Total Synthesis of Elfamycins: Aurodox and Efrotomycin. 1. Strategy and Construction of Key Intermediates

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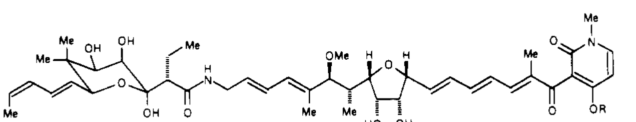
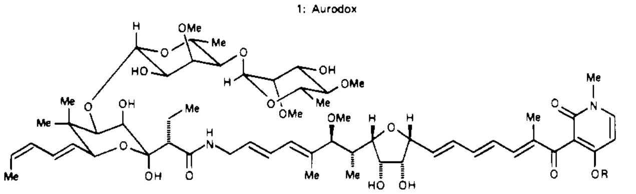
Abstract: The strategy for the total synthesis of aurodox (**1**) and efrotomycin (**2**) and the construction of key intermediates IV–VIII are described.

The elfamycins are a newly discovered class of narrow-spectrum antibiotics whose number and importance are rapidly increasing. Aurodox (goldinomycin, **1**), the most well-known member of this group, was isolated from *Streptomyces goldiniensis* and structurally elucidated by a Hoffmann–La Roche group,[1] whereas efrotomycin (**2**), the newest and most complex member of the group, is produced by *Nocardia lactamdurans* and was discovered and structurally elucidated by a Merck, Sharp & Dohme group.[2]



1: Aurodox



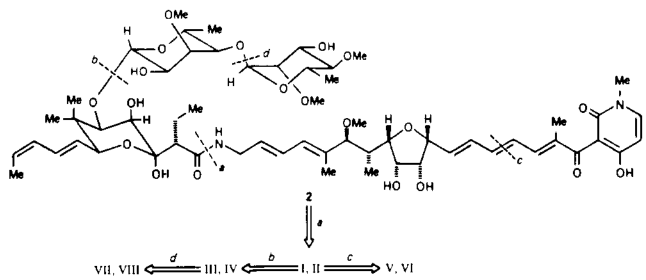
2: Efrotomycin

In addition to their action against *baccilli* and dysentery, these compounds exhibit potent growth-promoting properties and are intended for veterinary use.[1–3] In this and the following paper in this issue,[4] we report the first total syntheses of the two most prominent members of the elfamycin family,[5] aurodox (**1**) and efrotomycin (**2**), in their naturally occurring enantiomeric forms and include a number of new synthetic methods and novel reactions.

Structurally, efrotomycin (**2**) includes 21 stereocenters and 7 geometrical stereosites.[6] The two O-glycoside bonds, the amide linkage, and the several olefinic moieties provide logical strategic locations for disconnection. Scheme I indicates (dotted lines) the main strategic bonds chosen for disconnection in the retrosynthetic analysis of this target molecule, unraveling key intermediates I–VIII.

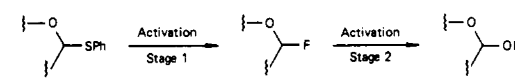
Leaving aside for the moment the tenuous nature of these targets and subtargets, two major problems in connection with the total synthesis of efrotomycin precipitate: (a) the stereoselective and efficient construction of the oligosaccharide segment of the molecule and (b) the stereocontrolled synthesis of the tetrahydrofuran system with its proper substituents on the same side of the ring (all-cis arrangement). As will become apparent in these papers, new solutions to these rather general problems were developed that may have important applications to other areas of organic synthesis and biosynthesis, particularly in saccharide and ionophore chemistry. Thus, implementation of the above strategy was preceded by (1) a search for a new and general technology suitable for building oligo- and polysaccharide chains

Scheme I. Strategic Bond Disconnections of Aurodox and Efrotomycin[a]

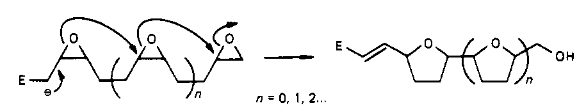


[a] For structures of intermediates see I–III, paper 2 in this series,[4] and IV–VIII, Schemes II–V, this paper.

and (2) an effort to develop tandem technology for the construction of tetrahydrofurans that could be applicable to higher homologues



(eq. 1)



(eq. 2)

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[‡] Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1985. J. S. Guggenheim Fellow, 1984.

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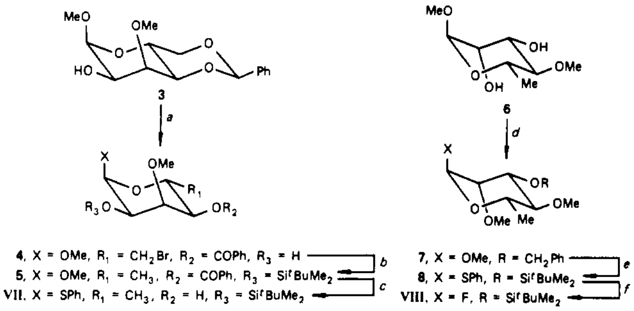
Scheme II. Construction of Carbohydrate Units VII and VIII[a]



[a] (a)[12] 1.1 equiv of NBS, catalytic AIBN, PhH, 25 °C, 100%. (b) (i) 1.5 equiv of n-Bu_3SnH, catalytic AIBN, PhH, 80 °C; (ii) 1.2 equiv of t-$BuMe_2SiCl$, 1.2 equiv of imidazole, DMF, 25 °C, 90% overall. (c) (i)[13] 5.0 equiv of $PhSSiMe_3$, 3.0 equiv of ZnI_2, 1.3 equiv of n-Bu_4NI, $ClCH_2CH_2Cl$, 70 °C; 0.5 equiv of K_2CO_3, MeOH, 0–25 °C, 78% overall. (d) (i) 1.0 equiv of n-Bu_2SnO, MeOH, Δ; (ii) 2.5 equiv of $PhCH_2Br$, DMF, 70 °C; (iii) 1.3 equiv of KH, 2.0 equiv of MeI, THF, 25 °C, 90% overall. (e) H_2, 5% PdC, EtOAc, 25 °C; (ii) 1.1 equiv of t-$BuMe_2SiCl$, 1.5 equiv of imidazole, DMF, 25 °C; (iii) as in (c) (i) above, 75% overall. (f)[7] 1.1 equiv of NBS, 1.2 equiv Et_2NSF_3, CH_2Cl_2, −15 °C, 88%.

based on oligoepoxide openings. Equations 1[7] and 2 outline these new technologies, the successful implementation of which is demonstrated in the present work.

What follows in this article is a description of the synthesis of the five key intermediates IV–VIII, whereas their coupling to the more advanced intermediates I–III and completion of the synthesis are reported in the following paper in this issue.[4]

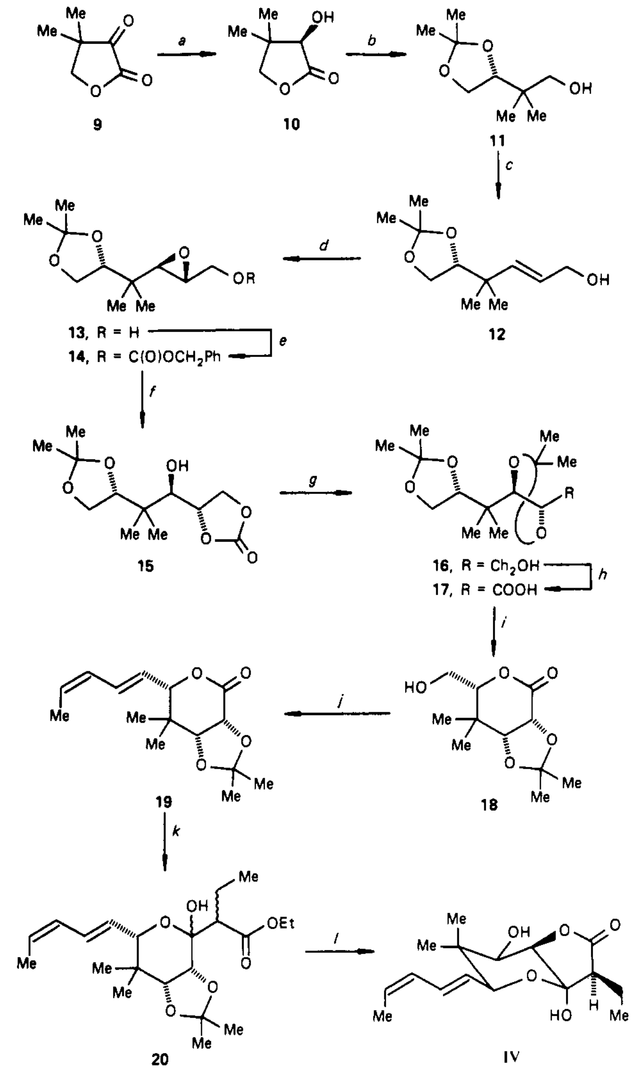
Scheme II summarizes the construction of the carbohydrate units VII (α:β, ca. 3:1) and VIII (α exclusively) from the readily available α-D-allose derivative **3** and L-(+)-rhamnose derivative **6**,[9] respectively.

Described in Scheme III is an asymmetric synthesis of key intermediate IV (goldinonolactone) which is a stable degradation product of aurodox.[1a] This construction begins which the prochiral precursor, ketolactone **9**, and follows an "acyclic stereoselection approach" in which all the stereocenters are introduced sequentially and with high stereocontrol. Chromatographic purification of synthetic IV and comparison with authentic material derived from aurodox[1a] proved its identity [^{1}H, NMR, MS, IR, UV, $[\alpha]_D$, and TLC].

The construction of the central backbone of the present targets, tetrahydrofuran fragment V, also followed an "acyclic stereoselection approach", starting with prochiral compounds [Scheme IV, 4-(benzyloxy)-1-lithio-1-yne + crotonaldehyde → **21**, 90% yield]. The oligoepoxide fragmentation strategy to tetrahydrofurans depicted in eq 2 served admirably in the present construction, leading from **25** to **26** in 90% overall yield [(i) KCH_2SOCH_3, THF–PhMe, (1:1), −20–25 °C, (ii) t-$BuMe_2SiCl$-imidazole, DMF, 0–25 °C].[10]

The synthesis of the requisite 2-pyridone fragment VI [colorless crystals, mp 110–111 °C (acetone–ether)] was achieved by starting with aldehyde **33**[11] and following the outline of Scheme V. This route featured an organotitanium reagent addition to aldehyde **33** (after fruitless experimentation with a number of more obvious

Scheme III. Construction of Goldinono Lactone (III)[a]



[a] (a)[14] Rh-complex-H_2. (b) 1.0 equiv of LAH, THF, 80 °C; (ii) Me_2CO, catalytic CSA, 25 °C, 70% overall. (c) 1.2-equiv of $(COCl)_2$, 1.2 equiv of Me_2SO, 5.0 equiv of Et_3N, CH_2Cl_2, −78–25 °C; (ii) 1.3 equiv of $(MeO)_2P(O)CH_2COOMe$, 1.2 equiv of t-BuOK, THF, 0–25 °C; (iii) 2.2 equiv of DIBAL, CH_2Cl_2, −78 °C, 85% overall. (d)[15] Sharpless AE: 2.0 equiv of t-BuOOH, 2.0 equiv of (−)-DET, 1.0 equiv of $Ti(i\text{-}PrO)_4$, CH_2Cl_2, −20 °C, 70% ee ⩾95. (e)[16] 1.1 equiv of $PhCH_2OCOCl$, 1.5 equiv of pyr, THF, −20 °C, 100%. (f)[16] 1.1 equiv of $AlCl_3$, ether, −20 °C, aqueous workup, 65%. (g) (i) 5.0 equiv of $(MeO)_2CMe_2$, catalytic CSA, PhH, Δ; (ii) 0.5 equiv of K_2CO_3, MeOH, 25 °C; (iii) catalytic CSA, CH_2Cl_2, 25 °C, 90% overall. (h)[17] catalytic RuO_2, 3.0 equiv of $NaIO_4$, $MeCN$-CCl_4-H_2O (1:1:1), 25 °C, 95%. (i) AcOH-H_2O (3:1), 25 °C, 48 h, 82%. (j) (i) 1.5 equiv of CrO_3·pyr·HCl, 4AMS, CH_2Cl_2, 0–25 °C; (ii)[18] 2.0 equiv of *cis*-crotyldiphenylphosphine oxide, 2.0 equiv of n-BuLi, THF, −110–25 °C, 72% overall. (k) 2.0 equiv of $CH_3CH_2CH_2COOEt$-2.0 equiv of LDA, THF, −78 °C, 85% + 10% recovered SM. (l) (i) AcOH-H_2O (7:3), 60 °C; (ii) 0.05 N aqueous NaOH-EtOH (1:4), 25 °C, 85% overall.

(6) These 28 stereoparameters offer the possibility of 268 435 460 stereoisomers from which only the 1 corresponding to efrotomycin (**2**) was targeted in this stereocontrolled total synthesis.

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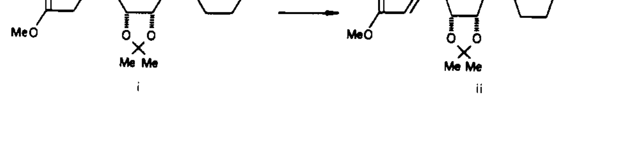
(10) This technology involving a zip-type reaction was readily extended to the triepoxide i which furnished, under similar treatment, the bis(tetrahydrofuran) system ii in >90% yield. We are currently examining similar systems and higher homologues in this series.



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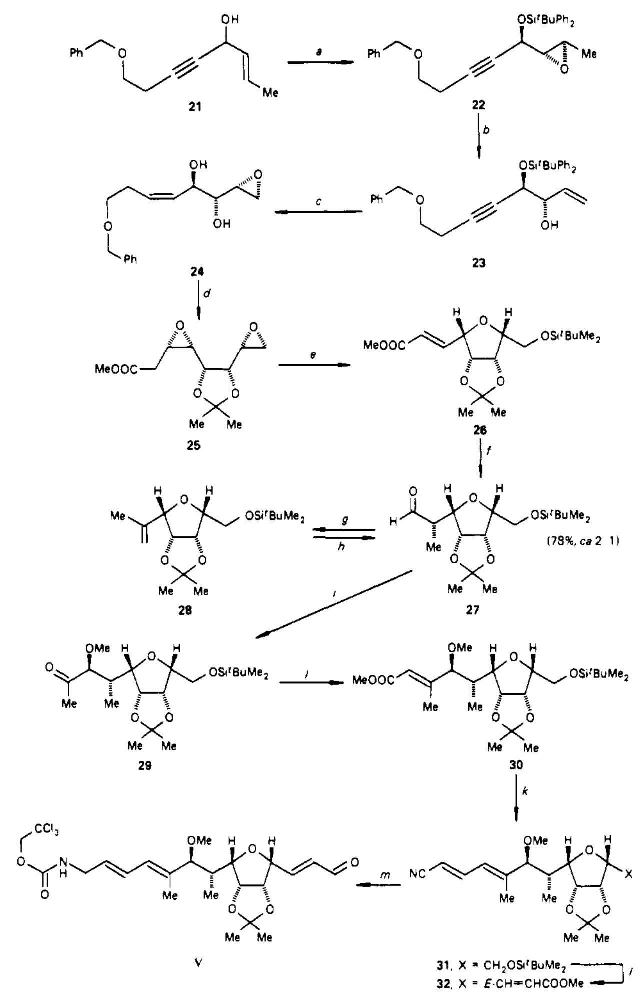
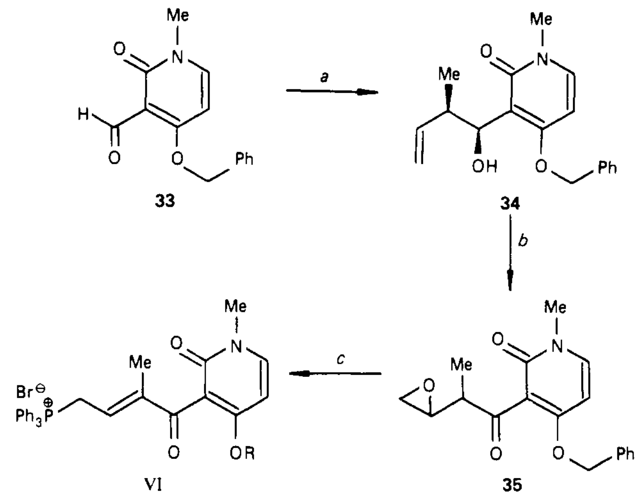
Scheme IV. Construction of Tetrahydrofuran Fragment V[a]



[a] (a) (i)[19] Sharpless KR: 0.6 equiv of t-BuOOH, 1.0 equiv of (-)-DET, 1.0 equiv of $Ti(OiPr)_4$, CH_2Cl_2, −20 °C; (ii) 1.2 equiv of t-$BuPh_2SiCl$, 1.3 equiv of imidazole, DMF, 0–25 °C, 30% overall yield, 50:1 selectivity. (b)[20] (i) 1.2 equiv of $NaBH_4$, 1.2 equiv of PhSeSePh, EtOH, 60 °C; (ii) 1.5 equiv of 30% H_2O_2, 0–25 °C, 75% overall. (c) (i)[15] Sharpless AE: 1.5 equiv of t-BuOOH, 2.0 equiv of (-)-DET, 2.0 equiv of $Ti(OiPr)_4$, CH_2Cl_2, −20 °C, 80%, ca. 30:1 selectivity; (ii) 1.2 equiv of n-Bu_4NF, THF, 0–25 °C; (iii) H_2, catalytic Lindlar, hexane, 25 °C, 85% overall. (d) (i)[16] 1.1 equiv of m-CPBA, CH_2Cl_2, −20 °C, 90%, ≥15:1 selectivity; (ii) Me_2CO, catalytic CSA, 25 °C; (iii) H_2, 5% Pd-C, EtOAc, 25 °C; (iv)[17] catalytic RuO_2, 1.2 equiv of $NaIO_4$, $MeCN-CCl_4-H_2O$, 25 °C; (v) CH_2N_2, ether, 0 °C. (e) (i) 1.1 equiv of KCH_2SOCH_3, PhMe-Me_2SO (1:1), −20–25 °C; (ii) 1.2 equiv of $BuMe_2SiCl$, 1.3 equiv of imidazole, DMF, 0–25 °C, 90% overall. (f) (i) 5.0 equiv of $LiCuMe_2$, ether, −78–0 °C; (ii) excess Me_3SiCl −78–0 °C; (iii) O_3, CH_2Cl_2, −78 °C then excess Me_2S, −78–25 °C, 78% overall, ca. 2:1 selectivity. (g) (i) 1.1 equiv of t-$BuNH_2$, BH_3, CH_2Cl_2, 0 °C; (ii)[21] 1.2 equiv of $MeO_2CNSO_2N^+Et_3$, PhH, 25–80 °C, 90% overall. (h) (i) 1.2 equiv of (+)-pinylborane, THF, 0 °C then $NaOH-H_2O$; (ii) 1.5 equiv of $(CF_3CO)_2O$, 1.5 equiv of Me_2SO, 5.0 equiv of Et_3N, CH_2Cl_2, −78–0 °C. (j) (i)[23] 2.0 equiv of LiCu(MeO)CH=CH_2, THF, −78–0 °C; (ii) 1.5 equiv of KH, 2.0 equiv of MeI, 0–25 °C; (iii) $AcOH-H_2O$ (3:1), 45 °C, 5 min, 70% overall, ca. 8:1 selectivity.[24] (j) 7.0 equiv of NaH, 7.0 equiv of $(MeO)_2$-$P(O)CH_2COOMe$, DMF, 25 °C, 90%, ca. 4:1 selectivity. (k) (i) 2.5 equiv of DIBAL, CH_2Cl_2, −78 °C; (ii) 1.5 equiv of CrO_3·pyr·HCl, 4AMS, CH_2Cl_2, 25 °C; (iii) 1.5 equiv of KO-t-Bu, 1.5 equiv of $(i\text{-}PrO)_2P(O)CH_2CN$, THF, −78 °C, 90% overall, ca. 10:1 selectivity. (l) (i) excess HF·pyr, CH_2Cl_2, 25 °C; (ii) 10.0 equiv of CrO_3·2pyr, celite, CH_2Cl_2, −10–0 °C; (iii) 1.2 equiv of $(MeO)_2$-$P(O)CH_2COOMe$, 1.2 equiv of KO-t-Bu, THF, −78–25 °C, 85% overall, ca. 7:1 selectivity. (m) (i) 3.1 equiv of DIBAL, 0.01 M ether solution, −78 °C, (ii) 10.0 equiv of $NaBH_4$, −78–25 °C; (iii) 0.9 equiv of Cl_3CCH_2OCOCl, 1.1 equiv of DMAP; (iv) 1.5 equiv of CrO_3·pyr·HCl, CH_2Cl_2, 0–25 °C, 60% overall.

Scheme V. Construction of 2-Pyridone Fragment VI[a]



[a] (a) 1.2 equiv of $MeCH{=}CHCH_2Ti(i\text{-}PrO)_3$, CH_2Cl_2, −78–(−40 °C), 95%, ca. 7:1 selectivity. (b) (i) 1.2 equiv of m-CPBA, CH_2Cl_2, NaH_2PO_4, 0 °C; (ii) Jones [O], acetone, −40–0 °C. (c) (i) 2.0 equiv of DBU, CH_2Cl_2, 25 °C, E exclusively; (ii) 1.1 equiv of CBr_4–1.1 equiv of PPh_3, CH_2Cl_2, 0 °C; (iii) 1.1 equiv of PPh_3, PhH, 45 °C, 60% overall for (b) and (c).

reagents) and a base-induced fragmentation of epoxide **35** to arrive stereoselectivity at the desired E geometry of the double bond.

With the five key intermediates (IV–VIII) at hand, the stage was now set for their coupling and completion of the total syntheses of aurodox (**1**) and efrotomycin (**2**). The following paper in this issue[4] describes the chemistry leading to these targets.

Experimental Section

General. ^1H NMR spectra were recorded on a Bruker WH-250 MHz spectrometer in $CDCl_3$ and are reported in δ from Me_4Si. IR spectra were recorded on Perkin-Elmer Model 281B or 781 infrared spectrophotometer, and the IR figures reported are ν_{max} in inverse centimeters.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV light and 7% phosphomolybdic acid in ethanol-heat as the developing agent. Preparative-layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere using dry freshly distilled solvents under anhydrous conditions unless otherwise noted. Ethereal solvents were dried and distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from calcium hydride. Amines were distilled under argon from calcium hydride. Reaction temperatures were externally measured. NMR multiplicities are reported by using the following abbreviations: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet; br, broad, J = coupling constant (hertz). Only the strongest and/or structurally most important peaks are reported for the IR. All yields refer to chromato-

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(24) Although the reaction of the corresponding titanium reagent [Weidmann, B.; Seebach, D. E. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31] resulted in higher stereoselectivity (ca. 15:1 by ^1H NMR), the yield was unsatisfactory. The yield with the lithium reagent [Baldwin, J. E.; Hofle, G. A.; Lever, O. W. *J. Am. Chem. Soc.* **1974**, *90*, 7125] was comparable to the cuprate but the stereoselectivity was only ca. 3:1 in favor of the desired product.
(25) This work was financially supported by the National Instiutes of Health, the Camille and Henry Dreyfus Foundation and Merck, Sharp & Dohme.

graphically and spectroscopically (^{1}H NMR) homogeneous materials.

Preparation of Key Intermediate VII from 5. Benzoate **5** (1.34 g, 3.27 mmol) in dichloroethane (16 mL) was treated with phenyltrimethylsilyl sulfide (2.98 mL, 16.34 mmol), zinc iodide (3.12 g, 9.80 mmol), and tetra-*n*-butylammonium iodide (1.57 g, 4.25 mmol) and the solution heated to 65 °C for 2.5 h. The reaction mixture was cooled and poured into saturated $Ba(OH)_2$ (30 mL). Extracting with methylene chloride (3 × 20 mL), combining the extracts, drying over $MgSO_4$ and concentrating gave a residue which was flash-chromatographed (silica, 5% ether in petroleum ether) to afford an inseparable 3:1 (α:β) anomeric mixture of thioglycosides. This mixture (1.0 g, 2.17 mmol) was dissolved in methanol (8 mL), and powdered potassium carbonate (200 mg) was added. After stirring at room temperature for 4.5 h, the solution was diluted with ether (40 mL) and filtered. Concentration of the filtrate in vacuo and purification of the residue by flash column chromatography (silica, 20% ether in petroleum ether) separated VII (608 mg, 73%) from its β anomer (199 mg, 24%). VII: mp 82–84 °C (from diisopropyl ether); R_f = 0.29 (silica, 30% ether in petroleum ether); $[\alpha]^{24}{}_D$ −14.61° (*c* 2.37, $CHCl_3$); IR (CCl_4 film) ν_{max} 3450, 2940, 2860, 1370, 1145, 1060, 875, 840, 775, 740, 690 cm^{-1}; ^{1}H NMR δ 7.50, 7.34 (multiplets, 5 H, Ph), 5.21 (d, J = 5.0 Hz, 1 H, H-1), 4.14 (d q, J = 10.0, 7.0 Hz, 1 H, H-5), 4.04 (dd, J = 5.0, 2.0 Hz, 1 H, H-2), 3.72 (s. 3 H, OMe) 3.65 (t, J = 3.0 Hz, 1 H, H-3), 3.20 (ddd, J = 3.0, 10.0, 11.0 Hz, 1 H, H-4), 2.50 (d, J = 11.0 Hz, 1 H, O*H*), 1.30 (d, J = 7.0 Hz, 3 H, H-6), 0.94 (s, 9 H, *t*-Bu), 0.10 and 0.09 (singlets, 3 H each, $SiMe_2$); HRMS calcd for $C_{19}H_{32}O_4SSi$ (M^+) 383.9537, found 383.9536.

Preparation of Key Intermediate VIII from 8. A methylene chloride (10 mL) solution of **8** (230 mg, 0.58 mmol) and (diethylamino)sulfur trifluoride (0.11 mL, 0.69 mmol) was cooled to −15 °C, and *N*-bromosuccinimide (113 mg, 0.64 mmol) was added. The reaction mixture became yellow as stirring continued over a 15-min period. The solution was poured into saturated $NaHCO_3$ (3 mL) and ether (15 mL). Separation of the organic phase, drying over $MgSO_4$, concentration at reduced pressure, and purification of the crude fluoride by using flash column chromatography (silica, 15% ether in petroleum ether) afforded VIII (157 mg, 88%). VIII: R_f = 0.18 (silica, 15% ether in petroleum ether); $[\alpha]^{24}{}_D$ +32.17° (*c* 0.83, $CHCl_3$); IR (neat) ν_{max} 2930, 2860, 1255, 1185, 1130, 1100, 960, 950, 870, 835 cm^{-1}; ^{1}H NMR δ 5.52 (dd, J = 0.3, 50.0 Hz, 1 H, H-1), 3.90 (ddd, J = 2.5, 9.5 Hz, 1 H, H-3), 3.72 (m, 1 H, H-5), 3.56 and 3.52 (singlets, 3 H each, OMe), 3.46 (br s, 1 H, H-2), 3.11 (t, J = 9.5 Hz, 1 H, H-4), 1.32 (d, J = 5.5 Hz, 3 H, H-6), 0.94 (s, 9 H, *t*-Bu), 0.14 and 0.12 (singlets, 3 H each, $SiMe_2$); HRMS calcd for $C_{14}H_{29}FO_4Si$ (M^+) 308.1817, found 308.1815.

Preparation of Key Intermediate Goldinonolactone IV from 19. To a solution of freshly distilled ethyl butyrate (0.46 mL, 3.50 mmol) in THF (9.5 mL) at −78 °C was added 1.0 equiv of LDA (14.0 mL of a 0.25 M solution in THF; 3.50 mmol). After stirring for 45 min at −78 °C, a solution of lactone **19** (300 mg, 1.02 mmol) in dry THF (2 mL) was added to the ester enolate. Saturated NH_4Cl (2 mL) was used to quench the reaction after ca. 10 min at −78 °C. Dilution with ether (75 mL), washing with water (10 mL), drying over $MgSO_4$, and removal of solvent in vacuo gave a diastereomeric mixture of lactols. The crude product was dissolved in 75% aqueous acetic acid (3 mL) and warmed to 50 °C. Stirring for 20 min, diluting with toluene (125 mL), drying over $MgSO_4$ and evaporating of solvents afforded the dihydroxy lactol also as a mixture of isomers. Only traces of goldinonolactone could be detected following this deprotection sequence as indicated by TLC (ether). Thus, the lactols were dissolved in a 0.05 N ethanolic NaOH solution (5 mL of 0.05 N NaOH in 80% aqueous ethanol), stirred at 0 °C for 20 min, and then acidified with dilute aqueous HCl to pH 3. Dilution with ether (50 mL), washing with water (2 × 10 mL) and brine (10 mL), drying $MgSO_4$, and removing solvents in vacuo gave a yellow oil. Purification of this oil using flash column chromatography (90% ether in petroleum ether) provided the desired lactone IV (213 mg, 71%) as an approximate 1:1 epimeric mixture at C-3. The mixture was further purified by preparative thin-layer chromatography (75% ether in petroleum ether, two developments), yielding a spectroscopically pure sample of IV, identical with an authentic sample derived by degradation of aurodox (IR, ^{1}H NMR, TLC). IV: R_f = 0.48 (silica, ether); $[\alpha]^{24}{}_D$ −87.31° (*c* 0.82, $CHCl_3$); IR (CCl_4 film) ν_{max} 3590, 3380, 2970, 2940, 1775 (lactone), 1690, 1090, 1065, 990 cm^{-1}; ^{1}H NMR δ 6.55 (d. J = 15.0, 11.0 Hz, 1 H, H-2′), 6.00 (t, J = 11.0 Hz, 1 H, H-3′), 5.58 (m, 2 H, H-1′,-4′), 4.44 (d, J = 5.0 Hz, 1 H, H-7a), 4.18 (d, J = 7.0 Hz, 1 H, H-5), 3.70 (dd, J = 5.0, 12.0 Hz, 1 H, H-7), 2.65 (t, J = 7.0 Hz, 1 H, H-3), 2.58 (s, 1 H, 3a-OH), 2.10 (d, J = 12.0 Hz, 1 H, 7-OH), 1.84 (m, 2 H, H-1″), 1.76 (dd, J = 7.0, 1.5 Hz, 3 H, H-5′), 1.16 (t, J = 7.0 Hz, 3 H, H-2″), 0.98 and 0.80 (singlets, 3 H each, 6-Me), HRMS calcd for $C_{16}H_{24}O_5$ (M^+) 296.1622, found 296.1617.

Preparation of Tetrahydrofuran 26 from 25. Dry dimethyl sulfoxide (10 mL) was added to potassium hydride (114 mg of a 35% oil dispersion), and the solution was stirred for 30 min. A portion of this solution (2 mL; 0.2 mmol) was added to **25** (50 mg, 0.19 mmol) in toluene (0.3 mL) at −20 °C. The reaction mixture was warmed to room temperature and stirred for 15 min and then diluted with ether (10 mL) and washed with water (3 × 2 mL). The ether was dried over $MgSO_4$, filtered, and removed under reduced pressure. Purification of the residue using flash column chromatography (silica, ether) afforded the desired unsaturated ester (45 mg, 90%). This ester (870 mg, 3.37 mmol) in dry dimethylformamide (3 mL) containing imidazole (367 mg, 5.39 mmol) was cooled to 0 °C, and *tert*-butylchlorodimethylsilane (560 mg, 3.71 mmol) was added. After stirring for 30 min at room temperature, the reaction mixture was diluted with ether (25 mL), washed with water (3 × 5 mL), and dried over $MgSO_4$. Filtration, followed by removal of solvents and flash column chromatography (silica, 20% ether in petroleum ether), gave silyl ether **26** (1.26 g, 100%). **26**: R_f = 0.39 (silica, 30% ether in petroleum ether); $[\alpha]^{24}{}_D$ +39.94° (*c* 1.0, CH_2Cl_2); IR (neat) ν_{max} 2960, 2940, 2860, 1735 (COOMe), 1675, 1385, 1375, 1260, 1100, 840, 780 cm^{-1}; ^{1}H NMR δ 6.99 (dd, J = 15.0, 5.0 Hz, 1 H, H-3), 6.12 (dd, J = 15.0, 1.5 Hz, 1 H, H-2), 4.76 (br s, 2 H, H-5, -6), 4.18 (br s, 1 H, H-4), 3.92 (m, 2 H, H-8), 3.75 (s, 3 H, COOMe), 3.70 (dd, J = 5.0, 0.5 Hz, 1 H, H-7), 1.46 and 1.30 (singlets, 6 H, acetonide), 0.94 (s, 9 H, *t*-BuSi), 0.10 (s, 6 H, Me_2Si); HRMS calcd for $C_{18}H_{32}O_6Si$ (M^+) 372.1966, found 372.1963.

Preparation of Key Intermediate V from 32. A solution of ester **32** (65 mg, 0.166 mmol) in dry diethyl ether (2 mL) cooled to −78 °C was reacted with DIBAL (0.66 mL of a 1 M solution in hexane, 0.66 mmol). After 1 h at −78 °C, the reaction mixture was carefully diluted with methanol (2 mL), and excess sodium borohydride (4 mg; 0.10 mmol) was added. The solution was slowly brought to 0 °C, stirred until effervescence ceased, diluted with ethyl acetate (10 mL), and washed with saturated sodium potassium tartrate (1 mL) and brine (1 mL). Drying over $MgSO_4$, evaporating of solvents, and azeotropic removing of water (3 × 10 mL, benzene) gave the corresponding amino alcohol. This crude product was dissolved in methylene chloride (1 mL), and 4-(dimethylamino)pyridine (4 mg, 0.032 mmol) and trichloroethyl chloroformate (0.02 mL, 0.15 mmol) were added at −40 °C. After 10 min the reaction mixture was diluted with ether (10 mL), washed with water (2 mL), saturated $CuSO_4$ (3 × 2 mL), water (2 mL), saturated $NaHCO_3$ (2 mL), and brine (1 mL), and dried over $MgSO_4$. Removal of solvents gave the crude carbamate. The carbamate was dissolved in methylene chloride, and activated MnO_2 (350 mg) was added. Stirring was continued overnight, and the solution was filtered through celite and the residue washed with methylene chloride (20 mL). The filtrate was concentrated and flash-chromatographed (65% ether in petroleum ether) to give key intermediate V (41.5 mg, 60%). V: R_f = 0.23 (silica, 60% ether in petroleum ether); $[\alpha]^{24}{}_D$ −31.47° (*c* 0.96, $CHCl_3$); IR (neat) ν_{max} 3460, 3000, 2920, 1730 (CHO), 1685 (carbamate), 1500, 1375, 1200, 1080, 970 cm^{-1}); ^{1}H NMR δ 9.62 (d, J = 7.0 Hz, 1 H, H-3″), 6.88 (dd, J = 15.0, 6.0 Hz, 1 H, H-1″), 6.64 (dd, J = 15.0, 10.0 Hz, 1 H, H-3′), 6.40 (ddd, J = 15.0, 7.0, 1.0 Hz, 1 H, H-2″), 6.00 (d, J = 10.0 Hz, 1 H, H-4′), 5.80 (dt, J = 15.0, 5.0 Hz, 1 H, H-2′), 4.91 (br s, 1 H, NH), 4.79 (m, 4 H, OCH_2CCl_3, H-3a, -6a), 4.20 (br s, 1 H, H-4), 3.95 (t, J = 6.0 Hz, 2 H, H-1′), 3.62 (m, 1 H, H-6), 3.34 (d, J = 9.0 Hz, 1 H, H-6′), 3.18 (s, 3 H, OMe), 2.32 (m, 1 H, H-7′), 1.82 (s, 3 H, 5′-Me), 1.41 and 1.31 (singlets, 3 H each, acetonide), 0.94 (d, J = 7.0 Hz, 3 H, 7′-Me). Anal. ($C_{23}H_{32}Cl_3NO_7$) C,H,N.

Preparation of Key Intermediate Phosphonium Salt VI from 35. Crude epoxy ketone **35** (ca. 1.4 mmol) was dissolved in methylene chloride (1.5 mL), and DBU (0.05 mL) was added. After the solution was stirred for 15 min at room temperature, most of the solvent was removed by using a gentle stream of argon. Purification of the dark residue by flash column chromatography (silica, 15% methanol in ether) provided the expected unsaturated alcohol (342 mg, 68% overall from **34**). This alcohol (48 mg, 0.15 mmol) in methylene chloride (0.5 mL) was cooled to 0 °C, and triphenylphosphine (47 mg, 0.18 mmol) was added followed by treatment with carbon tetrabromide (56 mg, 0.16 mmol). After 2 min the solution was concentrated and flash-chromatographed (silica, 8% methanol in ether) directly to give the corresponding bromide (53 mg, 92%). To this bromide (46 mg, 0.12 mmol) in benzene (1 mL) was added recrystallized triphenylphosphine (47 mg, 0.18 mmol), and the reaction was warmed to 40 °C and stirred at that temperature for 3 h. When cooled, a crystalline product appeared which was removed and washed with several portions of ether. Thorough drying of the cream-colored salt in vacuo gave VI (73 mg, 94%), mp 170–172 °C (from ether–CH_2Cl_2). VI: R_f = 0.10 (95% methanol in ether); IR ($CHCl_3$ film) ν_{max} 2940, 1650, 1590, 1545, 1480, 1440, 1110, 680 cm^{-1}; ^{1}H NMR 7.90–7.20 (multiplets, 20 H, Ph), 7.42 (d, J = 7.5 Hz, 1 H, H-6), 6.46 (m, 1 H, H-2′), 6.11 (d, J = 7.5 Hz, 1 H, H-5), 5.08 (s, 2 H, OCH_2Ph), 4.90 (dd, J = 17.5, 10.0 Hz, 2 H, H-1′), 3.18 (s, 3 H, NMe), 1.36 (d, J = 5.0 Hz, 3 H, 3′-Me). Anal. ($C_{36}H_{33}BrNO_3P$) C, H, P.