Crystallization of the neutral product from isopropyl ether at 0° gave the **keto ester**: mp 55.5–56°; ir 1710–1745 (C=O); nmr 1.66 (s, 3, C—Me), 3.60 (s, 3, OMe), 7.22 (s, 4, aromatic **H**).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.55; H, 6.45. Found: C, 71.75; H, 6.55.

1,2,3,4-Tetrahydro-2α-hydroxy-1β-methyl-1α-naphthoic Acid (**35a**).—The foregoing keto ester (6.76 g) was reduced in methanol with sodium or potassium borohydride, exactly as described for the preparation of the hydroxy acid **28a** (see above). The crude corresponding hydroxy ester (**28b**), ir 3600, 1730, was obtained in theoretical yield.

The latter (1.04 g) was hydrolyzed with ethanolic potassium hydroxide as described for **5**, giving the **acid**: 0.97 g; mp 144–147° (raised to 150–150.5° after recrystallization from tetrahydrofuran–cyclohexane); ir (KBr) 1700 broad (carboxyl), 1255, 1040, 740.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.85. Found: C, 70.15; H, 7.1.

2,7-Dimethoxy-1-naphthoic Acid (**36a**).—This was at first prepared as reported previously,[29] except that the butyllithium solution was added to the solution of 1-bromo-2,7-dimethoxynaphthalene. A 76% of the acid mp 107–108° (lit.[29] mp 112–113°), was obtained.

The following procedure proved more convenient and gave better yields: 1-bromo-2,7-dimethoxynaphthalene (75 g), magnesium ribbon (8.8 g), and tetrahydrofuran (freshly distilled from calcium hydride, 580 ml) were stirred vigorously under nitrogen, and methyl iodide (2 ml) was added. The mixture was cautiously heated to reflux whereupon the reaction started. After refluxing for 1.5 hr, the solution was cooled to −10° (ice–salt), and dry carbon dioxide was bubbled in at a rate keeping the temperature below −2°. When absorption was complete as shown by a drop in temperature, the mixture was acidified with 2 *N* sulfuric acid and extracted with four portions of ether. The ether layers were extracted with 1 *N* sodium hydroxide, and the extracts were again washed with ether and acidified. The acid was isolated with ether, yielding 59 g (91%), mp 106–108°, raised by crystallization from benzene to 109–111°.

1,4,5,8-Tetrahydro-2,7-dimethoxy-1-naphthoic Acid (**37a**).—This was prepared from the dimethoxy acid **36a** by reduction with lithium and ethanol in liquid ammonia, exactly as described for 2-methoxy-1-naphthoic acid (see above and ref 27). The product was obtained in 40–50% yield, mp 118–119° dec.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.85. Found: C, 66.35; H, 6.7.

Attempted methylation of this acid with methyl iodide, using either potassium or lithium amide in liquid ammonia, as described for the preparation of acid **26a**, was unsuccessful.

1,4-Dihydro-2,7-dimethoxy-1-methyl-1-naphthoic Acid (**38a**). This was prepared by treatment of the acid **36a** (35 g) with sodium (2.5 mol/equiv) in ether and liquid ammonia, followed by alkylation with methyl iodide, exactly as described for the preparation of acid **33a**. The crude product (37 g) had mp 121–123°, raised to 127.5–128° dec after crystallization from ether–hexane; ir 1720–1690 (carboxyl C=O), 1620, 1040; nmr 1.65 (s, 3, C—Me), 3.45–3.52 (m, 2, benzyl —CH_2—), 3.60 (s, 3, OMe), 3.75 (s, 3, OMe), 4.97 (t, 1, J = 3 cps, =3H—), 6.67–7.25 (m, 3, aromatic **H**), 11.5 (s, 1, CO_2H).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.75; H, 6.5. Found: C, 68.05; H, 6.3.

The **methyl ester** (**38b**), prepared with ethereal diazomethane, had mp 78–79° (from hexane); ir 1740 (ester C=O), 1690 (C=C), 1620.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9. Found: C, 68.8; H, 7.05.

Methyl 1,2,3,4-Tetrahydro-7-methoxy-1-methyl-2-oxonaphthalene-1-carboxylate (**39**).—The foregoing ester (21.2 g) was cleaved by acid exactly as described for the methyl esters **26b** and **33b**. The resulting **keto ester** (18.6 g) had mp 55.5–56° (from hexane); ir 1745 (ester C=O), 1720 (ketone C=O), 1615; nmr 1.58 (s, 3, C—Me), 2.32–3.20 (m, 4, —CH_2—), 3.58 (s, 3, OMe), 3.73 (s, 3, OMe), 6.57–7.20 (m, 3, aromatic **H**).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.75; H, 6.5. Found: C, 67.95; H, 6.35.

1,2,3,4-Tetrahydro-2α-hydroxy-7-methoxy-1β-methyl-1α-naphthoic Acid (**40a**).—The above keto ester was reduced with borohydride in methanol exactly as described for **34b**. The resulting **hydroxy ester** (22.1 g) had mp 61–61.5°; ir 3500–3600 (broad, OH), 1710–1730 (carbonyls), 1615; nmr 1.68 (s, 3, C—Me), 3.17 (s, 1, disappears with trifluoroacetic acid, OH), 3.70 (s, 3, OMe), 3.78 (s, 3, OMe), 6.4–7.3 (m, 3, aromatic **H**).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.2; H, 7.25. Found: C, 66.95; H, 7.0.

Hydrolysis of the hydroxy ester, again as described above, gave in 89% yield the **hydroxy acid**: mp 168.5–169°, not raised by further crystallization from tetrahydrofuran–cyclohexane; ir (KBr) 1700–1730 (carboxyl), 1620.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.85. Found: C, 66.15; H, 6.75.

1,2,3,4,5,8-Hexahydro-2α-hydroxy-7-methoxy-1β-methyl-1α-naphthoic Acid (**41a**).—To liquid ammonia (200 ml) was added a solution of the hydroxy acid **40a** (4.00 g) in dry ethanol (60 ml) and tetrahydrofuran (40 ml). The mixture was cooled in Dry Ice–acetone, and sodium (9.4 g) was added with stirring during 30 min. After stirring for another 1 hr, the cooling bath was removed, and the mixture kept under a Dry Ice condenser until the color was discharged (15–30 min). After addition of ammonium chloride (22 g), the ammonia was allowed to evaporate, finally together with the solvents *in vacuo*. Chloroform (200 ml) was added; the mixture was cooled to 0° and acidified with vigorous stirring to pH 4 using 2 *N* sodium dihydrogen phosphate. The aqueous layer was extracted five times with more chloroform; the combined extracts were washed with saturated sodium chloride solution and dried (Na_2SO_4), and the chloroform was removed. The residue crystallized on treatment with isopropyl ether to give the acid (2.53 g): mp 102–103° dec; uv λ_{max} 206 mμ, (log ε 3.69); ir 1720–1740 (carboxyl), 1680 (C=C).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.6. Found: C, 64.85; H, 7.65.

For the next step the crude material could be used without crystallization.

Methyl 1,2,3,4,5,6,7,8-Octahydro-2α-hydroxy-1β-methyl-2-oxonaphthalene-1α-carboxylate (**42**).—The crude acid **41a**, prepared from 24 g of acid **40a**, was converted into its methyl ester using ethereal diazomethane. The latter was cleaved with hydrochloric acid in methanol–tetrahydrofuran as described for the cleavage of the ester **26b**. The resulting **hydroxyketo ester** crystallized from isopropyl ether to give 11.6 g: mp 77–78°, raised to 78–78.5° on further crystallization; ir 3400–3600 (broad, OH), 1720 (C=O); nmr 1.36 (s, 3, C—Me), 3.70 (s, 3, OMe), no vinyl **H**.

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.6. Found: C 65.45; H, 7.85.

7,7-Ethylenedioxy-1,2,3,4,5,6,7,8-octahydro-2α-hydroxy-1β-methyl-1α-naphthoic Acid (**43**).—The above keto ester (8.65 g) was dissolved in benzene (430 ml); *p*-toluenesulfonic acid (350 mg) and ethylene glycol (7.8 ml) were added, and the reaction was refluxed overnight with azeotropic removal of water. After cooling, the solution was washed with sodium chloride solution and dried, and the solvent was removed. The residue (9.9 g) was refluxed under nitrogen for 16 hr in ethanolic potassium hydroxide (10%, 100 ml), after which the ethanol was removed *in vacuo*, the residue dissolved in water, the solution was washed with ether and acidified cautiously at 0° under ethyl acetate. The aqueous phase was extracted with more ethyl acetate; the combined extracts were washed with saturated sodium chloride solution, dried, treated with charcoal, filtered, and concentrated to *ca.* 50 ml. Hexane was added (*ca.* 100 ml), whereupon the **acid** crystallized, giving 5.8 g: mp 101–108°, raised to 110–110.5° upon recrystallization from ether–hexane; ir 1690–1730; nmr 1.36 (s, 3, C—Me), 4.0 (s, 4, ketal ring —CH_2—), 7.0–7.2 (m, 2, OH and CO_2H).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.65; H, 7.5. Found: C, 62.6; H, 7.75.

7,7-Ethylenedioxydecahydro-2α,10α-dihydroxy-9β-iodo-1β-methyl-1α-naphthoic Acid 1→10-Lactone (44).—The above acid (3.31 g) was dissolved in sodium bicarbonate solution (0.5 *N*, 123 ml), and to this was added a solution of iodine (9.2 g) and potassium iodide (22 g) in water (62 ml). The mixture was left overnight in the dark, whereupon an excess of sodium thiosulfate solution was added and the product was extracted with ethyl acetate. The extracts were washed with sodium chloride solution and dried, and the solvent removed, leaving a crystalline residue which on trituration with isopropyl ether gave 3.45 g of the crude iodo lactone, mp 86°. Several recrystallizations from isopropyl ether and from dichloromethane–isopropyl ether gave the pure compound: mp 107° (vigorous dec); ir 3610 and 3570 (OH), 1780 (lactone C=O); nmr 1.25 (s, 3, C—Me), 4.00 (s, 4, ketal ring —CH_2—).

Anal. Calcd for $C_{14}H_{19}IO_5$: C, 42.65; H, 4.85; I, 32.2. Found: C, 42.6; H, 4.95; I, 32.3.

Deiodination of the Iodo Lactone 44. A.—The iodo lactone (500 mg) was dissolved in dry dimethyl sulfoxide (5 ml) under nitrogen, and ethanethiol (1.24 g) was added by a solution of chromous acetate (2 g) dissolved in dimethyl sulfoxide (10 ml). The mixture was stirred for 5 hr at room temperature, and the solvents were then removed, finally in a high vacuum. The residue was taken up in benzene–chloroform (1:2), and the organic layer was washed with water and sodium chloride solution; each washing was back-extracted. After drying and removal of solvents, the residue was treated with a small amount of isopropyl ether and allowed to crystallize at 0°, to give 332 mg of a mixture of the isomeric hydroxy lactones **45** [mp 127–135°; ir 3580 (OH), 1775 (lactone C=O)]; 145 mg of this mixture was recrystallized from benzene to give i [113 mg; mp 128–141°; nmr (DMSO-d_6) 1.00 and 1.07 (s, ratio 3:2, both C—Me), 3.2 (s, 4, ketal —CH_2—)] and ii [20 mg; mp 129–140°; with similar properties]. The mass spectrum of both fractions showed *m/e* 268 (calcd 268.3). Fraction i was analyzed.

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.65; H, 7.5. Found: C, 62.1; H, 7.25.

Repetition of the reaction using reversal of the order of addition of reactants and reduction of the time gave similar results.

B.—Lithium aluminum hydride (120 mg) was stirred in absolute ether (4 ml) for 15 min, after which tri-*n*-butyltin chloride (780 mg) in ether (4 ml) was added with stirring at 0°. The mixture was stirred for another 15 min at 0° and then at room temperature for 3.5 hr. Dry ethanol (1.0 ml) in ether (3 ml) was then added, and after evolution of hydrogen ceased, a solution of the iodo lactone (496 mg) in ethyl acetate (*ca.* 5 ml) was added during 10 min. The mixture was left overnight at room temperature; more ethyl acetate was added; the solution was washed with water and dried; and the solvent was removed. The residue (1.1 g) was chromatographed over Florisil (33 g) in benzene, and the chromatogram eluted with benzene–chloroform mixtures, which eluted tin compounds which were not examined further. Elution with chloroform gave a mixture of hydroxy lactones **45** which crystallized readily but had wide melting point ranges; they gave only one spot on tlc in a variety of systems. The eluates were concentrated in two separate consecutive fractions: (i) 210 mg, which on crystallization from isopropyl ether gave 106 mg [mp 138–148°; nmr (DMSO-d_6) 1.00 and 1.07 (s, ratio 2:5, both C—Me)]; (ii) 136 mg gave after crystallization from isopropyl ether 44 mg [mp 157–169°; here the nmr peaks at 1.00 and 1.07 were in a ratio of 1:6; concentration of the mother liquor gave material of mp 128–140°]. Material of mp 128–141° (104 mg) was acetylated by treatment with acetic anhydride (0.1 ml) in pyridine (0.5 ml) at room temperature overnight; the usual work-up gave a mixture of acetates (98 mg): mp 116–136°; ir 1780 (lactone C=O), 1735 (acetate C=O) and 1245 (complex); nmr 1.08 and 1.17 (ratio 3:2).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.9; H, 7.15. Found: C, 61.9; H, 7.1.

This mixture could likewise not be resolved by chromatography or crystallization.

Registry No.—**3,** 17953-50-3; **4,** 17968-32-0; **5,** 17968-33-1; **6,** 17968-34-2; **9a,** 13878-71-2; **10,** 18006-18-3; **11,** 18006-19-4; **12,** 18006-20-7; gibberellic acid, 77065; **14a,** 17968-35-3; **14b,** 17968-36-4; **15a,** 17968-37-5; **15b,** 18006-21-8; **15c,** 17968-38-6; **16,** 17968-39-7; **17,** 17968-40-0; **20a,** 17968-41-1; **21,** 17968-42-2; **22,** 17968-43-3; **23,** 18026-65-8; **24,** 17968-44-4; **25b,** 17953-52-5; **26a,** 17953-53-6; **26b,** 17953-54-7; **28a,** 17968-45-5; **29,** 17968-46-6; **30,** 18026-66-9; **31,** 17968-47-7; **32,** 17968-48-8; **33a,** 13878-70-1; **33b,** 17953-56-9; **34,** 17953-57-0; **35a,** 18006-22-9; **36a,** 17953-58-1; **37a,** 17953-59-2; **38a,** 13878-72-3; **38b,** 17953-61-6; **39,** 17953-62-7; **40a** hydroxy ester, 17968-49-9; **40a** hydroxy acid, 17968-50-2; **41a,** 17968-51-3; **42,** 17968-52-4; **43,** 17968-53-5; **44,** 17968-54-6; **45,** 17968-55-7.

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