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.

Acknowledgment.—The authors are grateful for the financial support provided by Public Health Service Grant AM 05014. Dr. E. O. Hornig and Professor K. L. Williamson kindly ran several nmr spectra. Mr. John L. Smith originally isolated compounds **10** and **11**.

A Synthesis of Podocarpic Acid[1]

THOMAS A. SPENCER,[2a] RICHARD J. FRIARY, WALTER W. SCHMIEGEL, JOSEPH F. SIMEONE, AND DAVID S. WATT[2b]

Department of Chemistry, Dartmouth College, Hanover, New Hampshire

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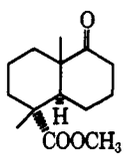
Reductive carbomethoxylation of α,β-unsaturated ketone **4** was investigated as a potential route to intermediates, such as keto ester **2**, with the podocarpic acid (**3**) stereochemistry. However, none of the desired **12** and only a low yield of isomeric **15** was obtained. Intermediate **2** 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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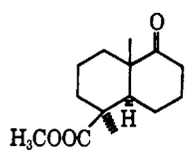

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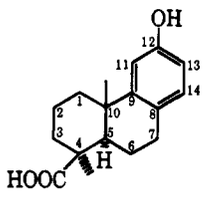

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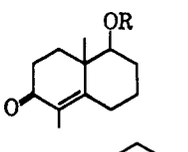
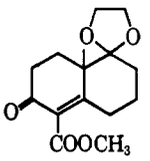
Reductive Carbomethoxylation of 4,10β-Dimethyl-9β-tetrahydropyranyloxy-$\Delta^{4,5}$-octalone-3 (4).—Stereoselective construction of the C_4 functionality of podocarpic acid (**3**) has only recently been achieved by several groups of investigators: Meyer[4] has reported a circuitous stereoselective 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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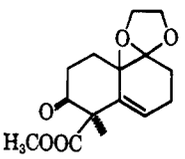

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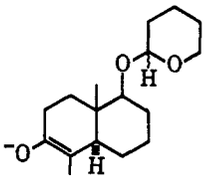

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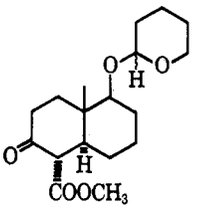

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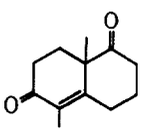


9

(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.

(3) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

(4) W. L. Meyer and K. K. Maheshwari, *Tetrahedron Letters*, 2175 (1964).

(5) S. W. Pelletier, R. L. Chappell, and S. Prabhakar, *ibid.*, 3489 (1966).

(6) *Cf.* E. Wenkert, *et al.*, *J. Am. Chem. Soc.*, **86**, 2038 (1964).

(7) Private communication from Dr. M. E. Kuehne, University of Vermont, 1966.

(8) E. J. Corey and R A. Sneen, *J. Am. Chem. Soc.*, **78**, 6271 (1956).

(9) E. J. Corey, *ibid.*, **75**, 2301 (1953); **76**, 175 (1954).

(10) *E.g.*, R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **31**, 2543 (1966).

(11) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).

(12) (a) V. F. Kucherov and A. Gurvich, *J. Gen. Chem. USSR*, **31**, 731 (1961); (b) Y. Kitahara, A. Yoshikoshi, and S. Oida, *Tetrahedron Letters*, 1763 (1964).

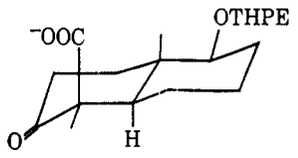
(13) M. Brown, Ph.D. Thesis, Stanford University, Stanford, Calif., 1963.

Oily **4** prepared by this route was reduced with lithium in ammonia to generate **7**, which was treated with carbon dioxide under various conditions[3] in the hope of forming **11**, followed by acidification, treatment with diazomethane, and methanolysis of the tetrahydropyranyl ether protecting group. The products thus obtained were chromatographed to afford four crystalline compounds, none of which was the desired **12**.

The major product (*ca.* 30% yield) from every run was hydroxy ketone **13**, mp 84–85°, resulting from simple reduction of **4**. The identity of **13** was evident from its origin, elemental analysis, and spectral properties. The assignment of the equatorial configuration to the secondary methyl group was confirmed by recovery of **13** after treatment with sodium methoxide in methanol.

Another product of reduction without carboxylation, diol **14**, mp 154–155°, was isolated on occasion in yields up to 7%. The β configuration is assigned to the C_3 hydroxyl group on the basis of the stereochemistry of closely analogous reductions.[14] Sodium borohydride reduction of **13** afforded **14**.

The only monocarbomethoxylation product ever obtained was the **4**α-ester **15**, the predominant product from methylation of **8**.[3] Using the best conditions developed for the carbomethoxylation of **16**,[3] the yield of **15** was only 16%. The nmr spectra of the crude products from two carbomethoxylations were determined to see if the characteristic shielded angular methyl peak of **12** (*vide infra*) could be detected. A small peak was found at δ 0.92 ppm which might be due to **12** (δ 0.93 ppm), but even if it were, it would amount to a yield of <1% of **12** in the reductive carbomethoxylation of **4**.



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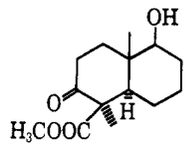

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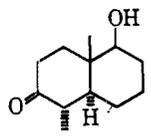

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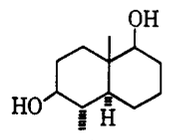

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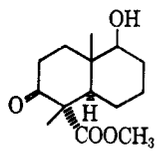

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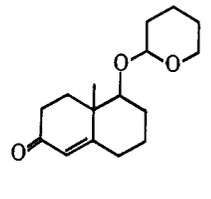
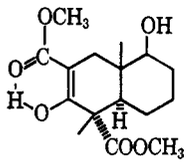


16

A fourth crystalline substance was obtained in trace amount during one of our initial attempts at reductive carbomethoxylation of **4**. This compound, mp 158–159°, had an elemental analysis consistent with dicarbomethoxylation and exhibited ultraviolet absorption at 254 mμ (ϵ 14,700) consistent with an enolized β-keto ester. On vigorous acid hydrolysis this substance yielded hydroxy ketone **13**. These data suggested that the compound was **17**, presumably formed by strong base (*e.g.*, amide anion) proton abstraction from a monocarboxylated species. Due to lack of material, no further work could be done on the compound itself. The infrared spectrum of **17** (λ_{max}^{KBr} 2.81, 5.80, 6.02, and 6.15 μ) showed very little if any absorption due to the O–H bond of the enolic hydroxyl, but comparison with the spectra of compound **18**[3] (λ_{max}^{KBr} 2.81, 6.05, and 6.20 μ), its monoacetate derivative (**19**), mp 130.5–131.5° (λ_{max}^{KBr} 5.76, 6.00, and 6.13 μ), and diacetate derivative (**20**), mp 97.5–98.5° (λ_{max}^{KBr} 5.66, 5.78, and 5.99 μ), indicated that this lack of prominent absorption was consistent with the structural assignment.

The failure to isolate any axial carbomethoxylation product and the low yield of **15** suggested that possibly the sterically congested axial carbonation product **11** was being formed, but was undergoing decarboxylation (either before or after protonation to the β-keto acid) at a rate which precluded trapping with diazomethane. In order to test this possibility, the presumably irreversible reactions of enolate anion **7** with methyl chloroformate and dimethyl carbonate were investigated. As expected,[15] however, these reagents afforded after methanolysis the O-carbomethoxylated **21** essentially exclusively, judging from the spectral properties of the crude product (λ_{max} 2.9 and 5.71 μ).

One further attempt to test this decarboxylation hypothesis was made. Sodium borohydride was added to the reaction mixture of **7**, ether, and Dry Ice in an attempt to reduce the ketone carbonyl group of **11** as it was formed, thereby preventing subsequent facile decarboxylation. The product hoped for, after acidification, esterification, and methanolysis, was dihydroxy ester **22**. However, the amount of carbomethoxylated material obtained by this procedure was less than was usually isolated from the standard reductive carbomethoxylations, and the products were not fully characterized. Since methods for synthesizing bicyclic intermediates with the podocarpic acid



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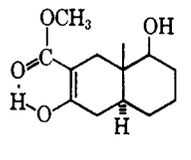

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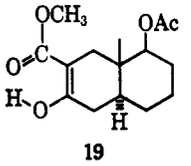

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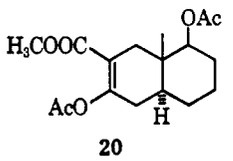

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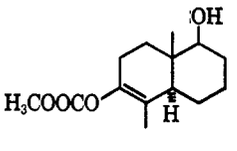

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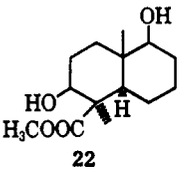

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(14) *E.g.*, C. Djerassi, M. Cais, and L. A. Mitscher, *J. Am. Chem. Soc.*, **81**, 2386 (1959).

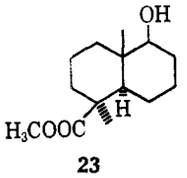
(15) See H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 273, for a discussion of this type of reaction; *cf.* ref 6.

(3) stereochemistry had become available,[5,7] experiments on the reductive carbomethoxylation of **4** were terminated.

Synthesis of Keto Ester 2.—One of the key steps in the synthesis of the bicyclic intermediate **1** with the abietic acid stereochemistry was stereoselective β methylation of **8** to afford **15** after methanolysis.[3] However, there was also formed a lesser amount of the α methylation product **12**, as indicated by isolation of the saponification-resistant hydroxy ester **23** from methylation products which had been carried through the reduction of the C_3 carbonyl group without separation of **15**.[3] Isolation of this **12** was originally undertaken in order to provide a sample for comparison with products from the reductive carbomethoxylation studies, but it transpired that the sole source of **12** was careful separation of methylation products.

When the residues from isolation of **15** were chromatographed, there were obtained, in addition to small amounts of **15** and **24**,[3] two crystalline dimethylation products. One, mp 94–95.5°, had spectral properties [$\delta_{TMS}^{CDCl_3}$ 1.07 (3 H, d, J = 6.5 Hz), 1.18 (3 H, s), 1.38 (3 H, s), 2.16 (1 H, s) and 3.72 ppm (3 H, s)] consistent with the expected product of dimethylation, **25**. The other, mp 121.5–123°, displayed λ_{max}^{KBr} 3.02, 5.73, and 5.95 μ and $\delta_{max}^{CDCl_3}$ 0.93 (3 H, s), 1.30 (3 H, s), 1.64 (1 H, s), 3.48 (3 H, s), 3.67 (3 H, s), and 4.70 (1 H, q), properties which suggested that it was the product of O-methylation, **26**. Confirmation of this assignment was obtained by acid hydrolysis of the substance to **15**; in fact, the decomposition of **26** to **15** on standing was difficult to prevent in the samples we had.

Repeated chromatography of the noncrystalline residues afforded fractions which had all the spectral properties, including the shielded angular methyl nmr peak at δ 0.92 ppm, expected from **12**. The yield of oily **12** of reasonable purity thus isolated was roughly 5% from **8**.



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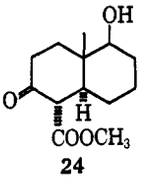

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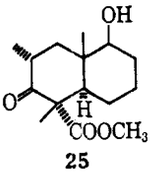

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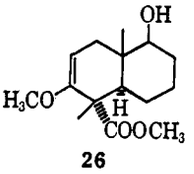

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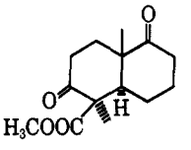
Proof that this material was indeed **12** was obtained by oxidation with Jones reagent to afford crystalline diketo ester **27**, mp 103–106° (δ 1.26 ppm[3]), in 73% yield. Similar oxidation of **15** afforded 78% of **28**, mp 134.5–136.5° (δ 1.35 ppm[3]). The isomeric ketones **12** and **15** were also both reduced with lithium aluminum hydride to the respective related triols **29**, mp 112–130°, and **30**, mp 197.5–199°. The odd melting point behavior of **29** and difficulty in securing good combustion analytical data for it led to its characterization as the well-behaved triacetate **31**, mp 121–122.5°. Triol **29** was also obtained by lithium aluminum hydride reduction of **27**.

The stereochemistry of the C_3 hydroxyls in **29** and **30** was assigned, as it was in **14**, on the basis of precedent.[5] The nmr spectrum of triacetate **31** was in agreement with this assignment, since all the signals for the protons on carbons bearing acetoxyl groups appeared at chemical shifts of δ <4.8 ppm, suggesting that the C_3 hydrogen was axial rather than equatorial.[16]



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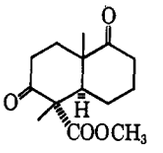

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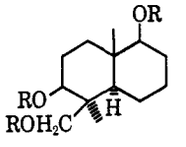
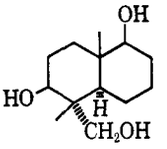


29, R = H
31, R = Ac



30

Conversion of **12** to **23**[3] was effected by preparation and Raney Ni reduction of the dithioketal derivative, but the yield of pure **23** was lower than that of **36** obtained in the corresponding reduction of **15**, perhaps because the remaining contaminants in the **12** used adversely affected the reactions or isolation. Oxidation of **23** afforded the desired **2**, mp 87.5–88.5°, in 91% yield.

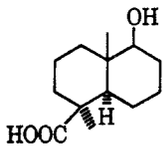
Hydroxy ester **23** was completely resistant to ordinary saponification conditions,[3] but could be converted to the corresponding acid **32**, mp 143–144°, in 70% yield by treatment with potassium hydroxide in diethylene glycol at 160–170° for 3 weeks.[17] Hydroxy acid **32** was oxidized to keto acid **33**, mp 156–157°, and, in order to confirm their structural assignments, **32** and **33** were transformed into **23** and **2**, respectively, by treatment with diazomethane. It is noteworthy that these two highly hindered acids appear to react slowly with diazomethane: starting material was recovered if the esterifications were worked up directly after addition of excess diazomethane.

This observation raised the possibility that failure to isolate **12** from reductive carbomethoxylation of **4** was caused by failure to esterify carboxylated material. However, in a few runs the separated "carboxylated" material had unpremeditatedly been allowed to stand in ethereal diazomethane for several hours, without any evidence of formation of substantial amounts of **12**. Furthermore, the total weight of material obtained as acidic product would have been greater if a useful yield of β-carboxylated material had been formed.

Keto acid **33** was also prepared by lithium aluminum hydride reduction of **23** to diol **34**, mp 144.5–145°, followed by chromic acid oxidation. The correspond-

(16) See N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 77–80, for a discussion of nmr spectra of equatorial *vs.* axial acetates.

(17) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 211 (1958).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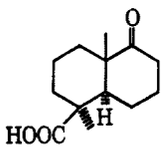
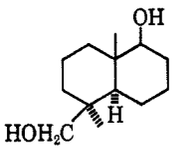
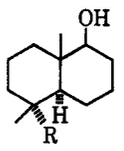

33


34

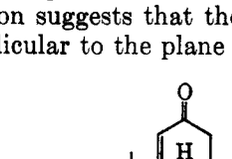

35, R = CH_2OH
36, R = $COOCH_3$

ing diol with the abietic acid stereochemistry **35**, mp 122–124°, was prepared by reduction of **36**.[3]

Synthesis of Podocarpic Acid.—With keto ester **2** in hand, completion of yet another[18] synthesis of podocarpic acid (**3**) appeared too convenient to ignore, for simply by Robinson annelation of **2**, one would gain access to tricyclic unsaturated ketone **37**, a dihydro derivative of the desired aromatic ring C system.

To facilitate annelation of **2**, it was converted to its hydroxymethylene derivative **38**, mp 132.5–134°, in 85% yield by the same procedure used with keto ester **1**.[3] The reaction of **38**, sodium methoxide, and 1-diethylaminobutanone-3 methiodide at room temperature afforded Michael adduct **39**, mp 100–101°, in 64% yield. Cyclization to **37** was accomplished in 84% yield by treatment of **39** with sodium methoxide in methanol at reflux. Racemic **37**, mp 158.5–160.5°, had solution infrared and nmr spectra identical with those of a sample of the *d*-enantiomer of **37**, mp 116–118°, derived from natural podocarpic acid.[19]

The stereochemistry of the C_8 protons in **37** and **39** is presumably β, as shown, since conformational principles and molecular models suggest that **37** and **39** will be the more stable epimers, and the reaction conditions leading to their formation should permit equilibration. The fact that the vinyl proton nmr peak of **37** is split into a doublet with J = 1.7 Hz by the C_8 proton suggests that the latter is approximately perpendicular to the plane formed by the carbons of the double bond and the vinyl proton.[20] However, either **37** or its C_8 epimer can adopt relatively favorable conformations in which this condition is met, and no experimental evidence on the stereochemical assignments at C_8 is available.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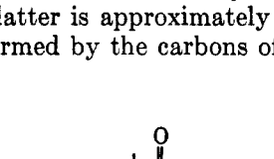
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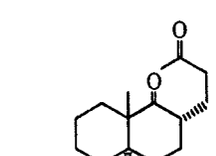
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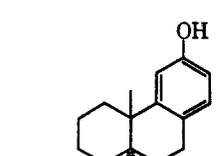
40

Oxidation of **37** to methyl *dl*-podocarpate (**40**), mp 184.5–185°, was readily accomplished by treatment with N-bromosuccinimide in refluxing carbon tetrachloride, which afforded 34% of crystalline **40** (13% over-all yield from **2**). This material had solution spectral properties identical with those of naturally derived methyl podocarpate, mp 210–211°. Since a conversion of methyl *d*-podocarpate to *d*-podocarpic acid has been recorded,[21] a formal total synthesis of the latter was completed with the isolation of *dl*-**40**.

Experimental Section[22]

4,10β-Dimethyl-9β-tetrahydropyranyloxy-$\Delta^{4,5}$-octalone-3 (4).—Tetrahydropyranyl ether **4** was prepared by the method of Brown.[13] Robinson annelation of methyldihydroresorcinol with ethyl vinyl ketone afforded 65% of enedione **9**, mp 45–46° (lit.[13] mp 41–42°; lit.[12a] mp 45–46°; lit.[12b] mp 39–40°). Selective sodium borohydride reduction of **9** afforded 70% of **10**, mp 86.5–88° (lit.[13] mp 89–91°). Upon reaction of **10** with dihydropyran in the presence of *p*-toluenesulfonic acid, tetrahydropyranyl ether **4** was obtained as an oil (λ_{max} 5.97 and 6.18 μ) which was purified by chromatography on alumina.

Reductive Carbomethoxylation of 4. Method A.—To a solution of 0.56 g (0.081 g-atom) of lithium wire in 250 ml of liquid ammonia (not redistilled) was added a solution of 6.3 g (0.023 mole) of **4** in 80 ml of anhydrous ether over a 10-min period. The ammonia was allowed to evaporate and was replaced by an equal volume of anhydrous ether. Carbon dioxide was bubbled from a cylinder into the reaction mixture for 4.5 hr at room temperature and for 0.5 hr at 0°. The mixture was acidified at 0° with 1 *M* hydrochloric acid saturated with sodium chloride. The ethereal layer was separated, washed with brine at 0°, dried over sodium sulfate and magnesium sulfate, and added to an ethereal solution of diazomethane. Excess diazomethane was decomposed with acetic acid and the solution was stripped of solvent to yield 8.5 g of oil.

This oil was then dissolved in 50 ml of methanol containing a trace of *p*-toluenesulfonic acid monohydrate, and the mixture was heated on the steam bath for 2 hr. Most of the methanol was evaporated and the residue was partitioned between water and ether. The dried ether layer yielded 5.6 g of oil which was chromatographed on 150 g of acid-washed alumina using ether–hexane and then acetone–ether mixtures.

With 4:1 ether–hexane was eluted 1.37 g (30%) of crude solid **4α,10β-dimethyl-9β-hydroxy-*trans*-decalone-3 (13)**. Recrystallization from acetone–hexane afforded the analytical sample: mp 84–85°; λ_{max}^{KBr} 2.85 (shoulder), 3.05, and 5.84 μ; $\delta_{TMS}^{CS_2}$ 0.88 (3 H, d, J = 7 Hz, H_3C—C—H), 1.02 (3 H, s, H_3C—C<), and 2.72 ppm (1 H, s, *H*O–).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.29.

With 1:1 ether–acetone was eluted 0.287 g (6%) of **4α,10β-dimethyl-*trans*-decalin-3β,9β-diol (14)**. Recrystallization from acetone–hexane afforded the analytical sample which had mp 154.5–155° and λ_{max}^{KBr} 3.0 μ.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.68; H, 11.26.

(18) For other syntheses, *cf.* (a) ref 4; (b) ref 6; (c) U. R. Ghatak, D. K. Dutta, and S. C. Ray, *J. Am. Chem. Soc.*, **82**, 1728 (1960); (d) F. E. King, T. J. King, and J. G. Topliff, *Chem. Ind.* (London), 113 (1956); (e) R. D. Haworth and B. P. Moore, *J. Chem. Soc.*, 633 (1946); (f) B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **22**, 165 (1945).

(19) R. H. Bible, Jr., and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961). We thank Dr. Bible for kindly sending us a sample of *d*-**37**.

(20) T. A. Wittstruck, S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1699 (1963).

(21) E. Wenkert and B. G. Jackson, *ibid.*, **80**, 217 (1958).

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

All noncrystalline residues were rechromatographed on 150 g of acid-washed alumina using acetone–hexane eluent mixtures. With 1:4 acetone–hexane was obtained 0.173 g (3%) of **4β,10β-dimethyl-4α-carbomethoxy-9β-hydroxy-*trans*-decalone-3** (**15**), mp 122–124°. Comparison of infrared spectra and an undepressed mixture melting point with an authentic sample of **15**[3] served to identify this material.

The diester **17** was not obtained from the experiment described above (although infrared spectra of certain fractions suggested its presence). From another, essentially identical, carbomethoxylation of 12.6 g (0.046 mole) of **4**, there was obtained, after chromatography with 4:1 ether–hexane, *ca.* 0.25 g of **4β,10β-dimethyl-2,4α-dicarbomethoxy-9β-hydroxy-*trans*-decalone-3** (**17**). Recrystallization of **17** from acetone–hexane afforded the analytical sample: mp 158–159°; λ_{max}^{EtOH} 254 mμ (ε 14,700); λ_{max}^{KBr} 2.81, 5.80, 6.02, and 6.15 μ; $\delta_{TMS}^{CS_2-CHCl_3}$ 0.88 (H_3C—C<), 1.37 (>C(CH_3)—COOCH_3), 2.3 (center of AB quartet from C_1 protons), 3.63 (-OCH_3), and 3.73 ppm (-OCH_3).

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.61; H, 7.77.

Reductive Carbomethoxylation of 4. Method B.—To a solution of 0.75 g (0.108 g-atom) of lithium wire in 500 ml of ammonia in a 2-l. three-necked flask equipped with a mechanical stirrer, reflux condenser (closed with a potassium hydroxide drying tube), and dropping funnel was added 6.3 g (0.023 mole) of **4** in 100 ml of anhydrous ether over a 5-min period with vigorous stirring. The reaction mixture was warmed to remove most of the ammonia and then 400 ml of anhydrous ether was added and the mixture was refluxed for 15 min to remove the remaining ammonia. The reaction mixture was cooled in a Dry Ice–acetone bath and *ca.* 100 g of Dry Ice which had been pulverized in a plastic bag was added through a powder funnel inside another large plastic bag. Careful precautions were taken to exclude moisture.

After addition of the Dry Ice, the funnel was replaced by a stopper, the cooling bath was removed, and the mixture was allowed to stir for 35 min. Then the mixture was again cooled in Dry Ice–acetone and 150 ml of water was added. The layers were separated and the *aqueous layer* was returned to the chilled (−10°) reaction vessel, to which was then added 200 ml of ether, followed by a mixture of 15 ml of concentrated hydrochloric acid and 15 g of ice, with stirring. The ether layer was separated, washed with brine at 0°, and poured through a dry filter paper into an ethereal solution of diazomethane. Acetic acid was added to destroy excess diazomethane and the ethereal solution was washed with sodium bicarbonate solution and brine, and dried over sodium sulfate and magnesium sulfate. Evaporation of the ether yielded 2.9 g of yellow oil, λ_{max} 5.74 and 5.84 μ. This oil was subjected to methanolysis (as in method A), affording 1.95 g of partially crystalline material from which was separated 0.94 g (16%) of **15**, mp 120–123°.

The initially separated ethereal layer containing neutral (uncarboxylated) components afforded, after methanolysis, 2.35 g of an oil. The infrared spectrum of this material suggested that it was a mixture of mostly **13** plus some unreduced **4**. It was not characterized further.

The nmr spectra of the crude "acidic layer" products, after methanolysis, from two reductive carbomethoxylations of **4** were determined. A signal at $\delta_{TMS}^{CDCl_3}$ 0.92 ppm was observed which could indicate the presence of **12** ($\delta_{TMS}^{CDCl_3}$ 0.93 ppm). The intensity of this signal was such that there could be only *ca.* 10% of **12** in these products, which themselves were obtained in only *ca.* 5% yield.

Reductive Carbomethoxylation of 4. Method C. Using Methyl Chloroformate.—To a stirred solution of 0.215 g (0.031 g-atom) of lithium wire in 150 ml of liquid ammonia was added a solution of 2.77 g of **4** in 30 ml of anhydrous ether. The ammonia was evaporated and replaced by anhydrous ether. A large excess (*ca.* 10 g) of redistilled methyl chloroformate in 30 ml of ether was added dropwise and the mixture was stirred for 3.5 hr. The mixture was partitioned between water and ether, and the ether layer was washed successively with water, sodium bicarbonate solution, and brine, and then dried over magnesium sulfate and evaporated. The resulting oil was methanolized in the usual manner (see method A) to yield 1.55 g of an oil which was chromatographed on silicic acid using a hexane–ether–acetone eluent progression. The major fraction, 0.88 g of oil eluted with 3:2 ether–hexane, was rechromatographed to afford an oil which had λ_{max} 2.9 and 5.71 μ and appeared to be fairly pure enol carbonate **21**. About an equal amount of **13** was also obtained in later fractions of the first chromatography.

An 0.080-g sample of **21** was treated with sodium hydroxide in 1:1 water–methanol at room temperature overnight. The usual work-up afforded 0.042 g of oil which had an infrared spectrum almost identical with that of **13**. This material was not characterized further.

Treatment of 13 with Sodium Methoxide.—To a solution of 0.063 g (3.2×10^{-4} mole) of **13** in 10 ml of anhydrous methanol was added a solution of *ca.* 0.5 g of sodium in 30 ml of anhydrous methanol. After standing at room temperature for 2 days the solution was acidified with concentrated hydrochloric acid, reduced in volume, and partitioned between water and ether. The ether layer afforded, after the usual work-up, 0.054 g of crystalline residue, mp 79–82°. Recrystallization from acetone–hexane gave material with mp 84–85°; the mixture melting point with known **13** was 84–85°.

Conversion of Diester 17 to 13.—To a mixture[23] of 5 ml of glacial acetic acid, 1.15 ml of concentrated hydrochloric acid, and 1.5 ml of water was added 0.100 g (3.2×10^{-4} mole) of pure diester **17**. The resulting solution was refluxed for 20 hr. The mixture was partitioned between water and ether, and acetic acid was removed by washing with sodium bicarbonate solution. The ether layer afforded a semisolid residue which was recrystallized from acetone–hexane to afford material, mp 84–85°, which was shown to be **13** by infrared spectrum and mixture melting point.

Sodium Borohydride Reduction of 13 to 14.—To a solution of 0.068 g (3.5×10^{-4} mole) of **13** in 15 ml of absolute ethanol was added 0.422 g of sodium borohydride in 40 ml of absolute ethanol. After 15 min at room temperature, the resulting solution was acidified with dilute hydrochloric acid, reduced in volume under aspirator vacuum, and partitioned between water and chloroform. The organic layer was washed with brine, dried over sodium sulfate and magnesium sulfate, and evaporated to yield 0.075 g of oily crystals, mp 145–152°. Recrystallization from hexane–acetone afforded material, mp 154–154.5°, which was shown to be **14** by an undepressed mixture melting point and comparison of infrared spectra.

2-Carbomethoxy-9β-acetoxy-10β-methyl-*trans*-decalone-3 (**19**).—To 3 g of acetic anhydride was added 0.090 g (3.8×10^{-4} mole) of 2-carbomethoxy-9β-hydroxy-10β-methyl-*trans*-decalone-3 (**18**),[3] mp 94.5–95.5° (λ_{max}^{KBr} 2.91, 6.06, and 6.21 μ), and 3 g of pyridine. This mixture was allowed to stand at room temperature for 2.5 hr and then was evaporated under reduced pressure at 40°. The residue crystallized to afford crude **19**, mp 115–123°, which was recrystallized from acetone–hexane to give pure monoacetate **19**: mp 130.5–131.5°; λ_{max}^{KBr} 5.76, 6.00, and 6.13 μ.

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.61; H, 7.71.

2-Carbomethoxy-3,9β-diacetoxy-10β-methyl-*trans*-Δ^{2,3}-octalin (**20**).—A reaction mixture like that described in the preparation of **19** was heated at 50° for 14 hr. Volatile materials were removed under reduced pressure at 80°. The residue was recrystallized from acetone–hexane to afford diacetate **20**: mp 97.5–98.5°; λ_{max}^{KBr} 5.66, 5.78, and 5.99 μ.

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.54; H, 7.18.

Chromatography of the Residues from Methylation of 8.—Noncrystalline residues (*ca.* 80 g) from several methylations of **8**,[3] after removal of the tetrahydropyranyl ether group and crystallization of the predominant product **15**, were combined and chromatographed on 1400 g of acid-washed alumina using an acetone–hexane eluent progression. Early fractions afforded *ca.* 40 g of oil which was rechromatographed as described below. Later fractions (*ca.* 14 g) afforded 3.35 g of **15**, mp 115–120°, and 1.51 g of **24**, mp 138–143°, after fractional crystallization and rechromatography.

Isolation of 26.—The 40 g of oil obtained above was rechromatographed on 1350 g of acid-washed alumina. Elution with 1:1 ether–hexane afforded 0.91 g of material, mp 99–115°, which was recrystallized from ether to afford 0.562 g of **26**, mp 116–119°. The analytical sample had mp 121.5–123°; λ_{max}^{KBr} 3.01, 5.72, and 5.95 μ; $\delta_{TMS}^{CDCl_3}$ 0.93 (3 H, s, H_3C—C<), 1.30 (3 H,

(23) W. S. Johnson, J. W. Petersen, and W. P. Schneider, *J. Am. Chem. Soc.*, **69**, 74 (1947).

s, >C(CH_3)—$COOCH_3$), 3.49 (3 H, s, $H_3COC(=)$-), 3.67 (3 H, s, H_3COOC-), and 4.68 ppm (1 H, q, $HC=C<$).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.19; H, 8.98.

To 0.125 g (4.67×10^{-4} mole) of **26** was added 20 ml of methanol and a solution of 5 ml of concentrated hydrochloric acid in 10 ml of water. The mixture was allowed to stand at room temperature for 2 hr, diluted with 35 ml of brine, and extracted with four 25-ml portions of ether. The extract was washed with two 20-ml portions of brine, dried over magnesium sulfate, filtered, and evaporated to give 0.106 g of colorless oil from which there was obtained 0.062 g (52%) of β-keto ester **15**, mp 119.5–121.5°, identified by mixture melting point and infrared spectrum.

Isolation of 12.—After separation of **26**, 28.3 g of residual oily fractions were recombined and chromatographed again on 900 g of alumina using a benzene–chloroform–ether progression. The only crystalline material obtained was *ca.* 0.7 g of **26**. Oily fractions weighing 23.1 g were again chromatographed, this time on Florisil, using ether–hexane and taking many fractions. The only crystalline material isolated was 0.795 g of **15**. About 12 g of oil was isolated which showed λ_{max} 3.0 and 5.80–5.85 μ (broad) and $\delta_{TMS}^{CCl_4}$ 0.93 (s), 1.25 (s), and 3.65 ppm (s). There was only a very weak peak at 1.04 ppm corresponding to the angular methyl of **15**. Integration of the 0.93-ppm peak characteristic of **12** *vs.* the total methoxyl methyl peak indicated presence of greater than 60% of **12**. One more chromatography of 2.77 g of this material afforded 1.94 g of the **12** used in the preparation of **27** below. The yield of this reasonably pure **12** thus isolable from methylation of **8** may be estimated at *ca.* 5%.

Isolation of 25.—From chromatography of another batch of methylation residues (31.3 g) there was obtained, upon elution with 2:3 ether–hexane of a 450-g, acid-washed alumina column, 3.28 g of the other dimethylation product, **2α,4β,10β-trimethyl-4α-carbomethoxy-9β-hydroxy-*trans*-decalone-3** (**25**), mp 85–90°. An analytical sample prepared by recrystallization from ether–hexane had mp 94–95.5°, and the following spectral properties: λ_{max}^{KBr} 2.80, 5.76 and 5.87 μ; $\delta_{TMS}^{CDCl_3}$ 1.07 (3 H, d, J = 6.5 Hz, H_3C—C—H), 1.18 (3 H, s, H_3C—C<), 1.38 (3 H, s, >C(CH_3)—$COOCH_3$), 2.16 (1 H, s, HO-), and 3.72 ppm (3 H, s, H_3-COOC-).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.75; H, 9.10.

4α,10β-Dimethyl-4β-carbomethoxy-*trans*-decalin-3,9-dione (**27**).—To an ice-cooled solution of 0.488 g (1.92×10^{-3} mole, if pure) of **12**, isolated as described above, in 20 ml of reagent grade acetone was added 2.3 ml of Jones reagent[24] dropwise from a buret. After being magnetically stirred for 5 min the mixture was diluted with 50 ml of brine and extracted with three 30-ml portions of ether. These extracts were washed with water and all combined aqueous layers were again extracted with ether. The organic layers were washed with saturated sodium bicarbonate solution, washed with brine, dried over magnesium sulfate, filtered, and evaporated to afford 0.456 g of pale yellow oil. Upon trituration with ether, the product crystallized to afford 0.353 g (73%) of diketo ester **27**, mp 103–104°. An analytical sample was prepared by recrystallization from ether–hexane as long needles: mp 103–106°; λ_{max}^{KBr} 5.76 and 5.85 μ; $\delta_{TMS}^{CDCl_3}$ 1.26 (3 H, s, H_3C—C<), 1.39 (3 H, s, >C(CH_3)—$COOCH_3$), and 3.74 ppm (3 H, s, H_3COOC-).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.69; H, 7.84.

4β,10β-Dimethyl-4α-carbomethoxy-*trans*-decalin-3,9-dione (**28**).—A solution of 0.556 g (2.18×10^{-3} mole) of **15**, mp 108–118°, in 25 ml of reagent grade acetone was treated with 2.6 ml of Jones reagent[24] exactly as in the preparation of **27**. A crude product of 0.584 g afforded 0.428 g (78%) of diketo ester **28**, mp 130–137°. An analytical sample prepared by recrystallization from acetone–hexane had mp 134.5–136.5°; λ_{max}^{KBr} 5.73 and 5.84 μ; $\delta_{TMS}^{CDCl_3}$ 1.35 (3 H, s, H_3C—C<), 1.45 (3 H, s, >C(CH_3)—$COOCH_3$), and 3.72 ppm (3 H, s, H_3COOC-).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.89; H, 8.17.

4α,10β-Dimethyl-4β-hydroxymethyl-*trans*-decalin-3β,9β-diol (**29**).—To a three-necked flask, equipped with magnetic stirring bar, condenser, and drying tube was added 0.75 g (1.98×10^{-2} mole) of lithium aluminum hydride (Metal Hydrides, Inc.) and then a solution of 0.758 g of oily **12** in 40 ml of dry tetrahydrofuran. The mixture was refluxed for 45 min and ice and sulfuric acid were added. The layers were separated, and the aqueous phase was extracted with two 25-ml portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and evaporated to afford 0.658 g of crude product, which was purified by chromatography on acid-washed alumina to afford 0.372 g of **29**, mp 127–131°; λ_{max}^{KBr} 3.05 μ; $\delta_{TMS}^{CDCl_3-DMSO-d_6}$ 0.78 (3 H, s, H_3C—C<) and 1.14 ppm (3 H, s, H_3C—C<). Recrystallization from acetone–hexane, ether, or methanol–ether all gave material of unpredictably varying melting point, ranging from 102–108, 113–120, 112–130, and once 133–135°. Satisfactory analytical data were not obtained for this substance.

Triol **29** was also prepared by similar lithium aluminum hydride reduction of pure **27**, which afforded 53% of **29**, mp 110–115°.

4α,10β-Dimethyl-4β-acetoxymethyl-3β,9β-diacetoxy-*trans*-decalin (**31**).—A solution of 0.160 g (7.0×10^{-4} mole) of **29**, mp 87–105°, in a mixture of 7 ml of pyridine and 5 ml of acetic anhydride was stirred at room temperature for 24 hr. The mixture was diluted with ether, washed with water, dilute hydrochloric acid, dilute sodium bicarbonate solution, and brine, dried over magnesium sulfate, filtered, and stripped to afford 0.204 g of oil which crystallized on standing under hexane. The solid was recrystallized several times to afford 0.049 g (20%) of **31**, mp 121–122.5°; λ_{max}^{KBr} 5.78 μ; $\delta_{TMS}^{CDCl_3}$ 1.01 (6 H, s, 2 H_3C—C<), 2.011 (3 H, s, H_3C-COO-), 2.015 (3 H, s, H_3C-COO-), 2.03 (3 H, s, H_3C-COO-), and 3.9–4.8 ppm (4 H, broad m, 2 AcO—CH< and AcO—CH_2).

Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.22; H, 8.52.

4β,10β-Dimethyl-4α-hydroxymethyl-*trans*-decalin-3β,9β-diol (**30**).—To a three-necked flask charged with 0.550 g (1.45×10^{-2} mole) of lithium aluminum hydride was added, dropwise over 5 min, a solution of 0.514 g (2.03×10^{-3} mole) of **15**, mp 118–122°, in 40 ml of dry ether. The solution was refluxed for 30 min; excess lithium aluminum hydride was decomposed by the addition of ice and then cold, concentrated sulfuric acid. The mixture was extracted with four 30-ml portions of ether and the extract was washed with brine. The solution was dried over magnesium sulfate, filtered, and evaporated to give 0.109 g (24%) of **30**, mp 172–175°. Several recrystallizations from hexane containing a little acetone furnished the analytical sample: mp 197.5–199°; λ_{max}^{KBr} 3.02 μ; $\delta_{TMS}^{CDCl_3-DMSO-d_6}$ 0.71 (3 H, s, H_3C—C<) and 0.84 ppm (3 H, s, H_3C—C<).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 68.38; H, 10.59. Found: C, 68.52; H, 10.62.

Conversion of 12 to 23.—To a solution of 0.960 g of oily **12** (purity estimated at >60%) in 3.5 ml of ethanedithiol (Aldrich) was added 0.7 ml of freshly distilled boron trifluoride etherate (Eastman), as described in the previous paper.[3] The mixture was allowed to stand for 5 hr at room temperature and was then poured slowly into 30 ml of 2 *M* sodium hydroxide solution cooled in an ice bath. The mixture was stirred for 15 min, and then the supernatant liquid was removed by pipet from a white, gummy precipitate. The process was repeated with 14 ml of 2 *M* sodium hydroxide solution. The residue was washed with three 10-ml portions of water in the same manner and then dried under high vacuum.

The dried, crude dithioketal was dissolved in 30 ml of absolute ethanol, to which was added *ca.* 20 g of Raney nickel, prepared as previously described,[3] in 15 ml of ethanol. The mixture was stirred at room temperature for 26 hr and filtered. The Raney nickel was washed with 1.5 l. of acetone, and the organic layers were refiltered and evaporated to afford 0.999 g of oil with an infrared spectrum like that of **23**.[3] Chromatography of this material on 30 g of acid-washed alumina afforded 0.202 g of **23**, mp 67–74°.

From this one preparation of **23** there was also isolated from the chromatography 0.027 g of another substance, mp 105–115°. Recrystallization from ether–hexane gave a pure specimen: mp 120–121°; λ_{max}^{KBr} 2.91 and 5.77 μ; $\delta_{TMS}^{CDCl_3}$ 0.75 (3 H, s), 1.17 (3 H, s), and 3.64 ppm (3 H, s).

Anal. Found: C, 70.34; H, 10.19.

These spectral and analytical properties were essentially identical with those of **23**. However, the fingerprint region of the infrared spectrum of the 120–121° compound was very different from that of **23**. An attempt to demonstrate by seeding that the 120–121° compound was a different crystalline

(24) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

form of **23** failed. Due to lack of material no further work was possible, and the identity of the substance remains in doubt.

4α,10β-Dimethyl-4β-carbomethoxy-*trans*-decalone-9 (2).—A solution of 0.610 g (2.54×10^{-3} mole) of hydroxy ester **23**, mp 73.5–76.5°, in 35 ml of reagent grade acetone was treated with Jones reagent[24] exactly as in the procedure for the preparation of **27** from **12** described above. The crude product, after washing with pentane, was 0.550 g (91%) of keto ester **2**, mp 85–89°. An analytical sample prepared by recrystallization from pentane had mp 87.5–88.5° and the following spectral properties: λ_{max}^{KBr} 5.80 μ (broad); $\delta_{TMS}^{CCl_4}$ 0.92 (3 H, s, H_3C—C<), 1.18 (3 H, s, >C(CH_3)—$COOCH_3$), and 3.64 ppm (3 H, s, H_3COOC–).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.59; H, 9.36.

4α,10β-Dimethyl-4β-carboxy-9β-hydroxy-*trans*-decalin (32).—A mixture of 0.252 g (1.05×10^{-3} mole) of hydroxy ester **23**, mp 73.5–76.5°, 1.40 g of potassium hydroxide, 1.0 ml of water, and 9.5 ml of diethylene glycol was heated to 160°.[17] After the water had evaporated, the mixture was blanketed with nitrogen and stoppered, and allowed to stand for 20 days at 165 ± 5°. The brown solution was diluted with water and extracted with chloroform. The aqueous phase was then acidified with dilute hydrochloric acid and extracted with chloroform. This organic layer was dried, filtered, and evaporated to afford 0.289 g of residue, which was chromatographed on 6 g of silicic acid. Elution with 7:3 ether–hexane afforded 0.165 g (70%) of hydroxy acid **32**, mp 139–142.5°. Recrystallization from ether–hexane afforded the analytical sample: mp 143–144.5°; λ_{max}^{KBr} 2.90, 3.0–4.3 (broad), and 5.88 μ.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80; neut equiv, 226. Found: C, 69.07; H, 9.73; neut equiv, 230.

Conversion of 32 to 23.—A solution of 0.040 g (1.8×10^{-4} mole) of **32** in 10 ml of anhydrous ether was treated with a large excess of ethereal diazomethane at room temperature for 2 hr. Evaporation and crystallization gave 0.019 g of **23**, mp 60–64°. Recrystallization from ether–hexane afforded 0.016 g, mp 73.5–75°, which was identified as **23** by its infrared spectrum. If the mixture was evaporated as soon as the diazomethane was added, acidic material was recovered.

4α,10β-Dimethyl-4β-carboxy-*trans*-decalone-9 (33).—To a solution of 0.032 g (1.42×10^{-4} mole) of hydroxy acid **32**, mp 139–142°, in 1.7 ml of distilled acetone was added dropwise 0.18 ml of Jones reagent.[24] The mixture, which had turned brown, was stirred for 5 min, diluted with brine, and extracted with ether. The ether layer was dried, filtered, and evaporated to give 0.028 g of white solid. Recrystallization from ether–hexane yielded 0.016 g (51%) of **33**, mp 154.5–156°. An analytical sample prepared by further recrystallization from ether–hexane had mp 156–157°; λ_{max}^{KBr} 3.0–4.4 (broad) and 5.84–5.92 μ.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.48; H, 9.01.

Keto acid **33** was also prepared by oxidation of diol **34** (*vide infra*) with Jones reagent[24] by the procedure used for the oxidation of **12** to **27** described above, except that the organic layer was not extracted with sodium bicarbonate solution. The yield of **33**, mp 135–140°, was 94%.

Conversion of 33 to 2.—A solution of 0.025 g (1.12×10^{-4} mole) of **33**, mp 146–155°, in 10 ml of anhydrous ether was treated with a large excess of freshly distilled ethereal diazomethane at room temperature for 2 hr. Evaporation afforded an oil which was identified as **2** by comparison of its infrared spectrum with that of an authentic sample. If the reaction mixture was evaporated as soon as the diazomethane was added, acidic material, mp 63–140°, was recovered.

4α,10β-Dimethyl-4β-hydroxymethyl-9β-hydroxy-*trans*-decalin (34).—A solution of 0.383 g (1.59×10^{-3} mole) of hydroxy ester **23**, mp 73–76°,[3] in 30 ml of dry ether was added to a suspension of 0.486 g of lithium aluminum hydride in 5 ml of ether. The mixture was refluxed for 2 hr and was then treated with ice, followed by cold concentrated sulfuric acid. The aqueous layer was thoroughly extracted with ether and the combined organic layers were dried over potassium carbonate, filtered, and evaporated to yield 0.326 g (96%) of white crystals, mp 138–148°. Recrystallization from ether afforded 0.279 g (82%) of **34**, mp 143–144°. The analytical sample had mp 144.5–145° and the following spectral properties: λ_{max}^{KBr} 3.0 μ; $\delta_{TMS}^{CDCl_3}$ 0.87 (3 H, s, H_3C—C<), 0.96 (3 H, s, H_3C—C<), and *ca.* 3.58 ppm (2 H, q, $HOCH_2$—C<).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.23; H, 11.22.

4β,10β-Dimethyl-4α-hydroxymethyl-9β-hydroxy-*trans*-decalin (35).—An 0.583-g sample of hydroxy ester **36**, mp 89–95°,[3] was treated in ether solution with excess lithium aluminum hydride for 24 hr. The mixture was treated with dilute sulfuric acid and worked up in the customary manner to afford 0.753 g of yellow oil from which 0.202 g (39%) of diol **35**, mp 116–128°, crystallized. An analytical sample, prepared by recrystallization from ether–hexane, had mp 122–124° and the following spectral properties: λ_{max}^{KBr} 3.05 μ; $\delta_{TMS}^{CDCl_3}$ 0.79 (3 H, s, H_3C—C<), 0.92 (3 H, s, H_3C—C<), and 3.25 ppm (2 H, q, $HOCH_2$—C<).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.39; H, 11.27.

4α,10β-Dimethyl-4β-carbomethoxy-8-hydroxymethylene-*trans*-decalone-9 (38).—According to the procedure used for preparation of the hydroxymethylene derivative of keto ester **1**,[3] 0.48 g of sodium hydride dispersion (Metal Hydrides, Inc.; 62.4% sodium hydride) was added to a solution of 0.594 g (2.49×10^{-3} mole) of keto ester **2**, mp 88–89.5°, in 5.2 ml of ethyl formate (dried by distillation from calcium chloride) immersed in an ice–ethanol bath. Methanol was added (three drops) and the mixture was magnetically stirred for 1.5 hr, after which time further stirring was impeded by precipitate. The ice–ethanol bath was removed, 10 ml of dry ether was added, stirring was resumed for an additional 3.5 hr, and 25 ml of ice and water was added, dissolving all the precipitate. The aqueous layer was extracted with 10 ml of ether to remove the sodium hydride dispersion mineral oil and any unchanged starting material. The combined ether layers were extracted with 10 ml of 2% aqueous sodium hydroxide, and the extract was combined with the original aqueous layer. Acidification of this cooled aqueous layer with cold, concentrated hydrochloric acid gave creamy, white crystals which were collected by filtration, washed with water, and air-dried. In this manner, there was obtained 0.563 g (85%) of α-formyl keto ester **38**, mp 135–137.5°. This α-formyl adduct gave an instantaneous, deep purple color with ferric chloride solution. Several recrystallizations from *n*-pentane containing a little ether furnished an analytical sample in the form of long, white needles: mp 132.5–134°; $\lambda_{max}^{95\%\ EtOH}$ 292 μ (ε 8200); λ_{max}^{KBr} 5.79 and 6.22 μ (broad); $\delta_{TMS}^{CDCl_3}$ 1.02 (3 H, s, H_3C—C<), 1.22 (3 H, s, >C(CH_3)—$COOCH_3$), 3.63 (3 H, s, H_3COOC–), 8.67 (1 H, d, $J \sim 2.5$ Hz, $HC(OH)=\rightleftharpoons HC(=O)$–), and 14.70 ppm (1 H, d, $J \sim 2.5$ Hz, HO–).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.51; H, 8.25.

4α,10β-Dimethyl-4β-carbomethoxy-8α-(3-oxobutyl)-*trans*-decalone-9 (39).—To a suspension of 0.563 g (2.12×10^{-3} mole) of hydroxymethylene ketone **38**, mp 135–137.5°, in 9 ml of dry methanol, immersed in an ice–ethanol bath, was added, at one time, a cooled solution of 0.056 g (2.43×10^{-3} g-atom) of sodium in 2 ml of methanol. When the starting material had dissolved, a cold solution of 1.3 g (4.56×10^{-3} mole) of the methiodide of 1-diethylaminobutanone-3,[25] mp 55–70°, in 2 ml of methanol was added from a dropping funnel over a period of 5 min. Upon completion of the addition, the reaction vessel was flushed several times with nitrogen. The ice–ethanol bath was removed, and the mixture was magnetically stirred for 20.5 hr in a nitrogen atmosphere protected from moisture by a drying tube filled with Drierite. The mixture was evaporated under reduced pressure to *ca.* one-half of its original volume, cooled, and acidified with 3 ml of 10% hydrochloric acid. The reaction mixture was diluted with brine and was extracted with ether and methylene chloride. The extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to afford 0.670 g of dark red oil, which was chromatographed on 33 g of acid-washed alumina. Elution with ether–pentane provided 0.410 g (64%) of crude, crystalline Michael adduct **39**. One recrystallization from hexane gave 0.365 g (57%) of **39**, mp 101–103°. Several recrystallizations from pentane containing a little ether gave an analytical sample as clusters of white needles: mp 100–101°; λ_{max}^{KBr} 5.78 and 5.84 μ; $\delta_{TMS}^{CDCl_3}$ 0.96 (3 H, s, H_3C—C<), 1.19 (3 H, s, >C(CH_3)—

(25) The methiodide was prepared according to E. C. duFeu, 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)].

$COOCH_3$), 2.12 (3 H, s, H_3C—C(=O)–), and 3.69 ppm (3 H, s, H_3COOC–).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.22.

4α,10β-Dimethyl-4β-carbomethoxy-1,2,3,4,5α,6,7,8β,10,12,13,14-dodecahydrophenanthrone-12 (37).—A cold solution of 0.061 g (2.65×10^{-3} g-atom) of sodium in 10 ml of dry methanol was added dropwise over 10 min to a solution of 0.365 g (1.18×10^{-3} mole) of Michael adduct **39**, mp 101–103°, in 15 ml of methanol immersed in an ice–ethanol bath. When the addition was complete, the bath was removed, the system was flushed with nitrogen several times and the mixture was refluxed for 8 hr. It was then cooled, diluted with brine, and extracted with ether. The ethereal extract was washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 0.365 g of crude enone **37**, mp 146–159°. One recrystallization from hexane gave 0.287 g (84%) of **37**, mp 159–164°. Further recrystallization from hexane did not sharpen the melting point. A specimen of **37** was purified by elution chromatography on alumina to mp 158.5–160.5°; it had the following spectral properties: λ_{max}^{KBr} 5.80, 6.00, and 6.16 μ; λ_{max}^{MeOH} 239 mμ (ε 22,000); $\delta_{TMS}^{CCl_4}$ 0.94 (3 H, s, H_3C—C<), 1.17 (3 H, s, >C(CH_3)—$COOCH_3$), 3.64 (3 H, s, H_3COOC–), and 5.72 ppm (1 H, d, J = 1.7 Hz, H—C(=)–).

A specimen of authentic naturally derived **37**,[19] mp 115.5–116.0° (lit.[19] mp 116–118°) had λ_{max}^{KBr} 5.80, 5.95, and 6.19 μ; the nmr spectrum of this material was identical with that of the 158.5–160.5° material.

Methyl *dl*-Podocarpate (40).—To a refluxing solution of 0.100 g (3.45×10^{-4} mole) of enone **37**, mp 159–164°, in 25 ml of dry carbon tetrachloride was added, at one time, 0.096 g (5.39×10^{-4} mole) of freshly recrystallized N-bromosuccinimide. The mixture was refluxed for 50 min, cooled, and partitioned between water and ether, whereupon crystals which had appeared during cooling dissolved. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 0.166 g of brown oil which was chromatographed on 10 g of acid-washed alumina. Two fractions, eluted successively with 8:1 and 9:1 ether–pentane, furnished 0.034 g (34%) of **40**, mp 172–180°. Several recrystallizations of **40** from hexane containing a little acetone gave an analytical sample which crystallized as long, white needles: mp 184.5–185° (lit.[18c] mp 193°); λ_{max}^{KBr} 2.86, 5.83, 6.18 μ. The infrared spectrum of **40** in chloroform solution was identical with that of an authentic sample of methyl *d*-podocarpate, mp 210–211.5°, prepared by treatment of *d*-podocarpic acid with diazomethane.

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.03; H, 8.20.

Registry No.—**2**, 15292-89-4; **3**, 15292-90-7; **12**, 15292-91-8; **13**, 15292-92-9; **14**, 15292-93-0; **15**, 15292-50-9; **17**, 15292-95-2; **19**, 15268-85-6; **20**, 15268-86-7; **23**, 15268-87-8; **24**, 15268-88-9; **25**, 15268-89-0; **26**, 15268-90-3; **27**, 15285-90-2; **28**, 15268-91-4; **29**, 15268-92-5; **30**, 15268-93-6; **31**, 15268-94-7; **32**, 15268-95-8; **33**, 15268-96-9; **34**, 15268-97-0; **35**, 15268-98-1; **37**, 15268-99-2; **38**, 15269-00-8; **39**, 15269-01-9; **40**, 15292-67-8.

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7-Deazaadenine Ribonucleosides. The Use of Periodate Oxidation in Degradation Studies[1a]

T. UEMATSU AND R. J. SUHADOLNIK[1b,c]

Research Laboratories, Department of Biochemistry, Albert Einstein Medical Center, Philadelphia, Pennsylvania

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A number of purine and pyrimidine ribonucleoside analogs have been synthesized in the search for purines possessing antitumor and antibacterial activity. Three naturally occurring, biologically active 7-deazaadenine ribonucleosides have been recently isolated from *Streptomyces*.[2,3] Two of these nucleosides are tubercidin (**1**) and toyocamycin (**3**).

The structure of tubercidin and toyocamycin have been reported,[4,5] as well as the synthesis of the aglycon of toyocamycin.[6] The proof of structure of toyocamycin did not proceed *via* the intact aglycon since the 7-deazaadenine nucleosides are not as easily hydrolyzed as purine nucleosides.[5] Ohkuma[5] and Suzuki and Maruma[7] reported the isolation of ribose from toyocomycin and tubercidin. The yields of ribose were very low, and the intact aglycon was not isolated. Refluxing 7-deazaadenine ribonucleosides in acidic phenylhydrazine solution does not cleave the N-ribosyl bond. A careful examination of the chemical reactions of the purine ribonucleosudes[8,9] indicated that the stability of the N-glycosyl bond of 7-deazaadenine ribonucleosides might be significantly lowered by altering the ribosyl portion of the nucleoside. This study reports on the periodate oxidation of the 7-deazaadenine ribonucleosides, tubercidin and toyocamycin, the isolation of the aglycones, and the isolation of carbon atoms 1 and 2 of the ribose moiety as glyoxal bisphenylosazone by employing the methods as described by Khym and Cohn[9] and Barry.[10] By using this procedure, 4-hydroxy-5-cyanopyrrolo-[2,3-*d*]pyrimidine (**8**) has also been isolated by two methods from toyocamycin. Method A (Scheme I, compounds **3**, **4**, **5**, **8**) affords a 71% yield compared to 19% for method B (Scheme I, compounds **3**, **7**, **8**). Compound **8** had not been previously reported in the degradation studies on toyocamycin as described by Ohkuma.[5] Subsequent treatment of **8** with hydriodic acid and red phosphorus allows the isolation of 4-hydroxypyrrolo[2,3-*d*]pyrimidine (**9**). The product is identical with chemically prepared 4-hydroxypyrrolo-

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