Stereospecific Syntheses of Deuterated Clovane and Caryolane Derivatives Related to the Cyclization of Caryophyllene[1a]

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Stereospecific syntheses of four deuterium-labeled compounds related to the cyclization of caryophyllene are described. The routes may be generally useful for introduction of deuterium at hindered sites. Caryolan-1-ol-9-one was converted by a series of reactions into caryol-9-en-1-ol (7) and caryol-9-en-1-ol-9-d (8). Caryolan-1-ol-9β-d (2b) and -9α-d (2a) were prepared by respective deuterioboration of 7 and hydroboration of 8, as their trimethylsilyl ethers, followed by removal of the C-10 hydroxyl group. Clovane-2β-ol-9-one was converted into clov-9-en-2β-ol (19) and into clov-9-en-2β-ol-9-d (20). Clovenic anhydride-6α-d (4a) and -6β-d (4b) were prepared by respective deuterioboration of 19 and hydroboration of 20, as their trimethylsilyl ethers, followed by removal of the C-10 function and oxidation of the five-membered ring. The reduction of ketone tosylhydrazones with lithium aluminum hydride followed by D₂O work-up was found to provide an effective route to monodeuterated olefins.

Caryophyllene (1) undergoes acid-catalyzed cyclization to give (among other products) caryolan-1-ol (2) and clov-2-ene (3).[2] Cyclization with D₂SO₄ leads to monodeuterated 2 and 3,[3] whose deuterium configurations are pertinent for mechanistic understanding of the

which are characteristic of nucleophilic substitutions at neopentyl positions.[5] Incorporation of deuterium of known configuration at the C-9 position in the caryolane and clovane systems was accomplished by deuterioboration[6] of olefins 7a and 19a, and by hydroboration[7] of deuterated olefins 8a and 20a. The known *cis* mechanism of hydroboration was used to determine deuterium configuration.

Caryolane System.—The preparation of caryolan-1-ol-9α-d (2a) and -9β-d (2b) is outlined in Scheme I.

1

2

3

2a, R₁ = H; R₂ = D
**b**, R₁ = D; R₂ = H

4a, R₁ = H; R₂ = D
b, R₁ = D; R₂ = H
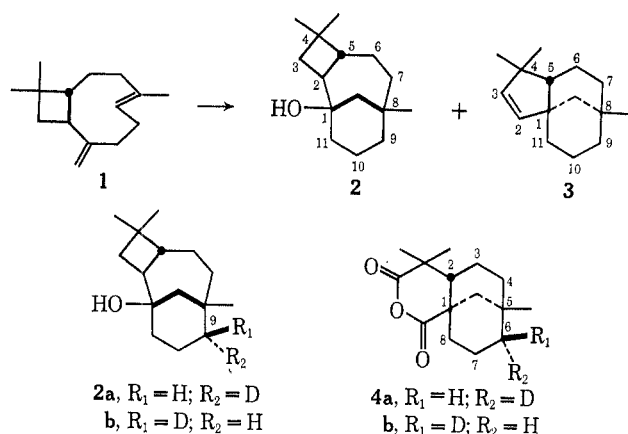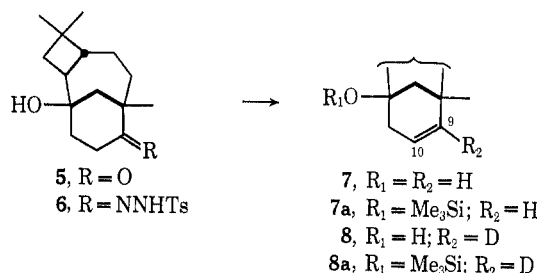
cyclizations. To permit a rigorous assignment of deuterium configurations in the cyclization products, we synthesized the following authentic deuterated compounds by stereospecific routes: caryolan-1-ol-9-α-d (2a) and -9β-d (2b) and clovenic anhydride-6α-d (4a) and -6β-d (4b).[4]

Attempts were initially made to prepare the desired deuterated compounds by direct deuteride displacements on appropriately functionalized C-9 derivatives of caryolane and clovane. However, such a route was vitiated by eliminations and molecular rearrangements,

SCHEME I

5, R = O
6, R = NNHTs

7, R₁ = R₂ = H
7a, R₁ = Me₃Si; R₂ = H
8, R₁ = H; R₂ = D
8a, R₁ = Me₃Si; R₂ = D
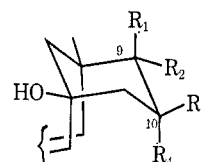
9, R₁ = OH; R₂ = R₃ = R₄ = H
10, R₁ = R₃ = R₄ = H; R₂ = OH
11, R₁ = R₂ = R₄ = H; R₃ = OH
12, R₁ = R₂ = R₃ = H; R₄ = OH
13, R₁ = OH; R₂ = R₄ = H; R₃ = D
14, R₁ = D; R₂ = R₄ = H; R₃ = OH
15, R₁ = OH; R₂ = D; R₃ = R₄ = H
16, R₁ = R₄ = H; R₂ = D; R₃ = OH

11 ⟶ C-10 tosylate **11a** ⟶ **2**
14 ⟶ C-10 tosylate **14a** ⟶ **2b**
16 ⟶ C-10 tosylate **16a** ⟶ **2a**

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(2) (a) A. Aebi, D. H. R. Barton, and A. S. Lindsey, *J. Chem. Soc.*, 3124 (1953); (b) A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsey, *ibid.*, 4659 (1954); (c) A. Nickon, *Perfumery Essent. Oil Record*, 45, 149 (1954); (d) W. Parker, R. A. Raphael, and J. S. Roberts, *Tetrahedron Lett.*, 2313 (1965).

(3) A. Nickon, F. Y. Edamura, T. Iwadare, K. Matsuo, F. J. Mc-Guire, and J. S. Roberts, *J. Amer. Chem. Soc.*, 90, 4196 (1968).

(4) Because clovene is a liquid, its solid anhydride 4, obtainable by oxidation of 3, was chosen as the compound for comparison. Note that the C-6 position in 4 corresponds to the C-9 position in 3.

(5) E. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden, New York, N. Y., 1959, p 277.

(6) H. C. Brown and K. J. Murray, *J. Org. Chem.*, 26, 631 (1961).

(7) (a) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962; (b) G. Zweifel and H. C. Brown, *Org. Reactions*, 13, 1 (1963).

Caryolan-1-ol-9-one (5)[8] was converted into its tosyl-hydrazone derivative 6. Caryol-9-en-1-ol (7) was obtained when 6 was treated with sodium methoxide in diethyl Carbitol (Bamford–Stevens[9] reaction under aprotic conditions[10-12]). Olefin 7 was also obtained when 6 was treated with lithium aluminum hydride (Caglioti[13] reaction). The structure of 7 was established by its infrared and nuclear magnetic resonance spectra, and by hydrogenation to the known alcohol 2. The position of the double bond was verified by hydro-boration experiments (described below), which gave C-9 and C-10 alcohols.

Deuterium incorporation was achieved by treatment of 6 with lithium aluminum hydride followed by work-up in D_2O, which gave caryol-9-en-1-ol-9-d (8, 6% d_0, 94% d_1). The nmr spectrum of 8 showed a one-proton triplet ($J = 3.5$ Hz) at δ 5.55 attributed to the C-10 proton.[14] The deuterium must therefore be located at C-9. Treatment of 6 with lithium aluminum deuteride, followed by H_2O work-up, gave 7 (96% d_0, 4% d_1); furthermore, deuterium was not incorporated into 7 when it was treated with $LiAlH_4$ followed by D_2O work-up. These results demonstrate that deuterium does not come from the reducing agent but rather by deuterolysis of some intermediate (eq 1) during work-up, and the method appears attractive for the preparation of monolabeled olefins.[16]

$$\text{(1)}$$
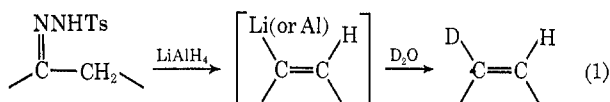
Hydroboration of hydroxy olefin caryol-9-en-1-ol (7) gave a mixture of all four possible diols (analyzed as their bistrimethylsilyl ethers[17] by gas chromatography): caryolane-1,9β-diol (9),[18] -1,9α-diol (10),[2b] -1,10β-diol (11), and -1,10α-diol (12). Attempts were made to optimize the formation of diol 11. No reaction occurred when the more selective reagent disiamyl-borane[19] was tried. The best results were obtained when the trimethylsilyl ether of caryol-9-en-1-ol (7a) was treated with externally generated[7b] diborane: 49% of a mixture[20] of 9 and 10, 37% 11, and 7% 12.

Diol 11 was isolated as its bistrimethylsilyl ether. The nmr of 11 and of its C-10 tosylate 11a showed symmetrical seven-line multiplets centered at δ 4.10 and 4.80, respectively, for the carbinyl proton at C-10. The relative band intensities were 1:2:3:4:3:2:1, with band separations of 5.5 Hz. The pattern results from two diaxial splittings of 11 Hz and two axial–equatorial splittings of 5.5 Hz. The carbinyl-proton must therefore be at C-10 and have axial character (hence equatorial hydroxyl group). Similar spectra have been reported for steroidal[21a] and bicyclo-[3.3.1]nonane[22,23] systems. The β assignment for the C-10 OH in 11 is based on the predominant β attack in hydroboration.[20] Our results thus show that the six-membered ring in 11 exists in a chairlike conformation.[24]

Similarly, caryolane-1,10β-diol-9β-d (14, 10–23% d_0, 76–84% d_1, 0–8% d_2) was prepared by deuterioboration of 7a.[25] The nmr of 14 and of its C-10 tosylate 14a showed symmetrical five-line multiplets with relative band intensities of 1:2:2:2:1 and band separations of 5.5 Hz. This pattern arises from one diaxial and two axial–equatorial splittings and is consistent with the assigned structure for 14 (equatorial OH at C-10 and axial deuterium at C-9). Caryolane-1,10β-diol-9α-d (16, >90% d_1) was prepared by hydroboration of deuterioolefin 8a.[26] The nmr of 16 and of its C-10 tosylate 16a showed symmetrical six-line multiplets with relative band intensities of 1:1:2:2:1:1 and band separations of 5.5 Hz. This pattern results from two diaxial and one axial–equatorial splittings, and is consistent with structure 16 (equatorial OH at C-10 and equatorial deuterium at C-9). A similar splitting pattern has been reported for a steroidal alcohol in the same sort of environment.[21b] The C–D stretching frequencies[27] in diols 14 (2145 cm⁻¹, axial D) and 16 (2158 cm⁻¹, equatorial D) substantiated the nmr assignments, although by itself the infrared criterion is not unequivocal.

Removal of the C-10 hydroxyl group in diols 11, 14, and 16 was accomplished by conversion into the corresponding tosylates 11a, 14a, and 16a, respectively, followed by displacement with lithium aluminum hydride. Thus 14 was converted into caryolan-1-ol-9β-d (2b, 98% pure, 20% d_0, 73% d_1, 7% d_2), and 16 was converted into caryolan-1-ol-9α-d (2a, 98% pure, 16% d_0, 84% d_1). Infrared spectra indicated that the deuterium retained its axial character in the conversion of 14 into 2b (2142 cm⁻¹), and its equatorial character

(8) D. H. R. Barton, T. Bruun, and A. S. Lindsey, *J. Chem. Soc.*, 2210 (1952).

(9) W. R. Bamford and T. S. Stevens, *ibid.*, 4735 (1952).

(10) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).

(11) L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **81**, 5512 (1959).

(12) Rearranged olefins resulted when protic solvents were used. Tosyl-hydrazone decompositions in protic media involve cationic intermediates, whereas under aprotic conditions carbenes are produced.[10,11]

(13) R. Caglioti and M. Magi, *Tetrahedron Lett.*, 1261 (1962); *Tetrahedron*, **19**, 1127 (1963).

(14) The nmr signal is assigned to the C-10 proton on the basis of the observed coupling constant, which is appropriate for vicinal but not for allylic coupling.[15]

(15) L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, London, 1959, p 85.

(16) After completion of our experiments, similar conclusions were drawn about the Caglioti reaction in steroid systems: M. Fisher, Z. Pelah, D. H. Williams, and C. Djerassi, *Chem. Ber.*, **98**, 3236 (1965).

(17) (a) R. Martin, *J. Amer. Chem. Soc.*, **74**, 3024 (1952); (b) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *ibid.*, **85**, 2497 (1963).

(18) W. Treibs, *Chem. Ber.*, **80**, 56 (1947).

(19) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 3222 (1960); **83**, 1241, (1961).

(20) (a) Although our glpc was known not to resolve 9 and 10, the product after isolation of this peak by preparative glpc was 9. Therefore, hydroboration of 7a occurs with predominant β attack at C-9 and at C-10. (b) This result agrees with reports that *exo* alcohols are obtained in hydroborations of bicyclo[3.3.1]non-2-ene[23] and of 1,5-dimethylbicyclo[3.3.1]non-2-ene.[22] (c) For references and stereochemical aspects of related ring systems, see E. Marvel and coworkers, *J. Org. Chem.*, **35**, 388, 391, 396 (1970).

(21) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 80, 180; (b) p 82.

(22) W. Macrosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, **30**, 2859 (1965).

(23) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

(24) An "equatorial" C-10 hydroxyl group would have the α configuration if the ring were in the boat conformation.

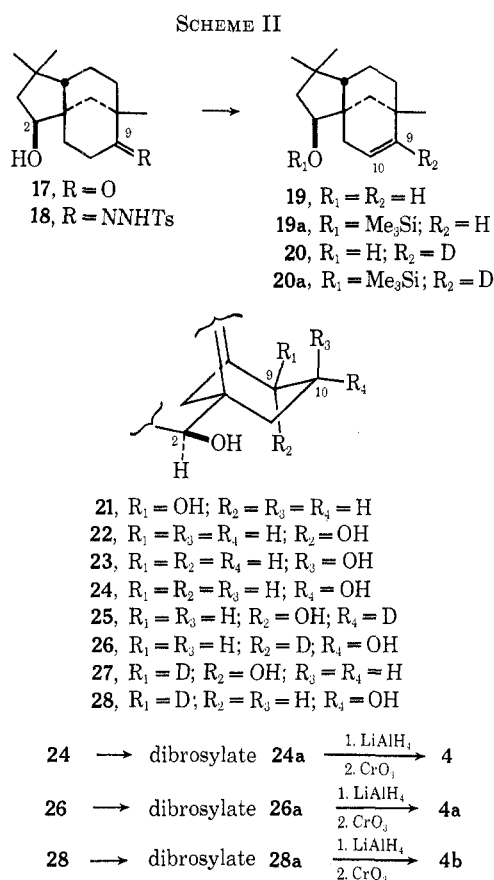(25) Caryolane-1,9β-diol-10β-d (13) was also isolated (18%) in this reaction.

(26) Caryolane-1,9β-diol-9α-d (15) was also isolated (14%).

(27) E. J. Corey, M. Howell, A. Boston, R. Young, and R. Sneen, *J. Amer. Chem. Soc.*, **78**, 5036 (1956).

in the conversion of **16** into **2a** (2155 cm^{-1}). Thus the six-membered ring very likely adopts the chairlike shape in all four compounds.[28]

A graded series of ten mixtures of caryolan-1-ol-9α-d (**2a**) and -9β-d (**2b**) were prepared and their infrared spectra were recorded for comparison with that of caryolan-1-ol obtained from D$_2$SO$_4$ cyclization of caryophyllene. On the basis of characteristic peaks in the fingerprint region, these mixtures showed that as little as 3% of **2a** could be detected when mixed with **2b**, whereas the lower limit of detection of **2b** is 10–15% when mixed with **2a**.

Clovane System.—Our preparation of clovenic anhydride-6α-d (**4a**) and -6β-d (**4b**) is outlined in Scheme II. A series of reactions analogous to that described

SCHEME II

17, R = O
18, R = NNHTs

19, R$_1$ = R$_2$ = H
19a, R$_1$ = Me$_3$Si; R$_2$ = H
20, R$_1$ = H; R$_2$ = D
20a, R$_1$ = Me$_3$Si; R$_2$ = D

21, R$_1$ = OH; R$_2$ = R$_3$ = R$_4$ = H
22, R$_1$ = R$_3$ = R$_4$ = H; R$_2$ = OH
23, R$_1$ = R$_2$ = R$_4$ = H; R$_3$ = OH
24, R$_1$ = R$_2$ = R$_3$ = H; R$_4$ = OH
25, R$_1$ = R$_3$ = H; R$_2$ = OH; R$_4$ = D
26, R$_1$ = R$_3$ = H; R$_2$ = D; R$_4$ = OH
27, R$_1$ = D; R$_2$ = OH; R$_3$ = R$_4$ = H
28, R$_1$ = D; R$_2$ = R$_3$ = H; R$_4$ = OH

24 ⟶ dibrosylate 24a $\xrightarrow[\text{2. CrO}_3]{\text{1. LiAlH}_4}$ 4

26 ⟶ dibrosylate 26a $\xrightarrow[\text{2. CrO}_3]{\text{1. LiAlH}_4}$ 4a

28 ⟶ dibrosylate 28a $\xrightarrow[\text{2. CrO}_3]{\text{1. LiAlH}_4}$ 4b

earlier for the caryolane system was used. Clov-9-en-2β-ol (**19**) was obtained by treatment of tosylhydrazone **18** (derived from clovan-2β-ol-9-one, **17**[29]) with sodium methoxide in diethyl Carbitol.[12] Olefin **19** was also obtained *via* the Caglioti reaction. The structure of **19** was established by spectral data, by hydrogenation to the known clovan-2β-ol,[29] and by the hydroboration results described below. The deuterio-olefin **20** (8% d_0, 92% d_1) was obtained from **18** by lithium aluminum hydride reduction with D$_2$O workup. The nmr spectrum of olefin **19** showed the C-9 proton as a six-line multiplet at δ 5.17 consisting of a

doublet (J = 10 Hz) of triplets (J = 2 Hz), and the C-10 proton as an eight-line multiplet at δ 5.68 consisting of a doublet (J = 10 Hz) further split into a doublet (J = 4.5 Hz) of doublets (J = 3 Hz). The nmr spectrum of **20** showed only a triplet (J = 3.5 Hz) at δ 5.68, assigned to the C-10 proton.[14]

Hydroboration of **19** gave a mixture of all four possible diols (analyzed as their bistrimethylsilyl ethers by gas chromatography): clovane-2β,9β-diol (**21**), -2β,9α-diol (**22**), -2β,10β-diol (**23**), and -2β,10α-diol (**24**). The C-9 epimers are known compounds.[2] No reaction occurred when disiamylborane[19] was tried in an attempt at greater selectivity. Hydroboration of the trimethylsilyl ether **19a** gave a mixture (1% **21**, 25% **22**, 2% **23**, and 61% **24**), from which pure diol **24** was obtained by preparative gas chromatography of the bistrimethylsilyl ether. The nmr spectra of diol **24** and of its dibrosylate derivative **24a** showed symmetrical seven-line multiplets (similar to those described earlier for caryolane derivatives **11** and **11a**) at δ 4.02 and 4.92, respectively, for the C-10 proton. Therefore, the C-10 hydroxyl in **24** has equatorial character. The results of hydroboration (predominant α attack)[20b,c] indicate that the C-10 hydroxyl also has the α configuration, and thus the six-membered ring containing C-10 exists in a chairlike conformation.

Clovane-2β,10α-diol-9α-d (**26**, 10% d_0, 89% d_1, 1% d_2) was prepared by deuterioboration of **19a**.[30] The nmr spectrum of **26** and of its dibrosylate **26a** showed symmetrical five-line multiplets (similar to those described for caryolane derivatives **14** and **14a**) for the C-10 proton, a result consistent with an axial α deuterium at C-9. Clovane-2β,10α-diol-9β-d (**28**, 6% d_0, 94% d_1) was obtained by hydroboration of the deuterio-olefin trimethylsilyl ether **20a**.[31] The nmr spectrum of **28** and of its dibrosylate **28a** showed symmetrical six-line multiplets (similar to those discussed earlier for caryolane derivatives **16** and **16a**) for the C-10 proton, a result consistent with an equatorial β deuterium at C-9.

Diol **24** was converted into the dibrosylate **24a**, which in turn was reduced with lithium aluminum hydride to a mixture that contained 23% clovene (**3**) and 31% clovan-2β-ol. Oxidative cleavage of the mixture with CrO$_3$ followed by pyrolysis of the dicarboxylic acid clovenic acid gave clovenic anhydride (**4**). Similarly, diol **26** was converted into clovenic anhydride-6α-d (**4a**, 99.3% pure, 3% d_0, 97% d_1) and diol **28** was converted into clovenic anhydride-6β-d (**4b**, 98.4% pure, 4% d_0, 96% d_1). Infrared spectra substantiated the axial character of the deuterium in **4a** (2142 cm^{-1}) as well as in **26** (2140 cm^{-1}), and the equatorial character of the deuterium in **4b** (2162 cm^{-1}) as well as in **28** (2152 cm^{-1}). The spectral results are therefore consistent with a chairlike conformation for all four compounds.[32]

Infrared spectra of a graded series of ten mixtures of clovenic anhydride-6α-d (**4a**) and -6β-d (**4b**) were recorded. Inspection of characteristic fingerprint bands revealed that as little as 3% of **4a** could be detected when mixed with **4b**; and as little as 4% of **4b** could be detected in a mixture with **4a**.

(28) The chairlike geometry for the cyclohexane ring in the caryolane skeleton is supported by X-ray studies on 1-chlorocaryolane: J. M. Robertson and G. Todd, *Chem. Ind.* (London), 437 (1953).

(29) D. H. R. Barton and A. Nickon, *J. Chem. Soc.*, 4665 (1954).

(30) Clovane-2β,9α-diol-10α-d (**25**) was also obtained (15%).

(31) A 9% yield of clovane-2β,9α-diol-9β-d (**27**) was also obtained.

(32) In bicyclo[3.3.1]nonane, the double chair (slightly flattened) is the preferred conformation: W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965); see also ref 20c.

Experimental Section[33]

Caryolan-1-ol-9-one p-Toluenesulfonylhydrazone (6).—Caryolan-1-ol-9-one[8] (5.00 g, 21.2 mmol) and p-toluenesulfonylhydrazine (4.72 g, 25.4 mmol) in methanol (50 ml) were refluxed overnight. Water (100 ml) was then added and the product was extracted with ether. Crystallization from ether–hexane afforded 7.37 g (86%) of 6 as white crystals, mp 145–152° dec. Two recrystallizations from ether–hexane gave a sample: mp 147–152° dec;[36] ir (CHCl₃) 3595 (OH), 3290 (NH), 1630 (C=N), 1600 (aromatic C=C), and 1325 and 1164 cm⁻¹ (SO₂).

Anal. Calcd for C₂₂H₃₂N₂O₃S (mol wt, 404.57): C, 65.31; H, 7.97. Found: C, 65.51; H, 8.15.

Caryol-9-en-1-ol (7). A. From the Aprotic Bamford–Stevens Reaction.—The general procedure of Friedman and Shechter[11] was used. Tosylhydrazone 6 (3.00 g, 7.4 mmol) was treated with sodium methoxide (3.0 g) in dry diethyl Carbitol (125 ml) for 2.5 hr under reflux. The cooled reaction mixture was diluted with water and extracted with ether. The extracts were washed with water, dried (MgSO₄), and evaporated. Two recrystallizations from ethanol–water and sublimation afforded 1.13 g (69%) of 7 as white needles: mp 102–102.5°; ir (CS₂) 3600 (OH), 3010 (olefinic CH), and 737 and 725 cm⁻¹ (cis-disubstituted olefin); nmr (CCl₄) δ 5.28–5.71 (m, 2, olefinic H).

Anal. Calcd for C₁₅H₂₄O (mol wt, 220.34): C, 81.76; H, 10.98. Found: C, 81.60; H, 10.86.

The 3,5-dinitrobenzoate of 7 was recrystallized from ethanol–water: mp 92.5–94°; ir (KBr) 3100 (aromatic CH), 3015 (olefinic CH), 1725 (C=O), and 1550 and 1350 cm⁻¹ (NO₂).

Anal. Calcd for C₂₂H₂₆N₂O₆ (mol wt, 414.44): C, 63.75; H, 6.32. Found: C, 63.79; H, 6.38.

Hydrogenation of 7 (0.062 g) with platinum oxide in ethyl acetate gave 0.058 g (93%) of caryolan-1-ol (2), mp 92.5–93.5°, identical with authentic 2 (lit.[8] mp 93–94°) by mixture melting point (93–94°) and infrared spectrum.

B. From the Caglioti Reaction.—The general procedure of Caglioti and Magi[13] was followed. Tosylhydrazone 6 (0.50 g, 1.24 mmol) was added to a slurry of lithium aluminum hydride (0.50 g, 13.2 mmol) in dry tetrahydrofuran (12 ml) under nitrogen. The mixture was refluxed for 21 hr, and then carefully treated successively with water (0.5 ml), 15% sodium hydroxide (0.5 ml), and water (1.5 ml). The mixture was stirred for 1.5 hr and filtered, and the precipitate was washed with warm ether (three 10-ml portions). The combined portions of ether and tetrahydrofuran were washed with water, dried, and evaporated to give a pale yellow solid (0.22 g, 81%). Infrared (CCl₄) indicated that this product consisted mainly of hydroxyolefin 7. Gas chromatography showed 80% 7, 2% caryolan-1-ol (2), 3% caryolan-1-ol-9-one, and 15% caryolane-1,9α-diol and caryolane-1,9β-diol. Sublimation of the crude solid followed by recrystallization from ethanol–water gave white, crystalline product

(0.11 g, 40%), mp 101–101.5°, identical by glpc and infrared spectrum with 7 obtained from the aprotic Bamford–Stevens reaction.

Caryol-9-en-1-ol-9-d (8).—Treatment of tosylhydrazone 6 (1.00 g, 2.47 mmol) with lithium aluminum hydride (1.00 g, 23.8 mmol) as described above, but with work-up with D₂O (1.0 ml, 99.5% isotopic purity), 15% sodium deuterioxide (1.0 ml), and D₂O (3.0 ml), successively, afforded 0.19 g (35%) of deuterioolefin 8 after sublimation and recrystallization from ethanol–water: mp 101–101–5°; identical with 7 by glpc; ir (CS₂) 3600 (OH), 3024 (olefinic CH), 2230 (olefinic CD), and 681 cm⁻¹ (cis-disubstituted olefin); nmr (CCl₄) δ 5.55 (t, 1, J = 3.5 Hz, olefinic H at C-10); 5–8% d₀, 92–95% d₁.

Treatment of tosylhydrazone 6 with lithium aluminum deuteride (Metal Hydrides, 99% minimum isotopic purity), followed by work-up in aqueous medium as above, gave in 26% yield a mixture of 96% 7 and 4% 8, as determined by mass spectral analysis (96% d₀ and 4% d₁) and by the relative intensities of infrared bands at 737 and 681 cm⁻¹. No detectable amount of deuterium (<3%) was observed (absence of infrared band at 681 cm⁻¹) when pure hydroxyolefin 7 was treated with lithium aluminum hydride and then with D₂O under the conditions of the Caglioti reaction.

Caryol-9-en-1-ol Trimethylsilyl Ether (7a).—The general procedure of Martin was followed.[17a] Freshly distilled trimethylsilyl chloride (2.00 ml, 1.68 g, 15.5 mmol) was added over a period of 5 min to 7 (0.800 g, 3.63 mmol) in dry pyridine (5 ml). After 5 hr at room temperature, the excess of trimethylsilyl chloride and most of the pyridine were removed *in vacuo*. Then dry benzene (30 ml) was added, the precipitated pyridine hydrochloride was filtered, and the solution was concentrated to give 1.09 g (100%) of 7a as a pale yellow oil: ir (CS₂) 3010 (olefinic CH), 1248 and 838 [Si(CH₃)₃], and 1120 cm⁻¹ (SiO). Hydroxyolefin 7 was readily recovered by hydrolysis of 7a with 50% aqueous methanol for 2 hr at reflux.[37]

Caryol-9-en-1-ol-9-d Trimethylsilyl Ether (8a).—In a similar manner deuterioolefin 8 was converted into its trimethylsilyl ether 8a: ir (CS₂) 3028 (olefinic CH), 2230 (olefinic CD), 1248 and 829 [Si(CH₃)₃], and 681 cm⁻¹ (cis-disubstituted olefin).

Caryolane-1,10β-diol (11). Hydroboration of 7a.—Diborane was generated[7b] by the addition (over a 1-hr period) of 1 M sodium borohydride in diglyme (18 ml, 18 mmol) to a stirred solution of freshly distilled boron trifluoride etherate (4.6 ml, 5.2 g, 37 mmol) in dry diglyme (4 ml). The gas was bubbled through a solution of sodium borohydride in diglyme to remove traces of boron trifluoride and then transferred with a slight flow of dry nitrogen into a separate vessel containing 7a (1.06 g, 3.63 mmol) in dry tetrahydrofuran (15 ml) at 25°. The generator was then heated at 60–70° for 1 hr to drive over all the diborane. The reaction mixture was carefully treated with water, and then with 3 N sodium hydroxide (5 ml) and 30% hydrogen peroxide (5 ml) for 2 hr. The product after work-up (0.86 g, 100%) was converted into a mixture of trimethylsilyl ethers by treatment with dry pyridine (10 ml) and trimethylsilyl chloride (3.0 ml) for 3.5 hr. Glpc analysis showed the trimethylsilyl ethers of the following diols: 37% 11, 7% 12, and 49% of a mixture[20a] of 10 and 9 (listed in order of increasing retention time). The two major components were isolated by preparative glpc.

Collection and hydrolysis (2-hr reflux with 50% aqueous methanol) of the first major component afforded 0.14 g (16%) of diol 11 after recrystallization from ether–hexane: mp 159–159.5°; ir (CHCl₃) 3600 (OH), 1095 (CO), and 1005 cm⁻¹; nmr (CDCl₃) δ 4.10 (seven-line multiplet, 1, H-10α, see discussion for interpretation). Four recrystallizations from ether–hexane gave the analytical sample, mp 160–160.5°.

Anal. Calcd for C₁₅H₂₆O₂ (mol wt, 238.36): C, 75.58; H, 11.00. Found: C, 75.58; H, 10.83.

Collection and hydrolysis of the second major component gave 0.25 g (29%) of caryolane-1,9β-diol (9) after recrystallization from ether–hexane: mp 105–106° (lit.[5,18] mp 106–107°); nmr (CDCl₃) δ 3.37 (poorly resolved triplet, 1, J = 2.5 Hz, H-9α); ir (CCl₄) 3625 and 3600 (OH), 1093 (CO), 1057, 1025, and 964 cm⁻¹, identical with ir spectrum of authentic 9.

Caryolane-1,10β-diol-9β-d (14). Deuterioboration of 7a.—In an analogous manner, 7a (1.06 g, 3.63 mmol) was treated with deuteriodiborane [generated from sodium borodeuteride (Metal Hydrides, 99.5% minimum isotopic purity) and boron trifluoride etherate] to give a mixture of deuterated diols after peroxide

(33) Melting points are corrected. Unless otherwise specified, sublimations were carried out at 40–60° (ca. 0.1–0.4 mm). Infrared spectra were recorded on Perkin-Elmer Models 21, 337, and 521 spectrophotometers. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 spectrometer in deuteriochloroform (unless otherwise specified) with tetramethylsilane as the internal standard. Analysis by gas–liquid partition chromatography (glpc) was carried out with a Perkin-Elmer Model 226 chromatograph, with 0.02-in. Golay capillary or 0.125-in. packed columns (SE-30 silicone gum rubber) operated at ca. 230°. Preparative glpc separations were performed with an Aerograph Autoprep Model A-700 instrument (Wilkins Instrument and Research, Inc.) with a 0.375 in. × 20 ft column packed with 30% SE-30 on Chromosorb P, operated at ca. 230°. Mass spectra were recorded with Consolidated Electrodynamics Corp. Model 21-103C, Associated Electrical Industries MS-9, and Hitachi Perkin-Elmer RMU-6D mass spectrometers. Isotopic distributions were calculated as described by Biemann.[34,35] Elemental analyses were performed by Mr. J. Walter at the Johns Hopkins University. Benzene was dried by distillation over sodium; pyridine was distilled over barium oxide. Ether, diglyme, tetrahydrofuran, and diethyl Carbitol were dried by distillation over lithium aluminum hydride.

(34) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 204 ff.

(35) Wherever possible, molecular ion peaks and several fragment ion peaks were used as the bases for these calculations. The ranges of calculated values are reported in the Experimental Section, but the values judged to be most reliable are reported in the discussion. Details are available in ref 1b.

(36) Earlier preparations gave a low-melting form of 6, mp 93–98° dec after recrystallization, which was identical (by ir spectrum, elemental analysis, and reactivity in the Bamford–Stevens reaction) with the higher melting form. Perhaps we are dealing with syn and anti isomers.

(37) A. Waiss, R. Lundin, and D. Stern, Tetrahedron Lett., 513 (1964).

oxidation. Preparative glpc separation (as the bistrimethylsilyl ether) of the first major component, followed by hydrolysis and recrystallization from ether–hexane, afforded 0.10 g (12%) of deuterated diol 14: mp 159–159.5°; ir (CHCl₃) 3600 (OH), 2145 (axial CD), 1091 (CO), 1026, and 1008 cm⁻¹; nmr (CDCl₃) δ 4.10 (five-line multiplet, 1, H-10α, see discussion for interpretation); 10–23% d_0, 76–84% d_1, 0–8% d_2.

Collection and hydrolysis of the second major component gave 0.15 g (18%) of caryolane-1,9β-diol-10β-*d* (13) after recrystallization from ether–hexane: mp 107.5–108.5°; ir (CCl₄) 3624 and 3600 (OH), 2160 (equatorial CD) 1090 (CO), 1042, 1032, and 965 cm⁻¹; nmr (CDCl₃) δ 3.38 (d, 1, *J* = 2.5 Hz, H-9α).

Caryolane-1,10β-diol-9α-*d* (16). Hydroboration of 8a.—In a similar manner deuterioolefin 8a (1.30 g, 4.42 mol) was treated with diborane to give a mixture of deuterated diols after peroxide oxidation. Preparative glpc separation (as the bistrimethylsilyl ether) of the first major component, followed by hydrolysis and recrystallization from ether–hexane, gave 0.10 g (10%) of deuterated diol 16: mp 159–159.5°; ir (CHCl₃) 3600 (OH), 2158 (equatorial CD), 1092 (CO), and 997 cm⁻¹; nmr (CDCl₃) δ 4.10 (six-line multiplet, 1, H-10α, see discussion for interpretation); 0–10% d_0, 90–100% d_1.

Collection and hydrolysis of the second major component gave 0.14 g (14%) of caryolane-1,9β-diol-9α-*d* (15) after recrystallization from ether–hexane: mp 106–107°; ir (CCl₄) 3623 and 3600 (OH), 2100 (broad, CD), 1091 (CO), and 1053 cm⁻¹; nmr (CDCl₃) no signal at δ 3.37.

Caryolane-1,10β-diol 10-Tosylate (11a).—Diol 11 (0.018 g, 0.076 mmol) was treated with a large excess of *p*-toluenesulfonyl chloride (0.073 g, 0.38 mmol) in pyridine (0.5 ml) for 42 hr at room temperature to give after work-up 0.029 g (97%) of 11a as a colorless oil: ir (CCl₄) 3600 (OH) and 1189 and 1178 cm⁻¹ (SO₂); nmr (CDCl₃) δ 2.45 (s, 3, aromatic CH₃), 4.80 (seven-line multiplet, 1, H-10α, see discussion), 7.31 (d, 2, *J* = 8 Hz, aromatic H), and 7.80 (d, 2, *J* = 8 Hz, aromatic H).

Caryolan-1-ol (2) by Lithium Aluminum Reduction of 11a.—Crude tosylate 11a (0.029 g) was dissolved in dry tetrahydrofuran (5 ml) and treated with lithium aluminum hydride (0.055 g, 1.4 mmol) for 52 hr at reflux. The product after work-up was sublimed to give oily crystals (0.009 g) shown by ir and glpc to consist of 78% caryolan-1-ol (2) and 22% caryol-9-en-1-ol (7).

Caryolane-1,10β-diol-9β-*d* 10-Tosylate (14a).—Diol 14 (0.10 g, 0.43 mmol) was converted in 87% yield into tosylate 14a: ir (CCl₄) 3600 (OH) 1189 and 1178 cm⁻¹ (SO₂); nmr (CDCl₃) δ 2.45 (s, 3, aromatic CH₃), 4.80 (five-line multiplet, 1, H-10α, see discussion), 7.31 (d, 2, *J* = 8 Hz, aromatic H), and 7.79 (d, 2, *J* = 8 Hz, aromatic H).

Caryolan-1-ol-9β-*d* (2b).—Crude tosylate 14a (0.146 g) in dry tetrahydrofuran (15 ml) was treated with lithium aluminum hydride (0.28 g, 7.4 mmol) for 52 hr at room temperature. The product after work-up was sublimed to give 0.062 g of a mixture of 2b plus olefinic material. The product was dissolved in carbon tetrachloride and treated with 0.35 *M* bromine in carbon tetrachloride (0.75 ml). Evaporation of excess bromine and solvent, followed by five fractional sublimations, gave 0.007 g (7% yield from the diol) of 2b: mp 89.5–91.5°; 98% pure by glpc; ir (CCl₄) 3608 (OH), 2142 (axial CD), 1092 (CO), 1058, 1043, and 1020 cm⁻¹; 15–22% d_0, 73–78% d_1, 6–8% d_2.

Caryolane-1,10β-diol-9α-*d* 10-Tosylate (16a).—Diol 16 (0.094 g, 0.39 mmol) was converted in 91% yield into tosylate 16a: ir (CCl₄) 3600 (OH) and 1189 and 1178 cm⁻¹ (SO₂); nmr (CDCl₃) δ 2.45 (s, 3, aromatic CH₃), 4.79 (six-line multiplet, 1, H-10α, see discussion), 7.31 (d, 2, *J* = 8 Hz, aromatic H), and 7.79 (d, 2, *J* = 8 Hz, aromatic H).

Caryolan-1-ol-9α-*d* (2a).—Crude tosylate 16a (0.135 g) in dry tetrahydrofuran (15 ml) was treated with lithium aluminum hydride (0.26 g, 6.9 mmol) for 60 hr at reflux. The product after work-up was sublimed to give 0.050 g of a mixture of 2a plus olefinic material. After purification by bromination and repeated sublimations we obtained 0.012 g (14% yield from the diol) of 2a: mp 93–94°; 98% pure by glpc; ir (CCl₄) 3608 (OH), 2155 (equatorial CD), 1091 (CO), 1063, and 1031 cm⁻¹; 12–17% d_0, 83–88% d_1, 0–1% d_2.

Infrared Spectra of Mixtures of 2a and 2b.—A graded series of ten mixtures ranging from pure 2a to pure 2b were prepared and their infrared spectra were recorded in CCl₄ solution with a Perkin-Elmer Model 521 grating spectrophotometer. The CD stretch and fingerprint regions were scale expanded (both ordinate and abscissa) to allow more detailed comparisons.[38] The 9α-*d* epimer 2a has a medium-intensity characteristic fingerprint band

at 1031 cm⁻¹ where the 9β-*d* epimer 2b has a minimum; 2b has weak, but characteristic, bands at 1043 and 1020 cm⁻¹ where 2a has only very weak absorption. The lower limits of detectability (see discussion) were determined from the mixtures on the basis of these bands.

Clovan-2β-ol-9-one *p*-Toluenesulfonylhydrazone (18).—The reaction of clovan-2β-ol-9-one[29] (12.6 g, 53.2 mmol) and tosylhydrazine (11.9 g, 63.9 mmol) in refluxing methanol (100 ml) gave, after crystallization from methanol–water, 18.4 g (86%) of tosylhydrazone 18: mp 146–152° dec; ir (KBr) 3480 (broad, bonded OH), 3100 (broad, bonded NH and aromatic CH), 1630 (CN), 1600 (aromatic C=C), 1322 and 1163 (SO₂), and 819 cm⁻¹ (aromatic CH).

Anal. Calcd for C₂₂H₃₂N₂O₃S (mol wt, 404.57: C, 65.31; H, 7.97. Found: C, 65.51; H, 7.77.

Clov-9-en-2β-ol (19). A. By the Aprotic Bamford–Stevens Reaction.—Tosylhydrazone 18 (3.20 g, 7.92 mmol) and sodium methoxide (3.00 g, 55.5 mmol) were heated in refluxing dry diethyl Carbitol (85 ml) for ¸2.5 hr under nitrogen. The product after work-up was an amorphous solid (1.91 g) which could not be crystallized from any of a number of solvents, but was sublimed to give 1.50 g (86%) of 19 as white crystals: mp 50–54°; 94% pure by glpc; ir (CS₂) 3615 (OH), 3010 (olefinic CH), 1645 (C=C), and 710 cm⁻¹ (*cis*-disubstituted olefin); nmr (CCl₄) δ 3.62 (doublet of doublets, 1, *J* = 5 and 2 Hz, H-2α), 5.17 (doublet of triplets, 1, *J* = 10 and 2 Hz, H-9), 5.68 (pair of doublets of doublets, 1, *J* = 10, 4.5 and 3 Hz, H-10). Purification by regeneration from the 3,5-dinitrobenzoate, followed by two sublimations, gave pure 19, mp 55.5–58.5°.

Anal. Calcd for C₁₅H₂₄O (mol wt, 220.34): C, 81.76; H, 10.98. Found: C, 81.88; H, 10.89.

The 3,5-dinitrobenzoate of 19 was recrystallized from hexane: mp 177–175.5°; ir (KBr) 3106 (aromatic CH), 3012 (olefinic CH), 1720 (C=C), and 1550 and 1348 cm⁻¹ (NO₂).

Anal. Calcd for C₂₂H₂₆N₂O₆ (mol wt, 414.44): C, 63.75; H, 6.32. Found: C, 63.97; H, 6.41.

Hydrogenation of 19 (0.18 g, 0.82 mmol) with platinum oxide in ethyl acetate gave 0.15 g (84%) of clovan-2β-ol after recrystallization from ethanol–water and sublimation: mp 93.5–94.5° (lit.[29] mp 95–96°); ir (CCl₄) 3620 (OH) and 1067 cm⁻¹ (CO); nmr (CDCl₃) δ 3.81 (doublet of doublets, 1, *J* = 9 and 6 Hz, H-2α). The 3,5-dinitrobenzoate of clovan-2β-ol had a melting point of 132–133° (lit.[29] mp 134–135°).

B. By the Caglioti Reaction.—The reaction of tosylhydrazone 18 (0.40 g, 0.99 mmol) with lithium aluminum hydride (0.40 g, 10.5 mmol) in dry tetrahydrofuran for 14 hr at reflux gave, after work-up, 0.14 g (64%) of a mixture consisting of 60% hydroxyolefin 19, 15% clovan-2β-ol, 21% clovane-2β,9α-diol and clovane-2β,9β-diol, and 4% unidentified material. Preparative glpc and sublimation gave pure 19, mp 55–57°, identical by ir spectrum with 19 obtained from the Bamford–Stevens reaction. The reaction of tosylhydrazone 18 with lithium aluminum tri-*t*-butoxy hydride gave a crude product which contained only 49% 19.

Clov-9-en-2β-ol-9-*d* (20).—Treatment of tosylhydrazone 18 (1.00 g, 2.47 mmol) with lithium aluminum hydride (1.00 g, 26.3 mmol) in dry tetrahydrofuran (30 ml) for 24 hr under reflux, followed by successive treatment with D₂O (1.0 ml), 15% sodium deuterioxide (1.0 ml), and D₂O (3.0 ml), gave 0.075 g (14%) of deuterioolefin 20 after preparative glpc and sublimation: mp 55.5–58°; identical with 19 by glpc; ir (CS₂) 3615 (OH), 3025 and 3012 (olefinic CH), 2240 (olefinic CD), and 671 cm⁻¹ (*cis*-disubstituted olefin); nmr (CCl₄) δ 3.62 (doublet of doublets, 1, *J* = 5 and 2 Hz, H-2α) and 5.68 (t, poorly resolved, 1, *J* = 3.5 Hz, H-10); 8% d_0 and 92% d_1.

Reaction of tosylhydrazone 18 with lithium aluminum deuteride, followed by D₂O work-up as above, also gave deuterioolefin 20 (11–12% d_0 and 88–89% d_1). Reaction of the tosylhydrazone with lithium aluminum deuteride followed by aqueous work-up gave olefin 19 (97% d_0 and 3% d_1). No detectable deuterium incorporation (<1%) was observed (absence of ir band at 671 cm⁻¹) when pure olefin 19 was treated with lithium aluminum hydride and D₂O under the conditions of the Caglioti reaction.

(38) Infrared CD stretching frequencies are useful for the qualitative assignment of axial or equatorial character in cyclohexane systems;[27] however, in our compounds as well as in the published literature[27] these bands are usually broad, unsymmetrical, and sometimes have multiple peaks, and are therefore unsuitable for quantitative determination of mixtures.

Clov-9-en-2β-ol Trimethylsilyl Ether (19a).—The reaction of hydroxyolefin 19 (1.50 g, 6.8 mmol) in dry pyridine (8 ml) with trimethylsilyl chloride (3.0 ml, 2.5 g, 23 mmol) at room temperature gave, after work-up as described above for 7a, 1.99 g (100%) of 19a as a pale yellow oil: >97% pure by glpc; ir (neat film) 3010 (olefinic CH), 1248 and 837 [Si(CH₃)₃], 1059 (SiO), 713 cm⁻¹ (cis-disubstituted olefin); nmr (CCl₄) δ 0.06 (s, 9, SiCH₃), 3.63 (doublet of doublets, 1, J = 5 and 2 Hz, H-2α), 5.21 (doublet of triplets, 1, J = 10 and 2 Hz, H-9), and 5.76 (poorly resolved doublet of triplets, 1, J = 10 and 3.5 Hz, respectively, H-10). Hydrolysis of 19a (2-hr reflux with 50% aqueous methanol) gave 19.

Clov-9-en-2β-ol-9-d Trimethylsilyl Ether (20a).—In a similar manner 20 was converted into its trimethylsilyl ether 20a: ir (CS₂) 3025 and 3012 (olefinic CH), 2240 (olefinic CD), 1247 and 838 [Si(CH₃)₃], 1058 and 1047 (SiO), 673 cm⁻¹ (cis-disubstituted olefin). Pure 20 could be regenerated by hydrolysis of 20a.

Clovane-2β,10α-diol (24). Hydroboration of 19a.—A slurry of lithium aluminum hydride (1.24 g, 32.6 mmol) in dry ether (15 ml) was added over a period of 15 min to a stirred, cooled (0°) solution of boron trifluoride etherate (5.5 ml, 6.17 g, 43.4 mmol) and olefin 19a (1.27 g, 4.34 mmol) in dry ether (30 ml) under nitrogen. The resulting mixture was stirred at 0° for 1 hr and then for 36 hr at room temperature. The reaction mixture was then oxidized with 3 N sodium hydroxide (5 ml) and 30% hydrogen peroxide (5 ml) for 2 hr. The product after work-up (1.03 g, 100%) was treated with dry pyridine (8 ml) and trimethylsilyl chloride (3 ml) for 2 hr. Glpc analysis showed the trimethylsilyl ethers of the following diols: 2% 23, 61% 24, 25% 22, and 1% 21 (listed in order of increasing retention time).

Preparative glpc and hydrolysis (2-hr reflux with 50% aqueous methanol) of the first major component afforded 0.27 g (26%) of the desired diol 24 after recrystallization from ether–hexane: mp 150.5–151.5° (first crop) and 145–147.5° (second crop); ir (CHCl₃) 3600 (OH), 1070 and 1021 (CO), and 997 cm⁻¹; nmr (CDCl₃) δ 3.81 (doublet of doublets, 1, J = 8 and 6 Hz, H-2α) and 4.02 (br m, 1, total width 32 Hz, H-10β).[39] Four additional recrystallizations from ether–hexane gave a sample, mp 155–155.5°.

Anal. Calcd for C₁₅H₂₆O₂ (mol wt, 238.36): C, 75.58; H, 11.00. Found: C, 75.38; H, 10.87.

Collection and hydrolysis of the second major component gave 0.11 g (10%) of clovane-2β,9α-diol (22) after recrystallization from ether–hexane: mp 151–152°; nmr (CDCl₃) δ 3.32 (br s, 1, H-9β) and 3.80 (doublet of doublets, 1, J = 10 and 6 Hz, H-2α); ir (CHCl₃) 3600 (OH), 1153, 1069, 1032, 990, 958, and 941 cm⁻¹, identical with the ir spectrum of authentic 22 (lit.[2a] mp 152–153°).

Clovane-2β,10α-diol-9α-d (26). Deuterioboration of 19a.—In an analogous fashion 19a (1.99 g, 6.88 mmol) was treated with lithium aluminum deuteride (Metal Hydrides, 99% minimum isotopic purity) and boron trifluoride etherate to give a mixture of deuterated diols after peroxide oxidation. Preparative glpc separation (as the bistrimethylsilyl ether) of the first major component, followed by hydrolysis and recrystallization from ether–hexane, afforded 0.20 g (12%) of deuterated diol 26: mp 151–152°; ir (CHCl₃) 3606 (OH), 2140 (axial CD), and 1070 and 1029 cm⁻¹ (CO); nmr (CDCl₃) δ 3.77 (doublet of doublets, 1, J = 8 and 6 Hz, H-2α) and 3.95 (br m, 1, total width 21 Hz, H-10β);[39] 9–11% d₀, 89–90% d₁, 0–1% d₂.

Collection and hydrolysis of the second major component gave 0.24 g (15%) of clovane-2β,9α-diol-10α-d (25) after recrystallization from ether–hexane: mp 151.5–152.5°; ir (CHCl₃) 3600 (OH), 2160 (equatorial CD), 1069 and 1048 (CO), and 990 cm⁻¹; nmr (CDCl₃) δ 3.30 (poorly resolved doublet, 1, J = 2 Hz, H-9β) and 3.79 (doublet of doublets, 1, J = 10 and 6 Hz, H-2α).

Clovane-2β,10α-diol-9β-d (28). Hydroboration of 20a.—Similarly, 20a (1.19 g, 4.07 mmol) was treated with lithium aluminum hydride and boron trifluoride etherate to give a mixture of deuterated diols after peroxide treatment. Preparative glpc separation (as the bistrimethylsilyl ether) of the first major component, followed by hydrolysis and recrystallization from ether–hexane, gave 0.12 g (12%) of deuterated diol 28: mp 152.5–153.5°; ir (CHCl₃) 3605 (OH), 2152 (equatorial CD), 1070 (CO), 1042, and 996 cm⁻¹; nmr (CDCl₃) δ 3.78 (doublet of doublets, 1, J = 8 and 6 Hz, H-2α) and 3.98 (br m, 1, total width 26 Hz, H-10β);[39] 6% d₀ and 94% d₁.

Collection and hydrolysis of the second major component gave

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(39) Part of this multiplet was obscured by the adjacent signal of H-2α.

0.09 g (9%) of clovane-2β,9α-diol-9β-d (27) after recrystallization from ether–hexane: mp 150.5–151.5°; ir (CHCl₃) 3600 (OH), 2100 (broad, CD), 1069 (CO), and 998 cm⁻¹; nmr (CDCl₃) δ 3.78 (doublet of doublets, 1, J = 10 and 6 Hz, H-2). There was also a weak signal at δ 3.30 which indicated the presence of ca. 9% unlabeled diol 22.

Clovane-2β,10α-diol Dibrosylate (24a).—Diol 24 (0.043 g, 0.18 mmol) was treated with brosyl chloride (0.11 g, 0.43 mmol) in dry pyridine (1.0 ml) for 24 hr at room temperature to give, after work-up and recrystallization from ether–hexane, 0.084 g (69%) of 24a: mp 114.5–115° dec; ir (CHCl₃) 1575 (aromatic C=C) and 1365 and 1176 cm⁻¹ (SO₂); nmr (CDCl₃) (δ 4.50 (t, 1, J = 6 Hz, H-2α), 4.92 (seven-line multiplet, 1, H-10β, see discussion for interpretation), and 7.72 (s, 8, aromatic H). Four recrystallizations from ether–hexane gave a sample, mp 114.5–115° dec.

Anal. Calcd for C₂₇H₃₂Br₂O₆S₂ (mol wt, 676.51): C, 47.94; H, 4.77. Found: C, 47.91; H, 4.86.

Clovenic Anhydride (4) from 24a.—Dibrosylate 24a (0.078 g, 0.115 mmol) in dry tetrahydrofuran (10 ml) under nitrogen was treated with lithium aluminum hydride (0.087 g, 2.3 mmol) for 34 hr under reflux. The product after work-up was a mixture (0.031 g) shown by ir and glpc to consist of 23% clov-2-ene (3), 11% clov-9-en-2β-ol (19), 31% clovan-2β-ol, plus several minor unidentified compounds. This product, in glacial acetic acid (5 ml), was oxidized with CrO₃ (0.25 g, in 0.25 ml of water) for 132 hr at room temperature. The excess of CrO₃ was destroyed with methanol, and most of the acetic acid was removed *in vacuo*. Ether extraction gave a crude product which was digested with 10% NaOH for 30 min at 100°. The alkaline solution was extracted with ether to remove any neutral material, and then acidified with 3 N HCl to precipitate clovenic acid (0.012 g). This material was pyrolyzed for 10 min at 195–200° in a glass tube closed at one end and then sublimed at 100–110° (0.2 mm) to give the known anhydride 4.

Clovane-2β,10α-diol-9α-d Dibrosylate (26a).—Diol 26 (0.13 g, 0.535 mmol) was converted in 71% yield into dibrosylate 26a: mp 113.5–114.5° dec; ir (CHCl₃) 2150 (CD), 1575 (aromatic C=C), and 1365 and 1175 cm⁻¹ (SO₂); nmr (CDCl₃) δ 4.49 (t, 1, J = 6 Hz, H-2α), 4.90 (five-line multiplet, 1, H-10β, see discussion), and 7.71 (s, 8, aromatic H).

Clovenic Anhydride-6α-d (4a).—Treatment of dibrosylate 26a (0.36 g, 0.53 mmol) with lithium aluminum hydride gave a crude mixture of products which was oxidized with CrO₃ (1.0 g, in 10 ml of water) as described above to give 0.043 g of crude deuterated clovenic acid. Pyrolysis and sublimation as described above for the preparation of 4 gave 0.033 g (25% yield from the dibrosylate) of 4a as oily crystals, 98% pure by glpc. Three fractional sublimations at 40–60° (0.2 mm) gave 0.0085 g (6% yield) of 4a: mp 47–48°; 99.3% pure by glpc; ir (CCl₄) 2161 (weak shoulder, CD), 2142 (axial CD),[38] 1808 and 1760 (anhydride C=O), 1085, 1073, 1038, 1028, 1018, 992 cm⁻¹; 2–4% d₀ and 96–98 d₁.

Clovane-2β,10α-diol-9β-d Dibrosylate (28a).—Diol 28 (0.054 g, 0.23 mmol) was converted in 71% yield into dibrosylate 28a: mp 114–115° dec; ir (CHCl₃) 2160 (equatorial CD), 1575 (aromatic C=C), and 1365 and 1175 cm⁻¹ (SO₂); nmr (CDCl₃) δ 4.50 (t, 1, J = 6, H-2α), 4.91 (six-line multiplet, 1, H-10β, see discussion), and 7.71 (s, 8, aromatic H).

Clovenic Anhydride-6β-d (4b).—Treatment of dibrosylate 28a (0.200 g, 0.295 mmol) with lithium aluminum hydride gave a crude mixture which was oxidized with CrO₃ to give 0.016 g of crude deuterated clovenic acid. Pyrolysis and sublimation gave 0.011 g (15% yield from the dibrosylate) of crude 4b. Fractional resublimation gave 0.0067 g (9%) of 4b: mp 46–47°; 98.4% pure by glpc; ir (CCl₄) 2162 (equatorial CD), 1808 and 1759 (anhydride C=O), 1089, 1048, 1029, 1010, and 1005 cm⁻¹; 4–6% d₀ and 94–96% d₁.

Infrared Spectra of Mixtures of 4a and 4b.—A graded series of ten mixtures ranging from pure 4a to pure 4b were prepared and their infrared spectra were recorded. The 6α-d epimer 4a has characteristic fingerprint bands at 1073 (w), 1038 (s), and 1018 cm⁻¹ (m), where the 6β-d epimer 4b has minima; 4b has characteristic bands at 1048 (s), where 4a has a weak shoulder, and at 1010 (m) and 1005 cm⁻¹ (m) where 4a has minima. The limits of detectability (see discussion) were determined from the mixtures on the basis of these bands.

86-9; **6**, 23736-87-0; **7**, 23736-88-1; **7** 3,5-dinitro-benzoate, 23809-49-6; **7a**, 23736-89-2; **8**, 23736-90-5; **8a**, 23736-91-6; **9**, 4870-61-5; **11**, 23809-50-9; **11a**, 23736-93-8; **13**, 23736-94-9; **14**, 23736-95-0; **14a**, 23736-96-1; **15**, 23736-97-2; **16**, 23809-51-0; **16a**, 23809-52-1; **18**, 23809-53-2; **19**, 23736-98-3; **19** 3,5-dinitrobenzoate, 23736-99-4; **19a**, 23737-00-0; **20**, 23809-54-3; **20a**, 23737-01-1; **22**, 23737-02-2; **24**, 23737-03-3; **24a**, 23809-55-4; **25**, 23809-56-5; **26**, 23737-04-4; **26a**, 23737-05-5; **27**, 23737-06-6; **28**, 23737-07-7; **28a**, 23737-08-8.

Halogenated Ketenes. XII. The Reaction of Some Acid Halides with Triethylamine. α-Halovinyl Esters[1,2]

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The reaction of triethylamine with an excess of some acid halides to produce α-halovinyl esters (enol esters of acid halides) has been investigated. The α-halovinyl esters produced are considered to be the result of acylation of an intermediate enolate ion. The reaction is most appropriate for disubstituted acetyl halides where at least one of the substituents is halogen. Some of the implications of the enolate ion intermediate are discussed and the synthesis of several representative examples of this new class of compounds is described.

It has recently been reported from this laboratory that in an attempted preparation of the dimer of methylchloroketene by the dehydrochlorination of α-chloropropionyl chloride, a novel compound was isolated.[4] This material was assigned the structure of a β-keto acid halide and was assumed to be the result of a reaction of methylchloroketene and the acid halide, since conducting the reaction in the presence of cyclopentadiene produced a good yield of cycloadduct. This type of reaction was described by

$$CH_3 \diagdown C=C=O + CH_3CHCCl \longrightarrow CH_3CHC-C-CCl$$
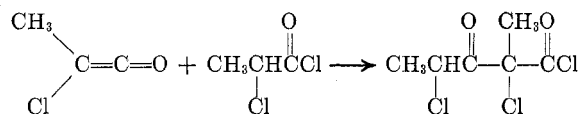
Staudinger, and by others since that time, and more recently by us.[5-9] Nevertheless, upon investigation of this situation further it has become apparent to us and others that the material produced is not a β-keto acid halide.

Dreiding and coworkers have recently confirmed and supplemented our initial report on the α-chloropropionyl chloride system, but have assigned the material the following structure.[10]

$$CH_3CHCOC=CCH_3$$
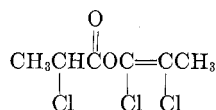
Lavanish has reported that similar results are obtained with dichloroacetyl chloride and triethylamine and assigns the structure as trichlorovinyl dichloroacetate.[11]

The purpose of this report is to correct our previous structure assignment and to reveal the results of a more extensive and comprehensive study of this reaction, which we believe involves the synthesis of a new class of compounds.

Results

In addition to the two systems that have already been reported, we have examined the reaction of triethylamine with a number of other acid halides in an effort to produce other α-halovinyl esters. This reaction may be represented as indicated.

$$2RC-CX + Et_3N \longrightarrow RC-COC=CR + Et_3NHX$$
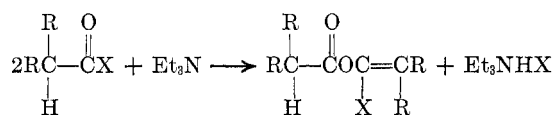
It becomes immediately apparent that this is not a general reaction of acid halides. Table I lists the acid halides which we found will react with a deficiency of triethylamine to produce the α-halovinyl esters.

Attempts to prepare α-halovinyl esters from several other acid halides were unsuccessful; *e.g.*, acetyl chloride, chloroacetyl chloride, propionyl chloride, isobutyryl chloride, α-phenylbutyryl chloride, and diphenylacetyl chloride did not produce α-halovinyl esters.

A different type of α-halovinyl ester was also prepared from α-chloropropionyl chloride. After the treatment of α-chloropropionyl chloride with a stoichiometric amount of triethylamine, a stoichiometric

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