yielded 979 mg (95%) of the keto alcohol **14** as a very viscous oil: IR (film) 3460, 1715, 1100, 1060 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 6.5 Hz), 1.69 (br s, 3 H), 1.82 (br s, 1 H, OH), 1.89–2.84 (m, 4 H), 2.99 (q, 1 H, J = 6.5 Hz), 3.38–3.76 (m, 2 H), 4.08 (s, 2 H), 4.14–4.26 (m, 1 H), 5.24–5.36 (m, 1 H); high-resolution mass spectrum calcd for $C_{12}H_{18}O_3$ m/e 210.12558, found m/e 210.12577.

Acknowledgment. We thank the National Institutes of Health for generous financial assistance.

Registry No. **3**, 75233-41-9; **4**, 41198-89-4; **5**, 75233-42-0; **6**, 75233-43-1; **8**, 75233-44-2; **9**, 75233-45-3; **10**, 75233-46-4; **11**, 75233-47-5; **12**, 6018-41-3; **13a**, 75233-48-6; **13b**, 75233-49-7; **14**, 75247-52-8; **15** (isomer 1), 75233-50-0; **15** (isomer 2), 75233-51-1; **16**, 75233-52-2; **17**, 75233-53-3; **18**, 75233-54-4; 4-methyl-1-(hydroxymethyl)-1-(2-hydroxy-4,6,9-trioxodec-1-yl)-2,5-cyclohexadiene, 75233-55-5; 1-[(benzoyloxymethyl)]-1-[(2-(benzoyloxy)-4,6,9-trioxodec-1-yl]-4-methyl-2,5-cyclohexadiene, 75233-56-6; (±)-(4α,4aβ,8aβ)-4a-(carbomethoxy)-3,4,4a,5,8,8a-hexahydro-4,7-dimethyl-2*H*-1-benzopyran-2-one, 75233-57-7; (±)-(4α,4aβ,8aβ)-4a-(carbomethoxy)-3,4,4a,5,8,8a-hexahydro-4,6-dimethyl-2*H*-1-benzopyran-2-one, 75233-57-7; (±)-(2α,4aβ,8aβ)-4a-(carbomethoxy)-4a,5,8,8a-tetrahydro-2-hydroxy-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran (isomer 1), 75233-58-8; (±)-(2α,4aβ,8aβ)-4a-(carbomethoxy)-4a,5,8,8a-tetrahydro-2-hydroxy-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran (isomer 2), 75233-59-9; (±)-(4aα,8aα)-4a,5,8,8a-tetrahydro-4a-(hydroxymethyl)-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran, 75233-60-2; 2-(2-nitroethoxy)tetrahydropyran, 75233-61-3; 3-hydroxy-2-nitro-1-(2-tetrahydropyranyloxy)butane (isomer 1), 75233-62-4; 3-hydroxy-2-nitro-1-(2-tetrahydropyranyloxy)butane (isomer 2), 75281-72-0; 2-nitroethanol, 625-48-9; dihydropyran, 25512-65-6; 4-methylcyclohexanone, 589-92-4; 1-cyano-1-hydroxy-4-methylcyclohexane, 933-45-9; *p*-toluic acid, 99-94-5; 4-methyl-2,5-cyclohexadienecarboxylic acid, 20646-36-0; glycidol, 556-52-5; (β-methoxyethoxy)methyl chloride, 3970-21-6; benzoyl chloride, 98-88-4; isoprene, 78-79-5.

Synthetic Studies toward Verrucarol. 2. Synthesis of the AB Ring System

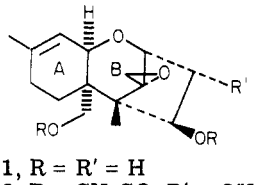
George A. Kraus* and Bruce Roth

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received June 24, 1980

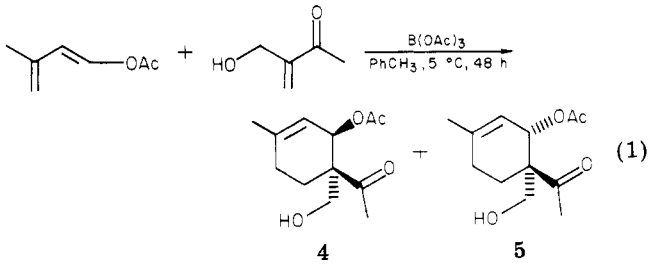
A route to the AB ring system of verrucarol is described. The successful scheme involved the formation of the A ring by a boron triacetate catalyzed Diels–Alder reaction. The second ring can be appended by an intramolecular Knoevenagel reaction to afford lactone **12b**. This lactone could be converted into the desired keto alcohol **3b** by reduction of the lactone and nitrile followed by an oxidation and Curtius degradation.

As indicated in the previous paper,[1] the biological activity and challenging structures of verrucarol (**1**) and



1, R = R′ = H
2, R = CH_3CO; R′ = OH

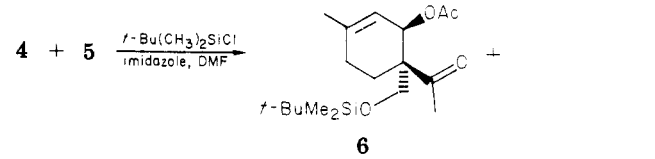
anguidin (**2**) have prompted considerable synthetic effort. Our initial successful preparation of a functionalized AB ring system for verrucarol involved a Diels–Alder reaction between isoprene and methyl coumalate followed by functional group modifications on the B ring. Although the ring-junction stereochemistry was unambiguously defined, our strategy mandated eventual isomerization of the trisubstituted olefin in ring A. In this paper an alternate strategy will be presented in which the trisubstituted olefin in ring A is regiospecifically introduced by a Lewis acid promoted Diels–Alder reaction. Subsequent transformations will afford ketol **3b**. The general plan is outlined in Scheme I. A Diels–Alder reaction between 1-acetoxy-3-methylbutadiene[2] and 3-(hydroxymethyl)-3-buten-2-one[3] afforded a mixture of diastereomeric acetoxy ketones **4** and **5** (3.5:1, eq 1). Stereochemistry was tentatively assigned



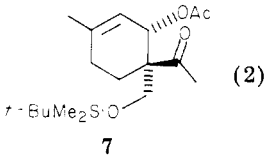
(1)

4 **5**

by comparison of the spectra of the silylated adducts **6** and **7** with the spectrum of **8**. Ketone **8** was the exclusive

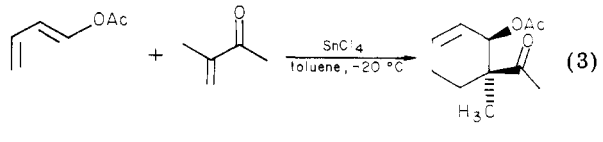


6



(2)

7



(3)

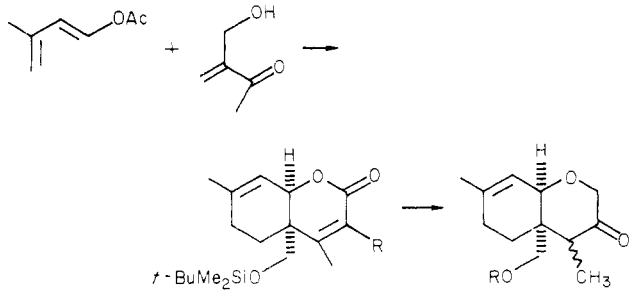
8

product from the tin tetrachloride catalyzed Diels–Alder reaction of 1-acetoxybutadiene and isopropenyl methyl

(1) Kraus, G. A.; Frazier, K. F. *J. Org. Chem.*, preceding paper in this issue.
(2) Cookson, R. C.; Cramp, M. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1980**, 197. Snider, B. B.; Amin, S. G. *Synth. Commun.* **1978**, *8*, 117–25.
(3) Gault, H.; Germann, L. A. *C. R. Hebd. Seances Acad. Sci.* **1933**, *197*, 620–1.

0022-3263/80/1945-4825$01.00/0

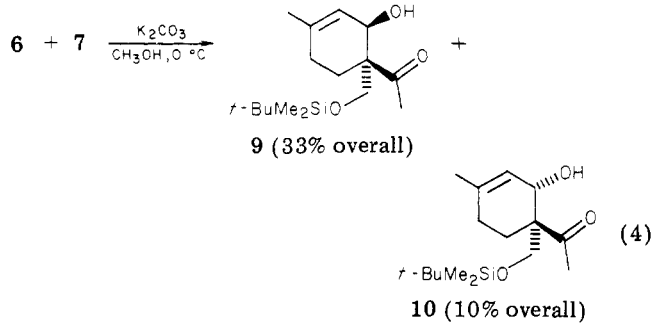
Scheme I



3a, R = t-BuMe$_2$Si
b, R = H

ketone.[4] The spectrum of 8 exhibits a doublet (J = 4.5 Hz) at δ 5.25 which represents the allylic methine proton. This compares closely to the value for 6 (J = 4.5 Hz at δ 5.23) but differs significantly from the corresponding signal for 7 at δ 4.12. Freshly prepared boron triacetate proved to be the Lewis acid catalyst of choice for obtaining an optimal yield of 4. Other catalysts such as aluminum chloride, tin tetrachloride, and boron trifluoride etherate either afforded inferior yields or showed lower selectivity. Interestingly, the thermal reaction (115 °C, 24 h) gave a 2:1 ratio where 5 predominated. Boron triacetate[5] does not catalyze the reaction of acetoxybutadiene and isopropenyl methyl ketone. In addition to 4 and 5, variable amounts of diene resulting from acetate elimination were obtained. Silylation was accomplished by the method of Corey.[8]

Saponification of the acetate was conducted under mild conditions (K_2CO_3, CH_3OH, 0 °C; eq 4) in order to avoid

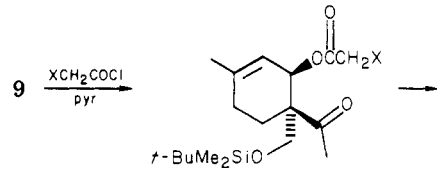


9 (33% overall)

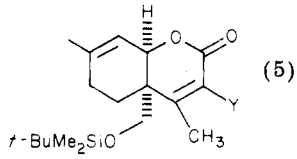
(4)

10 (10% overall)

epimerization by a process which would involve an initial retro aldol condensation followed by realdolization. Hydroxy ketone 10 (which could be conveniently separated from 9 at this point in the sequence) has been converted into an equal mixture of 9 and 10 with a catalytic amount of benzyltrimethylammonium hydroxide. Attempted epimerization of ketone 10 with triphenylphosphine, diethyl azodicarboxylate, and formic acid[6] led to recovery of starting materials. The reaction of 9 with acid chlorides and pyridine afforded esters 11a–c in excellent yields (eq 5). Ester 11a could be transformed into lactone 12a by reaction with neat trimethyl phosphite at 95 °C followed by cyclization with sodium hydride in THF at 0 °C. The overall yield from 9 to 12a was 67%. Our strategy for the conversion of 12a into desired hydroxy ketone 3 involved reduction of the lactone to an ether and the selective transformation of the olefin in ring B to a ketone. The initial phase of this plan was efficiently accomplished by



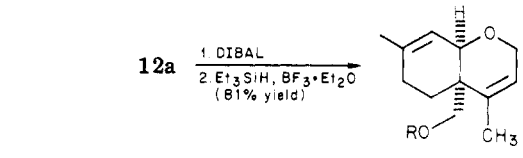
11a, X = Br
b, X = CN
c, X = CO_2Et



(5)

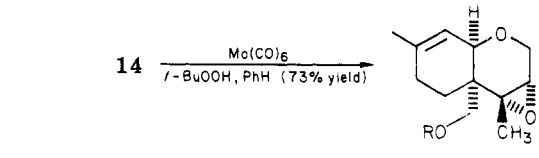
12a, Y = H
b, Y = CN

using a modification of a reduction procedure developed by Doyle and co-workers.[7] Reduction of 12a with diisobutylaluminum hydride (DIBAL) afforded an unstable lactol which could be reduced to allylic ether 13 with triethylsilane and boron trifluoride etherate at −78 °C (eq 6). Notably, no olefin migration was observed as evidenced by the NMR of the crude product. Removal of the alcohol protecting group with tetrabutylammonium fluoride[8] produced alcohol 14 in 88% yield. Examination of molecular models indicated that the conformation of 14 that was most consistent with the observed coupling constants had the hydroxymethyl group in close proximity to the olefin in ring B.[26] Therefore, directed epoxidation using the method of Sharpless[9] was attempted and proved to be highly selective. No other products were isolated. In support of the selectivity and identity of epoxide 15 (eq 7) the regioisomeric epoxide was synthesized by a four-step



(6)

13, R = $SiMe_2$-t-Bu
14, R = H



(7)

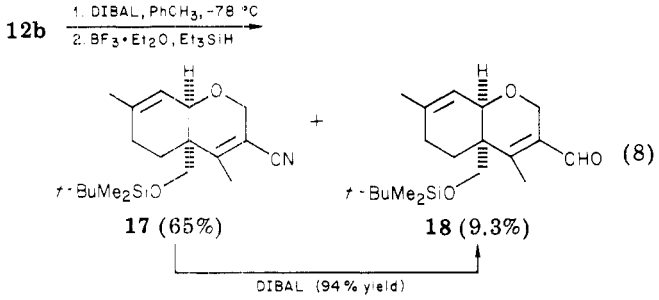
15, R = H
16, R = $COCH_3$

sequence[10] starting from 12a. Acetylation with acetic anhydride and triethylamine afforded 16 in 70% yield. Unfortunately, all attempts to convert epoxide 16 to a ketone failed. Epoxide isomerization[11] (BF_3·Et_2O, PhH;[12] lithium perchlorate in refluxing benzene;[13] NaI, Me_2SO;[14]

(4) Run by Hirohiko Sugimoto. In this case the thermal reaction afforded a mixture of stereoisomers of which 8 was the major isomer.
(5) Pictet, A.; Geleznoff, A. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2219.
(6) Bose, A. K.; Lal, B.; Hoffman, W. A.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619.
(7) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675.
(8) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(9) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
(10) (a) MCPBA, CH_2Cl_2, 0 °C; (b) DIBAL, $PhCH_3$, −78 °C; (c) pTSA, CH_3OH; (d) BF_3·Et_2O, Et_3SiH, CH_2Cl_2, −78 °C.
(11) Weissberger, A. "Heterocyclic Compounds"; Interscience: New York, 1964; p 231–61.
(12) Henbest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957**, 4596.
(13) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1968**, *90*, 4193.

$SnCl_4$, toluene, 0 °C[15]) led to decomposition of **16**. Alternatively, **3** could be approached from an α-hydroxy ketone by reductive elimination. This plan would also permit regioselective formation of an enol acetate or enol silyl ether. Acid-catalyzed opening of the epoxide **16** to a diol[16] followed by attempted oxidation [*N*-chlorosuccinimide, dimethyl sulfide;[17] *N*-bromosuccinimide in aqueous dioxane;[18] dimethyl sulfoxide (Me_2SO), dicyclohexylcarbodiimide, and various acids;[19] Me_2SO, acetic anhydride[20]] failed to yield the desired hydroxy ketone. In all cases unreacted diol was recovered.

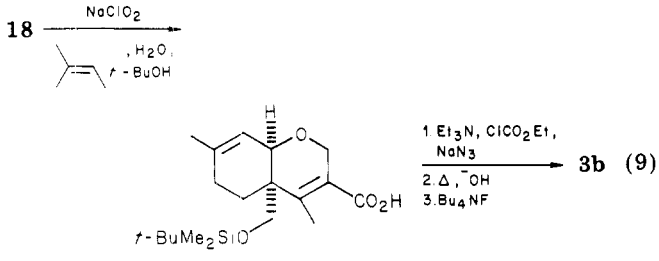
As a consequence of our failure to transform expoxide **16** into the desired ketone **3**, cyano ester **11b** was synthesized and cyclized to provide **12b** in 75% yield from **9**. The corresponding diester **11c** failed to cyclize. Cyanolactone **12b** could be reduced to a cyano lactol by using DIBAL in toluene at −78 °C which in turn could be reduced to **17** with boron trifluoride etherate and triethylsilane (eq 8). A minor product isolated in the conversion



(8)

of **12b** to **17** was aldehyde **18**. The DIBAL reduction of **17** provided **18** in 94% yield.

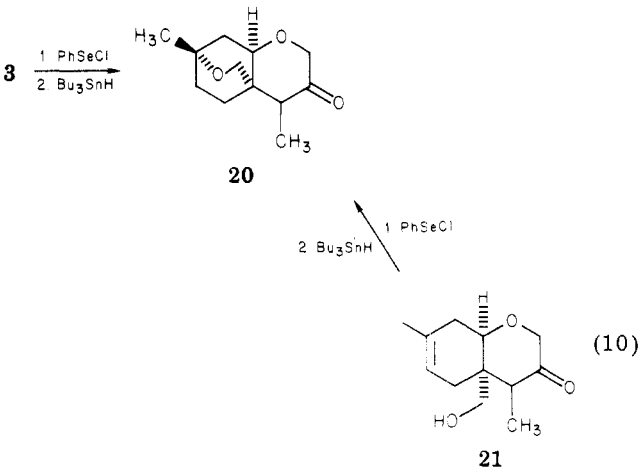
Aldehyde **18** was oxidized to acid **19** in 80% yield by using sodium chlorite in aqueous *tert*-butyl alcohol[21] with 2-methyl-2-butene as a chlorine scavenger (eq 9). A more



(9)

19

direct route to acid **19** would involve saponification. However, nitrile **17** proved to be resistant to a variety of hydrolysis procedures.[22] Acid **19** could be transformed into the desired hydroxy ketone **3** by Curtius degradation[23] and desilylation[8] in 75% yield. As an additional proof of structure, hydroxy ketone **3** was converted into ether **20** (eq 10) by cyclization with phenylselenyl chloride[24] followed by reductive deselenylation. Ether **20** could then be compared with the products obtained by the same reaction sequence on isomeric hydroxy ketone **21**.[25] The cis



(10)

ring junction in **21** had been unambiguously defined by the synthetic approach. Both comparison of the ^1H NMR and ^{13}C NMR spectra and coinjection on capillary gas chromatography indicated that the products obtained by both routes were identical.

The hydroxy ketone **3** is available in 11 steps in 10.4% overall yield. The conversion of **3** into verrucarol requires the introduction of a functionalized two-carbon bridge and the transformation of the ketone into an epoxide. Schemes to accomplish this goal are under active investigation.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether, THF, benzene, and toluene were distilled from $LiAlH_4$ prior to usage. Dichloromethane was distilled from P_2O_5. All organic extracts were dried over Na_2SO_4, except where otherwise noted. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on either a Hitachi Perkin-Elmer R-20B 60-MHz or a Varian HA-100 100-MHz instrument. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier transform spectrometer. Both proton and carbon chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

***cis*-1-[1-[(*tert*-Butyldimethylsiloxy)methyl]-2-hydroxy-4-methyl-3-cyclohexenyl]-1-ethanone (9).** Boron triacetate (76 g, 405 mmol) was added in one portion to a rapidly stirred solution of 3-(hydroxymethyl)-3-buten-2-one (27 g, 270 mmol), 1-acetoxy-3-methylbutadiene (37.8 g, 300 mmol), and hydroquinone (2 g) in 600 mL of dry toluene cooled to 0 °C. The resulting suspension was stored at 5 °C for 2 days. The now dark brown suspension was placed in an ice bath and the catalyst destroyed by slow addition of aqueous bicarbonate with vigorous stirring. When the mixture had assumed a bright yellow-orange color, it was transferred to a separatory funnel and partitioned between water (500 mL) and ether (1 L). The organic layer was washed with water (2 × 200 mL), bicarbonate (2 × 250 mL), and brine (100 mL). Drying and removal of the solvents afforded 46.2 g of a bright orange oil, which was estimated to be a 3:1 mixture of compounds **4** and **5** by NMR and TLC data.

After dissolution of the crude mixture of diastereomers in dry *N,N*-dimethylformamide (100 mL), *tert*-butyldimethylchlorosilane (46.5 g, 308 mmol) and imidazole (81.6 g, 1200 mmol) were added.

(14) Bethell, D.; Kenner, G. W. Powers, P. J. *J. Chem. Soc., Chem. Commun.* **1968**, 227.
(15) Bang, L.; Ourisson, G. *Tetrahedron* **1973**, *29*, 2097.
(16) Fieser, L. F.; Goto, T. *J. Am. Chem. Soc.* **1960**, *82*, 1693.
(17) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.
(18) Fieser, L. F.; Rajagopalan, S. *J. Am. Chem. Soc.* **1949**, *71*, 3938.
(19) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661.
(20) Butterworth, R. F.; Hanessian, S. *Synthesis* **1971**, 70.
(21) Lindgren, B. O.; Hilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–90.
(22) (a) Gassman, P. G.; Schenk, W. M. *J. Org. Chem.* **1977**, *42*, 918. (b) Hall, J. H.; Gisler, M. *Ibid.* **1976**, *41*, 3769.
(23) Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511.
(24) Nicolaou, K. C.; Seitz, S. P.; Sipro, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884.
(25) This experiment was performed on the mixture of regioisomers described in the previous paper. The regioisomeric ethers obtained by the selenylation–deselenylation procedure were completely separable under the VPC conditions described in the Experimental Section.
(26) As noted by a referee, several conformations of the *cis*-oxadecalin ring are possible. It may be that steric factors control the site of epoxidation.

The mixture was stirred at 45 °C for 4.5 h and then partitioned between hexanes (600 mL) and water (150 mL). The organic layer was washed with water (100 mL) and brine (100 mL) and dried. Removal of the solvents yielded 68 g of silylated material.

The crude mixture of acetates was dissolved in dry methanol (500 mL) and cooled to 0 °C. Potassium carbonate (69 g, 500 mmol) was added and the mixture stirred vigorously. When the reaction was judged complete by TLC analysis (4–5 h), it was acidified with 6 N HCL (pH 3), and the methanol was removed under reduced pressure. The residue was taken up in ether (500 mL) and washed with water (150 mL), 1 N HCl (150 mL), bicarbonate (150 mL), and brine (100 mL). The ether layer was dried, and the solvents were removed. The residue was chromatographed (silica gel, 30:1 hexanes–EtOAc) to afford two major substances. The undesired diastereomer **10**: R_f (3:1 hexane–EtOAc) 0.35; 8.3 g (10%); IR (film) 3450, 2960, 2860, 1715, 1255, 1105 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.88 (s, 9 H), 1.68 (br s, 3 H), 1.8–2.0 (m, 4 H), 2.22 (s, 3 H), 2.60 (br s, 1 H, OH), 3.76, 3.92 (AB q, J = 10 Hz, 2 H), 4.58 (m, 1 H), 5.50 (m, 1 H); 90-MHz ^{13}C NMR ($CDCl_3$) δ -5.72, 18.14, 22.89, 24.00, 25.82, 27.44, 27.77, 55.67, 65.17, 67.70, 123.49, 137.28. Major isomer **9**: 27.4 g (33%); R_f (3:1 hexane–EtOAc) 0.21; IR (film) 3440, 1715 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.88 (s, 9 H), 1.70 (br s, 3 H), 1.97 (br s, 4 H), 2.24 (s, 3 H), 2.67 (d, J = 6 Hz, 1 H, OH), 3.60, 3.74 (AB q, J = 11 Hz, 2 H), 4.16 (m, 1 H), 5.52 (m, 1 H, collapses to d, J = 5 Hz, on irradiation at δ 1.70); 90-MHz ^{13}C NMR ($CDCl_3$) δ 18.141, 22.108, 23.020, 25.817, 27.507, 27.898, 56.250, 65.484, 68.086, 122.906, 137.733, 213.104; high-resolution mass spectrum calcd for $C_{16}H_{30}O_3Si$ m/e 298.196 43, found m/e 298.196 45.

***cis*-1-[1-[(*tert*-Butyldimethylsiloxy)methyl]-2-[(bromoacetyl)oxy]-4-methyl-3-cyclohexenyl]-1-ethanone (11a).** To a 0 °C solution of alcohol **9** (2.25 g, 7.55 mmol) and dry pyridine (1.45 mL, 18 mmol) in dichloromethane (11 mL) was added a solution of bromoacetyl bromide (1.43 mL, 15.1 mmol) in dry THF (13 mL) dropwise over a period of 10 min. The resulting suspension was stirred a further 30 min and then poured into 200 mL of ether. The organic layer was washed with water (30 mL), 1 N HCl (2 × 20 mL), bicarbonate (2 × 20 mL), and brine (20 mL). Drying and removal of the solvents afforded a quantitative yield of bromoacetate **11a**: IR (film) 2980, 2960, 2870, 1740, 1715, 1275, 1105, 835, 770 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.89 (s, 9 H), 1.72 (m, 3 H), 2.0–2.2 (m, 4 H), 2.17 (s, 3 H), 3.43, 3.72 (AB q, J = 10 Hz, 2 H), 3.73 (s, 2 H), 5.27 (br d, J = 5 Hz, 1 H), 5.60 (m, 1 H, collapses to d, J = 5 Hz, on irradiation at δ 1.72); high-resolution mass spectrum calcd for $C_{14}H_{22}O_4BrSi$ (parent ion – 57) m/e 361.047 07, found m/e 361.046 03.

(±)-(4aα,8aα)-4a-[(*tert*-Butyldimethylsiloxy)methyl]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran-2-one (12a). Bromoacetate **11a** (1.694 g, 4.04 mmol) and trimethyl phosphite (1.42 mL, 16 mol) were heated together at 90–95 °C under nitrogen for 12 h. After the mixture cooled to room temperature, the excess phosphite was removed under vacuum (~1 mm, 10 h, room temperature), affording the crude phosphonate: high-resolution mass spectrum calcd for $C_{20}H_{37}O_7PSi$ m/e 448.204 63, found m/e 448.204 72.

The crude phosphonate was dissolved in 16 mL of anhydrous THF and the mixture added dropwise to a suspension of sodium hydride (pentane washed) in 5 mL of anhydrous THF at 0 °C under nitrogen. After the completion of hydrogen evolution, the cooling bath was removed and the solution allowed to warm to room temperature. When all the starting material was judged to be consumed by TLC analysis, the suspension was poured into ice–water. The aqueous layer was extracted with ether (3 × 50 mL), and the combined ether layers were washed with water (15 mL) and brine (15 mL). Drying and removal of the solvents gave an oil, which was chromatographed (silica gel, 10:1 hexanes–EtOAc), affording 1.604 g (67%) of a pale yellow oil: R_f (3:1 hexanes–EtOAc) 0.25; IR (film) 2980, 2970, 1725 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.88 (s, 9 H), 1.71 (br s, 3 H), 1.8–1.96 (m, 4 H), 1.90 (d, J = 1.6 Hz, 3 H), 3.57, 3.68 (AB q, J = 9.6 Hz, 2 H), 4.94 (m, 1 H), 5.44 (m, 1 H), 5.84 (q, J = 1.6 Hz, 1 H); 90-MHz ^{13}C NMR δ 18.199, 18.625, 22.878, 25.224, 25.655, 27.268, 42.143, 65.533, 75.919, 119.187, 119.720, 138.800, 160.355, 163.707; high-resolution mass spectrum calcd for $C_{18}H_{30}O_3Si$ m/e 322.196 43, found m/e 322.196 47.

(±)-(4aα,8aα)-4a-[(*tert*-Butyldimethylsiloxy)methyl]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran (13). Diisobutylaluminum hydride (1.0 M, hexanes) was added portionwise to a 0.3 M toluene solution of the unsaturated lactone **12a** (2.372 g, 7.37 mmol) cooled to –78 °C (dry ice–CH_3OH bath) until TLC analysis judged the reaction complete. It was then poured into a rapidly stirred mixture of ice (25 g) and acetic acid (7 mL). Chloroform (50 mL) was added and the two-phase system stirred vigorously for 10 min. Another 100-mL portion of chloroform was added and vigorous stirring continued until two distinct layers formed when the stirring was halted (typically 30–60 min). The layers were separated, and the organic layer was washed with bicarbonate (2 × 100 mL) and brine (75 mL). Drying and removal of the solvents afforded a colorless oil which was used without purification.

The crude lactol and triethylsilane (1.22 g, 10.5 mmol) in dichloromethane (25 mL) were cooled to –78 °C under nitrogen. Dropwise addition of boron trifluoride etherate (0.95 mL, 7.7 mmol) gave a light brown solution which was stirred a further 15 min and then quenched by addition of approximately 10 mL of aqueous bicarbonate. The cooling bath was removed and the solution allowed to warm to room temperature with vigorous stirring. After the mixture was transferred to a separatory funnel, ether (100 mL) was added and the whole washed with bicarbonate (20 mL) and brine (20 mL). Drying and removal of the solvents afforded a crude yellow oil which was chromatographed (silica gel, 25:1 hexanes–EtOAc) to yield **13** (1.83 g, 81%) as a colorless oil: R_f (3:1 hexanes–EtOAc) 0.61; IR (film) 2980, 2970, 2870, 1110 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.7–2.0 (m, 10 H), 3.50, 3.72 (AB q, J = 10 Hz), 4.02 (q, J = 2.5 Hz, 2 H), 4.20 (m, 1 H), 5.44 (m, 2 H); 90-MHz ^{13}C NMR ($CDCl_3$) δ 18.314, 23.135, 25.579, 25.898, 27.523, 41.124, 62.469, 65.511, 70.917, 121.353, 123.412, 134.517, 139.014; high-resolution mass spectrum calcd for $C_{18}H_{32}O_2Si$ m/e 308.217 17, found m/e 308.216 45.

(±)-(4aα,8aα)-4,7-Dimethyl-4a-(hydroxymethyl)-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran (14). Silyl ether **13** (1.68 g, 5.45 mmol) and tetra-*n*-butylammonium fluoride (0.75 M in THF, 20 mL, 15 mmol) were stirred 2 h at room temperature. The light yellow solution was poured into 75 mL of bicarbonate. The aqueous layer was extracted twice with ether (100 mL), and the combined ether layers were washed with bicarbonate (25 mL) and brine (25 mL). Drying and removal of solvents afforded a light yellow oil which was chromatographed (silica gel, 5:1 hexanes–EtOAc), providing 0.93 g (88%) of alcohol **14** as a colorless oil: R_f (3:1 benzene–acetone) 0.15; IR (film) 3450, 2980, 1675, 1450, 1115 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 1.7–2.05 (m, 10 H), 2.95 (br s, 1 H, OH), 3.53, 3.70 (br AB q, J = 11 Hz, 2 H), 4.04 (m, 2 H), 4.34 (m, 1 H), 5.35 (m, 1 H), 5.62 (m, 1 H, collapses to t, J = 3 Hz, on irradiation at δ 1.702 and to a br s on irradiation at δ 4.04); 90-MHz ^{13}C NMR ($CDCl_3$) 17.46, 22.914, 25.865, 26.894, 40.492, 61.837, 68.175, 74.561, 120.779, 125.058, 132.372, 139.631; high-resolution mass spectrum calcd for $C_{12}H_{18}O_2$ m/e 194.130 68, found 194.130 09.

(±)-(3α,4α,4aα,8aα)-4,7-Dimethyl-4a-(hydroxymethyl)-3,4,4a,5,6,8a-hexahydro-2*H*-1-benzopyran 3,4-Epoxide (15). *tert*-Butyl hydroperoxide (0.12 mL, 1.25 mmol) in 1.25 mL of benzene was dried over sodium sulfate. The resulting clear solution was added to a 0.3 M benzene solution of alcohol **14** (0.202 g, 1.04 mmol) and hexacarbonylmolybdenum (0.025 g). The whole was heated at reflux for 1.5 h. The cooled solution was filtered through silica gel (20 g, 5:1 hexanes–EtOAc as eluant) to provide, in the order of elution, 40 mg (20%) of recovered **14** and 0.16 g (73%, 91% based on recovered **14**) of epoxide **15** as a colorless oil: R_f (3:1 hexanes–EtOAc) 0.10; IR (film) 3450, 1135 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 1.46 (s, 3 H), 1.72 (br s, 3 H), 1.9–2.1 (m, 4 H), 2.50 (br s, 1 H, OH), 3.04 (d, J = 4 Hz, 1 H), 3.5–3.9 (m, 4 H), 4.14 (dd, J = 4, 13 Hz, 1 H), 5.46 (m, 1 H); 90-MHz ^{13}C NMR ($CDCl_3$) 19.093, 22.939, 22.048, 27.436, 39.246, 58.694, 61.891, 64.058, 64.383, 68.121, 119.532, 139.252; high-resolution mass spectrum calcd for $C_{11}H_{15}O_2$ (P – 31 = loss of CH_3O) m/e 179.107 21, found 179.107 84.

(±)-(4aα,8aα)-4a-[(*tert*-Butyldimethylsiloxy)methyl]-4,7-dimethyl-2-oxo-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran-3-carbonitrile (12b). Cyanoacetyl chloride (15.53 g, 150 mmol) in 50 mL of anhydrous ether was added dropwise to a rapidly stirred solution of alcohol **9** (17.9 g, 60 mmol) and pyridine (14.54

mL, 180 mmol) in dichloromethane (120 mL) cooled to 0 °C under nitrogen. The mixture was stirred 15 min beyond the completion of addition and then poured into 1 L of ether. The organic layer was washed consecutively with water (2 × 100 mL), 1 N HCl (2 × 100 mL), 1:1 bicarbonate–brine (2 × 100 mL), and slightly acidic brine (100 mL). The dried solution was poured through a pad of 1:1 Celite (filter aid)–silica gel (50 g), and the solvents were removed to afford pure cyano ester **11b** (22 g, 100%).

The cyanoacetate (20.2 g, 80 mmol) and 1,5-diazobicyclo-[4.3.0]non-5-ene (1.0 mL, 8 mmol) were heated to reflux in benzene (150 mL) with azeotropic removal of water. After 30 min, the solution was cooled, diluted with ether (500 mL), and washed with 1 N HCl (2 × 300 mL), bicarbonate (2 × 300 mL), and slightly acidic brine (100 mL). Drying and removal of the solvents afforded a crude solid which was recrystallized from 50:1 hexanes–EtOAc, yielding 18.15 g (52.3 mmol) of light yellow crystals (mp 145–0146 °C). Chromatography (SiO_2, 10:1 hexanes–EtOAc) of the mother liquors afforded a further 2.81 g (7.7 mmol) of crystals (60 mmol total, 75%): IR (film) 2980, 2240, 1735, 840 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.10 (6 H, s), 0.88 (9 H, s), 1.74 (br s, 3 H), 1.9–2.1 (m, 4 H), 2.37 (s, 3 H), 3.68, 3.86 (AB q, J = 11 Hz, 2 H), 4.97 (m, 1 H), 5.43 (m, 1 H); 90-MHz ^{13}C NMR ($CDCl_3$) 17.948, 18.598, 22.630, 25.231, 26.857, 43.830, 65.875, 76.510, 108.081, 113.283, 118.486, 140.011, 158.48, 174.998. Anal. Calcd for $C_{19}H_{29}NO_3Si$: C, 65.71; H, 8.36. Found: C, 65.79; H, 8.28.

(±)-(4aα,8aα)-4a-[(*tert*-Butyldimethylsiloxy)methyl]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran-3-carbonitrile (17). Diisobutylaluminum hydride (21.7 mL of a 1.0 M hexane solution) was added dropwise to a stirred solution of lactone **12b** (6.85 g, 19.74 mmol) in 85 mL of toluene cooled to −78 °C under nitrogen. The light brown solution was stirred a further 60 min after the addition was complete and then poured into a rapidly stirred mixture of acetic acid (25 mL) and ice (100 g). Chloroform (500 mL) was added, followed by 1 N HCl (100 mL). Stirring was continued until both layers clarified (2–3 h). The layers were separated, and the organic layer was washed with 1 N HCl (100 mL), bicarbonate (2 × 100 mL), and brine (100 mL). The dried solution was filtered through a pad of 1:1 silica gel–Celite (50 g), and the solvents were removed under reduced pressure.

The crude lactols were dissolved in dichloromethane (60 mL) and cooled to −78 °C under nitrogen. Triethylsilane (3.40 g, 29 mmol) was added, followed by dropwise addition of boron trifluoride etherate (2.64 mL, 21.5 mmol). The reaction mixture was stirred for 15 min beyond the completion of the addition, bicarbonate (25 mL) was added with vigorous stirring, and the cooling bath was removed. On attainment of room temperature, the two-phase system was poured into ether (300 mL) and the organic layer washed with bicarbonate (50 mL) and brine (50 mL). Drying and removal of the solvents afforded a crude yellow oil, which was chromatographed (silica gel, 25:1 hexanes–EtOAc) to provide two major products. Nitrile **17**: 4.27 g (65%); R_f (4:1 hexanes–EtOAc) 0.50; mp 75–76 °C (from hexanes); IR (film) 2980, 2880, 2205, 1120 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.91 (s, 9 H), 1.72 (br s, 3 H), 1.8–2.0 (m, 4 H), 2.07 (t, J = 2 Hz, 3 H), 3.57, 3.70 (AB q, J = 10 Hz, 2 H), 4.16 (m, 3 H), 5.44 (m, 1 H); high-resolution mass spectrum calcd for $C_{15}H_{22}O_2NSi$ (P − 57 = 276) m/e 276.141 03, found m/e 276.141 99. Aldehyde **18**: 0.91 g (9.3%); R_f (4:1 hexanes–EtOAc) 0.40; colorless oil; IR (film) 2950, 2920, 2850, 2740, 1708, 1655, 1240, 1090, 825 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.73 (br s, 3 H), 1.9 (m, 4 H), 2.23 (t, J = 1.5 Hz, 3 H), 3.63, 3.78 (AB q, J = 11 Hz, 2 H), 4.12 (br s, 1 H, collapses to d, J = 3 Hz, on irradiation at δ 1.73), 4.27 (m, 2 H, collapses to AB q, δ 4.20, 4.36, J = 16 Hz, on irradiation at δ 2.23), 5.46 (br s, 1 H, collapses to d, J = 3 H, on irradiation at δ 1.73), 10.10 (s, 1 H); 90-MHz ^{13}C NMR ($CDCl_3$) δ −5.656, 11.901, 18.144, 23.086, 25.167, 25.752, 27.378, 42.855, 61.908, 64.835, 71.142, 120.499, 134.22, 139.293, 156.590, 189.495; high-resolution mass spectrum calcd for $C_{19}H_{32}O_3Si$ m/e 336.212 08, found 336.212 01.

(±)-(4aα,8aα)-4a-[(*tert*-Butyldimethylsiloxy)methyl]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran-3-carboxaldehyde (18). To a 0.3 M toluene solution of nitrile **17** (2.98 g, 8.95 mmol) cooled to −78 °C under nitrogen was added 9.0 mL of a 1.0 M hexanes solution of diisobutylaluminum hydride. Thirty minutes after the addition was complete, the solution was poured into a rapidly stirred slurry of acetic acid (10 mL) and ice (25 g). Chloroform (200 mL) and 1 N HCl (25 mL) were added, and vigorous stirring was continued until both layers clarified. The layers were separated, and the organic layer was washed with bicarbonate (50 mL) and brine (50 mL). Drying and removal of solvents afforded 2.82 g of aldehyde **18** as a colorless oil which was used without purification (94% yield from nitrile **17**, 70% overall yield from lactone **12b**).

(±)-(4aα,8aα)-4a-[(*tert*-Butyldimethylsiloxy)methyl]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran-3-carboxylic Acid (19). A solution of sodium chlorite (1.41 g of commercial 85%, 12.5 mmol) in 10 mL of NaH_2PO_4 pH 3.5 buffer was added dropwise to a rapidly stirred solution of aldehyde **18** (3.36 g, 10 mmol) and 2-methyl-2-butene (10.6 mL, 100 mmol) in 50 mL of *tert*-butyl alcohol at room temperature. The resulting light yellow solution was stirred 8 h at ambient temperature. It was made basic with 6 N NaOH (pH 10), and the *tert*-butyl alcohol was removed at reduced pressure. The residue was dissolved in water and extracted twice with hexanes. The water layer was acidified (6 N HCl, pH 3) and extracted twice with ether (100 mL). The organic layer was washed with water (25 mL) and brine (25 mL). Drying and removal of solvents afforded a colorless solid which was recrystallized from hexanes to provide 2.5 g of colorless plates (mp 143–145 °C). Chromatography (silica gel, 5:1 hexanes–EtOAc) provided a further 0.35 g of crystals: 2.85 g total (80%); IR (film) 3400, 2970, 1700 cm^{-1}; 100-MHz NMR ($CDCl_3$) 0.10 (s, 6 H), 0.91 (s, 9 H), 1.72 (br s, 3 H), 1.8–2.0 (m, 4 H), 2.17 (t, J = 2 Hz, 3 H), 3.56, 3.78 (AB q, J = 11 Hz, 2 H), 4.22 (br s, 1 H, collapses to d, J = 4 Hz, on irradiation at δ 1.73), 4.32 (m, 2 H), 5.46 (br s, 1 H, collapses to d, J = 4 Hz, on irradiation at δ 1.73), 7.2 (var, br s, 1 H, OH). Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.77; H, 9.09. Found: C, 64.90; H, 9.20.

(±)-(4aα,8aα)-4a-[(*tert*-Butyldimethylsiloxy)methyl]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran-3(4*H*)-one (3a). Ethyl chloroformate (neat, 0.5 mL, 5.2 mmol) was added to a 0 °C THF (10 mL) solution of acid **19** (1.3 g, 3.95 mmol) and triethylamine (0.66 mL, 4.75 mmol) under nitrogen. The resulting suspension was stirred 60 min, and then sodium azide (0.51 g, 8.0 mmol) in 3 mL of water was added dropwise. The initially homogeneous solution was stirred 3 h at 0 °C before being partitioned between toluene (50 mL) and water. The organic layer was washed with water (10 mL) and brine (10 mL) and dried briefly over $MgSO_4$.

The filtered solution was concentrated to approximately 25 mL and heated at reflux for 30 min to effect rearrangement to the isocyanate. The toluene was removed under reduced pressure and replaced with 20 mL of THF. NaOH (5 mL of a 1 N solution) was added and the two-phase system stirred vigorously for 2 h. After the mixture was cooled to 0 °C, 6 N HCl was added to pH 3 and stirring continued a further 2 h. The inhomogeneous mixture was poured into ether (100 mL) and the organic material washed with bicarbonate (15 mL), water (10 mL), and brine. Drying and removal of solvents afforded a crude yellow oil, which was chromatographed (silica gel, 20:1 hexanes–EtOAc) to provide 0.79 g (62%) of ketone **3a** as a mixture of diastereomers: R_f (3:1 hexanes–EtOAc) minor isomer 0.60, major 0.55; IR (film) 2950, 2860, 1730, 1095 cm^{-1}; 100-MHz NMR ($CDCl_3$) for major isomer δ 0.10 (s, 6 H), 0.89 (s, 9 H), 1.13 (d, J = 7 Hz, 3 H), 1.7–2.0 (m, 7 H), 2.52 (q, J = 7 Hz, 1 H), 3.34, 3.48 (AB q, J = 10 Hz, 2 H), 3.9–4.1 (m, 3 H), 5.55 (m, 1 H); 90-MHz ^{13}C NMR ($CDCl_3$) δ −5.787, 6.698, 18.143, 23.411, 25.752, 26.922, 28.483, 43.505, 47.277, 64.250, 73.355, 74.256, 120.697, 138.841, 211.546; high-resolution mass spectrum calcd for $C_14H_{23}O_3Si$ (loss of C_4H_9) m/e 267.141 65, found m/e 267.141 06.

(±)-(4aα,8aα)-4,7-Dimethyl-4a-(hydroxymethyl)-4a,5,6,8a-tetrahydro-2*H*-1-benzopyran-3(4*H*)-one (3b). The silyl ether **3a** (0.56 g, 1.73 mmol) and tetra-*n*-butylammonium fluoride (4.7 mL of a 0.75 M THF solution, 3.5 mmol) were stirred at room temperature for 2 h. The light yellow solution was poured into ether (100 mL) and washed with bicarbonate (15 mL) and brine (10 mL). Drying and removal of solvents afforded a light yellow oil which was chromatographed (silica gel, 5:1 hexanes–EtOAc) to provide 0.308 g (85%) of alcohol **3b** as a colorless oil: R_f (3:1 benzene–acetone) 0.27; IR (film) 3450, 1720, 1090 cm^{-1}; 100-MHz NMR ($CDCl_3$) for major isomer δ 1.16 (d, J = 7 Hz, 3 H), 1.5–2.2 (m, 7 H), 2.60 (q, J = 7 Hz, 1 H), 3.55 (m, 2 H), 4.0 (m, 2 H), 4.26

(br s, 1 H), 5.52 (br s, 1 H); high-resolution mass spectrum calcd for $C_{12}H_{18}O_3$ m/e 210.125 60, found m/e 210.126 05.

(±)-(4aα,7α,8aβ)-4,7-Dimethyl-4a,7-ethano-4a,7,8,8a-tetrahydro-2*H*,5*H*-pyrano[4,3-*b*]pyran-3(4*H*)-one (20). Phenylselenyl chloride (0.086 g, 0.56 mmol) in dichloromethane (1.0 mL) was added dropwise to a solution of keto alcohol **3b** in dichloromethane (2.0 mL) cooled to −78 °C under nitrogen. At the completion of addition, the cooling bath was removed and the light orange solution allowed to warm to room temperature. Removal of solvents and chromatography (silica gel, 10:1 hexanes–EtOAc) afforded the crude selenide which was dissolved in toluene (5 mL) and heated to reflux with tri-*n*-butyltin hydride (0.22 mL, 0.82 mmol) and a catalytic amount of azobis(isobutyrylnitrile). After 60 min, the solution was cooled to room temperature. Concentration and chromatography (silica gel, 10:1 hexanes–EtOAc) provided ether **20** as a colorless oil: R_t 9.38 min (175 °C, isothermal, 6 ft × $^1/_4$ in., 5% SE-30 capillary column gas chromatograph); IR (film 2960, 1725, 1150 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.98 (d, J = 7 Hz, 3 H), 1.14 (s, 3 HO), 1.3–1.8 (m, 6 H), 2.30 (q, J = 7 Hz, 1 H), 3.60 (m, 1 H), 4.1 (m, 4 H); high-resolution mass spectrum calcd for $C_{12}H_{18}O_3$ m/e 210.125 60, found m/e 210.126 85.

Acknowledgment. We thank the National Institutes of Health (Grant No. CA23663) for generous financial assistance.

Registry No. 3a (isomer 1), 75233-76-0; **3a** (isomer 2), 75233-77-1; **3b**, 75233-78-2; **4**, 75247-61-9; **5**, 75233-79-3; **6**, 75233-80-6; **7**, 75233-81-7; **9**, 75233-82-8; **10**, 75233-83-9; **11a**, 75233-84-0; **11a** phosphonate, 75233-85-1; **11b**, 75247-62-0; **12a**, 75247-63-1; **12a** lactol, 75233-86-2; **12b**, 75233-87-3; **12b** lactol (isomer 1), 75233-88-4; **12b** lactol (isomer 2), 75233-89-5; **13**, 75233-90-8; **14**, 75233-91-9; **15**, 75233-92-0; **17**, 75233-93-1; **18**, 75233-94-2; **19**, 75233-95-3; **20**, 75233-96-4; 3-(hydroxymethyl)-3-buten-2-one, 73255-29-5; 1-acetoxy-3-methyl-1,3-butadiene, 17616-47-6; bromoacetyl bromide, 598-21-0; cyanoacetyl chloride, 16130-58-8.

Synthesis and Properties of 2′-Deoxy-2′-thiocytidine

Arvind D. Patel, Wayne H. Schrier, and Joseph Nagyvary*

Department of Biochemistry and Biophysics, Texas A&M University, College Station, Texas 77843

Received May 22, 1980

In order to assess the significance of the 2′-position of nucleosides, the nucleoside analogue 2′-deoxy-2′-thiocytidine was synthesized by using 2,2′-anhydro-1-β-D-arabinosylcytosine and P_2S_5 as starting materials. Several thiophosphorylated derivatives were also obtained as synthetic intermediates and characterized by NMR spectroscopy and elemental analysis. The main stable intermediate was 2′-deoxy-2′-thiocytidine 2′,3′-phosphorodithioate which was subjected to iodine oxidation, alkaline hydrolysis, and finally, a dephosphorylation step, yielding the title compound 2′-*S*-dCyd, or its disulfide. According to NMR and ORD data, the 2′-carbon of the nucleoside is in the endo orientation, and the rotation of the cytosine moiety is restricted. The most outstanding chemical property of 2′-*S*-dCyd is the lability of the glycosidic bond, owing to an intramolecular displacement reaction. The rate of decomposition could be conveniently studied by ORD spectroscopy as a function of pH, ionic strength, and temperature. Slightly different first-order kinetics were observed for the nucleoside and its 3′-phosphate.

In the past decade numerous 2′-substituted nucleoside analogues[1–4] have been prepared for the study of structure–function relationships in nucleic acids. Of these analogues, only the 2′-amino and thio substituents possess the capacity to hydrogen bond as hydrogen donors. Since the closest analogue of OH is the SH group, the thorough study of 2′-deoxy-2′-thionucleosides seems to be overdue. To this date work with 2′-deoxy-2′-thionucleosides has not progressed much beyond the point of successful or unsuccessful chemical synthesis.

Previous experiments[5–8] have shown that the classical chemical routes for the introduction of a 2′-thio (erythro) substituent, i.e., displacement on a nucleoside of a threo substituent with thioacetate or thiobenzoate, require protected nucleosides and deblocking procedures which result in cleavage of the glycosidic bond. Only one analogue, 2′-deoxy-2′-thiouridine was chemically characterized,[9,10] but it was not investigated biochemically or biologically. Derivatives of 2′-deoxy-2′-thioadenosine were prepared,[5–8] but the free nucleoside was too labile to be isolated.

We have concentrated our efforts on the synthesis of the cytidine analogue 2′-deoxy-2′-thiocytidine because of its expected stability and biological activity. Our attempts to obtain 2′-*S*-dCyd[11] in a manner analogous to Imazawa's method by reacting anhydro-araC[11] with thioacetate were not successful, and only cytosine was formed. We found it necessary to introduce a thio nucleophile as a 3′ neighboring group which could then react selectively with the 2′-carbon. The use of a thiophosphorylated precursor allowed the introduction of cis 3′-O, 2′-S substitution without the use of blocking groups. The conditions for the hydrolysis and oxidation of the phosphorodithioate esters were mild and yielded a stable disulfide of 2′-*S*-dCyd. This convenient storage form, in turn, could be quantitatively reduced to the thiol by using β-mercaptoethanol.

In our first attempt[12] we used dithiophosphate as a thiophosphorylating agent, but the lability of this compound made it unsuitable for large-scale preparation of 2′-*S*-dCyd. In the same communication we also noted the felicitous peculiarity of anhydro-araC chemistry which features a reversal in the customary reactivities of the 5′ and 3′ OH groups. This becomes understandable in view of the X-ray diffraction data which reveal an interaction

(1) F. Rottman and K. Heinlein, *Biochemistry*, 7, 2634–2639 (1968).
(2) J. Hobbs, H. Sternbach, M. Sprinzl, and F. Eckstein, *Biochemistry*, 11, 4336–4344 (1972).
(3) M. Ikehara, N. Kakiuchi, and T. Fukui, *Nucleic Acids Res.*, 5, 3315–3324 (1978).
(4) M. Ikehara and Y. Takatsuka, *Chem. Pharm. Bull.*, 26, 985–988 (1978).
(5) L. Goodman and J. E. Christensen, *J. Org. Chem.*, 28, 2610–2613 (1963).
(6) K. J. Ryan, E. M. Acton, and L. Goodman, *J. Org. Chem.*, 36, 2646–2657 (1971).
(7) R. S. Ranganathan, *Tetrahedron Lett.*, 1291–1294 (1977).
(8) R. Mengel and H. Griesser, *Tetrahedron Lett.*, 1177–1180 (1977).
(9) M. Imazawa, T. Ueda, and T. Ukita, *Tetrahedron Lett.*, 4807–4810 (1970).
(10) M. Imazawa, T. Ueda, and T. Ukita, *Chem. Pharm. Bull.*, 23, 604–610 (1975).
(11) Abbreviations: 2′-*S*-dCyd, 2′-deoxy-2′-thiocytidine; 2′-*S*-dCyd-2′,3′-P and 2′-*S*-dCyd-2′,2′-PS are the corresponding cyclic phosphorothioate and phosphorodithioate; anhydro-araC, 2,2′-anhydro-1-β-D-arabinosylcytosine.
(12) E. Bradbury and J. Nagyvary, *Nucleic Acids Res.*, 3, 2437–2443 (1976).

0022-3263/80/1945-4830$01.00/0