Tripyranoside Precursors for Ansamycins. Pyranosidic Homologation. 6[1,2]

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The primary and secondary alcohols of the dipyranoses **6** and **9a** are used as implements for elaborating the upper pyranoside rings of the tripyranoses **27** and **28**, respectively. Compound **27** contains seven of the eight chiral centers of rifamycin S, while **28** fixes seven of the nine chiral centers of streptovaricin A. For the synthetic procedures, the primary alcohol is oxidized to an aldehyde, which is subjected to olefination with a phosphorane of the type $PH_3P{=}CHCH(OR)_2$. Treatment with pyridinium *p*-toluenesulfonate, specifically, in the presence of an alcohol causes cyclization with the secondary alcohol, resulting in a hexenopyranoside, which is glycosidated in situ by the alcohol. the resulting hexenopyranoside is then epoxidized, and for this process, a new procedure was developed that involves hydroxylation with osmium tetraoxide and treatment of the cis diol so formed with phosgene iminium chloride (Viehe's salt) to give a chloro carbamate, which then reacts with methoxide to give the desired epoxide. Opening of the ring with dimethylmagnesium then completes the requirements for the upper ring.

In the preceding paper,[5] the tripyranoses **27b** and **28** (Scheme VI) were identified as possible precursors for the ansa chains of rifamycin S and streptovaricin A, and synthetic routes to the lower dipyranose moieties **6** and **9a** respectively were explored. An attractive aspect of the retrosynthetic analysis upon which this approach is based[6] is the fact that the upper pyranoside rings of **27** and **28** share the same stereochemical features, thereby allowing the development of a common synthetic plan. In this paper, we give details of our work that has been concerned with this structural feature.

Retrosynthetic Plan. The retrosynthetic plan called for the preparation of an unsaturated sugar, IV, whose resemblance to the well-known hex-2-enopyranoside **14** (Scheme V) is obvious. We had hoped to avail ourselves of published procedures[7] for the preparation of epoxides (e.g., **15**) and for their subsequent cleavage to give **17**.[8] The key intermediate for this sequence was deemed to be the *Z*-alkene II, which could be obtained via olefination of an aldehyde resulting from oxidation of the primary hydroxyl of I. Procedures for preparation of the required *Z*-alkenes (e.g., IIa) were available;[9,10] however, the subsequent step was a matter of some concern because if the aldehyde IIb was liberated during the cyclization, an equilibrium might ensue in which the more stable *E*-isomer III would accumulate. The detailed work of Bestmann[9] had given substance to these concerns, since the conditions for liberation of the *Z*-enals (e.g., IIb) from their precursors (IIa) also caused isomerization of the *E* isomer. Nevertheless, it was our hope that if a hemiacetal (e.g., IVa) could be glycosidated in situ to give IVb, then the equilibrating mixture of enals IIb and III would be drained off with the formation of IVb. Equilibrating conditions would further serve to ensure preponderance of the desired axially oriented alkoxyl in IVb, an expression of the anomeric effect,[11] which is well precedented in the formation of hex-2-enopyranosides (related to **14**) by means of the Ferrier rearrangement.[12]

Results and Discussion

The easily prepared glucoside **1**[13] was a convenient model for this study. The projected cyclization (e.g., II → IV) would necessitate that the secondary hydroxyl of the precursor be free, and hence it was expedient to avoid protection of this center in the first place. Conditions for this selective oxidation **1** → **2** were therefore explored (Scheme II).

Moffatt[14] and Swern[15] oxidations of **1** were only partially successful, and although lead tetraacetate–pyridine[16] did afford **2** cleanly, the reagent was found difficult to purify. Chromium and manganese reagents led to decomposition, as was apparent from the formation of benzaldehyde. Molecular oxygen catalyzed by palladium, platinum,[17] or ruthenium complexes[18] gave very low yields of **2**. The best oxidation medium proved to be a modification of the Corey–Kim procedure,[19] using thioanisole–*N*-chlorosuccimide and diisopropylethylamine.

For the olefination step, the readily prepared phosphorane obtainable from **3**,[10] was chosen for initial examination. Stereoselectivity in these condensations is known to be greatly influenced by solvent and metal salt content.[20]

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(2) For part 5, see ref 5.

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(4) Taken from Ph.D. Theses at the University of Maryland: L.M., 1983; B.F.M., 1984; D.R.M., 1986. Present addresses: L.M., Domtar Research Centre, Senneville, Quebec, Canada; B.M.; Rorer Central Research, 808 Business Center Drive, Building 3, Horsham, PA 19044; D. R.M., Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, NC 27706.

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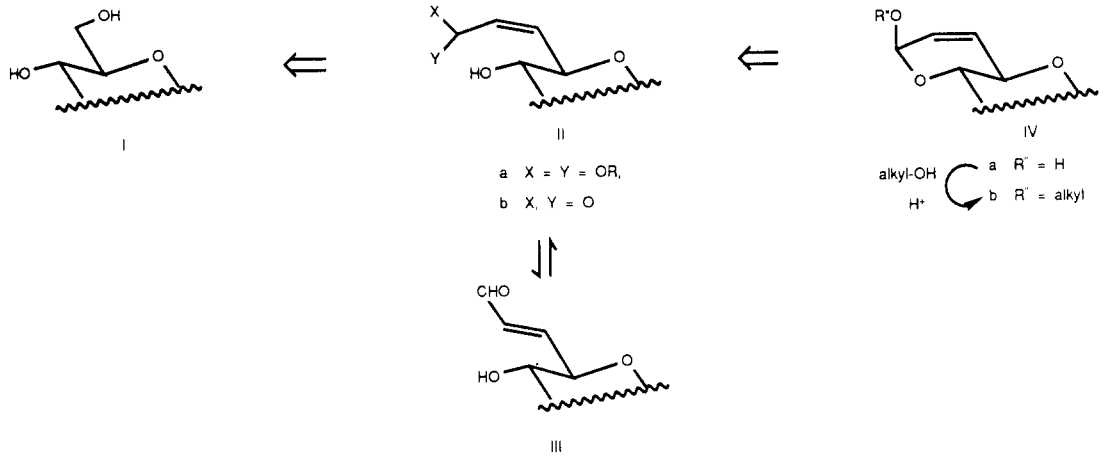
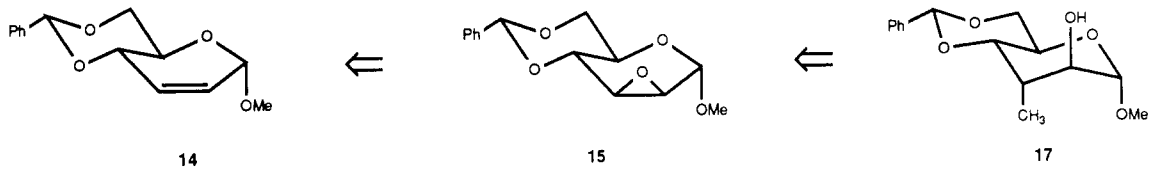
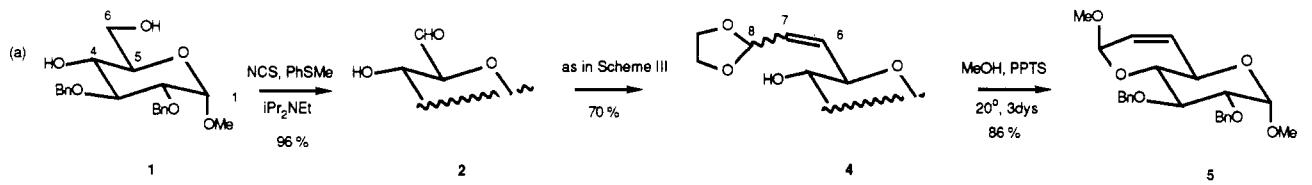
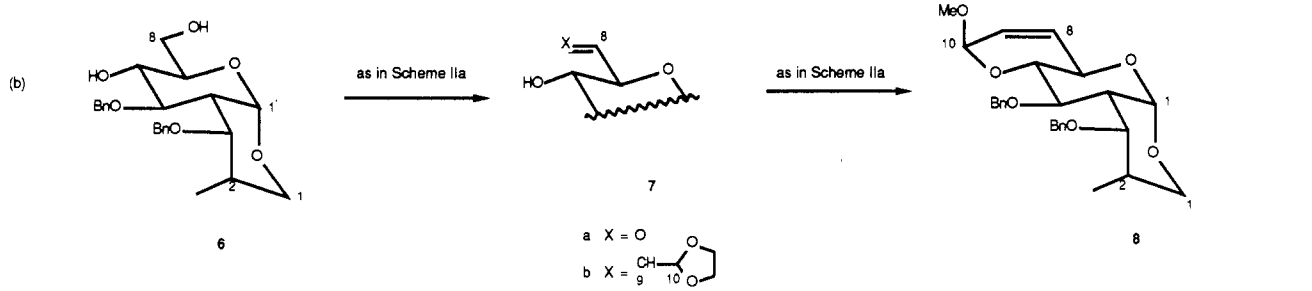
Scheme I



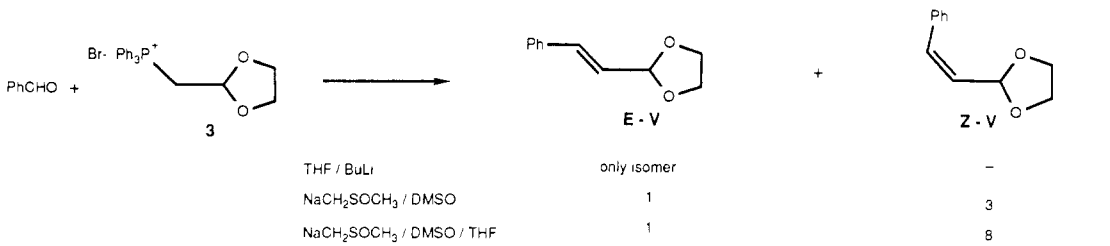


Scheme II





Scheme III



Accordingly, the stereoselectivity was first examined by using benzaldehyde. When the reagent was generated from the phosphonium bromide **3** in tetrahydrofuran with butyllithium, the only product observed was the *E*-isomer V (Scheme III). On the other hand, with dimsylsodium in dimethyl sulfoxide, a *Z*/*E* ratio of 3:1 was obtained, and addition of tetrahydrofuran to this medium raised the *Z*/*E* ratio to 8:1. The last conditions were, therefore, adopted.

Thus, reaction of hydroxy aldehyde **2** with excess of the phosphorane from **3** in a 1:1 mixture of dimethyl sulfoxide in tetrahydrofuran gave the acetal **4** as a 7:1 *Z*/*E* mixture

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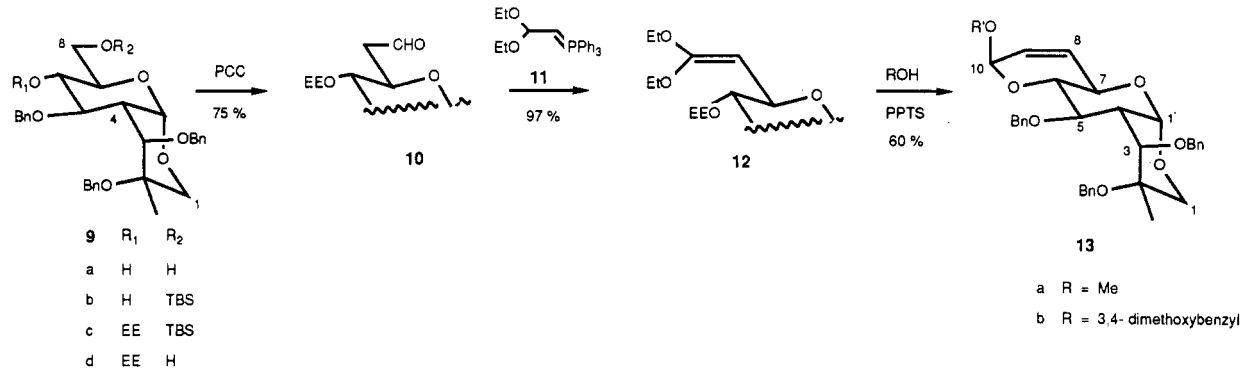
Scheme IV



in 70% yield. Treatment of this mixture with pyridinium *p*-toluene sulfonate[21] in dry methanolic solution at 20 °C for 3 days afforded dipyranoside **5** in 86% yield.

Application of the above procedure (Scheme IIa) to the dipyranosidic diol **6**[5] afforded the enoside **8** via the intermediates **7a** and **7b** as shown in Scheme IIb. The overall yields for these transformations was an encouraging 58% when the reactions were carried out at approximately 0.5-mmol levels. However, on larger scales, the selective oxidation of the primary alcohol proved to be more troublesome and the resulting hydroxy aldehyde **7a** more difficult to purify.

Both of the foregoing problems could be solved simultaneously by abandoning our initial desire to keep the secondary hydroxyl (of II, Scheme I) unprotected. However, the protecting group used would have to be compatible with the in situ cyclization/glycosidation, which led to the smooth formation of **5** and **8** (Scheme II). The α-ethoxyethyl protecting group was the obvious choice, since it is readily cleaved by use of Grieco's acid (PPTS)[21] under conditions that are comparable to those used in the formation of the enosides **5** and **8**. The success of this approach is exemplified in Scheme IV with the diol **9a**. Routine procedures afforded the 6-*O*-α-ethoxyethyl derivative **9d**, which was smoothly oxidized with pyridinium chlorochromate[22] or Swern's oxalyl chloride procedure,[15b] to afford the aldehyde **10** in 75–80% yield.

A second departure from the procedure outlined in Scheme IIa concerned the use of (2,2-diethoxyethylidene)triphenylphosphorane (**11**) for the olefination step. First, this reagent had been shown by Bestmann and co-workers[9] to give somewhat higher yields of *Z*-alkenes, and secondly, it was our hope that the subsequent cyclization/glycosidation would proceed with greater facility than with the corresponding dioxolanes used in Scheme II. These adjustments were indeed beneficial, since the acetal **12** was obtained in 97% yield and the cyclization/glycosidation afforded the axial methyl enonside **13a** in 60% yield. The latter reaction is particularly gratifying in view of the multiple equilibria which are conceivable for this substrate in the course of going from **12** to **13**. A comparable reaction using 3,4-dimethoxybenzyl alcohol in benzene solution afforded the 3,4-dimethoxybenzyl analogue **13b** in 59% yield.

The next step was the epoxidation of the enosides, and the readily available sugar **14** (Scheme V) was a convenient model. Epoxidation of this substrate with benzonitrile–hydrogen peroxide had been reported[7] to give a 3:2 mixture of the diastereomeric epoxides **15** and **16** in low yields. With *m*-chloroperbenzoic acid, the yields increased to 55% and the ratio improved to 4:1.

In view of these unencouraging literature reports, indirect methods were explored. Brown and Sweet[23] had studied the bromination of 2-methoxy-5,6-dihydropyran and found that the methoxyl group had directed the stereoselectivity of bromonium ion toward syn addition. Horton and co-workers[24] had made a similar observation in connection with the reaction of **14** with acetyl hypobromite. Thus, the latter reaction had been found to give products derived from exclusive bromonium ion attack at the more hindered α face of **14**.

Accordingly, treatment of **14** with *N*-bromosuccinimide in aqueous dimethoxyethane gave **18** as a mixture of major and minor products, which was treated directly with sodium hydride in *N*,*N*-dimethylformamide. Compound **15** was obtained as the exclusive product in 83% overall yield. In a similar manner, the olefinic tripyranoside **8** afforded the epoxide **18** (Scheme VI) as the only product in 78% yield.

While the bromohydrin route for epoxidation of the methyl glycoside **8** was satisfactory, it transpired that it could not be used for the 3,4-dimethoxybenzyl analogue **13b**. It therefore became necessary to develop an alternative method for epoxidation of these sensitive substrates.[25] We noted that Copeland and Stick[26] had observed that reaction of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**20**) with phosgene iminium chloride (**21**) had given the cyclic iminium carbonate **22**, which upon refluxing in 1,2-dichloroethane had given the chloro carbamate **23**. We were encouraged to find that treatment of **23** with sodium methoxide in methanol under reflux gave epoxide **15** in excellent yield.

Since the hydroxylation of **14** was already known to give **20**,[27] we clearly had the rudiments of an acceptable alternative. Indeed, the 3,4-dimethoxybenzyl enoside **13b** was hydroxylated by the Kelly procedure,[28] and the resulting cis diol **24** (Scheme VI) was converted into epoxide **26** via the chloro carbamate intermediate **25** in 69% overall yield.

The final step was the cleavage of the epoxides. Lithium dimethyl cuprate, which had worked well for Fraser-Reid and Hicks[8a] for the opening of **15** to give **17** (Scheme Vd), failed completely with **19**. The higher order cuprates of Lipshutz[29] fared equally as bad. However, Parker and

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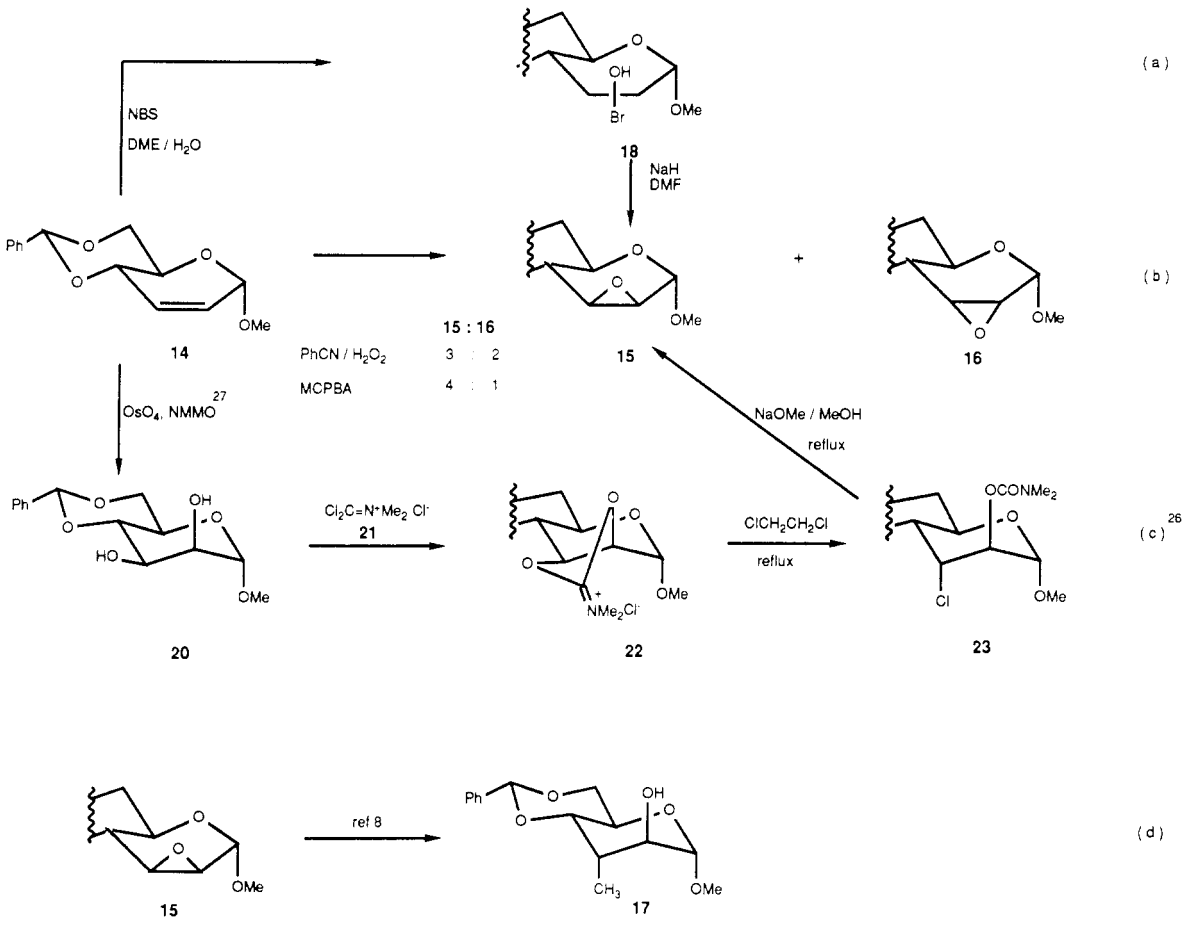
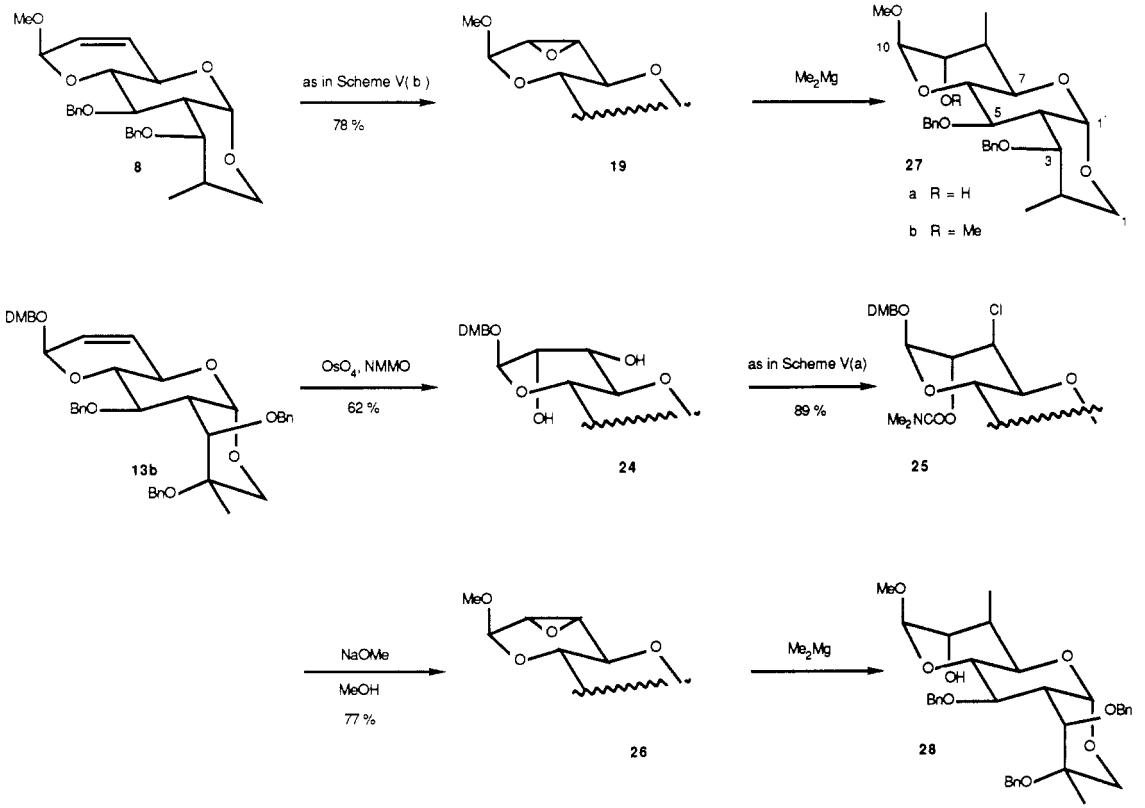
Scheme V



Scheme VI



Babine[8b] had shown that dimethylmagnesium was an excellent reagent for opening **15**. In an effort to prepare this reagent by a more expedient route than that which has been published,[30] methylmagnesium chloride was treated

with 1 equiv of methyllithium in toluene. The formation of white precipitate, deemed to be lithium chloride, was taken to indicate the presence of dimethylmagnesium in solution. Exposure of the tricyclic epoxides **19** and **26** to a large excess of this reagent gave the alcohols **27a** and **28**, respectively, as the only products in 73% and 92% yields, respectively. The stereochemistry at the newly created centers was apparent from the values $J_{8,9}$ = 3.8 and 3.7 Hz, respectively. Methylation of the former then gave **27b**.

This paper and the accompanying paper[5] show that the tripyranoses **27** and **28** can be obtained from levoglucosan (1,6-anhydro-β-D-glucopyranose) by a process of pyranoside homologation. Excellent degrees of stereocontrol have been achieved throughout by use of reactions that (usually) led to the desired product only, thereby making separation of isomers unnecessary. Assignments of configuration(s) made logically on the basis of mechanistic considerations are independently verified by simple ^{1}H NMR analyses. The attributes of stereocontrol and structure verification common to most carbohydrate reactions have, therefore, been preserved.[31] Compound **27** contains seven of the eight chiral centers of streptovaricin A.[5] Studies related to the development of the remaining chiral center(s) and to the unravelling of the tripyranose skeleta are under way and will be reported in due course.

Experimental Section

For the General Procedures, see ref 5. The numbering sequences used for reporting NMR data are shown in the various schemes.

Methyl 2,3-Di-*O*-benzyl-α-D-*gluco*-hexodialdo-1,5-pyranoside (2). *N*-Chlorosuccinimide (800 mg, 6.0 mmol) was added to a solution of thioanisole (0.78 mL, 818 mg, 6.6 mmol) in dry CH_2Cl_2 (20 mL) under argon at −20 °C. After 30 min, a solution of the diol **1**[13] (1.220 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise, and after an additional 30 min, diisopropylethylamine (1.05 mL, 6.0 mmol) was added dropwise. After stirring at −20 °C for 20 min, the reaction mixture was warmed to 0 °C. TLC indicated that the starting diol **1** (R_f 0.24, F) had formed a clean product (R_f 0.40). The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed successively with saturated sodium bicarbonate solution and dilute hydrochloric acid, dried ($MgSO_4$), and evaporated. Column chromatography (EtOAc) provided the title hydroxy aldehyde **2** monohydrate as a pale yellow syrup (1.0976 g, 96%): $[\alpha]_D^{25}$ +17.1° (*c* 1.10, $CHCl_3$); IR 3483 (s), 3061, 3025, 2920 (s) cm^{-1}; ^{1}H NMR (60 MHz) δ 2.64 (br s, ca. 2 H, OH), 3.32 (s, 3 H, OCH_3), 3.70 (m, 5 H), 4.75 (m, 5 H), 7.20 (m, 10 H, Ph), 9.67 (s, weak signal, H1). Anal. Calcd for $C_{21}H_{24}O_6 \cdot H_2O$: C, 64.77; H, 6.47. Found: C, 64.73; H, 6.23.

Ethylene Acetal of Methyl 2,3-Di-*O*-benzyl-α-D-*gluco*-oct-6(*Z*/*E*)-enodialdo-1,5-pyranoside (4). 1,3-Dioxolan-2-ylmethylphosphonium bromide (**3**)[10] (2.58 g, 6.5 mmol) was added to a stirred solution of dimsylsodium (5.25 mmol) in dry dimethyl sulfoxide (10 mL) and dry tetrahydrofuran (10 mL) at 10 °C under argon to give a deep red solution of the corresponding phosphorane. Addition of a solution of the aldehyde **2** (803.5 mg, 2.16 mmol, TLC R_f 0.15, D) in 10 mL of dry THF produced a clean product (R_f 0.29) in 10 min. The mixture was poured into water and extracted repeatedly with ethyl acetate. After drying ($MgSO_4$), filtration, and evaporation, the resulting residue was chromatographed (E) to provide the title dioxolane **4** (*Z*/*E* = 7:1) as a colorless syrup (659.5 mg, 70%): ^{1}H NMR (200 MHz) δ 2.56 (d, *J* = 2.6 Hz, 1 H, OH, D_2O ex), 3.34 (ddd, *J* = 9.6, 9.0, 2.6 Hz, 1 H, H4), 3.41 (s, 3 H, OCH_3), 3.51 (dd, *J* = 9.8, 7.6 Hz, 1 H, H5), 3.84 (dd, *J* = 9.8, 9.0 Hz, 1 H, H3), 3.96 (m, 4 H, CH_2CH_2), 4.44 (dd, *J* = 9.6, 7.6 Hz, 1 H, H5), 4.59 (d, *J* = 3.6 Hz, 1 H, H1), 4.72 (AB q, *J* = 12.0 Hz, Δδ = 0.12 ppm, 2 H, Ph″CH_2), 4.90 (AB q, *J* = 11.0 Hz, Δδ = 0.10 ppm, 2 H, Ph′CH_2), 5.27 (d, *J* = 5.6 Hz, H8E), 5.68 (d, *J* = 6.0 Hz, H8*Z*), 5.66 (dd, *J* = 11.0, 7.6 Hz, H6*Z*), 5.75 (dd, *J* = 11.0, 6.0 Hz, H7*Z*), 5.82 (ddd, *J* = 15.8, 5.6, 1.5 Hz, H7*E*), 6.03 (dd, *J* = 15.8, 5.2 Hz, H6*E*), 7.33 (m, 10 H, Ph); HRMS, *m*/*e* for $C_{25}H_{30}O_7$ calcd 442.1991, Found 442.1992.

(8*S*,6*Z*)-Dimethyl 2,3-Di-*O*-benzyl-α-D-*gluco*-oct-6-enodialdo-1,5:4,8-dipyranoside (5). The dioxolane **4** (225.2 mg, 0.51 mmol) and pyridinium *p*-toluenesulfonate[31] were dissolved in dry MeOH (10 mL) and stirred under argon at 20 °C in a flask covered with aluminum foil. After 60 h, TLC (D) indicated only a trace of **4** (R_f 0.37) (23.4 mg recovered) along with a clean product (R_f 0.55). Solid potassium carbonate (20 mg) was added to the solution, and the methanol was evaporated. The residue was partitioned between ether (20 mL) and water (10 mL), and the ether phase was washed with saturated sodium bicarbonate solution, dried (K_2CO_3), filtered, and evaporated. Column chromatography (D) gave the title dipyranoside **5** as a colorless syrup (179.2 mg, 86%): $[\alpha_D^{25}$ + 3.6° (*c* 1.86, $CHCl_3$); ^{1}H NMR (200 MHz) δ 3.39 (s, 3 H, O″CH_3), 3.46 (s, 3 H, O′CH_3), 3.52 (dd, *J* = 9.8, 3.8 Hz, 1 H, H2), 3.60 (t, *J* = 9.8 Hz, 1 H, H4), 3.91 (t, *J* = 9.8 Hz, 1 H, H3), 4.13 (brd, *J* = 9.8 Hz, 1 H, H5), 4.58 (d, *J* = 3.8 Hz, 1 H, H1), 4.47 (AB q, *J* = 12.0 Hz, Δδ = 1.7 ppm, 2 H, Ph″CH_2), 4.90 (AB q, *J* = 11.4, Δδ = 0.08 ppm, 2 H, Ph′CH_2), 4.92 (m, 1 H, H8), 5.71 (dt, *J* = 10.0, 2.2, 2.2 Hz, 1 H, H6), 5.97 (dt, *J* = 10.0, 1.0, 1.0 Hz, 1 H, H7), 7.35 (m, 10 H, *Ph*). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.85; H, 6.84. Found: C, 69.43; H, 6.84.

Unsaturated Tripyranoside 8. The identical procedure described above for the preparation of **2** (Scheme II) was followed for the selective oxidation of the diol **6**[5] (204 mg, 0.49 mmol), affording the hydroxy aldehyde **7a** as a partially hydrated, waxy material: $[\alpha]_D^{25}$ −16.5° (*c* 1.22, $CHCl_3$); IR 3410 (sb), 3062 (w), 3039 (w), 2900 (s) cm^{-1}; ^{1}H NMR (100 MHz) δ 1.18 (d, *J* = 7.2 Hz, C2CH_3), 2.05 (m, 1 H, H2), 2.32 (m, 1 H, H4), 3.80 (m, ca. 6 H), 4.65 (m, 6 H), 5.08 (d, *J* = 3.6 Hz, 1 H, H1′), 7.26 (m, 10 H), 9.78 (s, ca. $^1/_2$ H, H8). Reaction of the resulting aldehyde (167 mg, 0.40 mmol) and the Wittig reagent **3** (1.25 mmol) was carried out, as described above for preparation of **4**. The aldehyde **7a** (TLC R_f 0.20, D) formed a clean product (R_f 0.38). Column chromatography provided the alkene mixture **7b** (*E*/*Z* = 4) as a colorless syrup (140.0 mg, 73%): ^{1}H NMR (200 MHz) δ 1.34 (d, *J* = 7.0 Hz, 3 H, C2CH_3), 2.10 (m, 1 H, H2), 2.46 (ddd, *J* = 8.5, 4.5, 3.0 Hz, 1 H, H4), 2.83 (d, *J* = 2.5 Hz, 1 H, OH, D_2O ex), 3.39 (dt, *J* = 9.0, 9.0, 2.5 Hz, 1 H, H6), 3.56 (dd, *J* = 12.0, 4.2 Hz, 1 H, H1a), 3.71 (t, *J* = 4.5 Hz, 1 H, H3), 3.90 (dd, *J* = 12.0, 3.0 Hz, 1 H, H1e), 3.90 (m, 4 H, CH_2CH_2), 3.98 (dd, *J* = 9.0, 8.5, 1 H, H5), 4.61 (AB q, *J* = 12.0 Hz, Δδ = 0.12 ppm, 2 H, Ph″CH_2), 4.71 (d, *J* = 3.0 Hz, 1 H, H1′), 4.73 (m, 1 H, H7), 4.79 (AB q, *J* = 11.5 Hz, Δδ = 0.07 ppm, 2 H, Ph′CH_2), 5.30 (d, *J* = 4.5 Hz, H10*E*), 5.56 (*J* = 4.4, 2.0 Hz, H10*Z*), 5.75 (dd, *J* = 12.0, 8.0 Hz, H8*Z*), 5.83 (ddd, *J* = 15.0, 4.5, 1.0 Hz, H9*E*), 6.05 (dd, *J* = 15.0, 5.6 Hz, H8*E*), 7.28 (m, 10 H, Ph). A portion of the material (130 mg, 0.27 mmol) was cyclized with PPTS (20 mg) and methanol (20 mL), as described for preparation of **5**. After 20 h, only a trace of starting **7b** (TLC R_f 0.52, D) remained (30 mg recovered) along with a new product (R_f 0.65). Column chromatography (C) provided the title tripyranose **8** as a pale yellow semisolid, mp 75–80 °C (78.8 mg, 70%): $[\alpha]_D^{25}$ −32.5° (*c* 0.49, $CHCl_3$); ^{1}H NMR (100 MHz) δ 1.33 (d, *J* = 7.0 Hz, 3 H, C2CH_3), 2.08 (m, 1 H, H2), 2.52 (ddd, *J* = 9.0, 5.0, 3.4 Hz, 1 H, H4), 3.43 (s, 3 H, OCH_3), 3.58 (dd, *J* = 12.0, 4.0 Hz, 1 H, H1a), 3.71 (t, *J* = 5.0 Hz, 1 H, H3), 3.72 (dd, *J* = 10.0, 9.0 Hz, 1 H, H6), 3.89 (dd, *J* = 12.0, 2.0 Hz, 1 H, H1e), 4.10 (t, *J* = 9.0 Hz, 1 H, H5), 4.46 (ddd, *J* = 10.0, 2.2, 1.2 Hz, 1 H, H7), 4.58 (AB q, *J* = 12.2 Hz, Δδ = 0.13 ppm, 2 H, Ph″CH_2), 4.75 (d, *J* = 3.4 Hz, 1 H, H1′), 4.84 (AB q, *J* = 11.0 Hz, Δδ = 0.10 ppm, 2 H, Ph′CH_2), 4.94 (m, 1 H, H10), 5.73 (t, *J* = 2.2 Hz, H8), 6.03 (t, *J* = 1.2 Hz, 1 H, H9), 7.26 (m, 10 H, Ph); MS, *m*/*e* 452 (M, 0.5), 450 (1.0), 420 (2.0), 391 (7), 330 (42), 239 (30), 223 (45), 149 (55), 117 (80), 111 (50), 97 (75), 91 (100), 83 (75), 71 (75), 57 (80), 55 (75). Anal. Calcd for $C_{27}H_{32}O_6$: C, 71.66; H, 7.13. Found: C, 71.25; H, 7.18.

Differentially Protected Dipyranoside 9d. The diol **9a**[5] (898 mg, 1.72 mmol) was selectively silylated (see the General Procedures),[5] and the resulting material **9b** was dissolved in methylene chloride (5 mL) and treated with ethyl vinyl ether (1 mL) and pyridinium *p*-toluenesulfonate[31] (20 mg). The resulting

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6-*O*-(α-ethoxyethyl) derivative **9c** was obtained as a pale yellow oil, which was dissolved in tetrahydrofuran (10 mL) and treated with tetra-*n*-butylammonium fluoride (1.2 mL of a 1 M tetrahydrofuran solution) at room temperature. After 3 h, the brown reaction mixture was concentrated in vacuo, and the oily residue was purified by flash chromatography (C) to give **9d** (842 mg, 83% overall from **9a**) as a colorless syrup. The physical properties for the diastereomeric mixture are as follows: TLC R_f 0.2, and 0.30 (D); IR (neat) 3460, 2925, 1448, 1065 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.82–1.40 (m, 9), 1.62 (br s, 1, OH, D_2O ex), 2.00–2.30 (m, 1 H4), 3.25–4.90 (m, 17), 5.12 (m, 1), 7.00–7.45 (m, 15, $PhCH_2$). Anal. Calcd for $C_{35}H_{44}O_8$: C, 70.92; H, 7.48. Found: C, 71.13; H, 7.64.

***E*/*Z* Unsaturated Tripyranoside 13a.** The alcohol **9d** (552 mg, 0.931 mmol) was oxidized with pyridinium chlorochromate in refluxing benzene, as described in the General Procedures. The resulting aldehyde **10** (409 mg, 75%) was obtained as a colorless syrup: TLC R_f 0.24 (C); IR (neat) 2875, 1735, 1455, 1380, 1070, 738, 705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00–1.50 (m, 9), 2.11 (m, 1), 3.30–3.80 (m, 4), 4.00–4.80 (m, 11), 5.10–5.30 (m, 1), 7.10–7.45 (m, 15), 9.82 (s, 1); HRMS, *m*/*e* ($M^+ - C_2H_4O$) calcd 546.2617, found 546.2615. (Formylmethylene)triphenylphosphorane[32] (**11**) (888 mg, 2.71 mmol) was boiled with freshly distilled bromoethane (40 mL) under an argon atmosphere overnight. Dry tetrahydrofuran (50 mL) was added, and after the mixture was refluxed for another 3 h, the excess bromoethane was removed by standard fractional distillation. the resulting solution was cooled to room temperature, and the oily product was treated with sodium ethoxide (3 equiv) prepared fresh from the reaction of oil-free sodium hydride and ethanol. The mixture was stirred for 0.5 h under an argon atmosphere, during which time the oily residue and sodium ethoxide dissolved, resulting in an orange-red solution of **11**. The aldehyde **10** (534 mg, 0.904 mmol) was added in tetrahydrofuran solution (5 mL) at room temperature. After 0.5 h, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ether. The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (C) gave **12** as a yellow syrup (608 mg, 97%). The physical properties for the diastereomeric mixture are as follows: TLC R_f 0.50 (1:2 ethyl acetate–hexane); IR (neat) 3060, 2970, 1455, 1380, 1062, 732 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80–1.50 (m, 15), 2.2 (m, 1), 3.35–3.80 (m, 9), 3.90–5.00 (m, 10), 5.10–5.20 (m, 1), 5.30–5.40 (m, 1), 5.65–5.83 (m, 2), 7.10–7.50 (m, 15); HRMS, *m*/*e* ($M^+ - C_2H_5OH$) calcd 644.3349, obsvd 644.3344. A solution of the unsaturated acetal **12** (455 mg, 0.659 mmol), pyridinium *p*-toluenesulfonate (0.1 equiv), and absolute methanol (40 mL) was refluxed in a round-bottom flask fitted with a magnetic stirring bar and a condenser under argon. After 24 h, the reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (C) to give **13a** as a pale yellow syrup (221 mg, 60%): TLC R_f 0.48 (C); $[\alpha]_D^{19}$ +99.7° (*c* 1.94, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.14 (s, 3, CH_3), 2.17 (m, 1, H4), 3.39 (s, 3, OCH_3), 3.61 (t, 1, $J_{5,6} = J_{6,7} = 9.0$ Hz, H6), 3.72 (d, 1, $J_{1a,1e} = 13.0$ Hz, H1a), 3.82 (br s, 1, H3), 4.13 (dd, 1, $J_{1e,3} = 1.8$ Hz, H1e), 4.34–4.77 (m, 8, H4, H6, $PhCH_2$), 4.87 (br s, 1, H10), 5.14 (d, 1, $J_{1',4} = 3.4$ Hz, H1′), 5.73 (dt, 1, $J_{9,10} = J_{7,9} = 1$ Hz, $J_{8,9} = 10.0$ Hz, H9), 6.03 (dt, 1, $J_{8,10} = J_{7,8} = 2.8$ Hz, H8), 7.18–7.45 (m, 15, $PhCH_2$). Anal. Calcd for $C_{34}H_{38}O_7$: C, 73.10; H, 6.86. Found: C, 73.36; H, 6.66.

Unsaturated Tripyranoside 13b. A solution of the unsaturated acetal **12** (506 mg, 0.73 mmol) in pyridinium *p*-toluenesulfonate[31] (180 mg, 0.73 mmol) and 3,4-dimethoxybenzyl alcohol (1.23 g, 1.4 mL, 7.3 mmol) in dry benzene (30 mL) was refluxed in a round-bottom flask fitted with a magnetic stirring bar, a Dean-Stark trap, and a condenser under argon. After 24 h, the reaction mixture was concentrated in vacuo and the residue purified by flash silica gel chromatography (C) to afford the enoside **13b** as a pale yellow syrup (300 mg, 59%): TLC R_f 0.24 (C); $[\alpha]_D^{20}$ +125° (*c* 0.28, $CHCl_3$); IR (neat) 3025, 2900, 1515, 1265, 1140, 1070, 1030, 750 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 3, CH_3), 2.18 (m, 1, H4), 3.67–3.90 (m, 3), 3.78 and 3.85 [2 s, 6, (3,4-di-CH_3OPhCH_2)], 4.16 (br d, 1, $J_{1a,1e} = 13.0$ Hz, H1e), 4.29–4.82 (m, 9), 5.06 (br s, 1, H10), 5.14 (d, 1, $J_{1,7} = 3.1$ Hz, H1′), 5.74 (br d, 1, $J_{8,9} = 10$ Hz, H9), 6.04 (br d, 1, H8), 6.82 [m, 3, (3,4-di-CH_3OPhCH_2)], 7.20–7.42 (m, 15, $PhCH_2$). Anal. Calcd for $C_{42}H_{46}O_9$: C, 72.60; H, 6.67. Found: C, 72.53; H, 6.89.

Methyl 2,3-Anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (15). A solution of methyl 4,6-*O*-benzylidene-α-D-erythrohex-2-enopyranoside (**14**)[33] (564.0 mg, 2 mmol) and *N*-bromosuccinimide (712 mg, 4 mmol) in a 3:1 mixture of dimethoxyethane and water (20 mL) was left in the dark at 20 °C. After 18 h, compound **14** (TLC R_f 0.75, C) was replaced by major (R_f 0.16) and minor (R_f 0.55 and 0.40) products, presumed to be isomers of **18**. The solution was diluted with ether (40 mL), washed with 5% sodium thiosulfate solution (20 mL) followed by water, dried ($MgSO_4$), filtered, and evaporated to a solid residue (770.3 mg). The crude product was dissolved in dry DMF (30 mL) at 0 °C and treated with sodium hydride (200 mg). After 20 min at 20 °C, TLC (C) indicated only a single product (R_f 0.40). The reaction was quenched by careful addition of ice (10 g). The mixture was partitioned between CH_2Cl_2 (100 mL) and water (100 mL), and the CH_2Cl_2 phase was washed with water, dried ($MgSO_4$), filtered, and evaporated to yield pure **15** as fan-shaped crystals (497.4 mg, 83%): mp 145.5–146 °C; $[\alpha]_D^{23}$ + 98.02° (*c* 1.77 in $CHCl_3$) [lit.[34] mp 145–147 °C; $[\alpha]_D^{15}$ +107° (*c* 1.6 in $CHCl_3$)].

Hydroxylation of the Enoside 13b To Give Diol 24. *N*-Methylmorpholine *N*-oxide (1.1 equiv, 60 wt % in water) and osmium tetraoxide (1 mol %, 2.5 wt % in *tert*-butyl alcohol) were added to a solution of the 3,4-dimethoxybenzyl enoside **13** (287 mg, 0.696 mmol) in acetone–water (5:1, 15 mL). The reaction mixture was stirred for 48 h at room temperature under argon and, upon completion (TLC, D), was quenched with sodium bisulfite (25 mg), diluted with water, and extracted with ethyl acetate. The combined ethyl acetate portions were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by filtration through a short silica gel column (D) to afford the diol **24** as a white solid (189 mg, 62%): mp 66–68 °C; TLC R_f 0.08 (D); $[\alpha_D^{19}$ +44.7° (*c* 1.1, $CHCl_3$); IR ($CDCl_3$) 3440, 3040, 2905, 1512, 1262, 1065 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.14 (s, 3, CH_3), 2.14 (m, 1, H4), 2.54 (br s, 1, OH, D_2O ex), 2.69 (br s, 1, OH, D_2O ex), 3.55–4.20 (m, 10), 3.77 and 3.86 [2 s, 6, (3,4-di-CH_3OPhCH_2)], 4.28–4.87 (m, 11), 4.90 (s, 1, H10), 5.12 (d, 1, $J_{1',7} = 3.1$ Hz, H1′), 6.82 [m, (3,4-di-CH_3OPhCH_2)], 7.20–7.50 (m, 15, $PhCH_2$). Anal. Calcd for $C_{42}H_{48}O_{11}$: C, 69.21; H, 6.64. Found: C, 69.06; H, 6.64.

Chloro Carbamate 25. A solution of the cis diol **24** (188 mg, 0.26 mmol) in dry 1,2-dichloroethane (10 mL) and triethylamine (1.0 mL) was treated with phosgene iminium chloride (1.5 equiv) and refluxed with vigorous stirring for 0.5–1 h under argon. The dark brown reaction mixture was cooled to room temperature, quenched with saturated sodium bicarbonate solution, and extracted with methylene chloride. The combined methylene chloride portions were washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was fractionated by flash column chromatography (D) to give **25** (186 mg, 89%): TLC R_f 0.28 (D); $[\alpha]_D^{19}$ +1.37° (*c* 1.61, $CHCl_3$); IR (neat) 3025, 2910, 1710, 1510, 1390, 1270, 1138, 1068 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (s, 3, CH_3), 2.22 (br d, 1, $J_{4,5} = 10.8$ Hz, H4), 2.93 and 2.94 (2 s, 6, Me_2NCO_2), 3.70–3.90 (m, 2), 3.79 and 3.86 [2 s, 6, (3,4-di-CH_3OPhCH_2)], 4.08–4.76 (m, 13), 4.80 (s, 1, H10), 5.13 (d, 1, $J_{8,9} = 2.5$ Hz, H9), 5.22 (d, 1, $J_{1',4} = 3.1$ Hz, H1′), 6.73–6.89 [m, 3, (3,4-di-CH_3OPhCH_2)], 7.12–7.40 (m, 15, $PhCH_2$); HRMS, *m*/*e* (M^+) calcd 817.3229, found 817.3230.

Epoxide 26. A solution of the chloro carbamate **25** (187 mg, 0.228 mmol) in absolute methanol was added to a freshly prepared solution of sodium methoxide (5 equiv) in absolute methanol (15 mL). The reaction mixture was refluxed for 6–8 h and monitored by TLC (D). Upon completion, the reaction mixture was concentrated in vacuo, and the residue was dissolved in methylene chloride and washed with water and saturated sodium chloride solutions. The methylene chloride layer was dried (Na_2SO_4), filtered, and concentrated in vacuo and the residue purified by flash chromatography (D) to afford **26** as a colorless syrup (125 mg, 77%): TLC R_f 0.41 (D); $[\alpha]_D^{19}$ +83.4° (*c* 1.25, $CHCl_3$); IR (neat) 3110, 2990, 1555, 1495, 1308, 1180, 1110, 1068, 795 cm^{-1}; 1H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 3, CH_3), 2.12 (m, 1, H4), 3.15 (d, 1, $J_{8,9} = 3.7$ Hz, H8), 3.39 (d, 1, H9), 3.54 (t, 1, $J_{6,7} = J_{5,6}$

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= 9.8 Hz, H6), 3.68-3.80 (m, 2, H3, H1a), 3.76 and 3.86 [2 s, 6, (3,4-di-CH_3OPhCH_2)], 3.95 (d, 1, H7), 4.17 (br d, 1, $J_{1a,1e}$ = 13.2 Hz, H1e), 4.23-4.74 [m, 8, PhCH_2, (3,4-di-CH_3OPhCH_2)], 5.06 (s, 1, H10), 5.13 (d, 1, $J_{1',4}$ = 3.2 Hz, H1'), 6.81 [br s, 3, (3,4-di-CH_3O*Ph*CH_2)], 7.12-7.40 (m, 15, *Ph*CH_2). Anal. Calcd for $C_{42}H_{46}O_{10}$: C, 75.92; H, 6.98. Found: C, 76.00; H, 6.91.

Epoxide 19 and Cleavage to Tripyranoside 27. The identical procedure given above for the preparation of **15** was followed for the epoxidation of the unsaturated tripyranoside **8** with the following amounts: **8** (78.8 mg, 0.17 mmol), NBS (100 mg, 0.5 mmol), DME-water (3:1, 10 mL), for 29 h. TLC (F) showed only a trace of **8** (R_f 0.58) along with major (R_f 0.12) and minor (R_f 0.64 and 0.40) products. Treatment of this mixture with sodium hydride (30 mg) in 10 mL of dry DMF, as described for **15**, produced one product (R_f 0.64) containing a trace of the alkene **8** (R_f 0.58, ca. 10 mg recovered). Column chromatography (B) provided the epoxide **19** as an off-white semisolid (48.2 mg, 73%). To a solution of methyllithium (1.6 M in ether, 1.25 mL, 2 mmol), at 0 °C under argon was added a solution of methylmagnesium chloride (2.8 M in THF, 0.71 mL, 2 mmol). After 30 min at 20 °C, toluene (25 mL) was added to the white mixture and the temperature raised to 80 °C. After an additional 30 min, the epoxide (30 mg, 0.064 mmol), dissolved in 5 mL of toluene, was added to the hot white mixture. After 2 h, TLC (F) indicated the formation of a major product (R_f 0.04) along with traces of other material (R_f 0.26 and 0.04). The reaction mixture was cooled to 0 °C, poured onto water (100 mL), and extracted with ether (100 mL). The ether phase was washed with 5 M NH_4Cl (50 mL), dried ($MgSO_4$), filtered, and evaporated to yield a semisolid. Column chromatography (C) gave the starting material (7.0 mg) and **27a** (20.2 mg, 73%): ^{1}H NMR (200 MHz) δ 1.08 (d, J = 7.0 Hz, 3 H, C8CH_3), 1.34 (d, J = 7.2 Hz, 3 H, C2CH_3). O-Methylation with sodium hydride-MeI in DMF gave the tripyranoside **27b** as a pale yellow semisolid: mp ca. 100 °C; $[\alpha]_D^{25}$ -30.6° (*c* 0.34, $CHCl_4$); ^{1}H NMR (200 MHz) δ 1.10 (d, J = 7.2 Hz, 3 H, C8CH_3, 1.36 (d, J = 7.2 Hz, 3 H, C2CH_3), 2.08 (m, 1 H, H2), 2.42 (m, 1 H, H8), 2.47 (ddd, J = 10.5, 5.2, 3.2 Hz, 1 H, H4), 3.21 (br s, 1 H, H9), 3.41 and 3.53 (2 s, 6 H, OCH_3), 3.59 (dd, J = 12.0, 4.0 Hz, 1 H, H1a), 3.71 (t, J = 5.2 Hz, 1 H, H3), 3.73 (dd, J = 10.5, 8.5 Hz, 1 H, H6), 3.89 (dd, J = 12.0, 2.0 Hz, 1 H, H1e), 4.17 (dd, J = 10.5, 8.5 Hz, 1 H, H5), 4.25 (dd, J = 10.5, 5.0 Hz, 1 H, H7), 4.58 (AB q, J = 12.0 Hz, $\Delta\delta$ = 0.1, ppm, 2 H, Ph''CH_2), 4.65 (d, J = 3.2 Hz, 1 H, H1'), 4.69 (s, 1 H, H10), 4.81 (ABq, J = 11.5 Hz, $\Delta\delta$ = 0.06 ppm, 2 H, PhCH_4), and 7.30 (m, 10 H, *Ph*). Anal. Calcd for $C_{29}H_{38}O_7$: C, 69.87; H, 7.63. Found: C, 69.54; H, 7.41.

Tripyranoside 28. Epoxide **26** (125 mg, 0.180 mmol) was cleaved with dimethylmagnesium by using a similar procedure to that described above for **19** → **27a**. The alcohol **28** was obtained as a colorless syrup (120 mg, 92%): TLC R_f 0.18 (D); $[\alpha]_D^{19}$ +30.8° (*c* 1.17, $CHCl_3$); IR (neat) 3465, 3015, 2910, 1590, 1515, 1450, 1265, 1135, 775 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.10-1.18 (overlapping d and s, 6, C8CH_3, C2CH_3), 1.77 (d, 1, $J_{9,OH}$ = 7.0 Hz, OH, D_2O ex), 2.12 (m, 1, H4), 2.33 (m, 1, H8), 3.67-3.81 (m, 2, H9, H1a), 3.78 and 3.86 [2 s, 6, (3,4-di-CH_3PhCH_2)], 4.17 (dd, 1, $J_{1e,3}$ = 1.6 Hz, $J_{1e,1a}$ = 13.2 Hz, H1e), 4.24 (dd, 1, $J_{7,8}$ = 5.6 Hz, $J_{6,7}$ = 10.4 Hz, H7), 4.32-4.81 [m, 9, PhCH_2, H10, (3,4-di-CH_3OPhCH_2)], 5.12 (d, 1, $J_{1',4}$ = 3.3 Hz, H1'), 6.80 [br s, 3, (3,4-di-CH_3O*Ph*CH_2)], 7.21-7.43 (m, 15, *Ph*CH_2). Anal. Calcd for $C_{43}H_{50}O_{10}$: C, 70.94; H, 7.58. Found: C, 71.02; H, 7.69.

Registry No. 1, 17791-36-5; 2, 89731-21-5; 3, 52509-14-5; (*Z*)-4, 89731-22-6; (*E*)-4, 89747-98-8; 5, 89731-19-1; 6, 88392-83-0; 7a, 88392-84-1; (*E*)-7b, 110046-70-3; (*Z*)-7b, 110115-19-0; 8, 88392-86-3, 9a, 110046-71-4; 9b, 110046-72-5; 9c (diastereomer 1), 110046-73-6; 9c (diastereomer 2), 110115-23-6; 9d (diastereomer 1), 110046-74-7; 9d (diastereomer 2), 110115-24-7; 10 (diastereomer 1), 110046-75-8; 10 (diastereomer 2), 110115-25-8; 11, 71276-94-3; 12 (diastereomer 1), 110046-76-9; 12 (diastereomer 2), 110115-26-9; 13a, 110046-77-0; 13b, 110046-78-1; 14, 3169-98-0; 15, 3150-16-1; 19, 88392-87-4; 24, 110115-20-3; 25, 110115-21-4; 26, 110115-22-5; 27a, 110046-79-2; 27b, 88392-88-5; 28, 110046-80-5; OCCH=PPh_3, 2136-75-6; 3,4-dimethoxybenzyl alcohol, 93-03-8.

Complementary Routes to "Remote" Tertiary Alcohols of Streptovaricin A[1,2]

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This paper describes a model study connected with the "pyranosidic homologation" approach to the ansa chain of streptovaricin A. Of the nine contiguous chiral centers present in this array, the C14 tertiary alcohol is the only one that cannot be accommodated on the tripyranoside backbone. In the present study, the anomeric center of a dipyranoside model is transformed into the δ-lactone **2** and thence into the isopropenyl center in **9**. For both compounds **2** and **9**, reliance is placed upon the adjacent C7 oxygen to provide a stereocontrolling force. In the first set of reactions, the lactone is elaborated into a methyl ketone, **3b**, to which vinylmagnesium bromide adds with only modest stereoselectivity to give the mixture of tertiary alcohols **4** and **5**. In the second set of reactions, the double bond in **9** reacts with complete stereoselectivity to give (a) a single diol, **7**, upon hydroxylation and (b) a single epoxide, **13**. Processing of the latter leads to the complementary diol **6**. The sense of stereoselectivity in the various reactions follows an internally consistent pattern, which lends confidence to the configurational assignments that have been made.

In the accompanying papers,[5] we gave details for the preparation of tripyranose derivatives (e.g., I), which are being investigated as precursors for the ansamycin antibiotics. The retrosynthetic plan[6a] on which this approach is based led to structures Ia and Ib, which are capable of accommodating eight contiguous chiral centers. Structure Ia is an adequate chiron for the eight contiguous chiral centers present in the ansa chain of rifamycin S;[6a] however,

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(2) Pyranosidic Homologation part 11. For part 5, see ref 5a.

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