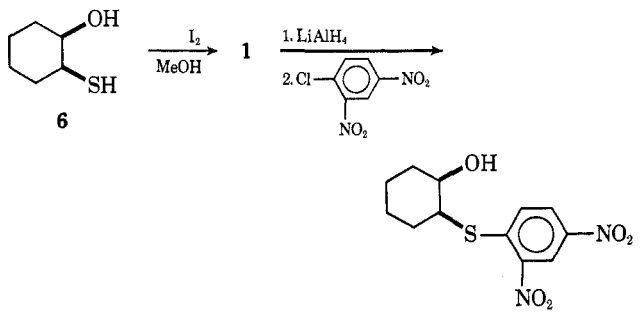
Oxidation of the known[7] *cis*-2-mercaptocyclohexanol (**6**) with iodine gave the cis,cis disulfide **1** melting at 85–88°. The molecular weight of the disulfide **1** was determined by mass spectrometry to be 262. The nonidentity of this material with the disulfide **2** was verified by depression of the mixture melting point and nonsuperposable ir and nmr spectra. The disulfide **1** was converted by reduction and derivatization to the known[7] *cis*-2-hydroxycyclohexyl 2,4-dinitrophenyl sulfide (**7**).



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It is of interest to note that the nmr spectrum of the cis,cis disulfide **1** shows the C-1 carbinyl proton as a multiplet centered at τ 5.95 and appearing 0.50 ppm downfield from the corresponding carbinyl proton of the trans,trans disulfide **2**. This data establishes[8] that the hydroxyl group is axial and the disulfide group is equatorial in the disulfide **1**, while both function groups, as expected, are equatorial in the disulfide **2**.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared spectra were obtained with Beckman IR-8 and IR-20A spectrophotometers. The nmr spectra were recorded at 60 MHz on a Varian A-60 spectrometer. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Solvents were removed *in vacuo* on a Buchler rotary evaporator.

trans,trans-**Bis(2-hydroxycyclohexyl) Trisulfide (3).**—A modified procedure for the preparation of trisulfides reported by Vineyard[3] was employed. *trans*-2-Mercaptocyclohexanol (**4**,[6] 14.9 g, 0.113 mol) was stirred with 0.5 ml of *n*-butylamine at room temperature. Recrystallized sulfur (2.5 g, 0.078 mol) was added over a 1-hr period after which the reaction mixture was stirred overnight. Benzene was added to the mixture and any solid material present was removed by filtration. The organic phase was washed with water, 6 *N* hydrochloric acid, 6 *N* sodium hydroxide, and water. After the mixture was dried over magnesium sulfate, the solvent was removed *in vacuo* to yield an oil. White crystals (2.0 g, 14%) were deposited from a solution of the oil in benzene–ligroin (bp 60–90°), mp 156–157° (lit.[4] 157–158°). This material was identical (mixture melting point, ir, nmr, mass spectrum) with material prepared following Mousseron's procedure:[2] ir (KBr) 3280 cm^{-1} (OH); nmr (DMSO-d_6) τ 5.15–5.34 (d, 2 H, OH), 6.35–6.91 (m, 2 H, CHOH), 7.05–7.65 (m, 2 H, CHS), and 7.70–9.20 (m, 16 H, methylene); molecular ion, *m/e* 294.

Anal. Calcd for $C_{12}H_{22}O_2S_3$ (294.5): C, 48.9; H, 7.53; S, 32.7. Found: C, 48.8; H, 7.66; S, 32.4.

The trisulfide **3** was reduced with lithium aluminum hydride in ether to give, as previously reported,[5] *trans*-2-mercaptocyclohexanol (**4**) in 40% yield: bp 95–97° (15 mm) [lit.[6] bp 100° (18 mm)]. The 2,4-dinitrophenyl thio ether of **4** was prepared[9] in a yield of 56%, mp 133–134° (lit.[4,6,7] mp 135°).

trans,trans-**Bis(2-hydroxycyclohexyl) Disulfide (2).**—To 4.4 g (0.033 mol) of *trans*-2-mercaptocyclohexanol (**4**), prepared according to Culvenor, *et al.*,[6] was added dropwise a solution containing 5.0 g of iodine/100 ml of methanol until a permanent brown color was obtained, following which the reaction mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium bisulfite was added dropwise until a colorless mixture resulted. The methanol was evaporated *in vacuo* and the remaining aqueous phase was extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated *in vacuo* to yield a pale yellow oil. The oil was taken up in hot ethyl acetate–*n*-hexane, whereupon a white solid crystallized upon cooling. The solid (2.4 g, 55%) was collected by filtration and air-dried: mp 83–84°; ir ($CHCl_3$) 3400 (OH), no absorption at 2500–2600 cm^{-1} (no SH); nmr ($CDCl_3$) τ 6.15–6.70 (m, 4 H, CHOH), 6.90–7.50 (m, 2 H, –CHS–), and 7.60–8.80 (m, 16 H, methylene); molecular ion, *m/e* 262.

Anal. Calcd for $C_{12}H_{22}O_2S_2$ (262.4): C, 54.9; H, 8.45; S, 24.4. Found: C, 54.8; H, 8.43; S, 24.2.

The disulfide **2** was reduced[5] with lithium aluminum hydride in ether to the trans compound **4**, which was characterized as the 2,4-dinitrophenyl thio ether derivative **5**,[9] mp 133–134° (lit.[4,6,7] mp 135°).

cis,cis-**Bis(2-hydroxycyclohexyl) Disulfide (1).**—*cis*-2-Mercaptocyclohexanol (**6**, 18.6 g, 0.14 mol), prepared according to procedure of Behringer and Kley,[7] was treated with iodine in methanol as was done in the preparation of the disulfide **2**. The pale yellow oil obtained was eluted through a silica gel column using benzene followed by chloroform. A small amount of white crystals formed within the oil; these crystals were collected and used as seed crystals in the subsequent recrystallization of **1**. The remaining oil was dissolved in hot ethyl acetate, to which ligroin (bp 60–90°) was added to the cloud point. After the solution was cooled to room temperature and seeded, white crystals of **1** were slowly deposited. The crystals were collected by filtration and air-dried (3.0 g, 18%): mp 82–85°; ir 3550 (OH), no absorption at 2500–2600 cm^{-1} (no SH); nmr ($CDCl_3$) τ 5.8–6.1 (m, 2 H, CHOH), 6.9–7.2 (m, 2 H, –CHS–), 7.58 (s, 2 H, OH), 7.9–8.9 (m, 16 H, methylene); molecular ion, *m/e* 262; with **2**, mmp 73–85°.

An analytical sample was prepared by recrystallization from ethyl acetate–ligroin (bp 60–90°), mp 85–88°.

Anal. Calcd for $C_{12}H_{22}O_2S_2$ (262.4): C, 54.9; H, 8.45. Found: C, 54.9; H, 8.60.

Reduction of the disulfide **1** with lithium aluminum hydride following the procedure reported[5] for the trans disulfide gave *cis*-2-mercaptocyclohexanol (**6**), as established by comparison of infrared spectra, in a yield of 70%. Following a previously reported procedure,[7] **6** was converted to *cis*-2-hydroxycyclohexyl 2,4-dinitrophenyl sulfide (**7**) in a yield of 33%, mp 141–143° (lit.[7] mp 143°).

Registry No.—**1**, 27040-92-2; **2**, 27040-93-3; **3**, 27040-94-4.

Acknowledgment.—Partial support is acknowledged to the U. S. Public Health Service, National Cancer Institute, Grant No. CA 10653.

(8) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 117.

(9) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed, Interscience, New York, N. Y., p 532, 1957.

Hydroformylation of 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose

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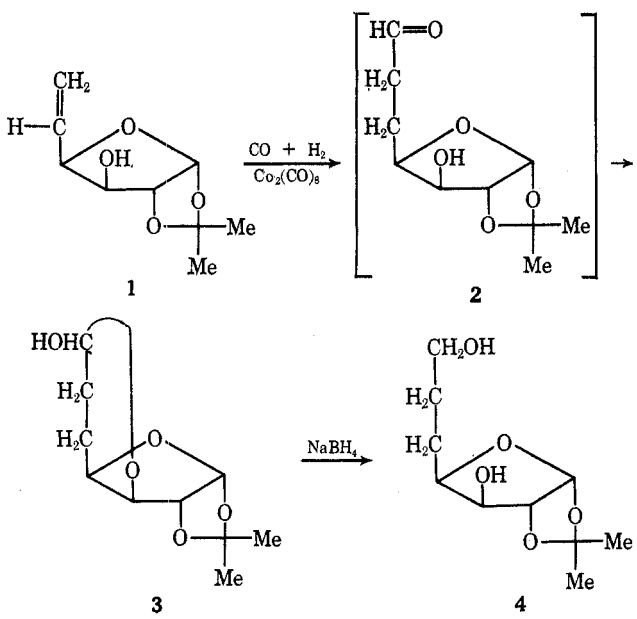
Hydroformylation of unsaturated sugar derivatives has posed a problem of great difficulty.[1] This difficulty

(1) (a) A. Rosenthal and D. Abson, *J. Amer. Chem. Soc.*, **86**, 5356 (1964). (b) A. Rosenthal, D. Abson, T. D. Field, H. J. Koch, and R. E. J. Mitchell, *Can. J. Chem.*, **45**, 1525 (1967); A. Rosenthal, *Advan. Carbohyd. Chem.*, **23**, 59 (1968).

arises from the fact that the initial products, namely the anhydrodeoxyaldoses, subsequently undergo hydrogenation to afford anhydrodeoxyalditols. In this communication we present a novel approach to this problem by designing a starting material having a free hydroxyl on a carbon atom of the ring which is subsequently capable of cyclizing with the *aldehydo* group to form a hemiacetal and thus possibly prevent the hydrogenation stage of the oxo reaction.

When 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**1**)[2] was allowed to react with carbon monoxide and hydrogen in the presence of preformed dicobalt octacarbonyl at 105° for 45 min, a mixture of three main components and traces of two additional compounds was obtained. The major component **3**, isolated in 51% yield, crystallized from the reaction mixture; ether–petroleum ether was used as solvent. The nuclear magnetic resonance (nmr) spectrum of **3**,



when compared with the spectra of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose and various 6-deoxyhexose derivatives,[3] conclusively shows that the formyl group is attached to position 6. If the hydroformylation had proceeded in such a manner as to add the formyl group at C-5 yielding a 6-deoxy derivative, the protons at C-6 would have appeared as a doublet at about τ 8.9. Instead, the 5,6-dideoxy protons of **3** gave a multiplet equal to four protons at τ 7.8–8.6. The nmr of **3** showed the absence of a formyl hydrogen and showed the presence of two hemiacetal hydrogens at τ 4.82 and 5.32 assigned to H-7e and H-7a, respectively.[1,4] Irradiation of either of these signals altered the signals at τ 7.8–8.6. Presumably, the free aldehyde group of the hydroformylation product **2** immediately cyclized with the free hydroxyl group on C-3 to give an α,β mixture of anomers possessing the tricyclic structure **3**. Further proof that **3** was a dialdose was provided by converting it into a crystalline phenylhydrazone derivative which possessed an isopropylidene group on C-1 and C-2. Reduction of **3** with sodium borohydride gave an aldose derivative with retention of the isopropylidene group. This new aldose had the same R_f as one of the minor components present in the hydroformylation product mixture. Presumably, the dialdose **2** underwent partial reduction during the hydroformylation reaction. The remaining products of the hydroformylation reaction could not be separated into pure compounds.

In order to study the effect of the free hydroxyl on C-3 of **1** in controlling the hydroformylation reaction compound **1** was converted into its 3-*O*-acetate derivative. The latter was then subjected to an oxo reaction. Surprisingly, a very complex mixture of products was obtained which could not be separated by chromatography. The unblocked oxo product mixture also could not be separated by paper chromatography.

(2) (a) H. Ohle and E. Dickhäuser, *Ber.* **58**, 2593 (1925); (b) J. K. N. Jones, and J. L. Thompson, *Can. J. Chem.*, **35**, 955 (1957); (c) L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, 1537 (1961); (d) D. Horton and W. N. Turner, *Tetrahedron Lett.*, 2531 (1964); (e) D. Horton and W. N. Turner, *Carbohyd. Res.*, **1**, 444 (1966).

(3) M. L. Wolfrom, K. Matsuda, F. Komitsky, Jr., and T. E. Whiteley, *J. Org. Chem.*, **28**, 3551 (1963), and references therein.

(4) P. W. K. Woo, H. W. Dion, and L. F. Johnson, *J. Amer. Chem. Soc.*, **84**, 1066 (1962).

Experimental Section

General Considerations.—Nmr spectra were obtained in deuteriochloroform solution (unless otherwise stated) with tetramethylsilane as the internal standard (set at τ 10) using a Varian A-60 spectrometer.[5] Mass spectra were obtained with an AEI MS9 spectrometer. All melting points (micro hot stage) are corrected. Silica gel G was used in the tlc with methyl ethyl ketone–water azeotrope as developer. Elemental analyses were performed by the Microanalytical Laboratory, University of British Columbia.

Hydroformylation of 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (1) to Yield 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose-α,β-D-7,3-pyranose (3).—A solution of compound **1** (1.40 g) and dicobalt octacarbonyl (0.30 g) in dry purified benzene (50 ml) was shaken with carbon monoxide (1100 psi) and hydrogen (1100 psi) in a high-pressure autoclave at a temperature of 105° for 45 min. The reaction mixture was transferred to a beaker and heated at 60–70° to decompose the catalyst. The reaction mixture was added to a short column of Celite–Norit and eluted with 99:1 benzene–ethanol. Evaporation of the eluent gave a syrup which was crystallized several times from ether–petroleum ether, bp 35–60°, to afford 0.82 g of the major compound **3** in 51% yield: mp 103–104°; $[\alpha]^{24}D$ +18° (*c* 1, water) which changed to +36° after 1.5 hr; R_f 0.81; nmr τ^{CDCl_3} 4.1 (t, H-1), 4.82 (t, H-7e), 5.32 (t, H-7a), 5.53 (overlapping peaks, H-2), 5.8 (s, H-3), 5.9 (m, H-4), 6.6 (broad peak, OH), 7.8–8.6 (m, equal to 4 hydrogens, assigned to H-5,6), 8.5, 8.7 (CMe_2). Irradiation at τ 4.82 and 5.32 altered the signals at τ 7.8–8.6.

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.60; H, 7.40; mol wt, 216. Found: C, 55.55; H, 7.10; *m/e* 201 [the base peak in the mass spectrum is at $M^+ - 15$ (loss of CH_3)].

The mother liquor consisted of a mixture of components one of which was the reduced compound **4** (about 5%). The remaining components could not be separated by chromatography.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose Phenylhydrazone.—To a solution of the sugar **3** (0.090 g) in 1 drop of water was added 4 drops of a solution of phenylhydrazine hydrochloride (0.20 g) in water (3 ml) containing sodium acetate (0.30 g). The reaction mixture was warmed on a steam bath for 1 min and then cooled in an ice–water bath to afford the crystalline phenylhydrazone derivative (0.056 g), in 49% yield: mp 146–149°; $[\alpha]^{24}D$ −32° (*c* 0.7, chloroform).

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.74; H, 7.18; N, 9.10. Found: C, 62.82; H, 7.25; N, 8.92.

7-*O*-Acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose-α,β-D-7,3-pyranose.—Compound **3** (0.040 g) was acetylated with acetic anhydride and pyridine at 0° under the usual conditions for 48 hr. After the pyridine and acetic anhydride were evaporated under reduced pressure, the product was passed through a short column of silica gel using ethyl ether as eluent to afford 0.032 g (60%) of a syrup, $[\alpha]^{24}D$ +54° (*c* 3,

(5) s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

chloroform). The product consisted of both α and β anomers as evidenced by tlc and nmr: τ^{CDCl_3} 3.95 and 4.45 (m, assigned to H-7e and H-7a), 4.15 (t, H-1), 5.30 (t, H-2), 8.20 (m, equal to four hydrogens on C-5 and C-6); the mixture could not be separated by tlc.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hepto-1,4-furanose (4).—Compound **3** (0.045 g) in methanol (20 ml) was reduced with sodium borohydride at 0° for 24 hr. After the reaction mixture was neutralized with acetic acid (2 ml), water (10 ml) was added and the mixture then passed consecutively through columns of Amberlite IR-120 (H^+) and Dowex A-4 (OH^-). The eluent was evaporated to dryness and benzene–ethanol was distilled from the syrup (0.035 g, 75%): $[\alpha]^{24}D$ +2° (*c* 2, ethanol); R_f 0.46; nmr τ^{D_2O} 6.25 (t, H-7), 8.10 (m, equal to 4 hydrogens, assigned to hydrogens on C-5 and C-6). Compound **4** had the same R_f as one of the components of the hydroformylation product mixture.

Reaction of 3-*O*-Acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose with Carbon Monoxide and Hydrogen.—The 3-*O*-acetate derivative of 1 was subjected to the usual oxo conditions[1] at 135° for 2 hr. The oxo product mixture could not be separated by chromatography. An aliquot of the oxo mixture was deacetylated with methanolic sodium methoxide and then deisopropylidenated[3] with Amberlite IR-120 (H^+) to yield a very complex mixture of free sugars which could not be separated by paper chromatography using 4:1:5 butanol–ethanol–water as developer.

Registry No.—**3** (7*R*), 27039-90-3; **3** (7*S*), 26988-37-4; **3** phenylhydrazone, 26988-64-7; **4**, 26988-65-8; 7-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose-α-D-7,3-pyranose, 26988-66-9; 7-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose-β-D-7,3-pyranose, 26988-67-0.

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The Stereoselective Total Synthesis of Racemic Nootkatone

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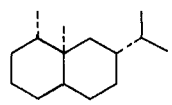
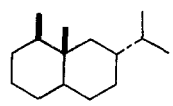
Considerable effort has been devoted over the past decade to the exploration of potential synthetic routes to compounds in the eremophilane–valencane family of sesquiterpenes.[1,2] A major problem in this connection has been the stereochemical control of the vicinal methyl groupings which characterize the members of this family. Several years ago we devised a straightforward solution to this problem based upon the stereoselective condensation of cyclohexanone derivatives with *trans*-3-penten-2-one.[1c] This report describes our application of that synthetic concept to the total synthesis of nootkatone (**11**), a sesquiterpene constituent of citrus fruit.[3]

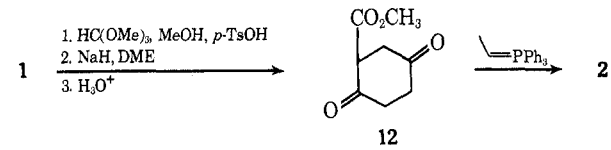


eremophilane skeleton



valencane skeleton

The requisite starting material for our synthesis, keto ester **2**, could be obtained directly in one step by treatment of dimethyl γ-ketopimelate (**1**)[4] with ethylidenetriphenylphosphorane in dimethyl sulfoxide (DMSO).[5] Evidently the basic reaction medium promotes Dieckmann cyclization of the γ-ketopimelate either prior to Wittig condensation or as a subsequent step. The unsaturated keto ester **2** could also be prepared through reaction of the diketo ester **12** with the ethylidene phosphorane in DMSO. Keto ester **12** was readily obtained from dimethyl γ-ketopimelate (**1**) *via* ketal formation, Dieckmann cyclization, and hydrolysis. This latter route to the keto ester **2**, though longer than the direct condensation–cyclization scheme, proceeded in higher overall yield.



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The stereochemically critical step of the synthesis, condensation of keto ester **2** with *trans*-3-penten-2-one, was effected in *tert*-amyl alcohol with potassium *tert*-amylate as the base. Aldol cyclization of the resulting Michael addition product in methanolic sodium methoxide then gave the bicyclic keto ester **3**, a 3:1 mixture of cis and trans CH_3, CO_2CH_3 isomers, and a 1:1 mixture of *Z* and *E*[6] double bond isomers according to the nmr spectrum. These conditions for the Michael–aldol sequence were selected on the basis of studies on related condensations.[1c,7] The desired cis isomer **3** could be readily separated from the mixture and purified through crystallization. Material thus secured still contained the *Z* and *E* double bond isomers[6] in nearly equal amounts.

Epoxidation of the ethylidene grouping of the dienone ester **3** followed by boron trifluoride etherate promoted rearrangement[8] of the resulting epoxide mixture (syn, anti, and α,β stereoisomers) led to a 2:1 mixture of

(1) (a) D. Herbst and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 4337 (1960); (b) R. F. Church, R. E. Ireland, and D. R. Shridhar, *J. Org. Chem.*, **27**, 707 (1962); (c) J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *Chem. Commun.*, 753 (1967); (d) R. M. Coates and J. E. Shaw, *ibid.*, 47 (1968); (e) R. M. Coates and J. E. Shaw, *ibid.*, 515 (1968); (f) C. Berger, M. Franck-Neumann, and G. Ourisson, *Tetrahedron Lett.*, 3451 (1968); (g) E. Piers and R. J. Keziere, *ibid.*, 583 (1968); (h) R. M. Coates and J. E. Shaw, *ibid.*, 5405 (1968); (i) S. Murayama, D. Chan, and M. Brown, *ibid.*, 3715 (1968); (j) H. Roebke, "Addition of Organocopper Reagents to Conjugated Ketones," Ph.D. Thesis, Northwestern University, 1968; (k) E. Piers, R. W. Britton, and W. Dewaal, *Can. J. Chem.*, **47**, 4307 (1969).

(2) Total syntheses of nootkatone have recently been reported by two groups: M. Pesaro, G. Bozatto, and P. Schudel, *Chem. Commun.*, 1152 (1968); H. C. Odom and A. R. Pinder, *ibid.*, 26 (1969). The approach used by the latter group is similar to that used in our synthesis of isonootkatone (ref 1c) except for the use of a 2-methylcyclohexanone rather than a 2-carbomethoxyl derivative in the stereochemically critical condensation with *trans*-2-penten-3-one. However, recent developments indicate that this step of the Odom–Pinder synthesis is markedly influenced by certain unknown experimental factors which drastically change the stereochemical outcome. The synthesis has therefore been retracted pending clarification of these factors: H. C. Odom, A. K. Torrence, and A. R. Pinder, "Synthetic Studies in the Eremophilane Sesquiterpene Group," presented at the Symposium on Synthesis and Substitutes for the Food Industry, American Chemical Society, Division of Agricultural and Food Chemistry, 158th National Meeting of the American Chemical Society, Sept 8-12, 1969, New York, N. Y., Abstract 48.

(3) W. D. Macleod, Jr., *Tetrahedron Lett.*, 4779 (1965).

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(5) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

(6) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *ibid.*, **90**, 509 (1968).

(7) T. M. Warne, Jr., "Total Synthesis of (±)-Isonootkatone," Ph.D. Thesis, Northwestern University, 1969.

(8) *Cf.* H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).