Organic and Biological Chemistry

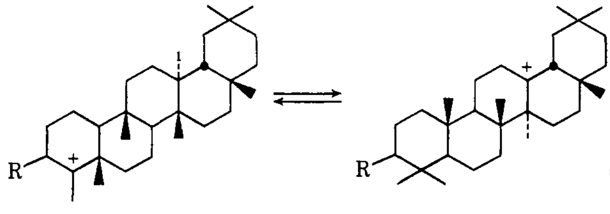
The Concertedness, or Lack Thereof, of a Multiple Carbonium Ion Rearrangement

Howard W. Whitlock, Jr., and A. H. Olson

Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received October 20, 1969*

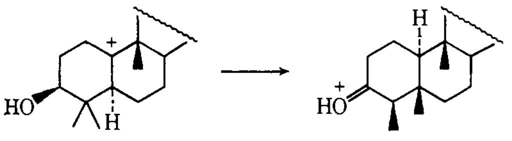
Abstract: The acid-catalyzed rearrangement of 2-hydroxy-1,1,10-trimethyl-8,9-epoxydecahydronaphthalene and its mono-*p*-nitrobenzoate is investigated and discussed. The results are consistent with a rate-determining formation of a set of rapidly interconverting carbonum ions that partitions itself among the observed products.

One of the fundamental transformations associated with terpene and steroid biosynthesis is that loosely referred to as "backbone"[1] rearrangements.[2] The most dramatic example of this complex series of hydrogen and methyl migrations is seen (eq 1) in the (presumed) biosynthesis of friedelin (R = OH, right to left) and the acid-catalyzed reverse of this skeletal isomerization[3] (R = H, left to right). The acid-catalyzed rearrangement of epoxides with accompanying backbone rearrangements is a closely related reaction that has been shown[4] to be a common response of steroidal epoxides toward Lewis acids.



(1)

It has been suggested[1] that this type of interconversion is a concerted process. One must, however, define a concerted process as one lacking in intermediates, and in this sense it is now generally conceded[5] that complex rearrangements of this type are not concerted. There is remarkably little experimental evidence on this point of concertedness. It is now clear that backbone rearrangements associated with triterpene biosynthesis proceed without the intermediacy of olefins.[6-10] Study of models of these rearrangements shows that by and large the same situation holds there.[11,12] It is difficult to assess the role of solvent captured species in a set of rapidly interconverting carbonium ions if they cannot be detected[13] but one may in general dismiss the concerted mechanism for rearrangements as extensive as that in eq 1 with the theoretical complaint that simultaneous migration of four methyls and two hydrogens would require a flattening of the six rings that would be energetically prohibitive.[14] In order to investigate the question of the concertedness of multiple carbonium ion rearrangements of this general type we have investigated the behavior of epoxide **4** toward acids (Figure 3). One may view the rearrangement observed (**4** → **10**) as a suitable model of the later rearrangement stages in the biosynthesis of friedelin (**1** → **2**). We conclude below that the formation of the "backbone" product **11** from **4** is *not* concerted but instead most likely involves a series of rapidly interconverting carbonium ions.



1 **2**

Results and Discussion

The synthesis of **4** and **4a** and of their monodeuterated derivatives **4**-d_1 and **4a**-d_1 (eq 2) is unexceptional and is presented in the Experimental Section. Stereoselective epoxidation of **3a**[15] (eq 2) is rationalized in terms of general attack of reagents on 9-methyloctalins at the side of the molecule away from the angular methyl group[16] and is ultimately confirmed by isolation of cyclic ketal **13** that must possess the stereochemistry shown.

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(1) G. Brownlie, F. S. Spring, R. Stephenson, and W. S. Strachan, *Chem. Ind.* (London), 1156 (1955).

(2) A comprehensive review of these rearrangements is found in J. F. King and P. de Mayo in" Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1964.

(3) E. J. Corey and J. J. Ursprung, *J. Amer. Chem. Soc.*, **78**, 183 (1956).

(4) J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **22**, 3195 (1966), and subsequent papers.

(5) But see J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *J. Chem. Soc., C*, 635 (1968).

(6) H. H. Rees, E. I. Mercer, and T. W. Goodman, *Biochem. J.*, **99**, 726 (1966).

(7) J. W. Cornforth, R. H. Cornforth, G. Donninger, G. Popjak, Y. Shimizu, S. Ichii, E. Forchielli, and E. Caspi, *J. Amer. Chem. Soc.*, **87**, 3224 (1965).

(8) J. W. Cornforth, R. H. Cornforth, A. Pelter, M. G. Horning, and G. Popjak, *Tetrahedron*, **5**, 311 (1959).

(9) R. K. Maudgal, T. T. Tchen, and K. Bloch, *J. Amer. Chem. Soc.*, **80**, 2589 (1958).

(10) T. T. Tchen and K. Bloch, *J. Biol. Chem.*, **226**, 931 (1957).

(11) H. W. Whitlock and M. C. Smith, *Tetrahedron Lett.*, 821 (1968).

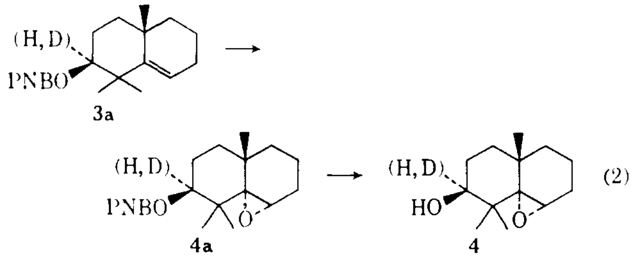
(12) R. M. Coates, *ibid.*, 4143 (1967).

(13) E. J. Corey, K. Lin, and H. Yamamoto, *J. Amer. Chem. Soc.*, **91**, 2133 (1969).

(14) See, for example, the calculated energy difference of *ca.* 15 kcal between half-planar and chair cyclohexane ring: J. B. Hendricksen, *J. Amer. Chem. Soc.*, **83**, 4537 (1961).

(15) The suffixed numbers refer to the indicated derivatives of the structure. "PNB" is an abbreviation for *p*-nitrobenzoyl.

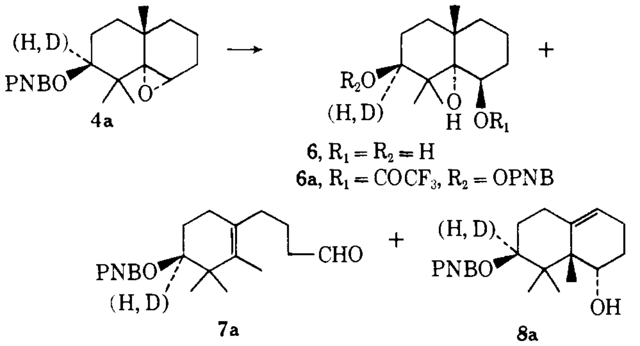
(16) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959.



3a 4a 4 (2)

Reaction of p-nitrobenzoate **4a** with trifluoroacetic acid in chloroform afforded three products, **6a**, **7a**, and **8a**, in 8, 72, and 13% yield, respectively (Scheme I). The structure of **6a** is based on its analysis, spectral properties, and saponification to **6**. The nmr spectrum of **6a** indicated the presence of two C*H*OAcyl part structures and a tertiary alcohol. Saponification of **6a** afforded triol **6** whose nmr spectrum showed the presence of both an axial and an equatorial secondary alcohol. The resonance due to the latter's C*H* group was absent in the triol derived from **4a**-d_1, thus indicating that the left-hand ring (assumed to be in a chair conformation) had undergone an even number of inversions. This is consistent with the assigned structure. Structure **6a** is the result of *trans*-diaxial opening of the epoxide ring and corresponds to the fluorohydrin commonly encountered in epoxide–boron trifluoride etherate rearrangements.[4]

Scheme I



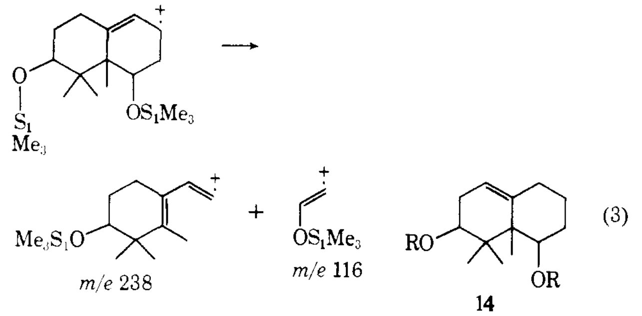
4a

6, $R_1 = R_2 = H$

6a, $R_1 = COCF_3$, $R_2 = OPNB$

7a **8a**

Compound **8a** is an olefinic diol mono-p-nitrobenzoate and is assigned a structure corresponding to a Westphalen[17–19] type of rearrangement. The position of the double bond is assigned on the basis of the observed mass spectral cracking pattern of the bistrimethylsilyl ether of **8**. Prominent peaks at m/e 238 and 116 corresponding to a retro-Diels–Alder fragmentation mode[20,21] are observed (eq 3) while peaks corresponding to the analogous cracking of the Δ^4 isomer **14** were not.



m/e 238 m/e 116 (3)

14

The major product, aldehyde **7a**, was isolated in 72% yield. Its structural assignment is based on nmr spectra of it and its derivatives and chemical manipulation of its functional groups as in Scheme II. Nmr spectra clearly showed the presence of a PNBO–CHCH$_2$ grouping and a –CH$_2$CH$_2$CHO group. In the nmr of **7a**-d_1, the deuterium is at the expected site, PNBO–CDCH$_2$, and is not present as a –CDO group. Conversion of **7** to a saturated ketone (no intense ultraviolet absorption) present in a six ring or open chain ($\lambda_{max}^{CHCl_3}$ 5.86 μ) eliminates from consideration structures such as **15** and **15a**, but not **16**, the result of an initial *cis* bond migration to **17**. Aldehyde **7a** does not correspond to any of the commonly encountered structural types in steroidal epoxide rearrangements.[4,22] It seems likely that the driving force for the fragmentation leading to **7a** (and **7**) arises in the steric congestion due to the three methyl groups on the decalin ring. Control experiments verify that the observed products represent the kinetically determined ones, as all products are stable under the reaction conditions. Aldehyde **7**, however, slowly polymerizes under the reaction conditions.

Trifluoroacetic acid in chloroform converts epoxy alcohol **4** into a mixture of four components: **7** and **8**, and two ketones assigned the structures **11** and **12**. If the composition of the reaction mixture is monitored with time it is seen that **11** appears initially and is replaced in time by **12**. Under conditions of the reaction as normally carried out **11** is converted almost completely to **12**. The overall structure and stereochemistry of **12** follow from its derivatization and reaction with methanol in the presence of p-toluenesulfonic acid to form a cyclic ketal, **13**. Ketal **13** possesses no carbonyl or hydroxyl group and is hydrolyzed under mild conditions with re-formation of **12**. The nmr spectra of both **11** and **12** show the presence of an isolated –CHCH$_3$ part structure.[23] Moreover, acid-catalyzed rearrangement of **4**-d_1 affords **11**-d_1 possessing a >CDCH$_3$ part structure. This not only fixes the stereochemistry of **11** (and hence of **12**), given the stereochemistry of **4**, but requires that the reaction be terminated by a hydride (or deuteride) shift as in the normal pinacol rearrangement[24–27] rather than proton elimination with subsequent ketonization of the enol. As required by the structure, conversion of **11** to **12** is accompanied by exchange of the enolizable methine hydrogen adjacent to the carbonyl group.

Reaction of **4** with boron trifluoride etherate in benzene, the more usual conditions for epoxide rearrangements,[4,23] affords a product mixture that is qualitatively similar to that above but which is accompanied by much nonvolatile and resinous material.

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(17) T. Westphalen, *Ber.*, 48, 1064 (1915).

(18) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(19) B. Ellis and V. Petrow, *ibid.*, 2246 (1952).

(20) H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, 21, 1855 (1965).

(21) A. F. Thomas and B. Willhalm, *Tetrahedron Lett.*, 5129 (1967).

(22) I. G. Gues and B. Marples, *ibid.*, 1947 (1969).

(23) T. G. Halsall, E. R. H. Jones, E. L. Tan, and G. R. Chaudhry [*J. Chem. Soc., C*, 1374 (1966)] have isolated species assigned structures similar to 11 in the rearrangement of several steroidal epoxides.

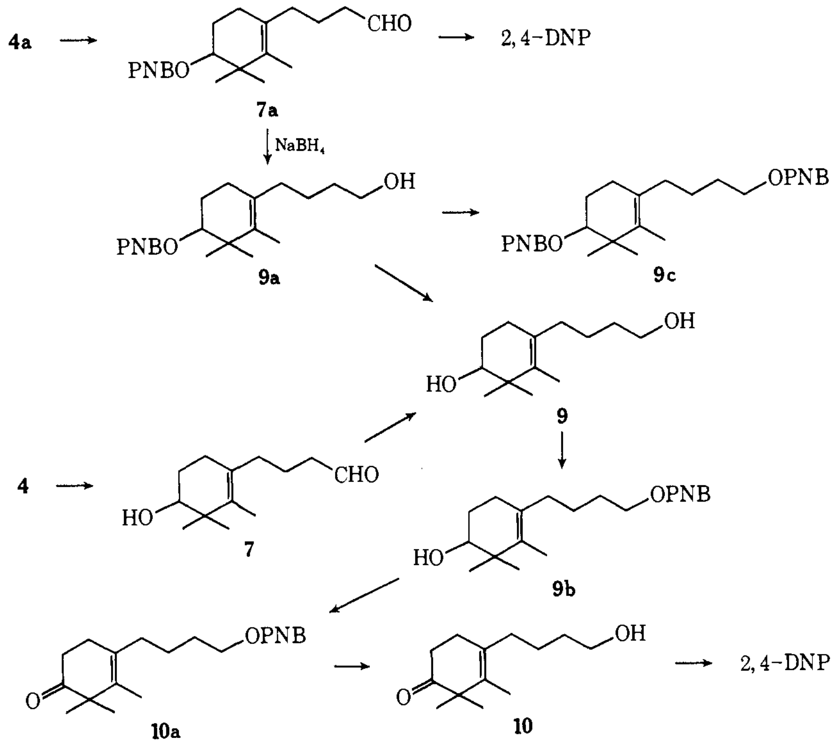
(24) C. J. Collins in "Carbonium Ions," Vol. 1, G. A. Olah and P. v. R. Schleyer, Ed., Interscience Publishers, New York, N. Y., 1968.

(25) W. B. Smith, R. W. Bowman, and T. J. Kmet, *J. Amer. Chem. Soc.*, 81, 997 (1959).

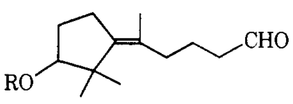
(26) C. J. Collins, *ibid.*, 77, 5517 (1955).

(27) C. J. Collins, W. T. Rainey, W. B. Smith, and L. A. Kaye, *ibid.*, 81, 460 (1959).

Scheme II



It is interesting to compare the rearrangements of **4** and **4a** and note the substantial effect of esterification of the secondary hydroxyl group on the product mixture. That fraction that appears as ketonic material in the rearrangement of **4** is diverted to aldehyde **7a** in the rearrangement of **4a**.



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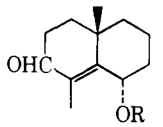
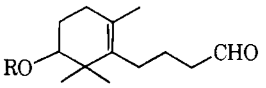


15a



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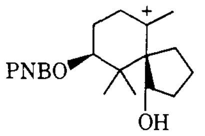

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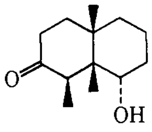
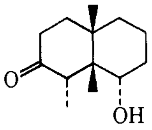


11



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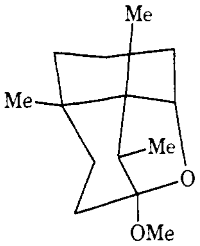

13

The kinetic isotope effect for disappearance of **4** *vs.* **4**-d_1 is unity within the limits of detection. A mixture of **4** and **4**-d_1, 53% d_0, 47% d_1, was allowed to react for approximately two half-lives. Recovered **4** had the isotopic composition 54% d_0, 46% d_1. An isotope effect on product ratios was easily discernible, however (Table I). The average yield[28] of **12** from **4** is 30% but drops to 22% when **4**-d_1 is used. Conversely the average yields of **7** and **8** from **4**, 33 and 11%, respectively, increase to 43% (**7**-d_1) and 13% (**8**-d_1) when **4**-d_1 is employed as starting material. We feel that the reproducibility of the experiments is such that these are real changes in rates leading to the various products and do not merely reflect variations in material balance. Our mechanistic interpretation of the lack of a kinetic isotope effect coupled with the presence of an isotope effect in the product ratio is presented in Scheme III. On the basis of irreversible rate determining formation of a set of rapidly interconverting carbonium ions, one of which may afford **11**, one calculates an isotope effect for B → **11** of 1.77. This is in good agreement with the range 1–3 found for other pinacol rearrangements.[24–27] The proposed rate-determining heterolysis of the carbon–oxygen bond of A to produce a set of rapidly converting cations B, C, and D which partition to the observed products at a rate less than that of their interconversion is in agreement with our data. The concerted scheme (eq 4) is ruled out. For a scheme of

Table I. Change in Product Ratio on Introduction of Deuterium at C-2 in **4**

	% yield			
Epoxide	**12**[a]	**7**[a]	**7**[b]	**8**[b]
4	29	35	33	12
4	28	31	35	11
4	34	37	31	9
4-d_1	21	45	41.4	12
4-d_1	23	46.5	38	14

[a] Estimated by quantitative tlc [J. H. Dhont and C. de Rooy, *Analyst*, **86**, 74 (1961); "Thin Layer Chromatography," E. Stahl, Ed., Springer Verlag, Berlin, 1965] of the 2,4-dinitrophenylhydrazone derivative. Control experiments indicate that the percentages quoted are ±2%. [b] By nmr. *p*-Dibromobenzene was used as an internal standard.

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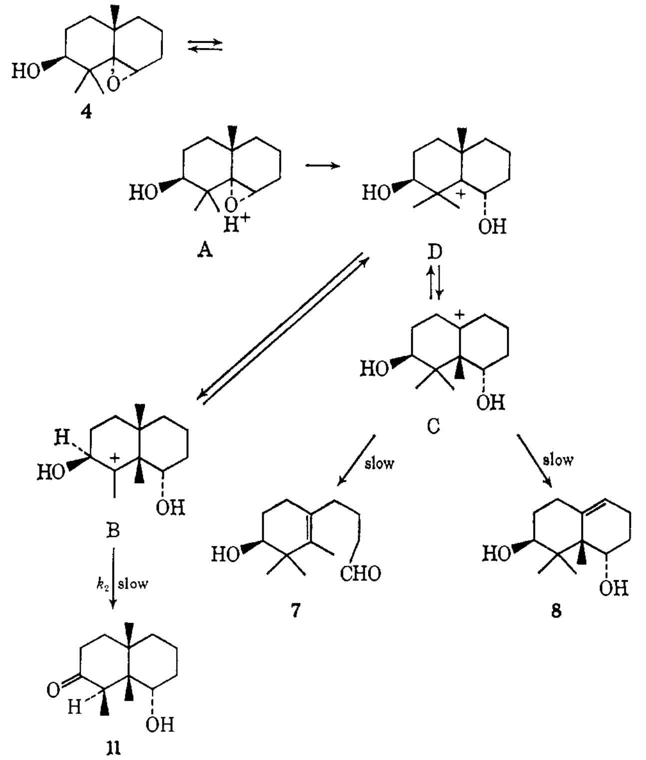
(28) The rather peculiar analytical methods were used because of lack of reproducibility of glpc, mostly due to instability of 7.

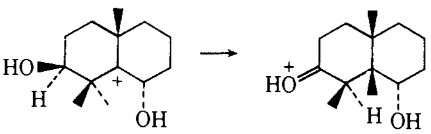
Scheme III



this type the kinetic isotope effect I_K $(-\nu_4/-\nu_{4d_1})$ is related to the isotope effect I (k_H'/k_D') by the relationship $I_K/I = (k + k')/(kI + k')$. For all $I \geq 1$, $I_K/I \leq 1$,

$$7 + 8 \xleftarrow{k} 4 \xrightarrow{k'} 11 \qquad (4)$$

and for our case one calculates I_K = *ca.* 1.2, well outside of the experimental error in measurement of the kinetic isotope effect. Scheme III could of course be modified by inclusion of other rapidly equilibrating ions and/or by replacement of any ions intermediate between D and **11** with a concerted transformation, without producing a scheme distinguishable from that shown. In particular one could eliminate B and propose a concerted collapse of D to **11** to be competing with stepwise formation of **7** and **8** (eq 5). We view



⇌ **11** (5)

D

this as unlikely on the (admittedly intuitive) basis that the observed isotope effect on formation of **11**, ~1.8, is too high for the concerted process.

Experimental Section[29,30]

10-Methyl-$\Delta^{1,9}$-octal-2-one was prepared by the procedure of Marshall and Fanta[31] from 2-methylcyclohexanone and methyl vinyl ketone in 30% yield, bp 99–102° (lit.[31] bp 82–83°).

1,1,10-Trimethyl-$\Delta^{8,9}$-octal-2-one (2). Alkylation of octalone **1** was accomplished by the procedure of Ringold and Rosenkranz[32] to afford the title compound in 86% yield, bp 62–64° (0.25 mm) (lit.[32] bp 105–107° (2 mm)).

1,1,10-Trimethyl-2-hydroxy-$\Delta^{8,10}$-octalin (3). Lithium aluminum hydride reduction of the above ketone afforded a quantitative field of the equatorial alcohol (**3**):[33,34] mp 80–82° after recrystallization from hexane; δ_{CDCl_3} 5.52 (1 H, H-8, triplet, J = 3.5 Hz), 3.25 (1 H, H-2, double doublet, J_a = 6 Hz, J_b = 7 Hz), 1.72 (1 H, OH, exchangeable with D_2O), 1.15, 1.11, 1.02 (3 H each, methyl singlets).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.13; H, 11.35.

The *p*-nitrobenzoate (**3a**), prepared by standard procedures, had mp 133–135° (from 95% ethanol); δ_{CDCl_3} 5.64 (1 H, H-8, triplet, J = 3.5 Hz), 4.78 (1 H, H-2, double doublet, J_a = 6 Hz, J_b = 7 Hz), and singlets at 1.27, 1.22, and 1.06 (methyls).

Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.05; H, 7.25; N, 4.13.

Use of lithium aluminum deuteride (98% deuterium) afforded the corresponding monodeuteriooctalin **3**-d_1; *p*-nitrobenzoate **3a**-d_1; mp 133–134°. The nmr spectrum of this was transparent at δ 4.78.

1,1,10-Trimethyl-2-*p*-nitrobenzoyloxy-$\Delta^{8,9}$-octalin α-Epoxide (4a). A solution of 13.6 g of olefin **3a** (0.04 mole) and 14 g (0.08 mole) of 85% technical *m*-chloroperbenzoic acid in 200 ml of benzene was held at 55–60° for 12 hr. The cooled reaction mixture was worked up and the neutral portion was evaporated to afford 14.1 g of white crystals. Examination of its nmr spectrum showed the presence of two signals, δ 3.12 and 3.33, in the ratio 7:3, corresponding to H-8 of the two epimeric epoxides. Fractional recrystallization of this from ethyl acetate–hexane afforded 5.21 g (37% yield) of the major isomer, **4a**: δ 3.12; mp 150–151°; δ_{CDCl_3} 5.06 (1 H, H-2, double doublet, J_a = 6.5 Hz, J_b = 9.0 Hz (100 MHz)), 3.12 (1 H, H-8, triplet, $J_{8,7}$ = 2.5 Hz), and three singlets at 1.33, 1.27, and 0.82 (methyls).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 67.01; H, 7.19; N, 3.83.

A pure sample of the minor product, presumably the β-epoxide, could not be isolated by fractional crystallization or chromatography. Epoxidation of the monodeuterio-*p*-nitrobenzoate **3a**-d_1 afforded the monodeuterioepoxide mixture. Fractional crystallization of this mixture afforded the α isomer **4a**-d_1, mp 150–151°.

1,1,10-Trimethyl-2β-hydroxy-8,9-octalin α-Oxide (4). A solution of 1.99 g of **4a** and 1.5 g of sodium hydroxide in 75 ml of 95% ethanol was stirred at 60° under a nitrogen atmosphere for 1 hr. The cooled reaction mixture was worked up and the crude product was sublimed at 45–50° (0.03 mm) to afford 1.15 g (98% yield) of **4** as white needles: mp 49–50°; δ_{CDCl_3} 3.55 (1 H, H-2, double doublet, J_a = 7 Hz, J_b = 9 Hz (100 MHz)), 3.08 (1 H, H-8, triplet, J = 2.5 Hz), 1.81 (1 H, OH, exchangeable with D_2O), and three singlets at 1.20, 1.08, and 0.85 (methyls).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.01; H, 10.39.

Saponification of the **4a**-d_1 afforded the monodeuterio epoxy alcohol **4**-d_1, mp 49–50°. Its nmr spectrum was comparable to that of the protio species except for the absence of the resonance at δ 3.55.

Isomerization of Epoxide 4a by Trifluoroacetic Acid. A solution of 0.600 g of **4a** and 10 ml of trifluoroacetic acid in 50 ml of chloroform was allowed to stand at 26° for 3.5 hr under an atmosphere of nitrogen. The reaction mixture was then added with vigorous stirring to 250 ml of 5% sodium bicarbonate solution. This was extracted with chloroform and the chloroform extracts were washed with water and saturated salt solution, dried over magnesium sulfate, and evaporated. The residual oil was triturated with ether and allowed to stand in the cold for 24 hr. Filtration afforded 58 mg of an insoluble material (**6a**). Recrystallization of this from benzene afforded an analytical sample: mp 221–222°; δ_{CDCl_3} 8.28 (4 H, ArH, broad singlet), 5.39 (2 H, C*H*OAcyl, broad multiplet), 1.70 (1 H, OH, exchangeable with D_2O), and three singlets at 1.50, 1.30, and 1.05 (methyls).

Anal. Calcd for $C_{22}H_{26}F_3NO_7$: C, 55.81; H, 5.54; N, 2.96. Found: C, 55.93; H, 5.56; N, 2.91.

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[29] Mass spectra were determined on an MS 902a or a CEC 103C. Low-voltage mass spectra were determined at 7–10 V nominal, and isotopic compositions were determined using experimentally determined P + 1 values. "Silylation" was accomplished with bistrimethylsilylacetamide according to literature procedures.[32] "Work-up" entailed extracting an aqueous mixture with ether, washing the ether extracts with water, drying over anhydrous sodium sulfate, and evaporating under reduced pressure.

[30] C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

[31] J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).

[32] H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957).

[33] F. Sondheimer and D. Elad, *J. Amer. Chem. Soc.*, **80**, 1967 (1958).

[34] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *ibid.*, **76**, 2852 (1954).

Saponification of **6a** was affected by refluxing a solution of 180 mg of it in a mixture of 1.5 ml of 10% sodium hydroxide and 6 ml of methanol for 90 min under an atmosphere of nitrogen. Work-up afforded 53 mg (61% yield) of 1,1,10-trimethyl-*trans*-decalin-2β,8β,9α-triol (**6**), mp 132–133°. The nmr of the analytical sample showed δ_{CDCl_3} 4.09 (1 H, H-8, triplet, $J_{8,7}$ = 2.5 Hz (100 MHz)), 3.86 (1 H, H-2, double doublet, J_a = 7 Hz, J_b = 8 Hz (100 MHz)), 1.40 (3 H, OH, exchangeable with D_2O), and three singlets at 1.12, 1.30, and 1.43 (quaternary methyls).

Anal. Calcd for a $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.26; H, 10.70.

The residual oil from the trituration was chromatographed on silica gel to afford the following products in order of elution.

(1) Aldehyde **7a** (434 mg, 72% yield) had R_f = 0.52 (silica gel G, 10% EtOAc–C_6H_6), a semisolid; δ_{CDCl_3} 9.80 (1 H, CHO, triplet, J = 2 Hz), 8.25 (4 H, ArH, broad singlet), 5.05 (1 H, H-2, multiplet, $v_{1/2}$ = 14 Hz), 1.66 (3 H, allylic methyl, broad singlet), and two sharp singlets at 1.15 and 1.10 (quaternary methyls). An analytical sample was obtained of the 2,4-dinitrophenylhydrazone **7b**: mp 128–129° (ethanol); δ_{CDCl_3} 7.60 (1 H, CH=N–, triplet, J = 7.60 Hz), 5.06 (1 H, C*H*OAcyl, double doublet, J_a = 6 Hz, J_b = 7 Hz (100 MHz)), 1.70 (3 H, allylic methyl, broad singlet), and two singlets at 1.17 and 1.11 (quaternary methyls). Examination of the 100-MHz spectrum of **7b** showed the methylene C*H*$_2$CH=N as a quartet centered at δ 2.38, with a peak separation of 6 Hz. Irradiation at δ 7.60 caused collapse of the 2.38 quartet to a triplet with a peak separation of 6.5 Hz.

Anal. Calcd for $C_{26}H_{29}N_5O_8$: C, 57.88; H, 5.42; N, 12.98. Found: C, 58.00; H, 5.56; N, 13.04.

(2) 1,1,9-Trimethyl-2-β-*p*-nitrobenzoyloxy-8α-hydroxy-$\Delta^{5,10}$-octalin (**8a**) (83 mg) had mp 115–117° (hexane); δ_{CDCl_3} 8.27 (4 H, Ar*H*, broad singlet), 5.53 (1 H, H-2, broad singlet, $v_{1/2}$ = 8 Hz), 5.03 (1 H, H-5, triplet, J = 3.5 Hz), 3.83 (1 H, H-8, double doublet), J_a = 5 Hz, J_b = 6 Hz), 1.63 (1 H, OH, exchangeable with D_2O), 1.45 (3 H, methyl, singlet), and 1.25 (6 H, two methyls, singlet).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.89; H, 6.97; N, 3.95.

Saponification of **8a** was affected by refluxing a solution of it in methanolic sodium hydroxide under a nitrogen atmosphere to afford the diol **8** in quantitative yield as an oil: δ_{CDCl_3} 5.45 (1 H, H-5, multiplet, $v_{1/2}$ = 8 Hz), 3.75 (1 H, H-2 or H-8, triplet, J = 5 Hz), 3.53 (1 H, H-2 or H-8, triplet, J = 4 Hz), 1.68 (2 H, O-*H*, exchangeable with D_2O), and three singlets at 1.35, 1.22, and 1.10 (methyls).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.33; H, 10.58.

The bistrimethylsilyl ether, prepared with bistrimethylsilylacetamide,[35] was purified by glpc: its mass spectrum showed a parent ion at *m/e* 354, and peaks at *m/e* 339, 238, 116, and 107.

On allowing **8a** to stand in chloroform–trifluoroacetic acid under the conditions of its formation, it was recovered unchanged.

Bis-*p*-nitrobenzoate 9c. Reduction of **7a** by sodium borohydride in ethanol followed by acylation with *p*-nitrobenzoyl chloride in pyridine afforded on work-up a 43% yield of the diol diester **9c**: mp 93–95° (aqueous ethanol); δ_{CDCl_3} 8.27 (8 H, Ar*H*, multiplet), 5.05 (1 H, C*H*OAcyl, double doublet, J_a = 7 Hz, J_b = 6 Hz), 4.42 (2 H, –C*H*$_2$OAcyl, triplet, J = 7 Hz), 1.68 (3 H, CH_3C=, broad singlet), and two methyl singlets at 1.15 and 1.10.

Anal. Calcd for $C_{27}H_{30}N_2O_8$: C, 63.52; H, 5.92; N, 5.49. Found: C, 63.63; H, 5.92; N, 5.86.

Stability of 7a under Acidic Conditions. To a solution of **7** (117 mg) in 8.5 ml of chloroform was added 1.7 ml of trifluoroacetic acid. The mixture was allowed to stand at room temperature for 3.5 hr. Work-up afforded a 91% yield of recovered aldehyde, identified by tlc and its nmr spectrum.

Keto Alcohol 10. Aldehyde **7a**, 811 mg, was reduced by sodium borohydride in absolute ethanol at room temperature. The crude alcohol, 721 mg, was saponified with ethanolic sodium hydroxide at reflux. The crude diol obtained on work-up was evaporatively distilled (90°, 0.2 mm) to afford 379 mg of a colorless oil, **9**, homogeneous by tlc. An analytical sample was prepared by conversion of the oily diol into the corresponding bistrimethylsilyl ether and purification of that by preparative glpc.

Anal. Calcd for $C_{19}H_{40}SiO_2$: C, 63.97; H, 11.30; Si, 15.75. Found: C, 63.83; H, 11.45; Si, 15.81.

A solution of *p*-nitrobenzoyl chloride (217 mg, 1.18 mmoles) and 261 mg (1.18 mmoles) of **9** in 3 ml of dry pyridine was allowed to stand at 26° for 2 hr. The reaction mixture was worked up to afford 266 mg of an oil whose tlc showed the presence of two components. Preparative tlc afforded the faster moving component, monoester **9b**, as an oil, 95 mg, homogeneous by tlc: δ_{CDCl_3} 8.20 (4 H, Ar*H*, broad singlet), 4.56 (2 H, –C*H*$_2$OAcyl, triplet, J = 6 Hz), 3.48 (1 H, C*H*OAcyl, double doublet, J_a = 4 Hz, J_b = 7 Hz), and three methyl singlets at 1.60, 1.05, and 1.00.

Jones oxidation[36] of diol monoester **9b** afforded an oil whose nmr spectrum was consistent with its assigned structure (**10a**). This was saponified with ethanolic sodium hydroxide at reflux for 1 hr. Work-up afforded an oil to which is assigned structure **10**. Its infrared spectrum showed maxima at 2.75 and 2.90 μ (OH) and at 5.86 μ (saturated carbonyl). Its nmr spectrum was consistent with the assigned structure: δ_{CDCl_3} 3.65 (2 H, –CH_2OAcyl, triplet, J = 6 Hz), 1.65 (3 H, CH_2=, broad singlet), 1.15 (6 H, *gem*-dimethyl, singlet). The mass spectrum showed a parent ion at *m/e* 210, and the ultraviolet spectrum showed only end absorption down to 210 mμ. An analytical sample of the trimethylsilyl ether was prepared by preparative gas chromatography.

Anal. Calcd for $C_{16}H_{30}SiO_2$: C, 68.02; H, 10.70. Found: C, 67.79; H, 10.61.

Rearrangement of 4 by Boron Trifluoride. To a solution of 500 mg of epoxy alcohol **4** in 25 ml of dry benzene at 27° under nitrogen was added in one portion 0.6 ml of freshly distilled boron trifluoride etherate. The reaction mixture became dark red immediately and a red precipitate appeared after approximately 1 min. The mixture was stirred for 10 min and then poured into aqueous sodium bicarbonate solution. Ether work-up afforded 506 mg of a light yellow oil. Tlc of this indicated the presence of two major components and at least three minor components. Evaporative distillation (130°, 0.03 mm) afforded 235 mg of a colorless oil. Repeated chromatography of this oil on alumina and silica gel afforded two major components.

(1) Component 1 was isolated in 18% yield (93 mg), a solid, mp 146–147° (hexane). It was ultimately identified as the more stable (**12**) of the two doubly rearranged compounds. Its infrared spectrum showed absorbances at 2.75 and 2.87 μ (OH) and at 5.87 μ (CO). Its nmr spectrum showed δ_{CDCl_3} 3.80 (1 H, broad singlet, $v_{1/2}$ = 7 Hz), 1.08 (3 H, C*H*$_3$CH, doublet, J = 7 Hz), and two singlets at 1.12 and 0.95 (quaternary methyls). The mass spectrum exhibited a parent ion at *m/e* 210 and a P − CH_3 peak at *m/e* 195. Examination of the 100-MHz spectrum showed a quartet at δ 2.33 which on irradiation at δ 1.08 collapsed to a singlet.

(2) Component 2 was isolated in 24% yield (125 mg), a solid (**11**), mp 136–137° (hexane). Its infrared spectrum also showed the presence of a hydroxyl group (2.75 μ, 2.90 μ) and a ketone (5.86 μ). Its nmr spectrum was similar to that of **12**: δ_{CDCl_3} 3.76 (1 H, broad singlet, $v_{1/2}$ = 6 Hz), 1.11 (3 H, C*H*$_3$CH, doublet, J = 7 Hz), and two singlets at 0.97 and 0.87 (quaternary methyls). Its mass spectrum showed a parent ion at *m/e* 210 and a P − CH_3 peak at *m/e* 195.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.34; H, 10.56.

Isomerization of 11 to 12. A solution of 38 mg of **11** and 2 ml of 10% aqueous sodium hydroxide in 4 ml of ethanol was allowed to stand at room temperature for 1 hr. The reaction mixture was worked up to afford 33.8 mg of a white solid. Comparison of its tlc (silica gel G, 5% methanol–chloroform), R_f 0.51 *vs.* R_f 0.51 for an authentic sample of **12** and R_f 0.40 for a sample of **11**, showed no spot for starting material (**11**). One recrystallization (hexane) afforded a sample, mp 145–146.5°, mixture melting point with a sample of **11**, mp 145–146.5°. The isomerization of **11**–**12** could also be carried out quantitatively with trifluoroacetic acid in chloroform.

Conversion of 12 to the Cyclic Ketal 13. A mixture of 88 mg of **12** and 29 mg of *p*-toluenesulfonic acid in 10 ml of anhydrous methanol was allowed to stand at room temperature for 5 hr. The reaction mixture was poured into saturated sodium bicarbonate solution and worked up to afford an oil that was evaporatively distilled (65°, 0.20 mm) to afford **13** as a colorless oil, 87 mg (92% yield), that was homogeneous by tlc and showed no hydroxyl or carbonyl peaks in its infrared spectrum. Its nmr spectrum was in agreement with the assigned structure: δ_{CDCl_3} 4.03 (1 H, CHO–, broad singlet, $v_{1/2}$ = 5 Hz), 3.35 (3 H, OCH_3, sharp singlet), 0.916 (3 H, C*H*$_3$CH, doublet, J = 7 Hz), and two singlets at 0.918 and 0.85 (quaternary methyls). Its mass spectrum showed a parent ion at *m/e* 224, and the base peak at *m/e* 139.

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(35) L. Birkofer, A. Ritter, and H. Dickopp, *Chem. Ber.*, **96**, 1473 (1963).

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Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.67; H, 10.60.

On being allowed to stand at room temperature in aqueous methanolic hydrochloric acid ketal **18** reverted to **12**.

Reaction of 40 mg of **12** with 45 mg of *p*-nitrobenzoyl chloride in 3 ml of pyridine afforded the corresponding *p*-nitrobenzoate **12a**, mp 148–149°, in 89% yield: δ_{CDCl_3} 8.21 (4 H, Ar*H*, broadened doublet), 5.30 (1 H, C*H*OAcyl, triplet, J = 4 Hz), 1.26 (3 H, C*H*$_3$CH, doublet, J = 7 Hz), and two quaternary methyl singlets at 1.16 and 0.86.

Anal. Calcd for $C_{20}H_{25}N_5O_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.91; H, 7.04; N, 3.96.

Rearrangement of 4 in Chloroform–Trifluoroacetic Acid. To a solution of 300 mg of **4** in 27 ml of dry chloroform at 26° under nitrogen was added in one portion 3.0 ml of trifluoroacetic acid. The reaction mixture was allowed to stand at room temperature for 60 min. It was then poured into saturated sodium bicarbonate solution and worked up to afford 324 mg of a light yellow oil. This oil was silylated and subjected to analysis by glpc. Glpc indicated the presence of four major (greater than 92% of the mixture) components. These were established to be, by comparison as shown below, and in order of elution, the silyl derivatives of **11**, **12**, **8**, and hydroxy aldehyde **7**. The peak due to hydroxy aldehyde **7** rapidly decreased in intensity as the sample was allowed to stand; it had vanished after 12 hr. The ratio of **12** to **11** was time dependent. At 60 min (and after silylation) the ratio was 64:1. When an aliquot was removed from the rearrangement reaction mixture after 10 min, analysis of the silyl ethers prepared as above showed the ratio of **12** to **11** to be 1:2.

Repeated column chromatography of the rearrangement reaction mixture afforded the above components. Aldehyde **7** was isolated in low yield as a colorless oil: δ_{CDCl_3} 9.70 (1 H, C*HO*, triplet, J = 2 Hz), and methyl singlets at 1.60, 1.05, and 1.00. Treatment of the reaction mixture with 2,4-dinitrophenylhydrazine reagent afforded the 2,4-dinitrophenylhydrazone derivative **7c** as yellow needles, mp 105–106° (aqueous ethanol). Its nmr spectrum was in agreement with the assigned structure: δ_{CDCl_3} 7.56 (1 H, C*H*= NNH, triplet, J = 6 Hz), 3.50 (1 H, C*H*OH, double doublet, J_a = 4 Hz, J_b = 6 Hz), a broadened singlet at 1.63, and sharp singlets at 1.07 and 1.01. Examination of the 100-MHz nmr spectrum showed the –C*H*$_2$CH=NNH group as a quartet at δ 2.40, which collapsed to a triplet, J = 6.5 Hz, on irradiation at δ 7.56.

Anal. Calcd for $C_{19}H_{26}N_4O_5$: C, 58.45; H, 6.71; N, 14.35. Found: C, 58.26; H, 6.61; N, 14.27.

Reaction of the 2,4-DNP derivative with *p*-nitrobenzoyl chloride in pyridine afforded the double derivative **7b**, identified by comparison with an authentic sample prepared from the *p*-nitrobenzoyloxy epoxide, by ir and mixture melting point. Both **12** and **11**, and **8** were isolated and compared with samples obtained *via* boron trifluoride catalyzed rearrangement of **4** by melting point and nmr spectra. In the time scale associated with the acid-catalyzed rearrangements, both aldehyde **7** and olefin diol **8** are stable. They do not therefore serve as intermediates in the formation of **12** or **11**.

For analysis of the rearrangement mixture by nmr **8** was detected by means of the δ 5.45 vinyl hydrogen signal, and aldehyde **7** was detected by its aldehyde proton at δ 9.70. The ratio of **12** to **8** as determined by glpc of the trimethylsilyl ethers was in agreement with the ratio determined by comparison of the isolated yield of the 2,4-DNP of **12** with the amount of **8** estimated by nmr. The instability of aldehyde **7** precluded the use of glpc as the sole analytical method.

It was established by comparison of the estimated yields by nmr spectrometry (using *p*-dibromobenzene as in internal standard) with the actual isolated yields of the 2,4-DNP derivatives of **12**, **11**, and **7** that both methods of analysis gave the same answer (see Table I). The results of a number of rearrangement experiments, using analysis by both nmr and isolation of the 2,4-DNP derivatives of **12**, **11**, and **7**, are listed in Table I.

Rearrangement of 4-*d*$_1$. Isolation of 11-*d*$_1$. To a solution of 300 mg of **4**-*d*$_1$ prepared as above in 27 ml of chloroform was added in one portion 3.0 ml of trifluoroacetic acid. The resulting solution was stirred at 26° under a nitrogen atmosphere for 10 min and was then poured into vigorously stirred sodium bicarbonate solution and worked up. The product, 308 mg of an oil, was subjected to preparative tlc (silica gel PF-254 (Brinkmann). The material at R_f 0.5 corresponding to **11** was collected. Its nmr spectrum was similar to that of **11** except that the peak at δ 1.11 which was a doublet in the case of **11** was now a singlet. It was contaminated with starting material. It was further purified by silylation followed by preparative glpc (20% Carbowax 20 on Chromosorb P, at 180°). The peak corresponding to the trimethylsilyl ether of **11** was collected and subjected to mass spectrometry. Analysis of the low voltage mass spectrum of this material showed its isotopic content to be d_0, 30.3; d_1, 69.4%.

Competitive Acid-Catalyzed Rearrangement of 4 and 4-*d*$_1$. The Kinetic Isotope Effect. A mixture of **4** and **4**-*d*$_1$ was prepared by dissolving 150 mg of each epoxide in 3 ml of ether and evaporating the solution to dryness. Low voltage mass spectrometry of the resulting mixture showed it to be d_0, 52.5%, d_1, 47.4%. This mixture was dissolved in 27 ml of chloroform and with stirring at 26° under nitrogen 3 ml of trifluoroacetic acid was added. After stirring for 20 min the reaction mixture was poured into sodium bicarbonate solution and worked up. Unreacted starting material was recovered by preparative tlc followed by silylation and collection of the peak corresponding to starting material. Analysis of this material, which was homogeneous by capillary gas chromatography, was analyzed by low voltage mass spectrometry. Its isotopic composition was d_0, 53.7%, d_1, 46.4%. The initial and final isotope values are considered to be within experimental error of one another.

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