Expeditious Synthesis of the Polypropionate Sector of Rifamycin S by Reiterative Diene–Aldehyde Cyclocondensation Reactions

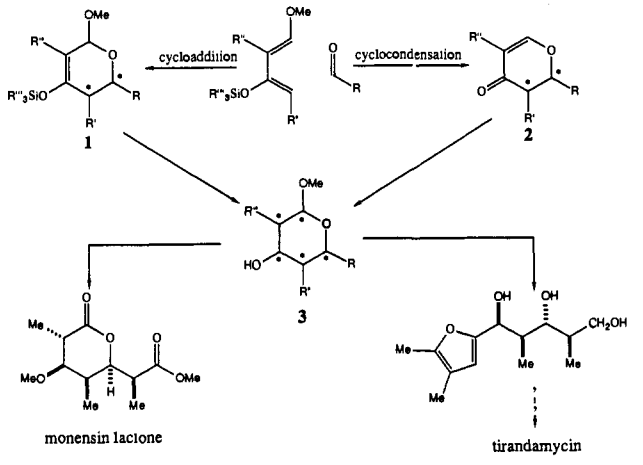
Samuel J. Danishefsky,* David C. Myles, and Daniel F. Harvey

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received July 7, 1986*

Abstract: Two Lewis acid catalyzed cyclocondensation reactions of activated dienes with β-oxygenated aldehydes are used in a rapid synthesis of the C_{19}–C_{29} polypropionate sector of rifamycin S. Both processes occur with essentially perfect diastereofacial selectivity in the Cram–Felkin sense. The first process (see **11** + **12** → **13**) occurs under the influence of titanium tetrachloride and is cis selective. The second process (see **25** + **35** → **34**) is mediated by the BF_3 etherate and is trans selective (ca. 4.5:1).

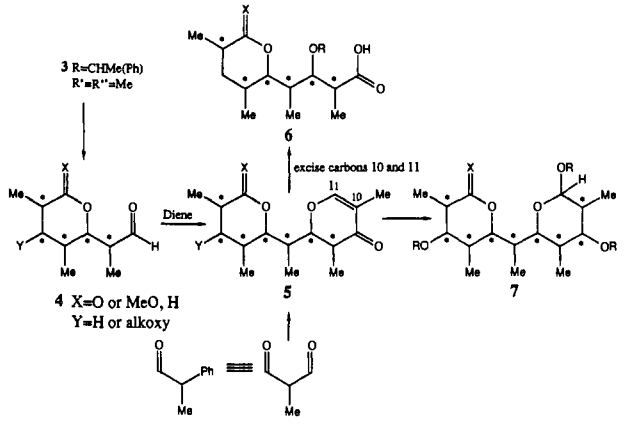
A recent report from our laboratory[1] identified a new strategy for the synthesis of polypropionate[2] segments of various natural products. A Lewis acid (L^+) mediated diene–aldehyde cyclocondensation reaction generates a pyran derivative. Advantage is taken of the remarkable ability of the L^+ catalyst to influence the diastereofacial and topographic[3] outcomes of the cyclocondensation reaction. Through a range of selective reactions, the initial cycloadduct **1** or cyclocondensation product **2** can be converted to stereochemically more advanced structures of the type **3**. Strong chiral biases of the pyranoid ring are exploited in this adjustment phase. If necessary, the ring can be cleaved with transferal of the stereochemical information to an acyclic fragment.

The synthesis of the "monensin lactone" was illustrative of this new approach.[1] The use of lanthanide catalysis in the cycloaddition reaction resulted in apparent endo addition,[4] leading to a cis relationship of R and R′ in structure **1**. In the approach to tirandamycin, the use of $Yb(fod)_3$ catalysis led to a cis relationship



of R and R′ in structure **2**. In this synthesis, new potentialities for stereochemical adjustments of pyran systems were developed, and a reductive version of the ring disconnection process was demonstrated. Aside from chirality which might be contained within the R, R′, or R″ groups of the aldehyde and the diene, the maximum number of nonanomeric stereogenic centers which can be correlated by this strategem is four.

The research described herein was addressed to the goal of synthesizing longer polypropionate domains by reiteration of the scheme proposed above. Two versions of this reiteration could be readily envisioned. In one plan, a new aldehyde group could be unveiled on the side chain. This group could function in another cyclocondensation reaction (see **4** → **5**). Two examples of this



reiterative version have been achieved in our laboratory. One example was used in the synthesis of the C_1–C_{10} fragment of 6a-deoxyerythronolide B (cf. compound **6**).[5] The second cyclocondensation reaction was conducted on a lactone aldehyde of the type **4** (X = O). Overall, 2-phenylpropanal had functioned as a "methylmalondialdehyde" equivalent. Unfortunately, the transformation of **4** → **5** lacked useful diastereofacial selectivity. Furthermore, for the erythronolide application,[5] it was necessary to excise carbons 10 and 11 of the bis(pyran) **5**, thus forfeiting access to two of the four potential stereogenic centers available by the method (cr. inter alia **2** → **3**, **5** → **6**, and **5** → **7**).

The reiteration reaction has also been carried out on the acetal aldehyde version of **4** (X = H, MeO). In this case much higher stereoselectivity was achieved in the formation of **5**. Furthermore, **5** was converted to the more advanced system **7**, containing nine contiguous nonanomeric stereogenic centers.[6]

In this paper we describe a different and more powerful reiterative strategy in which the successor aldehyde is fashioned from the anomeric carbon of its predecessor pyranoid. This new aldehyde participates in another cyclocondensation reaction, thus extending the polypropionate connectivity (**3** → **8** → **9**). As implied in structure **9**, there is a possibility for repeating "disconnects" and "reiterations". The issue of a diastereofacial control will be implicit in each cyclocondensation reaction. The extent of this control will, to no small extent, determine the attractiveness of the overall strategy.

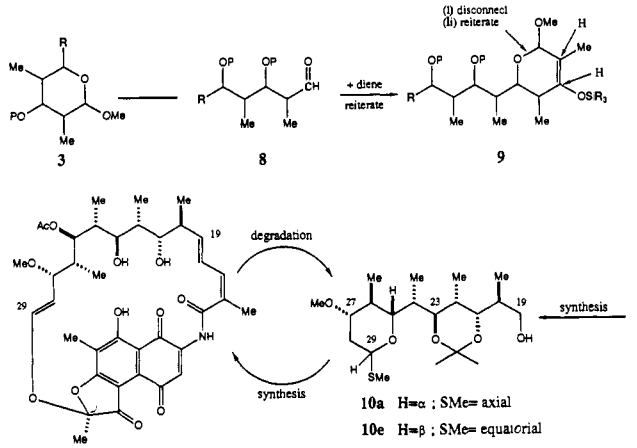
There is no dearth of synthetic targets which fall, in principle, under the scope of this formulation. Of particular interest, for

(1) Danishefsky, S. J.; Harvey, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 6647.
(2) "Polypropionate segment" here implies that these are substructures containing repeating 1,3-diol units bearing branched functionality at C_2. This type of structure can be viewed as arising from the formal condensation of propionate units.
(3) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.
(4) Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 3716.
(5) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.
(6) Harvey, D. F. Ph.D. Dissertation, Yale University, 1985.

0002-7863/87/1509-0862$01.50/0

illustrative purposes, was the synthesis of the polypropionate domain of the ansa-antibiotic rifamycin S.[7] The only total synthesis of rifamycin S has been accomplished by Kishi and collaborators in a feat which must be regarded as one of the milestones in contemporary organic synthesis.[8] The Kishi success was followed by several other reports which described the preparation of polypropionate substructures of rifamycin S.[9] In conceptual terms, though not always in fact, these syntheses merged with specific ansa fragments used in the Kishi synthesis.

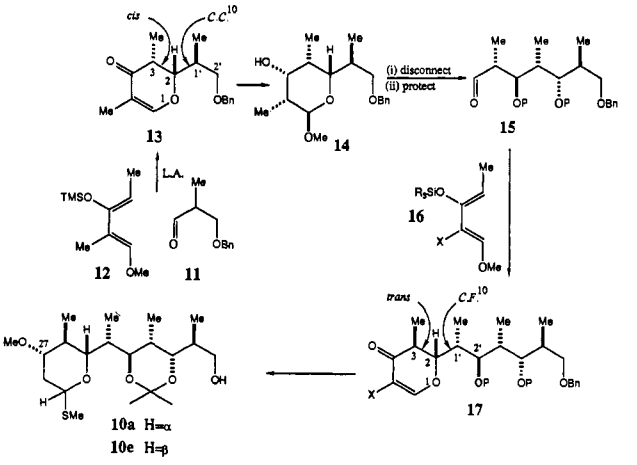
In the effort described here, the goal structures were the thiomethyl anomers **10a,e**. These compounds, in optically active form, were obtained by Kishi via total synthesis, as well as by degradation of rifamycin S.[8] They were actual intermediates in



the reconstruction of rifamycin S. Thus, in a formal sense, a relationship between a synthesis of compounds **10** and a total synthesis of rifamycin S had been established. Also, the possibility of achieving a direct spectral comparison of our synthetic material with one of the anomers of **10** loomed large in formulating our specific target.

Synthetic Strategy

The plan to reach compound **10** envisioned the intermediacy of pyrone **17**. It was assumed that an equatorial alcohol function could be introduced at C_{27} (rifamycin S numbering) and that this alcohol could be methylated. To reach the Kishi intermediate



10, it would also be necessary to introduce an anomeric thiomethyl group at C_{29} and to cleave the benzyl ether at C_{19} in an unspecified order. In keeping with the perception discussed above, system **17** would arise from a cyclocondensation reaction of diene type **16** with aldehyde **15**. As we began the exploration, the nature of X in diene **16** awaited precise definition. This matter will be considered in detail (vide supra).

Given the central algorithm, aldehyde **15** is seen to be the formal hydrolysis product of the branched pyranoid intermediate **14**. Suitable provision for protection of the 1,3-diol would be built into the plan. It seemed not improbable that pyrone **13** might serve as a precursor of **14**. Compound **13** is viewed, in our construct, as the cyclocondensation product of diene **12** with aldehyde **11**, both known compounds. Following previous protocols, the requisite cyclocondensation of **11** + **12** leading to **13** is described as cis at the topographic level and the apparent result of chelation control (C.C.)[10] in its diastereofacial sense. Indeed, in an earlier publication[3] this very reaction had been described with virtual stereocontrol in the desired sense under the governance of titanium tetrachloride in CH_2Cl_2.

Both antipodes of aldehyde **11** are well-known and available.[11] *It was the nature of our plan that the single stereogenic center in this compound would control, in a serial fashion, the sense of emergence of seven new contiguous stereogenic centers through the use of achiral reagents functioning under substrate control.*[12] The feasability of this proposal could be tested with racemic **11**. Thus, it was with this substance and thence with racemic **13**[13] that we began.

Discussion of Results

Reduction of compound **13** with lithium aluminum hydride in ether afforded, in greater than 90% yield, the equatorial alcohol **18**.[14] Although the configuration of the alcohol in compound **18** was that needed to reach target system **10**, the plan which we wished to institute to achieve control at C_{24} called for a temporary forfeiture of the advantage already secured at C_{23}. Treatment of **18** with methanol in the presence of *p*-TsOH brought about the expected Ferrier rearrangement,[15] providing compound **19** in 92% yield. The stereochemical sense[16] of the next reaction, i.e., hydroboration (BH_3·THF), was from the β-face, i.e., trans to the substituents at the 5- and 6-positions of the pyran. Oxidation of the crude borane with alkaline hydrogen peroxide afforded compound **20** in 68% yield. The stereochemistry at C_{24} had now been arranged in the desired sense. The need to achieve overall inversion of the configuration at C_{23} was now addressed. Compound **20**

(7) (a) Sensi, P.; Greco, A.; Ballota, R. *Antib. Ann.* **1960**, 262. (b) Brufani, M.; Fedali, W.; Giacomelo, G.; Vaciago, A. *Experientia* **1964**, *24*, 339.

(8) (a) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. (b) Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. (c) Nagaoka, H.; Kishi, Y. *Tetrahedron*, **1981**, *37*, 3873.

(9) (a) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528. (b) Hanessian, S.; Pougnyt, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289. (c) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (d) Nakatta, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chim. Soc. Jpn.* **1981**, *54*, 1749. (e) Tschamber, T.; Waespe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 621.

(10) For purposes of this paper, the descriptors "C.F." and "C.C." are used to convey the diastereofacial[3] sense of the cyclocondensation process. C.F. implies that the product is in accord with the correlative rules advanced by Cram and Felkin. The predictions from both the Cram and Felkin analyses converge, though from quite different bases. In the C.F. case (**15** → **17**), placing the 1′,2′ bond at the side chain antiperiplanar to the 2,3 bond of the pyrone results in the methyl group at C_1· appearing syn to the pyranoid oxygen (O_1). The descriptor C.C. is used to denote the apparent result of chelation control (i.e., cyclic Cram model) in the cyclocondensation reaction. In the case at hand (**11** → **13**), with the same disposition of the 1′,2′ and 2,3 bonds, the methyl group at 1′ will be anti to the pyranoid oxygen (O_1). For crucial references see ref 3 above and inter alia. (a) Cram. D. J.; Abd. Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cherest, M.; Felkin, H.; Prudert, N. *Tetrahedron Lett.* **1968**, 2199. (c) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (d) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245. (e) Still, W. C.; McDonald, J. H *Tetrahedron Lett.* **1980**, 1031.

(11) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347 and references cited therein.

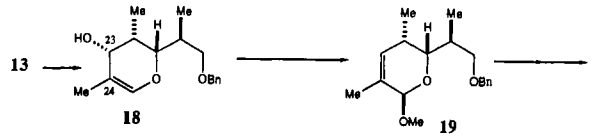
(12) For an alternative strategy of asymmetric synthesis based on the powerful strategy of reagent control see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Eng.* **1985**, *24*, 1.

(13) A previous publication from this laboratory describes the synthesis of **13** in a 55% yield.[3] Further experimentation led to an increased yield of 80% (see Experimental Section).

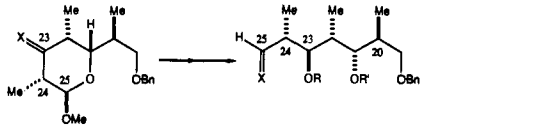
(14) A small amount (ca. 4%) of the tetrahydropyrone **18a** corresponding to conjugate reduction of **13** was also isolated from this reaction (see Experimental Section).

(15) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.

(16) Several other compounds were also obtained from this reaction. Structures were not assigned to these byproducts.



18 19

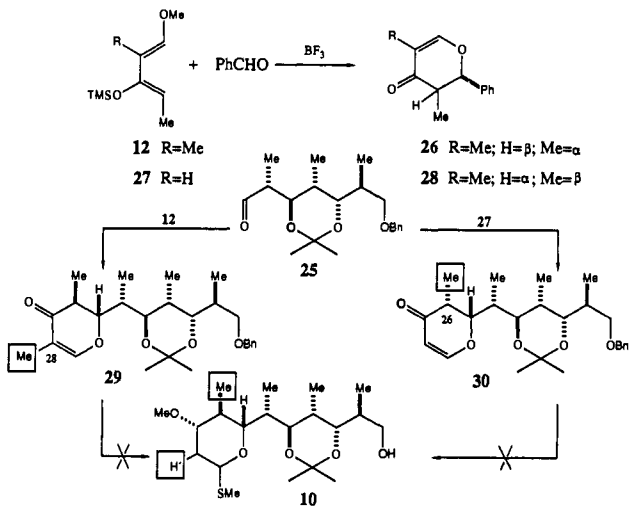


20 X=β OH;α H
21 X=O
22 X=α OH;β H
23 X= -S(CH$_2$)$_3$S- ; R=R'=H
24 X= -S(CH$_2$)$_3$S- ; R,R'= C(Me)$_2$
25 X=O; R,R'= C(Me)$_2$

was subjected to the action of oxalyl chloride and Me_2SO in CH_2Cl_2, followed by triethylamine.[17] The crude ketone **21**, thus obtained, was subjected to the action of sodium borohydride in methanol to afford the α-alcohol **22**.

The pyran matrix had successfully encoded the configurational specifications for C_{24}–C_{20} (inclusive) of the ansa sector, **10**. Attentions were now directed to the disconnection phase with a view to unveiling an aldehyde function at C_{25} (at this stage the anomeric carbon of compound **22**). Treatment of **22** with 1,3-propanedithiol in the presence of BF_3 etherate provided an 86% yield of compound **23**. At this stage, a promising possibility for engaging the 1,3-diol as a cyclic acetonide presented itself. Indeed, reaction of diol **23** with 2,2-dimethoxypropane in the presence of camphorsulfonic acid afforded an 87% yield of acetonide **24**. Treatment of **24** with *N*-bromosuccinimide in aqueous acetone liberated the aldehyde **25** in 85% yield.[18] Compound **25** was obtained as apparently a single entity through workups and purification practices which would not have been likely to have separated epimers at C_{24}. Thus, epimerization, which could potentially have accompanied transformations **22** → **23** and **24** → **25**, had been avoided. The stage was now set for the reiterative cyclocondensation.

The sense of the cyclocondensation reaction required to reach the goal system **10** would be trans at the topographic level[3] and in accord with (C.F.)[10] formulations, in its diastereofacial sense. With diene **12** and benzaldehyde, the use of BF_3 etherate catalysis strongly favored trans isomer **26**.[19] Previous studies[3] of cyclo-



12 R=Me
27 R=H
26 R=Me; H=β; Me=α
28 R=Me; H=α; Me=β
25
29
30
10

condensation reactions of β-alkoxyaldehydes similar to **25**, with diene **12** under BF_3 etherate catalysis, indicated a substantial selectivity in the direction of the desired (C.F.)[10] mode. However, for the purpose at hand, the methyl group at C_2 of diene **12** was not only unnecessary but was also a serious complicating factor. No ready solution to the problem of demethylation of the unwanted group from C_{28} of the polypropionate precursor seemed to be available.

Precedents from our own work indicated that recourse to the desmethyl diene ***27*** *would not bring forth a favorable outcome. Thus, the primary cyclocondensation product of diene* ***27*** *with benzaldehyde was, in fact, the cis disubstituted dihydropyrone* ***28***.[5] Preliminary experiments involving cyclocondensation of aldehyde **25** with dienes **12** and **27** indicated that this trend was applicable.[6,20] Diene **12**, upon cyclocondensation with aldehyde **25** in methylene chloride mediated by BF_3 etherate afforded primarily the trans system **29** containing the extraneous methyl group at C_{28}. Conversely, diene **27**, upon cyclocondensation with **25** under the same conditions, afforded predominantly pyrone **30**, which was, as required, unsubstituted at C_{28}. However, its configuration at C_{26} is epimeric with that required.

The origin of the dramatic effect of the substitution state at C_2 of dienes such as **12** and **27** on the topography of the cyclocondensation reaction is currently a matter of conjecture. However, even lacking a satisfactory level of understanding, a solution to the conundrum implicit in the relationship of structures **29**, **30**, and **10** could be advanced. It was proposed to employ a diene such as **16**, which would have an X substituent at C_2. This function would provide the same trans guidance as does the C_2 methyl group in diene **12**. Having served this purpose, the X group would be replaced by a hydrogen.

Given these requirements, and with ease of synthesis as another important consideration, the diene **33** emerged as an attractive possibility. The compound was in fact synthesized from the well-known enone **31**[21] in three steps. Treatment of **31** with phenylsulfenyl chloride gave an unstable 1-chloro-2-thiophenyl adduct. Dehydrohalogenation of the crude adduct was smoothly accomplished with triethylamine, affording an 80% yield of enone **32**, apparently as a single geometric isomer, shown as the *Z* system. Enol silylation of **32** using trimethylsilyl triflate afforded a near quantitative yield of a single diene formulated as **33**. The homogeneous character of **33** stands in contrast to **27**, which is obtained as ca. a 3.5:1 mixture of *Z*:*E* isomers upon enol silylation of its enone precursor.[5] The situation with **32** is very similar to that which pertains in the enol silylation leading to diene **12**,[22] wherein a single geometric isomer is produced. Apparently the presence of a substituent at C_2 favors formation of a single silyloxy diene with a *Z* configuration at C_4. The setting for the all crucial cyclocondensation reaction of aldehyde **25** with diene **33** was at hand.

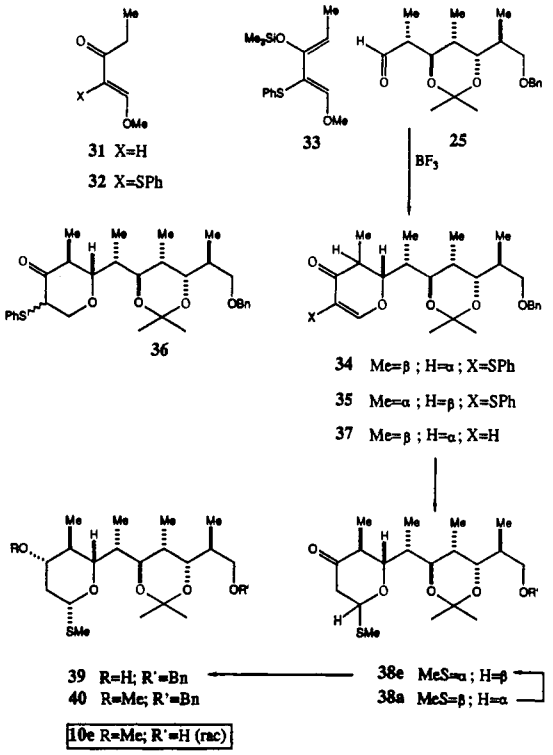
Reaction was carried out in methylene chloride using 2 equiv of diene **35** and 1 equiv of aldehyde **25** in the presence of BF_3 etherate at −78 °C. Aqueous workup produced a 4.5:1 ratio of trans:cis-pyrones **34**:**35**. The two substances were cleanly separated on silica gel to afford a 57% yield of homogeneous **34** and a 13% yield of **35**. At this stage we could assign, by NMR analysis, the pyrones as belonging to the trans and cis disubstituted series, respectively. That the major product **34** in fact belongs to the C.F.[10] series, as shown, was not rigorously known at the time but is now confirmed by its conversion to target system **10** of rigorously established stereochemistry (vide infra). By analogy, but without comparable certitude, the minor cis product is formulated as also belonging to the C.F.[10] series.

We note the absence of observable aldol-type intermediates under these conditions. Thus, the mechanistic classification which we would provide, based on earlier work,[5] would be a siloxonium pathway wherein carbon–carbon bond formation between C_4 of the diene and the aldehyde carbon produces a product with a high proclivity for cyclization. The process corresponding to the major product **36** is of threo topography in an aldol-type[5] view (or exo from the standpoint of a cycloaddition reaction), leading to a trans

(17) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(18) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(19) Danishefsky, S. J.; Chao, K.-H.; Shulte, G. *J. Org. Chem.* **1985**, *50*, 4650.
(20) Myles, D. C., unpublished results.
(21) Hills, P. R.; McQuillin, F. G. *J. Chem. Soc.* **1953**, 4060.
(22) Danishefsky, S. J.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

2,3-disubstitution pattern. By suitable manipulation of the diene and the reaction conditions, it might yet be possible to improve still further upon the stereochemical margin favoring the trans isomer. However, from a practical standpoint, the problem had substantially been solved.

The program to remove the phenylthio group started with conjugate reduction of the double bond through the action of L-Selectride. This provided the epimeric sulfide mixture **36**. Oxidation of this material with *m*-chloroperoxybenzoic acid, followed by thermolytic fragmentation in toluene, afforded an 83% yield of the dihydropyrone **37**.



Since Kishi had obtained both **10a** and **10e** in his rifamycin synthesis,[8] either of these thio anomers would have constituted an acceptable target system. However, in practice, **10e** became our goal. The reason for this is apparent from consideration of previous work from our laboratory on the sense of reduction of 2-alkoxytetrahydro-4-pyrones.[23] It had been shown that in the equatorial methoxy anomer series, the course of reduction of the 4-ketone with metal hydrides, *including even Selectrides*, produces equatorial alcohol. With axial methoxy anomers, L-Selectride affords substantially axial alcohol while sodium borohydride gives mixtures. By extension it seemed likely that reduction of the ketone of the equatorial thiomethyl anomer constituted our best chance to attain a stereospecific route to the required equatorial alcohol at C_{27}.

Treatment of dihydropyrone **37** with methanethiol in tetrahydrofuran, containing tetra-*N*-butylammonium fluoride afforded a 2:1 mixture of **38e**:**38a**. These compounds were readily separable by chromatography on silica gel.[24] The minor compound **38a**, upon resubjection to the same reaction conditions, afforded again a 2:1 mixture of **38e**:**38a**. Apparently, at least under these conditions, this is the thermodynamic ratio of the thio anomers. After a single recycle, the yield of **38e** was 75%.

In keeping with analogies from our anomeric alkoxy compounds,[23] reduction of **38e** with sodium borohydride in ethanol produced substantially (77% isolated yield) the equatorial alcohol **39** with only traces (<5%) of the axial epimer. Methylation of the C_{28} hydroxyl group was accomplished (92%) through the action of sodium hydride and methyl iodide in tetrahydrofuran, leading to **40**. Finally, treatment of compound **40** with sodium in ammonia resulted in its debenzylation with the isolation of *rac*-**10e** in 80% yield. *The richly detailed NMR spectrum of rac-**10e**, measured at 490 MHz in $CDCl_3$ was identical with that obtained from an authentic specimen furnished by Prof. Kishi.* The infrared and mass spectra were consistent with the assignment. There can be no doubt that the reiterative cyclocondensation strategy has achieved a total synthesis of *rac*-**10e**, expressing all of the polypropionate stereochemical information of rifamycin S. By associating our work in the racemic series with that of Kishi, a formal claim, regarding the total synthesis of rifamycin S, could be registered.

We note in summary that a total of 18 discrete chemical steps were employed in this linear synthesis. This count neglects a variety of opportunities for consolidation which could be implemented if a serious process research effort were pursued. The applicability of this new strategy to the synthesis of other natural products containing polypropionate domains is a matter of continuing interest in our laboratory.

Experimental Section

(±)-[2α(*R),3α]-2,3-Dihydro-3,5-dimethyl-2-[1-methyl-2-(phenylmethoxy)ethyl]-4*H*-pyran-4-one (13).** A solution of 3-(benzyloxy)-2-methyl-1-propanal (**11**, 1.51 g, 8.49 mmol) in CH_2Cl_2 (85 mL) was cooled to −78 °C and treated with $TiCl_4$ (1.70 g, 8.96 mmol). After 5 min, diene **12** (2.10 g, 10.5 mmol) was added. After 30 min, saturated $NaHCO_3$ solution (50 mL) was added, and the system was warmed to room temperature. Extracting with ether, drying ($MgSO_4$), and concentrating in vacuo gave a slightly yellow oil. Silica gel chromatography gave 1.85 g (80%) of 2,3-dihydropyrone **13**.

1,5-Anhydro-2,4,6-trideoxy-2,4,6-trimethyl-7-*O*-(phenylmethyl)-DL-*manno*-hept-1-enitol (18) and 1,5-Anhydro-2,4,6-trideoxy-2,4,6-trimethyl-7-*O*-(phenylmethyl)-DL-*gluco*-3-heptulose (18a). To a suspension of LAH (294 mg, 7.75 mmol) in Et_2O (100 mL) at −78 °C was slowly added a solution of dihydropyrone **13** (1.93 g, 7.04 mmol) in Et_2O (30 mL). After the solution was stirred for approximately 5 min, a saturated sodium potassium tartrate solution (approximately 30 mL) was carefully added, the reaction mixture warmed to 25 °C, diluted with water (100 mL) and Et_2O (100 mL), and stirred for 3 h. After separation of the organic phase and extraction with Et_2O (3 × 150 mL), the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatography gave 76 mg (4%) of ketone **18a** and 1.77 g (91%) of alcohol **18**. Ketone **18a**: IR ($CHCl_3$) 3000, 2960, 2930, 2845, 1710, 1450, 1380, 1240, 1200, 1115, 1090 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H), 4.52 (AB_q, J = 12.2 δ = 31.0 Hz, 2 H), 4.14 (dd, J = 11.1, 7.3 Hz, 1 H) 3.62 (dd, J = 8.8, 3.0 Hz, 1 H), 3.50 (dd, J = 8.8, 6.2 Hz, 1 H), 3.39 (dd, J = 10.1, 2.3 Hz, 1 H), 3.14 (t, J = 11.3 Hz, 1 H), 2.82 (m, 1 H), 2.5 (dq, J = 2.3, 7.2 Hz, 1 H), 2.04–1.98 (m, 1 H), 1.16 (d, J = 7.2 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); MS, *m/e* (%) 276 (M^+, 4), 259 (3), 258 (11), 200 (3), 186 (7), 185 (63), 171 (3), 170 (25), 167 (19), 161 (12), 160 (49), 152 (10), 145 (23), 129 (26), 128 (15), 127 (100), 111 (20), 107 (32), 99 (12), 98 (46), 92 (10), 91 (62), 87 (15), 83 (13), 57 (11). Alcohol **18**: mp 59.5–60.5 °C; IR ($CHCl_3$) 3600, 3450 (br), 3000, 2970, 2935, 2920, 2880, 2855, 1665, 1450, 1380, 1370, 1155, 1100, 1070, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H), 6.09 (s, 1 H), 4.52 (AB_q, J = 12.1, δ = 15.2 Hz, 2 H), 4.42 (br t, J = 7.0 Hz, 1 H), 3.71 (br d, J = 10.3 Hz, 1 H), 3.62 (dd, J = 8.9, 3.1 Hz, 1 H), 3.47 (dd, J = 8.9, 6.3 Hz, 1 H), 2.21–2.16 (m, 1 H), 2.05–1.98 (m, 1 H), 1.59 (s, 3 H), 1.35 (d, J = 7.0 Hz, 1 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H); MS *m/e* (%) 276 (M^+, 2), 187 (4), 167 (4), 111 (7), 109 (15), 107 (6), 101 (9), 99 (4), 98 (5), 97 (4), 95 (5), 92 (11), 91 (100), 87 (11), 85 (11), 83 (13), 82 (13), 69 (42); exact mass calcd 276.1726, found 276.1728.

(±)-[2α(*S),3α,6β]-3,6-Dihydro-6-methoxy-3,5-dimethyl-2-[1-methyl-2-(phenylmethoxy)ethyl]-2*H*-pyran (19).** A solution of alcohol **18** (1.77 g, 6.4 mmol) in MeOH (25 mL) containing *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol) was kept at room temperature for 10 h. Saturated $NaHCO_3$ solution (10 mL) and H_2O (200 mL) were then added, and the aqueous phase was extracted with Et_2O (4 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Silica gel chromatography gave 1.70 g (92%) of olefin **19**: IR ($CHCl_3$) 3000, 2960, 2950, 2910, 2870, 1450, 1375, 1185, 1090, 1055, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5 H), 5.68 (d, J = 5.7 Hz, 1 H), 4.59 (s, 1 H), 4.53 (s, 2 H), 3.78 (dd, J = 8.7, 7.2 Hz, 1 H), 3.69 (dd, J = 10.6, 2.9 Hz, 1 H), 3.49 (dd, J = 8.7, 7.2 Hz, 1 H), 3.38 (s, 3 H), 2.07–2.02 (m, 1 H), 1.98–1.92 (m, 1 H), 1.69 (s, 3 H), 0.99 (d, J = 6.8 Hz, 3 H),

(23) Danishefsky, S. J.; Langer, M. E. *J. Org. Chem.* **1985**, *50*, 3672.
(24) Pyrone **38e** was found on standing to equilibrate to a mixture of **38e**, **38a**, and **37**. Therefore, it was normally reduced to pyran **39** immediately following chromatography (see Experimental Section).

0.91 (d, J = 6.9 Hz, 3 H); MS, m/e (%) 290 (M^+, 0.3), 289 (0.4), 275 (0.3), 272 (0.6), 260 (1.5), 259 (8.4), 258 (20.3), 199 (2), 184 (6), 171 (9), 169 (2), 168 (4), 167 (25), 166 (5), 161 (2), 153 (14), 152 (33), 151 (8), 150 (2), 149 (3), 141 (5), 139 (6), 137 (8), 134 (5), 126 (5), 125 (5), 123 (9), 121 (8), 113 (15), 112 (100), 111 (20), 109 (21), 97 (29), 95 (7), 91 (30), 85 (6), 81 (6); exact mass calcd 290.1882; found 290.1889.

Methyl (±)-2,4,6-Trideoxy-2,4,6-trimethyl-7-*O*-(phenylmethyl)-D-*glycero*-α-D-*ido*-heptopyranoside (20). Pyran **19** (1.70 g, 5.86 mmol), in THF (25 mL), was cooled to 0 °C and treated with BH_3·THF solution (8.8 mL of a 1.0 M solution in THF (Aldrich), 8.8 mmol). After 30 min at 0 °C, the reaction mixture was slowly warmed to 15 °C over a 5.5-h period. The crude product was treated with 30% H_2O_2 solution (5.0 mL), H_2O (10 mL), and NaOH (1.40 g). After stirring for 12 h at room temperature, the reaction mixture was diluted with H_2O (150 mL) and extracted with CH_2Cl_2 (4 × 150 mL), and combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatography gave 1.23 g (68%) of alcohol **20**: IR ($CHCl_3$) 3510 (br), 3000, 2960, 2910, 1490, 1475, 1460, 1450, 1410, 1380, 1365, 1325, 1235, 1190, 1150, 1105, 1095, 1075, 1040, 990, 970 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5 H), 4.52 (s, 2 H), 4.48 (s, 1 H), 3.94 (dd, J = 10.6, 3.0 Hz, m, 1 H), 3.68 (dd, J = 8.5, 3.0 Hz, 1 H), 3.56 (dd, J = 8.6, 6.4 Hz, 1 H), 3.52 (m, 1 H), 3.32 (s, 3 H), 3.23 (d, J = 9.0 Hz, 1 H), 1.99–1.92 (m, 2 H), 1.89–1.85 (m, 1 H), 1.10 (d, J = 7.7 Hz, 3 H), 1.03 (d, J = 7.5 Hz, 3 H), 0.99 (d, J = 6.8 Hz, 3 H); MS, m/e (%) 276 (M^+ − 32, 16), 188 (12), 187 (46), 185 (33), 179 (12), 173 (10), 141 (9), 139 (20), 129 (24), 127 (10), 111 (17), 109 (13), 107 (16), 101 (42), 99 (20), 92 (16), 91 (100), 87 (16), 85 (12), 83 (22), 82 (10), 73 (16), 72 (92), 69 (20); exact mass calcd 308.1988, found 308.1970.

Methyl (±)-2,4,6-Trideoxy-2,4,6-trimethyl-7-*O*-(phenylmethyl)-D-*glycero*-α-D-*talo*-heptopyranoside (22). To a solution of oxalyl chloride (189 mg, 1.49 mmol) in CH_2Cl_2 (2.0 mL) cooled to −78 °C, was added, dropwise, Me_2SO (233 mg, 2.98 mmol). The resultant mixture was stirred for 5 min, and alcohol **20** (92 mg, 0.298 mmol, 1.0 mL) was slowly added at −78 °C. After 10 min at −78 °C, triethylamine (606 mg, 5.95 mmol) was added, and the reaction mixture was warmed to room temperature. After 10 min at room temperature, H_2O (5 mL) was added. The aqueous phase was extracted with Et_2O (4 × 15 mL), and the organic phase was dried ($MgSO_4$). Concentration in vacuo gave crude ketone **21**, which was not characterized. The crude ketone **21** was dissolved in MeOH (8 mL), cooled to −25 °C, and treated with solid $NaBH_4$ (56 mg, 1.49 mmol). After 20 min at −25 °C, saturated NH_4Cl solution (5 mL) was added, and the reaction mixture was warmed to room temperature. Water (20 mL) was then added, and the aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL). Drying ($MgSO_4$) concentration in vacuo, and silica gel chromatography gave starting alcohol **20** (6 mg, 6%) and alcohol **22** (79.1 mg, 86%). Alcohol **22**: IR ($CHCl_3$) 3600, 3450 (br), 3000, 2960, 2900, 1485, 1450, 1370, 1235, 1125, 1070, 1025, 990, 960, 950 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5 H), 4.54–4.48 (m, 3 H), 4.12 (br q, J = 5.3 Hz, 1 H), 3.68–3.65 (m, 2 H), 3.54 (dd, J = 8.5, 6.3 Hz, 1 H), 3.27 (s, 3 H), 2.07–1.96 (m, 3 H), 1.43, (d, J = 5.1 Hz, 1 H), 1.05 (d, J = 7.5 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H); MS, m/e (%) 277 (4), 276 (M^+ − 32, 7), 259 (2), 258 (2), 236 (3), 219 (10), 207 (8), 187 (18), 185 (13), 179 (16), 177 (11), 169 (11), 167 (11), 129 (31), 127 (13), 112 (13), 111 (11), 109 (25), 107 (33), 101 (52), 99 (20), 97 (10), 92 (35), 92 (100), 87 (27), 85 (18), 83 (24), 82 (13), 79 (15), 77 (15), 73 (42), 72 (97), 71 (23), 69 (47), 54 (25), 59 (20), 58 (31), 57 (39), 55 (23); exact mass calcd 308.1988, found 308.1981.

(±)-2,4,6-Trideoxy-2,4,6-trimethyl-7-*O*-(phenylmethyl)-D-*glycero*-D-*talo*-heptose Cyclic 1,3-Propanediyl Mercaptal (23). To a solution of alcohol **22** (65 mg, 0.211 mmol) and 1,3-propanedithiol (35 mg, 0.32 mmol) in CH_2Cl_2 (2.1 mL) at −78 °C was added BF_3·Et_2O. After 40 min at −78 °C, the reaction mixture was warmed to 0 °C for 20 min and then quenched with saturated $NaHCO_3$ solution (3.0 mL). Extraction with Et_2O (4 × 15 mL), drying ($MgSO_4$), concentration in vacuo, and slow silica gel chromatography gave diol **23** in 84% yield (68 mg): IR ($CHCl_3$) 3440 (br), 3000, 2960, 2930, 2900, 1450, 1420, 1380, 1360, 1270, 1245, 1100, 1070 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5 H), 4.90 (d, J = 2.3 Hz, 1 H), 4.53 (AB_q, J = 11.8, δ = 15.3 Hz, 2 H), 4.34 (s, 1 H), 3.86 (overlapping doublets, [3.86, d, J = 8.9 Hz] [3.85, d, J = 9.4 Hz], 2 H), 3.62 (dd, J = 9.2, 4.0 Hz, 1 H), 3.57 (td, J = 9.5, 2.6 Hz, 1 H), 3.48 (t, J = 9.3 Hz, 1 H), 3.08 (td, J = 13.2, 2.4 Hz, 1 H), 2.94 (td, J = 13.2, 2.3 Hz, 1 H), 2.85 (m, 2 H), 2.19–2.10 (m, 2 H), 2.07–2.01 (m, 1 H), 1.90–1.76 (m, 2 H), 1.13 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.75 (d, J = 6.9 Hz, 3 H); MS, m/e (%) 384 (M^+, 2), 366 (4), 275 (6), 188 (5), 187 (12), 178 (8), 177 (13), 176 (100), 175 (7), 161 (8), 160 (16), 159 (40), 149 (6), 148 (22), 147 (17), 146 (20), 129 (20), 121 (10), 120 (6), 199 (85), 107 (6), 91 (45), 87 (6); exact mass calcd 384.1793, found 284.1781.

(±)-2,4,6-Trideoxy-2,4,6-trimethyl-3,5-*O*-(1-methylethylidene)-7-*O*-(phenylmethyl)-D-*glycero*-D-*talo*-heptose Cyclic 1,3-Propanediyl Mercaptal (24). To a solution of diol **23** (66 mg, 0.173 mmol) in 2,2-dimethoxypropane (1.0 mL) was added *dl*-10-camphorsulfonic acid monohydrate (4 mg, 0.016 mmol). After 6 h at room temperature, saturated $NaHCO_3$ solution (3.0 mL) was added, and the resulting aqueous phase was extracted with Et_2O (4 × 15 mL). Drying ($MgSO_4$), concentration in vacuo, and silica gel chromatography gave acetonide **24** (64 mg) in 87% yield: IR ($CHCl_3$) 2980, 2930, 2895, 1450, 1430, 1420, 1410, 1380, 1350, 1270, 1210, 1180, 1135, 1090, 1070, 1020, 1000, 965 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5 H), 4.58 (d, J = 3.0 Hz, 1 H), 4.50 (s, 2 H), 3.66 (dd, J = 10.8, 3.7 Hz, 1 H), 3.58 (dd, J = 8.7, 3.0 Hz, 1 H), 3.44 (dd, J = 8.7, 6.2 Hz, 1 H), 3.38 (dd, J = 9.4, 6.4 Hz, 1 H), 3.01 (td, J = 13.0, 2.3 Hz, 1 H), 2.88–2.83 (m, 3 H), 2.15–2.08 (m, 1 H), 2.04–1.98 (m, 1 H), 1.90–1.80 (m, 2 H), 1.76–1.70 (m, 1 H), 1.35 (s, 3 H), 1.29 (s, 3 H), 1.09 (d, J = 7.1 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.7 Hz, 3 H); MS, m/e (%) 425 (6), 424 (M^+, 25), 367 (7), 366 (32), 350 (8), 349 (18), 348 (70), 291 (9), 277 (8), 275 (6), 260 (13), 259 (69), 245 (6), 227 (5), 220 (18), 217 (5), 185 (6), 183 (7), 177 (5), 176 (15), 175 (37), 167 (5), 159 (7), 149 (8), 148 (19), 147 (22), 146 (100), 121 (8), 119 (60), 111 (8), 92 (5), 91 (55); exact mass calcd 424.2106, found 424.2108.

(±)-2,4,6-Trideoxy-2,4,6-trimethyl-3,5-*O*-(1-methylethylidene)-7-*O*-(phenylmethyl)-D-*glycero*-D-*talo*-heptose (25). A solution of the dithiane **24** (21 mg, 0.051 mmol) in 95% acetone–H_2O (1.0 mL) was added to a cold (−25 °C) solution of *N*-bromosuccinamide (73 mg, 0.41 mmol) in 95% acetone–H_2O. After 2 min, a solution of Na_2SO_3 (ca. 1 M) was added dropwise until the yellow had disappeared. Dilution with water (15 mL) and extraction with ether (4 × 20 mL) followed by drying ($MgSO_4$), concentration in vacuo, and silica gel chromatography gave aldehyde **25** (14 mg) in 83% yield: IR ($CHCl_3$) 2980, 2930, 2870, 2850, 1725, 1450, 1380, 1210, 1180, 1140, 1090, 1070, 1050, 1020, 995 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 9.74 (d, J = 2.6 Hz, 1 H), 7.37–7.26 (m, 5 H), 4.49 (s, 2 H), 3.70 (dd, J = 10.8, 4.1 Hz, 1 H), 3.56 (dd, J = 8.7, 3.0 Hz, 1 H), 3.47 (dd, J = 6.9, 6.1 Hz, 1 H), 3.45 (dd, J = 8.7, 6.0 Hz, 1 H), 2.47 (ddq, J = 2.6, 6., 7.0 Hz, 1 H), 1.94 (dp, J = 4.1, 6.8 Hz, 1 H), 1.88–1.81 (m, 1 H), 1.33 (s, 3 H), 1.27 (s, 3 H), 1.15 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H); MS, m/e (%) 319 (M^+ − 15, 2), 218 (2), 179 (12), 170 (2), 149 (4), 129 (3), 127 (2), 111 (4), 109 (3), 108 (2), 107 (17), 100 (3), 99 (4), 98 (8), 97 (3), 95 (3), 92 (10), 91 (100), 85 (4), 83 (7), 82 (2), 71 (3), 70 (3), 69 (19), 68 (2), 59 (31); exact mass calcd 334.2144, found 334.2139.

5-Methoxy-4-(phenylthio)penten-3-one (32). A solution of 5-methoxypenten-3-one (**31**, 4.0 g, 35.1 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C in an ice bath and treated with phenylsulfenyl chloride (15.0 g, 104 mmol, 2.97 equiv). After stirring for 5 min at 0 °C, triethylamine (30.0 mL, 408 mmol, 11.7 equiv) was added dropwise over 2 min. A colorless precipitate formed immediately. The slurry was then diluted with 100 mL of water, the phases were separated, and the aqueous phase was extracted (3 × 100 mL) with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. Silica gel chromatography of the resulting dark-yellow oil afforded 6.25 g (80.2%) of a slightly yellow oil which solidified on standing: IR ($CDCl_3$) 2982, 2942, 1678, 1588, 1480, 1442, 1272, 1134, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.90 (s, 1 H), 7.13 (m, 5 H), 3.97 (s, 3 H) 2.66 (q, J = 6.90 Hz, 2 H), 0.99 (t, J = 6.90 Hz, 3 H); EI-MS, m/e (%) 222 (M^+, 100), 193 (30), 165 (50), 150 (10), 135 (48), 134 (9), 122 (16), 121 (46), 117 (16), 109 (16), 100 (9), 91 (15).

(*Z*,*E*)-(1-Ethylidene-3-methoxy-2-(phenylthio)-2-propenyl)trimethylsilane (33). To a 0 °C solution of enone **32** (1.51 g, 6.80 mmol) and triethylamine (3.44 g, 34.0 mmol) in ether (25 mL) was added trimethylsilyl trifluoromethanesulfonate (1.89 g, 8.5 mmol). After 30 min, an oily precipitate was discarded and the reaction quenched with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted (2 × 50 mL) with Et_2O. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated to afford 1.92 g (96%) of crude **33**. This material was routinely used in this form but could be chromatographed on silica gel (5% triethylamine, 20% ether, 75% hexanes) to afford, typically, 40–50% yield of purified **33**: IR ($CDCl_3$) 2960, 2935, 1668 1612, 1560, 1480, 1310, 1255, 1238, 1139, 1052, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.16–7.13 (m, 5 H), 7.01 (s, 1 H), 5.30 (q, J = 6.96 Hz, 1 H), 3.72 (s, 3 H), 1.52 (d, J = 6.98 Hz, 3 H), 0.719 (s, 9 H). EI-MS, m/e (%) 222 (100), 193 (31), 165 (60), 150 (13), 137 (11), 135 (69), 134 (14), 122 (26), 121 (71), 117 (24), 109 (29), 105 (11), 91 (24).

(±)-1,5-Anhydro-4,6,8,10-tetradeoxy-4,6,8,10-tetramethyl-7,9-*O*-(1-methylethylidene)-2-*S*-phenyl-11-*O*-(phenylmethyl)-2-thio-D-*arabino*-L-*manno*-undec-1-en-3-ulose (34). A solution of aldehyde **25** (451 mg, 1.35 mmol) and diene **33** (794.3 mg, 2.7 mmol, 2.0 equiv.) in CH_2Cl_2 (30 mL) was cooled to −78 °C. This was treated with BF_3·Et_2O (383 mg, 2.7 mmol, 2 equiv). The resultant system was allowed to stir for 15 min,

quenched with sodium bicarbonate solution (1.0 M), and allowed to warm to room temperature. The phases were separated, and the aqueous phase was extracted (3 × 60 mL) with ether. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo, giving a yellow oil which was chromatographed (20% ethyl acetate in hexanes, silica gel) to afford 403 mg (57%) of **34** and 90 mg (13%) of **35**. Pyrone **34**: IR ($CDCl_3$) 2990, 1682, 1575, 1382, 1252, 1116 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.90 (s, 1 H), 7.35–7.12 (m, 10 H), 4.66 (dd, J = 13.1, 1.4 Hz, 1 H), 4.50 (s, 2 H), 3.71 (dd, J = 10.8, 3.7, 1 H), 3.60–3.44 (AB of ABx, J_{ab} = 8.63, J_{ax} = 2.97, J_{bx} = 5.96 Hz, 2 H), 3.39 (dd, J = 9.81, 6.42 Hz, 1 H), 2.76–2.62 (dq, J = 13.85, 6.93 Hz, 1 H), 1.95–1.74 (m, 3 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 1.12 (d, J = 6.89 (d, J = 6.89 Hz, 3 H), 1.03–0.97 (m, 9 H); MS, M^+ calcd 524.2597, obsd 524.2597. Anal. Calcd for $C_{31}H_{41}O_5S$: C, 70.99; H, 7.82; S, 6.11. Found: C, 70.76, H, 7.58; S, 6.27. Pyrone **35**: IR 2992, 2940, 2881, 1682, 1572, 1457, 1382, 1256, 1227 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.86 (s, 1 H), 7.32–7.10 (m, 10 H), 4.57–4.53 (dd, J = 6.39, 3.49 Hz, 1 H), 4.45 (s, 2 H), 3.65–3.59 (dd, J = 10.81, 3.76 Hz, 1 H), 3.54–3.39 (AB of ABx, J_{ab} = 8.61, J_{ax} = 2.96, J_{bx} = 5.79 Hz, 2 H), 3.19 (dd, J = 6.93, 6.95 Hz, 1 H) 2.77 (dq J = 13.80, 6.91 Hz, 1 H), 1.88–1.72 (m, 2 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.16 (d J = 7.29 Hz, 3 H), 1.09 (d, J = 6.94 Hz, 3 H), 0.93 (d, J = 6.79 Hz, 3 H), 0.89 (d, J = 6.66 Hz, 3 H); EI-MS m/e (%) 525 (7), 466 (10), 289 (2), 288 (6), 277 (3), 276 (10), 260 (1), 259 (4), 220 (7), 219 (28), 207 (3), 206 (4), 179 (6), 178 (4), 151 (6), 139 (5), 137 (9), 123 (5), 121 (10), 111 (7), 109 (9), 107 (4), 105 (6), 99 (7), 95 (6), 92 (9), 91 (100), 69 (12).

(±)-1,5-Anhydro-2,4,6,8,10-pentadeoxy-4,6,8,10-tetramethyl-7,9-*O*-(1-methylethylidene)-11-*O*-(phenylmethyl)-D-*arabino*-L-*manno*-undec-1-en-3-ulose (37). A solution of pyrone **34** (258 mg, 0.492 mmol) in THF (25.0 mL) at −78 °C was treated with lithium di-*sec*-butylborohydride (0.615 mL, 1.0 M in THF, Aldrich). After stirring for 5 min, sodium bicarbonate solution (25 mL, in 1.0 M in water) was added. The solution was then extracted with ether (3 × 50 mL), and the organic phases were combined, dried ($MgSO_4$), and concentrated to afford crude **(±)-2-(*R*)-1,5-anhydro-4,6,8,10-tetradeoxy-4,6,8,10-tetramethyl-7,9-*O*-(1-methylethylidene)-2-*S*-phenyl-11-*O*-(phenylmethyl)-2-thio-D-*arabino*-L-*manno*-3-undeculose (36)**, as a slightly yellow oil. An ethereal solution of this material was passed through a plug of silica gel, concentrated in vacuo, and used directly in the next experiment.

Compound **36**, prepared as above, was dissolved in toluene (15 mL) and the solution cooled to 0 °C. To this solution was added a solution of *m*-chloroperoxybenzoic acid (5.0 mL, 0.1 M in toluene), and the resultant system was stirred for 10 min. The mixture was then treated with methyl sulfide (0.10 mL) and neutralized with triethylamine (ca. 0.05 mL). This mixture was heated to reflux for 35 min. It was cooled to room temperature, concentrated in vacuo, and chromatographed (20% ether in hexanes, silica gel) to afford 175 mg (85%) of **37** as a colorless oil: IR ($CDCl_3$) 2918, 1676, 1609, 1382, 1262, 1230, 1056, 1030 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.36–7.28 (m, 6 H), 5.38 (d, J = 5.83 Hz, 1 H), 4.48 (dd, J = 13.91, 1.49 Hz, 1 H), 4.49 (s, 2 H), 2.70 (dd, J = 10.77, 3.65 Hz, 1 H), 3.60–3.43 (AB of ABX, J_{ab} = 8.60, J_{ax} = 2.87, J_{bx} = 5.96 Hz, 2 H), 3.39 (dd J = 9.79, 6.56 Hz, 1 H), 2.57 (dq, J = 7.01, 14.01 Hz, 1 H), 1.92–1.77 (m, 3 H), 1.30 (s, 3 H), 1.26 (s, 3 H), 1.07 (d, J = 6.92 Hz, 3 H), 0.99–0.90 (m, 9 H); MS, M^+ calcd 416.2563, found 416.2565.

Methyl (±)-2,4,6,8,10-Pentadeoxy-4,6,8,10-tetramethyl-7,9-*O*-(1-methylethylidene)-11-*O*-(phenylmethyl)-1-thio-D-*manno*-β-L-*galacto*-undecopyranoside (39). A solution of pyrone **37** (89 mg, 0.213 mmol) and tetra-*n*-butylammonium fluoride (0.5 mL, 1.0 M) in THF (20 mL) was cooled to ca. −15 °C in an ice–methanol bath. Methanethiol (15 drops, Matheson) was then introduced into the solution via a dry ice condenser. After stirring for 45 min, the solution was diluted with 1:1 ether:hexanes (20.0 mL), washed through a plug of silica gel with ether, and concentrated in vacuo. The residue was rapidly chromatographed (15% ether in hexanes, silica gel) to afford 58 mg (58%) of the equatorial sulfide, methyl **(±)-2,4,6,8,10-pentadeoxy-4,6,8,10-tetramethyl-7,9-*O*-(1-methylethylidene)-11-*O*-(phenylmethyl)-1-thio-D-*arabino*-β-L-*manno*-undecopyranosid-3-ulose (38e)** and 30 mg (30%) of the axial sulfide **(38a)** containing a small amount of starting material. In a separate experiment, 30 mg of this latter mixture was resubjected to the preceding conditions to yield an additional 17.0 mg of the desired product, giving a combined total yield of 75%. **38e**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.24 (m, 5 H), 4.60 (dd, J = 12.1, 4.2 Hz, 1 H), 4.48 (s, 2 H), 3.75–3.32 (m, 5 H), 2.69–2.40 (m, 3 H), 2.23 (s, 3 H), 1.93–1.69 (m, 3 H), 1.28 (s, 3 H), 1.22 (s, 3 H), 1.03–0.92 (m, 12 H).

A solution of the equatorial sulfide **38e**[25] (58 mg, 0.124 mmol) in ethanol (10.0 mL) was cooled to −78 °C and treated with sodium borohydride (2.0 mL, 0.1 M in ethanol). After 10 min, acetone (1.0 mL) followed by sodium bicarbonate solution (25 mL, 1.0 M) was added and the mixture warmed to room temperature. The mixture was then extracted with ether (3 × 35 mL) and the organic phases were combined, dried ($MgSO_4$), and concentrated. Column chromatography (20% ether in hexanes, silica gel) afforded 47 mg (81%) of alcohol **39**: IR ($CDCl_3$) 3620, 2978, 2923, 1455, 1380 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5 H), 4.49 (s, 2 H), 4.40 (dd, J = 11.66, 1.92 Hz, 1 H), 3.66 (dd, J = 10.80, 3.68 Hz, 1 H), 3.60–3.32 (m, 7 H), 2.19 (s, 3 H), 1.90–1.41 (m, 4 H), 1.29 (s, 3 H), 1.26 (s, 3 H), 0.98–0.89 (m, 12 H); EI-MS, m/e (%) 466 (M^+, <1), 451 (6), 419 (12), 343 (14), 268 (8), 165 (11), 153 (13), 139 (25), 107 (20), 91 (100), 69 (47); CI-MS m/e (%) 484 (M^+, 18, 5), 467 (M^+, 100), 419 (58), 401 (18), 391 (21), 361 (43), 343 (93), 277 (20), 196 (19), 108 (27), 91 (35).

Methyl (±)-2,4,6,8,10-Pentadeoxy-4,6,8,10-tetramethyl-3-*O*-methyl-7,9-*O*-(1-methylethylidene)-11-*O*-(phenylmethyl)-1-thio-D-*manno*-β-L-*galacto*-undecopyranoside (40). A solution of the alcohol **39** (116 mg, 0.249 mmol) in tetrahydrofuran (5.0 mL) was treated with sodium hydride (ca. 150 mg) and stirred for 5 min. To this was added freshly distilled methyl iodide (ca. 0.40 mL). The mixture was heated to reflux for 1 h. After cooling to room temperature, the mixture was diluted with 1:1 ether:hexanes (20 mL) and filtered through a pad of Celite. The solution was then concentrated in vacuo and the resulting oil chromatographed (10% ether in hexanes, silica gel) to afford 111.0 mg (92%) of **40**: IR ($CDCl_3$) 2990, 2912, 1455, 1380, 1228, 1082 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5 H), 4.49 (s, 2 H), 4.37 (dd, J = 11.74, 1.73 Hz, 1 H), 3.66 (dd, J = 10.84, 3.64 Hz, 1 H), 3.60–3.32 (m, 6 H), 3.37 (s, 3 H), 3.01–2.91 (m, 1 H), 2.35–2.28 (m, 1 H), 2.20 (s, 3 H), 1.88–1.35 (m, 4 H), 1.29 (s, 3 H), 1.26 (s, 3 H), 0.98–0.89 (m, 12 H); EI-MS m/e (%) 480 (M^+, <1), 465 (5), 433 (19), 343 (18), 197 (19), 153 (21), 107 (26), 91 (100); CI-MS (NH_3) 498 (M + 18, 5), 481 (M + 1, 100), 433 (97), 391 (30), 375 (62), 360 (23), 343 (69), 297 (12), 277 (22), 235 (16), 197 (32), 108 (27), 95 (37).

Methyl (±)-2,4,6,8,10-Pentadeoxy-4,6,8,10-tetramethyl-3-*O*-methyl-7,9-*O*-(1-methylethylidene)-1-thio-D-*manno*-β-L-*galacto*-undecopyranoside (10e). Anhydrous ammonia (ca. 10 mL) at −78 °C was treated with solid sodium (ca. 15 mg). After the mixture stirred for 5 min, a solution of the benzyl ether **40** (60 mg, 0.125 mmol) in THF (3.0 mL) was added. The mixture was then rapidly (10 s) quenched with solid ammonium chloride (2.0 g). The ammonia evaporated as the mixture slowly warmed to room temperature. The colorless paste was then dissolved in water and the solution extracted (4 × 3.0 mL) with ether. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (20% ether in hexanes) to yield 30 mg (80%) of anomer **10e**: IR ($CDCl_3$) 3500 (br), 2980, 2925, 1463, 1372, 1232, 1084, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.37 (dd, J = 11.74, 1.74 Hz, 1 H), 3.68 (dd, J = 14.13, 3.72 Hz, 1 H), 3.61–3.34 (m, 3 H), 3.37 (s, 3 H), 3.20 (br d, J = 8.38 Hz, 1 H), 2.96 (dt, J = 10.49, 4.51 Hz, 1 H), 2.33 (m, 1 H), 2.20 (s, 3 H), 1.95–1.92 (m, 1 H), 1.83–1.76 (m, 2 H), 1.55–1.25 (m, 4 H), 1.37 (s, 3 H), 1.31 (s, 3 H), 0.95 (d, J = 6.71 Hz, 3 H), 0.91 (d, J = 8.07 Hz, 3 H), 0.90 (d, J = 6.50 Hz, 3 H) 0.78 (d, J = 6.88 Hz, 3 H).

Acknowledgment. This work was supported by PHS Grant AI 16943. A Dox Fellowship to D.C.M. is gratefully acknowledged. We thank Prof. Y. Kishi for authentic samples of **10e** and **10a**. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Registry No. (±)-**10e**, 105616-13-5; (±)-**11**, 74130-31-7; **12**, 72486-93-2; (±)-**13**, 105926-77-0; (±)-**18**, 105539-44-4; (±)-**18a**, 105581-62-2; (±)-**19**, 105562-31-0; (±)-**20**, 105539-45-5; (±)-**21**, 105539-46-6; (±)-**22**, 105616-10-2; (±)-**23**, 105539-47-7; (±)-**24**, 105539-48-8; (±)-**25**, 105539-49-9; **31**, 56279-28-8; **32**, 105539-50-2; **33**, 105539-51-3; (±)-**34**, 105539-52-4; (±)-**35**, 105616-11-3; (±)-**36**, 105539-53-5; (±)-**37**, 105539-54-6; (±)-**38a**, 105616-12-4; (±)-**38e**, 105539-55-7; (±)-**39**, 105539-56-8; (±)-**40**, 105539-57-9; rifamycin S, 13553-79-2.

(25) A small amount (2 mg, 4%) of another product of similar chromatographic mobility to **30** was also isolated from this reaction. This is presumed to be the hydroxyl epimer of **39**.