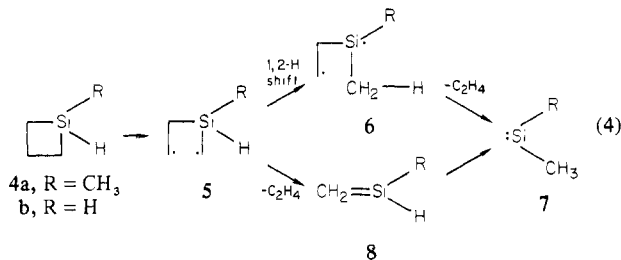


As pyrolysis temperatures were raised from 556 to 697 °C, the ratio of methylsilylene to silene products, 2:3, increased from 1.2 to 5.1. While the decrease in silene products and increase in methylsilylene products might be attributed to isomerization of silene to methylsilylene,¹⁰ it is also possible that the change in product ratios may originate from a branching step prior to silene formation (*vide infra*).

It is of interest to consider these results in light of the recent work of Barton and co-workers,¹¹ who demonstrated that 1-methylsilene, generated thermally at 450 °C from a methylsilabicyclooctadiene, adds to dienes in the typical Diels-Alder fashion. These authors suggested that formation of a methyl-substituted silylene from a hydridosilacyclobutane might be accommodated by the following sequence (eq 4): ring opening of



4 via C-C bond cleavage affords the 1,4-biradical 5, which isomerizes to the 1,3-biradical 6. Homolysis of another Si-C bond in 6 can account for a methylsilylene (7) and ethylene. The key step, a 1,2-hydrogen shift from silicon to carbon (5 → 6), is expected to be exothermic by roughly 8 kcal/mol.¹² If the barrier height for this hydrogen shift were less than the barrier for cleavage of the opposing silicon-carbon bond, a methylsilylene could be formed without intervention of a silene.

Although both reaction sequences 5 → 6 → 7 and 5 → 8 → 7 are reasonable pathways leading to methylsilylene, an analysis of the temperature dependence of methylsilylene to silene products ratios, 2:3, permits a distinction. The major decomposition pathway of 4 likely involves the 1,4-biradical 5. Subsequent isomerization to give the 1,3-biradical 6 or fragmentation to give the silene 8 would be expected to proceed with low and comparable activation energies.¹³ However, the activation entropy for the 1,2-H shift from 5 to 6 is likely to be significantly lower than the entropy of fragmentation to 8. Therefore, over the relatively large temperature range 556-697 °C, the change in relative rates of fragmentation to isomerization should be determined by entropy and favor the silene pathway. We observe the opposite, a considerable decrease in silene products and an increase in methylsilylene products. Consistent with our observation is the isomerization of silene to methylsilylene in the high-temperature range.

It is important to point out that the kinetic arguments presented here for rapid isomerization of silene to methylsilylene at these temperatures are not in conflict with the theoretical studies of Schaefer¹⁴ nor the experimental contributions of Barton.¹¹ Currently our efforts are directed toward elucidating the reversible reaction pathway between hydridosilenes and hydridosilacyclobutanes and measuring the activation barrier for the isomerization.¹⁵

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Acknowledgment. We gratefully acknowledge the Robert A. Welch Foundation, the North Texas State Faculty Research Fund, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No. 1, 7049-25-4; 2, 55544-25-7; 3, 84057-67-0; silacyclobutane, 287-29-6; 1,3-butadiene, 106-99-0.

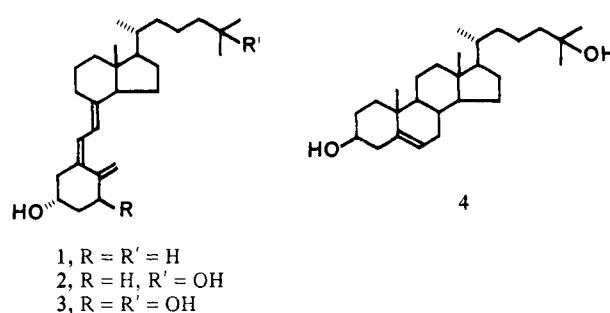
Partial Synthesis of (20R)-25-Hydroxycholesterol Involving a Nickel(II)-Promoted Dienol Rearrangement

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The recognition that 25-hydroxycholecalciferol (2) and



1α,25-dihydroxycholecalciferol (3) exhibit increased calcium transport, bone mineral mobilization, and calcification relative to vitamin D₃ (1) has generated interest in the synthesis of 25-hydroxy-substituted cholestanes. Considerable synthetic activity has focused on the partial synthesis¹ of (20R)-25-hydroxycholesterol (4), which has served as a progenitor of 2² and 3.³ We report a new partial synthesis of 4 from pregnenolone (5) that employs a new approach for assembling steroid side chains and relies on an intriguing dienol rearrangement to transform a C-20 hydroxy steroid to a C-25 hydroxy steroid.

We have investigated an approach to the cholestane side chain based on the sequential construction of the C-20,22 and C-24,25 bonds as summarized in Scheme I. Metalation of 1-(methylthio)-1-(trimethylsilyl)-2-propene (6) using *sec*-butyllithium (1.3

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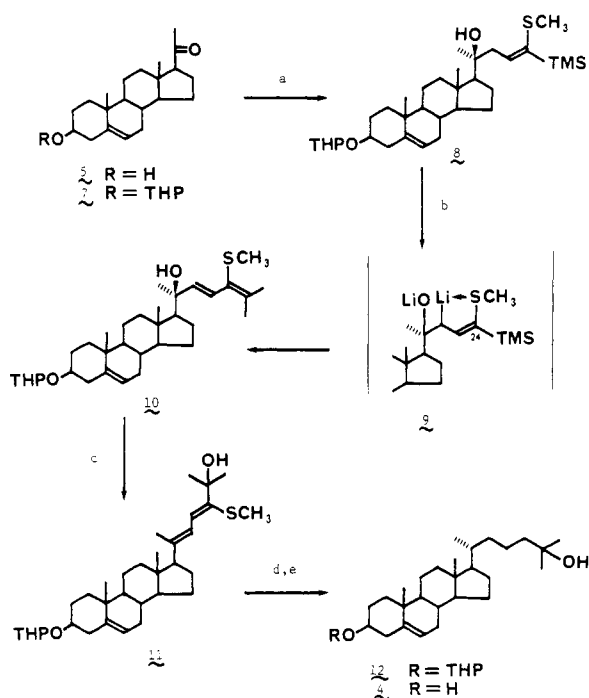
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(4) Compound 6 was prepared from allyl methyl thioether according to Kyler and Watt (Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1981**, *46*, 5182).

(5) All new compounds had satisfactory IR, NMR, and mass spectral and C, H combustion (or high-resolution mass spectral) data.

Scheme I

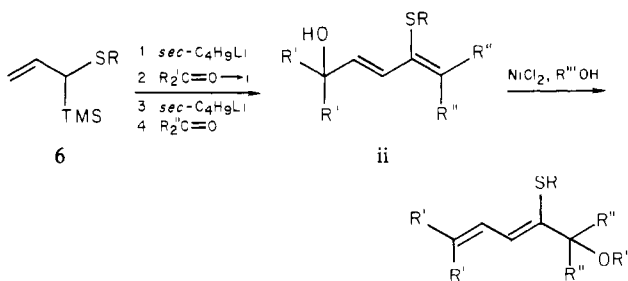


^a $\text{CH}_2=\text{CHCH}(\text{SCH}_3)\text{Si}(\text{CH}_3)_3$ (6), *sec*-C₄H₉Li. ^b *sec*-C₄H₉Li followed by acetone; ^c NiCl₂, 40% aqueous *t*-C₄H₉OH, 60 °C. ^d Ra Ni, C₂H₅OH, 50 °C. ^e *p*-TsOH, CH₃OH.

equiv, 10% HMPA-THF, -78 °C, 2 h) and condensation with the tetrahydropyran ether⁶ 7 of pregnenolone furnished regio- and stereoselectively the α -(trimethylsilyl)thioenol ether⁸ 8 in 54% yield. The 20*S* and 23*Z* stereochemistry in 8 was assigned by comparison to similar adducts obtained previously.⁴ Conversion of 8 to a dianion 9 (1.5 equiv of *sec*-butyllithium, 10% HMPA-THF, -78 °C, 2 h) and a regioselective Peterson olefination reaction at C-24 in 9 using acetone (30 equiv, inverse addition, 0 °C) furnished the dienol⁵ 10 in 80% yield. This dienol synthesis involving the coupling of 6 with two different carbonyl compounds is a general process, as illustrated in Table I.⁵

Dienol rearrangements⁸ in systems bearing terminal alkoxy⁹ or halogen substituents¹⁰ lead to unsaturated carbonyl compounds. Analogous rearrangements in systems bearing an internal substituent such as the methylthio group in 10 have not been investigated in detail. Exposure of dienol 10 to nickel chloride (2 equiv) in 40% aqueous *tert*-butyl alcohol at 60 °C for 24 h led to the rearranged dienol 11 in 70% yield. In contrast, simple Brønsted acids led to a 20,22,24-triene⁵ as the predominant product. Other Lewis acids including nickel acetate, nickel bis-(acetylacetonate), palladium chloride, and cupric acetate were less effective than nickel chloride for reasons that, at the moment, are obscure. The 20(22)*E*,23*Z* stereochemistry in 11 was tentatively assigned on the basis of the following ¹H NMR observations: (1) the absence of long-range coupling¹¹ between the C-21

Table I. Sequential Condensation of 1-(Alkylthio)- or 1-(Arylthio)-1-(trimethylsilyl)-2-propenes with Carbonyl Compounds and Dienol Rearrangements Promoted by Nickel Chloride



R	R ₂ 'C=O	R ₂ ''C=O	R ^{'''} OH	isolated yields, %		
				i	ii	iii
CH ₃	cyclododecanone	acetone		62	79	
<i>n</i> -C ₄ H ₉	cyclododecanone	acetone		50	63	
C ₆ H ₅	cyclododecanone	acetone	H ₂ O ^a	59	37	44
CH ₃	7	acetone	H ₂ O ^a	54	80	70
C ₆ H ₅	7	acetone	H ₂ O ^a	57	54	73
C ₆ H ₅	7	3-pentanone		57	60	
C ₆ H ₅	6β-methoxy-3α,5α-cyclopropan-20-one	acetone		53	73	
C ₆ H ₅	3β-methoxy-5-pregnen-20-one	acetone	H ₂ O ^a	59	39	46
C ₆ H ₅	3β-methoxy-5-pregnen-20-one	acetone	CH ₃ OH	59	39	84
C ₆ H ₅	3β-methoxy-5-pregnen-20-one	acetone	C ₂ H ₅ OH	59	39	68

^a Experiments leading to rearranged dienols were conducted in 40% aqueous *tert*-butyl alcohol.

methyl and C-22 vinyl proton in 11; (2) the small, downfield chemical shift of the C-23 vinyl proton in the methylsulfinyl and methylsulfonyl derivatives^{5,12} obtained from the oxidation of 11; (3) the trans coupling of the C-23 and C-24 vinyl protons in the desulfurized dienol⁵ derived from the deactivated Raney nickel¹³ reduction of 11. The rearrangement process appears to be general in that various dienols bearing methylthio or phenylthio substituents undergo analogous rearrangements and various solvents such as methanol or ethanol lead to rearranged products⁵ bearing terminal methoxy or ethoxy groups, respectively, as summarized in Table I.

Stereoselective reduction^{14,15} of the rearranged dienol 11 using Raney nickel in ethanol at 50 °C and methanolysis of the tetrahydropyran ether 12 provided (20*R*)-25-hydroxycholesterol (4) in 52% yield. The synthetic material was identical with an authentic sample. Reduction of 11 using deactivated Raney nickel indicated that the rate of reduction of the functionality in 11 decreased in the following order: CH₃S >> Δ²³ > Δ²⁰⁽²²⁾ >> Δ⁵. The high degree of C-20 stereoselectivity observed in the reduction of 11 (20*R*:20*S* ≈ 4:1) is also consistent with the 20(22)*E* stereochemistry in 11, which in related systems¹⁴ led to a predominance of the 20*R* diastereomer. In summary, we have developed an efficient, six-step synthesis of (20*R*)-25-hydroxycholesterol (4) from pregnenolone (5) that illustrates both a new method for cholestane synthesis as well as a useful dienol rearrangement.

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Acknowledgment. We thank The National Institutes of Health (Grant CA 30065) for their generous financial support. We also thank the BSRG Committee for partial support from BSRG Grant SO7BR07157 awarded by the Biomedical Research Support Grant Program, Dr. Richard Heppner of the Laramie Energy Technology Center for determining mass spectra, The National Science Foundation (Grant CHE-8026553) for funds to purchase a JEOL 270-MHz NMR spectrometer, and Drs. J. J. Partridge, Jr., W. G. Salmond, and R. Chorvat for various authentic samples.

Registry No. 4, 55064-27-2; 6 (R = CH₃), 84051-40-1; 6 (R = C₄H₉), 84029-11-8; 6 (R = C₆H₅), 78905-13-2; 7, 35961-41-2; 8, 84056-75-7; 10, 84056-76-8; 11, 84051-41-2; 11 (methylsulfinyl derivative), 84051-42-3; 11 (methylsulfonyl derivative), 84051-43-4; 11 (desulfurized diene), 84051-44-5; 12, 55064-27-2; i (R = CH₃, R₂' = (CH₂)₁₁), 84051-45-6; i (R = C₄H₉, R₂' = (CH₂)₁₁), 84051-46-7; i (R = C₆H₅, R₂' = (CH₂)₁₁), 83862-54-8; i (R = C₆H₅, R₂' = 3β-tetrahydropyranyloxy-preg-5-en-20-yl), 79409-72-6; i (R = C₆H₅, R₂' = 6β-methoxy-3α,5α-cyclopregnan-20-yl), 84051-47-8; i (R = C₆H₅, R₂' = 3β-methoxy-5-pregnen-20-yl), 83862-55-9; ii (R, R'' = CH₃, R₂' = (CH₂)₁₁), 84051-48-9; ii (R = C₄H₉, R₂' = (CH₂)₁₁, R'' = CH₃), 84051-49-0; ii (R = C₆H₅, R₂' = (CH₂)₁₁, R'' = CH₃), 84051-50-3; ii (R = C₆H₅, R₂' = 3β-tetrahydropyranyloxy-preg-5-en-20-yl, R'' = CH₃), 84051-51-4; ii (R = C₆H₅, R₂' = 3β-tetrahydropyranyloxy-preg-5-en-20-yl, R'' = C₂H₅), 84056-77-9; ii (R = C₆H₅, R₂' = 6β-methoxy-3α,5α-cyclopregnan-20-yl, R'' = CH₃), 84051-52-5; ii (R = C₆H₅, R₂' = 3β-methoxy-5-pregnen-20-yl, R'' = CH₃), 84051-53-6; iii (R = CH₃, R₂' = (CH₂)₁₁, R''' = CH₃, R'''' = H), 84051-54-7; iii (R = C₆H₅, R₂' = 3β-tetrahydropyranyloxy-preg-5-en-20-yl, R'' = CH₃, R''' = H), 84051-55-8; iii (R = C₆H₅, R₂' = 3β-methoxy-5-pregnen-20-yl, R'' = CH₃, R''' = H), 84051-56-9; iii (R = C₆H₅, R₂' = 3β-methoxy-5-pregnen-20-yl, R'', R''' = CH₃), 84056-97-3; iii (R = C₆H₅, R₂' = 3β-methoxy-5-pregnen-20-yl, R'' = CH₃, R''' = C₂H₅), 84051-57-0; NiCl₂, 7718-54-9; cyclododecanone, 830-13-7; 6β-methoxy-3α,5α-cyclopregnan-20-one, 32249-55-1; 3β-methoxy-5-pregnen-20-one, 511-26-2; 3-pentanone, 96-22-0; acetone, 67-64-1.

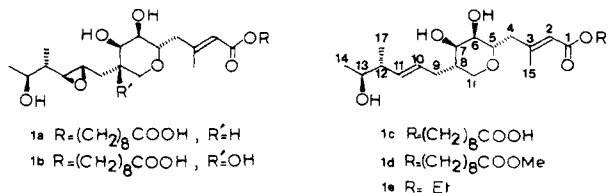
Total Synthesis of (+)-Methyl Pseudomonate C from Carbohydrates

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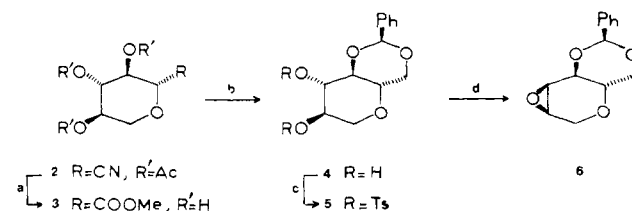
Pseudomonic acids A (1a), B (1b), and C (1c) are members



of a new group of metabolites with antimicrobial and antimycoplasmal activity, produced by submerged fermentations of a strain of *Pseudomonas fluorescens*.¹⁻³ The stability and the natural scarcity of pseudomonic acid C, which has been isolated³ as its methyl ester 1d, qualify it as an attractive synthetic target. We report the first enantiospecific total synthesis of 1d, which makes use of carbohydrates as chiral templates. While this work was in progress, total syntheses of (±)-pseudomonic acid C emerged.^{4,5}

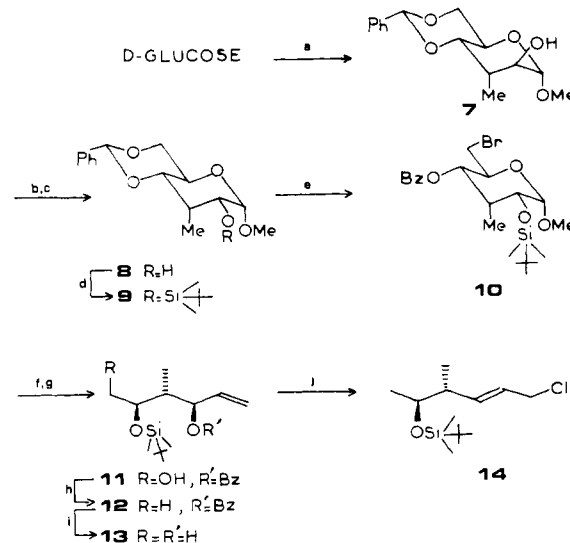
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Scheme I^a



^a Reagents: (a) (1) MeONa, (2) NaOH, (3) MeOH-HCl, 70%; (b) (1) LiAlH₄, (2) PhCH(OMe)₂, TsOH, 85%; (c) TsCl, pyridine, 70%; (d) MeONa, CHCl₃, room temperature, 24 h, quantitative.

Scheme II^a



Other synthetic efforts have been published,⁶ giving evidence of the popularity of this target.

The crystalline cyanide 2, readily available⁷ from D-xylose, was converted into the ester 3,⁸ then into the acetal 4. Tosylation of 4 produced 5, which was next quantitatively converted into the epoxide 6, as illustrated in Scheme I. No trace of the isomeric epoxide 6 was present in the reaction mixture.⁹

Our approach was based on the idea that the rigid tricyclic epoxide 6 would probably undergo a regiospecific opening upon treatment with a suitable allylic anion, thus adorning the core with the left side appendage. With this idea in mind we then prepared the chiral chloride 14 from D-glucose, as shown in Scheme II. The key reaction of this sequence was the treatment of the bromide 10 with activated zinc,¹⁰ generating an aldehyde which was reduced into the alcohol 11.

The copper-catalyzed¹¹ (CuI) ring opening of epoxide 6 with Grignard reagent derived from 14 (2 equiv, THF, -30 °C, 10 min)

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