Fungal Extractives. 10.[1a] An Alternative Synthesis of the Velleral Skeleton[1b]

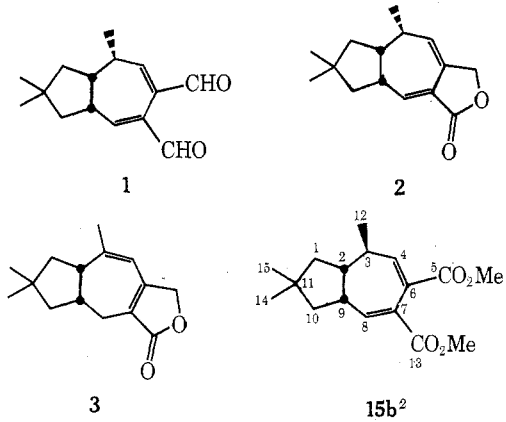
T. Fex, J. Froborg,* G. Magnusson, and S. Thorén

Organic Chemistry 2, Chemical Center, The Lund Institute of Technology, Box 740, S-220 07 Lund 7, Sweden

Received May 12, 1976

An improved synthetic route to the hydroazulenic skeleton of the fungal sesquiterpenoid velleral (**1**, *Lactarius vellereus* and *L. pergamenus*, Russulaceae) is described. 2-Carbomethoxy-4,4-dimethylcyclohexanone (**4**) was transformed in a convenient six-step sequence to 4,7,7-trimethylbicyclo[3.3.0]octan-2-one (**9**). The morpholine enamine of **9** (**13**) was converted to the racemic velleral derivative 2,2,4-trimethyl-1,3,4*H*-6,7-bis(methoxycarbonyl)-azulene (**15a**) via a 1,2 addition of dimethyl acetylenedicarboxylate, electrocyclic opening of the cyclobutene ring to give compound **14**, and subsequent hydrogenolytic deamination of **14** with diborane. The relative stereostructure of ketone **9** was determined with the aid of computer analysis of $Eu(fod)_3$-induced chemical shifts of the corresponding alcohol (**11**).

In previous publications we have reported the structures of five sesquiterpenoids from basidiomycetes of the genus *Lactarius* with the lactarane skeleton[2] [velleral (**1**), vellerolactone (**2**), pyrovellerolactone (**3**), and two furan alcohols].[3] Recently we also described a synthesis of the velleral skeleton which gave compound **15b**, a C-3 epimer of the natural product, and further a total synthesis of (±)-pyrovellerolactone.[1a] (There has recently been a revision in the position of the lactone carbonyl group[4] of the lactarorufins from *L. rufus* and *L. necator*,[5] which are closely related to **2** and **3**. The accepted position is now the opposite to that assigned to **2** and **3**. In view of these findings a reinvestigation of **2** and **3** is being undertaken. However, the product of the synthesis of the racemate of **3** is definitely the racemate of the true natural product.)

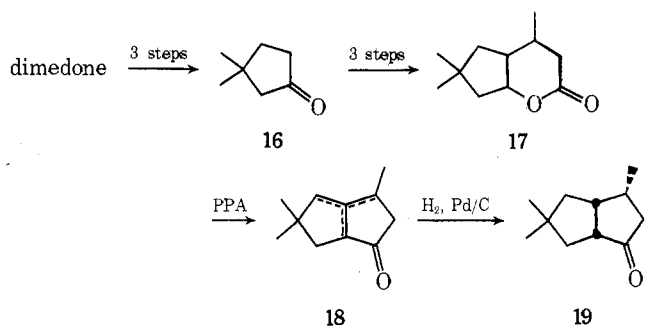


We now wish to report an efficient synthesis of the velleral skeleton with correct relative stereostructure. The present approach to a synthesis of the velleral derivative (**15a**), a potential precursor to velleral (**1**), vellerolactone (**2**), and possibly other members of the lactarane group terpenoids, was based on a firm control of the two major structural features of the velleral molecule: (a) the cis ring junction/trans methyl group, (b) the 1,3-diene unit with oxidized substituents in 2 and 3 positions.

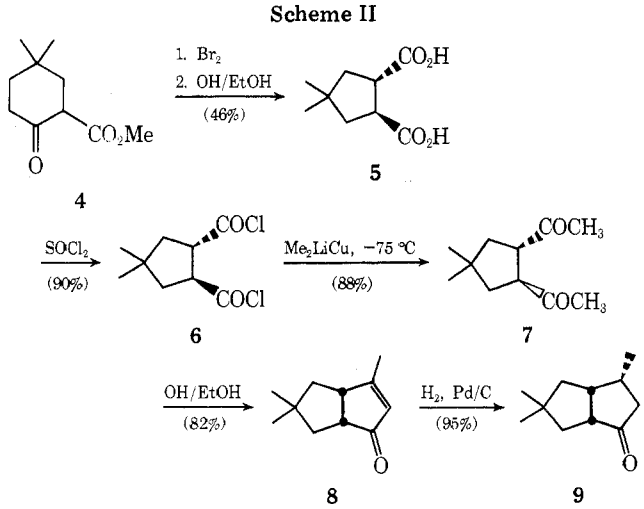
In order to meet the stereostructural requirements, attempts were made to prepare 4,7,7-trimethylbicyclo-[3.3.0]octen-2-one (**18**, mixture of isomers). Hydrogenation of the double bond would give a ketone (**9**) with correct relative configuration at the three epimeric carbon atoms. The lactone **17** would be a key substance in this route (Scheme I).

Lactone **17** was prepared by Michael addition of the pyrrolidine enamine of 3,3-dimethylcyclopentanone (**16**) to ethyl crotonate,[6] followed by borohydride reduction of the keto acid and ring closure. Ketone **16** was conveniently prepared in good yield from dimedone via the 2-azo derivative,[7] Wolff rearrangement,[8] and decarboxylation. However, attempted conversion of lactone **17** to mixtures of unsaturated ketones (**18**) by intramolecular acylation in strong acid media, e.g., polyphosphoric acid[9,10] or phosphorus pentoxide–methanesulfonic acid,[11] in our hands gave only low yields (<5%) of **18** and much polymeric material. An alternative route was therefore devised (Scheme II): 2-carbomethoxy-4,4-dimethylcyclohexanone (**4**)[12,13] was brominated; on treatment with alkali it underwent a Favorskii rearrangement giving 4,4-dimethylcyclopentane-*trans*-1,2-dicarboxylic acid (**5**). Bisalkylation of the diacid (**5**) with methyllithium in ether gave only a poor yield of the dimethyl ketone **7**, probably depending on low solubility of the dilithium salt (cf. ref 15). In an improved procedure the diacyl chloride (**6**) was treated with lithium dimethylcuprate at −75 °C for 20 min which gave **7** in 88% yield. To our knowledge this is the first successful preparation

Scheme I



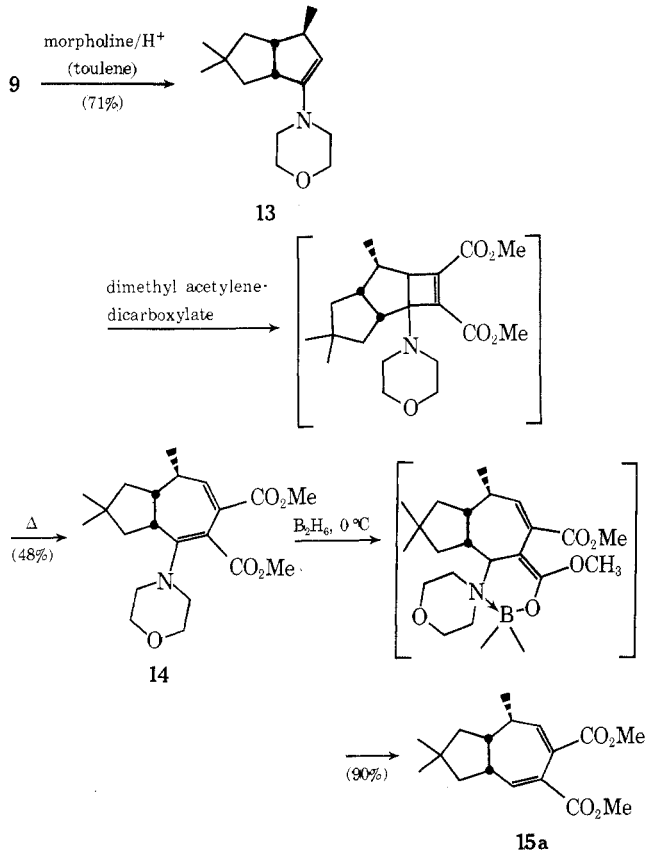
Scheme II



of bismethyl 1,4-diketones from 1,2-diacyl halides by this method.[14] Base-catalyzed intramolecular aldol condensation of the diketone (7) afforded 4,7,7-trimethylbicyclo[3.3.0]-oct-3-en-2-one (8). Compound 8 has been synthesized by Miyano et al.;[15] this synthesis is more laborious and longer and some of the earlier steps in the sequence are difficult to reproduce.[16] Catalytic hydrogenation of 8 gave 4,7,7-trimethylbicyclo[3.3.0]octan-2-one (9). GLC and ^{1}H NMR analysis showed a single product and stereochemical considerations suggested a selective attack of hydrogen from the convex side of 8, which should lead to the relative stereostructure 9. However, an independent, thorough stereostructural investigation of 9 was desirable and a computer analysis of the LIS of alcohol 11 was therefore carried out (vide infra).

The construction of the functionalized part of the velleral skeleton was based on the addition of an acetylene 1,2-diester to the enamine of cyclopentanone, forming a cyclobutene. These fused four-membered ring compounds easily undergo thermal electrocyclic ring opening to cyclohepta-1,3-dienes with ester functions in 2 and 3 positions.[17] Under carefully controlled conditions the morpholine enamine 13 was allowed to react with dimethyl acetylenedicarboxylate to give a cyclobutene derivative, which was not isolated. The crude product on refluxing in diglyme for 2 h rearranged to the crystalline dienamine 14 (Scheme III). The corresponding reaction with the enamine of pyrrolidine was found to be complex. This unexpectedly large difference between the morpholino and pyrrolidino derivatives must presumably be due to some subtle conformational effect.

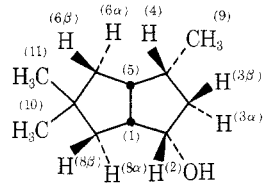
Scheme III



Removal of the nitrogen moiety was accomplished according to a recently developed method.[18] The dienamine 14 was reacted with diborane at 0 °C. Warming at room temperature gave the oily velleral derivative **15a**. The reaction apparently proceeds (cf. ref 18) via an unstable adduct (Scheme III) which decomposes on slight heating. In this postulated reaction mechanism the allylic positions in 14 and **15a** escape epimerization, which is a further considerable advantage over the obvious hydrolysis–reduction–elimination alternative. The velleral derivative **15a** gave spectral data with minor but relevant differences from data for the isomer **15b** synthesized earlier.[1a]

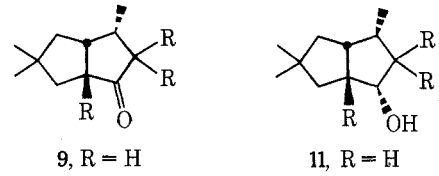
The stereostructure of ketone 9 could not be solved unambiguously with ordinary NMR techniques. The keto function was reduced with $LiAlH_4$ and ^{1}H NMR spectra were recorded of the alcohol 11 with $Eu(fod)_3$ added to the solution. Interpretation and assignment of the LIS experiment was made with the help of conformational analysis combined with decoupling experiments carried out on the alcohol 11 and on its trideuterated derivative 12 (Chart I). A comparison of the experimentally and theoretically induced shifts of the four possible isomers (Chart II) was made using the LISRIT computer program.[19] One isomer, I, gave a very good agreement factor[20] (R = 3.9%) and lanthanide–oxygen distance (r = 3.6 Å). The three remaining isomers either gave r values far outside reasonable limits or r values that allowed them to be rejected with high statistical significance[21] (>99.5%). Experimental and calculated chemical shifts for 11 (isomer I) are shown in Table I.

Table I. Eu(fod)$_3$-Induced and Calculated Proton Chemical Shifts of 11



Proton no.	Induced shift, Hz	
	Obsd	Calcd[19]
1	216	214
2	448	451
3α	256	265
3β	334	317
4	116	114
5	100	109
6α	122	109
6β	84	75
8α	329	334
8β	220	226
9	65	58
10	55	66
11	63	66

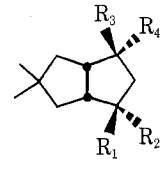
Chart I



9, R = H
10, R = D

11, R = H
12, R = D

Chart II



I, $R_1 = R_3 = H$; $R_2 = OH$; $R_4 = CH_3$
II, $R_2 = R_3 = H$; $R_1 = OH$; $R_4 = CH_3$
III, $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = CH_3$
IV, $R_2 = R_4 = H$; $R_1 = OH$; $R_3 = CH_3$

Experimental Section

NMR spectra were run on JEOL 60 and Xl-100 instruments in $CDCl_3$with Me_4Si as internal standard. Ir spectra were run as liquid films unless otherwise stated. Melting points are uncorrected.

4,4-Dimethylcyclopentane-*trans*-1,2-dicarboxylic acid (5) was prepared by the general procedure of Eisenbraun et al.:[22] yield 46%; mp 174–176 °C (lit.[15] 175–176 °C); ir ν 1700 (C=O), 1395, 1375 cm^{-1} (*gem*-CH_3); NMR acetone-d_6) δ 3.40–3.10 (m, 2), 1.90–1.60 (m, 4), 1.05 (s, 6).

4,4-Dimethylcyclopentane-*trans*-1,2-dicarboxylic Acid Chloride (6). The diacid (**5**, 31.5 g, 0.17 mol) was dissolved in benzene (600 ml) and pyridine (18 ml). Thionyl chloride (55 ml) was added and the mixture ws stirred (magnet) for 3 h. The bulk of the benzene ws evaporated and the residue was filtered, evaporated, and distilled, giving pure **6**: 34.0 g (90%); bp 74–75 °C (1 mm); $n^{23}D$ 1.4788; ir ν 1790 (C=O), 1395, 1375 cm^{-1} (*gem*-CH_3); NMR δ 3.95–3.60 (m, 2), 2.20–1.85 (m, 4), 1.05 (s, 6).

***trans*-1,2-Diacetyl-4,4-dimethylcyclopentane (7).** Methyllithium (0.42 mol) was added to cuprous iodide (39.9 g, 0.21 mol) in ether (200 ml) at −5 °C (magnet). The reaction mixture was cooled to −75 °C and the diacid chloride (**6**, 6.90 g, 30.6 mmol) was added dropwise. After 20 min, absolute methanol (30 ml) was added (vigorous stirring) at −75 °C. The reaction mixture was allowed to reach room temperature and was then poured into saturated ammonium chloride solution (500 ml). The ether phase was separated and the water phase extracted with ether (2 × 150 ml). The combined ether extracts were dried (Na_2SO_4), filtered, and evaporated, giving practically pure **7** (4.9 g, 88%). Distillatior gave an analytical sample: bp 99–100 °C (12 mm); $n^{23}D$ 1.4542; ir ν 1710 (C=O), 1390, 1370 cm^{-1} (*gem*-CH_3); NMR δ 3.65–3.25 (m, 2), 2.15 (s, 6), 2.00–1.40 (m, 4), 1.02 (s, 6); mass spectrum *m/e* (rel intensity) 182 (M^+, 4, $C_{11}H_{18}O_2$), 167 (4), 139 (99), 42 (100, base peak).

Anal. Calcd for $C_{11}H_{18}O_2$: mol wt, 182.1307. Found: mol wt 182.1329 (M^+).

4,7,7-Trimethylbicyclo[3.3.0]oct-3-en-2-one (8). The diketone (**7**, 4.1 g, 22.5 mmol) was dissolved in ethanolic sodium hydroxide (0.5 M, 20 ml) and the solution was refluxed for 4 h. The reaction mixture was cooled, evaporated, diluted with water, and extracted with ether. Drying of the ether phase (Na_2SO_4), filtration, evaporation, and distillation gave the ketone **8**: yield 3.0 g (82%); bp 115–116 °C (11 mm); $n^{23}D$ 1.4915; ir ν 3050 (=CH–), 1695 (C=O), 1620 (C=C), 1385, 1370 cm^{-1} (*gem*-CH_3); NMR δ 5.75 (broad s, 1), 2.10 (s, 3), 1.00 (s, 6).

Anal. Calcd for $C_{11}H_{16}O$: mol wt, 164.1201. Found: mol wt, 164.1209 (M^+).

4,7,7-Trimethylbicyclo[3.3.0]octan-2-one (9). The α,β-unsaturated ketone (**8**, 3.0 g) in absolute ethanol (50 ml) was hydrogenated (Pd/C, 300 mg, 760 mm, room temperature). Filtration and distillation gave the ketone **9**: yield 2.9 g (95%); bp 98 °C (12 mm); $n^{23}D$ 1.4633; ir ν 1735 (C=O), 1385, 1370 cm^{-1} (*gem*-CH_3); NMR δ 1.05 (d, 3, J = 6 Hz), 1.05 (s, 3). 0.95 (s, 3); mass spectrum *m/e* (rel intensity) 166 (M^+, 72, $C_{11}H_{18}O$), 151 (100, base peak), 136 (34).

Anal. Calcd for $C_{11}H_{18}O$: mol wt, 166.1358. Found: mol wt, 166.1350 (M^+).

4,7,7-Trimethyl-*1,3,3-d*$_3$-bicyclo[3.3.0]octan-2-one (10). The ketone (**9**, 0.5 mmol) was dissolved in deuteriomethanolic sodium methoxide (5 mg, 5 ml) and the solution was refluxed for 20 h. On working up this gave a practically pure **10** (NMR) which was used directly in the next step.

4,7,7-Trimethylbicyclo[3.3.0]octan-2-ol (11). The ketone (**9**, 166 mg, 1 mmol) in dry ether (10 ml) was added to a suspension of lithium aluminum hydride (125 mg, 3 mmol) in dry ether (15 ml) and refluxed for 2 h. Workup (potassium sodium tartrate solution) of the reaction mixture gave almost pure bicyclo alcohol (**9**), 120 mg, 72%). Sublimation (0.1 mm) gave an analytical sample: mp 63–65 °C; ir ν 3400 (OH), 1380, 1365 cm^{-1} (*gem*-CH_3); NMR δ 4.30–4.00 (m, 1), 2.90–2.37 (m, 2), 2.10–1.63 (m, 2 + OH), 1.50–1.14 (m, 5), 1.10 (s, 3), 0.92 (s, 3), 0.89 (d, 3, J = 6 Hz); mass spectrum *m/e* (rel intensity) 168 (M^+, 1, $C_{11}H_{20}O$), 150 (23), 135 (42), 124 (66), 109 (81), 95 (100, base peak).

Anal. Calcd for $C_{11}H_{20}O$: mol wt, 168.1514. Found: mol wt, 168.1519 (M^+).

4,7,7-Trimethyl-*1,3,3-d*$_3$-bicyclo[3.3.0]octan-2-ol (12) was prepared from **10** as above: NMR δ 4.13 (broad s, 1), 2.70–2.40 (m, 1), 2.04–1.75 (m, 1 + OH), 1.37–1.14 (m, 4), 1.10 (s, 3), 0.92 (s, 3), 0.89 (d, 3, J = 6 Hz); mass spectrum *m/e* (rel intensity) 171 (M^+, 1, $C_{11}H_{17}D_3O$), 153 (24), 138 (35), 125 (57), 110 (98), 96 (100, base peak).

Anal. Calcd for $C_{11}H_{17}D_3O$: mol wt, 171.1700. Found: mol wt, 171.1713 (M^+).

2-(*N*-Morpholino)-4,7,7-trimethylbicyclo[3.3.0]oct-2-ene (13). The ketone (**9**, 0.74 g), morpholine (1.10 g), and *p*-toluenesulfonic acid (ca. 1 mg) were dissolved in toluene and refluxed in a Soxhlet apparatus (linde 3A molecular sieve) for 6 h. Evaporation of the toluene and distillation gave the morpholine enamine (**13**): yield 0.74 g (71%); bp 89–90 °C (0.2 mm); ir ν 3070 (=CH–), 1640 (C=CN), 1390, 1375, cm^{-1} (*gem*-CH_3); NMR δ 4.05 (broad s, 1), 3.60 (t, 4, J = 7 Hz), 1.10 (s, 3), 0.95 (s, 3), 0.93 (d, 3, J = 6 Hz); mass spectrum *m/e* (rel intensity) 235 (M^+, 2, $C_{15}H_{25}NO$), 220 (10), 166 (16), 151 (22), 69 (100, base peak).

Anal. Calcd for $C_{15}H_{25}NO$: mol wt, 235.1936. Found: mol wt, 235.1944 (M^+).

8-(*N*-Morpholino)-2,2,4-trimethyl-1,3,4*H*-6,7-bis(methoxycarbonyl)azulene (14). Dimethyl acetylenedicarboxylate (440 mg) in dry toluene (20 ml) was added very slowly under nitrogen to a solution of freshly distilled **13** (740 mg) and hydroquinone (ca. 0.1 mg) in dry toluene (6 ml). After evaporation, the oily residue was refluxed in diglyme for 2 h. Solvent removal and trituration of the residue with cold ether gave crystalline **14**. Recrystallization from hexane gave pure **14**: yield 570 mg (48%); mp 164.0–164.5 °C; ir (KBr) ν 1720–1700 (s), 1620 (m), 1555 (s), 1380, 1360 cm^{-1} (*gem*-CH_3); NMR δ 6.70 (d, 1, J = 7 Hz), 3.72 (s, 3), 3.65 (s, 3), 1.03 (d, 3, J = 6 Hz), 1.03 (s, 3), 0.93 (s, 3); mass spectrum *m/e* (rel intensity) 377 (M^+, 50, $C_{21}H_{31}O_5N$), 362 (39), 318 (100, base peak).

Anal. Calcd for $C_{21}H_{31}O_5N$: mol wt, 377.2202. Found: mol wt, 377.2212 (M^+).

2,2,4-Trimethyl-1,3,4*H*-6,7-bis(methoxycarbonyl)azulene (15a) was prepared by diborane reduction of **14** as previously described.[18] Column chromatography (SiO_2, EtOAc/hexane, 1/1) gave **15a** (90%): ir ν 1730 (C=O), 1635, 1590, 1385, 1370 cm^{-1} (*gem*-CH_3); NMR δ 7.60 (d, 1, J = 8.7 Hz), 7.00 (d, 1, J = 6.0 Hz), 3.75 (s, 6), 1.07 (d, 3, J = 6 Hz), 1.00 (s, 3), 0.92 (s, 3); mass spectrum *m/e* (rel intensity) 292 (M^+, 19, $C_{17}H_{24}O_4$), 260 (100, base peak).

Anal. Calcd for $C_{17}H_{24}O_4$: mol wt, 292.1675. Found: mol wt, 292.1713 (M^+).

Acknowledgments. We thank Professor B. Wickberg for stimulating discussions, Dr. P. Stilbs for guidance in computer calculations, Dr. T. Drakenberg for running NMR spectra, and Dr. B. Thomas for linguistic criticism. This work was in part supported by the Swedish Natural Science Research Council.

Registry No.—5, 60064-68-8; **6,** 60064-69-9; **7,** 60064-70-2; **8,** 60064-71-3; **9,** 60064-73-5; **10,** 60064-72-4; **11,** 60064-74-6; **12,** 60064-75-7; **13,** 60064-76-8; **14,** 60064-77-9; **15a,** 60064-78-0; morpholine, 110-91-8; dimethyl acetylenedicarboxylate, 762-42-5.

References and Notes

(1) (a) Part IX: J. Froborg, G. Magnusson, and S. Thorén, *J. Org. Chem.*, **40**, 1595 (1975). (b) Presented in part at VI Conference on Isoprenoids, Torun, Poland, Sept 1975.
(2) The present numbering of the lactarane skeleton was suggested by Professor Sukh Dev.
(3) G. Magnusson et al., *Acta Chem. Scand., Ser. B*, **28**, 841 (1974).
(4) W. Daniewski, M. Kocór, and J. Król, personal communications (in press).
(5) E. Baranowska and W. Daniewski, *Bull. Acad. Pol. Sci., Ser. Chim.*, **20**, 313 (1972).
(6) G. Stork et al., *J. Am. Chem. Soc.*, **85**, 207 (1963).
(7) M. Regitz et al., *Org. Synth.*, **48**, 36 (1972).
(8) I. K. Korobitsyna and V. A. Nikolaev, *J. Org. Chem. USSR (Engl. Transl.)*, **7**, 411 (1974).
(9) S. Dev and C. Rai, *J. Indian Chem. Soc.*, **34**, 266 (1957).
(10) S. B. Kulkarni and S. Dev, *Tetrahedron*, **24**, 553 (1968).
(11) P. E. Eaton et al., *J. Org. Chem.*, **38**, 4071 (1973).
(12) Y. Chan and W. W. Epstein, *Org. Synth.*, **53**, 48 (1974).
(13) J. Froborg, G. Magnusson, and S. Thorén, *J. Org. Chem.*, **39**, 848 (1974).
(14) G. Posner et al., *J. Am. Chem. Soc.*, **94**, 5106 (1972).
(15) K. Miyano et al., *Tetrahedron Lett.*, 1545 (1974).
(16) Experiments in our laboratory to prepare the dibromide **2** (cf. ref 15) under the conditions reported were unsuccessful, as the corresponding diol formed adducts with acetic acid, which were not investigated further.
(17) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963).
(18) J. Froborg, G. Magnusson, and S. Thorén, *Tetrahedron Lett.*, 1621 (1975).
(19) P. Stilbs, *Chem. Scr.*, **7**, 59 (1975).
(20) R. E. Davis, M. R. Willcott, and R. E. Lenkinski, *J. Am. Chem. Soc.*, **94**, 1744 (1972).
(21) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).
(22) E. J. Eisenbraun et al., *J. Org. Chem.*, **32**, 3010 (1967).