Syntheses of Methyl Deisopropyldehydroabietate. Diterpenoid Synthesis by the AB → ABC Approach[1]

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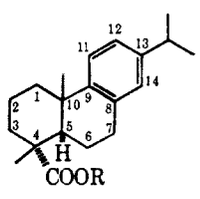
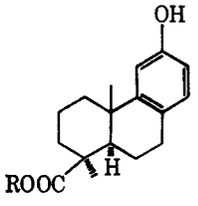
An efficient, stereoselective synthesis of the bicyclic keto ester **3**, a useful intermediate for elaboration of diterpenoid natural products stereochemically related to dehydroabietic acid (**1**), is described. The key step is reductive carbomethoxylation of **4**, which establishes the AB-*trans* fusion and introduces the C_4 carbomethoxyl group. Conversion of **3** into methyl *dl*-deisopropyldehydroabietate (**23**) by two routes is described. Nmr data are tabulated showing how the shielding effect of the C_4 axial carbomethoxyl group can be used to distinguish compounds with stereochemistry related to podocarpic acid (**2**) from compounds related to **1**.

Total synthesis of the tricyclic diterpene resin acids, typified by dehydroabietic acid (**1**) and podocarpic acid (**2**), has been accomplished by a variety of methods. Stork's pioneering synthesis of **1**[3] may be cited as an example of the approaches[4] involving addition of ring A to a preformed BC nucleus. Ireland's stereoselective, high-yield synthesis of **1**[5] notably exemplifies the closure of ring B in a suitable AC system, a tactic which has found favor with a number of investigators.[6]

In this and the following paper[7] most of our work of the last few years in developing effective syntheses of intermediates corresponding to rings A and B of such diterpenoid systems and some applications of these intermediates to the elaboration of tricyclic natural products are described. Preliminary reports of portions of this research have been published,[8] as have recent studies based on this AB → ABC approach by other workers.[9]



1, R = H
36, R = CH_3

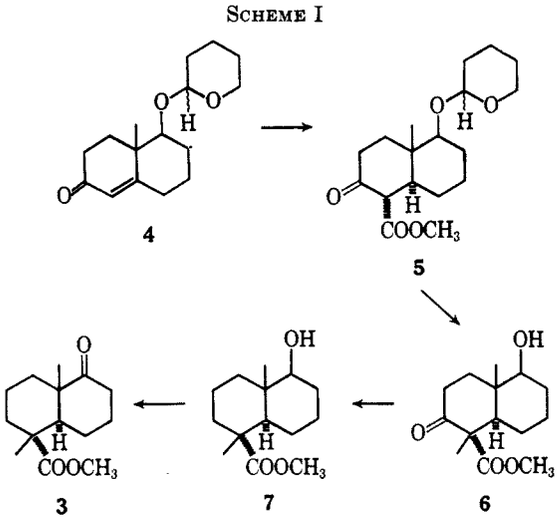


2, R = H
37, R = CH_3

The challenge in synthesis of a suitable bicyclic AB intermediate, for example, keto ester **3**, is primarily stereochemical. Introduction of the methyl and carboxyl groups at C_4 with the desired orientation and establishment of a *trans* ring fusion are central to such an endeavor, as indeed they are to any synthesis of **1** or **2**.

An efficient solution to these problems is represented by **4** → **5** → **6** → **7** → **3** as shown in Scheme I. If the

SCHEME I



readily accessible **4**[10] were to be reduced with lithium in ammonia, and if the resulting enolate anion could be carboxylated according to the method developed by Stork,[11] one step could serve both to form the desired *trans* ring fusion[12] and to introduce, after esterification, the carbomethoxyl function at C_4. Methylation of β-keto ester **5** could lead to compounds useful for the synthesis of either the dehydroabietic acid (**1**) or podocarpic acid (**2**) type, but would be expected[4a] to result in stereoselective formation of **6**. With the desired stereochemistry thus established, the reactions leading from **6** to **3** would be expected to be routine.

The realization of this proposed synthesis of **3** and the conversion of **3** to methyl *dl*-deisopropyldehydro-

(1) Portions of this work were presented at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstract K17.

(2) (a) Alfred P. Sloan Foundation Research Fellow; (b) Goodyear Foundation Fellow, 1963–1964; (c) Dartmouth College Senior Fellow, 1961–1962.

(3) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 259 (1956); **84**, 284 (1962).

(4) *Cf.* (a) E. Wenkert, *et al.*, *ibid.*, **86**, 2038 (1964); (b) W. L. Meyer and K. K. Maheshwari, *Tetrahedron Letters*, 2175 (1964).

(5) R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **27**, 703 (1962); **31**, 2543 (1966).

(6) (a) U. R. Ghatak, D. K. Datta, and S. C. Ray, *J. Am. Chem. Soc.*, **82**, 1728 (1960); (b) F. E. King, T. J. King, and J. G. Topliss, *Chem. Ind.* (London), 113 (1956); (c) R. D. Haworth and B. P. Moore, *J. Chem. Soc.*, 633 (1946); (d) B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **22**, 165 (1945).

(7) T. A. Spencer, R. J. Friary, W. W. Schmiegel, J. F. Simeone, and D. S. Watt, *J. Org. Chem.*, **33**, 719 (1968).

(8) (a) T. A. Spencer, T. D. Weaver, M. A. Schwartz, W. J. Greco, Jr., and J. L. Smith, *Chem. Ind.* (London), 577 (1964); (b) T. A. Spencer, R. M. Villarica, D. L. Storm, T. D. Weaver, R. J. Friary, J. Posler, and P. R. Shafer, *J. Am. Chem. Soc.*, **89**, 5497 (1967).

(9) (a) W. L. Meyer and C. W. Sigel, *Tetrahedron Letters*, 2485 (1967); (b) A. C. Ghosh, K. Mori, A. C. Rieke, S. K. Roy, and D. M. S. Wheeler, *J. Org. Chem.*, **32**, 722 (1967), and previous papers in this series; (c) C. T. Mathew, G. C. Banerjee, and P. C. Dutta, *ibid.*, **30**, 2754 (1965).

(10) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 3441 (1957).

(11) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965). The procedure involving treatment with lithium in ammonia, followed by carbonation, acidification, and esterification with diazomethane is referred to as "reductive carbomethoxylation" in this and the following paper.

(12) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).

abietate (**23**) by two routes are delineated in this paper. In addition, nmr data are tabulated which show that the shielding effect of the axial carbomethoxyl group of compounds with the podocarpic acid (**2**) stereochemistry can be used to distinguish readily between these substances and their isomers with the dehydroabietic acid (**1**) stereochemistry.

Synthesis of Intermediate 3.—The Stork reductive carbomethoxylation procedure[11] was first applied to alcohol **9**, which was prepared as described by Robinson annelation[13] of methyldihydroresorcinol to give **8**,[14] followed by selective sodium borohydride reduction of the unconjugated carbonyl group.[15] Treatment of **9** sequentially with lithium in ammonia, carbon dioxide, and, after acidification, diazomethane afforded two monocarbomethoxylated products.

One of these, mp 93–94°, obtained in 12% yield, exhibited spectral properties, *e.g.*, λ_{max}^{EtOH} 255 mμ (ε 8500), characteristic of an enolized β-keto ester. The other, mp 138–140°, was nonenolic. Since *trans* fused 4-carboalkoxy-3-ketones are nonenolic,[16] the 138–140° substance was assigned the desired structure **10**, and the enolic 93–94° β-keto ester was assigned structure **11**. Chemical confirmation of these assignments was obtained by conversion of **12**, previously prepared in our laboratory,[17] to **10** upon treatment with sodium methoxide in methanol. Consistent with its assigned structure, **11** was hydrolyzed and decarboxylated to the known hydroxy ketone **13**.[18] The latter substance was also the third major product isolable from the reductive carbomethoxylations of **9**.

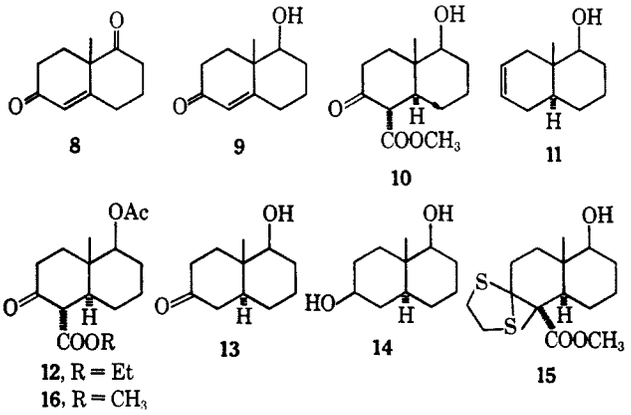
The considerable amount of C_2 carbomethoxylation product obtained indicated that equilibration of the initially generated C_4 enolate anion to the more stable[19] C_2 enolate anion had occurred, apparently facilitated by the presence of the free hydroxyl group at C_9. It is noteworthy that such equilibration was not observed in the reductive *methylation* of 4-methyltestosterone, despite the presence of the free hydroxyl group at C_{17}.[11]

When the tetrahydropyranyl ether **4**[10] derived from **9** was used in the same reductive carbomethoxylation procedure, the yield of **10**, after removal of the protecting group by acid-catalyzed methanolysis, increased to 30%. There was also isolated **13** (11%), and a small amount of diol **14**,[15,18] but none of the enolic 2-carbomethoxy compound **11**, and it was clear that protection of the hydroxyl group was important.

Considerable effort was expended trying to improve the yield in this key step. The best procedure found included separation of neutral (uncarboxylated) material before acidification prior to esterification. This modification permitted direct isolation of tetrahydropyranyl ether **5** in up to 68% yield of material, mp 102–122°, suitable for use in the next step, as a mixture of the two tetrahydropyranyl ethers **5a**, mp 130–131.5°, and **5b**, mp 117.5–118.5°, epimeric at the asymmetric center of the protecting group.

Methylation of **5**, using sodium hydride, *t*-butyl alcohol, and methyl iodide in dimethoxyethane, followed by methanolysis of the tetrahydropyranyl ether protecting group, did afford selectively one isomer, mp 122–124°, in up to 62% yield.[20] This compound was identified as **6**, the product of stereoelectronically controlled axial methylation,[4a] by the chemical shift of the angular methyl peak in its nmr spectrum (as discussed below), and eventually by its conversion to *dl*-**23**. There was also formed approximately one-tenth as much of the isomeric C_4 α-methylated product. Isolation and identification of this substance and other products from the methylation of **5** are described in the succeeding paper.[7]

As expected, conversion of **6** to **3** proceeded smoothly. Preparation of ethylene dithioketal **15**, mp 149–150.5°, and Raney nickel reduction afforded 90% of hydroxy ester **7**, mp 95–96°.[17b] Oxidation of **7** with chromic acid yielded 97% of **3**, mp 82–83°. This desired intermediate was thus available in 37% over-all yield from **4**.



Initially, the C_4 methylation had been conducted with acetate **16**, mp 128.5–131°, derived from **10**, as in the case of the corresponding ethyl ester **12**.[17b] The entire crude methylation product mixture, assumed to contain largely **17**, was carried through the dithioketal preparation and Raney nickel desulfurization. The resulting material, presumably principally **18**, was refluxed with 4 *N* sodium hydroxide solution for 36 hr, affording hydroxy acid **19**[17b] in 49% over-all yield from **16**. Oxidation of **19** afforded keto acid **20**, mp 183–185°, and conversion of **20** to **3** was effected with diazomethane.

The saponification which afforded **19** also yielded a smaller amount of neutral material. The well-known[21] resistance to hydrolysis of axial C_4 esters

(13) This term for the well-known ring extension reaction continues to receive various spellings, *e.g.*, "annealation," E. E. Smissman, T. L. Lemke, and O. Kristiansen, *J. Am. Chem. Soc.*, **88**, 334 (1966); "annellation," ref 4a; and "annulation," E. J. Corey and S. Nozoe, *J. Am. Chem. Soc.*, **87**, 5728 (1965). Although "annulation" appears to be the correct form (*cf.* "Webster's Third New International Dictionary," Unabridged, G. & C. Merriam Co., Springfield, Mass., 1961, p 88), "annelation" is the spelling of prior and most common usage; *e.g.*, W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960).

(14) S. Ramachandran and M. S. Newman, *Org. Syn.*, **41**, 38 (1961).

(15) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960); *cf.* ref 10.

(16) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959).

(17) (a) See ref 8a; (b) T. A. Spencer, T. D. Weaver, and W. J. Greco, Jr., *J. Org. Chem.*, **30**, 3333 (1965).

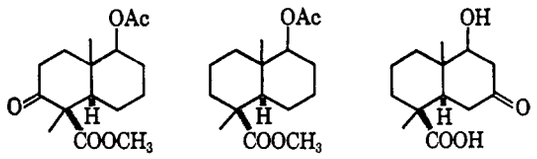
(18) A. J. Birch, E. Pride, and H. Smith, *J. Chem. Soc.*, 4688 (1958).

(19) R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957).

(20) As we have noted before (ref 17b), methylation of these nonenolic β-keto esters is a much less facile process than methylation of an "ordinary" enolic β-keto ester. A variety of conditions was tried, including those used by Wenkert (ref 4a), and good results (*ca.* 50% of **6** or better) could be obtained, although not always, with several different procedures. No evidence was obtained that different conditions gave different ratios of β- to α-methylation.

(21) See, *e.g.*, (a) C. L. Graham and F. J. McQuillin, *J. Chem. Soc.*, 4634 (1963); (b) F. E. King, D. H. Godson, and T. J. King, *ibid.*, 1117 (1955); (c) W. P. Campbell and D. Todd, *J. Am. Chem. Soc.*, **64**, 928 (1942).

of the podocarpic acid (2) type suggested that any of the isomeric methylation product **21** which had been formed would, after having been converted to **22**, now be found in this neutral material. Chromatography of the saponification-resistant residue did indeed afford hydroxy ester **22**, mp 73–74°. Further conversions of **22** are described in the succeeding paper.[7]



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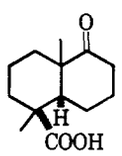

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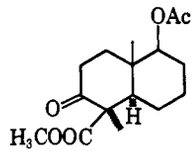

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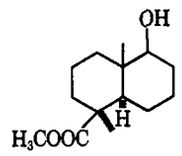

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Distinction between hydroxy esters **22** and **7** could be made not only on the basis of their relative susceptibility to hydrolysis, but also by reference to their nmr spectra. The singlet for the angular methyl group of **22** appears at δ 0.58 ppm, shielded by 0.25 ppm relative to the analogous resonance for **7** at 0.83 ppm. This 1,3-diaxial shielding by a carbonyl group has been noted by Wenkert and coworkers.[22] It is a very effective method of distinguishing between C_4 stereoisomers, as documented in Table I. It is noteworthy that a C_3 carbonyl group tends to reduce the magnitude of this shielding. This is reasonable, since the presumed twisting of ring A to some extent to relieve the interaction between the 4β and 9β substituents is easier in a cyclohexanone ring.

Syntheses of Methyl *dl*-Deisopropyldehydroabietate (23).—The choice of the deisopropyldehydroabietic acid (**24**) system as our first tricyclic synthetic goal was dictated by a preparation of *dl*-**24** which had just been published by Mathew and Dutta.[23] Their synthesis[24] proceeded *via* an intermediate keto acid, mp 141°, claimed to have structure **20**, but different from our keto acid **20**, mp 183–185°.[25] In order to clarify the situation, the reaction sequence used by Dutta[23] for synthesis of *dl*-**24** was applied to our 183–185° material. Accordingly, keto ester **3** was subjected to the Mannich condensation, which required vigorous conditions, *e.g.*, cyclohexanol as solvent at 110°, in order to afford **25**. The crude Mannich base was treated with the sodium salt of methyl acetoacetate to produce tricyclic α,β-unsaturated ketone **26**, mp 90.5–91° (21% over-all yield from **3**), which again differed from a compound, mp 101°, which had been assigned this structure.[23] The 90.5–91° enone was reduced with sodium borohydride to **27**, which, without purification, was heated with palladium on carbon at 235° for 1 hr to afford methyl *dl*-deisopropyldehydroabietate (**23**), mp 112.5–113.5°. This material was identical in all respects with *dl*-**23** prepared by Dutta[23] from his 101° enone and had a solution infrared spectrum identical with that of *d*-**23** prepared by Wenkert.[26]

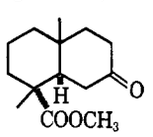
It was therefore clear that isolation of *dl*-**23** from the above sequence was useless as proof of the structures of precursory compounds. Dutta[9c] subsequently showed that the harsh treatment with palladium on carbon induced ani nteresting isomerization of the A,B ring fusion from *cis* to *trans*, and that his substances of mp 141 and 101° were really **28** and **29**. Further confirmation of the stereochem-

TABLE I

CHEMICAL SHIFTS OF THE ANGULAR METHYL GROUP IN PAIRS OF COMPOUNDS DIFFERING ONLY IN RELATIVE CONFIGURATIONS OF $-COOCH_3$ AND $-CH_3$ AT C_4

Compd with C_4 $-COOCH_3$ α	Chemical shift δ, ppm rel to TMS	Compd with C_4 $-COOCH_3$ β	Chemical shift δ, ppm rel to TMS
A3[a]	1.13 (CCl_4)[b]	B2[c]	0.91 (CCl_4)
A7	0.83 (CS_2)	A22	0.58[d] (CS_2)
A6	1.04 (CS_2–$CDCl_3$)	B12	0.92 (CCl_4)
A26	1.14 (CCl_4)	B37	0.94 (CCl_4)
A32	1.10 (CCl_4)	B39	0.86 ($CDCl_3$)
A31	1.18 (CCl_4)	B38	1.02 ($CDCl_3$)
B28	1.35 ($CDCl_3$)	B27	1.26 ($CDCl_3$)
A33	1.20 ($CDCl_3$)	A37	1.02 ($CDCl_3$)
A38[e]	1.05 (CS_2)	A39[e]	0.89 (CS_2)

[a] The letter A means that the number which follows refers to the compound designated by that number in this paper. [b] The solvent in which each nmr spectrum was determined is listed parenthetically after the δ value. [c] The letter B means that the number which follows refers to the compound designated by that number in the succeeding paper (ref 7). [d] The corresponding ethyl ester (ref 17b) has $\delta_{TMS}^{CCl_4}$ 0.68 ppm for the angular methyl group. [e] See T. A. Spencer, M. A. Schwartz, and K. B. Sharpless, *J. Org. Chem.*, **29**, 782 (1964), for preparation of **39** and the origin of **38**, which was subsequently isolated by us as



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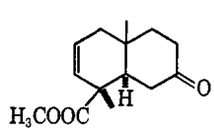

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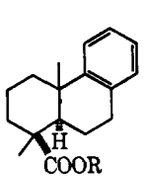
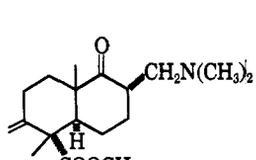
an impure solid, mp 77–84°. Pure **38**, mp 84–85.5°, has recently been reported (ref 9a).



23, R = CH_3
24, R = H



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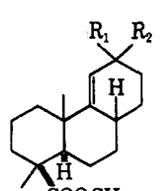
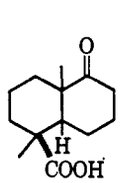


26, $R_1 = R_2 = O$
27, $R_1 = R_2$ = OH,H



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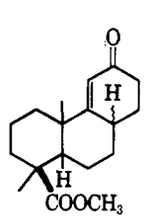

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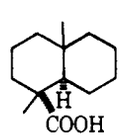

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(22) E. Wenkert, *et al.*, *J. Org. Chem.*, **30**, 713 (1965). We thank Professor W. L. Meyer for calling to our attention the Ph.D. dissertation of R. W. J. Carney, Iowa State University, 1962, in which this phenomenon is discussed, prior to publication of the Wenkert article.

(23) C. T. Mathew and P. C. Dutta, *Proc. Chem. Soc.*, 135 (1963).

(24) For other syntheses of *dl*-**24**, see (a) ref 4a; (b) ref 6a; (c) S. N. Mahapatra and R. M. Dodson, *Chem. Ind.* (London), 253 (1963); and (d) J. A. Barltrop and A. C. Day, *Tetrahedron*, **14**, 310 (1961).

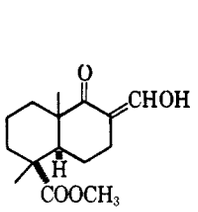
(25) Comparison of infrared spectra using a sample kindly furnished by Dr. Dutta confirmed that the compounds were not the same.

(26) See ref 4a. We thank Dr. Wenkert for kindly furnishing a sample of *d*-**23**.

istry of our keto acid **20** was obtained by its Wolff–Kishner reduction to acid **30**, mp 105–107°, which was found to be identical with a known sample of **30**.[27]

Finally, we chose to complete a synthesis of *dl*-**23** using mild conditions which would not be suspect of causing changes in stereochemistry. A more efficient method of preparing enone **26** was developed which consisted in conversion of **3** to its hydroxymethylene derivative **31**, mp 57.5–59.5° (91% yield), followed by Robinson annelation with 1-diethylaminobutanone-3 methiodide. Treatment of initially isolated oily Michael adduct **32** with sodium methoxide in methanol at reflux was required to effect formation of **26**, which was obtained in 54% over-all yield from **3** by this route. The C_8 hydrogen of **32**, like those of **25** and **26**, is assigned the presumably more stable β configuration, as discussed in the succeeding paper.[7]

Oxidation of **26** to the phenol **33** was readily accomplished in 40% yield with N-bromosuccinimide. Deoxygenation of **33** to *dl*-**23** was conducted by the Kenner method,[28] which required, in this instance, not only preparation of **34** with diethyl phosphite and reduction of **34** with lithium in ammonia, but also oxidation of the predominant resulting product **35** to the acid (*dl*-**24**) and reesterification.[29] This sequence was conducted without characterization of intermediate substances, and afforded *dl*-**23** which was identical with the material obtained by palladium-on-carbon aromatization.



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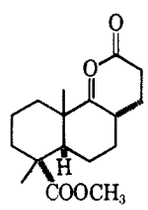

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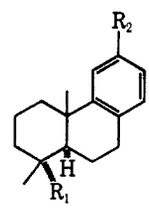

33, R_1 = $COOCH_3$; R_2 = OH
34, R_1 = $COOCH_3$; R_2 = $OPOEt_2$
35, R_1 = CH_2OH; R_2 = H

Experimental Section[30]

10β-Methyl-9β-hydroxy-Δ^{4,5}-octalone-3 (**9**).—10-Methyl-Δ^{4,5}-octalin-3,9-dione (**8**), prepared in the usual manner,[14] was selectively reduced to **9** (typical bp 130° at 0.2 mm) in 80–85% yield according to the procedure of Boyce and Whitehurst,[15] except that the 1 equiv of sodium borohydride used was not purified.[17b]

Reductive Carbomethoxylation of 9.—To a solution of 0.70 g (0.10 g-atom) of lithium in 250 ml of liquid ammonia (not redistilled) was added dropwise over 5 min a solution of 4.99 g (0.0277 mole) of hydroxyenone **9**, bp 131–132° (0.2 mm), which had been dried by evaporation from it of 21 ml of benzene, in 80 ml of anhydrous ether. As soon as the addition was completed, the ammonia was evaporated (warm water bath) and replaced with anhydrous ether which was refluxed to remove the last traces of ammonia. Into the resulting whitish suspension in *ca.* 250 ml of ether was bubbled carbon dioxide gas through a Drierite drying tube and a gas dispersion tube for 2.75 hr; ether was added to keep the volume constant during this time. The mixture was cooled to −15° in an ice–salt bath and slowly acidified with cold 1 *M* hydrochloric acid saturated with sodium chloride (some effervescence). The layers were quickly separated, and the ether layer was washed with cold brine, dried rapidly over sodium sulfate, and poured into a solution of excess diazomethane in ether at 0°. Then the original aqueous layer was again extracted with ether, and this second ether extract was also dried and added to the ethereal diazomethane. The excess diazomethane (the solution was still bright yellow) was decomposed with 1 *M* hydrochloric acid. The mixture was washed and dried as above, and evaporated to afford 4.5 g of oil which was chromatographed on 160 g of acid-washed alumina. With 2:3 ether–hexane there was eluted 1.06 g of material which was crystallized from ether–hexane to afford 0.803 g (12%) of **2-carbomethoxy-9β-hydroxy-10β-methyl-*trans*-decalone-3** (**11**), mp 89–95°. Further recrystallization from ether afforded pure **11**: mp 93–94°; λ_{max}^{EtOH} 255 mμ (ε 8500); $\lambda_{max}^{CHCl_3}$ 2.9, 6.01, and 6.17 μ.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.32; H, 8.18.

With 9:1 ether–acetone there was eluted 2.19 g of material which was crystallized from ether to afford 1.20 g (18%) of **4α-carbomethoxy-9β-hydroxy-10β-methyl-*trans*-decalone-3** (**10**), mp 105–130°. Further recrystallization from ether afforded pure **10**: mp 134–136° (samples of **10** often melted higher, *e.g.*, 138–140°); $\lambda_{max}^{CHCl_3}$ 2.9, 5.74, and 5.84 μ; $\delta_{TMS}^{CS_2-CDCl_3}$ 1.02 (3 H, s, H_3C—C<) and 3.64 (3 H, s, H_3COOC–) ppm.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.12; H, 8.23.

Conversion of 11 to 13.—To a solution of 0.835 g of **11**, mp 89–95°, in 10 ml of methanol was added 30 ml of 3 *M* sodium hydroxide solution, and the mixture was refluxed for 18 hr. The cloudy, yellow mixture was then acidified with hydrochloric acid (effervescence) and extracted with chloroform. Standard work-up of the chloroform layer afforded 0.810 g of oil, from which was crystallized 0.091 g of **13**, mp 69–71° (lit.[18] mp 68–70°), which was identified by comparison of its infrared spectrum with that of an authentic sample.

Conversion of 12 to 10.—To a solution of 0.44 g of sodium in 25 ml of methanol was added 0.081 g of **12**,[17b] mp 96–99°. The mixture was allowed to stand at room temperature for 15 min, diluted with water and chloroform, and acidified with 1 *M* hydrochloric acid. The chloroform layer was separated, dried, filtered, and evaporated to afford 0.053 g of yellow oil which crystallized upon seeding to give 0.034 g of **10**, mp 115–125°. After recrystallization from ether to mp 131–133°, the material was identified by infrared spectrum and a mixture melting point determination with authentic **10**.

10β-Methyl-9β-tetrahydropyranyloxy-Δ^{4,5}-octalone-3 (**4**).—The tetrahydropyranyl ether **4**[10] was best prepared by bubbling hydrogen chloride into a solution of **9** (195 g, 1.08 moles) and dihydropyran (137 g, 1.63 moles) in methylene chloride (600 ml) until the mixture grew warm. After the resulting solution had been allowed to stand for 3 hr at room temperature it was diluted with 400 ml of methylene chloride, washed with 400 ml of saturated sodium bicarbonate solution and two 400-ml portions of brine, filtered, and evaporated (high vacuum at 50°) to give 299 g of oily product, λ_{max} 5.96 and 6.16 μ. This material crystallized when mixed with 75 ml of ether. The solid was collected and washed with two 250-ml portions of ether on a sintered glass funnel. A total of 249.0 g (86%) of white crystalline **4** was thus obtained, mp 55–60° (lit.[10] mp 68–74°).

Reductive Carbomethoxylation of 4. Method A. Isolation of 10.—To a solution of 0.55 g (0.078 g-atom) of lithium in 200 ml of liquid ammonia (not redistilled) was added dropwise over 5 min a solution of 6.9 g (0.026 mole) of **4**, mp 57–60°, in 80 ml of anhydrous ether. The procedure followed was exactly that used in the reductive carbomethoxylation of **9** except that carbon dioxide was bubbled in for 3.75 hr. There was obtained 7.0 g of viscous oil which was dissolved in 30 ml of methanol containing a pinch of *p*-toluenesulfonic acid monohydrate and

(27) See ref 21a. We thank Dr. McQuillin for kindly furnishing a sample of **30**.

(28) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

(29) E. Wenkert and B. G. Jackson [*J. Am. Chem. Soc.*, **80**, 217 (1958)] effected direct deoxygenation of methyl podocarpate (*d*-**37**) to methyl desoxypodocarpate in 54% yield by the Kenner method and also showed that equatorial carbomethoxyl groups, such as that of **34**, are reduced by this procedure.

(30) Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were taken in an open capillary or on a hot stage; those of analytical samples are corrected. Boiling points are uncorrected. Ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb Spectronic 505 spectrometer. Infrared spectra were determined on either a Perkin-Elmer Model 21 or Model 137 recording spectrophotometer. Nmr spectra were determined either on a Varian A-60 spectrometer located at the University of Massachusetts, or on a Varian DA-60-IL spectrometer at Dartmouth. Brine refers to saturated aqueous sodium chloride solution.

this mixture was refluxed for 45 min. Solid potassium carbonate was added and the mixture was diluted with ether, washed with brine, dried over sodium sulfate, filtered, and evaporated to afford 5.6 g of orange oil, from which 1.320 g of **10**, mp 120–134°, crystallized upon trituration with ether. Chromatography of the residues on acid-washed alumina afforded 0.538 g more of **10**, mp 130–140°, for a total yield of 1.858 g (30%). There was also eluted from the column just before **10** 0.507 g of hydroxy ketone **13**, mp 70–72° (lit.[18] mp 68–70°).

In a different run there was also isolated a 7% yield of **10β-methyl-*trans*-decalin-3β,9β-diol (14)**, mp 136–137° (lit.[18] mp 132–133°; lit.[15] mp 133°).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.89; H, 10.87.

4α-Carbomethoxy-9β-acetoxy-10β-methyl-*trans*-decalone-3 (16).—A solution of 17.7 g (0.0738 mole) of hydroxy keto ester **10**, mp 121–140°, in a mixture of 100 ml of dry pyridine and 70 ml of acetic anhydride was allowed to stand for 15 hr at room temperature. The solution was then diluted with 700 ml of ether and was washed successively with two 200-ml portions of water, two 200-ml portions of 1 *M* hydrochloric acid, 60 ml of 10% sodium bicarbonate solution, and brine. The ether layer was dried, filtered, and evaporated. The solid residue was dried under high vacuum at 70° for 1 hr to give 19.7 g (95%) of **16**, mp 110–126°. Recrystallization from acetone–hexane afforded 16.5 g of **16**: mp 128.5–131°; λ_{max}^{KBr} 5.78 μ (broad).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.94; H, 8.00.

4β,10β-Dimethyl-4α-carboxy-9β-hydroxy-*trans*-decalin (19) from 16.—By a procedure analogous to that used in the conversion of **12** to **19**,[17b] 3.57 g (0.0126 mole) of **16**, mp 125–128°, was methylated to afford 2.95 g of oily product.

According to a procedure of Fieser,[31] this product was dissolved in 10 ml of ethanedithiol and was treated with 2.2 ml of freshly distilled boron trifluoride etherate, bp 125–126°. After standing at room temperature for 7 hr, the solution was diluted with 75 ml of ether and was washed with four 30-ml portions of 1 *N* sodium hydroxide solution and 10 ml of brine. The ether solution was dried over sodium sulfate, filtered, and evaporated. The residue was dried at room temperature under high vacuum for 15 hr. The residue was rinsed thoroughly with 1 *M* sodium hydroxide solution, then with water, and was dried under high vacuum at room temperature to give 2.57 g of semisolid product.

The 2.57 g of impure dithioketal prepared above was dissolved in 300 ml of absolute ethanol and treated with 30 g of Raney nickel, prepared as described below. The mixture was refluxed for 6 hr and was filtered, while still hot, through filter-cel. The catalyst was rinsed well with hot ethanol. Evaporation of the ethanol afforded 2.0 g of oil, to which was added 100 ml of 4 *M* sodium hydroxide solution containing 15 ml of ethanol. The mixture was stirred and heated at reflux for 36 hr. The ethanol was removed by distillation and the alkaline solution was extracted with three 50-ml portions of ether. The aqueous layer was poured slowly into 35 ml of stirred, ice-cold 6 *M* hydrochloric acid. The precipitate which formed was collected by filtration and was dried to give 1.39 g (49% from **16**) of hydroxy acid **19**, mp 195–207°.

Desulfurization of pure dithioketal **15**, mp 147–150° (*vide infra*), and hydrolysis, by the procedures just described, afforded 73% of **19**, mp 210–216°. This material was recrystallized from acetone–hexane to give **19**, mp 222–223° (lit.[17b] mp 216–218°).

4α,10β-Dimethyl-4β-carbomethoxy-9β-hydroxy-*trans*-decalin (22).—The ether extracts from the saponification reaction mixture for the preparation of hydroxy acid **19** were washed with brine and dried over magnesium sulfate. The ether was evaporated to give 0.301 g of oil, which was chromatographed, using an ether–hexane solvent system, on 10 g of Merck acid-washed alumina. There was obtained 0.146 g of solid material, which was recrystallized from hexane to give 0.130 g (4% from **16**) of hydroxy ester **22**, mp 70–73°. Five recrystallizations from hexane afforded pure **22**: mp 72.5–73.5°; $\lambda_{max}^{CHCl_3}$ 2.9 and 5.81 μ; $\delta_{TMS}^{CS_2}$ 0.58 (3 H, s, H_3C—C⩽), 1.09 (3 H, s, H_3C—C—$COOCH_3$), and 3.53 ppm (3 H, s, H_3COOC–).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.06; H, 10.15.

(31) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

4β,10β-Dimethyl-4α-carboxy-*trans*-decalone-9 (20).—According to a procedure of Fieser,[32] a well-stirred solution of 2.07 g (9.15×10^{-3} mole) of hydroxy acid **19**, mp 218.5–220°, in 75 ml of glacial acetic acid was treated gradually with a solution of 2.98 g of potassium chromate in 5.6 ml of water. The resulting suspension was allowed to stir for 30 hr, and then was filtered through filter-cel. The filtrate was heated to 40° under high vacuum to remove the acetic acid and water. The residue was dissolved in 50 ml of 4 *M* sodium hydroxide solution, and the alkaline solution was poured slowly, with stirring, into 60 ml of ice-cold 6 *M* hydrochloric acid. The resulting precipitate was collected, rinsed with water, and dried to give 1.90 g (93%) of keto acid **20**, mp 179–184°. Recrystallization from acetone–hexane afforded 1.56 g, mp 183–187°. The analytical sample had mp 183–184.5° and λ_{max}^{KBr} 5.84 and 5.88 μ.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.76; H, 9.03.

Conversion of 20 to 4β,10β-Dimethyl-4α-carboxy-*trans*-decalin (30).—According to the Huang-Minlon procedure,[33] a mixture of 0.150 g (6.70×10^{-4} mole) of **20**, mp 184–186°, 0.20 g of potassium hydroxide, 0.24 ml of 85% hydrazine hydrate, and 3 ml of diethylene glycol was heated for 1 hr at a bath temperature of 115°. Another 0.1 ml of 85% hydrazine hydrate was added and the mixture was heated for another hour at 115°. Then the temperature was raised gradually to 190° and maintained at 190–195° for 4.5 hr under a nitrogen atmosphere. The mixture was poured into cold 6 *M* hydrochloric acid to afford 0.114 g of gummy precipitate which was chromatographed on silicic acid to afford 0.019 g of **30**, plus some unchanged **20**. Recrystallization of this **30** from heptane gave material with mp 105–107.5. This was identified by comparison with a sample of **30**, mp 102–106°, prepared by the method of McQuillin.[21a]

Reductive Carbomethoxylation of 4. Method B. Isolation of 5.—To a 2-l., three-necked flask equipped with a mechanical stirrer and a reflux condenser was added 800 ml of liquid ammonia. To this was added 2.8 g (0.4 g-atom) of lithium wire (47.5 cm) which had been cut into 2- to 3-in. lengths, quickly rinsed with hexane to remove mineral oil, and dried quickly with a towel. The blue mixture was stirred for 10 min and then a solution of 26.4 g (0.1 mole) of **4** in 300 ml of anhydrous ether was added rapidly (4–5 min) from a pressure-equalizing dropping funnel while very vigorous stirring was maintained. As soon as the addition was complete, a steam bath was applied to the flask and the ammonia was evaporated as quickly as possible through the condenser (15–20 min). When the coating of ice around the flask melted, 500 ml of anhydrous ether was added and a Drierite drying tube was attached to the condenser. The mixture was refluxed for 15 min to drive off any residual ammonia and was then cooled to Dry Ice–acetone temperature.

During this cooling period a piece of Dry Ice was chipped on all sides to about 200 g, and then pulverized inside a cloth bag inside a large dry plastic bag. This fine powder was then added to the cold reaction mixture through a powder funnel which was also encased in a larger plastic bag. Care was taken to exclude moisture. The mixture was removed from the Dry Ice–acetone bath and allowed to stir for 30 min, and then for 30 min more in a room-temperature water bath. Then the mixture was recooled in a Dry Ice–acetone bath and 500 g of powdered Dry Ice was added, followed by 500 ml of cold distilled water. The contents of the flask were transferred to a separatory funnel, and the reaction flask was rinsed with cold water which was added to the funnel. The ether layer was separated and set aside; subsequent evaporation of this layer yielded 7.5 g of oil.

The aqueous layer was mixed with 500 ml of cold ether, cooled with stirring in a Dry Ice–acetone bath, and carefully acidified with a mixture of 50 ml of concentrated hydrochloric acid and 50 g of ice. The aqueous layer turned cloudy and then clear as the freed acid dissolved in the ether layer. The layers were separated, and the water layer was extracted with two 250-ml portions of cold ether. The combined, very cold, ether layers were washed with two 250-ml portions of very cold brine, and then allowed to filter into an ethereal solution of diazomethane. After 30 min, just enough acetic acid was added to dispel *partially* the yellow diazomethane color, and the solvent was evaporated at aspirator pressure. Upon

(32) L. F. Fieser and S. Rajagopalan, *ibid.*, **72**, 5530 (1950).

(33) Huang-Minlon, *ibid.*, **71**, 3301 (1949).

trituration of the residue with 100 ml of ether, followed by evaporation, there was obtained 21.8 g (68%) of **5** as a creamy solid, mp 102–122°. This product was of sufficiently good quality for use in the next step. Recrystallization from ether often effected separation of **5** into two compounds whose behavior and spectra indicated that they were epimers in the tetrahydropyranyl ether side chain. Typically, 22.5 g of **5** yielded 8.5 g of **5a**, mp 118–125°, and 8.5 g of **5b**, mp 103–108°.

Recrystallization of **5a** from ether gave an analytical sample: mp 130–131.5°; λ_{max}^{KBr} 5.72 and 5.82 μ; $\delta_{TMS}^{CS_2-CHCl_3}$ 1.06 (3 H, s, H_3C—C<) and 3.63 ppm (3 H, s, H_3COOC–).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.50; H, 8.61.

Recrystallization of **5b** from ether gave an analytical sample: mp 117–118.5°; λ_{max}^{KBr} 5.72 and 5.82 μ (different in the 7–12-μ region from **5a**); $\delta_{TMS}^{CS_2-CHCl_3}$ 1.03 (3 H, s, H_3C—C<) and 3.58 ppm (3 H, s, H_3COOC–).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.49; H, 8.63.

Both pure **5a** and pure **5b** were unchanged by potassium carbonate in methanol. Both gave quantitative yields of **10** upon acid-catalyzed methanolysis. Both gave approximately the same yield of **6** when separately methylated.

4β,10β-Dimethyl-4α-carbomethoxy-9β-hydroxy-*trans*-decalone-3 (6).—To a solution of 0.999 g (3.06×10^{-3} mole) of **5**, mp 97–119°, in 50 ml of dimethoxyethane, which had been distilled from sodium and then redistilled (bp 83–84°) from lithium aluminum hydride directly into the reaction flask, was added 0.163 g (4.2×10^{-3} mole) of sodium hydride mineral oil dispersion (Metal Hydrides, Inc., 62.4% sodium hydride) under a nitrogen atmosphere. Eight drops of dried *t*-butyl alcohol were added and the mixture was stirred for 12 min until evolution of gas had ceased. Over a 5-min period 5 ml of freshly distilled methyl iodide was added dropwise and the resulting mixture was refluxed for 3.5 hr. Then 15 ml of water was added, and the mixture was evaporated. The residue was dissolved in 150 ml of ether, washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 1.06 g of oil. This oil was dissolved in 85 ml of methanol containing a pinch of *p*-toluenesulfonic acid monohydrate and the mixture was allowed to stand at room temperature for an hour, boiled to a volume of 25 ml, and evaporated. The residue was partitioned between ether and brine. The ether layer was dried, filtered, and evaporated to afford 0.888 g of oil which crystallized from ether to give 0.484 g (62%) of **6**, mp 110–116°. Recrystallization from ether–hexane afforded an analytical sample: mp 122–124°; λ_{max}^{KBr} 2.81, 5.72, and 5.90 μ; $\delta_{TMS}^{CS_2-CDCl_3}$ 1.04 (3 H, s, H_3C—C<), 1.29 (3 H, s, H_3C—C—$COOCH_3$), and 3.64 ppm (3 H, s, H_3COOC–).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.04; H, 8.60.

Isolation and identification of the substances present in the methylation residues are described in the following paper.[7]

4β,10β-Dimethyl-4α-carbomethoxy-9β-hydroxy-*trans*-decalin (7) from 6.—A solution of 11.3 g (4.45×10^{-2} mole) of **6**, mp 114–118°, in 40 ml of ethanedithiol (Aldrich, as supplied), prepared by heating on a steam bath, was cooled and treated with 8 ml of freshly distilled boron trifluoride etherate. The resulting purple mixture was allowed to stand at room temperature for 6 hr and then was poured slowly into 500 ml of vigorously stirred 2 *M* sodium hydroxide solution which was cooled in an ice–ethanol bath. After 15 min of additional stirring the precipitate which had formed was collected by filtration, washed with four 100-ml portions of water, and dried at aspirator pressure on a steam bath for 6 hr to afford 16 g of white gummy solid.

Pure dithioketal **15** could be isolated from such products by washing with ether to give solid, mp 134–142°, followed by recrystallization from acetone–hexane to give an analytical sample: mp 149–150.5°; λ_{max}^{KBr} 2.99 and 5.75 μ; $\delta_{TMS}^{CS_2-CHCl_3}$ 0.91 (3 H, s, H_3C—C<), 1.39 (3 H, s, >C(CH_3)—$COOCH_3$), 2.14 (1 H, s, HO–), 3.07–3.16 (4 H, –SCH_2CH_2S–), and 3.60 ppm (3 H, s, H_3COOC–).

Anal. Calcd for $C_{16}H_{26}O_3S_2$: C, 58.14; H, 7.93. Found: C, 57.96; H, 7.87.

The entire 16 g of product described above was reduced with Raney nickel catalyst prepared from 1 lb of No. 2813 Raney Nickel Catalyst Powder (W. R. Grace & Co.) by the following modification of the procedure of Mozingo.[34] To a vigorously stirred (Hershberg) solution of 580 g of sodium hydroxide in 2100 ml of distilled water in a 4-l. beaker cooled in an ice–ethanol bath was added by spatula over a 50-min period 1 lb of the Raney nickel alloy at a rate such as to maintain a temperature of 50 ± 2°. Ethanol was squirted into the mixture as needed to prevent excessive foaming. At the end of the addition the mixture was gently stirred for 50 min. *Ca.* 1500 ml of water was added, the mixture was stirred and allowed to settle, and the supernatant liquid was decanted. The beaker was four-fifths filled with water, and the stirring, settling, decantation process was repeated. After this washing process was done five more times, 600 ml of absolute alcohol was added (heat evolved), the mixture was stirred for 5 min and allowed to settle, and the supernatant liquid was decanted. This process was repeated five times. The catalyst was kept in a bottle filled with absolute ethanol until it was used.

The 16 g of crude thioketal **15** was mixed with this Raney nickel catalyst in absolute ethanol (total volume 900 ml) and was stirred at room temperature for 25 hr. The mixture was then filtered and the catalyst was washed with seven 300-ml portions of acetone. The organic layers were reduced in volume, filtered through Super-Cel, and evaporated to give 13 g of oil which crystallized from hexane in two crops amounting to 9.58 g (90%) of hydroxy ester **7**, mp 93.5–96°. Pure **7** has mp 95–96°;[17b] $\delta_{TMS}^{CS_2}$ 0.83 (3 H, s, H_3C—C<), 1.09 (3 H, s, >C(CH_3)—$COOCH_3$), and 3.52 ppm (3 H, s, H_3COOC–).

4β,10β-Dimethyl-4α-carbomethoxy-*trans*-decalone-9 (3).—According to a procedure of Elks, Phillips, and Wall,[35] a solution of 50.0 g (0.208 mole) of hydroxy ester **7**, mp 95–97°, in 3000 ml of stirred, refluxing acetone was treated over a 5-min period with 730 ml of a solution of 49.0 g of potassium dichromate and 150 g of concentrated sulfuric acid diluted to 1000 ml with water. The reaction mixture was refluxed for 5 min, and then concentrated on a rotary evaporator over a 45-min period to a volume of 800 ml. This concentrate was extracted with three 500-ml portions of ether. The ethereal extracts were washed with 250 ml of brine containing 2 g of sodium thiosulfate and with 200 ml of brine, filtered by gravity through a dry filter paper, and evaporated to afford 50 g of product which crystallized in several crops from cold hexane to afford a total of 48.14 g (97%) of **3**, mp 74–82°. Recrystallization from pentane afforded an analytical sample: mp 82–83°; $\lambda_{max}^{CHCl_3}$ 5.80 and 5.84 μ; $\delta_{TMS}^{CCl_4}$ 1.13 (3 H, s, H_3C—C<), 1.21 (3 H, s, >C(CH_3)—$COOCH_3$), and 3.61 ppm (3 H, s, H_3COOC–).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.32. Found: C, 70.48; H, 9.37.

Keto ester **3** was also prepared by esterification of keto acid **20** with diazomethane in ether in the usual manner.

4β,10β-Dimethyl-4α-carbomethoxy-8-hydroxymethylene-*trans*-decalone-9 (31).—To a stirred solution of 4.78 g (2.01×10^{-2} mole) of keto ester **3**, mp 80–82°, in 45 ml of ethyl formate (freshly distilled), immersed in an ice–ethanol bath under a nitrogen atmosphere, was added 3.84 g of sodium hydride dispersion (Metal Hydrides, Inc., 62.4% sodium hydride) and then 0.75 ml of absolute methanol. The mixture was stirred in the cold until the precipitate became so thick that stirring was impeded, whereupon 10 ml of anhydrous ether was added and the mixture was stirred for 7 hr at room temperature. Ice was added and the basic aqueous mixture was extracted twice with ether to remove the sodium hydride dispersion mineral oil and any unreacted **3**. The combined ether layers were extracted with dilute base and the aqueous layers were combined and frozen in a Dry Ice–acetone bath. The frozen mixture was acidified with 9 *M* hydrochloric acid, and nitrogen was bubbled through the aqueous acidic liquid for 45 min, during which time crystals formed. The solid was collected by filtration, pulverized, and washed with water until the filtrate was not acidic to litmus paper. After drying *in vacuo* at 35° for *ca.* 2 hr, the product consisted of 4.83 g (91%) of **31**: mp 57.5–59.5°; λ_{max}^{EtOH} 282 mμ (ϵ 11,500); λ_{max}^{KBr} 5.78, 6.08, and 6.30 μ; $\delta_{TMS}^{CCl_4}$ 1.18 (3 H, s, H_3C—C<), 1.20 (>C(CH_3)—$COOCH_3$), 3.62 (3 H, s, H_3COOC–), 8.38 (1 H, d, J = 3.5 Hz, H—C(OH)= ⇌ H—C(=O)—), and 14.52 ppm (1 H, d, J = 3.5 Hz, HO–).

Analytical data were obtained on **4β,10β-dimethyl-4α-carbomethoxy-8-acetoxymethylene-*trans*-decalone-9** prepared from

(34) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

(35) J. Elks, G. H. Phillips, and W. F. Wall, *J. Chem. Soc.*, 4001 (1958).

31 with acetic anhydride and *p*-toluenesulfonic acid at reflux. The acetoxymethylene derivative was recrystallized from ether–hexane to mp 107.5–109.5°; λ_{max}^{EtOH} 252 mμ (ε 14,000); λ_{max}^{KBr} 5.63, 5.78, 5.88, and 6.14 μ; $\delta_{TMS}^{CCl_4}$ 1.07 (3 H, s, H_3C–C<), 1.21 (3 H, s, >C(CH_3)—$COOCH_3$), 2.18 (3 H, s, H_3CCOO–), 3.62 (3 H, s, H_3COOC–), and 7.78 ppm (1 H, apparent t, $HC(OAc)$=C).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.08; H, 7.76.

4β,10β-Dimethyl-4α-carbomethoxy-1,2,3,4,5α,6,7,8β,10,12,13,14-dodecahydrophenanthrone-12 (26).—To a solution of 4.83 g (1.81×10^{-2} mole) of hydroxymethylene ketone **31**, mp 57.5–59.5°, in 40 ml of anhydrous methanol cooled in an ice–ethanol bath under a nitrogen atmosphere was added a solution of 0.43 g (1.80×10^{-2} g-atom) of sodium in 20 ml of anhydrous methanol. To this cooled stirred mixture was added dropwise over 20 min a cold solution of 1-diethylaminobutanone-3-methiodide,[36] prepared from 5.75 g (4.0×10^{-2} mole) of 1-diethylaminobutanone-3 and 5.75 g (4.0×10^{-2} mole) of methyl iodide, in 17 ml of methanol. The resulting mixture was stirred at room temperature for 20 hr and then was reduced in volume on a rotary evaporator at room temperature, acidified with dilute hydrochloric acid, and extracted several times with ether. The ether extracts were washed with water and brine, dried, filtered, and evaporated to afford 5.14 g of an oil, which on the basis of its nmr spectrum [$\delta_{TMS}^{CCl_4}$ 1.10 (3 H, s, H_3C—C<), 1.20 (3 H, s, >C(CH_3)—$COOCH_3$), 2.04 (3 H, s, H_3CCO–), and 3.60 ppm (3 H, s, H_3COOC–)] was judged to be largely Michael adduct **32**.

This 5.14 g of product was dissolved in 60 ml of methanol containing 0.710 g of sodium under nitrogen. The mixture was stirred at room temperature overnight and then refluxed for 7 hr. The mixture was evaporated and the residue was extracted thoroughly with ether. The ether extracts were washed, dried, and evaporated in the usual manner to afford 4.42 g of oil from which crystallized 1.78 g of **26**, mp 82–90°. Chromatography of the residual oil on acid-washed alumina afforded an additional 1.38 g, mp 74–91°, bringing the total yield of crystalline **26** to 3.16 g (54%). Recrystallization from ether–pentane gave the analytical sample: mp 90.5–91°; λ_{max}^{EtOH} 239 mμ (ε 16,000); λ_{max}^{KBr} 5.77, 6.00, and 6.21 μ; $\delta_{TMS}^{CCl_4}$ 1.14 (3 H, s, H_3C—C<), 1.16 (3 H, s, >C(CH_3)—$COOCH_3$), 3.56 (3 H, s, H_3COOC–), and 5.63 ppm (1 H, d, J = 1.7 Hz, –C(H)=C<).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.52; H, 8.98.

Preparation of 26 *via* Mannich Reaction of 3.—To a solution of 1.25 g (5.25×10^{-3} mole) of keto ester **3**, mp 77–81°, in 3 ml of redistilled cyclohexanol, bp 161°, was added 0.450 g (5.52×10^{-3} mole) of recrystallized, dry dimethylamine hydrochloride. While the resulting suspension was stirred and heated at 110° under nitrogen, it was treated with 0.309 g of paraformaldehyde in five portions over a period of 75 min. The reaction mixture was then diluted with 90 ml of ether, and the ether solution was extracted with two 45-ml portions of water. The combined aqueous extracts were washed with four 75-ml portions of ether, and then were carefully saturated at 0° with potassium carbonate. The Mannich base then was taken up in 150 ml of ether. The ether solution was dried over magnesium sulfate, and the ether was evaporated to afford 0.723 g of semisolid product. After being washed with hexane a sample of **25** had mp 80–85°; λ_{max}^{KBr} 5.77 and 5.88 μ.

A solution of this 0.723 g of the Mannich base **25** in 15 ml of absolute methanol was added slowly to a well-stirred solution of the sodium salt of methyl acetoacetate, prepared by treating a solution of 0.113 g (4.90×10^{-3} g-atom) of sodium in 2.5 ml of absolute methanol with 0.53 ml (4.9×10^{-3} mole) of methyl acetoacetate, bp 168–169°.[37] The resulting mixture was refluxed in a dry nitrogen atmosphere for 7 hr and diluted with 50 ml of water, and the methanol was removed by distillation under reduced pressure. The product separated as a gum, which was taken up with two 50-ml portions of ether. The combined ether extracts were washed with brine and dried over magnesium sulfate. Evaporation of the ether left 0.704 g of pale yellow oil, which was chromatographed on 20 g of Merck acid-washed alumina. Elution with 1:1 ether–hexane afforded 0.320 g (21%) of **26**, mp 83–90°.

(36) The methiodide was prepared according to E. C. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937) from 1-diethylaminobutanone-3 prepared according to A. L. Wilds, R. M. Nowak, and K. E. McCaleb [*Org. Syn.*, **37**, 18 (1957)].

(37) Procedure of A. V. Logan, E. N. Marvell, R. Lapore, and D. C. Bush, *J. Am. Chem. Soc.*, **76**, 4127 (1954).

Methyl *dl*-Deisopropyldehydroabietate (23).—To a magnetically stirred solution of 0.100 g (3.45×10^{-4} mole) of **26**, mp 83–90°, in 10 ml of absolute methanol was added slowly a solution of 0.131 g of sodium borohydride in 15 ml of absolute methanol. After the mixture had been stirred for 30 min, more (0.131 g) sodium borohydride in 15 ml of absolute methanol was added. After 60 min more the mixture was diluted with 40 ml of water and most of the methanol was removed at reduced pressure. The mixture was extracted with ether, which was washed with brine, dried over magnesium sulfate, and evaporated to give 0.101 g of colorless, very viscous oil, λ_{max}^{KBr} 2.91, 5.77, and 6.04 μ.

A mixture of the above product and 0.10 g of 10% palladium on carbon was heated at 235° for 1 hr[9c] under an atmosphere of nitrogen. The catalyst was continuously extracted for 4 hr with acetone in a Soxhlet extractor. Evaporation of the solvent afforded 0.084 g of product, which was chromatographed on 2.5 g of Merck acid-washed alumina. Elution with 3:100 ether–hexane gave 0.015 g of an oily solid, which was recrystallized twice from pentane to give 0.006 g of pure *dl*-**23**, mp 112.5–113.5°, the chloroform solution infrared spectrum of which was identical with that of a sample of methyl *d*-deisopropyldehydroabietate, mp 102.5–105°, kindly provided by Professor E. Wenkert.[26] The infrared spectrum was also identical with that of a sample of *dl*-**23**, mp 112°, kindly supplied by Professor P. C. Dutta.[9c] The mixture melting point of our *dl*-**23** and Dutta's synthetic *dl*-**23** showed no depression.

Methyl 12-Hydroxydeisopropyldehydroabietate (33).—To a refluxing solution of 0.275 g (9.5×10^{-4} mole) of enone **26**, mp 82–86°, in 30 ml of carbon tetrachloride was added, at one time, 0.264 g (1.48×10^{-3} mole) of freshly recrystallized N-bromosuccinimide. The mixture was refluxed for 2 hr, cooled, diluted with 50 ml of ether, washed twice with 10 ml of water, washed twice with 25 ml of brine, dried over magnesium sulfate, filtered, and evaporated. The residue was triturated with hexane containing a little acetone, and yielded upon standing overnight in the refrigerator 0.110 g (40%) of **33**, mp 138–142°. Recrystallization from ether–hexane and sublimation were used to purify **33**, which was obtained melting sharply at 149.5–151° and 174–175°. These samples both gave poor elemental analysis, although all spectral evidence indicated that they were pure **33**: λ_{max}^{KBr} 3.1, 5.78, 6.08, and 6.23 μ; $\delta_{TMS}^{CCl_4}$ 1.20 (3 H, s, H_3C—C<), 1.27 (3 H, s, >C(CH_3)—$COOCH_3$), 3.66 (3 H, s, H_3COOC–), and 6.5–7.0 ppm (3 H, m, aromatic H's).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.20; H, 8.62.

Conversion of 33 to *dl*-23.—According to the procedure of Kenner,[38] a mixture of 0.196 g (6.8×10^{-4} mole) of **33**, mp 133–137°, 0.45 ml of triethylamine, 0.40 ml of diethyl phosphite, 1.5 ml of dry tetrahydrofuran, and 7 ml of carbon tetrachloride was refluxed for 16 hr, during which time a precipitate separated and the solution became dark red. The mixture was diluted with 40 ml of ether, washed with dilute hydrochloric acid, dilute sodium hydroxide solution, water, and brine, dried over magnesium sulfate, filtered, and evaporated to afford 0.268 g of brown oil, presumed to contain **34**.

Without purification, 0.109 g of this oil was dissolved in 2 ml of dry tetrahydrofuran and added to a solution of 0.007 g of lithium in 20 ml of liquid ammonia. After 5 min, excess ammonium chloride was added and the ammonia was evaporated. The residue was taken up in chloroform and washed with dilute acid, dilute base, water, and brine, dried over magnesium sulfate, filtered, and evaporated to afford 0.092 g of oil, which showed only a weak infrared band at 5.8 μ. Chromatography on alumina afforded 0.020 g of material, mp 85–96°, with λ_{max}^{KBr} 3.0 μ, assumed to be carbinol **35**.

The 0.020 g of **35** was dissolved in 2 ml of acetone and treated with 1 ml of Jones reagent.[38] After 5 min, this mixture was poured into 30 ml of brine which was extracted with ether. The ether layers were washed, dried, filtered, and evaporated to afford 0.019 g of crude *dl*-**24**, mp 142–148°. This substance was treated with freshly distilled ethereal diazomethane, and the product was purified by chromatography on alumina and recrystallization from pentane to afford 0.005 g of *dl*-**23**, mp 111.5–114.0°, which had an infrared spectrum identical with that of *dl*-**23** prepared as described above.

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Registry No.—**3**, 15292-47-4; **5A**, α-H epimer, 15292-48-5; **5B**, β-H epimer, 15292-49-6; **6**, 15292-50-9; **7**, 15292-51-0; **10**, 15268-88-9; **11**, 15292-53-2; **14**, 15292-54-3; **15**, 15292-55-4; **16**, 15292-56-5; **19**, 15268-95-8; **20**, 15268-96-9; **22**, 15268-87-8; **23**, 15292-60-1; **25**, 15292-61-2; **26**, 15292-62-3; **31**, 15292-63-4; **32**, 15292-64-5; **33**, 15292-65-6; **35**, 15292-66-7; **37**, 15292-67-8; 4β,10β-dimethyl-4α-carbomethoxy-8-acetoxymethylene-*trans*-decalone-9, 15292-68-9.

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A Synthesis of Podocarpic Acid[1]

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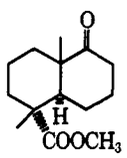
Reductive carbomethoxylation of α,β-unsaturated ketone **4** was investigated as a potential route to intermediates, such as keto ester **2**, with the podocarpic acid (**3**) stereochemistry. However, none of the desired **12** and only a low yield of isomeric **15** was obtained. Intermediate **2** was prepared instead from **12** isolated from methylation of **8**. Other products from this methylation and several related bicyclic terpenoid substances, such as triols **29** and **30**, are described. Methyl *dl*-podocarpate (**40**) was synthesized from **2** *via* Robinson annelation in 13% over-all yield.

The efficient, stereoselective synthesis of bicyclic keto ester **1** with the abietic acid stereochemistry was described in the preceding paper.[3] The results of some investigations designed to achieve a stereoselective synthesis of the corresponding intermediate **2** with the podocarpic acid (**3**) stereochemistry and a synthesis of **3** are delineated in this paper.



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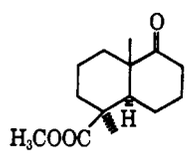

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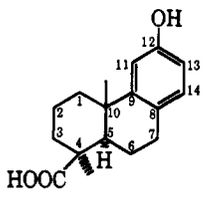

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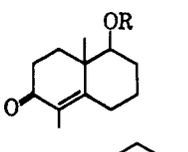
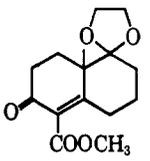
Reductive Carbomethoxylation of 4,10β-Dimethyl-9β-tetrahydropyranyloxy-$\Delta^{4,5}$-octalone-3 (4).—Stereoselective construction of the C_4 functionality of podocarpic acid (**3**) has only recently been achieved by several groups of investigators: Meyer[4] has reported a circuitous stereoselective route to **3**; Pelletier[5] has demonstrated that, as expected,[6] methylation of unsaturated β-keto ester **5** affords selectively the α-methylated **6**; Kuehne[7] has shown that methylation of β-keto nitriles leads to products with equatorial methyl, in contrast to the results obtained with saturated β-keto esters.[3,6]

Our approach had as its key step introduction of the axial carboxylate function by stereoelectronically controlled carbonation of enolate anion **7**, analogous to the predominantly β methylation of the corresponding enolate anion of **8**. In addition to a stereoselective route to **2**, this approach would, if successful, provide evidence that carbonation, like protonation,[8] bromination,[9] and alkylation,[10] is influenced by stereoelectronic factors.

Since enolate anion **7** is presumably unstable relative to its C_2 isomer, it can be efficiently generated only indirectly, as by metal–ammonia reduction of α,β-unsaturated ketone **4**.[11] Preparation of **4** has been previously accomplished by condensation of methyldihydroresorcinol with ethyl vinyl ketone to give **9**,[12] followed by selective sodium borohydride reduction to **10**,[13] and protection of the hydroxyl group.[13]





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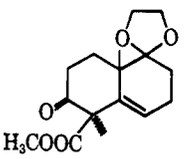

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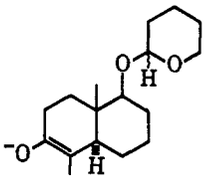

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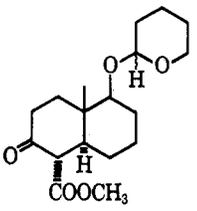

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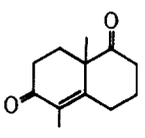

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(1) Portions of this work were presented at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstract K17.

(2) (a) Alfred P. Sloan Foundation Research Fellow; (b) recipient of support under the terms of an institutional research training grant from the U. S. Public Health Service, summer 1966.

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