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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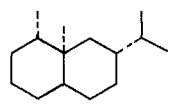
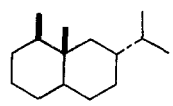
Considerable effort has been devoted over the past decade to the exploration of potential synthetic routes to compounds in the eremophilane–valencane family of sesquiterpenes.[1,2] A major problem in this connection has been the stereochemical control of the vicinal methyl groupings which characterize 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]

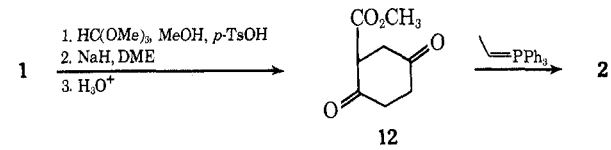


eremophilane skeleton



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.



12

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).

(4) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Amer. Chem. Soc.*, **74**, 1401 (1952).

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

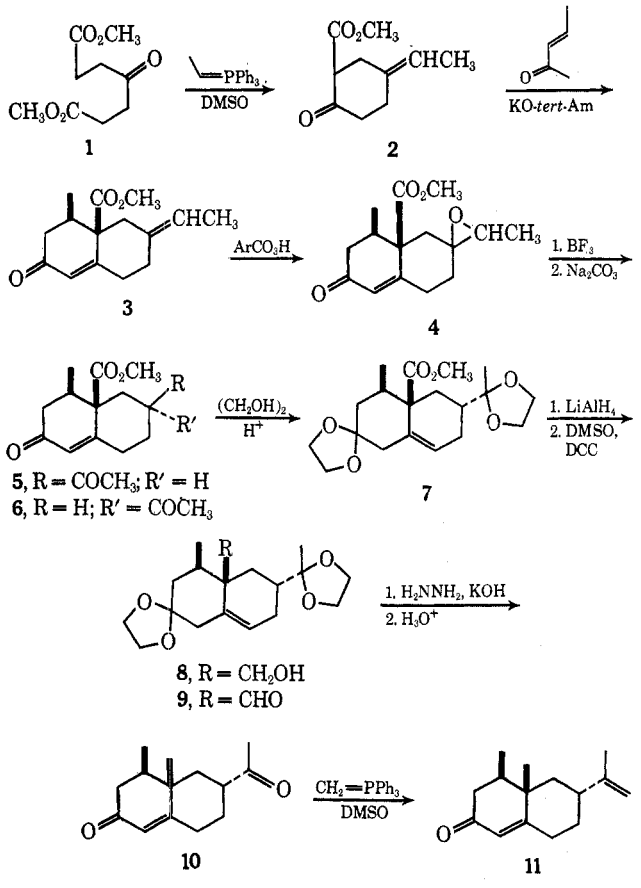
(6) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *ibid.*, **90**, 509 (1968).

(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).

β- and α-acetyl derivatives **5** and **6**. Assuming that the epoxide rearrangement proceeds with inversion of the oxirane-linked cyclohexane carbon, this finding indicates that a similar mixture of β- and α-epoxide stereoisomers must be produced upon epoxidation of olefin **3**. This result would not have been expected on the basis of steric considerations.

The less stable predominant β-acetyl isomer **5** could be isolated and purified by crystallization from the mixture. Basic treatment effected its conversion to the more stable α isomer **6**. Ketalization of this material then gave the bis-ketal derivative **7**. Attempts to convert the β-acetyl isomer **5** to ketal **7** directly were not successful. Only partial equilibration of the side chain could be realized and a mixture of stereoisomeric ketals resulted.



Reduction of the bis-ketal ester **7** with lithium aluminum hydride in ether and Moffatt oxidation[9] of the resulting alcohol **8** led to the aldehyde **9** in high overall yield. Wolff–Kishner reduction of this aldehyde and subsequent hydrolysis of the bis-ketal product afforded the dione **10**. Initially we examined a number of schemes of the type $CO_2CH_3 \rightarrow CH_2OH \rightarrow CH_2Y \rightarrow CH_3$ for effecting the methoxycarbonyl to methyl conversion in compounds related to keto ester **6**. In all cases the final step, reduction of the neopentyl sulfonic ester or halide by a variety of methods, gave little or none of the desired product.[7]

The final synthetic operation, conversion of the dione **10** to racemic nootkatone (**11**), was accomplished through a selective Wittig reaction using methylenetriphenylphosphorane in DMSO.[5] The spectral properties of material thus secured exactly matched those of authentic nootkatone.

(9) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).

Experimental Section[10]

Methyl 4-Ethylidene-2-oxocyclohexanecarboxylate (2). A. *Via* Condensation of Dimethyl γ-Ketopimelate with Ethylidenetriphenylphosphorane.—A solution of 2.00 g of dimethyl γ-ketopimelate (**1**)[4] in 22 ml of DMSO was added dropwise to a solution of ethylidenetriphenylphosphorane prepared from 9.20 g of triphenylethylphosphonium bromide and 1.01 g of 56% NaH dispersion, from which the mineral oil had been removed by pentane washing, in 94 ml of DMSO.[5,10a] The mixture was stirred at room temperature for 4 hr and the product was isolated *via* pentane extraction.[10b] Filtration through 10 g of silica gel with benzene and distillation of the filtrate afforded 0.71 g (40%) of keto ester **2**: bp 75° (bath temperature) (0.05 mm); $\delta_{TMS}^{CCl_4}$ 12.05 and 12.08 [enol OH (*Z* and *E* isomers)], 5.41 (vinyl CH, J = 6.2 Hz), 3.78 and 3.82 (CH_3O–), and 1.62 ppm (vinyl CH_3, J = 6.2 Hz).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.1; H, 7.7.

B. *Via* Diketo Ester 12.—A solution of 2.02 g of dimethyl γ-ketopimelate and 0.2 g of *p*-toluenesulfonic acid in 18.0 ml of trimethyl orthoformate and 12 ml of methanol was heated at 50° with stirring for 72 hr.[10a] The solution was poured into aqueous sodium bicarbonate and the product was isolated with ether[10b] affording 2.42 g (98%) of the ketal diester: bp 90° (0.10 mm); λ_{max}^{film} 5.75 μ; $\delta_{TMS}^{CCl_4}$ 3.58 (CO_2CH_3) and 3.08 ppm (OCH_3).

Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.0; H, 8.0.

A 1.98-g sample of the ketal in 20 ml of 1,2-dimethoxyethane was stirred with NaH (0.41 g of 57% oil dispersion washed with pentane to remove the oil) at 50° for 9 hr.[10a] Most of the solvent was removed under reduced pressure, the residue was acidified with ethereal acetic acid, and the product was isolated with ether[10b] affording 1.53 g (99%) of ketal keto ester: bp 112° (0.2 mm); λ_{max}^{film} 6.01 and 6.08 μ; $\delta_{TMS}^{CCl_4}$ 11.95 (enol H), 3.69 (CO_2CH_3), and 3.12 ppm (OCH_3).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.8; H, 7.6.

A 40-g sample of ketal keto ester comparable to that described above was stirred at room temperature for 12 hr with 250 ml of acetone, 35 ml of water, and 1 ml of concentrated HCl.[10a] The solution was concentrated under reduced pressure and the product was isolated with benzene[10b] affording 25.7 g (82%) of solid diketo ester **12**: mp 34–37°; λ_{max}^{KBr} 5.82, 6.01 and 6.15 μ; $\delta_{TMS}^{CCl_4}$ 12.10 (enol H) and 3.76 ppm (CO_2CH_3).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.7; H, 6.0.

To a solution of ethylidenetriphenylphosphorane, prepared as described above from 55 g of ethyltriphenylphosphonium bromide and 5.9 g of 57% NaH oil dispersion in 345 ml of DMSO, was added a solution of 10.0 g of diketo ester **12** in 100 ml of DMSO.[10a] The solution was stirred for 4 hr and the product was isolated with pentane[10b] affording 8.50 g (79%) of keto ester **2**, bp 75° (0.05 mm).

Condensation of Keto Ester 2 with *trans*-3-Penten-2-one.—To a solution of 2.00 g of keto ester **2** in 10 ml of KO-*tert*-Am in *tert*-AmOH (from 0.05 g of K) at −10° was added portionwise with stirring, 1.35 g of *trans*-3-penten-2-one.[10a] The solution was allowed to stand at 0° for 18 hr and the product was isolated with ether.[10b] The material thus obtained was treated with 10 ml of 2.3 *M* methanolic NaOMe at room temperature for 22 hr to effect aldol cyclization.[10a] Isolation *via* extraction with ether[10b] afforded 2.04 g (75%) of pale yellow solid keto ester **3** (a mixture of *Z* and *E* isomers): λ_{max}^{KBr} 5.80, 6.01 μ; $\delta_{TMS}^{CCl_4}$ 5.92 (vinylic CH), 5.35 (vinylic CH, quartet, J = 6.2 Hz), 3.71 (OCH_3), 1.60 and 1.70 ppm [vinylic CH_3 (*Z* and *E* isomers) doublet, J = 6.2 Hz].

Purification *via* short-path distillation, recrystallization from hexane, and, finally, sublimation gave material of mp 93–102°.

(10) (a) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132) was used to maintain a nitrogen atmosphere. (b) The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. (c) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.6; H, 8.2.

Conversion of the Dienone Ester 3 to the Enedione Ester 6.—A solution of 1.02 g of dienone ester **3** in 20 ml of DME and 10 ml of water was stirred at room temperature with 0.83 g of 97% *m*-chloroperoxybenzoic acid for 5 hr. The product was isolated with ether[10b] (10% KOH wash to remove acidic material) affording 1.02 g of crude epoxide **4**, a mixture of stereoisomers. This material was dissolved in 50 ml of benzene and 1.0 ml of boron trifluoride etherate was added *via* hypodermic syringe.[8,10a] After 1.5 min aqueous sodium bicarbonate was added, and the product was isolated with benzene[10a] to give 0.88 g (88%) of a colorless semisolid mixture of acetyl epimers **5** and **6** (2:1 according to the integrated nmr spectrum). The major isomer **5** was purified by recrystallization from hexane–ether to give a white solid: mp 148–148.5°; λ_{max}^{KBr} 5.80, 5.88, and 6.00 μ; $\delta_{TMS}^{CCl_4}$ 5.96 (vinylic CH), 3.62 (OCH_3), and 2.30 ppm (CH_3CO).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.0; H, 7.5.

A 0.44-g sample of the aforementioned 2:1 mixture of enediones **5** and **6** was stirred at room temperature with 25 ml of MeOH, 1 ml of water, and 0.03 g of sodium carbonate for 5 hr.[10a] Isolation with benzene[10b] afforded 0.44 g (99%) of oily enedione **6**: λ_{max}^{film} 5.78, 5.85, and 6.01 μ; $\delta_{TMS}^{CCl_4}$ 5.93 (vinylic CH), 3.73 (CH_3O), 2.17 (CH_3CO), and 0.98 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.4; H, 7.8.

Conversion of the Enedione Ester 6 to the Bis-Ketal Aldehyde 9.—A solution of 0.44 g of enedione ester **6** in 40 ml of benzene containing 6 ml of ethylene glycol and 0.13 g of *p*-toluenesulfonic acid was stirred at reflux with a Dean–Stark trap for 12 hr.[10a] Solid sodium bicarbonate was added and the product was isolated with benzene[10b] affording 0.58 g (95%) of bis-ketal ester **7**: λ_{max}^{film} 5.78 μ; $\delta_{TMS}^{CCl_4}$ 5.58 (vinylic CH), 3.82 ($-OCH_2CH_2O-$), 3.63 (CH_3O), 1.20 (CH_3), and 0.95 ppm (CH_3, unresolved doublet).

The above material in 50 ml of ether was treated with 0.50 g of lithium aluminum hydride and the mixture was stirred at reflux for 24 hr. Water (0.5 ml), 15% aqueous NaOH (0.5 ml), and water (1.5 ml) were added in turn, stirring was continued for 0.5 hr, and the mixture was filtered. Removal of ether under reduced pressure left 0.50 g (95%) of bis-ketal alcohol **8**: λ_{max}^{film} 3.0 and 9.51 μ; $\delta_{TMS}^{CDCl_3}$ 5.60 (vinyl H, unresolved triplet), 3.87 ($-OCH_2-CH_2O-$), 1.24 (CH_3), and 0.98 ppm (CH_3, unresolved doublet).

The above alcohol in 3 ml of DMSO was treated with 0.12 ml of pyridine, 0.06 ml of trifluoroacetic acid, and 0.94 g of dicyclohexylcarbodiimide in 3 ml of benzene.[9,10a] After stirring for 18 hr at room temperature, the mixture was poured into 25 ml of ethyl acetate, and a solution of 0.42 g of oxalic acid in 4 ml of MeOH was added. After 0.5 hr, the mixture was filtered and the filtrate was washed with water, aqueous sodium bicarbonate, and saturated brine and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure left 0.46 g (93%) of bis-ketal aldehyde **9**: λ_{max}^{film} 3.7 and 5.81 μ; $\delta_{TMS}^{CCl_4}$ 9.75 (CHO), 5.68 (vinyl H, unresolved triplet), 3.91 ($-OCH_2CH_2O-$), 1.27 (CH_3), and 1.10 ppm (CH_3, unresolved doublet).

Conversion of the Bis-Ketal Aldehyde 9 to the Enedione 10.—A solution of 0.46 g of bis-ketal aldehyde **9** in 25 ml of ethylene glycol and 3.5 ml of 85% hydrazine hydrate was heated at 120° with stirring for 1 hr.[10a] The solution was allowed to cool, 1.5 g of KOH was added, and the temperature was increased to 205° and maintained near that point for 2 hr. The solution was allowed to cool and the product isolated with ether.[10b] The resulting material in solution with 10 ml of acetone, 1 ml of water, and 3 drops of concentrated HCl was stirred at reflux for 1 hr.[10a] Extraction with benzene[10b] followed by short-path distillation at 130° (0.01 mm) afforded 0.24 g (78%) of pale yellow enedione. Further purification by preparative layer chromatography (silica gel) and short-path distillation yielded the analytical sample: λ_{max}^{film} 5.85 and 6.00 μ; $\delta_{TMS}^{CCl_4}$ 5.93 (vinylic CH), 2.07 (CH_3CO), 1.04 (angular CH_3), and 0.93 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{14}H_{20}O$: C, 76.33; H, 9.15. Found: C, 76.1; H, 9.3.

A solution of methylenetriphenylphosphorane was prepared as previously described from 0.48 g of NaH and 7.65 g of methyl triphenylphosphonium bromide in 40 ml of DMSO. A 2.60-ml sample was removed *via* syringe and added to 248 mg of enedione **10** in 2 ml of DMSO. The mixture was stirred at room temperature for 4 hr, and the product was isolated with pentane[10b] and chromatographed on silica gel to give 55 mg of (±)-nootkatone: mp 44–45°; λ_{max}^{film} 5.98 (CO), 6.16 (C=C), and 11.3 μ (C=CH_2); $\delta_{TMS}^{CCl_4}$ 5.60 (H-4), 4.66 (C=CH_2, doublet, J = 1 Hz), 1.66 (vinyl CH_3), 1.10 (angular CH_3), and 0.95 ppm (CH_3, doublet, J = 6 Hz). The spectral characteristics of the synthetic material were identical with those of the natural material.[3]

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.39; H, 10.16.

An early fraction amounting to 8 mg was obtained with hexane elution. This material exhibited spectral properties suggestive of the expected bis condensation product of dione **10**.

Registry No.—**1** dimethyl ketal, 27024-77-7; ketal keto ester [bp 112° (0.2 mm)], 27024-78-8; **2**, 27024-79-9; **3** (cis), 27024-80-2; **3** (trans), 27024-81-3; **5**, 27024-82-4; **6**, 27024-83-5; **7**, 27024-84-6; **8**, 27024-85-7; **9**, 27024-86-8; **10**, 27024-87-9; **11**, 20071-81-2; **12**, 27024-89-1.

Acknowledgment.—We are indebted to the National Institutes of Health for their support of this work through a research grant (5 R01 CA1 1089) and a predoctoral fellowship (1 F01 GM-41, 100). We thank Dr. R. E. Erickson, Givandan Corporation, Clifton, N. J., for a sample of natural nootkatone.

Lincomycin. XII.[1] The Preparation of Methyl *N*-Methyl-α-thiolincosaminide

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Cleavage of the antibiotic lincomycin in refluxing hydrazine hydrate led to the isolation of methyl 6-amino-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (methyl α-thiolincosaminide) (MTL) (**1**) in good yield.[2] Treatment of this sugar with triphenylphosphine dichloride afforded methyl 7(*S*)-chloro-7-deoxy-α-thiolincosaminide which when coupled with various 4-alkyl-L-prolines gave a series of potent antibacterial and antimalarial agents.[3] Further chemical transformations of methyl α-thiolincosaminide (**1**) to form methyl *N*-methyl-α-thiolincosaminide (**8**) and methyl *N*,*N*-dimethyl-α-thiolincosaminide (**2**) are now described.

Reductive alkylation of methyl α-thiolincosaminide (**1**) with excess formaldehyde readily formed *N*,*N*-dimethyl sugar **2**. In the presence of but 1 molar equiv of formaldehyde, reductive alkylation gave no evidence of the mono-*N*-methyl sugar **8**, but only a lowered yield of **2** and unreacted amino sugar **1**.

Examination by tlc (thin layer chromatography) of partially completed reductive alkylations revealed the presence of two new compounds both less polar than starting sugar **1** as well as *N*,*N*-dimethyl sugar **2**. These compounds could not be detected after further reduction. After separation by chromatography, the least polar of these intermediates was shown to be the initial condensation product of **1** with 2 mol of formaldehyde. This compound was assigned structure **3** on

(1) Previous paper in this sequence: R. D. Birkenmeyer and F. Kagan, *J. Med. Chem.*, **13**, 616 (1970).

(2) W. Schroeder, B. Bannister, and H. Hoeksema, *J. Amer. Chem. Soc.*, **89**, 2448 (1967).

(3) B. J. Magerlein and F. Kagan, *J. Med. Chem.*, **12**, 780 (1969).