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ASSEMBLY OF THE C19–C29 ALIPHATIC SEGMENT OF RIFAMYCIN S FROM D-GLUCOSE BY THE CHIRON APPROACH[1]

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Abstract—We describe a stereocontrolled method for the construction of the aliphatic chain of rifamycin S, based on a strategy that utilizes carbohydrates as optically active precursors.

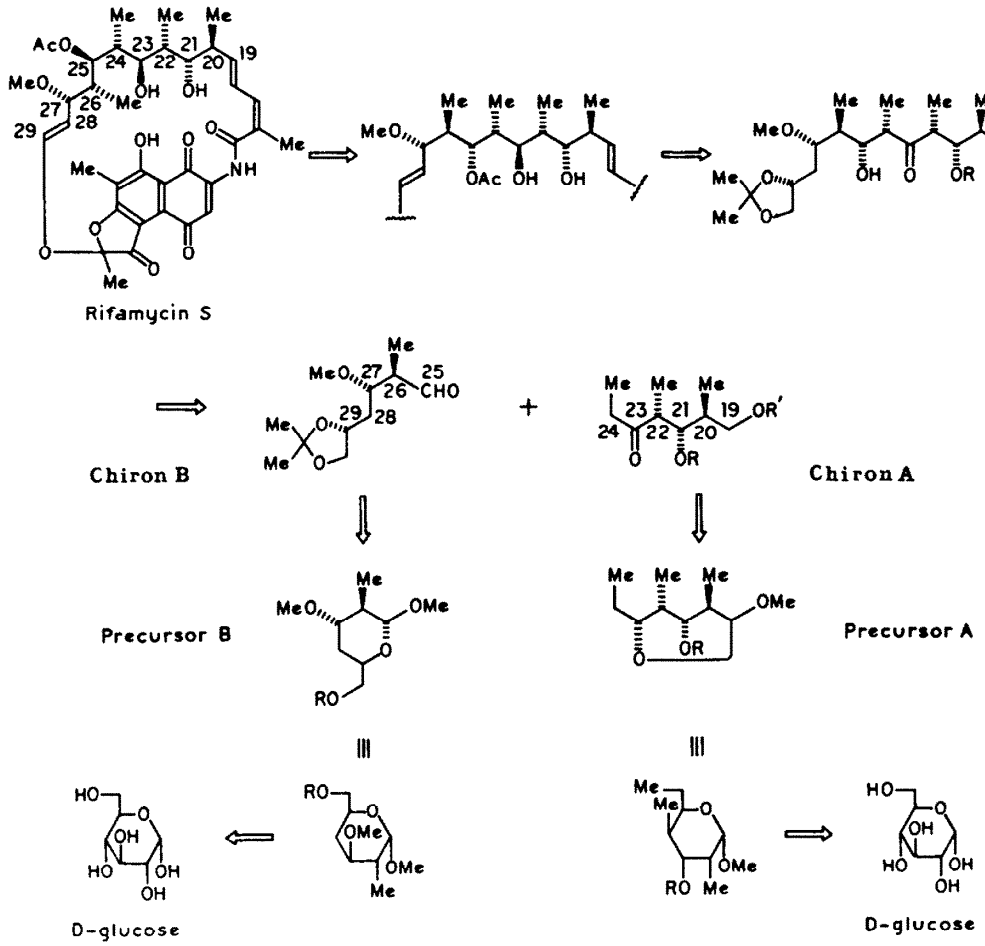
Rifamycin S, a member of the tuberculostatic group of ansamycin antibiotics has been the subject of elegant studies since its isolation in 1960.[2] Its constitutional structure,[3] X-ray crystallographic analysis[4] as well as related studies on other members of the same class have revealed unique structural features.[5] Thus, rifamycin S embodies an "ansa" chain which encompasses the carboxylic acid portion, C15–C29. Within this unit is found an aliphatic chain, C19–C29 which consists of a sequential array of alternating Me and OH groups corresponding to eight contiguous asymmetric centers. This pattern is a direct result of a biosynthetic pathway involving propionate units which can also be found in a large number of other natural products such as the macrolide group of antiobiotics. To complete the structurally intriguing features in rifamycin S, notice should be made of the "aromatic" naphthoquinone unit, which is connected to the ansa chain by amide and acetal linkages.

The total synthesis of natural products of the ansa or macrolide types has been a veritable challenge over the last ten years, and several targets have been recently conquered.[6] Kishi's[7] total synthesis of rifamycin S in 1980 highlighted other notable achievements in this area. Examination of the structure of this formidable target reveals a number of challenges not the least of which is the assembly of the aliphatic portion harboring eight of the nine asymmetric centers in the antibiotic. Closer scrutiny of this segment of the molecule reveals aspects of hidden symmetry that have been exploited by Kishi[7] and Masamune[8] and their respective coworkers. For example, (*S*)-3-hydroxyisobutyric acid available from enzymatic oxidation of isobutyric acid,[9] was a chiral building block in the Kishi synthesis where it was extended in either direction to build the growing chain of the ansa unit. Masamune *et al.*[8] recognized C_S symmetry in a hypothetical intermediate and used retrograde reasoning to provide two enantiomeric 5-carbon units which were used to generate the seven asymmetric centers found at C20–C22 and C24–C27 in the chain by aldol methodology.

There is yet another element of hidden symmetry in the aliphatic segment of rifamycin S, one which can be unveiled and related to carbohydrates.[10] This can be achieved by considering the retrosynthetic analysis shown in Scheme 1, where bond disconnection is effected between C24 and C25 to generate two six-carbon chirons† A and B encompassing C19–C24 and C25–C29 of the ansa chain. Each chiron can be derived from two precursors, A and B respectively, which in turn can be prepared from D-glucose by systematic modification of functionality to achieve the desired level of overlap. In such a strategy, the design element relies heavily on aspects of pattern recognition of flexible carbon frameworks in the target and chiral precursor. The stereochemical features, conformational bias and structures combine to provide the synthetic chemist with a "chiral template"[10] suitable for systematic chemical manipulation based on a great deal of predictive power. By generating precursors such as A and B, one also has the advantage of using synthetic intermediates common to both, since the pattern and nature of substitution at C20, C21 and C26, C27 are the same in the target. Identical and opposite stereochemcial relationships can be seen at C20/C26 and C21/C27 respectively. For the purposes of generating the two precursors one has the added convenience of manipulating a readily available and cheap sugar such as D-glucose, although the synthetic blueprint shown in Scheme 1 calls for an eventual oxidation at C5 in precursor A to provide the CO group in chiron A, and an oxidative cleavage of the diol unit in chiron B. Having reached the level of chiral and functional overlap required in the two precursors, hence the corresponding segments of the ansa chain, based on the template effect, one can, after necessary functional group adjustments, generate chirons A and B and continue the synthesis with acyclic units. This feature of manipulating *cyclic* and/or *acyclic* modifications of carbohydrates independently or in tandem, offers operational amenities and a flexibility in design which is not shared by the great majority of the other common chiral building blocks such as amino acids, hydroxy acids, and terpenes.

With chirons A and B in sight, it becomes evident that the assembly of the functionalized ansa chain

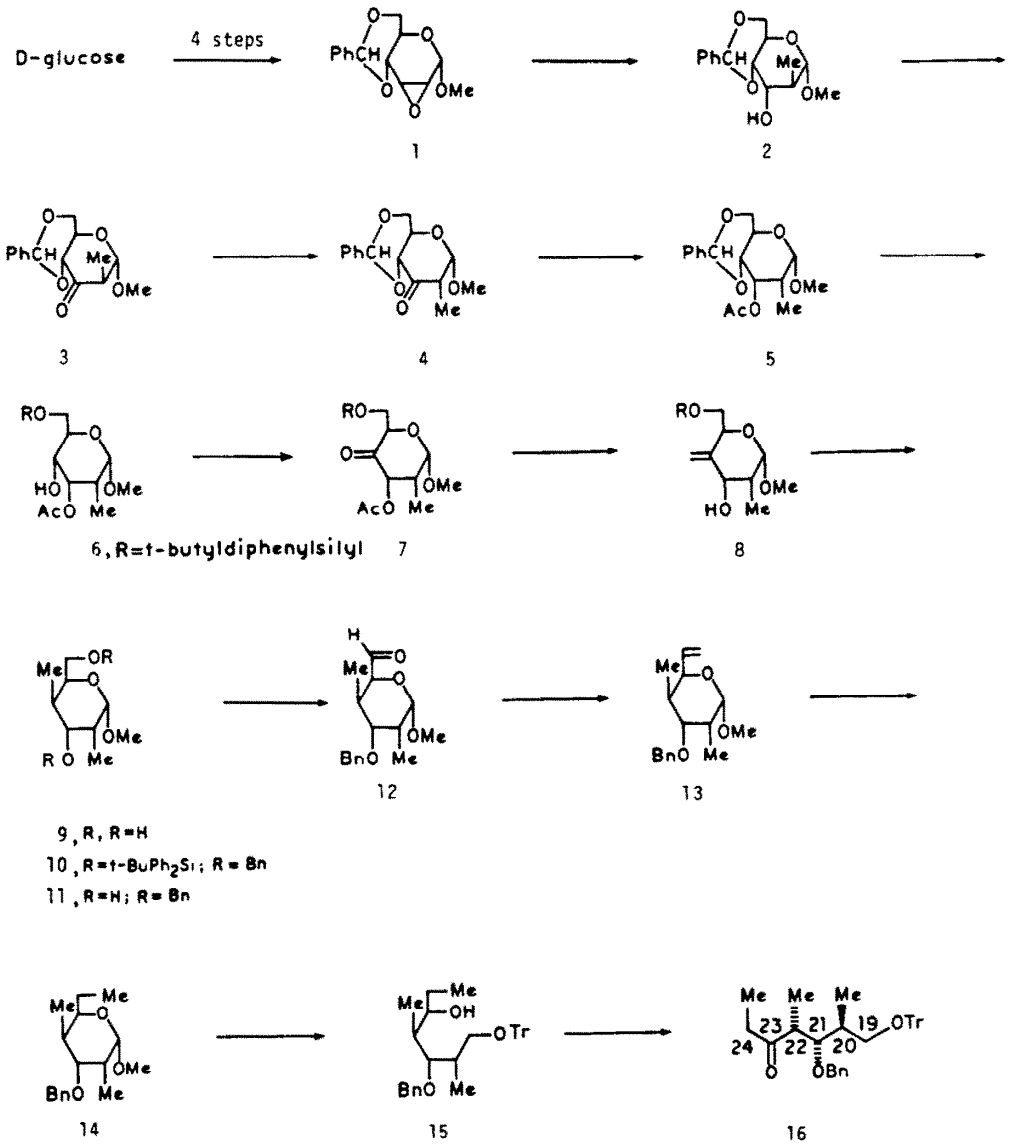
†See for example, S. Hanessian, In *Total Synthesis of Natural Products—The "Chiron" Approach* (Edited by J. E. Baldwin). Pergamon Press, Oxford (1983); See also, A. S. Dreiding and K. Wirth, *Match* 341 (1980) for a mathematical interpretation of this term.



Scheme 1.

must rely on two stereocontrolled processes, namely, C–C bond formation at the C24–C25 junction, followed by reduction of the C23 CO function. It is clear from the structures of chirons A and B that bridging would be best accomplished by a stereocontrolled cross aldol condensation.[11] Deployed with a synthetic blueprint such as the one outlined in Scheme 1, we set out to test its feasibility. Our objectives were thus to synthesize the two chirons and related derivatives in enantiomerically pure form, to explore methods for assembling the aliphatic portion of the ansa chain, and finally to secure evidence for the structural and stereochemical identity of such a fragment by comparison with an authentic degradation product obtained from the antibiotic.

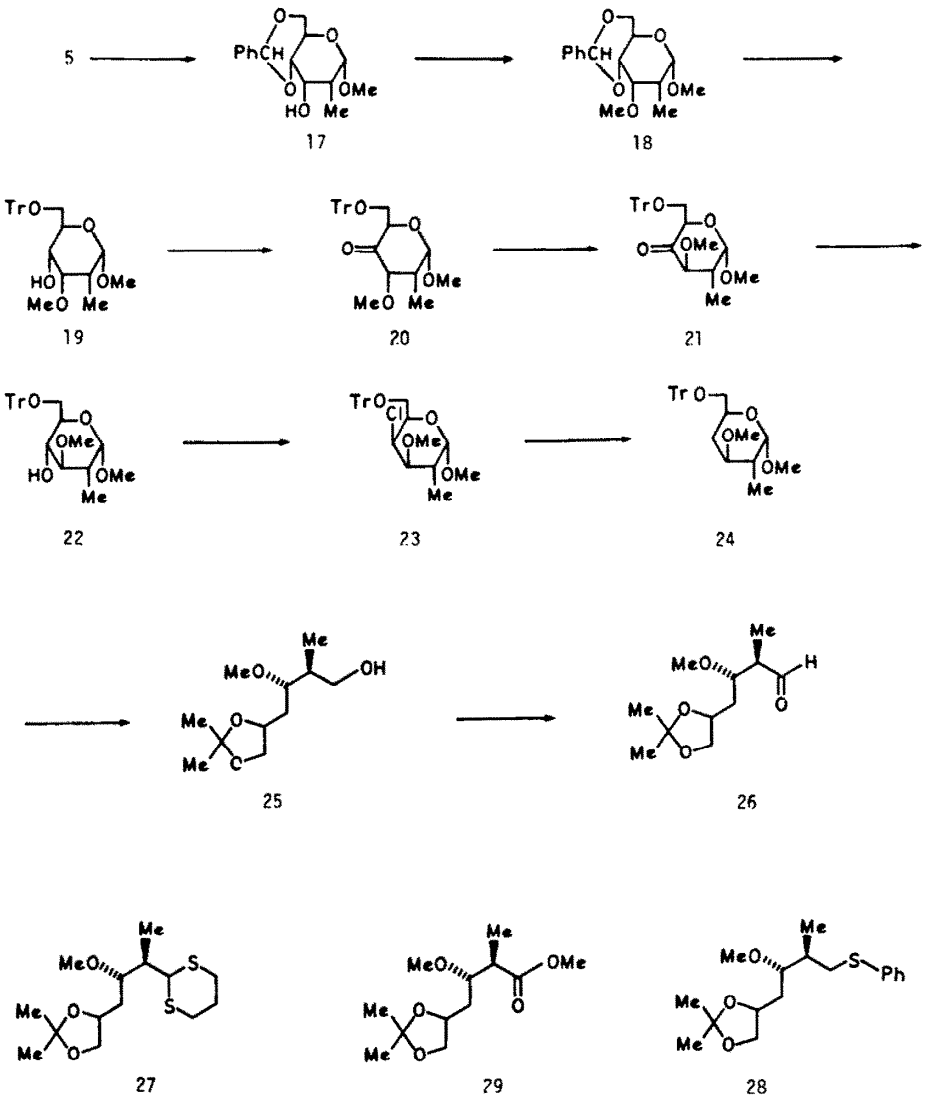
Scheme 2 outlines the route to chiron A, which involves the transformation of D-glucose into the known 2-C-Me derivative **2**[12,13] in high overall yield utilizing crystalline intermediates. It was known from previous experience in connection with the assembly of the erythronolide A framework,[13] that the inversion of configuration at C2 was a facile process. Thus, oxidation to the crystalline ketone **3** and base catalyzed epimerization led to the equally crystalline, epimerized derivative **4** in good overall yield. Reduction of the ketone function in **4** followed a predictable course due to the α-orientation of the anomeric substituent and the inherent conformational bias provided by the bicyclic system. The axial alcohol thus formed was acetylated to give **5** in excellent yield. The choice of ester protecting group was dictated by subsequent transformations which necessitated mild and selective deprotection. With the C-Me and OH substituents situated regio and stereospecifically, it was necessary to focus on the placement of an axial C-Me group at C4. Wittig methodology was therefore contemplated and a need for further functional group adjustments became evident. Thus, the O-t-butyldiphenylsilyl protecting group[14] was found most suitable for the primary OH group as in **6**. Oxidation with pyridinium chlorochromate[15] (PCC) afforded the ketone **7** which was subjected to a Wittig reaction with methylenetriphenylphosphorane. The product of this reaction was a mixture of the expected exocyclic allylic olefin **8** and the corresponding acetate. Mild base treatment gave the desired **8** in good yield. Spectroscopic data provided the needed assurance that epimerization had not occurred. The choice of the allylic alcohol for the stereoselective reduction of the double bond was based on previous experience[10] with O-substituted derivatives where mixtures rich in the undesired equatorial C-Me isomer resulted. It was therefore reasoned that the presence of an α-oriented OH group would have a directing effect in the catalytic hydrogenation. However, this anticipated effect was not experimentally observed until a number of catalysts were tried. The best combination



Scheme 2.

proved to be palladium hydroxide on charcoal[16] in dioxane as the solvent which gave the desired C4 axial Me isomer and its epimer in a ratio of 4 : 1. Desilylation gave the crystalline diol **9** whose spectroscopic properties were in agreement with its structure. With the pattern of substitution corresponding to C20–C22 in hand, by taking advantage of the template effect provided by the cyclic carbohydrate, it was now necessary to proceed toward chiron A with acyclic structures. There remained to chain extend the C-chain, and to generate a ketonic function after appropriate protection of OH groups. Thus, O-benzylation, desilylation and oxidation with PCC gave the aldehydo derivative **12** which was chain extended to **13** and **14**. Mild acid hydrolysis, followed by sodium borohydride reduction and selective tritylation of the primary OH group gave the acyclic analog **15**. Finally, oxidation with PCC gave chiron A, **16** as a crystalline solid.

The synthetic route to chiron B was executed uneventfully and is shown in Scheme 3. Compound **4** which was an intermediate in the synthesis of chiron A was the starting point. Its stereocontrolled reduction led to the crystalline **17** which was methylated to give another crystalline intermediate. Following a previous protocol[13] in the macrolide series the orientation of the C3 OMe group was inverted to provide the absolute stereochemistry required in the target. This was achieved by relying on the thermodynamically favored equatorial orientation of substituents in 6-membered ring systems. Thus a sequence involving functional group modifications led to **20** which, when subjected to mild basic treatment afforded the epimerized ketone **21** as a crystalline derivative in good overall yield. With the C- and O-Me groups introduced virtually regio- and stereospecifically there remained to effect deoxygenation at C4 and effect further transforms to give the desired acyclic chiron B. Reduction of **21** to **22** followed by chlorination with sulfuryl chloride[17] to **23**, and subsequent reductive dechlorination with tri-n-butyltin hydride in the presence of azobisisobutyronitrile gave the dideoxy derivative **24** in good yield. Acid hydrolysis, reduction of the resulting



Scheme 3.

lactol and formation of the isopropylidene acetal led to the acyclic derivative **25**, which upon oxidation with PCC gave the desired chiron B, **26** as a relatively unstable syrup. It was also deemed of interest to prepare other derivatives representing this segment of the target which could be used as nucleophilic or electrophilic counterparts in C–C bond forming reactions. The dithian analog **27** was thus easily obtained from the aldehyde **26**. In another instance, the alcohol **25** was transformed directly into the phenylthio ether **28**, by treatment with diphenyldisulfide and tri-n-butylphosphine.[18] As an electrophilic component, the ester **29** was obtained from **25** by oxidation with ruthenium tetroxide followed by esterification. Unfortunately C–C bond forming reactions with derivatives **27–29** with appropriate counterparts representing the C19–C24 portion were either unsuccessful or hampered by low yields. Therefore the originally intended aldol strategy shown in Scheme 1 became all the more critical for the completion of our synthesis.

Examination of the structure of the expected aldol product **30** (Scheme 4) reveals that a 24*S*, 25*R* *syn* relationship must be generated.† It is well known that an aldol condensation between an aldehyde and a lithium enolate with a *Z*-configuration leads to a preponderance of the aldol product with a *syn* orientation at the newly formed center.[11] Since the present case represents a unique example of two highly functionalized chiral counterparts, a higher order of double stereodifferentiation was to be expected.[19] By assuming a Felkin-type model[20] and invoking the oxygen of the benzyloxy group of the *Z*-enolate portion in a Li-coordinated specie, one could rationalize the distinct preponderance of the *syn* diastereomer. Although inspection of models appears to favor the formation of the desired 24*S*, 24*R* isomer as in **30** rather than the other *syn* isomer, the bias is not overwhelming (Fig. 1). In the event, formation of the *Z*-enolate from 16 at −78°, and addition of the aldehyde **26** gave after 10 min, a mixture of products which showed a major component by TLC. Column

†The sense of chirality at these two centers is in fact *S* and *R* respectively in rifamycin S itself.

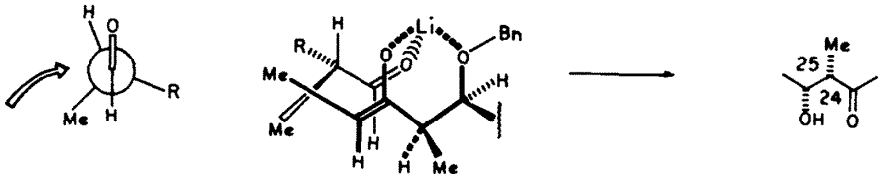
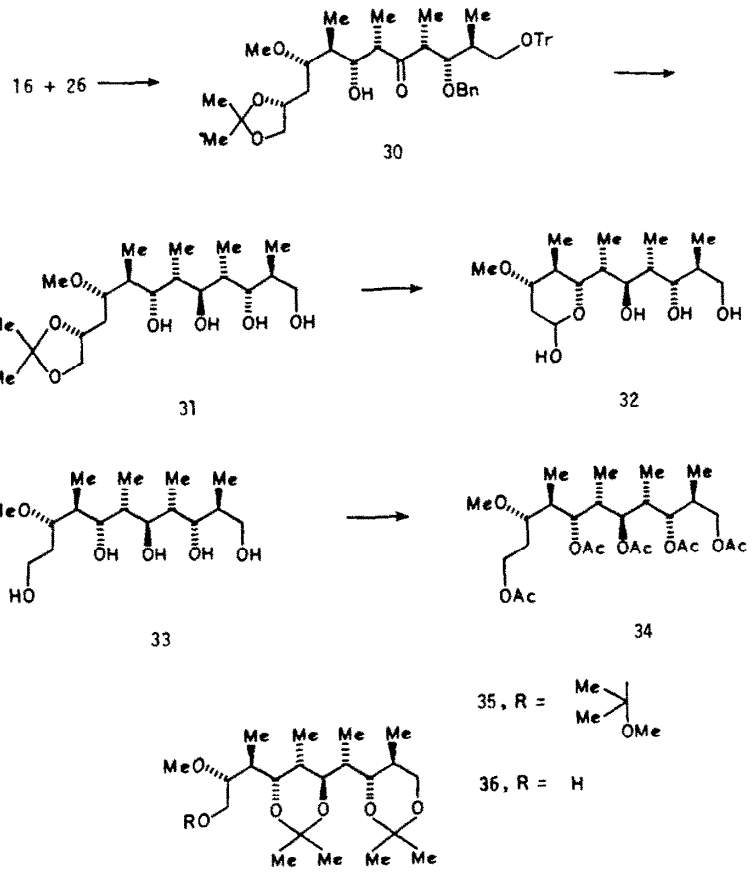


Fig. 1. Proposed lithium coordinate[19] intermediate in the aldol condensation leading to the 24*S*, 25*R syn* product.

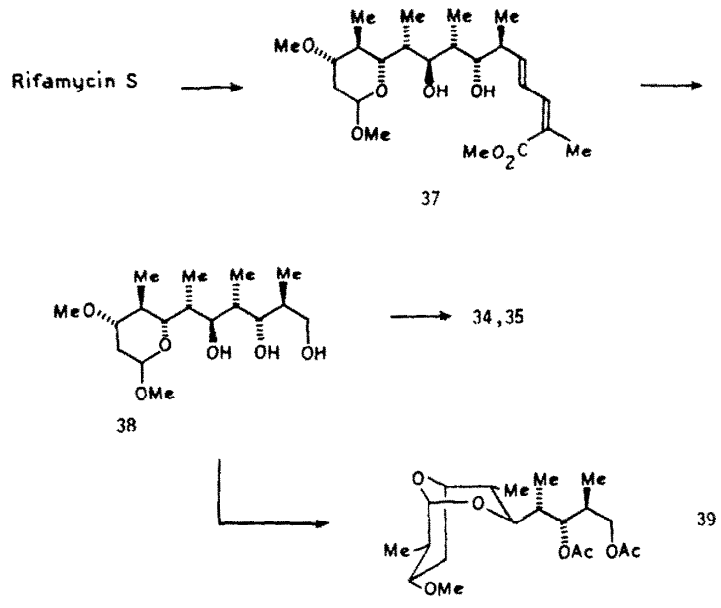
chromatography gave a 76% yield of a mixture of two compounds (7 : 3 ration by NMR analysis), which could not be separated at this stage, but were separated after reduction. The major component in the mixture was later found to be the desired isomer **30**. The identity of the minor isomer was not studied although it might be assumed to be the other *syn* diastereomeric isomer (24*R*, 25*S*) corresponding to the structure **30**. Dibal was found to be the reducing agent of choice after several unsuccessful attempts to achieve stereoselective reduction of the CO group in **30**. Thus with sodium borohydride, lithium aluminum hydride and diborane there was formed either equivalent amounts of two epimers or a preponderance of what turned out to be the wrong epimer at C23. Dibal on the other hand gave a better than 10 : 1 stereoselectivity which could be rationalized based on a OH assisted intramolecular delivery of hydride in a preferred conformation where 1,3-diaxial interactions of C22 and C24 Me groups are minimized although this argument is speculative at this point. Catalytic hydrogenation of the purified Dibal reduction product led to the tetrol **31**. Since structure **31** contains all eight chiral centers (C20–C27) present in the target, it was of paramount importance to secure an appropriate degradation product from rifamycin S itself, that contained the same intact sequence to be able to establish the constitutional and configurational identity of the aldol product and its derivatives. By a previously reported procedure,[21] it was possible to convert rifamycin S into the modified ansa chain derivative **37** (Scheme 5). Ozonolysis, followed by reduction of the corresponding aldehyde (or lactol) gave **38**, which upon treatment with aqueous acid, hydride reduction and acetalization led to the crystalline bis-acetal hemiacetal derivative **35**. Alternatively when the pentol was acetylated, the syrupy pentaacetate **34** was produced, the structure of which was corroborated by high field NMR as well as 2-D NMR spectroscopy. Upon treatment of **38** with aqueous acetic acid at 70° followed by acetylation, a new product was formed to which we assign structure **39** based on detailed ^{1}H NMR spectroscopy, including decoupling experiments. This product presumably results from intramolecular cyclization of the C23 OH group (rifamycin numbering) onto the transient oxonium ion generated during the hydrolysis.

Having access to authentic derivatives such as **34** and **35**, we turned our attention to the synthetic sample **31** and the prospects of its chemical modification. Thus, mild acid hydrolysis, followed by periodate cleavage of the vicinal diol system led to the lactol **32** (Scheme 4), which, without further characterization was reduced to the pentol **33**. Acetylation on the one hand, and acetalation on the other produced derivatives which were completely identical with the samples derived from rifamycin S. Figure 2 shows the 400MHz spectrum of synthetic **34** and a 2-D NMR analysis of the C-Me region. Compounds **33–36** can be used as representative of the C19–C29 acyclic segment of rifamycin S and should be easily converted to one of Kishi's[7] advanced intermediates. Thus, the assembly of this segment may also be regarded as a formal synthesis of the optically active antibiotic itself, and demonstrates the utility of the carbohydrate-derived chirons in the synthesis of natural products that are biosynthesized via the propionate route. Kinoshita *et al.*[22] have described another route to the acyclic segment of rifamycin S based on a carbohydrate precursor approach where the template effect was utilized to generate two chirons that were bridged to give the ansa chain. Fraser–Reid *et al.*[23] have reported on a strategy that utilizes "pyranosidic homologation" to construct a bicyclic growing chain with predetermined functionality based on inherent conformational bias (template effect) as well as stereoelectronic control dictated by the anomeric effect of hemiacetal linkages.

As in the case of the acyclic structures shown in expessions **27–29**, it was also possible to obtain a derivative corresponding to the C19–C24 segment to act as an electrophilic component (Scheme 6). Toward this end, the epoxide **43** was considered to be a useful target since, in addition to providing a reactive extremity corresponding to C24, the desired sense of chirality at C23 could be introduced during the formation of the epoxide itself. Acid hydrolysis of **10** was not easily achieved without accompanying β-elimination of the benzyloxy group. Thus, an alternative, indirect method was sought to produce the desired lactol. Treatment of **10** with ethanethiol in the presence of zinc chloride as catalyst resulted in transglycosylation to give the corresponding thioglycoside **40** as an anomeric mixture. Clean transformation of the thioglycoside to the corresponding lactol was observed upon treatment with aqueous bromine, presumably though the intermediacy of a sulfonium intermediate which was prone to hydrolysis. Reduction of the lactol to the alditol **41**, tritylation and mesylation of the remaining OH group gave **42**. Upon treatment with fluoride ion, it was possible to desilylate and intramolecularly displace the mesylate group to the desired epoxide **43** and attain the sense of chirality required at C23. Even though **43** lacks a Me group at C24 (rifamycin numbering) it was intended as a useful nearest neighbor model to attempt a C–C bond forming reaction with a nucleophilic counterpart representing the C25–C29 segment. To this end the dithian derivative **27** seemed ideal. Although 1,3-dithian and some of its derivatives are exceedingly useful acyl anion equivalents,[24]



Scheme 4.



Scheme 5.

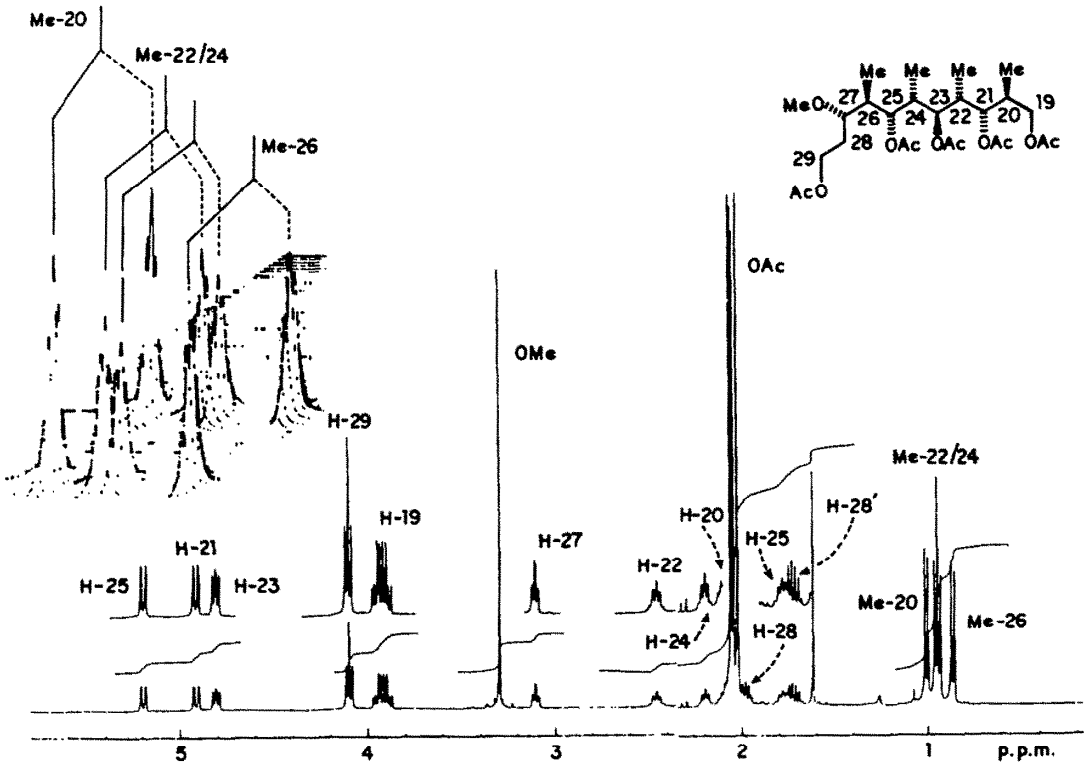
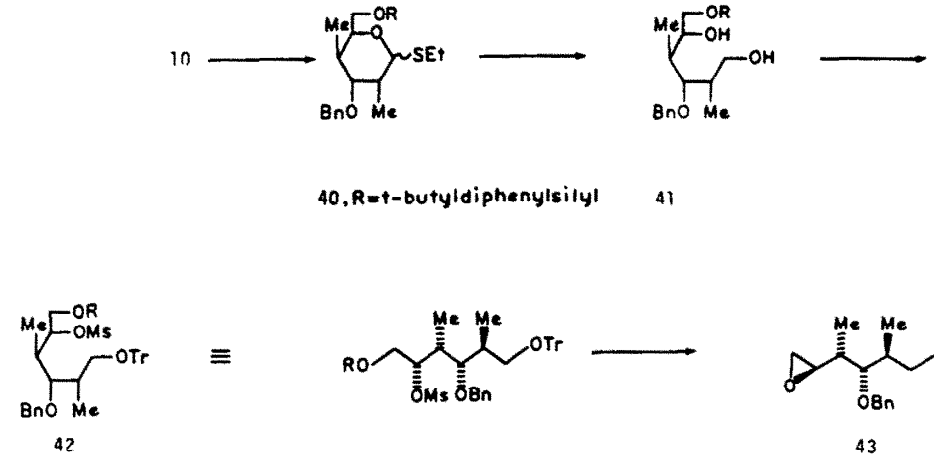


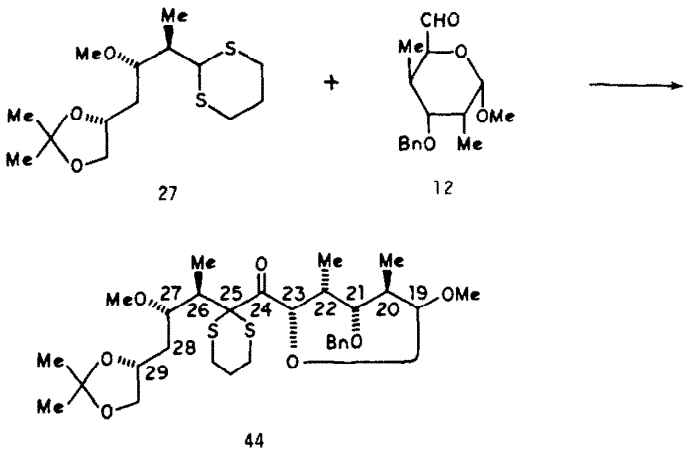
Fig. 2.



Scheme 6.

and the generation of the anions is routinely done with a base such as n-BuLi, examples of the preparation of anions from highly functionalized dithians such as **27** are not numerous. In those cases where anion formation and its subsequent utilization was demonstrated, the normal protocol was not followed. A dithian not too different from **27** was used by Corey *et al.* in their total synthesis of (±)-N-methylmaysenine,[25] where temperature control and nature of solvent proved to be critical for a reaction with an aldehyde. Sum and Weiler[26] utilized t-BuLi in hexanes to generate the anion from a functionalized dithian and used EtI in HMPA as an electrophile. We were not surprised therefore early on in this project[10] that the generation of an anion from **27** was not easily achieved. Using t-BuLi in hexanes, we were able to effect condensation with *p*-chlorobenzaldehyde as a model and to isolate a 25% yield of condensation product as a mixture of benzylic alcohols. We were however unsuccessful in effecting epoxide opening in **43** under the same conditions.

Some measure of success was secured in a condensation with aldehyde **12** to give the potential rifamycin S precursor **44** (Scheme 7). Further elaboration of **44** would require epimerization at C23 and functional group adjustments at C24/C25. In view of the



Scheme 7.

inefficient condensation, this initial approach[10] was not pursued further and our efforts were directed to the aldol route described above.

EXPERIMENTAL

M.ps are uncorrected. Optical rotations were measured on a Perkin–Elmer automatic spectropolarimeter, model 141. IR spectra were recorded on a Perkin Elmer mode 638 spectrometer.

NMR spected were recorded on Bruker spectrometers at 400, 90 or 80 MHz in $CDCl_3$ as solvent. The ^{13}C NMR spectra were recorded at 22.6 MHz. Chemical shifts are reported in ppm downfield from TMS as the internal standard. Mass spectra were recorded in the electron impact mode on an AEI-902 mass spectrometer and in the direct chemical ionization mode on a VG-1202 quadrupole spectrometer. All organic solvents were dried by standard techniques. Convential processing of mixtures consisted of extraction with an organic solvent (CH_2Cl_2 or EtOAc), drying over $MgSO_4$, filtration and evaporation to dryness. This layer chromatography was done on silica gel GF_{254} precoated plates and the spots were detected by viewing under UV light, $KMnO_4$ aq or the ceric ammonium sulfate "dip" procedure. Column chromatography was done on F. Merck silica gel 60 (0.04–0.06 mm, 230–400 mesh, ASTM).

Methyl 4,6 - O - *benzylidene* - 2 - *deoxy* - 2 - C - *methyl*- α - D - *arabino* - *hexopyranoside*, **3**. A soln containing 40.15 g (0.143 mole) of **2** in a mixture of dimethylsulfoxide (325 ml) and Ac_2O (130 ml) was stirred overnight at room temp. The soln was added dropwise and with stirring to an aqueous soln containing 200 g of $NaHCO_3$ and ice-cubes (total volume 5 lt). The precipitated crystalline product was separated by filtration, washed with cold water and dried in a desiccator to give 39.04 g (98%) of **3**. An analytical sample was obtained after recrystallization from a mixture of ether and hexane, m.p. 125.5–127°; $[\alpha]_D^{25} + 75.2°$ (*c* 1.11, $CHCl_3$); IR, γ_{max} (KBr): 1735 cm^{-1} (C=O); NMR: δ (ppm) 1.32 (d, J = 8 Hz, C2 Me); 2.73 (q, J = 8 Hz, H1); 3.33 (s, OMe); 3.60–4.65 (multiplets, 4H, H4–H6,6'; 4.73 (s, H1); 5.57 (s, PhCH); 7.20–7.65 (m, arom.). (Found: C, 64.56; H, 6.54. Calc. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52%).

Methyl 4,6 - O - *benzylidene* - 2 - *deoxy* - 2 - C - *methyl*- α - D - *ribo* - *hexopyranoside*, **4**. The preceding **3** (47.8 g, 0.172 mole) in 1320 mL dry MeOH was treated at 0° with 8 mL of a 1M soln of NaOMe in MeOH. After a few min. the title product crystalized out. After a further 4 hr, the crystals were filtered, washed with MeOH, then ether and dried to give 40.50 g (85%) of the epimerized **4**, m.p. 195–197°. This product was used as such for further steps. An analytical sample was obtained by recrystallization from $CHCl_3$-ether, m.p. 199–201°; $[\alpha]_D^{25} + 143.6°$ (*c* 0.52, $CHCl_3$); IR: γ_{max} (KBr): 1730 cm^{-1} (C=O); NMR: δ (ppm) 1.07 (d, J = 7 Hz, C2 Me); 2.85 (m, H2); 3.35 (s, OMe); 3.70–4.50 (m, H_4–H6,6'); 4.93 (d, $J_{1,2} = 4$ Hz, H1); 5.55 (s, PhCH); 7.20–7.65 (m, arom.). (Found: C, 64.52; H, 6.56. Calc. for $C_{15}H_{18}O_5$: C, 64.47; H, 6.52%.)

Methyl 3 - O - *acetyl* - 4,6 - O - *benzylidene* - 2 - C -*methyl*- α - D - *allopyranoside*, **5**. To a soln of **4** (58.30 g, 0.21 mole) in a mixture of DMF (1400 mL) and MeOH (1400 mL) was added $NaBH_4$ (11.89 g, 0.315 mole). After stirring at room temp. for 90 min, MeOH was removed by evaporation, the soln was diluted with ether, washed with brine, then water and the organic phase was processed as usual to give 54–56 g (95–96%) of the desired alcohol. An analytical sample was obtained after recrystallization from a mixture of CH_2Cl_2–ether and petroleum ether (b.p. 30–60°), m.p. 121.5–122.5°; $[\alpha]_D^{25} + 129.4°$ (*c*, 0.50, $CHCl_3$); NMR: δ (ppm) 1.10 (d, J = 7 Hz, C2 Me); 1.97 (m, H_2); 2.85 (m, OH); 3.40 (s, OMe); 3.5–4.5 (m, H3–H6,6'); 4.55 (d, $J_{1,2} = 3$ Hz, H1); 5.60 (s, PhCH); 7.25–7.80 (m, arom.). (Found: C, 64.23; 7.27. Calc. for $C_{15}H_{20}O_5$: C, 64.27; 7.19%.)

An amount of the above product (28 g) in 200 mL of CH_2Cl_2, 50 mL of pyridine, and 0.1 g of N,N-dimethylaminopyridine was acetylated with 40 mL Ac_2O. After stirring the soln overnight, it was diluted with CH_2Cl_2, extracted with $KHSO_4$ and processed to give a crystalline product (29.3g, 91%). Recrystallization from EtOAc and hexane gave **5**, m.p. 102–103°; $[\alpha]_D + 98.9°$ (*c* 1, 2 $CHCl_3$).

Methyl 3 - O - *acetyl* - 6 - O - *t* - *butyldiphenylsilyl* - 2-*deoxy* - C - *methyl* - α - D - *allopyranoside*, **6**. An amount of the preceding compound (10 g) was stirred in a soln of water and AcOH (15 mL, 3 : 7). After 15 hr, toluene was added and the soln evaporated at room temp. Toluene was again added and the evaporation repeated several times to give a crystalline residue. Trituration with hexanes and decanation removed traces of benzaldehyde. The residue was dissolved in 50 mL of pyridine and 10 mL of t-butyldiphenylsilyl chloride was added. After stirring overnight at 0°, the soln was diluted with water then CH_2Cl_2 and the organic phase was processed by washing successively with $KHSO_4$, $NaHCO_2$ and water. Flash chromatography of the residue after evaporation (EtOAc-hexanes, 1 : 9, silica), gave 17.5 g (88%) of the title compound as a syrup; $[\alpha]_D^{25} + 56.1°$ (*c* 1, $CHCl_3$).

Methyl 3 - O - *acetyl* - 6 - O - *t* - *butyldiphenylsilyl* - 2 - *deoxy* - 2 - C - *methyl* - α - D - *ribo* - *hexopyranosid* - 3 - *ulose*, **7**. A soln of **6** (2.17 g, 4.49 mmole) in 20 mL of dry CH_2Cl_2 containing 5.3 gm of 4Å molecular sieves (dried at 400°), was treated with pyridinium chlorochromate (2.9 g, 3 equiv.). After gentle stirring for 3 hr, the mixture was filtered over a bed of Florisil, the residue was washed with ether and the filtrates were evaporated to dryness. Flash chromatography (EtOAc–hexanes, 1 : 4) gave the title ketone as a chromatographically homogeneous syrup in almost quan-

titative yield, $[\alpha]_D$ + 125.6° (*c* 10.5, $CHCl_3$); IR: γ_{max} (film): 1740 cm^{-1} (C=O); NMR: δ (ppm) 0.98 (d, C2 Me); 2.19 (s, OAc); 3.44 (s, OMe); 5.15 (d, $J_{1,2}$ = 5.3 Hz, H1); 5.79 (d, $J_{3,4}$ = 4.3 Hz, H3), etc. This material was used as such in the subsequent step.

Methyl 6 - O - *t* - *butyldiphenylsilyl* - 2,4 - *dideoxy* - 2 - C - *methyl* - 4 - C - *methylene* - α - D - *ribo hexopyranoside*, **8**. A soln containing methyltriphenylphosphonium bromide (13.3 g, 2.5 equiv) in 100 mL of toluene was treated with 19.3 mL (2 equiv, 1.6 M soln) of n-BuLi. After stirring the pale yellow soln at room temp. for 20 min, the temp. was lowered to −20° and the ketone **7** (7 g, 14.9 mmole) in 20 mL of toluene was added with a double-tip needle under argon pressure. The reaction was continued at 0° for 2.5 hr, then treated with a few drops of acetone to decompose excess reagent. Evaporation gave a residue which contained a mixture of the title compound and the corresponding acetate. Treatment with a 1% methanolic solution of KCN resulted in smooth deacetylation to give **8** as a syrup after flash chromatography. Yield 5.6 g (88%); $[\alpha]_D$ + 104.3° (*c* 1.14, $CHCl_3$); NMR: δ (ppm) 1.06 (d, C2 Me); 3.41 (*s*, OMe); 4.50 (d, $J_{1,2}$ = 2.8 Hz, H1); 5.01, 4.86 (CH_2=), etc.

Methyl 2,4 - *dideoxy* - 2,4 - *di* - C - *methyl* - α - D - *gulopyranoside*, **9**. To a soln containing **8** (1 g) in 35 mL of dioxane was added 100 mg fo 20% palladium hydroxide on C. H_2 gas was bubbled through the suspension with stirring for 24 hr. Filtration and evaporation gave a syrup which showed a spot of slightly higher R_f than the starting olefin (EtOAc–hexanes, 1 : 4), yield 1 g. Treatment of a portion (0.498 g) with a soln of tetra-n-butylammonium fluoride (1M, 1.2 mL) in 15 mL of dry oxolane during 6 hr, followed by evaporation, washing the residue with brine from a CH_2Cl_2 soln gave a syrup which exhibited two spots on TLC (EtOAc–hexanes, 1 : 4). Flash chromatography gave **9** (0.75 g), m.p. 73–74°; $[\alpha]^{25}$ + 121.3° (*c* 1.3, $CHCl_3$) and its C4 epimer (0.2 g), syrup, $[\alpha]^{25}$ + 116° (*c*, 1.5, $CHCl_3$). For **9**, NMR: δ (ppm) 0.98 (d, C4 Me), 1.09 (d, C2 Me); 3.38 (S, OMe); 4.63 (d, $J_{1,2}$ = 3.2 Hz, H1); etc. ^{13}C NMR (ppm) from TMS): 11.02 (C4 Me), 12.7 (C2 Me); 32.47 (C4); 37.05 (C2); 55.3 (OMe); 63.97 (C6); 66.03 (C3); 74.88 (C5); 102.68 (C1); Mass spect. *m/e* 159 (M^+–MeO). For the C4 equatorial isomer, NMR; δ (ppm) 0.89 (d, C4 Me); 1.05 (d, C2 Me); 3.4 (s, OMe); 4.59 (d, $J_{1,2}$ = 3.2 Hz, H1); etc. ^{13}C NMR (ppm) from TMS): 13 (C4 Me); 13.6 (C2 Me); 36.6 (C4); 38.6 (C2); 55.4 (OMe); 63.52 (C6); 69.12 (C3); 73.24 (C5); 102.89 (C1); Mass. spec. *m/e* 159 (M^+–MeO).

Methyl 3 - O - *benzyl* - 6 - O - *t* - *butyldiphenylsilyl* 2,4-*dideoxy* - 2,4 - *di* - C - *methyl* - α - D - *gulopyranoside*, **10**. The mixture of epimeric compounds resulting from the hydrogenation of **8** (1.2 g, 2.8 mmole) in 10 mL of DMF containing 0.66 mL of benzyl bromide was treated with 0.1 g of NaH at 0°. After stirring overnight, the soln was diluted with $NaHCO_3$ aq and extracted with ether. Processing the organic phase and flash column chromatography (EtOAc–hexanes 15 : 85) gave **10** (R_f 0.55, EtOAc–hexanes, 15 : 85), (0.98 g) and its C4 epimer (R_f 0.57) (0.245 g) total yield 82%. For **10**, $[\alpha]_D$ + 25.6° (*c* 1.2, $CHCl_3$); NMR: δ (ppm) 0.79 (d, C4 Me); 0.94 (d, C2 Me); 1.08 (s, t-Bu); 3.18 (t, H3); 3.38 (s, OMe); 3.65 (dd, H6,6'); 4.53 (d, $J_{1,2}$ = 3.6 H1); 4.58 (q, CH_2Ph); 7.29–7.72 (arom.), etc. For the C4 epimer $[\alpha]_D$ + 67.9° (*c* 1.2, $CHCl_3$); NMR: δ (ppm) 0.85 (t, C2, C4 Me); 1.05 (s, t-Bu); 1.88–1.97 (m, H2, H4); 3.36 (OMe); 3.45 (m, H3); 3.79–3.89 (m, H5, H6,6'); 4.54 (d, = $J_{1,2}$ 3.8 Hz, H1); 4.63 (s, CH_2Ph); 7.22–7.75 (arom.), etc. (Found: C, 74.37; H, 10.71. Calc. for $C_{32}H_{42}O_4Si$: C, 74.40; H, 11.03%.)

Methyl 3 - O - *benzyl* - 2,4 - *dideoxy* - 2,4 - *di* - C - *methyl*-α - D - *gulopyranoside*, **11**. A soln of **10** (0.362 g, 0.7 mmole) in 5 mL of oxolane was treated with 0.7 mL of a 1M solution of tetra-n-butylammonium fluoride. After stirring overnight at room temp., the soln was evaporated to dryness and the residue was flash chromatographed ($CHCl_3$–MeOH, 10 : 2) to give 0.148 g (76%) of the expected product **11**; m.p. 60.5–61.5°; $[\alpha]_D$ + 53.8° (*c* 1.1, $CHCl_3$); NMR: δ (ppm) 0.88 (C4 Me); 0.95 (C2 Me); 1.94–2.06 (m, H2, H4); 3.17 (t, H3); 3.40 (s, OMe); 4.25 (m, H5), 4.49 (d, $J_{1,2}$ = 3.9 Hz, H1); 4.52 (d, CH_2Ph); 7.30–7.56 (arom.); etc. (Found: C, 68.30; H, 8.55. Calc. for $C_{16}H_{24}O_4$: C, 68.53; H, 8.64%.)

Methyl 6 - *aldehydo* - 3 - O - *benzyl*- 2,4 - *dideoxy* - 2,4-*di* - C - *methyl* - α - D - *gulopyranoside*, **12**. A soln containing **11** (1.45 g, 5.17 mmole) in CH_2Cl_2 (10 mL) was added to a soln of oxalyl chloride (0.7 mL) in CH_2Cl_2 (50 mL) and DMSO (0.5 mL) over 10 min at −60°. Et_3N 3.6 mL) was added over 5 min and the soln was stirred for a few min, then the cooling bath was removed. After a further 20 min, the soln was diluted with CH_2Cl_2, and washed with $KHSO_4$, brine then water. Usual processing of the organic phase gave 1.25 g (86%) of the title aldehyde as a chromatographically homogeneous semi-crystalline solid which was used as such in the next step; $[\alpha]_D$ + 51.1° (*c* 1.3, $CHCl_3$); NMR: δ (ppm) 0.91 (C4 Me); 0.96 (C2 Me); 2.03 (m, H2); 2.41 (m. H4); 3.25 (s, H3); 3.42 (s, OMe); 4.62 (d, CH_2Ph); 9.67 (CHO).

Methyl 3 - O - *benzyl* - 2,4,6,7 - *tetradeoxy* - 2,4 - *di* - C-*methyl* - α - D - *gulo* - *hept* - 6 - *enopyranoside*, **13**. To a soln of methylenetriphenylphosphorane (prepared from 2.94 g of the phosphonium bromide, 0.8 g of resublimed t-BuOK, in 10 mL of dry oxolane) was added to aldehyde **12** (0.763 g, 2.74 mmole) in oxolane (2.7 mL) over a period of a few min with external cooling. After stirring for 10 min at 0°, the soln was diluted with NH_4Cl aq, then with ether and the organic layer was processed as usual to give syrup. Flash chromatography gave **13** (0.66 g, 87.5%) as a syrup: $[\alpha]_D$56.4°(*c* 3.4, $CHCl_3$); NMR: δ (ppm) 0.87 (C4 Me); 0.95 (d C2 Me); 9.96 (m, H2, H4); 3.23 (t, H3); 3.37 (s, OMe); 4.56 (d, CH_2Ph); 5.19 (m, $H_{7,7'}$); 5.89 (m, H6); 7.34 (arom.); etc; Mass. spec. M^+ 276.

Methyl 3 - O - *benzyl* - 2,4,6,7 - *tetradeoxy* - 2,4 - *di* - C-*methyl* - α - D - *gulo* - *heptopyranoside*, **14**. A soln containing **13** (0.69 g) in 20 mL of benzene was hydrogenated in the presence of 5% Rh-on-Al catalyst (70 mg) during 3 hr. Filtration of the suspension and chromatographic separation of the evaporated residue (EtOAc–hexane 1 : 4) gave the title product in quantitative yield (0.7 g) as a syrup; $[\alpha]_D$ + 37° (*c* 2.5, $CHCl_3$); NMR: δ (ppm) 0.95 (C2, C4, C7, Me); 1.50 (m, H6,6'); 1.96 (m, H2, H4); 3.19 (s, $J_{2,3} = J_{3,4}$ = 3.2 Hz, H3); 3.38 (s, OMe); 3.99 (m, H5); 4.45 (d, $J_{1,2}$ = 4.2 Hz, H1); 4.52 (d, CH_2Ph); 7.33 (arom.); Mass. spec. M^+ 278.

3 - O - *Benzyl* - 2,4,6,7 - *tetradeoxy* - 2,4 - *di* - C - *methyl*-1 - O - *triphenylmethyl* - D - *gulo* - *heptitol*, **15**. The preceding compound (0.69 g, 2.48 mmole) was stirred in 22% aqueous AcOH (8 mL) at 50° for 1 hr. Evaporation with toluene gave a chromatographically homogeneous syrup which was reduced with $NaBH_4$ (93 mg) in 10 mL of EtOH. After stirring for 6 hr an additional 47 mg of $NaBH_4$ was added and the addition repeated after a further 24 hr. The chromatographically homogeneous product **15** (EtOAc–hexanes) was isolated by treatment with AcOH, evaporation and flash chromatography to give a syrup, 0.57 g (76%); $[\alpha]_D$ + 11.6° (*c* 2.1, $CHCl_3$). The product was used as such in the next step.

A soln of the preceding compound (0.57 g, 2.14 mmole) in 5 mL of pyridine was treated with trityl chloride (0.72 g, 1.2 equiv). After stirring at 65° for 20 hr, the soln was evaporated, and the residue was dissolved in CH_2Cl_2. Processing of the organic phase in the usual way and flash column chromatography (EtOAc–hexanes, 5 : 95) gave 1.02 g (quant) of product. Crystallization from ether and hexanes gave material showing m.p. 95–96° and $[\alpha]_D$ + 12.1° (*c* 1.0, $CHCl_3$). NMR: δ (ppm) 0.97 (d, Me); 1.08 (d, Me), etc. (Found: C, 82.33; H, 7.65. Calc. for $C_{35}H_{40}O_3$: C, 82.62; H, 7.90%.)

3 - O - *Benzyl* - 2,4,6,7 - *tetradeoxy* - 5 - *keto* - 2,4 - *di*-C - *methyl* - 1 - O - *triphenyl* - *methyl* - L - *lyxo* - *heptitol*, **16**. A soln of **15** (0.785 g, 1.55 mmole) in 10 mL of CH_2Cl_2 was added dropwise to a cooled mixture containing 1.33 g of pyridinium chlorochromate, 1 g of flame dried 3Å molecular sieves and 0.255 g of anhyd. NaOAc in 30 mL of

CH_2Cl_2. After stirring at 0° for 1.5 hr, ether was added and the suspension was filtered through a layer of Florosil. Processing the filtrates and flash chromatography gave 0.61 g (78%) of the title compound as a crystalline solid, m.p. 91–92°; $[\alpha]_D$ – 8.9° (*c* 1, $CHCl_3$); NMR (400 MHz); δ (ppm) 1.08 (C2 Me); 1.11 (C4 Me); 2.42 (q, H6); 2.71 (q, $J_{4,3} = 5$ Hz; $J_{4,5} = 7$ Hz, H4); 3.2 (CH_2OTr); 3.81 (q, $J_{3,2} = 7$ Hz; $J_{3,4} = 5$ Hz, H3), etc. (Found: C, 82.71: H, 7.29 Calc. for $C_{35}H_{38}O_3$, C 82.95; H, 7.57%.)

Methyl 4,6 - O - *benzylidene* - 2 - *deoxy* - 2 - C - *methyl*- 3 - O - *methyl* - α - D - *allopyranoside*, **18**. A soln containing 77 g (0.27 mole) of **17** (see preparation of **5**) in 450 mL of DMF was added to a suspension of NaH (19.83 g, 0.82 mole) in 240 mL of DMF. After stirring for 30 min the mixture was cooled to 0° and 137 mL (2.2 mole) of MeI was added slowly. After stirring for 2 hr at 0°, and overnight at room temp, MeOH was added to destroy excess reagent, the suspension was diluted with ether (6 × 400 mL) and water (200 mL) was added. Processing the organic phase as usual gave 75 g (93%) of **18** as a crystalline product. Recrystallization from CH_2Cl_2–petroleum ether (b.p. 30–60°) gave pure product, 62–69 g (76–85%); m.p. 140–141°; $[\alpha]_D$ + 115.4° (*c* 0.51, $CHCl_3$); NMR: δ (ppm) 1.07 (d, C2 Me); 1.97 (m, H2); 3.3–4.4, H3–H6,6'); 3.42 (s, C1 OMe); 3.60 (s, C3 OMe); 4.47 (d, $J_{1,2} = 4$ Hz, H1); 5.53 (s, CHPh); 7.25–7.70 (arom.); (Found: C, 65.65; 7.49. Calc. for C, 65.29; H, 7.53%.)

Methyl 2 - *deoxy* - 2 - C - *methyl* - 3 - *methyl* - 6 - O - *triphenylmethy*- α - D - *allopyranoside*, **19**. A soln containing 29.6 g (100.8 mmoles) of **18** 900 mL of EtOAc was hydrogenated in the presence of 20% Pd-C (2.96 g). After 20 hr the catalyst was filtered and the filtrate was evaporated to a syrup (20.76 g, quant). Chromatographic and spectroscopic examination indicated that hydrogenolysis of the benzylidene acetal was complete.

Treatment of **18** (4.4 g) in water (255 mL) and MeOH (90 mL) in the presence of *p*-toluenesulfonic acid 2.19 g (1.5 hr, 25°) gave similar results.

Tritylation of the above product (20.76 g, 100.8 mmoles) in pyridine (200 mL) with 30.97 g (111 mmoles) of trityl chloride during 72 hr at room temp, followed by dropwise addition of the soln to ice-water (4 lt) gave a syrup. The supernatant was decanted, the syrup was dissolved in ether and the soln processed as usual to give a solid which was recrystallized from ether–pentane to give the desired product in over 80% yield; m.p. 135–137°; $[\alpha]_D$ + 79.8° (*c* 0.5, $CHCl_3$); NMR: δ (ppm) 1.08 (d, C2 Me); 1.95 (m, H2); 2.45 (m, OH); 3.3–4.1 (m, H3–H6,6'); 3.45 (S, Cl OMe); 3.53 (S, C3 OMe); 4.50 (d, $J_{1,2} = 4$ Hz, H1); 7.10–7.70 (arom.). (Found: C, 75.24; H, 7.09. Calc. for $C_{28}H_{32}O_5$: C, 74.98; H, 7.19%.)

Since the crude product was found to be contaminated with traces of triphenylmethanol, it was found to be more practical to proceed to the next step without recrystallization.

Methyl 2 - *deoxy* - 2 - C - *methyl* - 3 - O - *methyl* - 6 - O - *triphenylmethyl* - α - D - *ribo* - *hexopyranosid* - 4 - *ulose*, **20**. To a soln containing 25.25 g (131.5 mmoles) of ethyldimethylaminopropyl carbodiimide hydrochloride in 200 mL of DMSO were added in succession 19.57 g (43.7 mmoles) of **19**, pyridine (5.2 mL, 64.5 mmoles) and trifluoracetic acid (4.4 mL, 59.4 mmoles) at 0°. After stirring at room temp for 18 hr, the soln was diluted with 200 mL of water, and extracted with ether. Processing of the organic phase gave 19.5 g (quant) of the expected ketone as a syrup. This material was utilized in the next step due to its relative instability. IR 1740 cm^{-1} (C=O); NMR: δ (ppm) 0.97 (d, C2 Me); 2.80 (m, H2); 3.40–3.70 (m, H6,6'; 3.43 (s, Cl–OMe); 3.47 (s, C3 OMe); 4.2–4.4 (m, H3, H5); 5.07 (d, $J_{1,2} = 6$ Hz, H1); 7.1–7.7 (m, arom.). Oxidation with pyridinium chlorochromate gave identical results.

Methyl 2 - *deoxy* - 2 - C - *methyl* - 3 - O - *methyl* - 6 - O - *triphenylmethyl* - α - D - *xylo* - *hexopyranosid* - 4 - *ulose*, **21**. Treatment of the preceding compound (18.17 g, 40.7 mmoles) in 70 mL of MeOH with 3 mL of a 1M NaOMe soln resulted in the direct crystallization from the soln of the desired product **21**. After sitting at – 20° for 27 hr the crystals were filtered, washed with MeOH and dried. The mother liquors were neutralized with Dowex-50(H^+) and the suspension filtered and evaporated to dryness to give additional product. The combined crops gave 14.55 g (80%) of epimerized ketone. Recrystallization from MeOH gave pure **21**, m.p. 137.5–139.5°; $[\alpha]_D$ + 130.1° (*c* 0.52, $CHCl_3$); IR (KBr) 1730 cm^{-1} (C=O); NMR: δ (ppm) 1.1 (d, C2 Me); 2.24 (m, H2); 3.2–3.7 (m, H6,6'); 3.45 (s, Cl OMe); 3.57 (S, C3 OMe); 3.77 (d, $J_{3,2} = 12$ Hz, H3); 4.33 (m, H5); 4.77 (d, $J_{1,2} = 3$ Hz, H1); 7.1–7.75 (m, arom.), etc. (Found: C, 75.07; H, 6.72. Calc. for $C_{28}H_{30}O_5$; C, 75.31; H, 6.77%.)

Methyl 2 - *deoxy* - 2 - C - *methyl* - 3 - O - *methyl* - 6 - O - *triphenylmethyl* - α - D - *glucopyranoside*, **22**. The preceding compound (3.45 g, 7.7 mmoles) was reduced with $NaBH_4$ (0.38 g) in a 1 : 1 mixture of DMF and MeOH (30 mL). After stirring for 1 hr, the soln was treated with AcOH at 0°, evaporated to dryness and the residue dissolved in CH_2Cl_2. Usual processing gave a pale yellow syrup which was chromatographically homogeneous (toluene–EtOAc 9 : 1) and was used as such in the next step.

Methyl 4 - *chloro* - 2,4 - *dideoxy* - 2 - C - *methyl* - 3 - O- *methyl* - 6 - O - *triphenylmethyl* - α - D - *galactopyranoside*, **23**. Compound **22** (3.46 g, 7.7 mmoles) was dissolved in 30 mL of dry pyridine and the soln was cooled to – 78°. Sulfuryl chloride (3.13 mL, 5 equiv) was added dropwise with stirring under an atmosphere of N_2. The pale yellow viscous soln was left at room temp overnight during which time the color changed to dark brown. The soln was poured into ice-water and stirred for 2 hr. Extraction with $CHCl_3$, washing the organic phase with cold dil H_2SO_4, then $NaHCO_3$ aq $Cu(NO_3)_2$ aq and finally water and drying gave a reddish syrup (3.6 g) which was chromatographically homogeneous (toluene–EtOAc, 9 : 1). This product was used as such in the next step.

Methyl 2,4 - *dideoxy* - 2 - C - *methyl* - 3 - O - *methyl* - 6 - O - *triphenylmethyl* - α - D - *xylo* - *hexopyranoside*, **24**. Compound **21** (3.6 g, 7.7 mmoles) was dissolved in dry toluene (100 mL) and 5.1 mL (2.5 equiv) of tri-n-butyltin hydride and 1.3 g of azobis-isobutyronitrile were added. After refluxing the soln for 5 hr under N_2, it was evaporated to dryness and the residue was flash chromatographed (hexane–EtOAc, 9 : 1) to give the title compound (3.3 g, quant) as a colorless syrup. An aliquot was purified by preparative TLC $[\alpha]_D$ + 76.1° (*c* 0.78, $CHCl_3$); NMR: δ (ppm) 1 (C2 Me); 3.38 (s, Cl OMe); 3.83 (s, C3 OMe); 4.61 (d, $J_{1,2} = 3.8$ Hz, H1), etc.

2,4 - *Dideoxy* - 5,6 - O - *isopropylidene* - 2 - C - *methyl*- 3 - O - *methyl* - D - *xylo* - *hexitol*, **25**. A soln of **24** (1.825 g, 4.22 mmoles) in a 7 : 3 mixture of AcOH and water was stirred at 80° for 2.5 hr. The soln was evaporated to dryness in the presence of toluene, the residue was dissolved in EtOH and 0.16 g of $NaBH_4$ was added. After stirring at room temp for 2.5 hr, the soln was treated with AcOH, then evaporated to dryness and the residue was flash chromatographed (CH_2Cl_2–MeOH, 93 : 7, then 80 : 20) to give the expected triol (0.94 g). Treatment of this product with 2,2-dimethoxypropane (3.9 mL) in oxolane 20 mL in the presence of *p*-toluenesulfonic acid (50 mg) for 30 min, followed by addition of solid $NaHCO_3$ and normal processing gave a syrup. Flash chromatography ($CHCl_3$–MeOH, 98 : 2) gave 0.9 g (78%) of the title compound as a syrup, NMR: δ (ppm) 0.88 (d, C2 Me); 2.39, 2.43 (CMe_2); 1.71–1.8 (m, H4); 2.12 (m, H2); 2.9 (OH); 3.45 (s, OMe, etc); Mass spec, *m/e* 219 ($M^+ + 1$).

Aldehydo 2,4 - *dideoxy* - 5,6 - O - *isopropylidene* - 2 - C- *methyl* - 3 - O - *methyl* - D - *xylo* - *hexose*, **26**. A soln of the preceding compound (0.5 g, 2.3 mmoles) in 60 mL of CH_2Cl_2 was treated with 1.98 g (4 equiv) of pyridinium chlorochromate, 1 g of 3Å molecular sieves and 0.38 g (2 equiv) of anhyd NaOAc. After 5 min of stirring, ether was

added, the mixture was transferred under argon unto a column containing Florisil, and the column washed with ether. The effluent was evaporated with minimum exposure to air and humidity. The syrupy residue was dried on a pump and stored at −10° under anhydrous conditions becasue of its tendency to hydrate, yield 0.36 g (72%). This aldehyde was prepared prior to further use and stored in oxolane containing molecular sieves at −10°. NMR: δ (ppm) 1.11 (s, C2 Me), 1.38, 1.43 (CMe_2); 1.70 (s, H4); 3.39 (s, OMe), 9.82 (CHO), etc.

Aldol product **30**. A soln of n-BuLi in hexanes (1.55M, 3°3 μL) was added dropwise and with stirring at −10° over 15 min to a soln containing diisopropylamine (70 μL) in 600 μL of THF under argon. After stirring for 15 min the soln was cooled to −78°. A soln of **16** (253 mg, 0.5 mmole) in 800 μL of THF was added dropwise over 2 min. The clear colorless soln was stirred at −78° for 2 hr, after which a soln of **26** (obtained from 60 mg, 0.28 mmole of **25** and stored over 4Å molecular sieves in 500 μL of THF) was added over 2 min. After stirring for 5 min at −78° TLC examination showed complete consumption of the aldehyde and the appearance of one major spot and two minor spots. The soln was treated with 1 mL of NH_4Cl aq, then allowed to warm to room temp. Extraction with CH_2Cl_2 and usual processing gave a colorless syrup which was flash chromatographed (EtOAc–hexanes, 1 : 4) to give the following fractions: recovered **16**, 150 mg; aldol product 152 mg (76% based on **26**) unknown component 10 mg. Analysis of the 400 MHz ^1H NMR spectrum showed the presence of an approx. 7 : 3 mixture of aldol products. For the major isomer: ppm (400 MHz), 0.75, 1.08, 1.1, 1.14 (C–Me20, 22, 24, 26); 1.37, 1.34 (Me_2C); 1.58 (H28a, o, J = 14 Hz; 8.2 Hz; 3.4 Hz; 1.74; (H28b, J = 14 Hz, 9.5 Hz; 4.6 Hz); 1.81 (H20, m); 1.95 (H26, q); 2.85 (H24, J = 7.08 Hz; 1.7 Hz; 3.15 (H25, J = 8.8 Hz; 5.86 Hz); 3.32 (H21, dd, J = 8.8 Hz; 4.6 Hz); (OMe); 3.72 (1H, dt); 3.96 – 3.95 (3H, m); 3.9 (1H, bd); 4.15 (1H, m); 4.40, 4.23 (CH_2Ph, J = 11 Hz); 7.09–7.44 (arom.). For the minor isomer: ppm 0.94, 1.08, 1.49 (C–Me); 1.37, 1.39(Me_2C); 4.22, 4.50 (CH_2Ph), etc. The chromatographically homogeneous syrupy aldol product consisting of a major component and a minor one (not separable) showed $[\alpha]_D$-17.6° (*c* 1.8, $CHCl_3$). (Found: C, 76.74; H, 7.88. Calc. for $C_{46}H_{58}O_7$: C, 76.40; H, 8.1%.)

Reduction and detritation of **30**—isolation of **31**. An amount of the aldol product **30** (150 mg) in 20 mL of toluene was treated at −78° with 6 mL of Dibol (1M in hexanes). After stirring at −78° for 2 hr, the soln was allowed to warm to 10°. It was treated with NaOH aq, the soln stirred vigorously and diluted with ether. Usual processing gave a syrup which was dried on a vacuum pump to give 142 mg of reduced product which exhibited a major component on TLC (hexanes–EtOAc, 3 : 2). Separation by preparative TLC gave 128 mg of the major expected product and 10 mg of the epimer.

Catalytic hydrogenation of the major product in 20 mL of MeOH in the presence of 60 mg of 10% Pd–C during 18 hr followed by filtration of the catalyst and evaporation gave a chromatographically homogeneous syrup in almost quantitative yield (68 mg); chromatographic separation (CH_2Cl_2–EtOH 96 : 4) to remove trace imputities gave 63 mg (93%) of **31** as of a clear syrup $[\alpha]_D$ − 3.2° (*c*, 0.43, EtOAc); M^+ 393 (M + H); 378 (M + H)–Me. (Found C, 60.88; H, 10.2. Calc. for $C_{20}H_{40}O_7$: C, 61.2; H, 10.27%).

Conversion of **31** to the pentol **33**. The preceding compound (60 mg) was dissolved in a 7 : 3 mixture of AcOH and water (10 ml) and the soln was stirred at 50° for 30 min. Toluene was added and the soln was evaporated to give a chromatographically homogeneous syrup (TLC CH_2Cl_2–EtOH 85 : 15); yield 50 mg. The product was dissolved in 5 mL of MeOH and 6 mL of a 0.02M soln of aqueous sodium metaperiodate was added at 0°. After stirring at room temp. for 30 min, TLC showed the appearance of a double spot with intermediate mobility, corresponding presumably to the two anomers of **32**. The mixture was treated directly with $NaBH_4$ (15 mg) and the soln was stirred for 30 min. Addition of AcOH and evaporation to dryness in the presence of toluene gave a semi-solid residue which was extracted with EtOAc several times to give a colorless syrup 45 mg (90%) which was characterized as the pentaacetate derivative **34** and the bisacetal hemiacetal **35** described below.

Preparation of the peracetylated pentol **34**. The preceding compound (20 mg) was dissolved in 12 mL of EtOAc and treated with 0.6 mL of Ac_2O and 6 mg of N,N-dimethylaminopyridine. After stirring overnight at 45° the soln was diluted with MeOH and stirred 1 hr at 45°. Toluene was added and the soln was evaporated to dryness to give a syrup which was purified from trace impurities by column chromatography (CH_2Cl_2–EtOH, 96 : 4) to give 25 mg (75%) of a colorless syrup; $[\alpha]_D$ + 0.38 (*c* 0.36, $CHCl_3$); *m/e* 473 (M + H)–AcOH; ppm (400 MHz)–0.86 (C26 Me); 0.93 (C24 Me); 0.95 (C22 Me); 1.00 (C20 Me); 1.71 (m, H28′ $J_{28',27} = J_{28',29} = 6.6$ Hz; $J_{28',28} = 14$ Hz); 1.76 (H26, m, $J_{26,27} = 1.6$ Hz; $J_{26,25} = 10$ Hz; $J_{26,Me} = 7$ Hz; 1.97, m (H28, m, $J_{28,27} = J_{28,29} = 6.6$ Hz; $J_{28,28'} = 14$ Hz); 2.01, 2.015, 2.03, 2.04, 2.05 (OAc); 2.04 (H20, m, $J_{20,19} = 4.5$ Hz; $J_{20,19} = 6.5$ Hz; $J_{20,21} = 9.8$ Hz; $J_{20,Me} = 6.9$ Hz; 2.18 (H24, m, $J_{24,25} = 1.2$ Hz; $J_{24,23} = 5.5$ Hz; $J_{24,Me} = 7.0$ OHz); 2.45 (H22, m, $J_{22,21} = 1.8$ Hz; $J_{22,23} = 8.1$ Hz; $J_{22,Me} = 6.9$ Hz); 3.10 (H27, m, $J_{27,26} = 1.6$ Hz; $J_{27,28} = J_{27,28'} = 6.6$ Hz); 3.29 (OMe); 3.88 (H19′, dd, $J_{19',20} = 6.5$ Hz; $J_{19',19} = 11$ Hz); 3.94 (H19, dd, $J_{19,20} = 6.5$ Hz; $J_{19',19} = 11$ Hz); 3.94 (H19, dd, $J_{19,20} = 4.5$ Hz; $J_{19,19'} = 11$ Ha); 4.09 (H29, 29′, t, $J_{29,28} = J_{29,29'} = 6.6$ Hz); 4.8 (H23, dd, $J_{23,24} = 5.5$ Hz; $J_{23,22} = 8.1$ Hz); 4.91 (H21, dd, $J_{21,22} = 1.8$ Hz, $J_{21,20} = 9.8$ Hz); $_{5,19}$H25, dd, $J_{24,25} = 1.2$ Hz; $J_{25,26} = 10$ Hz). (Found: C, 58.33; H, 8.14. Calc. for $C_{26}H_{44}O_{11}$: C, 58.62; H, 8.38%.) This material was identical in all respects with a sample obtained from the degradation rifamycin S (Ir, NMR, MS).

Preparation of the acetal **35**. Compound **33** (20 mg) was dissolved in 1 mL of 1,1-dimethoxypropane, 2 mg of camphorsulfonic acid was added and the soln was stirred at room temp overnight. The soln was poured into $NaHCO_3$ aq, ether was added and the organic layer was processed as usual to give a colorless syrup which was homogeneous on TLC (toluene–EtOAc, 4 : 1). A small quantity of more polar material could be observed which corresponds to the cleavage of the terminal acyclic acetal appendage. Chromatographed separation gave the acetal **35** as a colorless syrup which crystallized, yield 18 mg, 51%, m.p. 73–74°; $[\alpha]_D$ + 20° (*c* 2.17, CCl_4), *m/e* 403 (M + H)–C_4H_9O; δ (ppm) (400 MHz): 0.69, 0.78, 0.8, 0.87 (C–Me 20, 22, 24, 26); 1.27, 1.32, 1.35 (15 H, CMe_2); 1.39 (3H, CMe of acyclic acetal); 3.22 (OMe, acetal); 3.36 (OMe, ether), etc. (Found: C, 61.87; H, 8.53. Calc. for $C_{26}H_{50}O_7$: C, 62.15; H, 8.86%.)

Treatment of this product (4.5 mg) in 2 mL of MeOH with 0.2 mL of 1N AcOH and evaporation to dryness in the presence of toluene (several times) gave **36** a colorless syrup (3.8 mg).

Isolation of **34** *and* **35** *from a degradation product of rifamycin S*. Compound **37** (694 mg) prepared from rifamycin according to a lit procedure,[21] was dissolved in CH_2Cl_2 (5 mL) and EtOH (20 mL), the soln was cooled to −78° and ozonized. The initally pale yellow soln became pale green after 90 min. After an additional 20 min N_2 was bubbled through the soln, followed by addition excess $NaBH_4$ (230 mg). After warming the soln to room temp, excess reducing agent was destroyed by addition of aqueous AcOH and the soln was evaporated in the presence of toluene. The residue was dissolved in $CHCl_3$ and added to a silica gel column. Washing the column with a mixture of $CHCl_2$ and MeOH (9 : 1) gave a pale yellow syrup which after drying in vacuum was transformed into a foam, yield 515 mg (91%).

Treatment of the above product (370 mg) with aqueous 60% AcOH (50 mL) at 70° for 1.5 hr gave a mixture of two products which were separated by chromatography on silica gel (CH_2Cl_2–acetone 5 : 4, containing 0.1% Et_3N, followed

by CH_2Cl_2–MeOH, 95.5 containing 0.1% Et_3N). The lactol **32** (78.8 mg) and a less polar product (76.7 mg) were thus isolated as chromatographically homogeneous syrups. Reduction of the lactol with $NaBH_4$ (15 mg) in 10 mL of 95% EtOH, followed by addition of aqueous AcOH after 2 hr, and conventional processing gave a syrup (31 mg) which was identical to **33** (TLC, NMR). Acetylation and acetylation as described before gave **34** and **35** which were identical with material obtained by the synthetic route (NMR $[\alpha]_D$, MS).

Acetylation of the less polar component (70 mg) in 1.5 mL of pyridine, 0.4 mL Ac_2O in the presence of 0.3 mg of N,N-dimethylaminopyridine (2 hr, 25°, 1 hr, 60°), gave after coevaporation with toluene, and column chromatography, 43 mg of a colorless syrup to which structure **39** was assigned based on high field NMR and decoupling studies. Mass spectral data: *m/e* 387 (M + H); ^{1}H NMR data (400 MHz); ppm 0.75 (C24 Me); 0.97 (C20 Me); 1.03 (C22 Me); 1.12 (C26 Me); 1.45 (H28, $J_{28,29} = 2.26$ Hz; $J_{28,27} = 9.4$ Hz; $J_{28,28'} = 14$ Hz; 1.74 (H26, $J_{26,Me} = 6$ Hz; $J_{26,25} = 4.1$ Hz; $J_{26,27} = 9$ Hz; 9.96 (H22, $J_{22,Me} = 6.8$ Hz; $J_{22,23} = 3.2$ Hz; $J_{22,21} = 2.4$ Hz); 2, 2.05 (OAc); 2.11 (H20, $J_{20,Me} = 6.8$ Hz; $J_{20,21} = 9$ Hz; $J_{20,19} = 4.1$ Hz; $J_{20,19} = 6.6$ Hz); 2.35 (H24, $J_{24,Me} = 7$ Hz; $J_{24,25} = 4.1$ Hz; $J_{24,23} = 11$ Hz); 2.53 (H28′, $J_{28,29} = 8.7$ Hz; $J_{28',27} = 6.3$ Hz; $J_{28',28} = 14$ Hz); 3.02 (H27, $J_{27,28} = 9.4$ Hz; $J_{27,28'} = 6.3$ Hz; $J_{27,26} = 9.4$ Hz); 3.61 (H25, $J_{25,26} = 4.1$ Hz; $J_{25,24} = 4.1$ Hz); 3.77 (H23, $J_{23,24} = 11$ Hz; $J_{23,22} = 3.2$ Hz); 3.93 (H19′, $J_{19',20} = 6.6$ Hz; $J_{19',19} = 11$ Hz); 4.01 (H19, $J_{19,20} = 4.1$ Hz; $J_{19,19'} = 11$ Hz); 5.15 (H21, $J_{21,22} = 2.4$ Hz; $J_{21,20} = 9$ Hz); 5.24 (H29, $J_{29,28} = 2.6$ Hz; $J_{29,28'} = 8.7$ Hz). (Found: C, 61.93; H, 8.6. Calc. for $C_{20}H_{34}O_7$: C, 62.15 H, 8.85%.)

Ethylthio 3 - O - *benzyl* - 2,4 - *dideoxy* - 2,4 - *di* - C -*methy*- 6 - O - *t* - *butyldiphenylsilyl* - α,β - D - *gulopyranoside*, **40**. A soln of **10** (237 mg, 0.45 mmole) was dissolved in 3 mL of ethanethiol and anhyd $ZnCl_2$ (45 mg) was added at −25°. After stirring for 30 min, the mixture was filtered through a plug of silica gel and the filtrate was evaporated to dryness. Chromatography on silica (EtOAc–hexanes gave the thioglycoside as a chromatographically homogeneous syrup (237 mg, 94%). (Found: C, 67.51; H, 7.88; S, 5.54. Calc. for $C_{33}H_{44}O_3$ SiS: C, 67.76; H, 8.1; S, 5.8%.)

3 - O - *Benzyl* - 2,4 - *dideoxy* - 2,4 - *di* - C - *methyl* - 5- O - *methylsulfonyl* - 1 - O - *triphenylmethyl* - D - *gulitol*, **42**. To a vigorously stirring suspension containing **40** (161 mg, 0.294 mmole), and 173 mg of $NaHCO_3$ in 6 mL of ether and 3 mL of water was added 2.2 mL (3 equiv) of Br_2 dropwise over 5 min. TLC showed almost transformation into the lactol (double spot) after 20 min the mixture was diluted with ether, extracted, washed with $Na_2S_2O_3$, then NaCl and processed in the usual manner to give a syrup. Chromatography over silica gave 120 mg (81%) of the lactol as a mixture of anomers. This product was dissolved in 2-propanol (5 mL) and a total of 24 mg of $NaBH_4$ was added over 24 hr. TLC examination showed conversion to a more polar component. The mixture was neutralized with AcOH, and the soln processed as usual. After chromatography on silica (EtOAc–hexanes, 1 : 4) **41** was isolated as a colorless syrup (110 mg). Tritylation with 75 mg of trityl chloride in 1 mL of pyridine (25°, 3 days) followed by addition of methanesulfonyl chloride (0.2 mL) and N,N-dimethylaminopyridine (25°, 3 days) and conventional workup, gave a syrup. Chromatography on silica (EtOAc–hexanes, 3 : 7) gave **42** as a colorless syrup (195 mg); $[\alpha]_D + 9.2°$ (*c* 1.2, $CHCl_3$). (Found: C, 74.11; H, 7.20; S, 3.63. Calc. for $C_{51}H_{58}O_6$ SiS: C, 74.04; H, 7.08; S, 3.87%.)

5,6 - *Anhydro* - 3 - O - *benzyl* - 2,4 - *dideoxy* - 2,4 - *di* - C - *methyl* - 1 - O - *triphenylmethyl* - L - *galactitol*, **43**. A soln containing **42** (128 mg) in 1 mL of oxolane was treated with a soln of tetra-n-butylammonium fluoride (0.3 mL, 1M). After stirring for overnight at room temp and 2 hr at 60°, the soln was evaporated to dryness and the residue was chromotographed on silica ($CHCl_3$–MeOH, 97 : 3) to give 35 mg of the epoxide **43**, as a syrup; $[\alpha]_D + 7.65°$ (*c* 0.51, $CHCl_3$); *m/e* 494 ($M^+ + H$).

2,4 - *Dideoxy* - 2 - C - *methyl* - 3 - O - *methyl* - 5,6 - O- *isopropylidene* - D - *xylo* - *hexose propylenedithioacetal*, **27**. A soln of **24** (520 mg) was hydrolyzed as described for the preparation of **25**. The resulting crystalline lactol was dissolved in CH_2Cl_2 (25 mL) and the soln was treated with propanedithiol (0.9 mL) and BF_3–etherate 0.3 mL. After stirring overnight at 0°, $Ba(OH)_2$ was added and the mixture stirred vigorously. Filtration, evaporation and chromatography of the residue gave a syrup (340 mg), which was dissolved in benzene (10 mL) and the soln was treated with 2,2-dimethoxypropane (22 mL) and camphosulfonic acid (30 mg). After stirring 1 hr at room temp, the solution was treated with Dowex-1 (OH^-), and the filtrate evaporated to dryness. Chromatography over silica (EtOAc–hexanes, 1 : 4) gave the title compound as a syrup (298 mg); $[\alpha]_D - 9.2°$ (*c* 0.5, $CHCl_3$). (Found: C, 54.11, H, 8.14; S, 20.36. Calc. for $C_{14}H_{26}O_3S_2$: C, 54.5; H, 8.51; S, 20.78%.)

Condensation of dithian **27** *with* **12**. A soln of t-BuLi (220 μL, 0.4 mmole, 1.8M in hexanes) was added dropwise to a soln of **27** (133 mg, 0.433 mmole) in 2.5 mL of hexanes at −15°. The soln was stirred at −15° for 1.5 hr then cooled to −78°. A soln of **12** (10 mg) in 0.5 mL of dry ether was added dropwise. After stirring at −78° for 4 hr, TLC indicated little if any reaction had taken place. After allowing the mixture to warm up to room temp, there were formed three new products of lower mobility. NH_4Cl was added, the soln processed by extraction and the syrupy residue was chromatographed on silica (EtOAc–hexanes, 1 : 4) to give 60 mg of recovered dithian, 4 mg of the condensation product **44** and the same amount of two components of lower mobility which were not investigated further. For **44**, δ (ppm, 400 MHz) 0.95, 1.02, 1.30 (C–Me); 1.43, 1.36 (Me_2C): 3.19 (t, H3); 3.46, 3.52 (OMe); 4.59 (d, $J_{1,2} = 4.3$ Hz, H1), 4.89 (CH_2Ph) etc. *m/e* 569 ($M^+ - Me$); 479 ($M^+ - Me–CH_2Ph$).

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