Resin Acids. XXII. An Unusual Decarboxylation Induced by a Degenerate Acyloin Rearrangement[1,2]

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Pyrolysis of a dihydroxylactone **2b**, prepared by oxidation of the levopimaric acid–formaldehyde adduct **1**, unexpectedly resulted in decarboxylation to methyl 13α-hydroxy-14-oxoabietan-18-oate (**5**) or to methyl 8α,14α-dihydroxy-12-abieten-18-oate (**8**) depending on the conditions. Decarboxylation of methyl 12α-carboxy-13α-hydroxy-14-oxoabietan-18-oate (**4a**) also gave **5**. These remarkable and unusually facile decarboxylations were traced to a degenerate acyloin rearrangement in 13-hydroxy-14-oxoabietanes which involves reversible migration of the C-12–C-13 and C-8–C-13 bonds. In the methyl ester **4b**, prepared by treatment of **2b** with methanolic HCl, the stable orientation of the carbomethoxy group was shown to be axial. Transformations of **5** and **8** which shed light on the stereochemistry of various 14-oxygenated abietanes are described.

In the preceding paper[1] we reported *inter alia* the unusual oxidation of the levopimaric acid–formaldehyde adduct **1** to the dihydroxylactone **2b**. When we subsequently attempted to assay the utility of **2** as a potential intermediate for the partial synthesis of other terpenoids, we discovered a seemingly unprecedented decarboxylation reaction which eventually could be traced to the existence of a degenerate acyloin rearrangement involving the transitory formation of a β-keto acid. These findings are described in the present communication. We also report the transformation of **2** to a number of 14-oxygenated abietanes by methods which shed light on the stereochemistry of previously reported compounds.

For realization of our initial objective we proposed to hydrolyze **2b** to **3a** and carry out a decarboxylation after oxidation and dehydration of **3a**. However, **3a** could not be isolated because of spontaneous relactonization to **2b**. Hence **2b** was exposed to methanolic hydrogen chloride in the expectation that diester **3b** would be formed. Instead, however, acid-catalyzed cleavage of the lactone function followed by pinacol rearrangement[3] and subsequent methylation with methanolic hydrogen chloride resulted in quantitative conversion of **2b** to a compound **4b**.[4] The infrared spectrum of this substance revealed the absence of the lactone function, but had three carbonyl bands at 1740, 1730, and 1710 cm^{-1}, the first two of which were due to carbomethoxy groups (nmr spectrum). That the third carbonyl band of 1710 cm^{-1} arose from a ketone group was clear from the CD curve, which exhibited the typical $n-\pi^*$ transition at 284 nm. The presence of a single tertiary hydroxyl group was indicated by a sharp one-proton nmr peak at 3.88 ppm which disappeared on D_2O exchange, and, in contrast to the situation prevailing in the precursors **1** and **2**,[1] the doublets of the isopropyl group were now widely separated, one of them being highly shielded (0.64 ppm).

While it was more than reasonable to assume that the configuration of the 13-hydroxyl and the isopropyl group had not been affected during the conversion of **2b** to **4b**, the stereochemistry at the two centers C-8 and C-12 which *were* involved demanded further study. As regards the configuration at C-8, exposure of **4b** to epimerizing conditions ($NaOH-CH_3OH$) resulted after remethylation with diazomethane in recovery of starting material accompanied by a small amount of **5**,[5] thus indicating that **4b** possessed the stable trans–anti–trans perhydrophenanthrene ring system. The strongly negative Cotton effect of **4b** ($a = -212$) was in accord with this conclusion.

The appearance of the H-12 resonance (slightly distorted triplet at 3.4 ppm) served as a means for investigating the orientation of the carbomethoxy group at C-12. The observed splitting (3 Hz) clearly excluded axial–axial coupling of H-12 to one of its neighbors at C-11 and led to the rather surprising conclusion that the carbomethoxy group was axial, in spite of its stability under epimerizing conditions. Such failure to epimerize under the influence of $NaOH-CH_3OH$ could be due either to the inability of the base to abstract H-12 or to the presence of potentially unfavorable interactions encountered by an equatorial carbomethoxy group, whatever its configuration, the equilibrium in favor of an axial orientation being reinforced by the 3-alkyl ketone effect. The ambiguity was resolved by subjecting **4b** to the action of $NaOD-CH_3OD$. In the recovered **4b**, H-12 had been completely replaced by deuterium as evidenced by the disappearance of the signal at 3.4 ppm. Hence the carbomethoxy group of **4b** prefers the axial orientation.[6]

However, this by no means settles the absolute configuration at C-12, since the requirement for an axial carbomethoxy group is satisfied by two structures: (1) **4b** with ring C in the usual chair conformation and the carbomethoxy group α as in **4A**; (2) **4'b** with ring C in the twist conformation and the carbomethoxy group β as in **4B**. If ring C were a chair, the greater

(1) Previous paper: W. Herz and V. Baburao, *J. Org. Chem.*, **36**, 3271 (1971).

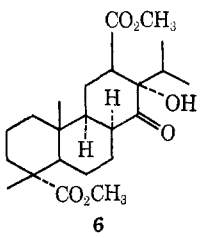
(2) Supported in part by a grant from the National Science Foundation (GP-12582).

(3) For similar hydride shifts in epoxides and glycols derived from Diels–Alder adducts of levopimaric acid, see (a) W. Herz, R. N. Mirrington, H. Young, and Y. Y. Lin, *J. Org. Chem.*, **33**, 4210 (1968); (b) W. Herz and R. C. Blackstone, *ibid.*, **34**, 1257 (1969).

(4) To substantiate the postulated last step, acid **4a**, prepared by cautious basic hydrolysis of **4b**, was reconverted to **4b** by the action of methanol–HCl.

(5) Structure assignment and mode of formation of this substance will be discussed subsequently.

(6) With the carbomethoxy group shown to be axial, the formal argument that in **4b** a cis B/C ring fusion might for some reason be more stable than a trans B/C junction could be discounted, since this would lead to formula **6** which can be dismissed because of the prohibitive interactions (model) and the negative Cotton effect.



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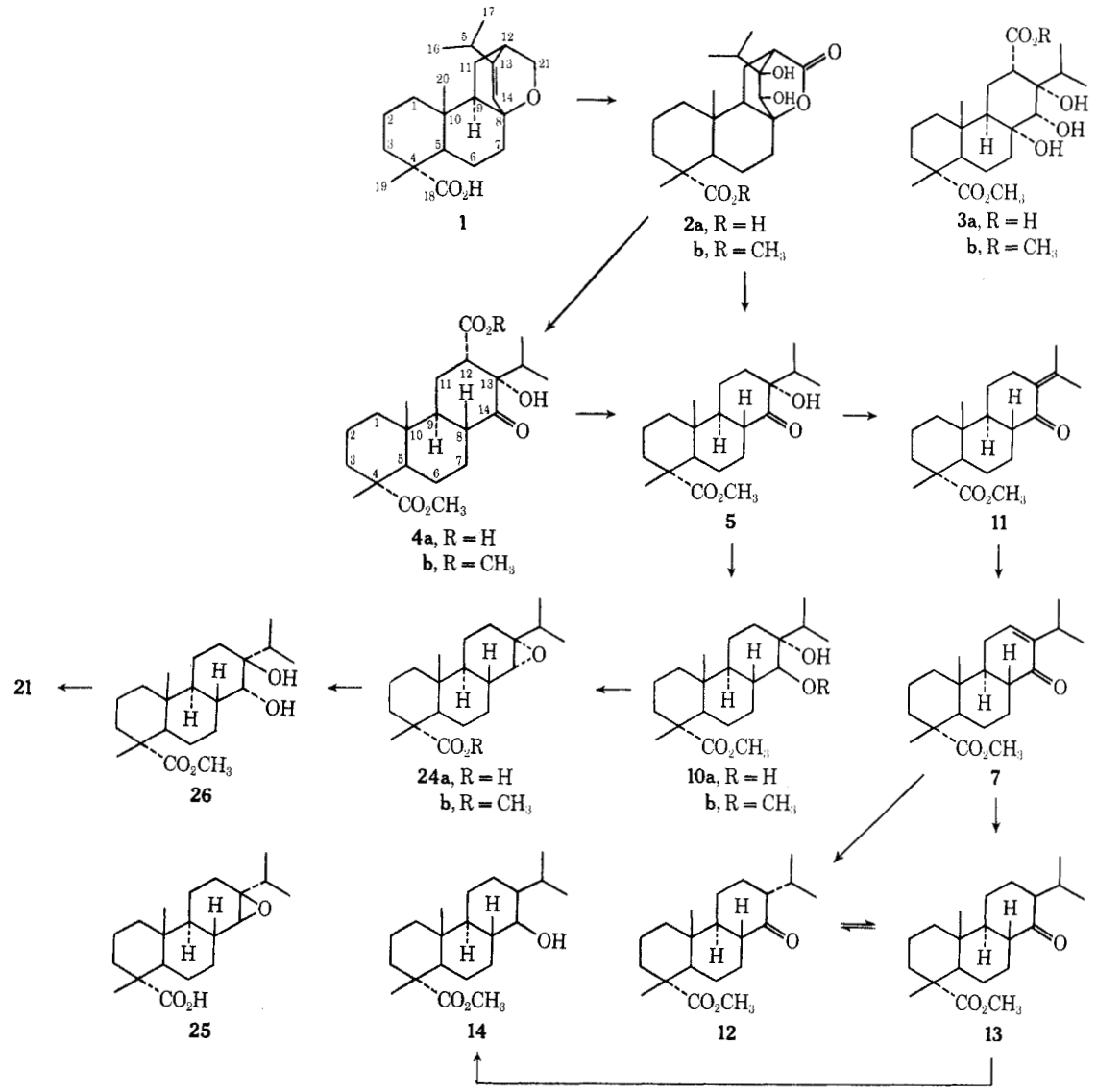
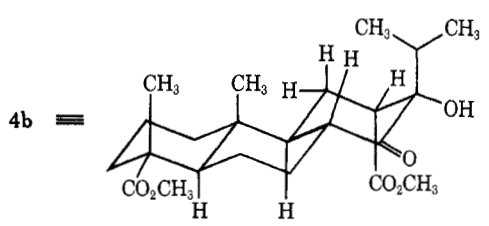
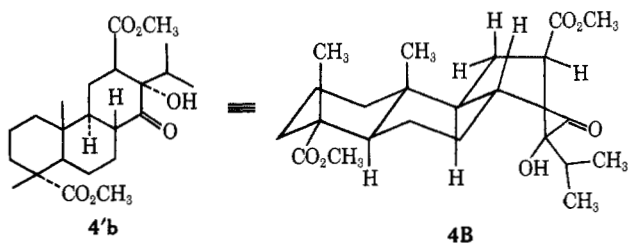


thermodynamic stability of **4b** (CO_2Me axial) over **4'b** (CO_2Me equatorial) would have to be attributed to the difference between one 1,3-diaxial H–CO_2Me interaction in **4b** on the one hand and the sum of one 1,3-H,H, and one skew CO_2Me–isopropyl interaction in **4'b** on the other. If ring C were in the flexible conformation, the greater stability of **4'b** (CO_2Me axial) over **4b** (CO_2Me equatorial) would have to be attributed to a rather tenuous difference between a H–CO_2Me flagpole interaction, reduced by twisting, in **4'b** on the one hand and the sum of a H–H flagpole (also reduced by twisting) and a skew CO_2Me–OH interaction of **4b** on the other.





We prefer **4A**, and hence configuration **4b**, on the following grounds. (1) **4b**, **5**, and **13** (*vide infra*) possess strongly negative Cotton effects of the same magnitude ($a = -212$, -207, and -172). Also the chemical shifts of their C-10 methyl and isopropyl methyl signals are almost identical (see Experimental Section). This suggests that the conformations of **4b**, **5**, and **13** are very similar, if not identical, and that conformational equilibria are not significantly affected by the presence or absence of the carbomethoxy group at C-12 and the α-hydroxyl group at C-13. (2) Conformations corresponding to **4B** would be expected to display considerably weaker Cotton effects than are actually observed.[7,8] (3) In conformations corresponding to **4B**

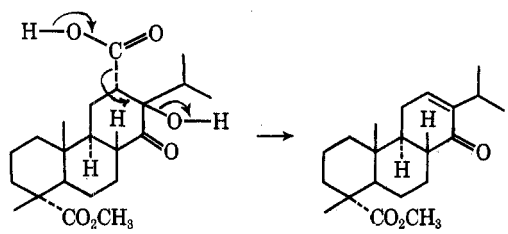
(7) On the other hand, if ring C were in a twist conformation, the "anti-octant" behavior of the hydroxyl group,[8] situated in a positive octant, might conceivably account for the amplitude drop in going from **5** to **13**. *A priori*, no appreciable change in amplitude would be expected if ring C were a chair. However, the drop and the simultaneous decrease in nonequivalence of the isopropyl methyls (see footnote 9) could easily be traced to a slight distortion of ring C of **13**, made now possible by the absence of the hydroxyl function to accommodate the axial isopropyl group.

(8) L. Bartlett, D. N. Kirk, W. Klyne, S. R. Wallis, H. Erdtman, and S. Thorén, *J. Chem. Soc.*, 2678 (1970).

the isopropyl methyls would not be expected to exhibit the degree of nonequivalence actually manifested in the nmr spectra of **4b**, **5**, and **13**, whereas models of structures corresponding to **4A** reveal that in the more heavily populated rotamers one of the methyl group is above and in the shielding cone of the ketone group in accordance with experimental observations.[9,10] (4) Lastly we note that **5** and **13** are reduced facilely by sodium borohydride in methanol at room temperature, hydride attack occurring exclusively from the α side, to give **10a** and **14** (*vide infra*). By contrast, **4b** is not reduced under these conditions, a result explicable on the basis of formula **4A**, where the axial and α oriented carbomethoxy group interferes with reagent approach from the α side, but not on the basis of formula **4B**.[11]

Thermal decarboxylation of **4a** was expected to provide the enone **7** by the process adumbrated in Scheme I.[12] However, the product, isolated in 70% yield by

SCHEME I



4a **7**

heating at 280°, was not **7**, but **5**, the minor product encountered earlier during the attempt to epimerize **4b**.[13] Some of the properties of this substance have been mentioned previously; the presence of strong intramolecular hydrogen bonding, the stability toward base, the ORD curve, and the similarity of its nmr spectrum to that of **4b** are entirely in agreement with its formulation as methyl 13α-hydroxy-14-oxoabietan-18-oate.[14]

The unexpectedly facile decarboxylation of **4a** to **5**, whose mechanism will be discussed subsequently, suggested that a thermal process involving intramolecular hydroxyl proton abstraction by the lactone ether oxygen of **2b** as illustrated in Scheme II (path a) might initiate rearrangement of **2b** to **4a** or its anion and that this would be followed by decarboxylation to **5**. This expectation was borne out in practice. When **2b** was heated to 280° for 10 min, two crystalline substances were isolated after column chromatography. The less polar compound (30% yield) was **5**; the more polar compound was shown to be **8** on the following grounds.

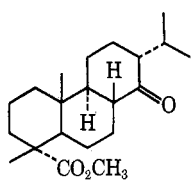
The presence of two ir bands at 3480 and 3360 cm^{-1}, a positive periodate test, and the formation of an acetonide established the presence of a vicinal glycol system whose hydroxyl groups were tertiary and secondary because the nmr spectrum contained only one characteristic low-field singlet at 4.22 ppm. The chemical shift of this signal indicated that it was allylic to a trisubstituted double bond (narrowly split vinyl multiplet at 5.58 ppm). The chemical shift of the C-10 methyl signal at 0.81 ppm was comparable to that found in a number of 8α-hydroxyabietanes[15] and not deshielded as would be expected in a 8β-hydroxyabietane. Oxidation of **8** afforded an α,β-unsaturated α-hydroxy ketone **9** (ir frequencies at 3400 and 1670 cm^{-1}) whose nmr spectrum exhibited a one-proton multiplet at 6.62 ppm typical of protons attached to the β position of an α,β-unsaturated ketone and a methyl signal at 0.67 ppm indicating a shielded C-10 methyl group.

The formation of **8** and **2b** can be rationalized by path b, Scheme II, or perhaps more plausibly by transformation of **2b** *via* lactone interchange into an unstable β-lactone A (path c) which undergoes facile decarboxylative elimination[16] (step d).[17]

The yield of **8** was improved to 60% and the yield of **5** was reduced to below 5% when the pyrolysis of **2b** was carried out in the presence of alumina. On the other hand, addition of catalytic amounts of manganese dioxide to **2b** increased the yield of **5** to 70% and completely suppressed the formation of **8**. In terms of Scheme II, the effect of alumina in promoting formation of **8** could perhaps be attributed to preferential coordination of the Lewis acid with the accessible carbonyl group. This would enhance the electrophilic character of C-21, thus favoring path b or c at the expense of path a. The effect of MnO_2 is more difficult to rationalize. It is possible that formation of a metal complex with the glycol system suppresses nucleophilic attack by the C-13 oxygen on the carbonyl group which is postulated to trigger the conversion of **2b** to **8**. Simultaneously the O–H bonds are weakened and proton transfer to the lactone ether oxygen is encouraged, thus lowering the energy of path a.

In order to shed light on the unusually facile and, we believe, unprecedented decarboxylation of **4a** to **5**, the reaction of **4b** with NaOD–CH_3OD was allowed to proceed for 20 hr. The resultant mixture of products was methylated and separated into **4b** and **5**. Mass spectrometric analysis of **4b** demonstrated the presence of 27% excess **4b**-d_2, 67% **4b**-d_3, 3% **4b**-d_4, and 3% **4b**-d_5.

(9) In **4b** the doublets are found at 0.90 and 0.64, in **5** at 1.00 and 0.67, and in **13** at 0.92 and 0.75 ppm. By comparison, the isopropyl doublets of i,[10] where, even though ring C is a chair, the relative orientation of isopropyl



i

and carbonyl groups reflects approximately the situation expected to prevail in the twist form **4B**, occur at 0.89 and 0.82 ppm.

(10) J. W. Huffmann, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966).

(11) That the previously mentioned difference between a 1,3-diaxial H,H and a skew carbomethoxy–isopropyl interaction in chair **4'b** is sufficient to make up the conformational free-energy difference between **4b** and **4'b** of more than 2.5 kcal necessary to account for the strongly preponderant, if not exclusive, presence of **4b** at equilibrium is not easily seen. It is probable that other factors also assist in lowering the conformational energy of **4b** or raising that of **4'b**.

(12) D. S. Noyce, S. K. Brauman, and F. B. Kirby, *J. Amer. Chem. Soc.*, **87**, 4355 (1965).

(13) The formation of **5** during the NaOH–MeOH treatment of **4b** was obviously the result of partial hydrolysis followed by decarboxylation.

(14) For naming and numbering of abietanes, see ref 6 of W. Herz and J. J. Schmid, *J. Org. Chem.*, **34**, 3464 (1969).

(15) W. Herz, R. C. Ligon, H. Kanno, W. H. Schuller, and R. V. Lawrence, *ibid.*, **35**, 3338 (1970).

(16) H. E. Zaugg, *Org. React.*, **8**, 305 (1954).

(17) Retention of the hydroxyl group at C-14 and α orientation of the hydroxyl group at C-8 requires that the path leading from **2b** to **8** not involve cleavage of the C-8–oxygen bond, since otherwise the inevitable 14 → 8 hydride shift[3] leading to a B/C transfusion intervenes.

The position of entry of two of the deuterium atoms was revealed by the nmr spectrum, which showed not only complete disappearance of the H-12 signal (*vide supra*) but collapse of the doublets of the isopropyl group. *Hence H-15 of* **4b** *had been replaced by deuterium* and the third deuterium atom must have entered at C-8.[18] Similarly, analysis of **5** showed the presence of 36% excess **5**-d_3 and 64% **5**-d_4. Again, the nmr spectrum demonstrated *complete substitution of H-15 by deuterium;* by analogy with **4b** it was assumed that the three remaining deuterium atoms had replaced H-8 and H-12. Decarboxylation of **4a** in a $NaOD-CH_3OD$ medium or treatment of **5** with $NaOH-CH_3OD$ also resulted in substitution of H-15 by deuterium.

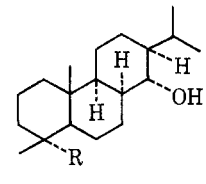
The surprising entry of deuterium into the 15 position of both **4b** and **5** indicated that decarboxylation of **4a** and deuterium exchange in **4b** and **5** involved identical or similar intermediates of a type that permits decarboxylation and quantitative incorporation of deuterium at positions which are not activated in the usual sense. To investigate the possible intervention of homoenolization[19] which affords such intermediates, we decided to study exchange reactions of derivatives of **4b** or **5** which lacked the 14-keto or the 13-hydroxyl group.

Attempts to functionalize the keto group of **4b** for eventual removal by conventional methods or to dehydrate **4b** under mild conditions resulted in recovery of starting material. Reaction of **5** with ethanedithiol took an unexpected course (see Experimental Section), but reduction of **5** with $NaBH_4$ gave a crystalline glycol **10a**. Its nmr spectrum exhibited a one-proton doublet at 3.25 ppm attributable to H-14, whose splitting (J = 10 Hz) clearly indicated its trans diaxial relationship to H-8. As expected, treatment of **10a** with CH_3OD-CH_3ONa and subsequent methylation resulted in recovery of starting material whose nmr and mass spectra showed no incorporation of deuterium.

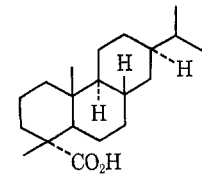
Treatment of **5** with thionyl chloride–pyridine and separation by preparative tlc afforded two α,β-unsaturared ketones, **7** and **11**. The chromophore of **7** was evidenced in the uv (λ_{max} 237 nm), ir (1680 and 1660 cm^{-1}), and nmr spectrum (H-12 triplet at 6.7 ppm, J = 4 Hz, allylic H-15 heptuplet at 2.85 ppm), that of **11** in the ir (cisoid α,β-unsaturated ketone because of the relative intensities of bands at 1680 and 1650 cm^{-1}) and nmr spectrum (two vinyl methyl signals at 1.80 and 1.96 ppm, no methyl doublets or vinyl proton multiplets). The additional observation that **11** was the product of kinetic control and that it was gradually converted to the equilibrium product **7** further supports the equatorial orientation of the hydroxyl group at C-13.

Catalytic hydrogenation (Pd/C) of **7** gave two saturated ketones separable by preparative tlc which had to be C-13 epimers. The less polar ketone, mp 74–76°, was identical with authentic **12** prepared in the course of earlier work,[10,20] a circumstance which clearly established the validity of the conclusions reached earlier with respect to the stereochemistry at C-8 of **4b**, **5**, and **7**. The more polar ketone, mp 128–130°, was therefore the C-13 epimer **13**. Its negative Cotton effect (a = −172), somewhat larger than that of **12**, showed that the octant rule can be applied safely to this system. $NaBH_4$ reduction of **13** gave alcohol **14**, which had an equatorial, hence β-oriented hydroxyl group (H-14 multiplet at 3.38 ppm, $W_{1/2}$ = 15 Hz).[21]

Treatment of **12** or **13** with $NaOCH_3-CH_3OH$ gave the same equilibrium mixture containing 90% **12** and 10% **13**; obviously, the stable orientation of H-8 in this system is β. Treatment of **12** with $NaOCH_3-CH_3OD$ gave an equilibrium mixture from which deuterated **12** (32% **12**-d_1 and 68% **12**-d_2 by mass spectrometric analysis) was isolated by preparative tlc. The nmr spectrum of the deuterated **12** retained the doublets of the isopropyl group in undiminished intensity. Obviously only H_8 and H_{13} had been exchanged by the usual enolization process and the idea that homoenolization might be responsible for deuterium incorporation only at C-13. The preparation of authentic **13** described in the present communication required revision of the structure assigned to B. Now a third 14-ketone, mp 134–135°, has been prepared[10] by reactions which unambiguously establish its stereochemistry as **17** and has been converted to **12** by treatment with base. Since there are only four possible ketones with a gross structure corresponding to **12** but differing from each other at C-8 and/or C-13, and since three of these (**12**, **13**, and **17**) are known, ketone B must have the stereochemistry represented by **18**. The transformation of **18** to **16** must therefore have been attended by epimerization at C-8 during the ketalization steps, an occurrence whose possibility has already been demonstrated by earlier work[10] in this laboratory.



15a, R = CH_2OH
b, R = CO_2H
c, R = CO_2CH_3



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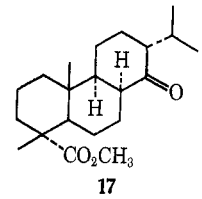

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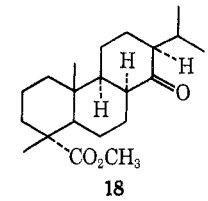

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Our conclusions on the structure of B were communicated to Professors Huffmann and Burgstahler who have incorporated them in more recently published material and have provided additional evidence for the new structural assignment,[23,24]

(18) This was not obvious from the nmr spectrum, since the H-8 signal of undeuterated **4b** is obscured. Prolongation of reflux time resulted in decrease and eventual disappearance of **4b**-d_2 and **5**-d_3. Simultaneously, the percentage of **4b**-d_3 and **5**-d_4 increased.

(19) A. Nickon and J. L. Lambert, *J. Amer. Chem. Soc.*, **84**, 4606 (1962); **88**, 1905 (1966), and references cited therein. For a recent report of cyclopropanol formation under homoenolization conditions, see P. S. Venkataramani, J. E. Karoglan, and W. Reusch, *ibid.*, **93**, 269 (1971). However, no example of homoenolization-induced decarboxylation has been reported.

(20) A. W. Burgstahler, J. N. Marx, and D. F. Zinkel, *J. Org. Chem.*, **34**, 1550 (1969).

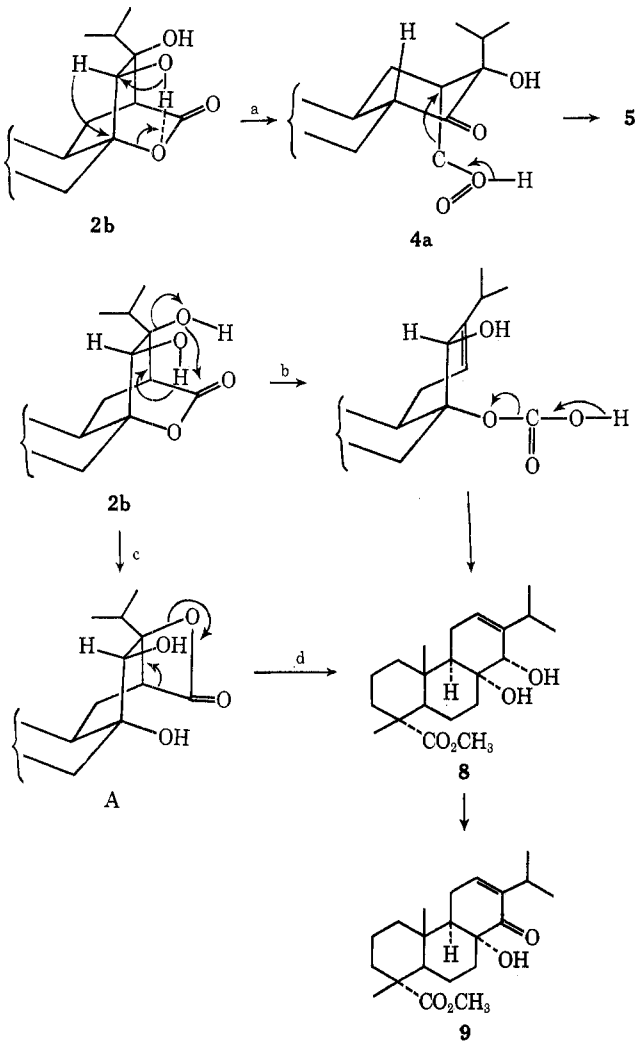
(21) While this work was in progress, Burgstahler and coworkers[20] reported preparation of a ketone B, mp 79–79.5°, for which formula **13** was proposed. Their reaction sequence started with 8(14)-abieten-18-oic acid, hydroboration–oxidation of which gave a diol **15a**. Oxidation of **15a** produced a noncrystalline keto acid methylated to a gummy ester B which was subsequently obtained in crystalline form by following the sequence methyl 8(14)-abieten-18-oate → **15c** → B. B was assigned formula **13** (presumably as the result of epimerization at C-8 but not at C-13 during the oxidation step), the configurational assignment for B being based on the negative ORD curve, the unhindered nature of the carbonyl group, and its conversion to the abietanoic acid **16** *via* the thioketal of B. Huffmann and Alford[22] also prepared A by a similar sequence. Both groups converted B to the ketone **12** by treatment with base, a reaction which they assumed involved epimer-

(22) J. W. Huffmann and J. Al Alford, Abstracts, Fifth International Symposium on the Chemistry of Natural Products, July 8–13, 1968, p 325.

(23) A. W. Burgstahler, J. N. Marx, and D. F. Zinkel, *J. Org. Chem.*, **34**, 3716 (1969) (correction).

(24) J. W. Huffman, J. A. Alford, and R. R. Sobti, *ibid.*, **35**, 473 (1970).

SCHEME II



poration at C-15 in **4b** and **5** and for decarboxylation of **4b** could be dismissed.

The experiments with **10a**, **12**, and **13** established, however, that both the C-13 hydroxyl and the 14-keto group were essential for the introduction of deuterium at C-12 and C-15 during the decarboxylation of **4a** and the exchange reaction of **5** and that the deuteration at these centers derives from a rearrangement in the course of which both H-12 protons and H-15 become enolic. This requirement is satisfied by invoking an acyloin rearrangement[25,26] which as particularized in Scheme III for **5** (R = H) must be degenerate. In the case of **4a**, whether it be formed from **4b** by pyrolysis or hydrolysis, Scheme III contains intermediates which as β-keto acids are subject to facile decarboxylation and are then in equilibrium with **5**.

(25) For base-catalyzed rearrangements of open-chain and monocyclic acyloins, see (a) D. B. Sharp and E. L. Miller, *J. Amer. Chem. Soc.*, **74**, 5643 (1952); (b) D. Y. Curtin and S. Leskowitz, *ibid.*, **73**, 2633 (1951); (c) I. Elphimoff-Felkin and A. Skrobek, *Bull. Soc. Chim. Fr.*, 742 (1959). Aspects of the base-catalyzed acyloin rearrangement of 17-hydroxypregnan-20-ones to D-homoandrostane derivatives are reviewed by (d) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 576; (e) N. L. Wendler in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1964, p 1099; (f) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, 1968, p 294; (g) D. N. Kirk and A. Mudd, *J. Chem. Soc. C*, 2045 (1970).

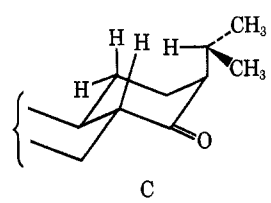
(26) Homoenolization has been excluded as a mechanism for the degenerate acyloin rearrangement of 1-hydroxynorbornan-2-one: A. Nickon, T. Nishida, and Y. Lin, *J. Amer. Chem. Soc.*, **91**, 6860 (1969). For the rearrangement of 3,3-dimethyl-1-hydroxynorbornanone, see A. Nickon, T. Nishida, J. Frank, and R. Muneyuki, *J. Org. Chem.*, **36**, 1075 (1971).

To explain the results of the deuterium exchange reaction, it was necessary to assume that the C-8–C-14 and the C-12–C-13 bonds migrate during the course of the reaction but that the overall result which produces no change in structure involves a degenerate acyloin rearrangement which would not have been detected in the absence of a carbomethoxy group at C-12 of **4b**. Thus reversible retrogression of **5** (or **4b**) by migration of the C-12–C-13 bond gives II, which can undergo deuterium exchange at C-15. Reversible ring expansion of II by migration of the C-8–C-14 bond either results in formation of ions III and IV which can undergo deuterium exchange at C-12, or leads to V, the precursor of stereoisomer **21** or **5**. Decarboxylation of **4a** presumably proceeds through an intermediate of type III or IV under basic conditions and probably under pyrolytic conditions as well.

The factors which favor ring expansion and contraction over methyl migration in the D-homoannulation of 17-hydroxy-20-keto steroids[25] (migration of a tertiary in preference to a primary center) are presumably not operative here, so that a direct path from I to III by migration of the isopropyl group is conceivable. However, even then, the return to **4b** or **5** would, because of the introduction of deuterium at C-15, require passage or leakage through ion II. Furthermore ion II (R = H) is required as an intermediate to account for the transformation of **21** to **5** (*vide infra*).

Scheme III suggests that **5** is in equilibrium not only with **20** and **22**, but also with the other three possible isomers **19**, **21**, and **23**, and that **5** represents the most stable isomer. This is reasonable because **19** and **23** are 1-acylcyclopentanols, which are known[25c] to be unstable with respect to the 2-alkyl-2-hydroxycyclohexanol systems represented by **5**, **20**, **21**, and **22**. Isomers **20** and **22**, although more stable than **19** and **23**, are undoubtedly less stable than **5** and **21**, due to the presence of extra interactions between H-7 and the axial substituent of C-14.

That **5** should be more stable than **21** as required by Scheme III seemed initially somewhat puzzling but can be rationalized since in the preferred conformation C[27] the interactions between methyl groups and the



axial hydrogens on ring C are minimized and since, due to the 2-alkyl ketone effect,[28] the conformational energy of an α-isopropyl group in cyclohexanones is 0.6 kcal/mol or less.[29,30] Thus even a small amount of assistance from another source can shift the equilibrium in favor

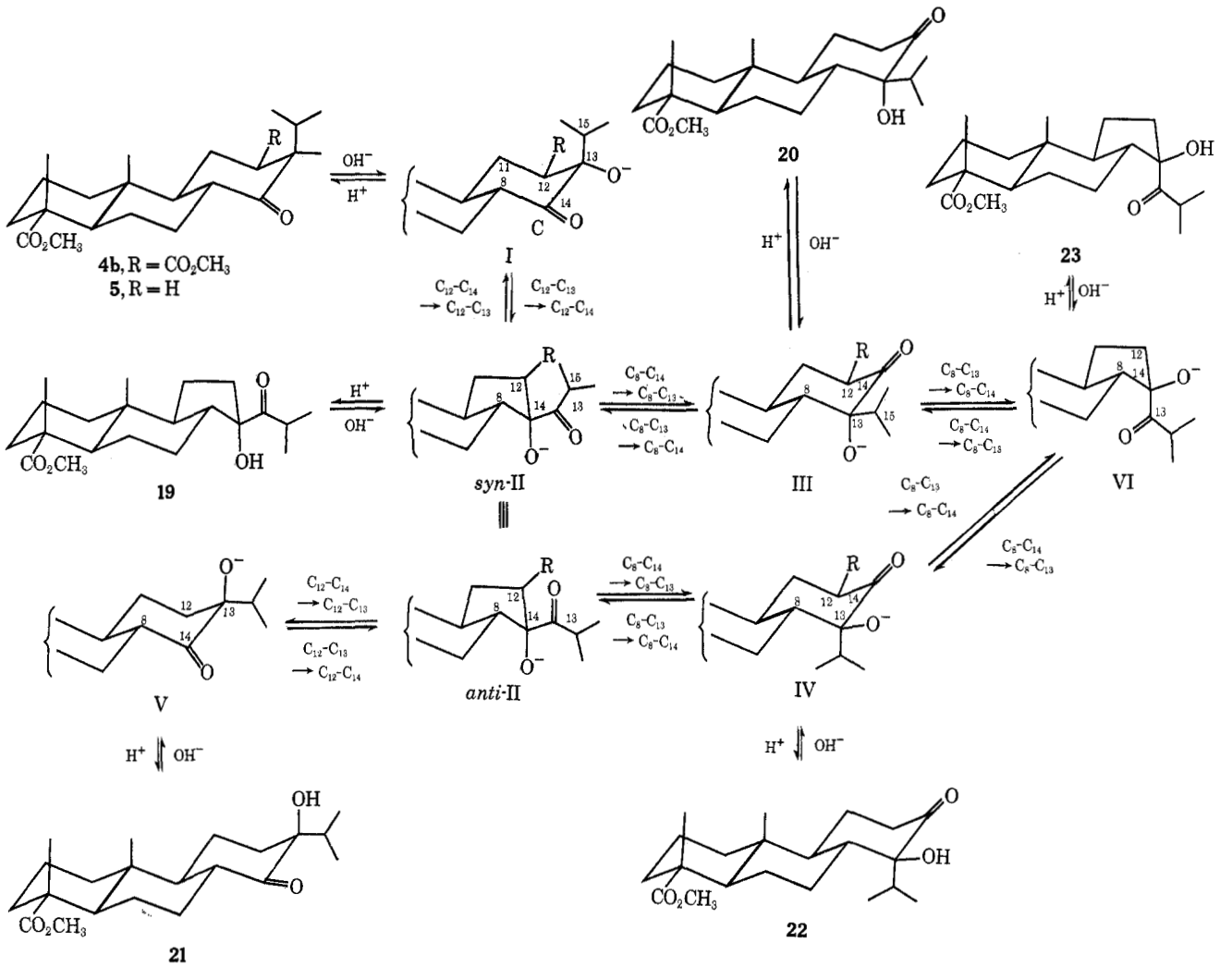
(27) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 458. The chemical shifts of the isopropyl doublets mentioned earlier support this conformation.

(28) Reference 25, p 113.

(29) B. Rickborn, *J. Amer. Chem. Soc.*, **84**, 2414 (1962).

(30) The equilibrium mixture of 2-isopropylcyclohexanone contains 66–67% of the equatorial and 29–34% of the axial conformer: C. Djerassi, P. A. Hart, and C. Beard, *ibid.*, **86**, 85 (1964).

SCHEME III



of an axial isopropyl group.[31] Although the conformational energy of a hydroxyl group in an α-ketol is not known, the presence of such a group may be expected to shift the equilibrium further toward **5**, particularly if, as is apparent from the models, the opportunity for strong intramolecular hydrogen bonding exists in **5**, as was in fact verified by experiment (*vide supra*), and not in **21**.

The likelihood of gaining access to the unstable isomers **19**, **20**, **22**, and **23** by synthesis for the purpose of testing all of the equilibria in Scheme III seemed very dubious. However, the preceding speculations on the relative stability order of **5** and **21**, and therefore the existence of the most important intermediate I, could be placed on a secure footing by successful transformation of **5** into **21**. The diol **10a** gave a gummy mesylate **10b** which was converted to the crystalline epoxide **24b** by refluxing with 5% methanolic sodium hydroxide.[32] Hydrolysis of **24b** gave **24a**, mp 214–216°, which was different from an acid, mp 226–228°, which has been prepared recently[24] by epoxidation of 13-abieten-18-oic acid and to which, on the basis of previous experience that reagent approach to 13-abietenes occurs preferentially from the β side, formula **25** had been tentatively assigned. The unambiguous synthesis of **24a** described here now confirms the conclusions reached by the Clemson workers.

Perchloric acid cleavage of **24b** gave a mixture from which a gummy diol was isolated after preparative tlc. Formation of the anticipated trans-diaxial glycol **26** was confirmed by the nmr spectrum, which displayed a broadened one-proton peak ($W_{1/2}$ = 5 Hz), thus indicating that the relationship of H-14 to H-8 was cis rather than trans. Oxidation of **26** furnished **21**, which could not be induced to crystallize and differed in other important respects from **5**. In line with the earlier discussion, there was no evidence of intramolecular hydrogen bonding. In the nmr spectrum the methyl doublets of **21** were almost superimposed (0.91 and 0.90 ppm) because the equatorial orientation of the isopropyl group removes the methyls from the shielding cone of the ketone function. The amplitude of the negative Cotton effect (a = −117) was considerably lower than that of **5**, perhaps because of the "*anti*-octant" behavior of the now axial hydroxyl group.[8]

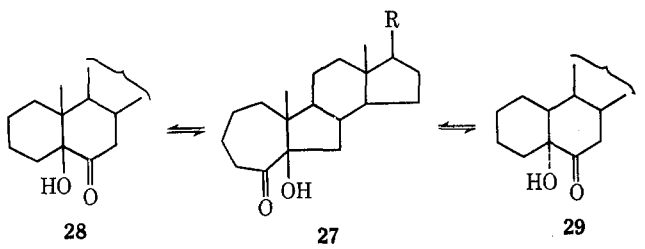
Treatment of **21** with 5% methanolic sodium hydroxide resulted in complete conversion to **5**. Rep-

(31) *Cf.* the situation prevailing in (+)-isomenthone, whose equilibrium mixture consists of 80–88% of the conformer with an axial and 12–20% of the conformer with an equatorial isopropyl group.[29]

(32) Although the stereochemistry of **24b** is without question because of its method of preparation, the half-height width of the H-14 signal (3 Hz) could not be used to confirm this, since models indicate that the H-8–H-14 dihedral angles would be almost the same irrespective of the orientation of the epoxide ring. However, in the β orientation one would expect deshielding of the C-10 methyl signal; this was not observed.

etition of the experiment with MeOD–CH_3ONA produced **5**, whose nmr spectrum showed complete incorporation of deuterium at H-15.[33] This result is in complete agreement with Scheme III.

Attempts were made to monitor the exchange reaction of **5** in an nmr tube in order to detect peaks caused by the presence of the unstable isomers. Such peaks could not be observed; hence it was assumed that the concentration of the isomers was sufficiently small (<5%) to excape detection. This failure parallels the results of Mazur and Nussim,[34] who effected complete rearrangement of the A-homo-B-nor steroid **27** to the cis ketol **28** with 2% methanolic KOH. Treatment of **28** and the trans ketol **29** separately with 10% methanolic KOH gave the same equilibrium mixture containing 92% **28** and 8% **29**. Although **28** and **29** are interconvertible only through **27**, the presence of the latter in the equilibrium mixture could not be detected.



28 **27** **29**

Experimental Section[35]

Methyl 12α-Carbomethoxy-13α-hydroxy-14-oxoabietan-18-oate (4b).—A solution of 25 g of **2b** in 500 ml of methanol saturated with gaseous HCl was allowed to stand overnight. Tlc of the wine red solution indicated disappearance of starting material. After removal of solvent, the residue was diluted with water, filtered, and washed repeatedly with cold water. Recrystallization from methanol–water gave 24.2 g (96%) of **4b** which had mp 139–140°; ir bands at 3480 (–OH), 1740, 1730 (two esters), and 1710 cm^{-1} (ketone); nmr signals at 3.88 (–OH), 3.60 (two methoxyls), 3.34 m, (H-12), 1.18 (C-4 methyl), 0.99 (C-10 methyl), 0.90 d and 0.64 d ppm (J = 6.5 Hz, isopropyl methyls); ORD curve $[\phi]_{298}$ −9280°, $[\phi]_{280}$ ±0°, $[\phi]_{254}$ +11,950°.

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88; O, 23.50. Found: C, 67.66; H, 9.08; O, 23.34.

Stirring of 1 g of **4b** with 10 ml of 2% methanolic sodium hydroxide at room temperature for 2 hr and evaporation of solvent at reduced pressure followed by addition of water and acidification gave 0.9 g of **4a**. Recrystallization from ether–hexane yielded the analytical sample which melted at 193–195°.

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.17; H, 8.83; O, 24.24.

Solution of **4a** in a methanolic solution of HCl overnight followed by the usual work-up gave a quantitative yield of **4b**.

Attempted Epimerizations of 4b. Isolation of 5. A.—A solution of 5 g of **4b** in 50 ml of 5% methanolic sodium hydroxide was refluxed for 18 hr. The solvent was removed at reduced pressure, water was added, and the mixture was acidified with 2 N HCl. The precipitate was washed with cold water, dried, and methylated with diazomethane. Evaporation of solvent gave a solid which contained **4b** and a minor component (tlc). Column chromatography gave 4.2 g of **4b**, identical in all respects with starting material. The minor component **5** had mp 160–161°; ir bands at 3480 (–OH), 1720 (ester), and 1700 cm^{-1} (ketone); nmr signals at 3.84 (–OH), 3.66 (methoxyl), 1.20 (C-4 methyl), 1.00 (C-10 methyl), 1.00 d and 0.67 d ppm (J = 6.5 Hz, isopropyl methyls); ORD curve $[\phi]_{400}$ −437°, $[\phi]_{310}$ −7145°, $[\phi]_{302}$ −8457°, $[\phi]_{286}$ ±0°, $[\phi]_{260}$ +12,250°, $[\phi]_{250}$ +11,370°. The position and shape of the hydroxyl band was not affected when the ir spectrum was run at different concentrations in CCl_4 solution indicating the existence of intramolecular hydrogen bonding.

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 71,77; H, 9.92; O, 18.58.

B.—A solution of 1 g of **4b** in 20 ml of 5% NaOD in CH_3OD was refluxed for 18 hr while being protected from atmospheric moisture, worked up as before but acidified with 2 ml of 38% DCl in D_2O prior to addition of water. The precipitate was filtered, washed with water, dried, methylated with diazomethane, and chromatographed. Nmr and mass spectra of the deuterated samples of **4b** and **5** were detailed in the Discussion. Prolongation of the reflux period resulted in an increase in the proportion of **4b**-d_3 and **5**-d_4.

Decarboxylation of 4a.—**4a** (0.5 g) was heated in a nitrogen atmosphere to 280° and held at this temperature for 5 min. Cooling and recrystallization of the product from chloroform–hexane afforded 0.32 g (70%) of **5**.

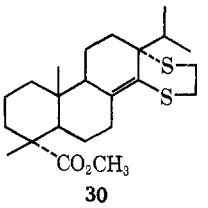
Pyrolysis of 2b. Preparation of 5 and 8. A.—Heating 5 g of **2b** to 280° in the manner described in the previous paragraph followed by chromatography of the crude product over alumina F-20 and elution with benzene afforded a 30% yield of **5** and 10% of a more polar substance **8** which melted at 136° after recrystallization from hexane. It had ir bands at 3480 and 3360 (two –OH) and 1720 cm^{-1} (ester), and nmr signals at 5.58 m ($W_{1/2}$ = 9 Hz, H-12), 4.22 br ($W_{1/2}$ = 6 Hz, H-14), 3.72 (methoxyl), 2.98 (two –OH), 1.18 (C-4 methyl), 1.06 d and 1.05 d (J = 7, isopropyl methyls), and 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 71.70; H, 9.95; O, 18.41.

B.—An intimate mixture of 5 g of **2b** and 10 g of alumina F-20 was heated in a nitrogen atmosphere at 280° for 10 min. Chromatographic separation of the crude product afforded a 60% yield of **8** and a 5% yield of **5**.

C.—A ground mixture of 2 g of **2b** and 0.2 g of MnO_2 (Baker analyzed) was heated at 280° for 10 min. Chromatographic separation gave 1.3 g (70%) of pure **5**.

A mixture of 1 g of **5**, 2 ml of ethanedithiol, and 0.5 ml of boron trifluoride etherate was left overnight and diluted with methanol. The precipitate was filtered and washed with methanol. Since tlc showed the presence of one main and several minor components, it was purified by preparative tlc. Elution with benzene–acetone (19:1) gave a major noncrystalline but homogeneous fraction which was not the expected thioketal because of the absence of hydroxyl peaks in the ir and nmr spectra and not a dehydration product because the nmr spectrum exhibited no signals characteristic of vinyl protons or vinyl methyl groups, but only the normal methyl doublets of the isopropyl group. The incorporation of ethylenedithiol was shown by the presence of a four-proton peak at 3.16 ppm. This material was tentatively assigned formula **30**. Raney nickel desulfurization furnished a



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mixture which exhibited neither –OH absorption in the ir nor vinyl proton peaks in the nmr indicating that **30** had been transformed into a mixture of esters of tetrahydroabietic acids.

Methyl 8α-Hydroxy-14-oxoabiet-12-en-18-oate (9).—To a solution of 0.5 g of **5** in 10 ml of acetone, Jones reagent was added with stirring and cooling until the yellow color of the reagent persisted (10 ml). The mixture was poured into water and extracted with ether. The washed and dried ether extracts gave 0.45 g of solid which was recrystallized from hexane–chloroform and then melted at 159.5–160°: ir bands at 3350, 1729, and 1668 cm^{-1}; nmr signals at 6.58 m (H-12), 3.69 (methoxyl), 2.20 (–OH), 1.10 (C-4 methyl), 1.03 d and 1.01 d (J = 6 Hz, isopropyl methyls), and 0.69 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36. Found: C, 72.19; H, 9.30; O, 18.50.

(33) Just as in the case of **4b** and **5** itself (footnote 18), the relative proportion of **5**-d_3 and **5**-d_4 depended on the reaction time (mass spectral analysis), although in every run, complete deuteration had taken place at C-15 (nmr analysis). We assume that deuterium exchange at C-8 which involves a sterically unfavorable abstraction and deuteration process is slower than exchange at C-12 and certainly slower than at C-15.

(34) Y. Mazur and M. Nussim, *Tetrahedron Lett.*, 817 (1961).

(35) For details concerning methods, see footnote 52 of ref 17. Mass spectra were run on a Nuclide 12 in medium-resolution mass spectrometer.

Methyl 13α,14β-Dihydroxyabietan-18-oate (10a).—A solution of 5 g of **5** in 60 ml of absolute ethanol containing 1 g of $NaBH_4$ was allowed to stand for 1 hr. Tlc of the mixture showed complete disappearance of starting material. Addition of water precipitated solid **10a** which was recrystallized from methanol (yield quantitative) and had mp 188–190°; $[\alpha]^{27}D$ −15.4° ($CHCl_3$); ir bands at 3580 and 3460 (–OH) and 1720 cm^{-1} (ester); nmr signals at 3.69 (methoxyl), 3.28 d (J = 10 Hz, H-14), 2.24 br (two –OH), 1.19 (C-4 methyl), 1.10 d and 0.90 d (J = 7 Hz, isopropyl methyls), and 0.88 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29; O, 18.15. Found: C, 71.76; H, 10.28; O, 18.24.

A solution of 0.2 g of **10a** in 5 ml of CH_3OD containing 0.2 g of CH_3ONa was refluxed for 18 hr and worked up as described for **4b** and **5**. Mass spectrometric analysis showed that recovered **10a** (yield quantitative) contained no excess deuterium.

Dehydration of 5. Preparation of 7 and 11.—To a solution of 5 g of **5** in 10 ml of pyridine was added at 0° dropwise 2 ml of thionyl chloride with stirring. The reaction was complete after about 6 hr; tlc showed two spots different from starting material. Dilution with water was followed by extraction with ether. Evaporation of the washed and dried extracts gave 4.5 g of residue. A 1-g portion of this was placed on a preparative tlc plate (20 × 40 cm) and developed with benzene–acetone (49:1). Two additional developments were required to separate the bands, which were separated and extracted with chloroform and chloroform–methanol (19:1). Band 1 gave 0.7 g of gummy **7**, which could be crystallized from hexane at −78° and then melted at 62–63°: ir bands at 1730 (ester), 1680, and 1660 cm^{-1} (α,β-unsaturated ketone); λ_{max} 237 nm (ε 7160); nmr signals at 6.72 t (J = 4Hz, H-12), 3.66 (methoxyl), 2.85 m (H-15), 120 (C-4 methyl), 1.00 d (J = 7 Hz, isopropyl methyls), and 0.98 ppm (C-10 methyl); ORD curve $[\phi]_{350}$ (first reading) −4420°, $[\phi]_{330}$ −4800°, $[\phi]_{300}$ −4060°, $[\phi]_{250}$ −9220°, $[\phi]_{235}$ ±0°, $[\phi]_{218}$ +11,070°, $[\phi]_{209}$ ±0°, $[\phi]_{200}$ −19,550° (last reading).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.40. Found: C, 75.78; H, 9.35; O, 14.61.

The more polar band on elution with chloroform and chloroform–methanol (19:1) gave 0.3 g of semicrystalline **11**, which was recrystallized from pentane and then melted at 138–140; ir bands at 1730 (ester), 1680, and 1650 cm^{-1} (α,β-unsaturated ketone, two bands of approximately equal intensity); nmr signals at 3.72 (methoxyl), 2.95 and 2.80 (vinyl methyls), 1.21 (C-4 methyl), and 0.96 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.99; H, 9.41; O, 14.79.

By following the dehydration reaction with tlc, it was noticed that **11** was formed first and that **7** was formed only after passage of time. When the reaction was complete (*i.e.*, after complete disappearance of starting material) the product consisted of **7** and **11**, but on standing all of the **11** was gradually converted to **7**.

Catalytic Hydrogenation of 7.—A solution of 0.5 g of **7** in 20 ml of absolute ethanol containing 0.1 g of 10% Pd/C was hydrogenated for 24 hr at 40 psi. Filtration and evaporation gave a residue which showed two spots of very similar R_f on tlc (benzene–methanol, 19:1). Preparative tlc gave two compounds. The less polar substance on recrystallization from methanol afforded 0.2 g of **12**, mp 74–76°, identical with authentic **12**.[10] The more polar substance **13** was recrystallized from cyclohexane: mp 128–130°; ir bands at 1720 (ester) and 1700 cm^{-1} (ketone); nmr signals at 3.61 (methoxyl), 1.16 (C-4 methyl), 0.97 (C-10 methyl), 0.92 d and 0.75 d (J = 7 Hz, isopropyl methyls); ORD curve $[\phi]_{319}$ −7770°, $[\phi]_{294}$ ±0°, $[\phi]_{283}$ +9390°.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.67; H, 10.34; O, 14.05.

A solution of 0.2 g of **13** in 10 ml of methanol containing 0.1 g of sodium methoxide was refluxed overnight. The usual work-up (which included remethylation with diazomethane) followed by preparative tlc resulted in isolation (prior to recrystallization) of **12** and **13** in the ratio 9:1. The same result was obtained when 0.2 g of **12** was refluxed with $NaOCH_3$–CH_3OH and worked up similarly. When a solution of 0.3 g of **13** in 10 ml of CH_3OD containing 0.1 g of sodium methoxide was refluxed overnight and worked up in the manner described for the exchange reaction of **4b**, 0.3 g of a mixture of deuterated **12** and **13** was obtained. Preparative tlc resulted in separation of **12**, which consisted of 32% excess **12**-d_1 and 68% **12**d_2 by mass spectrometric analysis. A more prolonged reflux period gave an increase in the proportion of **12**-d_2.

Methyl 12α,13α-Epoxyabietan-18-oate (24b).—A solution of 2 g of **10a** in 6 ml of pyridine was mixed with 1 g of methanesulfonyl chloride at 0°, allowed to stand in the refrigerator for 18 hr, poured into cold water, and extracted with ether. The washed and dried ether extracts were evaporated and the gummy residue of **10b**, which was homogeneous by tlc criteria, was refluxed with 20 ml of 5% methanolic sodium hydroxide for 5 hr. Evaporation at reduced pressure and addition of water gave a 90% yield of solid **24b**, which was recrystallized from methanol: mp 115–116°; ir band at 1720 cm^{-1} (ester); nmr signals at 3.66 (methoxyl), 2.80 br ($W_{1/2}$ = 3 Hz, H-14), 1.15 (C-4 methyl), 0.92 d and 0.91 d (J = 6.5 Hz, isopropyl methyls), and 0.80 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; 0, 14.35. Found: C, 75.22; H, 10.25; O, 14.70.

Hydrolysis of 0.15 g of **24b** with 15 ml of 5% methanolic sodium hydroxide for 18 hr gave a quantitative yield of **24a**, which was recrystallized from acetone–hexane and melted at 214–216°: $[\alpha]^{27}D$ +8.6° ($CHCl_3$); nmr signals at 2.81 br (H-14), 1.15 (C-4 methyl), 0.91 d and 0.90 d (J = 6.5Hz, isopropyl methyls), and 0.80 ppm (C-10 methyls).

A pure sample of the acid **25**, mp 226–228°, $[\alpha]$ +11°, was no longer available, but the mixture melting point of **24a** with a sample of mp 213–215° supplied by Professor Huffmann was depressed to below 200° and their spectra (KBr pellets) were different.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; O, 14.98. Found: C, 74.97; H, 9.74; O, 15.02.

Methyl 13β,14α-Dihydroxyabietan-18-oate (26).—A solution of 1 g of **24b** in 20 ml of tetrahydrofuran containing 2–3 drops of 87% perchloric acid was stirred at room temperature for 1 hr. Tlc showed a mixture with one major spot (40%). The usual work-up followed by preparative tlc gave 0.3 g of a homogeneous gum which had ir bands at 3505, 3480 (hydroxyl groups), and 1710 cm^{-1} (ester); nmr signals at 3.70 (methoxyl), 3.48 br ($W_{1/2}$ = 5 Hz, H-14), 1.20 (C-4 methyl), 0.91 d and 0.90 d (J = 7 Hz, isopropyl methyls), and 0.90 (C-10 methyl).

Methyl 13β-Hydroxy-14-oxoabietan-14-oate (21).—Jones reagent (2 ml) was added to a solution of 0.5 g of **26** in 10 ml of acetone with stirring at ice bath temperature. The reaction was quenched with water after 20 min and extracted with ether. The washed and dried ether layer was removed. The gummy residue (**21**), wt 0.5 g, was purified by chromatography, but could not be induced to solidify. The substance displayed ir bands at 3480 (intermolecularly bonded –OH, displaced to 3580 cm^{-1} in dilute CCl_4), 1730 (ester), and 1715 cm^{-1} (ketone), and nmr peaks at 3.70 (methoxyl), 1.20 (C-4 methyl), 1.00 (C-10 methyl), 0.91 d and 0.90 d (J = 7 Hz, isopropyl methyls); ORD curve $[\phi]_{326}$ −5675°, $[\phi]_{304}$ ±0°, $[\phi]_{250}$ +6040°.

A solution of 0.2 g of **21** in 10 ml of 5% methanolic sodium hydroxide was refluxed overnight. The reaction was worked up in the usual way (this included remethylation with diazomethane) and afforded 0.18 g of recrystallized **5**, mp 160–161°. The reaction was repeated with $NaOCH_3$–CH_3OD and quenched after 2 hr by the addition of water before it was complete. Tlc indicated the presence of a mixture of **21** and **5**. Separation by column chromatography gave pure **5**, whose nmr spectrum indicated that H-15 had been completely replaced by deuterium. Mass spectrometric analysis indicated the presence only of **5**-d_3 and **5**-d_4.

Registry No.—**4a**, 32111-48-1; **4b**, 32111-49-2; **5**, 32111-50-5; **7**, 32111-51-6; **8**, 32111-52-7; **9**, 32111-53-8; **10a**, 32111-54-9; **11**, 32111-55-0; **13**, 19426-98-3; **21**, 32111-57-2; **24a**, 32207-39-9; **24b**, 32111-58-3; **25**, 22565-87-3; **26**, 32111-60-7.