Anal. Calcd for $C_{23}H_{30}N_6O_8S$·HCl: C, 47.06; H, 5.32; N, 14.32. Found: C, 47.71; H, 5.47; N, 13.88.

Methyl *N*-Acetyl-2-(ethylthio)-L-tryptophanoate (7). A solution of **2** (258 mg, 1.0 mmol), ethanethiol (0.75 mL, 10 mmol), dioxane (6 mL), and 0.2 M NH_4CO_3 (3 mL) was shaken in a sealed tube at 55 °C overnight and then lyophilized. The residue was chromatographed on a Sephadex column with 40% ethanol. Homogeneous fractions were pooled and lyophilized. Crystallization of the pasty residue (176 mg, 55%) was unsuccessful. The material was homogeneous by HPLC with a retention time of 19 min (60% → 90% B).

Mass spectra (CI), *m/e* 323 (6%), 322 (20%), 321 (100%, P + 1), 277 (9%), 261 (52%), 215 (5%); (EI), *m/e* 320 (4%), 261 (5%), 232 (3%), 190 (100%), 162 (19%), 157 (10%), 130 (27%), 117 (7%); ^{1}H NMR ($CDCl_3$) 8.59 (s, 1, $N_{ind}H$), 7.52 (d, 7.5, 1, H_4), 7.4-7.05 (m, 3, H_{5-7}), 6.23 (d, 7, 1, NHAc), 4.93 (5 lines, 2 overlapping triplets, 6, 1, α-H), 3.69 (s, 3, OCH_3), 3.39 (7 lines, *J* = 14, 6, and 7, 2 protons, β-H), 2.76 (q, 7, 2, SCH_2), 1.95 (s, 3, NAc), 1.25 (5 lines, 2 overlapping triplets), ca. 7, 3, SCH_2CH_3).

Methyl *N*-Acetyl-2-[(2-hydroxyethyl)thio]-L-tryptophanoate (8). A solution of **2** (103 mg, 0.4 mmol), 2-mercaptoethanol (0.28 mL, 4 mmol), dioxane (3.5 mL), and 0.5 M NH_4HCO_3 (2.0 mL) was shaken for 6 h at 55 °C and lyophilized. The residue was purified on a Sephadex column with 30% ethanol as described above and yielded 97 mg (72%) of pasty solid which was homogeneous on HPLC; retention time, 11 min (60% → 90% B). The ^{1}H NMR spectrum indicated some 30% 2-mercaptoethanol disulfide: mass spectra (CI), *m/e* 337 (P + 1, 100%), 261 (55%), 255 (19%); (EI), *m/e* 336 (3%), 304 (4%), 277 (3%), 245 (8%), 232 (3%), 206 (100%), 188 (8%), 162 (68%), 130 (17%), 128 (8%), 117 (9%); ^{1}H NMR ($CDCl_3$) 9.25 (s, 1, $N_{ind}H$, exchanges with CD_3OD), 7.48 (d, 7.5, 1, H_4), 7.27 (d, 7.5, 1, H_7), 7.20 (t, 7.5, 1, H_6), 7.11 (t, 7.5, 1, H_5), 6.27 (d, 7, 1, NHAc, slow exchange), 4.93 (q, 6, 1, α-H), 3.80 (t, 5.5, 2, CH_2OH), 3.68 (s, 3, OCH_3), 3.39 (7 lines, *J* = 14 and 6, 2 protons, β-H), 2.91 (5 lines, overlapping triplets, *J* = 5.5, ~3, SCH_2 and $(SCH_2CH_2OH)_2$ impurity), 1.94 (s, 3, NAc). Also a triplet (approximately 1 proton) noted at 3.91 (*J* = 6) corresponding to CH_2OH protons of impurity.

Methyl *N*-Acetyl-2-(*S*-cysteinyl)-L-tryptophanoate (9). A solution of **2** (103 mg, 0.4 mmol), L-cysteine (194 mg, 1.6 mmol), dioxane (3.5 mL), and 0.5 M NH_4CO_3 (4.5 mL) was shaken at 55 °C for 2 h and filtered to remove precipitated cystine. The filtrate was acidified with 6 M HCl and lyophilized. The residue was purified on a Sephadex column with water yielding 101 mg (61%) of fluffy powder; retention time on HPLC 28 min (20% → 60% B); $[\alpha]^{20}_D$ +14° (*c* 0.28, water).

Anal. Calcd for $C_{17}H_{21}N_3O_5S$·HCl: C, 49.10; H, 5.33; N, 10.10. Found: C, 50.26; H, 5.59; N, 10.88.

Mass spectra (CI), *m/e* 345 (3%), 307 (16%), 293 (84%), 275 (22%), 261 (100%); (EI), *m/e* 306 (7%), 258 (22%), 216 (18%), 187 (17%), 176 (100%), 162 (40%), 161 (54%). ^{1}H NMR (CD_3OD): strong solvent impurities at δ 3.23 and 4.95 obscure some signals; nevertheless sharp singlets at 1.89 (NDAc) and 3.52 (CO_2CH_3) and an 8-line ABX spectrum) (δ_A = 2.94, δ_B = 3.21, J_{AB} = 14, J_{AX} = 8.5, J_{BX} = 7), most probably for the β-CH_2 of the tryptophyl side chain, can be discerned. A spectrum in CD_3CN containing ca. 10% CD_3OD exhibits impurity signals at 1.93 and 3.0 but again, sharp singlets at 1.80 and 3.46 are seen and a triplet (*J* = 7) at 4.60 for the tryptophyl α-H is evident. Both spectra show the usual aromatic pattern. While complicated by the poor solubility of **9** (ca. 10 mg/mL), these spectra are consistent with a single diastereomer only of **9** and strongly suggest that no racemization of **2** or **9** occurs during the thiolysis reaction.

Methyl *N*-Acetyl-2-[N_α-(γ-glutamyl)cysteinylglycyl-*S*]-L-tryptophanoate (10). The reaction was conducted with **2** (103 mg, 0.4 mmol), glutathione (492 mg, 1.6 mmol), dioxane (3.5 mL), and 0.5 M NH_4HCO_3 (4.5 mL) at 55 °C for 6 h. After lyophilization, the residue was dissolved in 1 M HCl (4 mL) and fractionated on a Sephadex column with water giving 164 mg (68%) of fluffy powder: retention time on HPLC, 24 min (20% → 60% B); $[\alpha]^{20}_D$ +17° (*c* 0.29, water).

Anal. Calcd for $C_{24}H_{31}N_5O_9S$·HCl: C, 47.88; H, 5.36; N, 11.63. Found: C, 48.71; H, 5.54; N, 11.88.

The reaction was also carried out at room temperature to give the same compound and was complete after 3 days.

Enzymatic Hydrolyses of 8 and 9. Compound **8** or **9** and α-chymotrypsin in a ratio of 20 to one were stirred at pH 8 (0.1 M NH_4HCO_3) for 4 h at 37 °C, then lyophilized, and analyzed by HPLC (20% → 60% B) to reveal a single major peak with a retention time of 4.5 or 16 min, respectively. Compounds **8** and **9** had retention times of 11 and 28 min, respectively, under these conditions.

Acknowledgment. We are grateful to Noel Whittaker (NIADDK) for determining the mass spectra reported herein.

Registry No. **1**, 21018-89-3; **2**, 25690-48-6; **3**, 92818-08-1; **4**, 92818-09-2; **5**·HCl, 92843-98-6; **6**·HCl, 92818-10-5; **7**, 92818-11-6; **8**, 92818-12-7; **9**·HCl, 92818-14-9; **10**·HCl, 92818-13-8; ethanethiol, 75-08-1; 2-mercaptoethanol, 60-24-2; L-cysteine, 52-90-4; glutathione, 70-18-8.

Synthesis of Protected Aminocyclohexanediols

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As the model study for the synthesis of aminocyclitols and amino sugars, 2-cyclohexen-1-ol (**1**) was converted to five of the seven possible (1,2,3)-aminocyclohexanediols in protected form (**4a**, **6a**, **11a**, **13a**, and **18a**). Two flexible new approaches were employed: (1) the preparation and iodocyclization of the unsaturated carbonimidothioate **2**, and (2) the preparation, rearrangement, and subsequent iodocyclization of unsaturated carbonimidate **8**. The alkene functionalization reactions allow a high measure of regio- and stereochemical control over the placement of the eventual amino and hydroxy groups.

The vicinal amino alcohol functionality is the principle structural characteristic of aminocyclitols and amino sugars.[1] In many of these compounds a second hydroxy group flanks the amino alcohol. In connection with our interest in the synthesis of aminocyclitol antibiotics,[2] we have developed methods for the regio- and stereospecific introduction of the cis, vicinal amino alcohol functionality.[3-5] We now report the optimization of these procedures

(1) Recent reviews: (a) Horton, D.; Wander, J. D. In "The Carbohydrates"; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1980; Vol. IB, pp 644-760. (b) Williams, N. R. *Carbohydr. Chem.* **1983**, *15* (Part 1), 91-105, 171-173, 176-198.

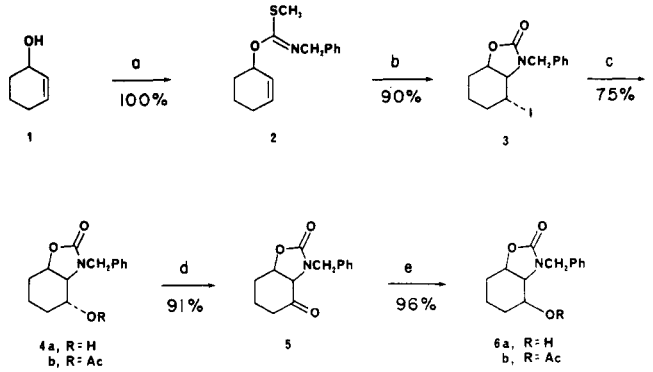
(2) Rinehart, K. L.; Suami, T. "Aminocyclitol Antibiotics"; American Chemical Society: Washington, DC, 1980.

(3) Knapp, S.; Patel, D. V. *Tetrahedron Lett.* **1982**, *23*, 3539.

(4) Knapp, S.; Patel, D. V. *J. Am. Chem. Soc.* **1983**, *105*, 6985.

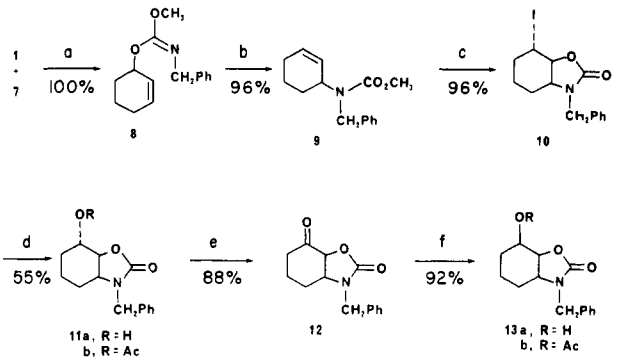
0022-3263/84/1949-5072$01.50/0

Scheme I. N-Cyclization[a]



[a] (a) NaH, $PhCH_2NCS$, CH_3I; (b) I_2, THF, aqueous Na_2SO_3; (c) $AgOCOCF_3$, CH_3NO_2; (d) pyridinium chlorochromate; (e) L-Selectride.

Scheme II. O-Cyclization[a]



[a] (a) KH; (b) toluene, reflux; (c) I_2, THF, aqueous Na_2SO_3; (d) $AgOCOCF_3$, CH_3NO_2; (e) pyridinium chlorochromate; (f) L-Selectride.

with 2-cyclohexen-1-ol (1) as the model and their extension to the synthesis of amino *diols*.[6]

Results

As reported previously,[4] sequential treatment of a tetrahydrofuran solution of **1** with sodium hydride, benzyl isothiocyanate, and iodomethane gave in quantitative yield the unsaturated carbonimidothioate **2** (Scheme I). Iodocyclization of **2** occurred upon treatment with iodine in tetrahydrofuran solution (aqueous sodium sulfite quench), leading to iodo carbamate **3**. We find this procedure superior to the use of bromonium bis(collidine) perchlorate[4] in terms of yield, economy, and ease of operation.

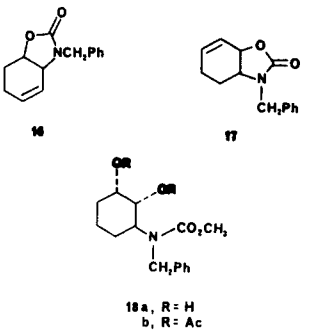
Treatment of **3** with silver(I) trifluoroacetate in nitromethane solution containing 0.9 equiv of added water gave the *exo*-hydroxy carbamate **4a** (characterized as its acetate, **4b**), accompanied by a small amount of alkene **16** (12%). The stereochemistry of **4a** was secured by its oxidation to ketone **5**, which in turn was reduced exclusively from the exo face to give the *endo*-hydroxy carbamate **6a** (characterized as its acetate, **6b**). Thus the silver assisted solvolysis of **3** is stereospecific within the limits of TLC detection, and both protected amino diols **4a** and **6a** are accessible in good yield.

The complementary model study is centered on an O-cyclization reaction and is displayed in Scheme II. Reaction of the potassium salt of **1** with methyl *N*-benzylchloroformimidate (**7**) gave the unsaturated carbonimidate **8**, which rearranged[3] in refluxing toluene to the carbamate **9**. Although we had employed silver-based reagents in our earlier efforts[3] to cyclize **9**, simply treating **9** with iodine in tetrahydrofuran solution (aqueous sodium sulfite quench) gave iodo carbamate **10** in high yield. Conversion to the *exo*-hydroxy carbamate **11a** (characterized as its acetate, **11b**) was carried out by using the reaction conditions which were successful for **4a**, but the product was accompanied by the *endo*-hydroxy carbamate **13a** (28%) and the alkene **17** (18%).

Since the reaction of **3** was significantly faster and more stereoselective than that of **10**, it is likely that the nearby nitrogen allows more equilibration of O-alkylated nitromethane-containing intermediates **14** or participates directly in the solvolysis to a greater extent (via **15**) compared with the nearby oxygen of **10**.[7] An explanation based on steric hindrance to approach of the nucleophile is weakened by the observation that the N-unsubstituted substrate **21** also undergoes stereospecific substitution (see Scheme III).

The structure of **11a** was proven by oxidation to the ketone **12**, then reduction to the *endo*-hydroxy carbamate **13a** (characterized as its acetate, **13b**). The mixture of **11a** and **13a** may also be taken through this sequence, giving **13a** in good overall yield. Thus in addition to **4a** and **6a**, the protected amino diols **11a** and **13a** are also readily prepared from **1**.

The dehydroiodination products **16** and **17** were independently synthesized in quantitative yield by DBU treatment of **3** and **10**, respectively. Alkenes **16** and **17** may be thought of as precursors for amino *triol* synthesis.



An additional pattern of amino diol substitution, which does not involve a cis, vicinal amino alcohol unit, may be reached from the 3-aminocyclohexene derivative **9**. Cis-hydroxylation of **9** catalyzed by osmium tetroxide gave in high yield a single diol, **18a** (characterized as its diacetate **18b**).

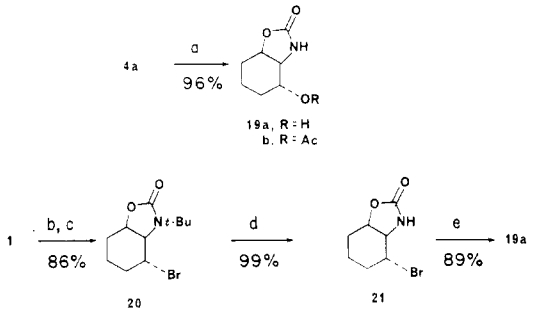
Finally, we report experimental conditions under which N-alkylated oxazolidinones may be deprotected (Scheme III). Treatment of **4a** with lithium metal in ammonia solution[6a] removed the benzyl group and produced **19a** (characterized as its acetate, **19b**). An independent preparation of **19a** was carried out starting with **20**, the product of a bromocyclization.[4] Treatment of **20** with trifluoroacetic acid[4] gave the dealkylated oxazolidinone **21**.

(5) Knapp, S.; Sebastian, M. J.; Ramanathan, H. *J. Org. Chem.* **1983**, *48*, 4786.

(6) Recent related work: (a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (b) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371. (c) Cardillo, G.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1489. (d) Pauls, H. W.; Fraser-Reid, B. *Ibid.* **1983**, 1031.

(7) For similar reactions see: (a) Kevill, D. N.; Johnson, G. H.; Likhite, V. V. *Chem. and Ind. (London)* **1969**, 1555. (b) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619.

Scheme III. Dealkylation of Oxazolidinones[a]



[a] (a) Li, NH_3, −33 °C; (b) NaH, *t*-BuNCS, CH_3I; (c) $Br(collidine)_2ClO_4$, aqueous Na_2CO_3; (d) TFA, 25 °C; (e) $AgOCOCF_3$, CH_3NO_2, reflux.

Stereospecific replacement of the bromide by hydroxyl was accomplished by treating **21** with silver(I) trifluoroacetate in nitromethane. The resulting hydroxy carbamate matched **19a**, and its acetate matched **19b**. The usefulness of *tert*-butyl as an N-protecting group was demonstrated in our synthesis of the aminocyclitol (±)-sporamine,[4] and we anticipate that the *N*-benzyl group will be appropriate for amino sugar synthesis.

Experimental Section

Apparatus and Reagents. Melting points were determined on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded by using a Perkin-Elmer Model 727B spectrophotometer (absorption maxima are in cm^{-1}). Proton nuclear magnetic resonance (NMR) spectra were obtained on deuteriochloroform solutions with a Varian Associates T-60 instrument unless otherwise specified. Chemical shifts are reported in parts per million downfield from tetramethylsilane and coupling constants are in hertz. Elemental analyses were obtained from Galbraith Laboratories (Knoxville, TN).

Precoated silica gel plates (Baker Si250F) were used for analytical thin-layer chromatography (TLC). E. Merck silica gel 60 (70–230 or 230–400 mesh) was employed for column chromatography. Tetrahydrofuran (THF) was distilled from benzophenone ketyl. Dichloromethane, nitromethane, pentane, and toluene were distilled from calcium hydride. Other reagents were obtained commercially and used as received unless otherwise specified. Organic solutions were dried over anhydrous sodium sulfate. All reactions were run under argon atmosphere.

***O*-3-Cyclohexenyl *S*-Methyl *N*-Benzylcarbonimidothioate (2).** A solution of 2-cyclohexen-1-ol (**1**, 1.963 g, 20 mmol) in 10 mL of THF was added dropwise to a suspension of oil-free sodium hydride (0.625 g, 26 mmol) in 25 mL of THF at 0 °C. After 30 min at 0 °C, a solution of 2.98 g (20 mmol) of benzyl isothiocyanate in 5 mL of THF was added. The reaction was stirred at 25 °C for 3 h, and then 4.98 mL (40 mmol) of iodomethane was added. The THF was removed by rotary evaporator and 20 mL of ether was added. The reaction mixture was filtered through Celite with ether wash (3 × 10 mL) and the combined organic extract was concentrated to give the carbonimidothiate **2** (5.25 g) in essentially quantitative yield: NMR 0.9–2.27 (m, 6 H), 2.40 (s, 3 H), 4.45 (s, 2 H), 5.27–5.77 (m, 1 H), 5.93 (m, 2 H), 7.30 (br s, 5 H); IR (film) 3075, 3050, 3025, 2925, 2850, 2820, 1700, 1630, 1580, 1495, 1450, 1430, 1390, 1355, 1310, 1220, 1170, 1080, 1060, 1025, 1005, 970, 910, 855, 840, 815, 765, 725, 695.

3-Benzyl-4-iodo-3aα,4β,5,6,7,7aα-hexahydrobenzoxazolin-2-one (3). A solution of 1.905 g (7.5 mmol) of iodine in 15 mL of THF was added to a solution of 1.305 g (5.0 mmol) of thiocarbonimadate **2** in 7.5 mL of THF. After 18 h at 25 °C, the reaction was quenched with saturated aqueous sodium sulfate and worked up as in the preparation of **10** to give a residue which crystallized from ether. Pure **3**, 1.604 g (90%), was collected: mp 87–89 °C; NMR 1.1–2.43 (m, 6 H), 3.88 (app t, J = 6, 1 H), 4.03–4.7 (m, 2 H), 4.53 (d, J = 15, 1 H), 4.85 (d, J = 15, 1 H), 7.33 (br s, 5 H); IR 3030, 2950, 2875, 1645, 1490, 1450, 1440, 1430, 1410, 1375, 1350, 1320, 1305, 1270, 1260, 1190, 1170, 1150, 1140, 1130, 1085, 1070, 1060, 1005, 960, 880, 765, 730, 700. Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.12; H, 4.48; N, 3.92; I, 35.55. Found: C, 47.27; H, 4.54; N, 3.90; I, 35.28.

3-Benzyl-4-hydroxy-3aα,4β,5,6,7,7aα-hexahydrobenzoxazolin-2-one (4a). A solution of 1.517 g (4.25 mmol) of **3** in 15 mL of nitromethane was stirred at 0 °C and treated with 1.409 g (6.375 mmol) of solid silver trifluoroacetate and 76.5 μL of water (4.25 mmol). Silver iodide began to precipitate immediately. After 2 h at 0 °C, the reaction mixture was worked up as for **11a** and chromatographed with 4:1 then 1:1 petroleum ether–ethyl ether as eluant. Collected in order of elution were the alkene **16** (117 mg, 12%) and **4a** (791 mg, 75%): NMR 1.1–2.2 (m, 6 H), 3.30 (app t, J = 6.5, 1 H), 3.40–3.97 (m, 2 H), 4.10–4.67 (m, 1 H), 4.40 (d, J= 15, 1 H), 4.82 (d, J = 15, 1 H), 7.27 (br s, 5 H); IR (film) 3415, 3020, 2940, 2860, 1735, 1695, 1440, 1420, 1360, 1300, 1255, 1220, 1200, 1180, 1160, 1125, 1105, 1065, 1040, 995, 965, 895, 870, 815, 760, 700, 680.

exo-Alcohol **4a** was further characterized as its acetate, **4b** (mp 82–83 °C from petroleum ether–ether): NMR 1.1–2.33 (m, 6 H), 2.03 (s, 3 H), 3.57 (app t, J = 6, 1 H), 4.4–5.27 (m, 2 H), 4.12 (d, J = 15, 1 H), 4.82 (d, J = 15, 1 H), 7.36 (br s, 5 H); IR (KBr) 2940, 1745, 1655, 1495, 1435, 1420, 1375, 1360, 1320, 1235, 1200, 1170, 1135, 1120, 1090, 1045, 1000, 945, 905, 835, 820, 765, 740, 705. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.54; H, 6.75; N, 4.82.

3-Benzyl-4-keto-3aα,4,5,6,7,7aα-hexahydrobenzoxazolin-2-one (5). Oxidation of 741 mg of **4a** as for **12** gave 661 mg (91%) of **5**. A sample crystallized from petroleum ether–ether had mp 56–57 °C: NMR 1.6–2.63 (m, 6 H), 3.77 (d, J = 8, 1 H), 4.7–5.07 (m, 1 H), 4.42 (d, J = 15, 1 H), 4.90 (d, J = 15, 1 H), 7.33 (s, 5 H); IR (KBr) 3015, 2950, 2920, 2850, 1750, 1645, 1600, 1580, 1525, 1495, 1440, 1420, 1375, 1360, 1340, 1330, 1300, 1265, 1245, 1215, 1200, 1160, 1120, 1090, 1075, 1045, 1015, 980, 920, 900, 880, 810, 760, 740, 700. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.61; H, 6.17; N, 5.72. Found: C, 68.57; H, 6.23; N, 5.76.

3-Benzyl-4-hydroxy-3aα,4α,5,6,7,7aα-hexahydrobenzoxazolin-2-one (6a). Reduction of 245 mg (1 mmol) of **5** as for **13a** gave 237 mg (96%) of **6a**: NMR 1.17–2.57 (m, 7 H), 3.45 (dd, J = 4, 6.5, 1 H), 3.83–4.27 (m, 1 H), 4.27–4.70 (m, 1 H), 4.25 (d, J = 15, 1 H), 4.88 (d, J = 15, 1 H), 7.33 (br s, 5 H); IR (film) 3400, 3010, 2945, 1850, 1725, 1490, 1420, 1340, 1260, 1220, 1195, 1175, 1120, 1090, 1070, 1050, 1040, 980, 965, 890, 865, 845, 815, 795, 760, 735, 700.

endo-Alcohol **6a** was also characterized as its acetate, **6b** (mp 87.5–88.5 °C from petroleum ether–ethyl ether): NMR 1.1–2.4 (m, 6 H), 2.10 (s, 3 H), 3.50 (dd, J = 4, 6.5, 1 H), 3.87 (d, J = 15, 1 H), 4.33–4.77 (m, 1 H), 4.83 (d, J = 15, 1 H), 5.03–5.33 (m, 1 H), 7.30 (br s, 5 H); IR (KBr) 3015, 2935, 1740, 1650, 1490, 1435, 1410, 1375, 1340, 1330, 1270, 1240, 1220, 1210, 1195, 1170, 1120, 1085, 1060, 1020, 1000, 970, 955, 920, 795, 760, 740, 700. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.60; H, 6.74; N, 4.74.

Methyl *N*-Benzylchloroformimidate (7). A solution of 1.88 g (10 mmol) of benzylimidoyl dichloride[8] in 5 mL of anhydrous ether was added to a suspension of freshly prepared sodium methoxide (0.594 g, 11 mmol) in 20 mL of ether. The mixture was heated at reflux for 48 h, after which time the NMR spectrum of an aliquot indicated the reaction was complete. The mixture was filtered through Celite and the solid residue washed with ether (3 × 10 mL). Concentration of the combined washes gave 1.84 g (100%) of product, pure by NMR analysis. NMR 3.9 (s, 3 H), 4.57 (s, 2 H), 7.33 (s, 5 H).

***O*-3-Cyclohexenyl *O'*-Methyl *N*-Benzylcarbonimidate (8).** A solution of 1.963 g (20 mmol) of 2-cyclohexen-1-ol (**1**) in 10 mL of THF was added by drops to a suspension of 25 mmol of oil-free potassium hydride in 25 mL of THF at 0 °C. The reaction was stirred at 0 °C for 15 min and 25 °C for 30 min and then cooled to −78 °C. A solution of **7** (3.67 g, 20 mmol) in 5 mL of THF was added, and the reaction was allowed to gradually warm to 25 °C. The THF was removed by rotary evaporator, ether (25 mL) was added, and the reaction mixture was filtered through Celite with ether rinse (3 × 20 mL). The combined organic solution was dried and concentrated to give 4.98 g of **8** (100%). The product was unstable toward chromatography and distillation but was pure

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enough as obtained for the subsequent step: NMR 1.47–2.37 (m, 6 H), 3.73 (s, 3 H), 3.83 (s, 3 H), 4.43 (s, 2 H), 4.83–5.57 (m, 1 H), 5.57–6.23 (m, 2 H), 7.37 (s, 5 H); IR (film) 3080, 3060, 3035, 2950, 2800, 1685, 1600, 1575, 1490, 1455, 1440, 1390, 1350, 1310, 1270, 1200, 1180, 1160, 1120, 1095, 1070, 1045, 1025, 1000, 945, 895, 810, 730, 695.

Methyl *N*-Benzyl-*N*-(3-cyclohexenyl)carbamate (9). A solution of 4.9 g (20 mmol) of **8** in 30 mL of toluene was heated at reflux for 24 h, cooled, and concentrated. Chromatography with 4:1 petroleum ether–ethyl ether as eluant gave 3.72 g (96%) of **9**: NMR 1.05–2.2 (m, 6 H), 3.72 (s, 3 H), 4.40 (br s, 2 H), 4.53–5.17 (m, 1 H), 5.23–6.1 (m, 2 H), 7.27 (br s, 5 H); IR (film) 3030, 2935, 2860, 1700, 1600, 1490, 1460, 1445, 1400, 1380, 1360, 1345, 1305, 1285, 1260, 1220, 1200, 1170, 1135, 1115, 1180, 1070, 1050, 1040, 1020, 1000, 940, 890, 790, 765, 745, 695. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.66; H, 7.80; N, 5.61.

3-Benzyl-7-iodo-3aα,4,5,6,7β,7aα-hexahydrobenzoxazolin-2-one (10). A solution of 305 mg (1.2 mmol) of iodine in 2 mL of THF was added to a solution of 245 mg (1.0 mmol) of **9** in 5 mL of THF and the mixture was stirred at 25 °C for 12 h. Saturated aqueous sodium sulfate was added until the iodine color disappeared, the THF was removed by rotary evaporator, and the residue was extracted with dichloromethane (3 × 10 mL). The combined organic extract was washed with brine, dried, and concentrated to give 342 mg (96%) of **10**, pure by TLC. A sample crystallized from dichloromethane–ethyl ether had mp 108–109 °C: NMR 1.13–2.23 (m, 6 H), 3.5–3.87 (m, 1 H), 4.13–4.83 (m, 2 H), 4.10 (d, J = 15.5, 1 H), 4.73 (d, J = 15.5, 1 H), 7.33 (br s, 5 H); IR (KBr) 3050, 3020, 2975, 2945, 2860, 1750, 1650, 1540, 1495, 1445, 1435, 1400, 1380, 1345, 1320, 1295, 1285, 1250, 1240, 1200, 1175, 1140, 1100, 1085, 1045, 1020, 970, 955, 920, 885, 860, 845, 820, 775, 740, 700, 680. Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.12, H, 4.48, I, 35.58; N, 3.92. Found: C, 47.28; H, 4.57; I, 35.71; N, 3.90.

3-Benzyl-7-hydroxy-3aα,4,5,6,7β,7aα-hexahydrobenzoxazolin-2-one (11a). A solution of 357 mg (1 mmol) of **10** in 4 mL of nitromethane was treated with 330 mg (1.5 mmol) of solid silver(I) trifluoroacetate and 16 μL (0.9 mmol) of water. The reaction mixture changed from homogeneous to cloudy during 15 min as silver iodide began to precipitate. After 20 h at 25 °C the reaction was complete, according to TLC analysis. The reaction mixture was diluted with 5 mL of ether and filtered, and the residue was washed with ether (2 × 5 mL). The combined organic extract was concentrated and chromatographed with 4:1 then 1:1 petroleum ether–ethyl ether as eluant. Collected in order of elution were the alkene **17** (42 mg, 18%), **11a** (137 mg, 55%), and **13a** (68 mg, 28%). **11a**: NMR 1.11–2.13 (m, 6 H), 3.27–4.40 (m, 4 H), 4.08 (d, J = 15, 1 H), 4.68 (d, J = 15, 1 H), 7.28 (br s, 5 H); IR (film) 3400, 3050, 3000, 2925, 2850, 1730, 1650, 1490, 1450, 1430, 1410, 1355, 1330, 1305, 1255, 1200, 1175, 1150, 1110, 1075, 1060, 970, 915, 860, 840, 800, 765, 720, 700. **13a**: NMR 1.57–2.97 (m, 6 H), 3.4–5.0 (m, 6 H), 7.32 (br s, 5 H); IR (film) 3400, 3040, 3010, 2925, 2850, 1730, 1490, 1430, 1355, 1340, 1300, 1250, 1225, 1200, 1160, 1095, 1065, 1040, 1000, 980, 755, 730, 700.

exo-Alcohol **11a** was also characterized as its acetate, **11b** (mp 109–110 °C from petroleum ether–ethyl ether): NMR 1.0–2.37 (m, 6 H), 2.05 (s, 3 H), 3.37–3.97 (m, 1 H), 4.10 (d, J = 15, 1 H), 4.39 (app t, J = 7, 1 H), 4.75 (d, J = 15, 1 H), 7.33 (br s, 5 H); IR (KBr) 2950, 2935, 2910, 2845, 1740, 1725, 1640, 1485, 1445, 1425, 1400, 1360, 1310, 1240, 1190, 1170, 1115, 1085, 1075, 1045, 1010, 970, 940, 855, 830, 810, 765, 730, 695. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.14; H, 6.65; N, 4.75.

endo-Alcohol **13a** was characterized as its acetate, **13b**: NMR 1.30–2.45 (br m, 6 H), 2.03 (s, 3 H), 4.10 (d, J = 15, 1 H), 4.82 (d, J = 15, 1 H), 3.8–5.0 (m, 3 H), 7.32 (s, 5 H); IR (film) 2950, 2925, 1740, 1490, 1450, 1435, 1420, 1370, 1360, 1330, 1240, 1160, 1090, 1080, 1035, 985, 750, 725, 700. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.20; H, 6.62; N, 4.69.

3-Benzyl-7-keto-3aα,4,5,6,7,7aα-hexahydrobenzoxazolin-2-one (12). A suspension of 100 mg (0.45 mmol) of pyridinium chlorochromate[9] in 2 mL of dichloromethane was stirred at 25 °C. A solution of 74 mg (0.3 mmol) of a mixture of **11a** and **13a** in 0.5 mL of dichloromethane was added all at once. After 15 h at 25 °C, the reaction mixture was triturated with ether (4 × 3 mL), and the combined organic extract was filtered through Celite, concentrated, and chromatographed with 1:1 petroleum ether–ethyl ether as eluant to give the ketone **12** (65 mg, 88%). A sample crystallized from petroleum ether–ethyl ether had mp 93–94 °C: NMR 1.47–2.73 (m, 6 H), 3.83–4.97 (m, 2 H), 4.12 (d, J = 15, 1 H), 4.75 (d, J = 15, 1 H), 7.33 (br s, 5 H); IR (KBr) 2925, 1740, 1720, 1480, 1445, 1430, 1395, 1380, 1355, 1340, 1320, 1305, 1245, 1205, 1190, 1160, 1100, 1080, 1060, 1045, 1015, 960, 915, 860, 765, 725, 700. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.61; H, 6.17; N, 5.71. Found: C, 68.60; H, 6.24; N, 5.56.

3-Benzyl-7-hydroxy-3a,4,5,6,7α,7aα-hexahydrobenzoxazolin-2-one (13a). A solution of L-Selectride[10] in THF (1M, 1 mL) was treated dropwise with a solution of **12** (122 mg, 0.5 mmol) in 2 mL of THF at −78 °C. The reaction was warmed to 25 °C over 1 h and then allowed to stand at 25 °C for 3 h. Water (0.8 mL) and ethanol (3 mL) were added. After 30 min 2 mL of 6 N sodium hydroxide and 3 mL of 30% aqueous hydrogen peroxide were added. After 30 min solid potassium carbonate was added and the aqueous phase was washed with ether (3 × 10 mL). The combined organic extract was dried, concentrated, and chromatographed with 2:1 ethyl ether–petroleum ether as the eluant. The *endo*-alcohol (114 mg, 92%) was collected and compared (TLC, NMR, IR) with **13a** prepared previously.

3-Benzyl-3aα,6,7,7aα-tetrahydrobenzoxazolin-2-one (16). Dehydroiodination of 357 mg (1 mmol) of **3** as described for **17** gave **16** in essentially quantitative yield: NMR 1.17–2.37 (m, 6 H), 3.6–4.07 (m, 1 H), 4.08 (d, J = 15, 1 H), 4.4–4.87 (m, 1 H), 4.82 (d, J = 15, 1 H), 5.5–6.3 (m, 2 H), 7.35 (br s, 5 H); IR (film) 3040, 3015, 2910, 2830, 1745, 1490, 1450, 1435, 1415, 1345, 1325, 1295, 1240, 1225, 1200, 1165, 1105, 1080, 1060, 1020, 975, 960, 840, 825, 780, 755, 700. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.29; H, 6.66; N, 5.99.

3-Benzyl-3aα,4,5,7aα-tetrahydrobenzoxazolin-2-one (17). A solution of 224 μL (1.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene[11] and 357 mg (1 mmol) of **10** in 5 mL of toluene was heated at reflux for 1.5 h. The reaction was cooled and washed with brine (3 × 10 mL). The combined aqueous layer was back extracted with dichloromethane (3 × 10 mL), and the combined organic extract was dried, concentrated, and chromatographed with 1:1 petroleum ether–ethyl ether as eluant to give **17** in essentially quantitative yield (230 mg): NMR 1.17–2.2 (m, 6 H), 3.53–3.93 (m, 1 H), 4.12 (d, J = 15, 1 H), 4.80 (d, J = 15, 1 H), 4.50–5.0 (m, 1 H), 5.5–6.37 (m, 2 H), 7.33 (br s, 5 H). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.10; H, 6.73, N, 6.20.

3β-(*N*-Benzyl-*N*-carbomethoxyamino)cyclohexane-1α,2α-diol (18a). Osmium tetraoxide (100 μL of a 2.5% by weight solution in *tert*-butyl alcohol, 0.01 mmol) was added to a solution of carbamate **9** (245 mg, 1 mmol) and *N*-methylmorpholine *N*-oxide (182 mg, 1.06 mmol) in 34 mL of acetone and 0.5 mL of water.[12] The reaction was stirred at 25 °C for 16 h, then solid sodium thiosulfate (1 g, 5.8 mmol), 1 g of Celite, and 10 mL of water were added, and stirring was continued for 3 h. The solution was filtered and acetone removed by rotary evaporation. The solid residue was washed with dichloromethane (3 × 15 mL), and the combined extract was dried and concentrated to give **18a**, weighing 288 mg (100%), pure by NMR and IR: NMR 0.90–2.1 (m, 6 H), 3.67 (s, 3 H), 3.2–4.8 (m, 7 H), 7.27 (s, 5 H); IR (film) 3450, 3060, 3040, 3010, 2935, 2850, 1680, 1600, 1535, 1495, 1470, 1450, 1405, 1375, 1355, 1305, 1265, 1240, 1205, 1170, 1125, 1100, 1020, 990, 970, 905, 870, 810, 765, 730, 695. The diol **18a** was further characterized as its diacetate, **18b**, mp 76–77 °C from ethyl ether–petroleum ether: NMR 1.07–2.20 (m, 6 H), 1.85 (s, 3 H), 2.06 (s, 3 H), 3.73 (s, 3 H), 4.40 (s, 2 H), 4.86–5.53 (m, 3 H), 7.27 (s, 5 H); IR (KBr) 3040, 3010, 2935, 2850, 1740, 1700, 1595, 1495, 1465, 1450, 1405, 1375, 1245, 1220, 1170, 1125, 1090, 1055, 1020,

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965, 925, 900, 885, 865, 855, 825, 805, 765, 730, 700. Anal. Calcd for $C_{19}H_{22}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.92; H, 6.85; N, 3.85.

3-*tert*-Butyl-4-bromo-3aα,4β,5,6,7,7aα-hexahydrobenzoxazolin-2-one (20). Treatment of the sodium salt of **1** with *tert*-butyl isothiocyanate, then iodomethane as in the preparation of **2**, gave *O*-3-cyclohexenyl *S*-methyl *N*-*tert*-butylthiocarbonimadate in quantitative yield: NMR 1.25 (s, 9 H), 1.4-2.2 (m, 6 H), 2.35 (s, 3 H), 4.95-5.4 (m, 1 H), 5.9 (app s, 2 H); IR (film) 3025, 2965, 2930, 2860, 2825, 1640, 1470, 1450, 1435, 1385, 1360, 1335, 1315, 1305, 1235, 1220, 1135, 1055, 1025, 1010, 965, 925, 915, 860, 840, 815, 800, 720. A 1 M solution of bromine in dichloromethane (11.75 mL, 11.75 mmol) was added dropwise to a suspension of silver(I) bis(collidine) perchlorate (5.5 g, 12 mmol) in 20 mL of dichloromethane. The bromine color was discharged and silver bromide precipitated during the addition. The reaction mixture was filtered and solvent removed to give white, crystalline bromonium bis(collidine) perchlorate, which was redissolved in 25 mL of dichloromethane. A solution of 2.27 g (10 mmol) of the carbonimidothioate in 5 mL of dichloromethane was added, and the reaction was stirred for 30 min. The reaction was quenched with saturated aqueous sodium carbonate, stirred for 15 h to complete the hydrolysis, and then filtered through Celite with dichloromethane rinse (2 × 10 mL). The aqueous layer was back extracted with dichloromethane (2 × 10 mL), and the combined organic extract was washed with 5% aqueous hydrochloric acid (2 × 10 mL) and saturated aqueous sodium bicarbonate (20 mL), dried, and concentrated. Chromatography with 4:1 petroleum ether-ethyl ether as eluant gave 2.374 g (86% yield) of **20**. A sample crystallized from petroleum ether-ethyl ether had mp 100-101 °C: NMR 1.50 (s, 9 H), 1.6-2.4 (m, 6 H), 3.9-4.34 (m, 2 H), 4.34-4.7 (m, 1 H); IR (KBr) 2965, 2915, 2875, 1730, 1660, 1525, 1480, 1460, 1445, 1395, 1365, 1340, 1310, 1290, 1270, 1230, 1205, 1175, 1155, 1140, 1100, 1050, 1025, 955, 890, 865, 825, 800, 760, 670, 655. Anal. Calcd for $C_{11}H_{18}BrNO_2$: C, 47.84; H, 6.57; Br, 28.93; N, 5.07. Found: C, 47.93; H, 6.60; Br, 28.94; N, 4.98.

4-Bromo-3aα,4β,5,6,7,7aα-hexahydrobenzoxazolin-2-(3*H*)-one (21). A solution of 276 mg (1 mmol) of **20** in 4 mL of trifluoroacetic acid was allowed to stand at 25 °C for 24 h. Removal of solvent and passage through a small silica column with 1:1 petroleum ether-ethyl ether as eluant gave acid-free **21**: 218 mg (99%); mp 125-126 °C (petroleum ether-ethyl ether); NMR 1.2-2.6 (m, 6 H), 3.6-4.2 (m, 2 H), 4.5-4.9 (m, 1 H), 5.87-6.4 (br s, 1 H); IR (KBr) 3250, 3125, 2950, 2940, 2860, 1750, 1640, 1545, 1445, 1420, 1385, 1365, 1350, 1320, 1285, 1250, 1235, 1205, 1175, 1115, 1075, 1040, 985, 965, 950, 880, 820, 765, 720, 700, 680, 640. Anal. Calcd for $C_7H_{10}BrNO_2$: C, 38.21; H, 4.58; Br, 36.31; N, 6.37. Found: C, 38.38; H, 4.57; Br, 36.50; N, 6.46.

4-Hydroxy-3aα,4β,5,6,7,7aα-hexahydrobenzoxazolin-2-(3*H*)-one (19a). A solution of 220 mg (1 mmol) of **21** in 5 mL of nitromethane was treated with 331.5 mg (1.5 mmol) of silver(I) trifluoroacetate and 16 μL (0.9 mmol) of water and then heated at reflux for 8 h. The reaction mixture was cooled, diluted with 5 mL of ether, and filtered through Celite with ether rinse (3 × 5 mL). The organic extract was dried, concentrated, and chromatographed with 1:1 then 1:4 petroleum ether-ethyl ether as eluant to give in order of elution the alkene (9.3 mg, 7%) and the alcohol **19a** (140 mg, 89%). **19a** was conveniently characterized as its acetate derivative **19b** (163 mg, 82% overall yield): mp 149-151 °C; NMR 1.1-2.47 (m, 6 H), 2.08 (s, 3 H), 3.58 (app t, J = 7, 1 H), 4.43-5.03 (m, 2 H), 6.63 (br s, 1 H); IR (KBr) 3260, 2935, 1740, 1720, 1440, 1415, 1375, 1360, 1300, 1235, 1220, 1170, 1100, 1075, 1060, 1040, 995, 915, 870, 840, 815, 770, 745, 710. Anal. Calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.58; N, 7.03. Found: C, 53.92; H, 6.75; N, 6.98.

Acetate **19b** was also prepared from **4a** as follows. A solution of 247 mg (1 mmol) of **4a** in 6 mL of ammonia was stirred at -33 °C. Freshly cut lithium metal (17 mg, 2.43 mmol) was added in two portions. The blue solution was stirred at -33 °C for 15 min, then excess solid ammonium chloride was added, and the ammonia was allowed to evaporate at 25 °C. The residue was triturated with dichloromethane (3 × 10 mL) with the aid of a sonicator, and the organic extract was concentrated to give 164 mg (96%) of crude **19a**. Acetylation and chromatography produced the acetate **19b** (87% overall yield from **21**), which was identical with that prepared previously according to melting point, NMR, IR, and TLC.

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Cyclonucleoside Formation and Ring Cleavage in the Reaction of 2',3'-*O*-Isopropylideneadenosine with Benzoyl Chloride and Its Substituted Derivatives

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Reaction conditions suitable for the formation of 8,5'-*O*-cycloadenosine derivatives in the reaction of 2',3'-*O*-isopropylideneadenosine (**1**) with benzoyl chloride and substituted benzoyl chlorides were investigated. Thus, reaction of **1** with *p*-toluyl chloride in a CH_2Cl_2-Et_3N mixture afforded 8,5'-*O*-cyclonucleosides **7** (34%) and **20** (11%), a noncyclized acylate **6** (30%), and a ring-cleaved imidazole compound **21** (12%). The structures of these compounds were determined by LSPD ^{13}C NMR.

The discovery that 2',3'-*O*-isopropylideneadenosine (**1**) (Chart I) was converted to its 8,5'-*O*-cyclonucleoside derivative **2**[1] prompted us to investigate the acylation of **1** using benzoyl chloride and substituted benzoyl chlorides with the aim of synthesizing the corresponding 8,5'-*O*-cyclonucleoside derivatives (Chart II).

In a reinvestigation of the preparation of **2**[2] 2',3'-*O*-isopropylideneadenosine was treated with phenyl chloroformate in pyridine following the method reported by Lyon and Reese[3] for the preparation of N^6,N^6-bis(phenoxycarbonyl)-2',3',5'-tri-*O*-acetyladenosine. 8,5'-*O*-cyclo-

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(2) The yield of the triacylated product **2** was low (6%) and the corresponding N^6,7-diacylate was predominant (29%) if the reaction was carried out in DMF-pyridine.[1]

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