Resin Acids. XXI.[1,2] Synthesis of Methyl Podocarp-8(14)-en-13-on-15-oate from the Levopimaric Acid–Formaldehyde Adduct

WERNER HERZ* AND V. BABURAO

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

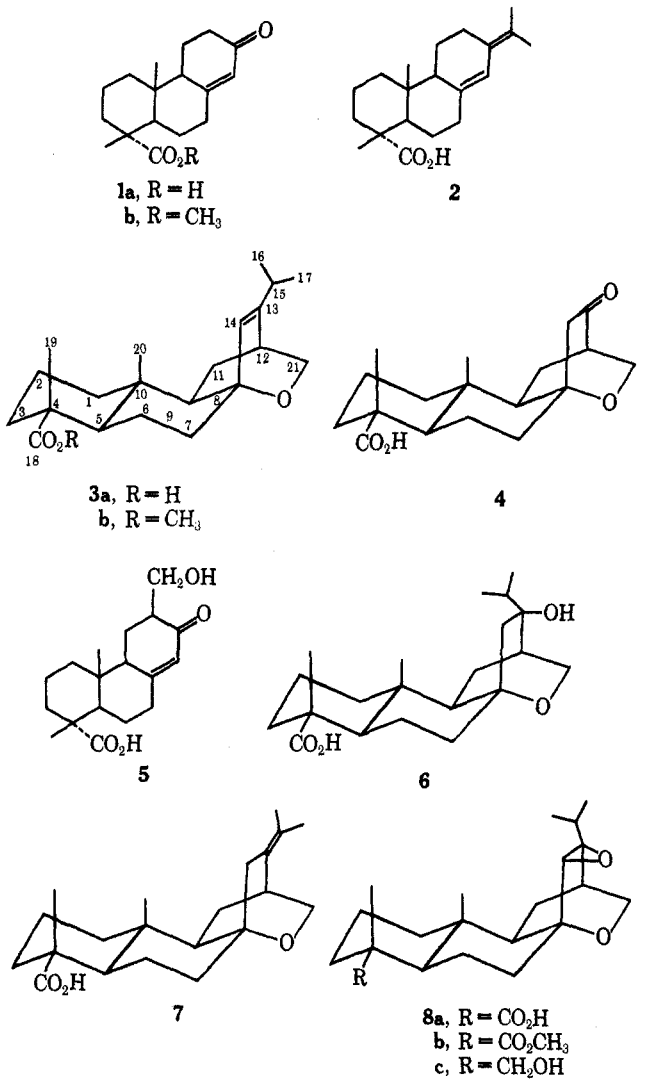
Received April 5, 1971

The transformation of the readily available levopimaric acid–formaldehyde adduct **3a** to the title compound **1b** by a convenient five-step sequence is described. Four of the steps proceed in quantitative or nearly quantitative yield. The first step involves an unusual oxidation of a cyclic ether to a δ lactone in the presence of a secondary hydroxyl group. In the last step three reactions, reductive elimination of an acetoxy group, β elimination of an acyloxy function, and decarboxylation, are effected at once.

The distribution of functional groups in (+)-podocarp-8(14)-en-13-on-15-oic acid (**1a**) makes this substance an attractive and potentially important starting material or relay for the synthesis of di- and triterpenoids. While the original method of preparation of **1a** by controlled ozonolysis of neoabietic acid (**2**)[3,4] as improved recently[5] is more convenient[6] than multistep routes[6,7] departing from dehydroabietic acid, studies on the use of **1a** have nevertheless been severely hampered by the relative scarcity of neoabietic acid whose isolation from pine gum or rosin in the requisite amounts is quite laborious.[8]

The levopimaric acid–formaldehyde adduct **3a** can be obtained very conveniently and in good yield from pine oleoresin.[9] It occurred to us that **3a** represented a potential precursor of **1a** if it could be transformed in good yield to **4**. The latter possesses the appropriate functionalities for an acid- or base-catalyzed cleavage to **5** which in turn could conceivably undergo a retro-aldol reaction to **1a**. In the following we describe the realization of our goal, albeit by a route which differs somewhat from the one envisioned originally.

Our previous experience with Diels–Alder adducts of levopimaric acid[10–12] indicated that reagent approach to the double bond of **3a** would, for steric reasons, occur from the side of the oxymethylene bridge and that oxymercuration–demercuration[13] would therefore result in the alcohol **6** by the mechanism suggested[14] for cis-oxymercuration of those olefins where back-side attack by an external nucleophile, and hence trans addition, is inhibited.[15] β elimination of the elements of water from **6** or an appropriate derivative should result in the isopropylidene compound **7** rather than **3a** because of the steric hindrance offered to attack of base on the bridge hydrogen trans to the hydroxyl group. Subsequent ozonolysis of **7** would furnish **4**.



In the event, **3b** was recovered unchanged from treatment with mercuric acetate–THF–H_2O although epoxidation proceeded normally to give **8b**. The stereochemistry assigned to this substance is based on analogy[11,12] and on the chemical shift (0.8 ppm) of the angular methyl group which would be expected to be more deshielded in the alternative arrangement with the oxygen atom oriented toward the C-10 methyl group. Acid-catalyzed ring opening of such epoxides does not produce glycols but 14 ketones for steric reasons that have been discussed previously;[11,12] similarly, treatment of **8b** with excess lithium **alumi-**

(1) Previous paper: W. Herz, R. C. Ligon, H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **35**, 3338 (1970).

(2) Supported in part by a grant from the National Science Foundation (GP-12582).

(3) G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.*, **70**, 339 (1948).

(4) W. M. Hoehn, U. S. Patent 2,682,555.

(5) S. W. Pelletier, K. N. Iyer, and C. W. J. Chang, *J. Org. Chem.*, **35**, 3535 (1970).

(6) A. W. Burgstahler and L. R. Worden, *J. Amer. Chem. Soc.*, **86**, 96 (1964).

(7) E. Wenkert, R. W. J. Carney, and C. Kaneko, *ibid.*, **33**, 4440 (1961).

(8) V. M. Loeblich and R. V. Lawrence, *J. Org. Chem.*, **21**, 610 (1956).

(9) B. A. Parkin, Jr., and G. W. Hedrick, *ibid.*, **30**, 2356 (1965).

(10) N. Halbrook, R. V. Lawrence, R. L. Dressler, R. C. Blackstone, and W. Herz, *ibid.*, **29**, 1017 (1964).

(11) W. Herz, R. N. Mirrington, H. Young, and Y. Y. Lin, *ibid.*, **33**, 4210 (1968).

(12) W. Herz and R. C. Blackstone, *ibid.*, **34**, 1257 (1969).

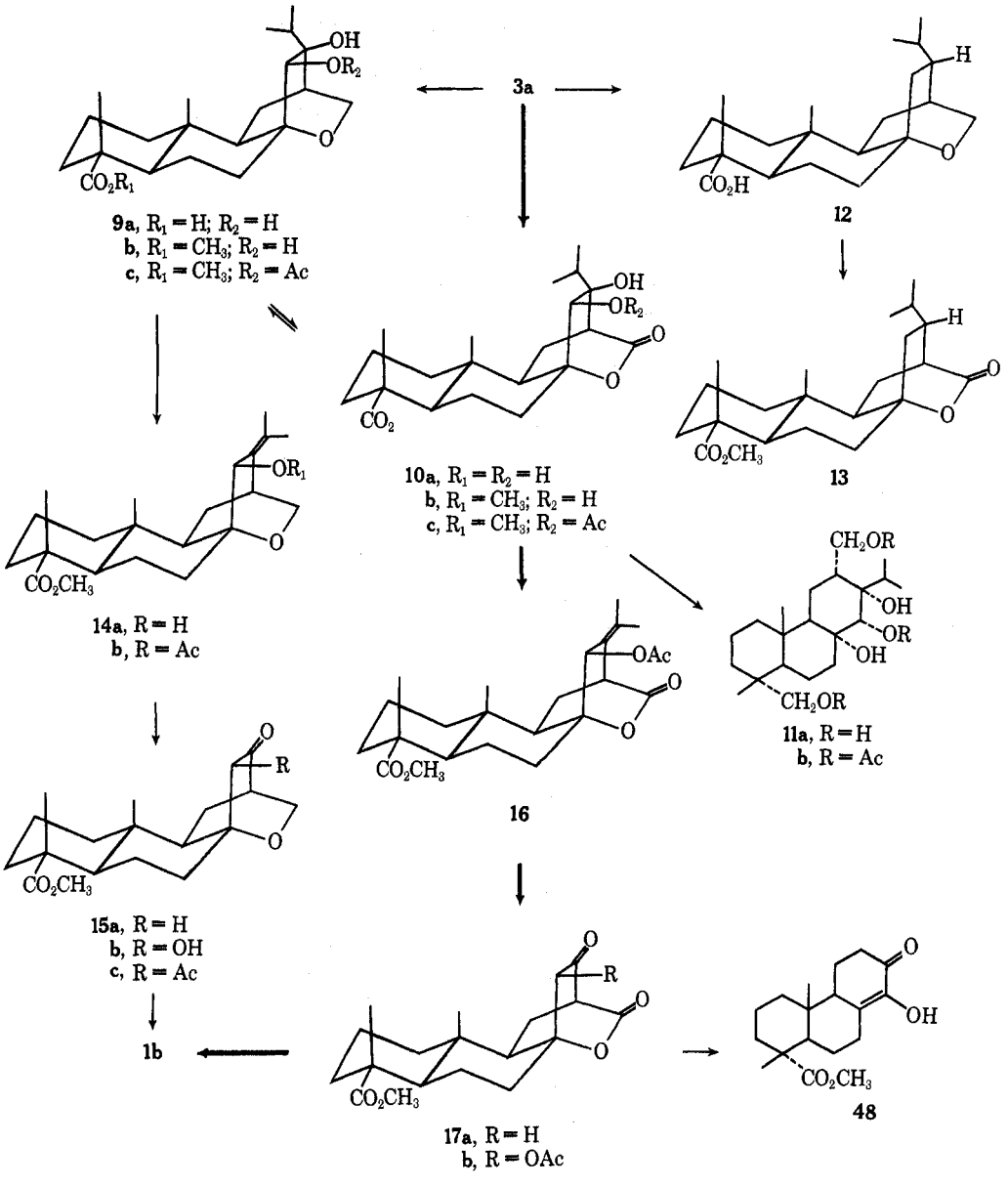
(13) The acid sensitivity of the adduct **3a** precluded adoption of more conventional hydration techniques.

(14) T. G. Traylor and A. W. Baker, *J. Amer. Chem. Soc.*, **85**, 2746 (1963); T. G. Traylor, *ibid.*, **86**, 244 (1964).

(15) Diels–Alder adducts of levopimaric acid fulfil this requirement.[11,12,16]

(16) N. Langlois and B. Gastambide, *Bull. Soc. Chim. Fr.*, 2966 (1965).

SCHEME I



num hydride produced only **8c** without affecting the oxide ring due to steric interference with nucleophilic attack from the rear. A different approach to **4** was therefore sought.

$KMnO_4$ oxidation of **3a** gave, after methylation with diazomethane, two substances, A and B. Limiting the amount of oxidizing agent[17] resulted in sole formation of more polar material A; treatment of **3a** with excess $KMnO_4$ or further oxidation of A resulted in quantitative conversion to the less polar substance B.

Structure **9b** (Scheme I) was assigned to A on the following grounds. The ir spectrum showed two hydroxyl bands and one carbonyl frequency at 1720 cm^{-1} associated with the ester function. In the nmr spectrum the broadened singlet of **3b** at 5.79 ppm due to the vinyl proton had been replaced by a sharp singlet at 3.48 ppm assignable to H-14, now geminal to a hydroxyl group. The C-10 methyl signal exhibited a normal chemical shift (0.90 ppm) instead of being characteristically shielded as in the precursor **3b**, but the two broadened doublets of the oxymethylene protons at 4.26 and 3.66 ppm had been retained. Formation of an acetonide established that the two hydroxyl groups were vicinal and cis. Since the acetonide and the cyclic manganate ester involved[18] in formation of a glycol possess large steric requirements, it could be surmised that only that glycol had been formed in which the hydroxyl groups were oriented toward the oxymethylene bridge, *i.e.*, **9b**. In the other arrangement, the C-10 methyl resonance should be deshielded by the 14-hydroxyl group; this was not observed.

Compound B also possessed two hydroxyl groups, one of which was strongly bonded intramolecularly, and two carbonyl groups (ir bands at 1720 and 1760 cm^{-1}). The second of these frequencies was attributed to a strained δ-lactone function as shown in **10b**, since

(17) The amount of $KMnO_4$ necessary to convert **3a** to **9b** or to **10b** exclusively was approximately 50% more than that calculated on the basis of complete reduction of Mn^{+7} to MnO_2 but corresponded approximately to reduction to Mn^{+5}. Consumption of oxidizing agent through conversion of **3a** or **9b** to a ketol (*cf.* R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, New York and Amsterdam, 1964, p 60) was not a factor.

(18) K. B. Wiberg and K. A. Saegebarth, *J. Amer. Chem. Soc.*, **79**, 2822 (1957).

the nmr spectrum lacked the peaks of the oxymethylene bridge but displayed a sharp one-proton signal at 4.2 ppm (H-14) and a one-proton doublet of doublets at 3.24 ppm (H-12, α to the lactone function). The proposed chemical relationship between **9b** and **10b** was demonstrated by reduction of **10b** to **9b** with the $NaBH_4$–BF_3 reagent. Lithium aluminum hydride reduction of **10b** gave a noncrystalline pentol **11a** which was characterized as the triacetate **11b**.

The formation of lactones from cyclic ethers by $KMnO_4$ oxidation has not to our knowledge been observed previously. The presence of the hydroxyl groups of **9b** is not responsible for this unusual oxidation reaction since $KMnO_4$ treatment of **12** followed by methylation gave a 60% yield of **13**. Presumably, by analogy with $KMnO_4$ oxidation of hydrocarbons,[19] permanganate ion abstracts a hydrogen atom from the oxymethylene group of **9a** or **12** and gives a radical pair which is trapped momentarily in the solvent cage. Recombination yields a hypomanganate ester which undergoes hydrolysis to a hemiacetal. Further oxidation of the latter affords **10a** and **13**. However, it is difficult to understand why oxidation of **9** and **12** should proceed so much more readily than that of ordinary ethers.

The observation that the secondary hydroxyl groups of **9a**, **9b**, **10a**, and **10b** were not affected by basic $KMnO_4$ while oxidation of the ether to a lactone, presumably a more difficult reaction, took place readily is worthy of comment. Other basic oxidizing agents were equally ineffective in attacking the secondary hydroxyl group of **9b** or **10b**,[20] presumably because its oxidation would require hydride abstraction in an extremely hindered environment. On the other hand, oxidation of similar, 14-hydroxy derivatives has been readily accomplished with chromic oxide in an acidic medium;[11,12] this reagent could not be tested in the present instance because of acid sensitivity of the oxymethylene bridge.

Treatment of **9b** with thionyl chloride–pyridine resulted in formation of a sulfite rather than in the hoped for elimination of the tertiary hydroxyl group. Protection of the secondary hydroxyl group prior to dehydration seemed therefore necessary and was effected by quantitative conversion of **9b** to the acetate **9c**.[21] Subsequent exposure to thionyl chloride–pyridine afforded a quantitative yield of **14b** which possessed the requisite spectral properties (downfield shift of the now allylic H-14 to 5.8 ppm, appearance of a complex one-proton signal at 2.73 ppm attributable to newly-allylic H-12, two vinyl methyl resonances) and was hydrolyzed to **14a** with dilute methanolic KOH. Ozonolysis of **14a** (ethyl acetate, −78°) and decomposition of the ozonide with dimethyl sulfide[22] furnished the ketol **15b** (54%) which was somewhat unstable. Ozonolysis of **14b** resulted in considerable improvement and gave a quantitative yield of noncrystalline **15c** which was characterized as the 2,4-dinitrophenylhydrazone.

Removal of the isopropyl group from the adduct **3a** had thus been accomplished in excellent overall yield. To achieve the cleavage reaction envisioned earlier without introducing complications, it was first necessary to remove the functional group at C-14. Attempts to effect reductive elimination of the acetoxy group with combinations of zinc and acetic acid, acetic anhydride, and formic acid or with calcium–liquid ammonia were frustrated by formation of polymeric material. Treatment of **15c** with chromous chloride resulted in a complex mixture which was refluxed with methanolic sodium hydroxide in an effort to convert **15a**, shown to be present by nmr analysis, to the desired enone **1b**. Analysis of the product indeed established the presence of **1b**, but the estimated yield was only 10–15%.

Lactone **10b** was now subjected to the reaction sequence which had been used successfully for deisopropylating **9b**, since it was hoped that the lactone analog **17** might be cleaved under the acid conditions of the chromous chloride reduction and might then be induced to decarboxylate fairly readily. This expectation was realized. Acetylation of **10b** to **10c** and dehydration of the latter to **16** proceeded in quantitative yield. Ozonolysis of **16** (ethyl acetate, −78°) followed by dimethyl sulfide work-up gave a 95% yield of the relatively unstable ketoacetate **17b** which could not be induced to crystallize but possessed spectral properties (sharp one-proton peak at 5.52 ppm due to H-14, broadened one-proton doublet at 3.5 ppm due to H-12, acetate singlet, two methyl singlets, and no vinyl methyl resonances) consonant with the assigned structure.

Attempts to remove the acetate function of **17b** reductively with zinc–acetic acid or calcium–liquid ammonia again yielded only polymeric material. When, on the other hand, a solution of **17** in tetrahydrofuran was refluxed with chromous chloride, chromatography of the crude product gave two crystalline compounds. The first, isolated in 40% yield, was indeed the desired **1b**; the second (20%) was the diosphenol **18** which has recently been encountered[23] as a transformation product of **1b**.

Formation of **1b** and **18** from **17b** can be rationalized as follows. Under the influence of the acidic reagent the normal reduction product **17a** undergoes β elimination of the lactone function to give the β-keto acid **19** which undergoes decarboxylation to **1b**. Formation of **18** is the result of acetate hydrolysis[24] and lactone cleavage prior to reductive elimination. Mild conditions should suppress this side reaction and, indeed, when the reduction was carried out at room temperature only **1b** was formed. However, the reaction proceeded only slowly at room temperature; after 1 week, the yield of **1b** did not exceed 40%. Nevertheless, since each of the preceding four steps **3** → **10a** → **10b** → **16** → **17b** proceeds in excellent yield, the new

(19) K. Wiberg, Ed., "Oxidation in Organic Chemistry," Academic Press, New York and London, 1965, p 37.

(20) Attempted oxidation of **9b** or **10b** with Sarett, Cornforth, and Collins reagent resulted in recovery of starting material. Use of Jones reagent gave complex mixtures due to acid-catalyzed ether cleavage.

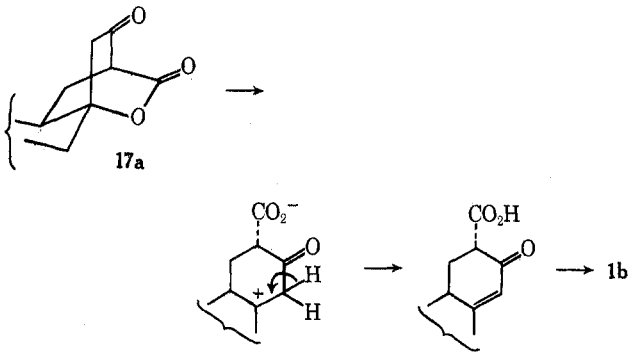
(21) The nmr spectrum of this substance (see Experimental Section) exhibited slight deshielding of the C-10 methyl group and some shielding of one of the methyls of the isopropyl group, indicating slight distortion of the C-13–C-14 bridge toward ring A probably due to dipolar interaction between the ether oxygen and the acetate function.

(22) J. J. Pappas, W. P. Keaveney, E. Grancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

(23) S. W. Pelletier, C. W. J. Chang, and K. N. Iyer, *J. Org. Chem.*, **34**, 3477 (1969).

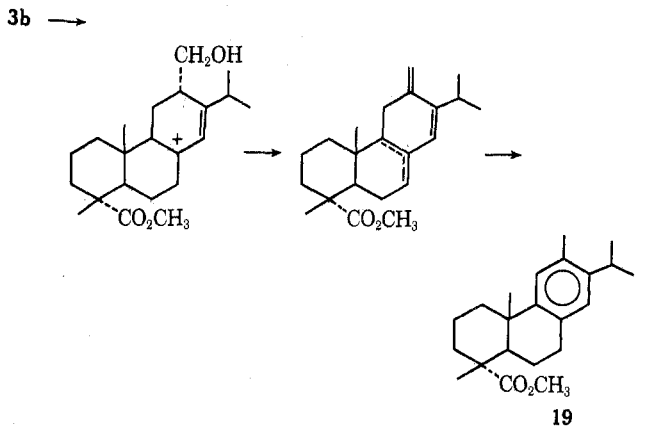
(24) As monitored by nmr spectroscopy, the initial step in the decomposition of **17b** prior to formation of intractable material is hydrolysis of the acetate function.

route to **1b** represents a useful alternative to its preparation from neoabietic acid.



17a

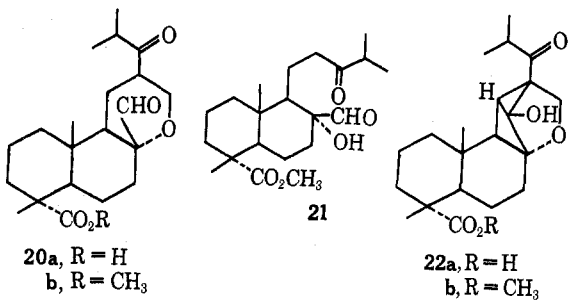
In the following, we briefly describe several other transformations of **3** or its derivatives which possess features of interest. In an attempt to introduce halogen at an allylic position with a view toward eventual removal of the isopropyl side chain, **3b** was refluxed with *N*-bromosuccinimide in benzene. This resulted not in substitution but in formation (90–95% yield) of methyl 12-methyldehydroabietate (**19**).[25] The same substance was obtained in practically quantitative yield by refluxing the adduct with iodine or *p*-toluenesulfonic acid in benzene, presumably by the path indicated below.[26]



19

Cleavage of the C-13,C-14 double bond of **3a** by ozonolysis[11,12] resulted in the formation of a complex mixture from which the ketoaldehyde **20** was isolated in low yield. A much better route to this substance was oxidation of **9a** with sodium metaperiodate. Acid treatment of **20** in an attempt to effect a retroaldol cleavage to **21** was unproductive; dilute base resulted in aldol condensation to **22** rather than retro-aldol reaction, as indicated by the nmr spectrum (H-14 at 4.10, H-15 at 4.16 and 3.74, H-16 at 2.98 ppm). Since the resonance of the C-10 methyl group at 0.91 ppm was not deshielded, the hydroxyl group of **22** is oriented toward the oxymethylene bridge. Efforts to utilize **20** and **22** for further studies are described in the Experimental Section.

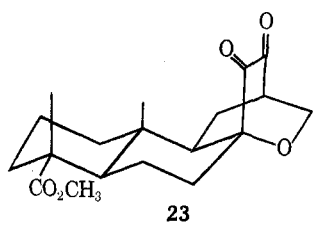
In one run involving chromous chloride reduction of **15c**, the reaction mixture was accidentally exposed to the atmosphere. Quenching of the reaction after several hours resulted in a 65% yield of **23**. In an attempt to determine the nature of the oxidizing agent, addition of chromic chloride without prior reduction to chromous chloride also effected conversion of **15c** to **23**. The nature of the reagent responsible for this unexpected oxidation of a ketol to a diketone is currently under investigation.



20a, R = H
b, R = CH_3

21

22a, R = H
b, R = CH_3



23

Experimental Section[27]

Epoxidation of 3b.—A solution of 2.0 g of **3b**, prepared as described[9] from **3a**,[28] and 1 g of *m*-chloroperbenzoic acid was stirred for 18 hr at room temperature and then washed several times with 5% KI solution, sodium thiosulfate solution, and water. The dried organic layer was evaporated at reduced pressure. The residue was taken up in ether and the ether extract washed, dried, and evaporated. The crystalline residue of **8b**, wt 2.1 g, was recrystallized from hexane and had mp 109–111°; ir bands at 1720 and 1230 cm^{-1} (ester); nmr signals at 3.94 and 3.52 (m, H-21), 3.62 (methoxyl), 3.12 (H-14), 1.17 (C-4 methyl), 0.80 (C-10 methyl), 1.06 and 0.78 ppm (d, J = 7 Hz, isopropyl methyls); $[\alpha]^{22}D$ +64.5° ($CHCl_3$).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45; O, 17.66. Found: C, 72.47; H, 9.44; O, 18.11.

Lithium aluminum hydride reduction of 1 g of **8b** in 30 ml of THF in the usual fashion gave, after acid hydrolysis and isolation of the product in the usual manner, 0.8 g of a gum which could not be induced to crystallize. The nmr spectrum indicated that the epoxide ring had been retained (H-14 signal at 3.12 ppm) but that the ester function had been reduced.

$KMnO_4$ Oxidation of 3a. A.—To a solution of 10 g of **3a** in 50 ml of 3% NaOH solution was added dropwise with stirring 4.5 g of $KMnO_4$[29] in 50 ml of water. Stirring was continued for an additional 15 min, following which the contents were mixed with a solution of 5 g of hydroxylamine hydrochloride in 50 ml of water. Addition of concentrated HCl, filtration, and washing with water gave 6.7 g of solid **9a** which was recrystallized from methanol–water and then melted at 279°.

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35; O, 21.83. Found: C, 68.88; H, 9.12; O, 22.22.

Methylation of **9a** with diazomethane gave **9b**, identical in all respects with a sample isolated from the mixture as described below.

B.—Oxidation of 10 g of **3a** in 50 ml of 4% sodium hydroxide solution with 10 g of $KMnO_4$ in 100 ml of water in the manner described above gave 9.2 g of solid product which was dissolved in chloroform–methanol and methylated with ethereal diazomethane. Removal of solvent gave 9.3 g of solid material which on tlc showed two spots of very similar R_f value. The material was extracted with three 20-ml portions of benzene–acetone (4:1). The residue **10b**, wt 1.5 g, was homogeneous on

(25) D. K. Black and G. W. Hedrick, *J. Org. Chem.*, **32**, 3758 (1967).

(26) In the case of the NBS reaction the acid catalyst may be the HBr contaminant usually present in commercial samples or may be produced by allylic substitution and spontaneous dehydrohalogenation.

(27) For details concerning methods, see W. Herz and J. Schmid, *J. Org. Chem.*, **34**, 3464 (1969), footnote 52.

(28) We would like to thank Dr. Glen W. Hedrick, Naval Stores Laboratory, Olustee, Fla., for a generous supply of the adduct **3a**.

(29) Use of less $KMnO_4$ resulted in formation of a mixture of **3a** and **9a**.

tlc. Evaporation of the extracts gave 6.7 g of a mixture which was dissolved in 10 ml of benzene–acetone (4:1) chromatographed over 100 g of F-20 alumina and eluted with benzene–acetone (4:1). The less polar fractions contained an additional 1.7 g of **10b**; the latter fractions eluted 6 g of **9b**.

Recrystallization of **9b** from methanol gave material which had mp 182–184°; $[\alpha]^{27}D$ +80.0° (EtOH); ir bands at 3520 and 3500 (hydroxyls) and 1720 cm^{-1} (ester); nmr signals at 4.27 and 3.67 (m, H-21), 3.7 (methoxyl), 3.48 and 2.98 (OH, exchangeable with D_2O), 1.18 (C-4 methyl), 0.9 (C-10 methyl), 0.93 and 0.97 ppm (d, J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54; O, 21.20. Found: C, 69.09; H, 9.44; O, 21.17.

Recrystallization of **10b** from methanol gave needles which had mp 279°; $[\alpha]^{27}D$ +43.5° ($CHCl_3$); ir bands at 3520 and 3340 (OH), 1760 (δ lactone), and 1720 cm^{-1} (ester); nmr signals (pyridine-d_5) at 5.84 and 4.48 (OH), 4.1 (H-14), 3.72 (methoxyl), 3.28 (m, H-12), 1.19 (C-4 methyl), 0.91 (C-10 methyl), 1.13 and 1.10 ppm (d, J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.34. Found: C, 66.69; H, 8.77; O, 24.19.

C.—Oxidation of 5 g of **3a** with 10 g of $KMnO_4$ and methylation of the product with CH_2N_2 gave 4.5 g (75%) of recrystallized **10b**.

Acetonide of 9b.—A mixture of 0.5 g of **9b**, 30 ml of anhydrous acetone, and 0.2 ml of 70–80% $HClO_4$ solution was stirred overnight and diluted with water. The precipitated acetonide was recrystallized from methanol (yield quantitative) and had mp 155–157°; ir band at 1720 cm^{-1} (ester); nmr signals at 4.16 (H-14), 4.16 and 3.67 (m, H-21), 3.73 (methoxyl), 1.62 and 1.55 (methyls of acetonide), 1.18 (C-4 methyl), 1.05 and 1.00 (d, J = 7 Hz, isopropyl methyls), 0.87 ppm (C-10 methyl).

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.32; H, 9.73; O, 18.99.

Sulfite of 9b.—Treatment of 0.5 g of **9b** in 2 ml of pyridine with 0.5 ml of thionyl chloride overnight in an atmosphere protected from moisture and decomposition by pouring over ice gave a solid. Recrystallization from methanol afforded the sulfite which had mp 137–138°; no hydroxyls in ir spectrum; nmr signals at 4.36 (H-14), 4.25 and 3.75 (m, H-21), 3.68 (methoxyl), 1.18 (C-4 methyl), 1.12 and 0.9 (d, J = 7 Hz, isopropyl methyls), 0.84 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{34}O_6S$: C, 62.06; H, 8.00; O, 22.55; S, 7.29. Found: C, 62.00; H, 7.98; O, 22.55; S, 7.50.

Hydrolysis of the sulfite with 5% NaOH solution at room temperature for 6 hr followed by acidification regenerated **9b** in quantitative yield.

Oxidation of 9a.—Oxidation of 5 g of **9a** with 6 g of $KMnO_4$ and methylation of the product with CH_2N_2 gave 5.25 g (~100%) of recrystallized **10b**.

Reduction of 10b. A.—A solution of 1 g of **10b** and 21 g of boron trifluoride etherate in 30 ml of anhydrous ether was added dropwise with cooling and stirring to 0.38 g of $NaBH_4$ in 15 ml of diglyme. The mixture was refluxed for 1 hr after the addition was complete, chilled, stirred with 10 ml of 37% H_2O_2 and 10 ml of 2% NaOH solution, and extracted with ether. The organic extract was washed, dried, and evaporated. The gummy residue was triturated with methanol and deposited 0.5 g of pure **9b**.

B.—Reduction of 1 g of **10b** in 20 ml of tetrahydrofuran with 1 g of $LiAlH_4$ in 20 ml of tetrahydrofuran in the usual manner, acid hydrolysis after stirring overnight, extraction with ether, and purification in the usual fashion gave 1 g of crude **11a**. This was dissolved in 3 ml of pyridine and stirred with 4 ml of acetic anhydride overnight. Chromatography of the product over silica gel and elution with benzene afforded **11b** which was recrystallized from hexane and had mp 147–148°; ir bands at 3580 and 3450 (OH) and 1745–1720 cm^{-1} (ester and three acetates); nmr signals at 5.17 (H-14), 4.7–3.5 (c, 5 protons, H-14, H-18, and H-21), 2.18, 2.02, 2.01 (3 acetates), 1.05 (C-4 methyl), 0.85 (C-10 methyl), 0.97 and 0.96 ppm (d, J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{27}H_{44}O_8$: C, 65.30; H, 8.93; O, 25.77. Found: C, 65.57; H, 8.86; O, 25.58.

Oxidation of 12.—Oxidation of 1.5 g of the dihydroadduct **12**[9] with 1.5 g of $KMnO_4$ and work-up in the manner described for **9a** gave 1.5 g of a gummy residue which was esterified with diazomethane. Several recrystallizations afforded **13** in 60% yield: mp 164–165°; ir bands at 1745 (lactone) and 1720 cm^{-1} (ester); nmr signals at 3.67 (methoxyl), 2.7 (c, $W_{1/2}$ = 7 Hz, H-12), 1.18 (C-4 methyl), 1.00 (C-10 methyl), 0.94 and 0.92 ppm (d, J = 6 Hz, isopropyl methyls).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45; O, 17.65. Found: C, 72.53; H, 9.61; O, 18.18.

Preparation of 14b.—A solution of 20 g of **9b** in 30 ml of dry pyridine was stirred overnight at room temperature with 35 ml of acetic anhydride in an atmosphere protected from moisture, poured on ice, and extracted with ether. The organic layer was washed, dried, and evaporated. The residue was recrystallized from methanol–water and afforded, in essentially quantitative yield, **9c**, which had mp 147–148°; ir bands at 3520 (OH) and 1730–1720 cm^{-1} (acetate and carbomethoxy); nmr signals at 4.9 (H-14), 4.24 and 3.6 (m, H-21), 3.58 (methoxyl), 2.58 (OH), 2.12 (acetate), 1.13 (C-4 methyl), 1.00 (C-10 methyl), 0.90 and ppm (d, J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06; O, 22.72. Found: C, 68.25; H, 8.53; O, 22.75.

Dehydration of 10 g of **9c** in 20 ml of dry pyridine was effected by adding dropwise 2.5 ml of thionyl chloride with stirring and cooling and continuing the stirring for 20 min after addition was complete. The mixture was poured on ice and extracted with ether. The washed and dried ether extract was evaporated and afforded 9.8 g of **14b** sufficiently pure for further work. Recrystallization from pentane gave **14b** which had mp 138–139°; ir bands at 1735 (acetate) and 1720 cm^{-1} (carbomethoxy); nmr signals at 5.8 (H-14), 3.88 (c, $W_{1/2}$ = 7 Hz, H-12), 2.09 (acetate), 1.71 and 1.58 (vinyl methyls of isopropylidene), 1.13 (C-4 methyl), 0.80 ppm (C-10 methyl).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; O, 19.78. Found: C, 70.82; H, 8.92; O, 20.18.

Hydrolysis of 14b and Ozonolysis of 14a.—A mixture of 1 g of **14b** and 10 ml of 2% methanolic sodium hydroxide was stirred at room temperature. After 5 min the solid had dissolved completely and tlc showed complete disappearance of starting material. Stirring was continued for an additional 5 min, the solution was diluted with water, and the precipitated **14a** (yield quantitative) was recrystallized from methanol–water. It had mp 144–145°; ir bands at 3450 (OH) and 1720 cm^{-1} (carbomethoxy); nmr signals at 4.25 (d, J = 10 Hz, H-14, collapsed to singlet on addition of D_2O), 3.84 (c, ($W_{1/2}$ = 4 Hz, H-21), 3.67 (methoxyl), 2.8 (c, $W_{1/2}$ = 7, H-12), 2.27 (d, OH), 1.81 and 1.71 (isopropylidene), 1.12 (C-4 methyl), 0.70 ppm (C-10 methyl). Because the product had a tendency to decompose on standing it was not analyzed. Reacetylation of **14a** with acetic anhydride pyridine gave **14b** in quantitative yield.

A solution of 2 g of **14a** in 50 ml of methylene chloride was cooled to 0° and ozonized until excess ozone was detected in the KI trap. The solution was flushed with dry nitrogen to remove excess ozone, mixed with 1 ml of dimethyl sulfide, and stirred overnight. The solvents were removed at reduced pressure and the residue was taken up in ether. Repeated washing of the extracts, drying, and evaporation gave 1.8 g of a gummy residue. Tlc (benzene–methanol 9:1) showed one major and several minor spots. Chromatography over silica gel and elution with chloroform afforded 1 g of **15b** which was recrystallized from pentane–methylene chloride and had mp 160–162°; ir bands at 3420 (hydroxyl) and 1730 and 1720 cm^{-1} (carbomethoxy and ketone); nmr signals at 4.02 (H-14), 4.02 (c, $W_{1/2}$ = 4 Hz, H-21), 3.67 (methoxyl), 1.16 (C-4 methyl), 0.88 ppm (C-10 methyl).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39; O, 23.78. Found: C, 67.78; H, 8.53; O, 23.57.

Ozonolysis of 14b.—Ozonolysis of 1 g of **14b** in 20 ml of methylene chloride at acetone–Dry Ice temperature and work-up in the manner described in the previous paragraph gave 0.8 g of a gummy ketoacetate **15c**, which had a complex set of ir bands at 1745–1720 cm^{-1} and nmr signals at 5.57 (H-14), 4.1 (m, $W_{1/2}$ = 4 Hz, H-21), 3.7 (methoxyl), 2.56 (c, $W^1/_2$ = 7 Hz, H-12), 2.20 (acetate), 1.18 (C-4 methyl), 1.01 ppm (C-10 methyl). The material decomposed on standing.

The 2,4-dinitrophenylhydrazone was recrystallized from methanol and melted at 179–181°.

Anal. Calcd for $C_{27}H_{34}N_4O_9$: C, 58.05; H, 6.14; N, 10.03. Found: C, 58.59; H, 6.28; N, 9.85.

To a solution of 2 g of **15c** in 30 ml of tetrahydrofuran in a flask protected from the atmosphere and swept with purified nitrogen was added with stirring 10 ml of aqueous chromous chloride solution from a Jones reductor.[30] The mixture was stirred overnight and extracted with chloroform. The organic extract was

(30) H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964).

washed, dried, and evaporated; although the gummy residue showed only one spot on tlc, the nmr spectrum revealed that it was a mixture of at least three components which could not be resolved ty tlc in various solvent systems. The crude product was therefore refluxed with 50 ml of 5% methanolic NaOH for 6 hr, concentrated at reduced pressure, diluted with water, and extracted with ether. The washed and dried ether extract yielded 1.5 g of a gummy residue which showed several spots on tlc one of which (10–15% of the mixture) corresponded to authentic **1b**.

Conversion of 10b to 1b.—A solution of 20 g of **10b** in 20 ml of pyridine was stirred overnight with 20 ml of acetic anhydridel Work-up in the manner described for **9c** and recrystallization from hexane gave a quantitative yield of **10c** which had mp 203–205°; ir bands at 3560 (OH), 1760 (lactone), 1740 (acetate), and 1730 cm^{-1} (carbomethoxy); nmr signals at 5.3 (H-14), 3.73 (methoxyl), 3.09 (c, H-12), 2.83 (OH), 2.27 (acetate), 1.20 (C-4 methyl), 1.11 (C-10 methyl), 0.98 and 0.85 ppm (d, J = 7 Hz, isopropyl).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31; O, 25.66. Found: C, 66.03; H, 8.50; O, 25.27.

Dehydration of 1.0 g of **10c** with thionyl chloride–pyridine and work-up in the manner described for **14b** gave a quantitative yield of **16** which was recrystallized from methanol–water and had mp 144–145°; $[\alpha]^{22}D$ +33.2° ($CHCl_3$); ir bands at 1760 (lactone), 1740 (acetate), 1725 (carbomethoxy), and 1670 cm^{-1} (weak, double bond); nmr signals at 6.07 (br, $W_{1/2}$ = 4 Hz, H-14), 3.70 (methoxyl), 3.7 (c, H-12), 2.10 (acetate), 1.82 and 1.63 (vinyl methyls), 1.20 (C-4 methyl), 0.90 ppm (C-10 methyl).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19; O, 22.94. Found: C, 68.70; H, 8.16; O, 23.39.

Ozonolysis of 5 g of **16** in 30 ml of methylene chloride at −78° and work-up with dimethyl sulfide in the manner described for **14a** gave 4.5 g (96%) of gummy **17b** whose nmr spectrum had signals at 5.57 (H-14), 3.65 (methoxyl), 3.48 (c, H-12), 2.16 (acetate), 1.18 (C-4 methyl), 1.12 ppm (C-10 methyl). Since this material was unstable at room temperature in air and decomposed during attempts at tlc purification, it was used directly for further experiments.

To a solution of 4 g of **17b** in 40 ml of deoxygenated tetrahydrofuran was added with stirring in a nitrogen atmosphere 25 ml of 1 N chromous chloride solution. After 8 days, solvent was removed at reduced pressure and the residue was extracted thoroughly with chloroform. The combined washed and dried chloroform extracts were evaporated and the residual gum, wt 3.5 g, whose major component was **1b** (tlc analysis) was chromatographed over alumina. Elution with benzene gave **1b** in 40% yield, mp 126–127°, whose physical properties (melting point, rotation, ir and nmr spectra) were in agreement with the literature values.

When the reaction mixture was refluxed for 24 hr and worked up as described above, chromatography of the crude product afforded a 40% yield of **1b** and a 20% yield of **18**, mp 124° (lit.[22] mp 124–125°); ir and nmr spectra were in accord with those reported previously.[22]

Methyl 12-Methyl-8,11,13-abietatrien-18-oate (19).—A solution of 1.5 g of **3b** in 50 ml of dry benzene was refluxed with 0.7 g of N-bromosuccinimide, cooled, and washed thoroughly with water. The dried benzene was evaporated and the solid residue, wt 1.3 g, mp 107–109°, was recrystallized from methanol–water. It had mp 113°; ir bands at 1720 and 1250 cm^{-1} (ester); nmr signals at 6.91 (H-11), 6.82 (H,14), 3.6 (methoxyl), 2.22 (C-12 methyl), 1.22 (C-4 methyl), 1.18 (C-10 methyl), 1.16 ppm (d, J = 7 Hz, two isopropyl methyls) in agreement with the literature values.[25]

The same compound was obtained in quantitative yield by refluxing 1.5 g of **3b** in 50 ml of dry benzene with 0.2 g of iodine or with 0.1 g of p-toluenesulfonic acid.

Periodate Cleavage of 9a.—A solution of 5 g of **9a** in 50 ml of methanol, 2 g of sodium metaperiodate in 10 ml of water, and 1 ml of concentrated HCl was stirred for 6 hr, concentrated at reduced pressure to remove methanol, and diluted with water. The precipitate of **20a**, obtained in quantitative yield, was recrystallized from methanol–water and then had mp 179–180°; ir bands at 1745, 1735, and 1720 cm^{-1}; nmr signals at 9.90 (aldehydic proton), 3.78 (c, H-21), 1.17 (C-4 methyl), 1.05 (d, J = 7 Hz, isopropyl methyls), 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.34; H, 8.82; O, 22.07.

Methylation with diazomethane and recrystallization from gave the methyl ester **20b** which had mp 102–104°; nmr signals at 9.83 (aldehyde), 3.78 (c, H-21), 3.67 (methoxyl), 1.11 (C-4 methyl), 1.07 (d, J = 7 Hz, isopropyl methyls), 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05; O, 21.13. Found: C, 69.68; H, 9.17; O, 21.30.

Preparation of 22a.—A solution of 2 g of **20a** in 30 ml of 2% methanolic sodium hydroxide was stirred for 1 hr, concentrated to small volume at reduced pressure, and diluted with water. Recrystallization from acetone–hexane gave **22a** which had mp 248°; ir bands at 3440 (OH), 3320 (carboxyl OH), 1730 (acid), and 1700 cm^{-1} (ketone); nmr signals at 4.10 (H-14), 4.16 and 3.74 (m, H-21), 2.98 (hept, J = 6.5 Hz, H-15), 1.20 (C-4 methyl), 1.1 (d center of two doublets, J = 6.5 Hz, isopropyls), 0.92 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.30; H, 8.90; O, 22.08.

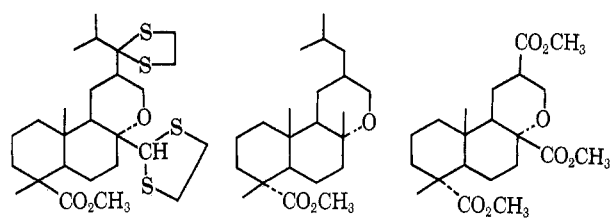
The ester **22b** was prepared by methylation of **22a** or by base treatment of **20b** and melted at 173°.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05; O, 21.13. Found: C, 69.75; H, 9.12; O, 21.25.

The ester **22b** was recovered quantitatively from an attempted reaction with m-chloroperbenzoic acid. Treatment of 2 g of **22b** with 3 ml of ethanedithiol and 0.5 ml of boron trifluoride etherate gave the gummy bisethylenedithiane derivative **24**, yield 1 g after preparative tlc (benzene–acetone 9:1), which had only one carbonyl absorption at 1720 cm^{-1} (ester) and nmr signals at 5.2 (H-14), 4.22 (m, H-21), 3.7 (methoxyl), 3.2 (br, $W_{1/2}$ = 3 Hz, 8 methylene protons α to S), 1.18 (C-4 methyl), 1.11 and 1.09 (d, J = 6 Hz, isopropyl methyls), 1.09 ppm (C-10 methyl). Attempts to restrict the reaction of **22b** with ethanedithiol to condensation with 1 mol equiv of dithiol were unsuccessful.

Desulfurization of 1 g of **24** in absolute methanol by refluxing with 10 g of Raney nickel for 18 hr, filtration, evaporation, and recrystallization of the solid residue from methanol–water gave a quantitative yield of **25** which had mp 62° and nmr signals at 3.72 (methoxyl), 3.57 (c, H-21), 1.22 (C-8 methyl), 1.18 (C-4 methyl), 0.90 and 0.86 (d, J = 6.5 Hz, isopropyl methyls), 0.80 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93; O, 13.69. Found: C, 75.10; H, 10.77; O, 13.95.



24 **25** **26**

Oxidation of 15c to 23.—A solution of 2 g of **15c** in 30 ml of tetrahydrofuran was mixed with 10 ml of the chromic chloride hexahydrate solution used for the preparation of chromous chloride with stirring. A white crystalline substance precipitated during this period. The mixture was diluted with water and filtered. Recrystallization from methanol–water gave a 65% yield of **23** which had mp 205–210°; a complex set of ir bands at 1730–1720 cm^{-1} (two ketones and ester); nmr signals at 4.0 and 3.73 (c, H-21), 3.66 (methoxyl), 1.17 (C-4 methyl), 0.92 ppm (C.10 methyl).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 67.83; H, 8.39; O, 23.78. Found: C, 67.77; H, 8.37; O, 23.68.

Oxidation of 1 g of **23** in 10 ml of methanol with 0.5 g of sodium metaperiodate in the manner described for the oxidation of **9b** gave a gum which was methylated by treatment with diazomethane and chromatographed over silica gel. Chloroform eluted 0.3 g of the homogeneous gummy triester **26** which had a complex ir band at 1730–1720 cm^{-1} (three carbomethoxyls) and nmr peaks at 3.88 and 3.66 (m, H-21), 3.63 (three methoxyls), 1.12 (C-4 methyl), 0.82 ppm (C-10 methyl).

Registry No.—**1b**, 5091-97-4; **8b**, 31579-57-4; **9a**, 31579-58-5; **9b**, 31579-59-6; **9b** acetonide, 31579-60-9;

9b sulfite, 31579-61-0; **9c**, 31579-62-1, **10b**, 31579-63-2; **10c**, 31579-64-3; **11b**, 31579-44-9; **13**, 31579-65-4; **14a**, 31579-66-5; **14b**, 31579-67-6; **15b**, 31579-45-0; **15c**, 31579-46-1; **15** 2,4-DNPH, 31579-47-2; **16**, 31579-48-3; **17b**, 31579-49-4; **20**, 31579-50-7; **20b**, 31579-51-8; **22a**, 31579-52-9; **22b**, 31579-53-0; **23**, 31579-54-1; **24**, 31579-55-2; **25**, 31579-56-3; **26**, 31579-68-7.

Steroids with Abnormal Internal Configuration. A Stereospecific Synthesis of 8α-Methyl Steroids[1]

WILLIAM G. DAUBEN* AND DWIGHT S. FULLERTON

Department of Chemistry, University of California, Berkeley, California 94720

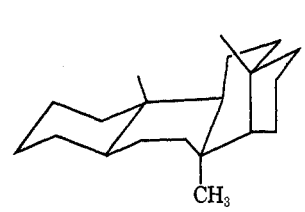
Received February 5, 1971

Stereospecific syntheses of 8α-methylcholestan-3β-ol-6-one acetate and 17-ethynyl-8α-methyltestosterone were accomplished. The synthetic scheme included a series of four reactions starting with steroid 5,7-dienes: hydroboration to the Δ^7-6α-ol, Simmons–Smith addition to form the 7α,8α-methano-6α-ol, Jones oxidation, and lithium in ammonia reductive ring opening to form the 8α-methyl-6-one. The configuration and conformation of the 8α-methyl compounds are discussed with the aid of spectral data. The 8α-methyl group was found to eliminate essentially all the androgenic and anabolic activities in standard biological tests.

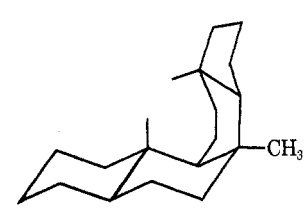
It has been well established that slight changes of the configuration of a biologically active molecule can vastly change its activity.[2] This characteristic has been studied in detail with steroids, where the effects upon biological activity of changing the configuration of substituents attached to carbon atoms on the periphery of the steroid nucleus are well documented.[3] However, the greatest changes in the overall shape of a steroid nucleus result from modification of the stereochemistry of the backbone of the molecule; of the backbone atoms, C-8 and C-9 cause the largest changes in molecular shape.

Several syntheses of 8-iso[4] and 9-iso steroids[5a] have been reported but less has been done with regard to the placement of a substituent at these centers.[5b] Continuing investigations of 8α-methyl steroid type antibiotics[6] have added interest in backbone substituted steroids. The preparation of an 8α-methyl steroid with other backbone carbon atoms possessing the natural configuration has been the basis of two studies.[7] The direct methylation of a 7-keto-9(11)-ene steroid has been reported to yield an 8α-methyl derivative;[8] the stereochemical assignment (first given as 8β)[9] is most likely correct but it is based upon tenuous spectroscopic interpretation. Recently an 8α-methylestrane derivative was prepared by hydrogenolysis of a bicyclobutane estrane precursor.[10] This synthetic route involved a nonstereospecific addition of dibromocarbene to a 6-ene, easily available only with ring-A aromatic steroids. The purpose of this present study was to develop a general, stereospecific synthesis of 8α-methyl steroids and then to evaluate such structural change upon hormonal activity.

The introduction of an 8α hydrogen or 8α substituent makes the B/C ring juncture cis, greatly changing the shape of the steroid nucleus. With the A/B and C/D ring junctures remaining trans, either ring B or ring C must be in a boat or twist conformation in these 8α steroids. In the C-boat or twist conformers, there is extreme steric hindrance because of the C-18 and C-19 angular methyl groups while the B-boat or twist conformers suffer only relatively minor hydrogen–angular methyl interactions. Thus, the B-boat or twist conformations would be preferred.



8α-methyl B boat



8α-methyl C boat

The B-boat conformers have a shape quite different from normal 8β steroids, but the distance between C-3 and C-17 remains approximately the same; for testosterone, 8-isotestosterone, and 8α-methyltestosterone, this distance on Dreiding models is virtually identical. If the C-3 to C-17 distance is important for biological activity, one would predict that 8α steroid hormones

(1) This work was supported, in part, by Grant No. CY-04284, National Cancer Institute, U. S. Public Health Service.

(2) For example, see A. Burger, "Medicinal Chemistry," 3rd ed, Wiley-Interscience, New York, N. Y., 1970.

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959; N. Applezweig, "Steroid Drugs," McGraw-Hill, New York, N. Y. 1962.

(4) W. G. Dauben and L. Ahramjian, *J. Amer. Chem. Soc.*, **78**, 633 (1956); C. Djerassi, H. Bendas, and A. Segaloff, *J. Org. Chem.*, **21**, 1056 (1956); C, Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6362, 6377 (1956); W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. I. Jones, *ibid.*, **80**, 661 (1958); G. C. Buzby, Jr., *et al.*, *J. Med. Chem.*, **9**, 338 (1966); K. Kuriyama, M. Moriyama, T. Iwata, and K. Tori, *Tetrahedron Lett.*, 1661 (1968); D. K. Banerjee, B. Sugavanam, and G. Nadamuni, *ibid.*, 2771 (1968); R. Bucourt, D. Hinaut, J. C. Gasc, and G. Nominé, *Bull. Soc. Chim. Fr.*, 1920 (1969); A. H. Emasry and O. Gisvold, *J. Pharm. Sci.*, **59**, 449 (1970); von C. Rufer, E. Schröder, and H. Gibian, *Justus Liebigs Ann. Chem.*, 211 (1967).

(5) (a) W. G. Dauben and G. J. Fonken, *J. Amer. Chem. Soc.*, **81**, 4060 (1959); J. Castells, E. R. H. Jones, G. D. Meakins, and R. W. J. Williams, *J. Chem. Soc.*, 1159 (1959); S. J. Halkes and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 889 (1965); H. Els, G. Englert, A. Fürst, P. Reusser, and A. J. Schocher, *Helv. Chim. Acta*, **52**, 1157 (1969). (b) J. W. ApSimon and R. R. King, *Can. J. Chem.*, **47**, 1989 (1969).

(6) The antibiotic activity of these compounds is described by W. O. Godtfredsen, W. von Daehne, L. Tybring, and S. Vangedal, *J. Med. Chem.*, **9**, 15 (1966).

(7) W. Nagata and coworkers have stereoselectively made 8β-methyl steroids: W. Nagata, Proceedings of the Symposium on Drug Research, Montreal, Canada, June 1966; Japanese Patent 3166 (1967).

(8) G. Amiard, R. Heymés, T. V. Thuong, and J. Mathieu, *Bull. Soc. Chim. Fr.*, 2321 (1965).

(9) G. Amiard, J. Mathieu, R. Heymés, and T. V. Thuong, *ibid.*, 1031 (1961).

(10) E. Galantay, N. Paolella, S. Barcza, R. V. Coombs, and H. P. Weber, *J. Amer. Chem. Soc.*, **92**, 5771 (1970).