Biogenetic-Like Rearrangements of Tetracyclic Diterpenes

ROBERT M. COATES* AND EDWARD F. BERTRAM[1]

Department of Chemistry, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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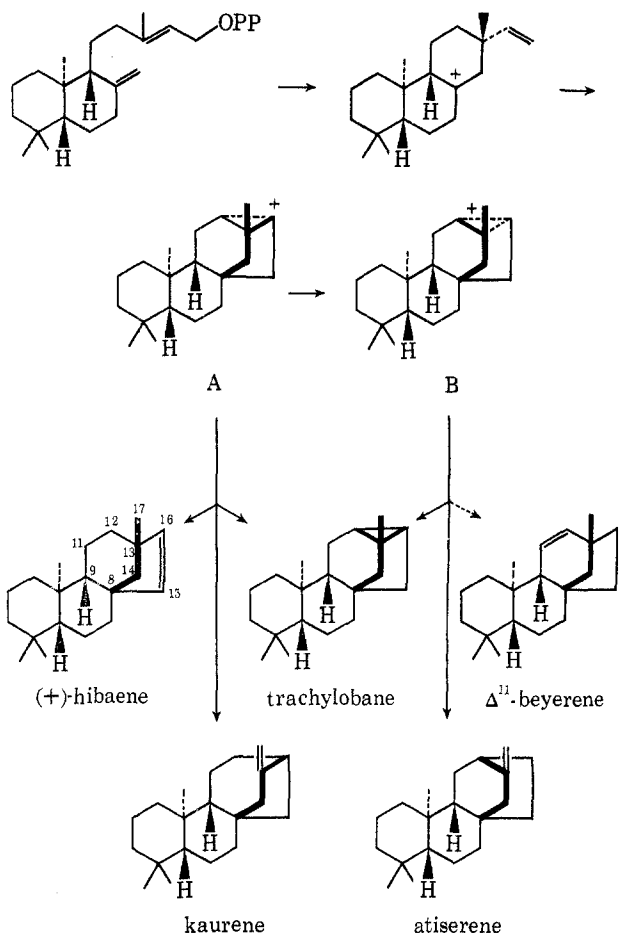
Nitrous acid deamination of methyl *ent*-16-aminobeyeran-19-oate (**1**) in acetic acid gives predominant rearrangement to methyl *ent*-16α-acetoxykauran-19-oate (**2b**) accompanied by small amounts of the isomeric kaurene esters **5** and **6**. Acetolysis of methyl *ent*-16β-tosyloxybeyeran-19-oate (**3c**) and decomposition of the tosylhydrazone **8** of methyl 16-ketobeyeran-19-oate under protic conditions afford the same rearranged, unsaturated esters **5** and **6**; in the latter reaction methyl *ent*-13aα,16-cycloatisan-19-oate (**9**), the C-4 epimer of methyl trachylobanoate, is also produced. Acetolysis of methyl 12β-tosyloxybeyeran-19-oate (**11c**) gives the isoatiserene ester **12** while formolysis of **11c** yields methyl *ent*-16-formyloxyatisan-19-oate (**14d**). Interconversion between these two Wagner–Meerwein rearrangement pairs is achieved through trifluoroacetolysis of **3c** and **11c**. Deuterium incorporation experiments shown that this rearrangement involves an intramolecular 12 $\rightleftarrows$ 16 hydride shift rather than an elimination–addition process by way of **9**. The various rearrangements observed formally correspond to the ring D rearrangements suggested for the biogenesis of these tetracyclic diterpenes.

The great majority of the naturally occurring tetracyclic diterpenes fall into two main classes in which the ethano bridge forming the D ring spans the 8 and either the 12 or 13 positions of the perhydrophenanthrene nucleus.[2,3] In the latter group the two-carbon bridge is found both cis and trans to the proton at C-9 (*e.g.*, kaurene and phyllocladene) and the C-17 carbon may be attached at either positions 13 or 16. Although these rather complex structural variations are inconsistent with the simple isoprene rule, a biogenetic scheme modified to permit skeletal rearrangements suggested by Wenkert[4] provides a concise rationale for the skeletal patterns within this family of natural products. The new diterpenes trachylobane[5a] and atiserene[5b] fit nicely into this biogenetic scheme[6,8–11] (Scheme I).

One particularly attractive feature of this biogenetic scheme is that the interconversions are quite analogous to the carbonium ion rearrangements of bridged bicyclic compounds.[12] It, therefore, seemed of interest to examine the cationic reactions of appropriately substituted tetracyclic diterpenes, to determine the extent to which the chemically induced reactions might follow, or deviate from, the pathways within this biogenetic scheme. In a separate paper we have set forth methods for modifying the available diterpene, isosteviol, with 12 and 16 substituents suitable for generation of carbonium ion intermediates.[13] In the following we describe in detail our investigation of the

SCHEME I



(1) Taken in part from the Ph.D. thesis of E. F. B., University of Illinois, 1970.

(2) (a) J. R. Hanson, "The Tetracyclic Diterpenes," Pergamon Press, London, 1968; (b) R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965).

(3) The numbering system used throughout this paper conforms to the recommendations ("The Common and Systematic Nomenclature of Cyclic Diterpenes," Third Revision, Oct 1968; Addenda and Corrigenda, Feb 1969) prepared by J. W. Rowe (Forest Products Laboratory, Forest Service, U. S. Department of Agriculture, Madison, Wis. 53705). Both common and systematic names are used in the text as seems appropriate; complete systematic names appear in the Experimental Section. We are grateful to Dr. Rowe for copies of these recommendations.

(4) E. Wenkert, *Chem. Ind. (London)*, 282 (1955).

(5) (a) G. Hugel, L. Lods, J. M. Mellor, D. W. Theobald, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2882, 2888 (1965); (b) A. H. Kapadi, R. R. Sobti, and S. Dev, *Tetrahedron Lett.*, 2729 (1965).

(6) A face-protonated trachylobane carbonium ion was originally suggested[4] as a possible single precursor to all of the various types of tetracyclic diterpenes. Since the face-protonated structure for the norbornyl cation has now been thoroughly discounted,[7] we prefer to use two separate carbonium ions, A and B. As will be seen, this accords with the chemical behavior.

(7) (a) C. J. Collins and M. H. Lietzke, *J. Amer. Chem. Soc.*, **89**, 6565 (1967); (b) G. A. Olah, A. M. White, J. R. DeMember, A. Commeyras, and C. Y. Lui, *ibid.*, **92**, 4627 (1970); (c) C. J. Collins, *Chem. Rev.*, **69**, 543 (1969).

(8) The reader may choose to consider the bridged representations A and B to correspond to either nonclassical, σ-bridged carbonium ions or transition states between two classical carbonium ions according to his preference. The 2-methylnorbornyl carbonium ion in superacid media is considered to be essentially classical according to spectral data.[7b]

(9) The available biosynthetic evidence is in agreement with these structural relationships; *cf.* J. R. Hanson and B. Achilladelis, *Perfum. Essent. Oil Rec.*, **59**, 802 (1968).

(10) The biosynthesis of some of these diterpenes has been carried out recently with soluble enzyme preparations: D. R. Robinson and C. A. West, *Biochemistry*, **9**, 70, 80 (1970), and references cited therein.

(11) To our knowledge, no naturally occurring Δ^{11}-beyerene derivatives (or their hydrated equivalents) have been isolated, although such compounds might be expected from Scheme I.

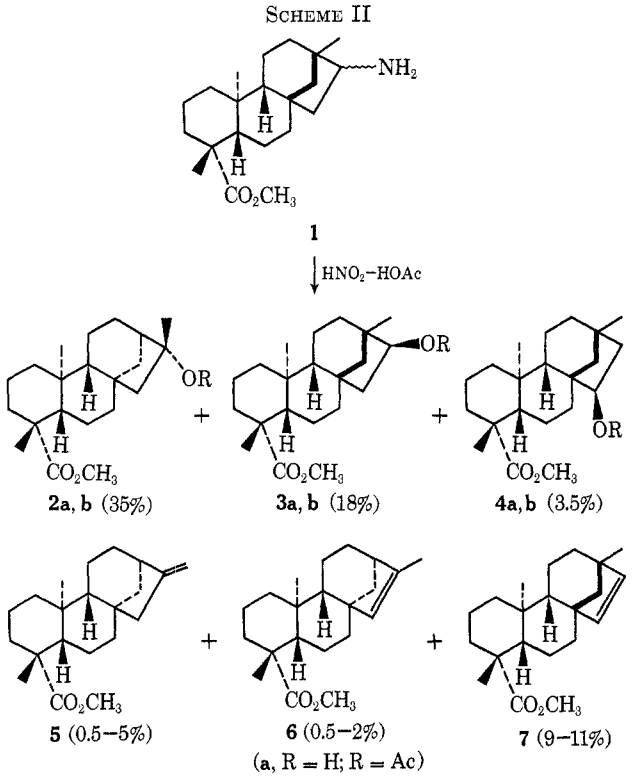
(12) (a) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Part 1, Chapter 3; (b) G. D. Sargent, *Quart. Rev., Chem. Soc.*, **20**, 301 (1966).

(13) R. M. Coates and E. F. Bertram, *J. Org. Chem.*, **36**, 2625 (1971).

biogenetic-like rearrangements of these isosteviol derivatives.[14,15]

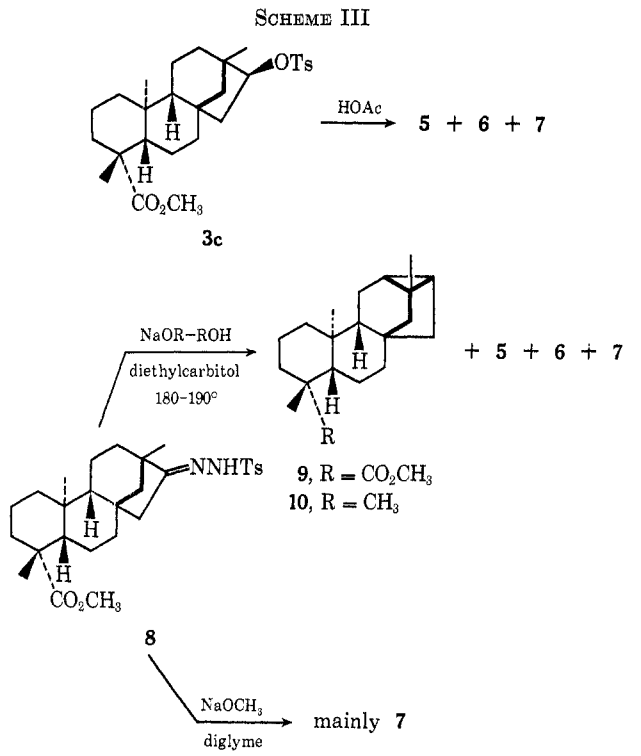
Three different methods for the generation of a cationic intermediate formally equivalent to A were examined: nitrous acid deamination of amine **1**, decomposition of tosylhydrazone **8**, and solvolysis of tosylate **3c**. Treatment of **1**, both as the free amine or in the form of its hydrochloride salt, with nitrous acid in acetic acid afforded a mixture consisting largely of acetates along with lesser amounts of olefinic products (Scheme II). The principal product, tertiary

SCHEME II



acetate **2b**, was identified by hydrolysis to the corresponding hydroxy ester **2a**[20] and dehydration with tosyl chloride in pyridine to a mixture of the exocyclic and endocyclic unsaturated esters **5** and **6**. The structure of the former was established by comparison with an authentic specimen derived from natural kauren-19-oic acid.[21] Iodine-catalyzed equilibration[19] of **5** gave rise to the double bond isomer **6**, and provided independent evidence in support of its constitution. The identity of the secondary acetates **3b** and **4b** was established by comparison with the acetates of the alcohols **3a** and **4a** obtained from hydroboration[18] of the known,[16b] unrearranged olefin **7**. Catalytic hydrogenation of the latter gave rise to methyl *ent*-beyeran-19-oate.[13] Acetolysis of the *exo* tosylate **3c** afforded a mixture of the same three unsaturated esters **5**–**7** in high yield (Scheme III).[22]

SCHEME III



Although none of the trachylobane-type product **9** was detected in the above product mixtures, decomposition of the tosylhydrazone **8** of the methyl ester of isosteviol in a variety of protic media yielded substantial proportions of the pentacyclic ester. With 10% ethylene glycol in diethyl carbitol containing 1.25 equiv of sodium glycolate, conditions which promote bicyclobutane formation from the tosylhydrazone of cyclopropanecarboxaldehyde,[23] **8** produces a mixture of esters in 59% yield. In addition to the same three olefinic esters (**5**–**7**) a fourth ester was obtained in 12% yield (21% of the ester mixture). The absence of both olefinic protons in the nmr spectrum and appreciable end absorption in the ultraviolet spectrum indicated the cyclopropane-containing structure **9**. Transformation

(14) Preliminary reports describing portions of this research are (a) R. M. Coates and E. F. Bertram, *Tetrahedron Lett.*, 5145 (1968); (b) *Chem. Commun.*, 797 (1969); (c) R. M. Coates, "Symposium on the Chemistry of Natural Products and Compounds of Biological Interest," Joint ACS-CIC Meeting, Toronto, Canada, May 1970.

(15) Concurrent, and in part, overlapping studies on the rearrangements of related tetracyclic diterpenes have been published.[16–19]

(16) Epoxide rearrangements: (a) A. H. Kapadi and S. Dev, *Tetrahedron Lett.*, 1255 (1965); (b) J. R. Hanson, *Tetrahedron*, **23**, 793 (1967); (c) A. Yoshikoshi, M. Kitahara, and Y. Kitahara, *ibid.*, **23**, 1175 (1967); (d) J. G. St. C. Buchanan and B. R. Davis, *Chem. Commun.*, 1142 (1967); P. A. Gunn, R. McCrindle, and R. G. Roy, *J. Chem. Soc. C* 1078 (1971); (e) J. R. Hanson, *Tetrahedron*, **26**, 2711 (1970).

(17) Acid-catalyzed rearrangements: (a) G. Hugel, L. Lods, J. M. Mellor, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2894 (1965); (b) A. J. McAlees, R. McCrindle, and R. D. H. Murray, *Chem. Ind. (London)*, 240 (1966); R. A. Appleton, A. J. McAlees, A, McCormick, R. McCrindle, and R. D. H. Murray, *J. Chem. Soc. C*, 2319 (1966); (c) L. H. Zalkow and A. C. Oehschalager, *J. Org. Chem.*, **32**, 808 (1967).

(18) Solvolytic rearrangements: (a) R. R. Sobti and S. Dev, *Tetrahedron Lett.*, 3939 (1966); (b) E. L. Ghisalberti and P. R. Jefferies, *Aust. J. Chem.*, **19**, 1759 (1966); (c) R. A. Appleton, P. A. Gunn, and R. McCrindle, *Chem. Commun.*, 1131 (1968); *J. Chem. Soc. C*, 1148 (1970).

(19) Iodine-catalyzed rearrangements: (a) K. Mori, M. Matsui, N. Ikekawa, and Y. Sumiki, *Tetrahedron Lett.*, 3395 (1966); K. Mori and M. Matsui, *Tetrahedron*, **24**, 3095 (1968); (b) ref 16c.

(20) The hydroxy acid corresponding to **2b** has recently been isolated: (a) E. P. Serebryakov, A. V. Simolin, V. F. Kucherov, and B. V. Rosynov, *Tetrahedron*, **26**, 5215 (1970); E. P. Serebryakov, N. S. Kobrina, A. V. Simolin, and V. F. Kucherov, *Chem. Ind. (London)*, 1770 (1968); (b) S. C. Pakrashi and E. Ali, *Indian J. Chem.*, **8**, 569 (1970). The properties of **2b** are in good agreement with those reported (see Experimental Section).

(21) C. A. Henrick and P. R. Jefferies, *Aust. J. Chem.*, **17**, 915 (1964). We are very grateful to Professor Jefferies for providing us with a sample of the kaurene ester **5**.

(22) For similar results see ref 18a,b.

(23) (a) J. A. Smith, H. Schechter, J. Bayless, and L. Friedman, *J. Amer. Chem. Soc.*, **87**, 659 (1965); J. Bayless, L. Friedman, J. A. Smith, F. B. Cook, and H. Schechter, *ibid.*, **87**, 661 (1965); see also (b) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959); (c) P. Clarke, M. C. Whiting, C. Papenmaier, and W. Reusch, *J. Org. Chem.*, **27**, 3356 (1962).

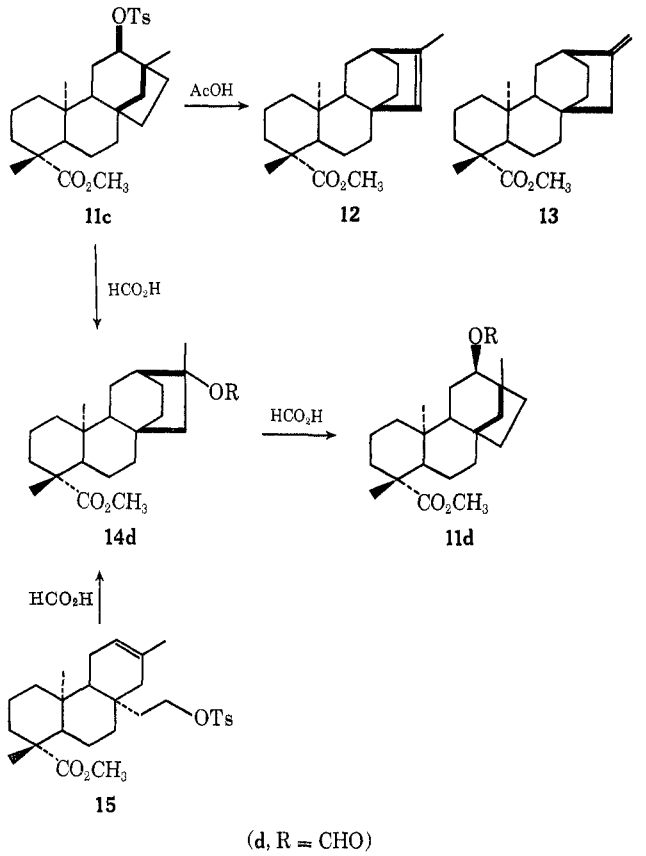
of the carboxyl group to a methyl group furnished the parent hydrocarbon, which proved to be identical with an authentic sample of trachylobane **10**.[5a,24-26]

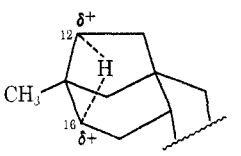
While all of the protic conditions employed for the tosylhydrazone decomposition afforded **9** in appreciable yields (4–14%, see Experimental Section), a reaction under aprotic conditions (sodium methoxide–diglyme) produced mainly the unrearranged olefinic ester **7**. These results provide an interesting contrast to the corresponding reactions of camphor tosylhydrazone, which give mainly tricyclene (cyclopropane formation) in aprotic media and rearranged olefin (camphene) under protic conditions.[27]

Solvolysis of the 12β tosylate **11c** provided a means for generating a cationic intermediate corresponding to B. In acetic acid, tosylate **11c** underwent Wagner–Meerwein rearrangement and elimination to the isoatiserene ester **12**[13] with little, if any, of the isomeric atiserene ester **13** present. Formolysis, on the other hand, gave rise to the corresponding rearranged substitution product **14d**. The tertiary alcohol (or formate) **14a(d)** upon heating in formic acid reverts to the 12β-beyerane derivative **11d**. The π route originating from tricyclic tosylate **15** also affords the 16-formyloxyatisan-19-oate **14d** upon formolysis,[13] thus implicating a common carbonium ion intermediate (Scheme IV).

The results presented to this point correspond well with the ring D rearrangements in the Wenkert biogenetic scheme (Scheme I). Cation A generated by chemical means does in fact undergo Wagner–Meerwein rearrangement to kaurenes[28a] and under certain conditions transannular proton elimination[28b] to the pentacyclic trachylobane nucleus. Similarly cation B gives the atiserene skeleton under solvolytic conditions. However, the one remaining step in this scheme, the interconversion A $\rightleftarrows$ B by means of a formal 12 $\rightleftarrows$ 16 hydride shift (crossover rearrangement) was not detected in the preceding experiments. This finding stands in contrast to the extremely facile 6 $\rightarrow$ 2 hydride shifts observed in norbornyl rearrangements.[7b] Furthermore, extensive transannular hydride shifts occur in the solvolysis of 5-*exo*-bicyclo[3.2.1]octyl tosylate[29] and the corresponding norditerpene, *ent*-16β-tosyloxy-17-norbeyerane.[18c] The evident inability of the 16 $\rightleftarrows$ 12 hydride shift to compete with nucleophilic capture and vicinal elimination in the above irreversible solvolysis reactions may be attributed to a combination of two factors. First, in the transition state for the 16 $\rightarrow$ 12 hydride shift, ring C must adopt a boatlike conformation in order that the 16β proton reach within bonding distance of C-12. This conformational strain must increase the energy of the transition state with respect to the norbornyl system. Second, the presence of the methyl group at C-13 must diminish the effective charge density at the 12 position, thus reducing the probability of hydrogen transfer.[30]

SCHEME IV





In order to increase the probability of the crossover rearrangement (A $\rightarrow$ B), we have examined the solvolysis of tosylates **3c** and **11c** in the less nucleophilic media, formic acid and trifluoroacetic acid.[31] A reduction in the rate of nucleophilic capture at the secondary positions (16 and 12) should enhance the relative rate of hydride shift, assuming that the solvent effect upon the latter process is negligible. The results are summarized in Scheme V.[30]

(24) We are grateful to Dr. G. Hugel and G. Ourisson for a sample of trachylobane.[5a]

(25) In view of the recent total synthesis of isosteviol by K. Mori, Y. Nakahara, and M. Matsui [*Tetrahedron Lett.*, 2411 (1970)], the production of **9** and **10** constitute formal total syntheses. Partial syntheses of methyl 13α,16-cycloatisan-19-oate (enantiomer of methyl trachylobanate)[5a] and (+)-**10** (enantiomer of **10**) from levopimaric acid have been reported by W. Herz, R. N. Mirrington, A. Young, and Y. Y. Lin, *J. Org. Chem.*, **33**, 4210 (1968).

(26) The corresponding acid (**9**, R = CO_2H), the C-4 epimer of the previously known trachyloban-18-oic acid,[5a] has recently been isolated from (a) the flowers of *Helianthus annuus* L. by J. St. Pyrek [*Tetrahedron*, **26**, 5029 (1970)] and (b) a *Solidago* species by R. McCrindle (private communication). A direct comparison performed by Professor McCrindle between the methyl ester of the latter and the ester **9** prepared in this work has established the identity of the two compounds.

(27) R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Amer. Chem. Soc.*, **89**, 1442 (1967), and references cited therein.

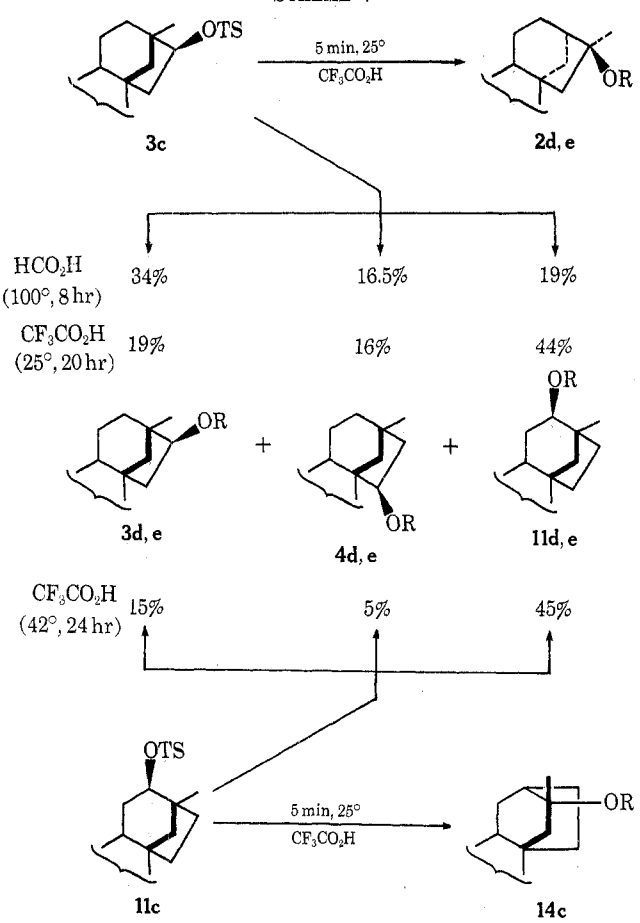
(28) (a) For other examples of this type of C–D rearrangement of beyerane derivatives see ref 16–18 (b). We are assuming that the mechanism of cyclopropane formation in the tosylhydrazone decomposition under protic conditions is cationic (diazonium ion formation with incorporation of a proton from solvent) rather than carbenoid, as has been established for the formation of bicyclobutane from cyclopropyl carboxaldehyde tosylhydrazone: F. Cook, H. Schechter, J. Bayless, L. Friedman, R. L. Foltz, and R. Randall, *J. Amer. Chem. Soc.*, **88**, 3872 (1966); K. B. Wiberg and J. M. Lavanish, *ibid.*, **88**, 5272 (1966).

(29) R. A. Appleton, J. C. Fairlie, R. McCrindle, and W. Parker, *J. Chem. Soc. C*, 1716 (1968).

(30) A small amount (0.5–14%) of crossover rearrangement was detected in the hydrogen chloride catalyzed isomerizations of tetracyclic diterpene hydrocarbons.[17b] A case of apparent crossover rearrangement has also been found in the phyllocladene series.[16d]

(31) P. E. Peterson, R. J. Bopp, D. M. Chevlie, E. L. Curran, D. E. Dillard, and R. J. Kamat, *J. Amer. Chem. Soc.*, **89**, 5902 (1967); J. E. Norlander and W. G. Deadman, *ibid.*, **90**, 1590 (1968); I. L. Reich, A. Diaz, and S. Winstein, *ibid.*, **91**, 5635 (1969).

SCHEME V



c, R = Ts; d, R = CHO; e, R = CF_3CO

Whereas acetolysis of **3c** affords only kaurane-type products (see above), extended formolysis gives 19% of the 12β formate **11d** along with the vicinal rearrangement product **4d**. In the less nucleophilic medium, trifluoroacetic acid, as much as 44% of the 12 substitution product is found. The reverse crossover rearrangement (B → A) is also seen in the trifluoroacetolysis of the 12β tosylate **11c**. In both cases, the initial products are the simple Wagner–Meerwein rearrangement isomers **2e** and **14e**.

The experimental observation of the 12 → 16 hydride shift raises the question of the mechanism of the process. The formation of a trachylobane intermediate, for which precedent now exists, followed by acid-catalyzed ring opening[17a] in the reverse sense would effect overall 12 → 16 hydride transfer. The other possibility is an intramolecular transfer of hydride between positions 12 and 16. These two alternatives were distinguished through solvolysis in deuteriotrifluoroacetic acid; a summary of the data is collected in Table I

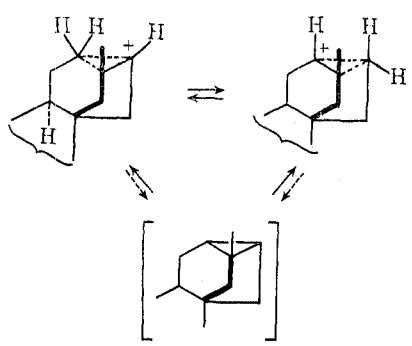


TABLE I

DEUTERIUM INCORPORATION DURING SOLVOLYSIS IN TRIFLUOROACETIC ACID-*O*-*d* WITH VARIOUS DITERPENE SUBSTRATES

	Deuterium incorporation[a]	
Substrate	Into **11b**[b]	Into other products
3c	77% d_5 (4.85)	**3b**,[b] 60% d_4 (3.56)
		4b,[b] 55% d_4 (3.27)
3c		**2a**,[c] 44% d_3 (3.25)
2a	69% d_5 (4.90)	
11a		**14a**,[c] 47% d_3 (4.18)
5	85% d_5 (4.95)	
12	85% d_5 (4.93)	
13	83% d_5 (4.90)	
9	76% d_6 (5.78)	

[a] Percentage of major deuterated species followed by the average deuterium content in parenthesis. Complete deuterium distribution data in Experimental Section. [b] Product isolated as acetate for convenience; deuterium distribution determined on M − 60 fragment. [c] Product isolated as alcohol; deuterium distribution determined on parent peak (M^+).

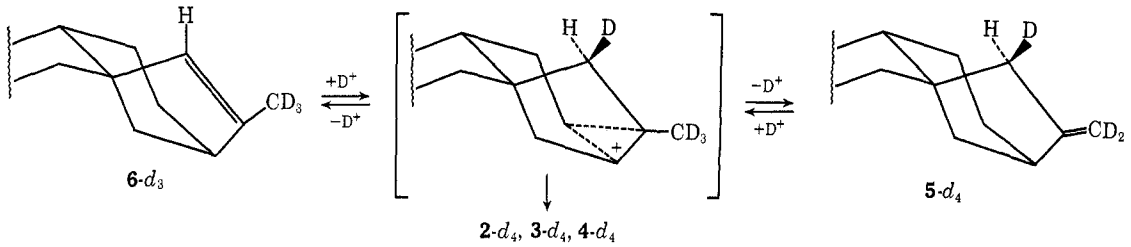
(complete deuterium distributions may be found in the Experimental Section).

From the extensive deuterium incorporation (three to six deuterium atoms), it is clear that extensive elimination–addition occurs in the trifluoroacetic acid medium. This conclusion is confirmed by conversion of the unsaturated esters **5**, **12**, and **13** to **11e** under the standard solvolysis conditions and with the same deuterium incorporation. The disappearance of the C-17 methyl resonance in the nmr spectra of the products locates approximately three of the deuterium atoms. There can be no deuterium at the carbinyl positions (*i.e.*, 12 and 16) of **11b** and **3b**, since the corresponding keto esters (**16** and **17**) had essentially the same deuterium content.

The remainder of the label would be expected to be situated on the carbon adjacent to the methyl group (*i.e.*, position 14 in **3b**, **4b**, and **11b**; position 15 in **2a** and **14a**) in the various products, since the label must be acquired in the deuteron addition to the unsaturated esters **6** and **12**. Some experimental support for this supposition was obtained by dehydration of the labeled **14a** (4.18 *d*, 47.1% d_5) with thionyl chloride in pyridine. The isomeric atiserene-type esters obtained (**12** and **13**) had average deuterium contents of 3.35 *d* and 3.48 *d* with the principal species being d_4 (51.3 and 55.5%) and with essentially no d_5. The nmr spectrum of labelled **13** exhibited a reduced intensity for the allylic methylene group (τ 8.04), and more quantitatively the spectrum of **12** showed only 0.1 proton for the vinyl hydrogen at C-15 (τ 4.42).

Submission of the cyclopropane-containing ester **9** to trifluoroacetic acid-*O*-*d* similarly afforded the 12β-substituted kaurane ester **11**, but now with the clean incorporation of six deuterium atoms. Since **11** was formed in all the other cases with incorporation of five atoms of deuterium (0–6% d_6), the observed crossover rearrangement in trifluoroacetic acid must occur predominantly by way of an intramolecular hydride transfer from C-12 to C-16.

The observation that products **2–4** apparently incorporate essentially one less deuterium atom than **11** is attributable to a highly stereoselective elimination–addition sequence with the tertiary kauranol ester **2**. Additions to trigonal carbons on the ethano bridge of kaurenes and beyerenes are well-known to proceed with high exo stereoselectivity.[32] Hence if the deuteron addition to the isokaurene **6** (and its microscopic reverse elimination) proceeds solely from the *exo* (α) side, there will be no opportunity for the endo proton to exchange. On the other hand, additions to atiserenes generally show little selectivity;[32] thus after the crossover rearrangement, nonselective elimination–addition ensues, resulting in the eventual exchange of the one remaining proton.



This investigation and complementary studies in other laboratories[16–19] have established that all of the individual ring D rearrangements in the Wenkert biogenetic scheme (Scheme I) can be mimicked by chemical means.[33] Despite these successes, however, it is clear that the chemical transformations, for the most part, lack the specificity normally found in enzyme-mediated biosynthetic reactions. We find, for example, that elimination under solvolytic conditions gives both kaurene and isokaurene esters, whereas, in the enzymatic biosynthesis of kaurene,[10] only the exocyclic isomer appears to be formed. Although we find that the 12 → 16 hydride shift can be observed in the poorly nucleophilic medium, trifluoroacetic acid, the rearrangement is accompanied by extensive elimination–addition, and under these conditions the product is a 12-substituted beyerane (**11**) rather than an atiserene (**12**). In contrast, the biosynthesis of the carbon nuclei of most terpenes from cyclic precursors appears to proceed in a "nonstop" manner, *i.e.*, without proton elimination *en route*.[36]

It is interesting, albeit highly speculative, to consider in closing the role which an enzyme (or enzymes) might play in the skeletal rearrangements of the actual biosynthetic process. First, the exocyclic specificity in the proton elimination might be effected by the location of a basic center near the C-17 methyl group in the enzyme–substrate complex. The efficiency of the crossover rearrangement could be enhanced through a conformational change imposed upon the diterpene substrate by the shape of the enzyme cavity. If ring C is forced to adopt a boat conformation, the 12 → 16 hydride shift might well occur with facility. Furthermore, it seems likely that a nucleophilic center(s) (and/or counterion) at the active site is closely associated with the various carbonium ions.[37] Reversible nucleophilic capture by this center would help maintain the stereospecificity of the rearrangement, moderate the reactivity of the cationic intermediate(s), and possibly avoid premature elimination.

Experimental Section[38]

Deamination of Methyl *ent*-16-Aminobeyeran-19-oate (1). A. As Hydrochloride.—Sodium nitrite (1.5 g, 21.6 mmol) was added in three equal portions to a solution of the hydrochloride of **1**[13] in acetic acid (25 ml) over a 2-hr period. After 12 hr at room temperature the solvent was evaporated, the residue was dissolved in hexane, and the hexane solution was washed twice with water and then dried (Na_2SO_4) and evaporated. The resulting mixture was separated into eight fractions by column chromatography on silica with chloroform as eluent.

The first fraction (34 mg) contained mainly methyl Δ^{15}-*ent*-beyeren-19-oate (**7**). Glpc analysis indicated the presence of small amounts of the kaurene esters (**5**:**6**:**7**, 5:5:90). The major component was isolated by crystallization from methanol, mp 111–112.5° (lit.[16b] mp 107–109°). The infrared spectrum is identical with a spectrum of **7** obtained from the decomposition of the tosylhydrazone **8**.

The third fraction (86 mg) was crystallized from hexane to give methyl *ent*-16α-acetoxybeyeran-19-oate (**26**): mp 144–148°; nmr τ 9.14, 8.81, 8.38, 8.02, 6.32 (all s, 3 H); ir 1720 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.40; H, 9.65.

The subsequent fractions contained mixtures of three acetates: **2b**, **3b**, and a third acetate. Preparative tlc (silica gel, 1:1 benzene–chloroform as eluent) upon fractions 5 and 6 (69 mg) enabled partial separation of **3b** (25.5 mg) essentially pure by glpc analysis. Several recrystallizations from methanol gave material with mp 91–92° (lit.[13] mp 91–92°). Direct comparison

(32) For specific references see ref 13.

(33) Three of the four preceding cyclization steps in the biogenetic scheme can be effected chemically. Acid-catalyzed cyclizations of acyclic precursors to the proper A–B bicyclic nucleus are well known.[34] In addition, the cationic cyclization of bicyclic diterpenes to the tricyclic stage has also recently been accomplished.[35a,b] Although further cyclization to tetracyclic beyerane derivatives was observed, the pathway is quite different from the biogenetic route in Scheme I.[35c]

(34) A. Eschenmosher, D. Felix, M. Gut, J. Meier, and P. Stadtler in "Biosynthesis of Terpenes and Sterols," Ciba Foundation Lectures, G. E. W. Wolstenholme and M. O'Connor, Ed., J. A. Churchill, London, 1959, p 217; G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5068 (1955); E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).

(35) (a) O. E. Edwards and R. S. Rosich, *Can. J. Chem.*, **46**, 1113 (1968); E. Wenkert and Z. Kumazawa, *Chem. Commun.*, 140 (1968); (b) T. McCreadie and K. H. Overton, *ibid.*, 288 (1968); *J. Chem. Soc. C*, 312 (1971); (c) O. E. Edwards and B. S. Mootoo, *Can. J. Chem.*, **47**, 1189 (1969); J.-L. Fourrey, J. Polonsky, and E. Wenkert, *Chem. Commun.*, 714 (1969); S. F. Hall and A. C. Oehlschlager, *ibid.*, 1157 (1969).

(36) See, for example, T. T. Tchen and K. Bloch, *J. Amer. Chem. Soc.*, **78**, 1516 (1956); E. Caspi, J. B. Greig, J. M. Zander, and A. Mandelbaum, *Chem. Commun.*, 28 (1969).

(37) The temporary participation of a nucleophilic center in enzyme-catalyzed olefin alkylation reactions has been suggested; *cf.* J. W. Cornforth, *Angew. Chem., Int. Ed. Engl.*, **7**, 903 (1968).

(38) Melting points were taken in open capillary tubes on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on Perkin-Elmer spectrophotometers, Models 137, 237, or 521. The nmr spectra were obtained in carbon tetrachloride (unless specified otherwise) using tetramethylsilane as internal standard on Varian Associates Models A-60A, A-56-60, or HA-100 spectrophotometers. The mass spectra were determined on an Atlas CH_4 mass spectrometer. Microanalyses were performed by Mr. J. Nemeth and associates at the University of Illinois. The gas chromatograph used was a Hi-Fi Model 600-D (Varian Aerograph) with a 6 ft × 0.125 in. column 5% SE-30 silicone rubber on 60–80 mesh DMCS Chromosorb W (usual temperatures: column 230°, injector 260°). The optical rotations were taken in a Zeiss polarimeter using chloroform as solvent. The ultraviolet spectra were taken on a Cary Model 14 spectrophotometer using ethanol as solvent.

TABLE II

YIELDS AND PRODUCT DISTRIBUTION FROM THE DECOMPOSITION OF TOSYLHYDRAZONE 8

Solvent	Base (equiv)	% yield (less polar fraction)	Relative yields,[e] % 9	5	6	7
DEC[a] + 1.25% H_2O	$NaOCH_3$ (2)	35	30	34	34.5[f]	
DEC + 2% H_2O	NaOH (1.6)	31.3	12.1	17.1	71.5[f]	
DEC + 1.25% H_2O[b]	NaOH (3)	49	24	28.7	6.6	42
DEC + 10% EG[c,d]	$NaOCH_3$ (3)	58	24.2	32.1	43.1[f]	
DEC + 10% EG[c]	$NaOCH_3$ (1)	52	14.8	17	11.2	59
DEC + 10% EG	Na (3)	40	23.6	29.2	6.6	34.8
DEC + 10% EG	Na (1.25)	59	21	35	7	35
Diglyme[c]	$NaOCH_3$ (1)	33		5	5	90

[a] DEC = diethylcarbitol. [b] Additional water added at intervals. [c] Salt formation before the solvent was added. [d] EG = ethylene glycol. [e] By glpc and nmr spectral analysis. [f] Yield of 6 + 7 (inseparable by glpc).

(tlc, glpc, ir, nmr, and mmp 91–93°) established its identity as methyl *ent*-16β-acetoxybeyeran-19-oate (**2b**). The third acetate is tentatively identified as *ent*-16α-acetoxybeyeran-19-oate[13] by glpc comparison.

By means of nmr and glpc analysis upon the mixed fractions, combined with the isolated materials, the following product distribution was calculated: **5** (0.5%), **6** (0.5%), **7** (9%), **2b** (35%), **3b** (15%), and the 16α acetate (<5%).

B. As Amine.—Three portions of sodium nitrite, 3.5 g (50.8 mmol), 2 g (29.0 mmol), and 0.5 g (7.2 mmol), were added to a solution of amine **1**[13] in acetic acid (100 ml) at 0, 0.5, and 15 hr, respectively. After 29 hr at room temperature the product was isolated as described in part A. Direct crystallization from methanol gave **3b** (0.5 g, mp 143–147°).

The mother liquor was evaporated and the residue was chromatographed on silica gel (200 g) using 5% ether in hexane as eluent. The early fractions afforded a mixture of the unsaturated esters (0.414 g) which according to glpc and nmr spectral analysis consisted of **5** (27%), **6** (14%), and **7** (59%). The following fractions gave additional tertiary acetate **3b** after recrystallization (mp 144–148°). The next fractions contained mixtures of **2b**, **3b**, **4b**, and the 16α acetate in varying proportions. From one fraction (502 mg) rich (~90%) in **3b**, crystallization twice from methanol gave pure material, mp 92–93.5°. The material recovered from the mother liquor and the following fraction (enriched in **4b**) were rechromatographed using chloroform as eluent. In this manner relatively pure **4b** was obtained, which after crystallization from methanol gave nmr, ir, glpc, and melting point characteristics identical with those of an authentic specimen.[13]

The final product distribution was estimated to be as follows: **5** (5%), **6** (2%), **7** (10%), **2b** (31%), **3b** (21%), **4b** (3.5%), and 16α acetate (4%).

Methyl *ent*-16α-Hydroxykauran-19-oate (2a).—A solution of **2b** (50 mg, 0.13 mmol) in excess 5% ethanolic sodium hydroxide was heated at reflux temperature for 3 hr. The alcohol was evaporated and the product was isolated by hexane extraction (see above). Recrystallization from hexane afforded the hydroxy ester **2a**: mp 154–155° (lit.[20a] mp 153–156°); nmr τ 9.18, 8.85, 8.70, 6.40 (all s, 3 H) (lit.[20a] τ 9.22, 8.88, 8.69); $[\alpha]^{25}D$ −76° (*c* 33); ir 1720, 3550 cm^{-1}.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.12; H, 10.19.

Methyl Δ[15]-*ent*-Kauren-19-oate (5) and Methyl Δ[16]-*ent*-Kaurene-19-oate (6).—A solution of hydroxy ester **2a** (58.5 mg, 0.17 mmol) and tosyl chloride (300 mg) in 15 ml of pyridine was heated under reflux for 3 hr. The cooled solution was added to dilute hydrochloric acid and the product was extracted from the resulting suspendion with three portions of hexane. The combined hexane extracts were washed once with dilute hydrochloric acid and twice with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on 20% silver nitrate silica gel with ethyl acetate–hexane as eluent. The first two fractions contained **5** (17 mg) and **6** (21 mg), respectively (ir, nmr, tlc, and glpc comparisons). A small amount of unreacted **2a** was found in a later fraction.

Tosylhydrazone 8 of Methyl *ent*-16-Ketobeyeran-19-oate (Isosteviol Methyl Ester).—A solution of isosteviol methyl ester (2.3 g, 6.9 mmol)[13] in 7 ml of glacial acetic acid was heated to reflux temperature. A 3-g (16.3 mmol) portion of *p*-toluenesulfonylhydrazine was slowly added to a second 7-ml portion of glacial acetic acid at reflux temperature. The two hot solutions were then combined and heated at reflux temperature for 1–2 min. After cooling, a fine white crystalline precipitate formed which was filtered and washed first with cold glacial acetic acid and then with 10–20% water in acetic acid. The yield of **8** was 3.36 g (95%): mp 214–215° (from chloroform and hexane); nmr (CDCl_3) τ 9.375, 9.00, 8.835, 7.57, and 6.35 (all s, 3 H), 2.70 and 2.17 (A_2B_2, 4 H, J = 8 Hz).

Anal. Calcd for $C_{28}H_{40}N_2O_4S$: C, 67.17; H, 8.05; N, 5.60; S, 6.40. Found: C, 66.91; H, 8.02; N, 5.77.

Decomposition of Tosylhydrazone 8.—Several different conditions were examined (see Table II for summary). A typical procedure is as follows.

The tosylhydrazone **8** (875 mg, 1.7 mmol) was allowed to react with sodium methoxide in methanol (6.0 mmol in 1 ml). The methanol was then removed by gentle heating under a light stream of dry nitrogen. The solvent was added, in this case 10% ethylene glycol in diethylcarbitol, and the solution was quickly brought to reflux temperature (180–190° bath temperature). After 3 hr at reflux temperature, the solution was cooled and the product was isolated by extraction with hexane. The crude product was separated into a less polar fraction (315 mg, 59%) and a more polar fraction by column chromatography on silica gel (chloroform as eluent).

Rechromatography of the less polar fraction on 30 g of 20% silver nitrate–silica gel eluting with 2–10% ethyl acetate–hexane afforded four components. The least polar, pentacyclic ester **9** (methyl *ent*-13α,16-cycloatisan-19-oate)[26] was recrystallized from methanol: mp 101–103° (lit.[26a] mp 98–100°); nmr τ 9.3–9.5 (m), 9.26 (s, 3 H), 8.87 (s, 6 H), 6.38 (s, 3 H) [lit.[26a] τ_{CDCl_3} 9.4 (m), 9.25 (s, 3 H), 8.88 (6 H), 6.40 (s, 3 H)]; $[\alpha]^{25}D$ −67° (*c* 4.5) [lit.[26a] $[\alpha]D$ −70.5° ($CHCl_3$)]; ir 1720 cm^{-1}; uv ϵ_{199} 845; mass spectrum *m/e* 316 (M^+).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.91. Found: C, 79.67; H, 10.11.

The second component was shown to be methyl Δ[16]-kauren-19-oate (**5**) by comparison (ir, mixture melting point, glpc) with an authentic sample:[21] mp 84–85° (lit.[21] mp 88–89°), mmp 83–86.5° (authentic sample, mp 86°); nmr τ 9.18, 8.87, 6.40 (all s, 3 H), 5.27 (m, 2 H); $[\alpha]^{25}D$ −102° (*c* 4.3) (lit.[21] $[\alpha]D$ −107°).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.17. Found: C, 79.57; H, 10.27.

Purification of the third component sometimes required a second column chromatography. An analytical sample was obtained by sublimation and after crystallization from methanol had mp 79–80°; nmr τ 9.165, 18.865, and 6.35 (all s, 3 H), 8.30 (d, 3 H, J = 1.8 Hz), 4.96 (m, 1 H), 4.96 (m, 1 H); $[\alpha]^{25}D$ −54° (*c* 4.1); ir (CCl_4) 1720, 875 cm^{-1}; uv ϵ_{199} 3843.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.92; H, 10.01.

Component four was the unrearranged unsaturated ester **7**: mp 115.1–115.6° (sublimed), 111–112° (recrystallized from methanol) (lit.[16b] mp 107–109°); nmr 9.46, 9.00, and 8.845 (all s, 3 H), 4.3 and 4.60 (AB, d, 2 H, J = 6 Hz); $[\alpha]^{25}D$ +2.48° (*c* 3.6); uv ϵ_{199} 9640.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.56; H, 10.17.

The results with other conditions are summarized in Table II.

Conversion of Methyl Δ[16]-*ent*-Kauren-19-oate (5) into Methyl Δ[15]-*ent*-Kauren-19-oate (6).—A few small crystals of iodine were added to a solution of unsaturated ester **5** (48.5 mg, 1.5 mmol) in xylene (5 ml), and the solution was heated at reflux for 20 min.[19] The reaction mixture was cooled and shaken with mercury (1 g) for several minutes. The precipitate which formed was filtered along with the excess mercury and washed with xylene. Glpc

analysis of the residue obtained after evaporation of the solvent showed three products present in the approximate ratio of 20:80:1 with retention times corresponding to those of **5**–**7**, respectively. Longer reaction times lead to an increase in the third component. Column chromatography on 20% silver nitrate–silica gel separated 25.5 mg of **6** and 11 mg of **5** in order of increasing "polarity." The major component was recrystallized from methanol and was identical (glpc, silver nitrate–silica gel tlc, nmr, and ir comparison) with a sample of **6** isolated from the tosylhydrazone decomposition above.

ent-**13α,16-Cycloatisan-19-ol.**—A 170-mg (0.43 mmol) sample of **5** was reduced with lithium aluminum hydride (excess) in dry tetrahydrofuran at reflux temperature for 12 hr. The excess lithium aluminum hydride was destroyed with wet tetrahydrofuran. The tetrahydrofuran was evaporated and the residue was dissolved in a hexane and dilute hydrochloric acid mixture. An extractive work-up afforded the pentacyclic alcohol (165 mg, 95%): mp 123–124.4°; nmr ($CDCl_3$) τ 9.23 and 9.39 (both broad m, 1 H), 9.08 (s, 6 H), 8.87 (s, 3 H), 7.76 (d, 1 H, J = 1.2 Hz), 6.52 and 6.36 (AB, d, 2 H, J = 11 Hz); $[\alpha]^{24}D$ −45.4 (*c* 4.2); ir (KBr) 3380 (OH), 3015 cm^{-1} (Δ H).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.05; H, 11.20.

ent-**13α-16-Cycloatisane (Trachylobane, 10).**—Oxidation of the pentacyclic alcohol above (60 mg, 0.2 mmol) was carried out with 1 g of the chromium trioxide–dipyridine complex[39] (freshly prepared) in 20 ml of dichloromethane. After 1 min, the mixture was filtered through 20 g of silica gel in a column using 1:4 ether–hexane as eluent. Glpc analysis showed the presence of a new compound with only a trace of starting alcohol; the ir spectrum had bands at 1705 and 2700 cm^{-1} appropriate for the corresponding aldehyde. A 50-mg (0.166 mmol) sample of the aldehyde and 500 mg of 98% hydrazine hydrate were added to a heavy glass tube containing 6 ml of methanol in which 1 g of sodium had been previously dissolved. The tube was sealed and placed in a high-pressure reaction bomb along with 30 ml of methanol. The bomb in turn was sealed and then heated to 210° for 3 hr. After cooling, the product was isolated by hexane extraction. The material obtained (25 mg, 63%) was homogeneous according to glpc analysis and had a retention time corresponding to authentic trachylobane[5a,24] by coinjection. The nmr spectra of the two samples are identical.

A more thorough comparison between hydrocarbon **9** and authentic trachylobane (mp 46–47.5° after recrystallization)[5a,24] was performed with material prepared from another Wolff–Kishner reduction. Repeated crystallization from methanol afforded a sample: mp 44.5–44.6°; mmp 45.5–47°; $[\alpha]^{24}D$ −37° (*c* 1.2) (lit. $[\alpha]D$ −43°).[5a] The ir and nmr spectra and tlc mobility of the two samples were identical.

Methyl *ent*-**16β-Tosyloxybeyeren-19-oate (3c).**—A solution of hydroxy ester **3a** (360 mg, 1.2 mmol)[13] and tosyl chloride (1.8 g, 10 mmol) in pyridine (25 ml) was allowed to stand for 24 hr at room temperature. After an extractive work-up and crystallization from hexane, tosylate **3c** (500 mg, 95%) was obtained: mp 96–97°; nmr ($CDCl_3$) τ 9.26, 9.17, 8.85, 8.57, and 6.39 (all s, 3 H), 5.56 (broad d, 1 H, J = 8 Hz), 2.66 and 2.21 (AB, 2 H each, J = 9 Hz).

Anal. Calcd for $C_{28}H_{40}O_5S$: C, 68.85; H, 8.20. Found: C, 69.33; H, 8.45.

Methyl *ent*-**12β-Tosyloxybeyeran-19-oate (11c).**—A solution of hydroxy ester **11a** (150 mg, 0.46 mmol)[13] and 1 g (5.4 mmol) of tosyl chloride in pyridine (10 ml) was allowed to stand for 15 hr at 10°. An extractive isolation procedure with hexane and recrystallization from hexane gave 200 mg (86%) of **11c**: mp 104.5–105.5°; nmr ($CDCl_3$) τ 9.37, 9.13, 8.86, 7.59, and 6.41 (all s, 3 H), 5.60 (s, 1 H, $W_{1/2}$ = 6 Hz), 2.66 and 2.21 (AB, 2 H each, J = 9 Hz); ir (KBr) 1725 cm^{-1}.

Anal. Calcd for $C_{28}H_{40}O_5S_1$: C, 68.85; H, 8.20. Found: C, 68.87; H, 8.22.

Isolation Procedures for Solvolysis Reactions. A.—The solvent (formic acid, acetic acid, or trifluoroacetic acid) was evaporated under reduced pressure with rotary evaporation, and the residue was subjected to hydrolysis with 5% sodium hydroxide in 95% ethanol for 1–2 hr at reflux temperature. The ethanol was removed by rotary evaporation and the product was isolated by extraction with hexane.

B.—After completion of part A, the crude product was heated with 10% acetic anhydride in pyridine for 3 hr at steam bath temperature. The solvents were removed by rotary evaporation and the acetylated product was isolated by hexane extraction.

Solvolysis of Tosylate 3c. A. Acetolysis.—A solution of tosylate **3c** (100 mg) in 50 ml of acetic acid (buffered by prior addition of sodium carbonate) was heated at reflux temperature for 15 hr. Glpc and nmr analysis of the product obtained after the isolation procedure A established that the material was a 1:2:1 mixture of the unsaturated esters **5**, **6**, and **7**, respectively.

B. Formolysis at Room Temperature.—A solution of tosylate **3c** (210 mg, 0.42 mmol) in 15 ml of formic acid (buffered by prior addition of sodium carbonate) was allowed to stand for 6–7 hr at room temperature. Hydroxy ester **2a** (100 mg, 70%), identified by melting point and mixture melting point, crystallized from a hexane solution of the crude product obtained by procedure A. Chromatography of the mother liquor afforded another 20 mg of **2a**.

C. Formolysis at Reflux.—A solution of **3c** (1.3 g, 2.6 mmol) in 65 ml of formic acid buffered with sodium carbonate (300 mg, 3.0 mmol) was heated at reflux temperature for 8 hr. The product obtained after isolation procedure B was chromatographed on 200 g of silica gel (5% ether–hexane as eluent). The first fraction contained a mixture of unsaturated esters (179 mg, 20%) which was not investigated further. The third fraction (161 mg) afforded methyl *ent*-12β-acetoxybeyeran-19-oate (**11b**) on crystallization from methanol. The identity of **11b** was established by comparison (melting point, glpc, nmr, and ir) with a previously prepared sample.[13] The fifth fraction (228 mg) was a mixture of **3b** and **4b** (glpc analysis). Crystallization from methanol provided 165 mg of **3b** identical (melting point, glpc, nmr, and ir) with a previous sample.[13] By means of rechromatography of the mixed fractions (**3b** and **4b**) on silica gel (chloroform as eluent) 135 mg of **4b** could be obtained. Crystallization from methanol afforded pure material identical (melting point, glpc, nmr, and ir) with that previously prepared.[13] The last fraction (79 mg), eluted with ether, proved to be mainly hydroxy ester **2a**. A final product distribution could be estimated from the isolated yields and analysis of the mixed fractions by glpc and nmr: **11b** (19%), **3b** (34%), **4b** (16%), and **2a** and/or **14a** (6%).

D. Trifluoroacetolysis.—A solution of **3c** (200 mg, 0.4 mmol) in 25 ml of trifluoroacetic acid buffered with sodium carbonate (200 mg, 1.9 mmol) was allowed to stand at room temperature for 48 hr. After isolation procedure B and purification as described in part C above, there was obtained **11b** (44%), **3b** (19%), and **4b** (19%).

E. Deuteriotrifluoroacetolysis.—The labeled solvent was prepared by adding 4.5 g (0.225 mol, 99.77% pure) of deuterium oxide to 50 g (0.237 mol) of trifluoroacetic anhydride, then buffered with 215 mg (0.002 mol, 0.004 equiv) of sodium carbonate making an 8×10^{-2} N solution of sodium trifluoroacetate. A solution of tosylate **3c** (900 mg, 1.8 mmol) in buffered deuteriotrifluoroacetic acid (55 ml) was allowed to stand at room temperature for 20 hr; then the product was isolated according to isolation procedure B. Direct crystallization from methanol at this stage gave 250 mg of **11b**. Further purification as described in part C afforded 104 mg (15%) of **3b** and 60 mg (10%) of **4b** as well as additional **11b** and mixed fractions.

The nmr spectrum of acetate **11b** was identical with that of **11b** previously prepared except for the absence of the C-17 methyl signal at τ 9.01. The mass spectrum, after correction for the natural abundance M + 1 and M + 2 peaks in unlabeled **11b**, indicated the following deuterium distribution per cent of each deuterated species, followed by the average deuterium content): (M − 60) 2 d_3, 16 d_4, 77 d_5, 5 d_6 (average, 4.85); (M − 75) 7 d_3, 16 d_4, 69 d_5, 5 d_6 (average 4.79).

The nmr spectrum of **3b** lacked the signal at τ 9.11. The mass spectrum gave the following deuterium distribution: (M − 60) 4 d_1, 7 d_2, 18 d_3, 60 d_4, 7 d_5 (average 3.56).

The nmr spectrum of **4b** had a reduced intensity for the methyl signal at τ 9.03 (s, 1 H). The mass spectrum gave the following deuterium distribution: (M^+) 5 d_0, 15 d_1, 7 d_2, 14 d_3, 48 d_4, 9 d_5 (average 3.23); (M − 60) 4 d_0, 12 d_1, 6 d_2, 14 d_3, 55 d_4, 8 d_5, 1 d_6 (average, 3.27).

Acetates **11b** and **3b** were hydrolyzed (see isolation procedure A for conditions) to the corresponding hydroxy esters **11a** and **3a**, then oxidized to the respective keto esters, methyl *ent*-12-ketobeyeran-19-oate (**16**) and methyl *ent*-16-ketobeyeran-19-oate (isosteviol methyl ester, **17**) with excess chromium trioxide dipyridine complex in methylene chloride[39] for 5–10 min at room temperature. After purification by column chromatography and recrystallization, the mass spectra were determined, leading to

(39) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

the following deuterium distribution data: **15** (M^+) 20 d_4, 77 d_5, 0 d_6, 4 d_7 (average, 4.96); **16** (M^+), 2 d_0, 5 d_1, 6 d_2, 18 d_3, 61 d_4, 7 d_5 (average, 3.50).

F. Brief Deuteriotrifluoroacetolysis.—A solution of tosylate **3c** (200 mg, 0.43 mmol) in 25 ml of buffered deuteriotrifluoroacetic acid was allowed to stand at room temperature for 5 min, then quenched quickly with 5% ethanolic potassium hydroxide. The alcohol solution was concentrated, water was added, and the product was isolated by extraction with hexane. Crystallization from hexane afforded 70 mg (52%) of tertiary hydroxy ester **2a**. The nmr spectrum of this material lacked the methyl peak at τ 8.69. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 3 d_1, 17 d_2, 44 d_3, 38 d_4 (average, 3.25).

Solvolysis of Tosylate 11c. A. Acetolysis.—Tosylate **11c** was subjected to acetolysis as above with **3c** for 25 hr at 85°. Evaporation of the acetic acid and isolation by hexane extraction afforded mainly methyl Δ^{15}-*ent*-atisen-19-oate (**12**) according to nmr analysis on the crude product.

B. Formolysis.—Tosylate **11c** (36 mg) was subjected to formolysis as described above with **3c** for 20 hr at room temperature. The nmr spectrum of the product obtained after isolation procedure A was identical with that of **14a** (methyl *ent*-16-hydroxyatisan-19-oate).[13]

C. Trifluoroacetolysis.—A 900-mg (1.8 mmol) portion of **11c** was added to 40 ml of buffered trifluoroacetic acid. After 5 min at room temperature, a 4-ml aliquot of the solution was removed and subjected to isolation procedure B. On crystallization of the residue from hexane, alcohol **14a** was obtained (by melting point, glpc, analysis, nmr, and ir spectral comparison).[13] After 20 hr at room temperature, a second 4-ml aliquot was removed and treated according to procedure B. Glpc and nmr spectral analyses on the product indicated the presence of **11b** (~80%) along with small amounts of **3b** and **4b**. The reaction was allowed to continue for 96 hr at room temperature and an additional 24 hr at 42°. Isolation according to isolation procedure B and purification by chromatography as described above (part C, formolysis of **3c**) gave **11b** (245 mg, 45%), **3b** (65 mg, 12%), and **4b** (25 mg, 5%). Acetates **11b** and **3b** were identified by melting point glpc and nmr and ir comparisons, acetate **4b** by glpc and nmr comparisons.

Deuteriotrifluoroacetolysis of Hydroxy Ester 11a.—A solution of **11a** in 20 ml of buffered deuteriotrifluoroacetic acid was allowed to stand for 15 min at room temperature. The product was then separated by isolation procedure A. Crystallization of the residue from hexane afforded labeled hydroxy ester **14a** (210 mg, 86%). The nmr spectrum was identical with that of unlabeled **14a**[13] except for the complete absence of the C-17 methyl signal at τ 8.71. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 1 d_1, 3 d_2, 12 d_3, 33 d_4, 47 d_5, 1 d_6 (average, 4.18); (M − 18) 3 d_2, 10 d_3, 34 d_4, 51 d_5 (average, 4.52).

The labeled hydroxy ester **14a** (190 mg, 0.57 mmol) was dehydrated with thionyl chloride (1 ml) in 20 ml of methylene chloride and 8 ml of pyridine and the resulting mixture of atiserene esters **12** and **13** was separated chromatographically on 18% silver nitrate–silica gel as previously described.[13] In the nmr spectrum of the labeled endocyclic isomer **12** (80 mg, 44%, mp 90–91°), the vinyl methyl group (τ 8.28) was reduced to $<1/4$ of the original intensity and the vinyl proton (τ 4.42) to ~0.1 H. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 5 d_0, 4 d_1, 9 d_2, 28 d_3, 51 d_4 4 d_5 (average 3.35). The nmr spectrum for the exocyclic isomer **13** (40 mg, 21%, mp 125.5–127°) showed a substantially reduced intensity for the vinyl protons (τ 5.3–5.4) and the allylic methylene group (τ 8.04). Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 7 d_0, 3 d_1, 9 d_2, 33 d_3, 55 d_4 (average 3.48).

Deuteriotrifluoroacetolysis of Other Diterpene Substrates.—In each of the following experiments, the substrate was subjected to solvolysis in buffered deuteriotrifluoroacetic acid (10–25 ml) for 20–21 hr at room temperature. After work-up by isolation procedure B, acetate **11b** was isolated by column chromatography and/or crystallization from methanol. The deuterium distribution data were obtained from the mass spectrum of **11b** after correction for ^{13}C natural abundance. The yields were estimated from glpc traces.

A.—Methyl *ent*-16α-hydroxykauran-19-oate (**2a**, 470 mg) in 55 ml of buffered deuteriotrifluoroacetic acid gave, after purification by column chromatography (see part C, formolysis of **3c**), **11b** (46%): (M − 60) 4 d_3, 23 d_4, 69 d_5, 5 d_6 (average, 4.78).

B.—Methyl Δ^{16}-*ent*-kauren-19-oate (**5**, 110 mg) in 55 ml of the labeled solvent gave, after purification by column chromatography, **11b** (45%): (M − 60), 11 d_4, 85 d_5, 5 d_6 (average, 4.95).

C.—Methyl Δ^{15}-*ent*-atisen-19-oate (**12**, 50 mg)[13] gave **11b** in ~80% yield: (M − 60) 11 d_4, 85 d_5, 4 d_6 (average 4.93).

D.—Methyl Δ^{16}-*ent*-atisen-19-oate (**13**, 56 gm)[13] gave **11b** in ~80% yield: (M − 60) 1 d_3, 12 d_4, 83 d_5, 4 d_6 (average 4.90).

E.—Methyl *ent*-13α,16-cycloatisan-19-oate (**9**, 24 mg) gave **11b** in ~80% yield: (M − 60) 4 d_4, 18 d_5, 76 d_6, 3 d_7 (average, 5.78); (M − 75) 20 d_5, 80 d_6, 1 d_7 (average, 5.85).

Registry No.—**1**, 21682-55-3; **2a**, 22376-08-5; **3c**, 31819-20-2; **5**, 5524-25-4; **6**, 18671-79-9; **7**, 14699-35-5; **8**, 21682-50-8; **11c**, 31819-24-6; **26**, 30288-12-1; *ent*-13α,16-cycloatisan-19-ol, 31819-26-8.

Studies on the Syntheses of Heterocyclic Compounds. CDL. Total Synthesis of Androcymbine

T. KAMETANI,* M. KOIZUMI, AND K. FUKUMOTO

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

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Photolysis of the diazonium salts **4** and **14** of 6,7-dimethoxy- (**3**) and 7-benzyloxy-6-methoxy-1-(2-amino-4-benzyloxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (**13**) gave *O*-benzylandrocymbine (**8**), which was debenzylated to afford (±)-androcymbine (**2**). Also the same reaction of a diazonium salt **19**, however, gave the abnormal product, homoproaporphine (**20**).

Androcymbine (**2**),[1] the principal member of a family of 1-phenethylisoquinoline alkaloids, has been biosynthesized from the diphenolic phenethylisoquinoline (**1**)[2] (Scheme I). Three synthetic methods have been developed for androcymbine-type compounds: the first by phenol oxidation,[3] the second by Pschorr reaction,[4] and the third by photolysis of diazonium salts.[5] Herein we wish to report the total synthesis of androcymbine by the photolysis of the diazonium salts **4** and **14** and the abnormal reaction during the photolysis of the phenolic diazonium salt **19**.

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