Application of Highly Stereocontrolled Glycosidations Employing 2,6-Anhydro-2-thio Sugars to the Syntheses of Erythromycin A and Olivomycin A Trisaccharide

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Abstract: The highly efficient syntheses of the erythromycin A (**1**) from its aglycon, (9*S*)-9-dihydroerythronolide A (**4**), and the C-D-E trisaccharide **3** of olivomycin A have been accomplished by the successful application of stereocontrolled glycosidations using 2,6-anhydro-2-thio sugars. The former synthesis includes the highly α-stereoselective glycosidation of the C5 desosaminated lactone **12** with phenyl 2,6-anhydro-4-*O*-benzyl-3-*C*-methyl-3-*O*-methyl-1,2-dithio-L-altropyranoside (**10**), which was achieved by using NIS−TfOH. The latter synthesis involves both the highly β-stereoselective glycosidation of 1,3-di-*O*-acetyl-2,6-anhydro-4-*O*-benzyl-2-thio-β-D-altropyranose (**23**), which was realized by employing TMSOTf, and the highly α-stereoselective glycosidation of phenyl 2,6-anhydro-3-*O*-(diethylisopropylsilyl)-4-*O*-isobutyryl-3-*C*-methyl-1,2-dithio-L-manno-pyranoside (**24**), which succeeded by utilizing NBS. Hydrogenolyses using Raney Ni as a catalyst and selective deprotections of the key glyco substances **17** and **22** led to the total syntheses of erythromycin A (**1**) and the C-D-E trisaccharide **3** of olivomycin A, respectively.

Introduction

Both erythromycin A (**1**) and olivomycin A (**2**) are very representative and useful antibiotics which have 2,6-dideoxy sugar(s) as their glycon moieties (Figure 1). A most typical and medicinally important macrolide antibiotic, erythromycin A (**1**),[1] isolated from a strain of *Saccharopolyspora erythraea*, has been widely studied for a long time and is still undoubtedly one of the most challenging target molecules for many synthetic organic chemists. Structurally, this macrolide is constructed from a 14-membered lactone with 10 asymmetric centers and two unique sugars. Although a vast number of synthetic studies[2] on erythromycins A and B including several elegant total syntheses of erythronolides A[3] and B,[4] the aglycons of erythromycins, have been reported so far, complete total synthesis of erythromycin A which has two sugars, L-cladinose and D-desosamine, was only accomplished by Woodward and his co-workers in 1981.[5] In this historic first total synthesis, *S*-pyrimidyl D-desosaminide and *S*-pyridyl L-cladinoside derivatives were effectively used for the glycosidation reactions. However, it was also made clear that one of the most difficult tasks after the aglycon synthesis was the stereoselective introduction of the acid-sensitive 2,6-dideoxy sugar, that is L-cladinose, to the extremely low reactive C3 hydroxyl group of the aglycon.[5]

On the other hand, olivomycin A (**2**),[6] produced by *Streptomyces olivoreticuli*, is a clinically effective member of the aureolic acid family of antibiotics, which also includes chromomycin A_3 and mithramycin as prominent members. They are structurally characterized by a complex tricyclic aglycon attached to various 2,6-dideoxy di- and trisaccharides. These

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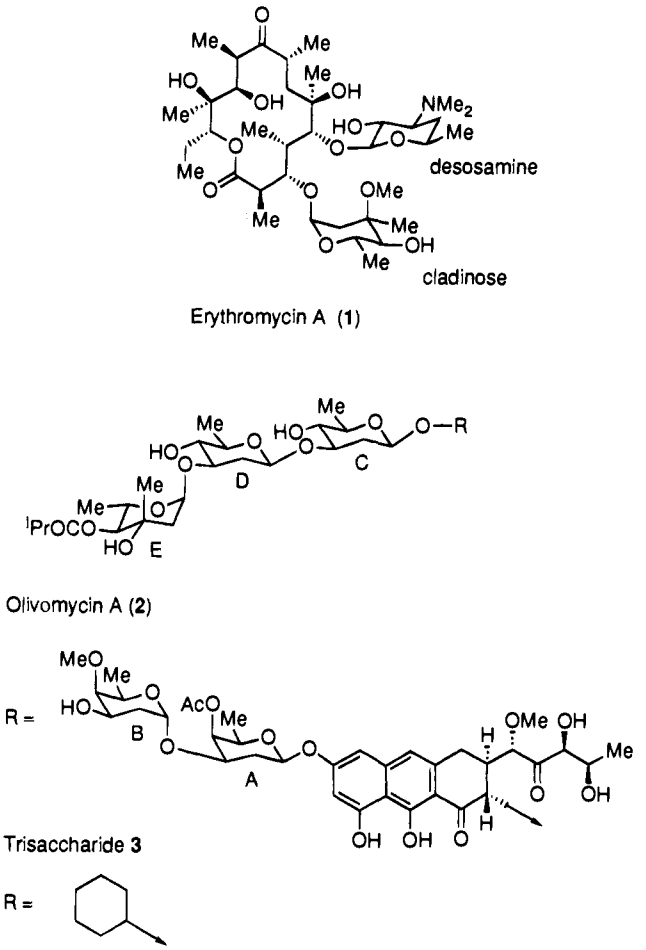

Figure 1. Molecular structures of erythromycin A (**1**), olivomycin A (**2**), and trisaccharide **3**.

compounds show significant anticancer activities which are supposed to result from the strong and selective inhibitions of the DNA-dependent RNA synthesis.[7] The mechanism of the activities involves the selective binding of these agents to two contiguous GC rich regions of the DNA duplexes in the minor groove and in the presence of divalent metal cations such as Mg(II).[8] The DNA binding site and the RNA synthesis inhibitory effect are influenced more by the carbohydrate moieties than by their aglycon parts, and the oligosaccharide chains are essential for their biological activities.[7,8] For this reason, synthesis of the di- and trisaccharides of these antibiotics has been a topic of great interest among several groups.[9] Especially, stereoselective formation of the 2,6-dideoxy-β-glycoside linkage, which is indispensable for the synthesis of these oligosaccharides, is still a formidable problem in glycoside synthesis.[10] In this context, Thiem has reported the pioneering synthesis of the C-D-E trisaccharide of chromomycin A_3 using 2,6-dideoxy-2-bromo-D-glucosyl bromides as the C and D sugar donors and a L-olivomycal derivative as the E ring precursor.[9g,i] Roush has recently synthesized the C-D-E trisaccharide of olivomycin A by employing 2-deoxy-2-(phenylthio)-α-D-glucotrichloroacetimidate and 2-deoxy-2-iodo-α-L-olivomycarosyl acetate as the glycosyl donors.[9j,k] Binkley,[9p,q,s] Crich,[9l,m] and Franck[9n,r,u,v] have also made significant contributions toward the synthesis of these substances.

Previously, we have disclosed a novel and powerful glycosidation method using 2,6-anhydro-2-thio sugars for the stereocontrolled synthesis of both 2,6-dideoxy-α- and β-glycosides.[11] In this paper, we now report the full account of the significant application of this method, that is the highly efficient syntheses of the erythromycin A (**1**) from its aglycon, (9*S*)-9-dihydroerythronolide A (**4**), and the C-D-E trisaccharide **3** of olivomycin A employing the stereocontrolled glycosidations of several kinds of 2,6-anhydro-2-thio sugars.[12]

Results and Discussion

Erythromycin A Synthesis. Our synthetic approach for the synthesis of erythromycin A (**1**) from its aglycon, (9*S*)-9-dihydroerythronolide A (**4**), began with the selective conversion of **4** into the C9- and C11-protected aglycon **7** in three steps (Scheme 1). (9*S*)-9-Dihydroerythronolide A (**4**) was synthesized by Kinoshita and Nakata in 1986[3c-e] and by Stork in 1987.[3f] Also, this aglycon **4** was readily prepared from natural erythromycin A.[13] Treatment of **4** with *p*-anisaldehyde dimethyl acetal and a catalytic amount of DL-10-camphorsulfonic acid (CSA) in CH_2Cl_2 at -30 °C afforded the C3- and C5-*p*-methoxybenzylidenated compound **5** in 87% yield with high regioselectivity. The isopropylidenation of **5** using 2-methoxypropene and pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 also proceeded regioselectively to give the C9 and C11 *O*-isopropylidene product **6** in quantitative yield. Subsequent reductive deprotection of the *p*-methoxybenzylidene group of **6** by hydrogenolysis using 20% $Pd(OH)_2$ on carbon as a catalyst in ethyl acetate gave the first key aglycon **7** in 95% yield. With

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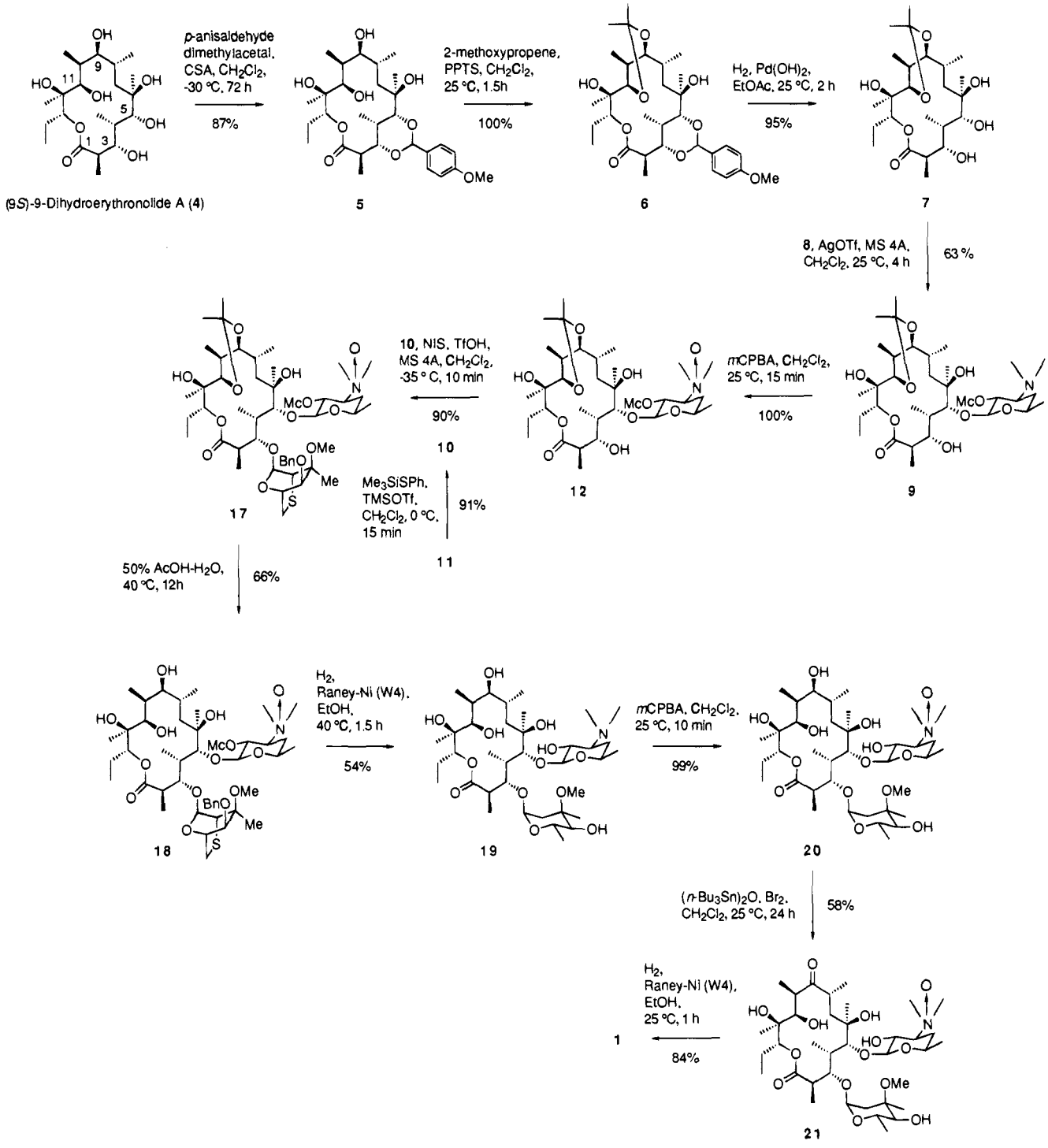
Scheme 1



the suitably protected aglycon **7** in hand, we turned our attention to the introduction of the D-desosamine moiety into **7**. The glycosidation of **7** (1 equiv) with the thioglycoside **8** (5.2 equiv) using the modified Woodward procedure[5] with AgOTf (6.4 equiv) and powdered molecular sieves 4A (MS 4A) in CH_2Cl_2–toluene at 0 → 25 °C for 4 h proceeded regio- and stereoselectively to afford the desired C5-glycosylated β-glycoside **9** as the sole anomer in 63% yield. The structure of **9** including the stereochemistry of the glycoside bond was confirmed by both ^{1}H-NMR analyses ($J_{1',2'}$ = 9.9 Hz) and identification with a sample prepared from (9*S*)-5-*O*-(β-D-desosaminyl)-9-dihydroerythronolide A.[14] Furthermore, it was found that MS 4A was an indispensable element in obtaining a high yield of **9** and the carbomethoxy protecting group at the C2 position of the glycosyl donor **8** was quite effective for the high β-stereoselectivity of the glycosidation.

On the other hand, the C1-activated 2,6-anhydro-C3-branched-2-thio glycosyl donor **10** corresponding to L-cladinose was effectively synthesized from the methyl 2,6-anhydro-C3-branched-2-thio glycoside **11**[15] using Nicolaou's method[16] with Me_3SiSPh and TMSOTf. The glycosidations of the C5-D-desosaminated lactone **9** with the phenythio glycoside **10** using several

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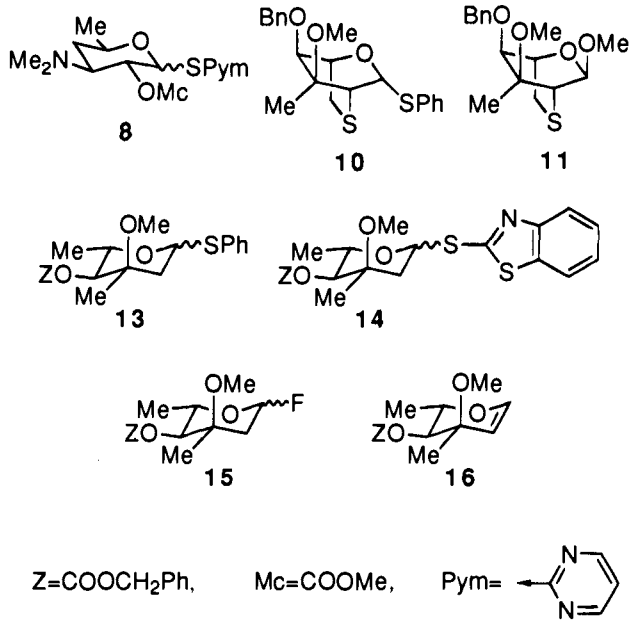

Figure 2. Several glycosyl donors for the synthesis of **1**.

activators such as *N*-bromosuccinimide[11a,e] (NBS) or *N*-iodosuccinimide (NIS) were first examined. However, it was found that only undesired products including *N*-formylated compounds as major components were isolated. Therefore, the *N,N*-dimethyl group of **9** was oxidized by *m*-chloroperoxybenzoic acid (*m*-CPBA) to give the corresponding *N*-oxide, the second key intermediate **12** in 99% yield. Even the glycosidation to the C3 hydroxyl group of **12** as well as that of **9**, predictively, posed an extremely difficult problem, which was due to the very low reactivity by steric hinderance at the C3 position and the formation of a hydrogen bond between its hydroxyl group and the C1 carbonyl group. Indeed, the glycosidations of **12** with several glycosyl donors, **13**, **14**, **15**, and **16** listed in Figure 2, using a number of appropriate procedures[10c] were not effective and the corresponding glycosylated products were not detected at all or isolated in very low yields. However, in drastic contrast, the glycosidation employing the 2,6-anhydro-2-thio sugar **10** worked very efficiently at this stage. Thus, the glycosidation of **12** (1 equiv) with the 2,6-anhydro-2-thio glycosyl donor **10** (2 equiv) in the presence of NIS, TfOH,[17] and MS 4A in degassed CH_2Cl_2 under argon at -35 °C proceeded very rapidly (10 min) to give the desired α-glycoside **17** in 90% yield with high stereocontrol as the sole isolated product.

With the fully glycosylated molecule **17** in hand, we then attempted the conversion of **17** into **1**. Deisopropylidenation of **17** under mild acidic conditions using 50% AcOH−H_2O afforded **18** in 66% yield with minimal cleavage of the glycoside bond of the 2,6-anhydro-2-thio sugar moiety in **18**. Subsequent treatment of **18** with H_2 in the presence of catalytic amounts of Raney Ni (W4) in EtOH caused the desulfurization of 2,6-anhydro-2-thio sugar, the reduction of *N*-oxide, and the removal of the benzyl and carbomethoxy groups at the same time to give (9*S*)-9-dihydroerythromycin A (**19**) in 54% yield. At this stage, we confirmed that the synthetic sample of **19** was identical to a sample of the naturally derived **19**[18] in all respects, including the stereochemistry of the glycoside bond of the cladinose moiety. To selectively oxidize the C9 hydroxyl group of **19**, the *N,N*-dimethyl group of **19** was again oxidized by *m*-CPBA to afford the corresponding *N*-oxide **20** in 99% yield. After **20** was subjected to many oxidation methods without success, its selective oxidation was eventually achieved under Saigo−Mukaiyama conditions.[19] Thus, treatment of **20** with 1.3 equiv of $(n\text{-}Bu_3Sn)_2O$ and 1.3 equiv of Br_2 in CH_2Cl_2 at 25 °C for 24 h produced the desired C9 keto compound **21**[20] in 58% yield. Finally, the *N*-oxide of **21** was reduced by standard hydrogenolysis using Raney Ni (W4) as a catalyst in EtOH to give **1** in 84% yield. The synthetic substance **1** thus obtained was found to be identical with an authentic sample of natural erythromycin A[21] in all respects.

Olivomycin A Trisaccharide Synthesis. The retrosynthetic analysis of the C-D-E trisaccharide **3** of olivomycin A using 2,6-anhydro-2-thio sugars is as follows. The synthesis of the trisaccharide **3** through the 2,6-anhydro-2-thio trisaccharide **22** would be possible and a good choice for reducing the deprotection steps. The 2,6-anhydro-2-thio-D-sugar **23** was selected for the β-stereoselective couplings of both the C and D sugar residues, and another 2,6-anhydro-2-thio-L-sugar **24** was chosen for the α-stereoselective connection of the E ring moiety. In the present synthesis, cyclohexanol (**25**), a secondary alcohol, was employed as a model alcohol of the aglycon olivin.[22] Furthermore, both key glycosyl donors **23** and **24** were effectively synthesized from the corresponding enantiomers of the 2,6-anhydro-2-thio sugar **26** by modifications and extensions of procedures previously reported from our laboratories.[15b]

We first examined the glycosidation of the C1 acetoxyl 2,6-anhydro-2-thio sugar **23** with cyclohexanol (**25**) (Scheme 2). The glycosyl donor **23** was rapidly prepared from the 2,6-anhydro-2-thio-D-sugar of **26**[15b] by acetolysis using acetic anhydride and TMSOTf. As expected from our preliminary results,[11c,e] it was found that **25** (2 equiv) was smoothly glycosylated with **23** (1 equiv) by using TMSOTf in CH_2Cl_2 at $-40 \rightarrow -20$ °C for 20 min to afford the desired β-glycoside **27** in 90% yield without any chromatographic evidence for the formation of the α-anomer. The coupling constant ($J_{1,2}$ = 3.6 Hz) and no observation of *w*-coupling between H1 and H3 in the ^{1}H-NMR spectrum indicated the β-linked structure **27**.[11e] The inversion of the configuration of the C3 position of the 2,6-anhydro-2-thioaltropyranoside **27** was stereoselectively achieved to give the 2,6-anhydro-2-thiomannopyranoside **30** in the following three steps. Deprotection of the acetyl group at the C3 position of **27** by methanolysis using NaOMe in MeOH,

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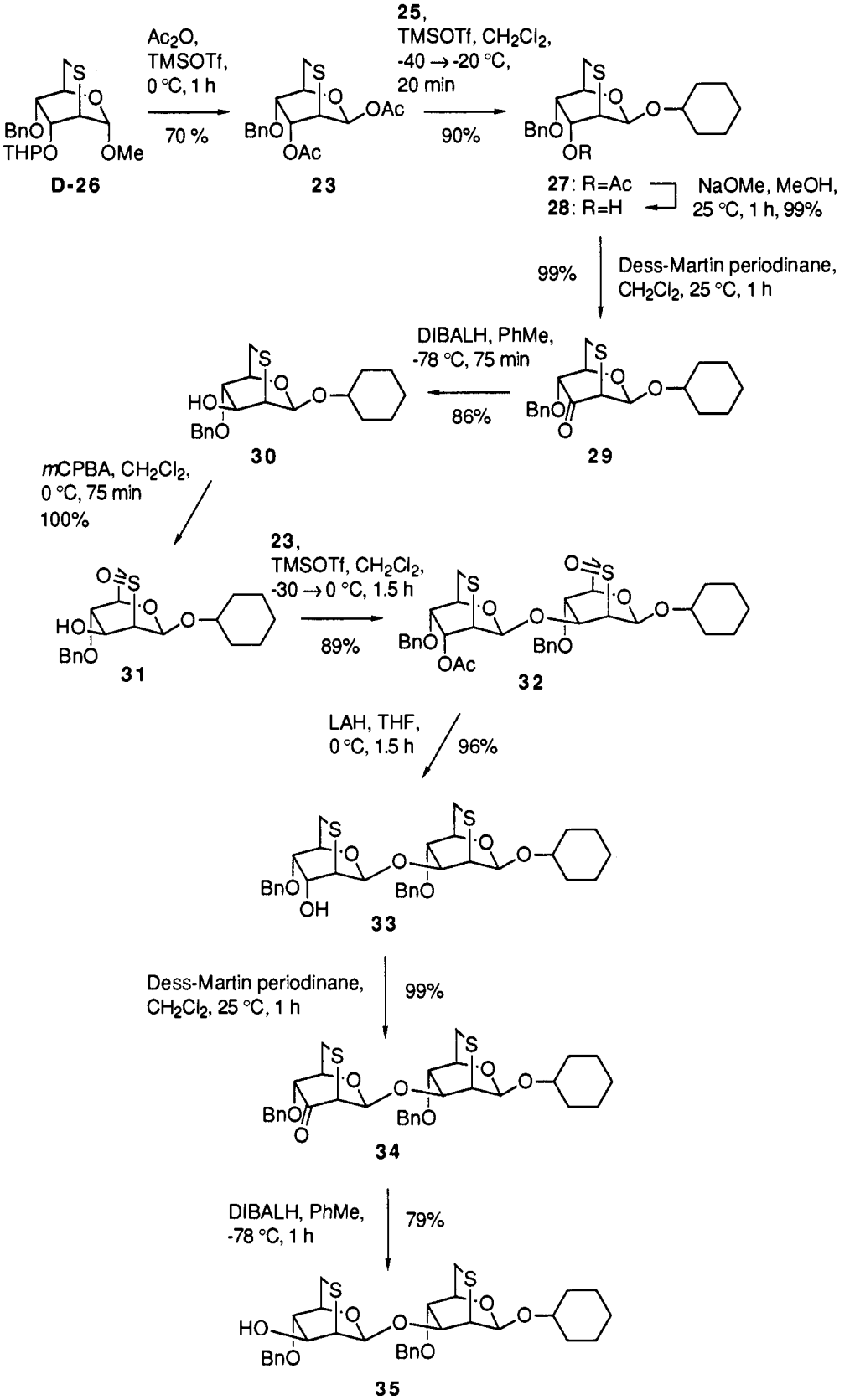
(22) For synthetic studies on olivin and chromomycinone, see: (a) Franck, R. W.; John, T. V. *J. Org. Chem.* **1980**, *45*, 1172. (b) Thiem, J.; Wessel, H. P. *Liebigs Ann. Chem.* **1981**, 2216. (c) Dodd, J. H.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4045. (d) Franck, R. W.; John, T. V. *J. Org. Chem.* **1983**, *48*, 3269. (e) Kraus, G. A.; Hagen, M. D. *J. Org. Chem.* **1983**, *48*, 3265. (f) Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2227. (g) Datta, S. C.; Franck, R. W.; Noire, P. D. *J. Org. Chem.* **1984**, *49*, 2785. (h) Franck, R. W.; Subramaniam, C. S.; John, T. V.; Blount, J. F. *Tetrahedron Lett.* **1984**, *25*, 2439. (i) Dodd, J. H.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811. (j) Franck, R. W.; Bhat, V.; Subramaniam, C. S. *J. Am. Chem. Soc.* **1986**, *108*, 2455. (k) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575. (l) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. (m) Roush, W. R.; Murphy, M. *J. Org. Chem.* **1992**, *57*, 6622.

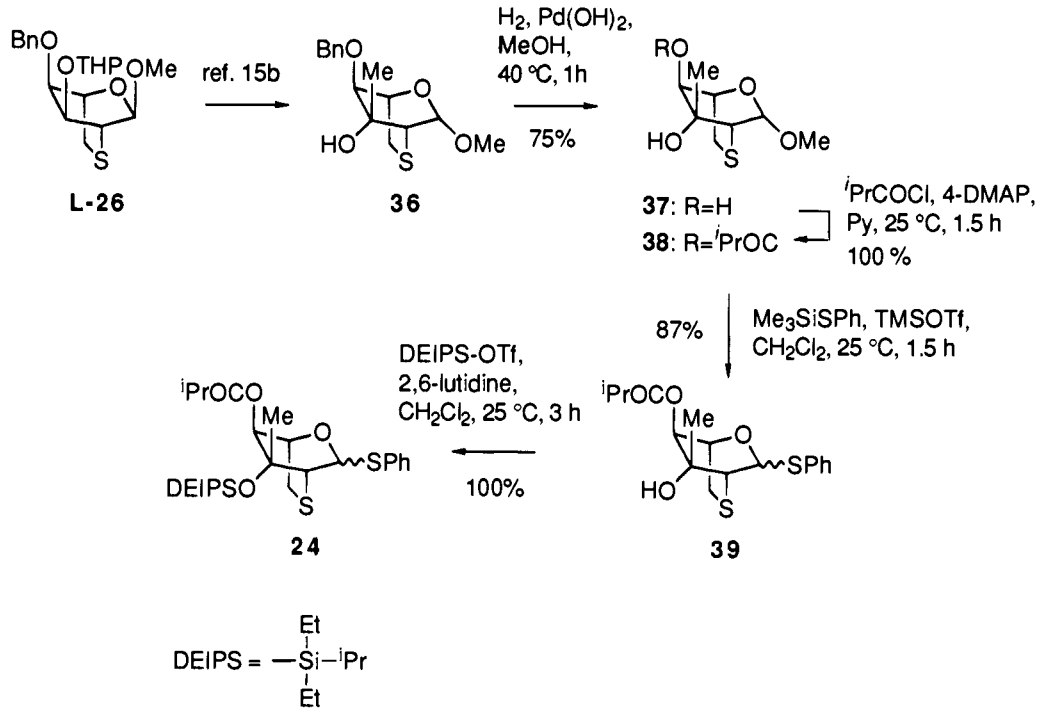
Scheme 2



followed by oxidation of the resulting alcohol **28** using Dess–Martin periodinane[23] in CH_2Cl_2, afforded the C3 keto compound **29** in 98% overall yield. Subsequent hydride reduction of **29** employing 3 equiv of diisobutylaluminum hydride (DIBALH) in toluene at −78 °C proceeded stereoselectively to give the desired **30** in 86% yield along with 6% of the C3 epimer **28**. The high stereoselectivity of the reduction is assumed to result from the repulsive interaction between the sulfur atom in **29** and the approaching hydride species.[15b] At this stage, because the next β-stereoselective glycosidation reaction using **23** with a Lewis acid in CH_2Cl_2 also proceeds under thermodynamic

(23) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

Scheme 3



conditions and is a reversible reaction,[11c,e] we needed to convert the 2,6-anhydro-2-thio glycoside **30** into the corresponding deactivated 2,6-anhydro-2-sulfinyl glycoside **31** by oxidation of the sulfide in **30**.[11d,e] As expected, the *m*-CPBA oxidation of **30** proceeded stereospecifically because of the induction of the hydroxyl group[24] at the C3 position to give the corresponding sulfoxide **31** in quantitative yield. The stereochemistry of the sulfoxide in **31** was clearly determined by its ^{1}H-NMR analysis based on the chemical shifts of H4.[11e,25]

The second glycosidation of the deactivated sugar **31** (1 equiv) with the activated sugar **23** (2 equiv) using TMSOTf that was performed in a manner similar to that for **27** was found to smoothly proceed to produce the 2,6-anhydro-2-thio β-disaccharide **32** in 89% yield without the detectable α-isomer. The disaccharide **32** was next converted into the glycosyl acceptor **35** *via* stereoselective inversion of the C3 position of the D ring by a way similar to that already described. Thus, treatment of **32** with lithium aluminum hydride (LAH) in THF at 0 °C gave the sulfide alcohol **33** in 96% yield followed by the reduction of the sulfoxide of the C ring. Subsequent oxidation of **33** using Dess–Martin periodinane afforded the ketone **34** in 96% yield. Selective reduction of **34** employing DIBALH in toluene at −78 °C also proceeded stereoselectively to give the desired **35** in 79% yield along with 7.6% of the C3′ epimer **33**. At this stage, deactivation of the disaccharide **35** was not necessary because the final α-stereoselective glycosidation reaction of the 2,6-anhydro-2-thio sugar **24** possessing a thiophenyl group utilizing NBS proceeded under kinetic conditions and is an irreversible rather than a reversible reaction.[11a,e]

On the other hand, the E sugar donor **24** was prepared from **36**, which was effectively synthesized from the L-isomer of **26** *via* stereoselective construction of the C3 configuration (Scheme 3).[15b] Thus, debenzylation of **36** by hydrogenolysis using H_2 and 20% $Pd(OH)_2$ on carbon as a catalyst in MeOH gave **37**, which was subjected to selective protection of the C4 hydroxyl group using isobutyryl chloride and a catalytic amount of 4-(dimethylamino)pyridine (4-DMAP) in pyridine to afford **38** in 75% overall yield. The methyl glycoside **38** was then converted into the corresponding thiophenyl glycoside **39** using Nicolaou's method with Me_3SiSPh and TMSOTf in 87% yield as a mixture of the α- and β-anomers in a ratio of 1:3. Silylation of **39** with a diethylisopropylsilyl (DEIPS) group[26–28] gave the glycosyl donor **24** in quantitative yield. In contrast to the corresponding triethylsilyl and *tert*-butyldimethylsilyl ethers, this silyl ether had sufficient stability under the following reactions conditions, while still offering reasonable lability in the final deprotection step using tetrabutylammonium fluoride (TBAF) in THF.

The final α-stereoselective glycosidation of the disaccharide **35** (1 equiv) with the thioglycoside **24** (1.7 equiv, α/β = 1/3) was completed by using NBS and MS 4A in CH_2Cl_2 at −30 → −20 °C for 30 min to give the 2,6-anhydro-2-thio trisaccharide **22** in 89% yield as the sole isolated anomer (Scheme 4). All of the 2,6-anhydro-2-thio systems in **22** were effectively transformed into the desired 2,6-dideoxy structures by hydrogenolysis using Raney Ni (W4) in EtOH–dioxane along with deprotection of two benzyl groups to afford the 2,6-dideoxy trisaccharide **40** in 76% yield. Finally, desilylation of the DEIPS group in **40** employing TBAF in THF furnished the targeted trisaccharide **3** of olivomycin A in high yield with three correct

(24) Henbest, H. B.; Wilson, A. L. *J. Chem. Soc., Chem. Commun.* **1957**, 1958.

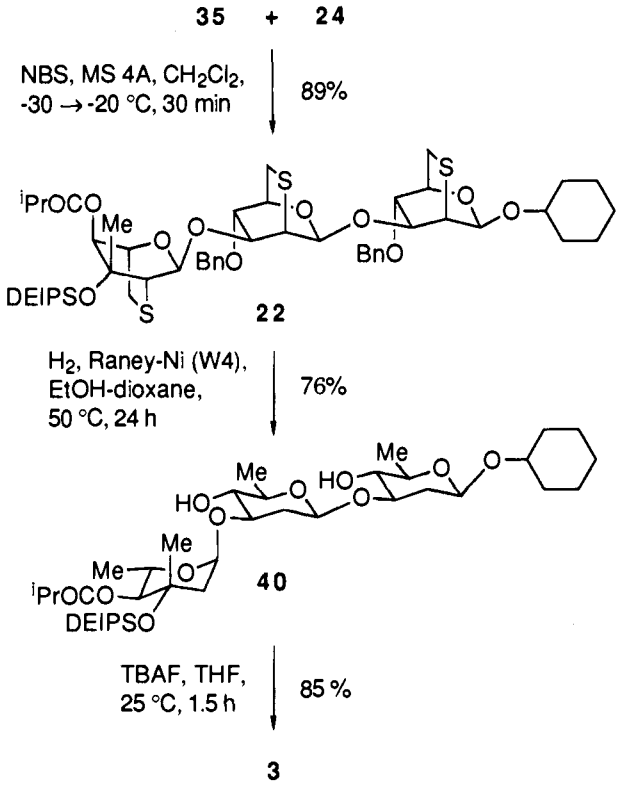
(25) Foster, A. B.; Duxbury, J. M.; Inch, T. D.; Webber, J. M. *J. Chem. Soc., Chem. Commun.* **1967**, 881.

(26) (a) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1986**, *27*, 4741. (b) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369. (c) Toshima, K.; Mukaiyama, S.; Kinoshita, M.; Tatsuta, T. *Tetrahedron Lett.* **1989**, *30*, 6413. (d) Toshima, K.; Misawa, M.; Ohta, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1989**, *30*, 6417. (e) Toshima, K.; Yanagawa, K.; Mukaiyama, S.; Tatsuta, K. *Tetrahedron Lett.* **1990**, *31*, 6697.

(27) For other application of the DEIPS protecting group to natural product synthesis, see: (a) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001. (b) Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5060. (c) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906. (d) Paterson, I.; Tillyer, R. D.; Smaill, J. B. *Tetrahedron Lett.* **1993**, *34*, 7137. (e) Oikawa, H.; Oikawa, M.; Ueno, T.; Ichihara, A. *Tetrahedron Lett.* **1994**, *35*, 4809.

(28) The silylating reagents DEIPS-Cl and DEIPS-OTf are now commercially available from Tokyo Kasei Kogyo Co., Ltd.

Scheme 4



anomeric configurations ($J_{1,2ax}$ and $J_{1',2'ax}$ = or $J_{1',2'ax}$ and $J_{1,2ax}$ = 10.0 and 9.8 Hz, $J_{1'',2''}$ = 3.6 and 2.4 Hz).

Conclusions

The present work provides the highly efficient syntheses of erythromycin A from its aglycon and the trisaccharide of olivomycin A using 2,6-anhydro-2-thio sugars. Remarkably, in both syntheses, the undesirable anomer was not detected in any of the glycosidation reactions. Therefore, these studies also clearly demonstrated the extremely high potentiality and the promising aspects of the glycosidations employing 2,6-anhydro-2-thio sugars in the syntheses of large and complex natural products.

Experimental Section

General Methods. Melting points were determined on a micro hot-stage Yanaco MP-S3. IR spectra were recorded on a Bio-Rad DIGILAB FTS-65 spectrometer. Optical rotations were measured on a JASCO DIP-360 photoelectric polarimeter, and ^{1}H-NMR spectra were measured on a JEOL GSX270 spectrometer in $CDCl_3$ using TMS as the internal standard unless otherwise noted. Silica gel TLC and column chromatography were performed on Merck TLC 60F-254 and Merck Kieselgel 60 or Fuji-Davison BW-820MH, respectively. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, organic solvents were purified and dried by the appropriate procedure and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

(9*S*)-9-Dihydro-3,5-*O*-(*p*-methoxybenzylidene)erythronolide A (5). To a solution of (9*S*)-9-dihydroerythronolide A (**4**) (1.09 g, 2.58 mmol) and *p*-anisaldehyde dimethyl acetal (2.08 mL, 12.9 mmol) in dry CH_2Cl_2 (54 mL) was added DL-10-camphorsulfonic acid (120 mg, 0.516 mmol) at −30 °C with stirring. After the resulting solution was stirred at −30 °C for 72 h, the reaction was quenched with $NaHCO_3$ and then the mixture was filtered. The filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography (130 g of silica gel, 6:1 hexane−acetone) gave **5** (1.21 g, 87%) as white crystals: R_f 0.31 (2:1 hexane−acetone); $[\alpha]^{30}_D$ +5.0° (*c* 0.92, $CHCl_3$); mp 134.0 ~ 135.0 °C (acetone−hexane, needles); ^{1}H-NMR δ 0.87 (3H, t, J = 7.2 Hz), 1.12 (3H, s), 1.14 (3H, d, J = 6.4 hz), 1.23 (3H, d, J = 6.4 Hz), 1.26 (3H, d, J = 6.4 Hz), 1.31 (3H, s), 1.32 (3H, d, J = 6.4 Hz), 1.2−1.6 (3H), 1.7−2.1 (4H, m), 2.38 (1H, d, J = 1.4 Hz), 2.63 (1H, d, J = 5.0 Hz), 2.89 (1H, dq, J = 11.6 and 6.4 Hz), 3.10 (1H, s), 3.14 (1H, m), 3.72 (1H, br s), 3.78 (1H, br d, J = 11.6 Hz), 3.82 (3H, s), 3.93 (1H, br s), 4.19 (1H, d, J = 1.4 Hz), 5.13 (1H, dd, J = 11.0 and 2.4 Hz), 5.60 (1H, s), 6.92 and 7.45 (each 2H, each d, J = 8.5 Hz). Anal. Calcd for $C_{29}H_{46}O_9$: C, 64.66; H, 8.61. Found: C, 64.96; H, 8.55.

(9*S*)-9-Dihydro-9,11-*O*-isopropylidene-3,5-*O*-(*p*-methoxybenzylidene)erythronolide A (6). To a stirred solution of **5** (552 mg, 1.03 mmol) and 2-methoxypropene (0.589 mL, 6.18 mmol) in dry CH_2Cl_2 (11 mL) was added pyridinium *p*-toluenesulfonate (259 mg, 1.03 mmol) under ice-cooling. After the resulting solution was stirred at 25 °C for 1.5 h, the reaction was quenched with $NaHCO_3$ and then the mixture was filtered. The filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography (60 g of silica gel, 3:1 hexane−acetone) gave **6** (596 mg, 100%) as a white foam: R_f 0.40 (3:1 hexane−acetone); $[\alpha]^{30}_D$ +3.5° (*c* 0.98, $CHCl_3$); ^{1}H-NMR δ 0.85 (3H, t, J = 7.4 Hz), 1.16 (3H, d, J = 6.4 Hz), 1.18 (3H, s), 1.25 (3H, d, J = 6.4 Hz), 1.27 (3H, d, J = 6.4 Hz), 1.30 (3H, d, J = 6.4 Hz), 1.32 (3H, s), 1.49 (6H, s), 1.2−1.6 (3H), 1.7−2.05 (3H, m), 2.18 (1H, m), 2.32 (1H, d, J = 1.6 Hz), 2.89 (1H, dq, J = 11.2 and 6.4 Hz), 2.97 (1H, d, J = 0.8 Hz), 3.15 (1H, d, J = 11.4 Hz), 3.62 (1H, d, J = 1.2 Hz), 3.81 (1H, br d, J = 10.3 Hz), 3.82 (3H, s), 4.00 (1H, br s), 5.08 (1H, dd, J = 11.2 and 2.3 Hz), 5.65 (1H, s), 6.92 and 7.43 (each 2H, each d, J = 8.5 Hz).

(9*S*)-9-Dihydro-9,11-*O*-isopropylideneerythronolide A (7). To a solution of **6** (533 mg, 0.920 mmol) in ethyl acetate (11 mL) was added 20% $Pd(OH)_2$ on carbon (266 mg). After the reaction mixture was vigorously stirred at 25 °C for 2 h under H_2, the mixture was filtered and the catalyst was washed with MeOH. The combined filtrate and washings were concentrated *in vacuo*. Purification of the residue by flash column chromatography (45 g of silica gel, 3:1 hexane−acetone) gave **7** (403 mg, 95%) as white needles: R_f 0.43 (2:1 hexane−acetone); $[\alpha]^{30}_D$ +27.0° (*c* 1.00, $CHCl_3$); mp 177.0 ~ 178.0 °C (chloroform−hexane, needles); ^{1}H-NMR δ 0.84 (3H, t, J = 7.6 Hz), 1.00 (3H, d, J = 7.4 Hz), 1.03 (3H, d, J = 7.4 Hz), 1.17 (3H, d, J = 7.4 Hz), 1.19 (3H, s), 1.25 (3H, d, J = 7.4 Hz), 1.27 (3H, s), 1.41 and 1.47 (each 3H, each s), 1.2−1.55 (3H), 1.7−2.05 (3H, m), 2.01 (1H, d, J = 4.4 Hz), 2.19 (1H, m), 2.56 (1H, s), 2.66 (1H, dq, J = 8.2 and 7.4 Hz), 2.78 (1H, d, J = 5.2 Hz), 3.52 (1H, dd, J = 3.4 and 3.4 Hz), 3.58 (1H, dd, J = 4.4 and 4.4 Hz), 3.60 (1H, d, J = 2.8 Hz), 3.89 (1H, m), 5.03 (1H, s), 5.06 (1H, dd, J = 10.6 and 2.4 Hz). Anal. Calcd for $C_{24}H_{44}O_8$: C, 62.58; H, 9.63. Found: C, 62.24; H, 9.40.

(9*S*)-9-Dihydro-9,11-*O*-isopropylidene-5-*O*-(2-*O*-(methoxycarbonyl)-*β*-D-desosaminyl)erythronolide A (9). To an ice-cold suspension of silver triflate (277 mg, 0.884 mmol) and powdered 4A molecular sieves (538 mg) in dry CH_2Cl_2−toluene (1:1) (3.55 mL) were added a solution of **7** (63.7 mg, 0.138 mmol) in dry CH_2Cl_2 (0.3 mL) and a solution of **8** (235 mg, 0.718 mmol) in dry CH_2Cl_2 (1.47 mL) under argon. After the reaction mixture was stirred at 25 °C for 4 h under the dark, the reaction was quenched with saturated aqueous $NaHCO_3$ (4 mL) and then the resulting mixture was extracted with EtOAc (3 mL × 3). The extracts were washed with saturated aqueous NaCl (8 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (10 g of silica gel, 4:1 toluene−acetone) gave **9** (59.1 mg, 63%) as white crystals: R_f 0.48 (1:1 toluene−acetone); $[\alpha]^{30}_D$ +1.7° (*c* 1.15, $CHCl_3$) [lit.[14] $[\alpha]^{31}_D$ +1.0° (*c* 1.14, $CHCl_3$)]; mp 167.5 ~ 169.0 °C (acetone−hexane, flakes) [lit.[14] mp 164−166 °C (1:1 acetone−hexane)]; ^{1}H-NMR δ 0.83 (3H, t, J = 7.6 hz), 0.92 (3H, d, J = 7.4 Hz), 0.97 (3H, d, J = 7.2 Hz), 1.16 (3H, d, J = 6.6 Hz), 1.20 (3H, s), 1.21 (3H, d, J = 6.8 Hz), 1.24 (3H, s), 1.26 (3H, d, J = 6.8 Hz), 1.45 and 1.47 (each 3H, each s), 1.2−1.8 (6H), 1.85−2.0 (2H, m), 2.05−2.3 (2H, m), 2.27 (6H, s), 2.58 (1H, br s), 2.66 (1H, dq, J = 10.2 and 6.8 Hz), 2.76 (1H, ddd, J = 12.5, 9.9, and 4.6 Hz), 3.42−3.58 (3H, m), 3.59−3.68 (2H, m), 3.77 (3H, s), 4.58 (1H, d, J = 9.9 Hz), 4.59 (1H, dd, J = 9.9 and 9.9 Hz), 5.13 (1H, dd, J = 11.6 and 2.3 Hz), 5.26 (1H, s). Anal. Calcd for $C_{34}H_{61}NO_{12}$: C, 60.42; H, 9.10; N, 2.07. Found: C, 60.19; H, 9.22; N, 2.15.

Phenyl 2,6-Anhydro-4-*O*-benzyl-3-*C*-methyl-3-*O*-methyl-1,2-dithio-β-L-altro-pyranoside (10), To a solution of **11** (1.09 g, 3.51 mmol) in dry CH_2Cl_2 (10.5 mL) were added Me_3SiSPh (3.20 mL, 17.6 mmol) and TMSOTf (0.814 mL, 4.23 mmol) at 0 °C under argon. After the resulting solution was stirred at 0 °C for 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and then the mixture was extracted with CH_2Cl_2 (10 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (100 g of silica gel, 4:1 hexane−ethyl acetate) afforded phenyl thioglycoside **10** (1.24 g, 91%) as a colorless oil: R_f 0.40 (4:1 hexane−ethyl acetate); ^{1}H-NMR δ 1.62 (3H, s), 2.58 (1H, dd, J = 11.8 and 3.4 Hz), 3.05 (1H, d, J = 3.4 Hz), 3.40 (3H, s), 3.48 (1H, s), 3.56 (1H, dd, J = 11.8 and 2.8 Hz), 4.33 (1H, dd, J = 3.4 and 2.8 Hz), 4.58 and 4.61 (each 1H, ABq, J = 12.1 Hz), 6.03 (1H, d, J = 3.4 Hz), 7.15−7.4 (8H, m), 7.5−7.6 (2H, m). Anal. Calcd for $C_{21}H_{24}O_3S_2$: C, 64.92; H, 6.23. Found: C, 64.68; H, 6.19.

(9*S*)-9-Dihydro-9,11-*O*-isopropylidene-5-*O*-(2-*O*-(methoxycarbonyl)-β-D-desosaminyl)erythronolide A *N*-Oxide (12), To a stirred solution of **9** (211 mg, 0.311 mmol) in dry CH_2Cl_2 (4.2 mL) was added *m*-chloroperoxybenzoic acid (108 mg, 0.622 mmol) at 25 °C. After the resulting mixture was stirred at 25 °C for 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (8 mL) and then the mixture was extracted with $CHCl_3$ (5 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (5 g of silica gel, 3:1 chloroform−methanol) gave **12** (215 mg, 100%) as colorless glassy solids: R_f 0.28 (5:1 chloroform−methanol); $[\alpha]^{30}_D$ −6.1° (*c* 1.05, $CHCl_3$); mp 136.0 ~ 137.0 °C (chloroform−hexane, flakes); ^{1}H-NMR δ 0.83 (3H, t, J = 7.6 Hz), 0.91 (3H, d, J = 7.6 Hz), 0.97 (3H, d, J = 7.6 Hz), 1.17 (3H, d, J = 6.6 Hz), 1.19 (3H, s), 1.24 (3H, s), 1.26 (3H, d, J = 6.4 Hz), 1.28 (3H, d, J = 6.6 Hz), 1.1−1.8 (5H), 1.85−2.0 (2H, m), 2.05−2.35 (2H, m), 1.45 and 1.47 (each 3H, each s), 2.58 (1H, br s), 2.67 (1H, dq, J = 10.2 and 6.6 Hz), 2.84 (1H, ddd, J = 13.0, 4.8, and 1.6 Hz), 3.09 and 3.26 (each 3H, each s), 3.45−3.75 (6H, m), 3.81 (3H, s), 4.75 (1H, d, J = 6.9 Hz), 4.87 (1H, dd, J = 10.0 and 6.9 Hz), 5.13 (1H, dd, J = 11.2 and 2.3 Hz), 5.24 (1H, s). Anal. Calcd for $C_{34}H_{61}NO_{13}$: C, 59.03; H, 8.89; N, 2.02. Found: C, 58.93; H, 9.03; N, 2.00.

(9*S*)-3-*O*-(2,6-Anhydro-4-*O*-benzyl-3-*C*-methyl-3-*O*-methyl-2-thio-α-L-altropyranosyl)-9-dihydro-9,11-*O*-isopropylidene-5-*O*-(2-*O*-(methoxycarbonyl)-β-D-desosaminyl)erythronolide A *N*-Oxide (17), To a suspension of **12** (76.0 mg, 0.110 mmol), **10** (90.0 mg, 0.232 mmol), and powdered 4A molecular sieves (116 mg) in dry degassed CH_2Cl_2 (1.7 mL) were added NIS (57.0 mg, 0255 mmol) and 0.15 M TfOH−CH_2Cl_2 (1.08 mL, 0.162 mmol) at −35 °C under argon. After the reaction mixture was stirred at −35 °C for 10 min, the mixture was diluted with ether (1.7 mL) and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (20 mL), and then the mixture was extracted with ether (20 mL × 3). The extracts were washed with saturated aqueous NaCl (40 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (20 g of silica gel, 10:1 chloroform−methanol) gave **17** (96.0 mg, 90%) as colorless glassy solids: R_f 0.50 (5:1 chloroform−methanol); $[\alpha]^{30}_D$ −24.4° (*c* 1.05, $CHCl_3$); mp 153.5 ~ 154.5 °C (toluene, needles); ^{1}H-NMR δ 0.83 (3H, t, J = 7.6 Hz), 0.92 (3H, d, J = 7.4 Hz), 0.95 (3H, d, J = 7.4 Hz), 1.12 (3H, d, J = 6.2 Hz), 1.15 (3H, s), 1.16 (3H, d, J = 6.4 Hz), 1.23 (3H, d, J = 7.0 Hz), 1.26 (3H, s), 1.48 and 1.49 (each 3H, each s), 1.55 (3H, s), 1.1−1.65 (4H), 1.8−2.3 (5H, m), 2.53 (1H, dd, J = 11.9 and 3.6 Hz), 2.59 (1H, s), 2.8−2.95 (2H, m), 2.97 and 3.07 (each 3H, each s), 3.08 (1H, dd, J = 11.9 and 2.4 Hz), 3.38 (3H, s), 3.41 (1H, s), 3.5−3.55 (2H, m), 3.68−3.87 (3H, m), 3.78 (3H, s), 4.05−4.2 (1H, m), 4.19 (1H, dd, J = 3.6 and 2.4 Hz), 4.58 and 4.86 (each 1H, ABq, J = 12.2 Hz), 4.82 (1H, dd, J = 10.0 and 7.8 Hz), 5.05 (1H, d, J = 7.8 Hz), 5.11 (1H, dd, J = 11.8 and 2.6 Hz), 5.13 (1H, s), 5.42 (1H, s), 7.2−7.4 (5H, m). Anal. Calcd. for $C_{49}H_{79}NO_{16}S$: C, 60.66; H, 8.21; N, 1.44. Found; C, 60.37; H, 8.10; N, 1.17.

(9*S*)-3-*O*-(2,6-Anhydro-4-*O*-benzyl-3-*C*-methyl-3-*O*-methyl-2-thio-α-L-altropyranosyl)-9-dihydro-5-*O*-(2-*O*-(methoxycarbonyl)-β-D-desosaminyl)erythronolide A *N*-Oxide (18), **17** (96.0 mg, 0.0980 mmol) was dissolved in 50% AcOH−H_2O (2.0 mL), and the resulting solution was warmed at 40 °C for 12 h. The reaction mixture was concentrated *in vacuo*. Purification of the residue by flash column chromatography (20 g of silica gel, 4:1 benzene−methanol) gave **18** (60.2 mg, 66%) as colorless glassy solids: R_f 0.48 (5:1 chloroform−methanol); $[\alpha]^{30}_D$ −24.9° (*c* 0.45, $CHCl_3$); mp 146.0 ~ 147.0 °C (chloroform−acetone, needles); ^{1}H-NMR δ 0.87 (3H, t, J = 7.6 Hz), 0.93 (3H, d, J = 7.4 Hz), 1.05 (3H, d, J = 6.6 Hz), 1.10 (3H, s), 1.15 (3H, d, J = 6.2 Hz), 1.17 (3H, d, J = 7.0 Hz), 1.21 (3H, s), 1.1−2.1 (9H), 1.23 (3H, d, J = 7.2 Hz), 1.56 (3H, s), 2.30 (1H, m), 2.54 (1H, dd, J = 11.8 and 3.6 Hz), 2.75−2.9 (2H, m), 2.93 (1H, s), 3.00 and 3.11 (each 3H, each s), 3.12 (1H, dd, J = 11.8 and 2.8 Hz), 3.31 (1H, m), 3.37 (3H, s), 3.42 (1H, s), 3.63 (1H, s), 3.7−3.95 (4H, m), 3.78 (3H, s), 4.12 (1H, m), 4.20 (1H, dd, J = 3.6 and 2.8 Hz), 4.42 (1H, br s), 4.59 and 4.84 (each 1H, ABq, J = 12.2 Hz), 4.83 (1H, dd, J = 9.8 and 7.7 Hz), 4.93 (1H, dd, J = 10.4 and 2.0 Hz), 5.08 (1H, d, J = 7.7 hz), 5.43 (1H, s), 7.2−7.4 (5H, m). Anal. Calcd for $C_{49}H_{79}NO_{16}S$: C, 59.40; H, 8.13; N, 1.51. Found: C, 59.16; H, 8.01; N, 1.88.

(9*S*)-9-Dihydroerythromycin A (19), To a solution of **18** (119 mg, 0.128 mmol) in EtOH (2.5 mL) was added a catalytic amount of Raney Ni (W4). After the reaction mixture was vigorously stirred at 40 °C for 1.5 h under H_2, the mixture was filtered and the catalyst was washed with MeOH. The combined filtrate and washings were concentrated *in vacuo*. Purification of the residue by flash column chromatography (20 g of silica gel, 3:1 chloroform−methanol) gave **19** (50.8 mg, 54%) as colorless glassy solids: R_f 0.17 (5:1 chloroform−methanol); $[\alpha]^{28}_D$ −46.2° (*c* 0.72, $CHCl_3$); mp 132.5 ~ 133.5 °C (isopropyl alcohol−water, needles), 129.0 ~ 130.0 °C (acetone−hexane, needles) [lit.[18] mp 133 ~ 135 °C (isopropyl alcohol−water)]; ^{1}H-NMR δ 0.89 (3H, t, J = 7.6 Hz), 1.08 (3H, d, J = 6.6 Hz), 1.10 (3H, d, J = 7.4 Hz), 1.11 (3H, s), 1.18 (3H, d, J = 6.8 Hz), 1.21 (3H, d, J = 7.0 Hz), 1.22 (3H, d, J = 6.4 Hz), 1.24 (3H, s), 1.28 (3H, s), 1.31 (3H, d, J = 6.2 Hz), 1.1−1.8 (6H), 1.82−2.07 (3H, m), 2.1−2.42 (3H, m), 2.30 (6H, s), 2.51 (1H, m), 2.75 (1H, dq, J = 6.6 and 6.6 Hz), 2.81 (1H, s), 3.04 (1H, br dd, J = 9.6 and 9.6 Hz), 3.30 (1H, dd, J = 10.2 and 7.7 Hz), 3.31 (3H, s), 3.39 (1H, br), 3.5−3.7 (2H, m), 3.69 (1H, d, J = 5.9 Hz), 3.75 (1H, s), 4.04 (1H, dq, J = 9.6 and 6.4 Hz), 4.10 (1H, dd, J = 6.2 and 2.4 Hz), 4.30 (1H, d, J = 1.6 hz), 4.38 (1H, br), 4.53 (1H, d, J = 7.7 Hz), 4.58 (1H, br), 4.89 (1H, dd, J = 9.8 and 2.6 Hz), 4.97 (1H, br d, J = 4.2 Hz).

(9*S*)-9-Dihydroerythromycin A *N*-Oxide (20), To a stirred solution of **19** (105 mg, 0.143 mmol) in dry CH_2Cl_2 (2.0 mL) was added *m*-chloroperoxybenzoic acid (49.0 mg, 0.286 mmol) at 25 °C. After the resulting mixture was stirred at 25 °C for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and then the mixture was extracted with $CHCl_3$ (7 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (15 g of silica gel, 3:1 chloroform−methanol) gave **20** (107 mg, 99%) as colorless glassy solids: R_f 0.50 (2:1 chloroform−methanol); $[\alpha]^{30}_D$ −57.1° (*c* 0.21, $CHCl_3$); mp 173.0 ~ 174.0 °C (chloroform−hexane); ^{1}H-NMR δ 0.89 (3H, t, J = 7.6 Hz), 1.09 (3H, d, J = 6.4 Hz), 1.10 (3H, s), 1.17 (3H, d, J = 7.0 Hz), 1.19 (3H, d, J = 6.6 Hz), 1.21 (3H, d, J = 6.6 Hz), 1.27 (3H, s), 1.28 (3H, d, J = 6.2 Hz), 1.29 (3H, s), 1.31 (3H, d, J = 6.2 Hz), 1.1−2.2 (10H), 2.3−2.45 (2H, m), 2.67 (1H, s), 2.83 (1H, dq, J = 6.4 and 6.4 Hz), 3.07 (1H, m), 3.20 (3H, s), 3.22 (3H, s), 3.32−3.5 (2H, m), 3.39 (3H, s), 3.62−3.77 (4H, m), 3.80 (1H, dd, J = 10.0 and 7.4 Hz), 4.02 (1H, dq, J = 9.6 and 6.2 Hz), 4.05−4.3 (4H, m), 4.68 (1H, d, J = 7.4 Hz), 4.82 (1H, dd, J = 10.0 and 2.2 Hz), 5.02 (1H, br d, J = 4.2 Hz). Anal. Calcd for $C_{37}H_{69}NO_{14}$: C, 59.10; H, 9.25; N, 1.86. Found: C, 58.75; H, 9.01; N, 1.59.

Erythromycin A *N*-Oxide (21), To a stirred solution of **20** (95.0 mg, 0.126 mmol) in dry CH_2Cl_2 (1 mL) was added bis(tri-*n*-butyltin) oxide (83.0 mg, 0.164 mmol) and 1 M Br_2−CH_2Cl_2 (0.164 mL, 0.164 mmol). After the resulting solution was stirred at 25 °C for 24 h, the mixture was concentrated *in vacuo*. Purification of the residue by flash column chromatography (20 g of silica gel, hexane, and then 4:1 chloroform−methanol) gave **21** (54.8 mg, 58%) as colorless glassy solids: R_f 0.53 (3:1 chloroform−methanol); $[\alpha]^{30}_D$ −82.8° (*c* 0.43, MeOH); mp 222.5 ~ 223.5 °C (methanol−ether) [lit.[20a] mp 218.0 ~ 222.0 °C (methanol−ether)]; ^{1}H-NMR (CD_3OD) δ 0.86 (3H, t, J = 7.8 Hz), 1.10 (3H, d, J = 7.0 Hz), 1.13 (3H, d, J = 7.0 Hz), 1.14 (3H, s), 1.20 (3H, d, J = 6.6 Hz), 1.22 (3H, d, J = 6.2 Hz), 1.25 (3H, d, J

= 6.2 Hz), 1.27 (3H, s), 1.28 (3H, d, J = 6.4 Hz), 1.39 (3H, s), 1.1−1.65 (3H), 1.8−1.95 (2H, m), 2.02 (1H, m), 2.13 (1H, m), 2.43 (1H, m), 2.45 (1H, br d, J = 15.3 Hz), 2.78 (1H, m), 2.92 (1H, dq, J = 9.4 and 7.0 Hz), 3.03 (1H, d, J = 9.9 Hz), 3.11 (1H, dq, J = 8.2 and 7.0 Hz), 3.19 (3H, s), 3.20 (3H, s), 3.37 (3H, s), 3.55 (1H, m), 3.68 (1H, dd, J = 10.4 and 7.0 Hz), 3.80 (1H, m), 3.88 (1H, d, J = 1.8 Hz), 3.95 (1H, d, J = 9.0 Hz), 4.12 (1H, dq, J = 9.9 and 6.2 Hz), 4.20 (1H, br d, J = 8.3 Hz), 4.61 (1H, d, J = 7.0 Hz), 4.91 (1H, br d, J = 4.4 Hz), 5.13 (1H, dd, J = 10.8 and 2.1 Hz). Anal. Calcd for $C_{37}H_{67}NO_{14}$: C, 59.26; H, 9.01; N, 1.87. Found: C, 59.12; H, 9.05; N, 1.89.

Erythromycin A (1), To a solution of **21** (18.0 mg, 0.0254 mmol) in EtOH (0.4 mL) was added a catalytic amount of Raney Ni (W4). After the reaction mixture was vigorously stirred at 25 °C for 1 h under H_2, the mixture was filtered and the catalyst was washed with MeOH. The combined filtrate and washings were concentrated *in vacuo*. The residue was dissolved $CHCl_3$ (4 mL) and washed with H_2O (4 mL). The water layer was extracted with $CHCl_3$ (4 mL × 3), and the extracts were concentrated *in vacuo*. Purification of the residue by flash column chromatography (2.5 g of silica gel, 3:1 chloroform−methanol) gave **1** (15.6 mg, 84%) as white crystals: R_f 0.42 (3:1 chloroform−methanol); $[\alpha]^{30}_D$ −75.4° (*c* 0.99, MeOH); mp 141.0 ~ 142.0 °C (chloroform) [lit.[20a] mp 135 ~ 140 °C (chloroform)]; mixture mp 139.5 ~ 141.5 °C; ^{1}H-NMR δ 0.83 (3H, t, J = 7.6 Hz), 1.11 (3H, d, J = 7.0 Hz), 1.12 (3H, s), 1.13 (3H, d, J = 7.0 Hz), 1.16 (3H, d, J = 7.0 Hz), 1.18 (3H, d, J = 7.0 Hz), 1.22 (3H, d, J = 6.2 Hz), 1.23 (3H, s), 1.28 (3H, d, J = 6.0 Hz), 1.47 (3H, s), 1.1−1.5 (3H, m), 1.57 (1H, dd, J = 15.2 and 4.4 Hz), 1.65−1.77 (2H, m), 1.8−2.1 (4H, m), 2.21 (1H, br d, J = 10.0 Hz), 2.3−2.4 (1H, m), 2.32 (6H, s), 2.49 (1H, m), 2.69 (1H, m), 2.88 (1H, dq, J = 9.2 and 7.0 Hz), 2.95−3.15 (3H, m), 3.24 (1H, dd, J = 10.0 and 7.8 Hz), 3.31 (3H, s), 3.5 (1H, m), 3.58 (1H, d, J = 7.9 Hz), 3.81 (1H, s), 3.90 (1H, br s), 3.99 (1H, dq, J = 9.0 and 6.0 Hz), 4.00 (1H, d, J = 9.3 Hz), 4.41 (1H, d, J = 7.8 Hz), 4.89 (1H, br d, J = 4.6 Hz), 5.03 (1H, dd, J = 11.0 and 2.0 Hz).

1,3-Di-*O*-acetyl-2,6-anhydro-4-*O*-benzyl-2-thio-β-D-altropyranose (23), To a stirred solution of D-**26** (2.58 g, 7.00 mmol) in acetic anhydride (50 mL) was added TMSOTf (0.135 mL, 0.700 mmol) under ice-cooling. After the resulting mixture was stirred under ice-cooling for 1 h, the reaction was made neutral with Et_3N and then the mixture was concentrated *in vacuo*. Purification of the residue by flash column chromatography (200 g of silica gel, 1:2 hexane−ether) gave **23** (1.78 g, 70%) as white crystals: R_f 0.57 (1:2 hexane−ether); $[\alpha]^{32}_D$ +9.6° (*c* 0.67, $CHCl_3$); mp 105.0 ~ 106.0 °C (hexane, needles); ^{1}H-NMR δ 2.09 (3H, s), 2.15 (3H, s), 2.58 (1H, dd, J = 11.9 and 3.0 Hz), 3.14 (1H, dd, J = 4.0 and 3.6 Hz), 3.27 (1H, dd, J = 11.9 and 2.9 Hz), 3.93 (1H, d, J = 8.2 Hz), 4.31 (1H, dd, J = 3.0 and 2.9 Hz), 4.52 and 4.58 (each 1H, ABq, J = 11.6 Hz), 5.62 (1H, dd, J = 8.2 and 4.0 Hz), 6.41 (1H, d, J = 3.6 Hz), 7.24−7.4 (5H, m). Anal. Calcd for $C_{17}H_{20}O_6S$: C, 57.94; H, 5.72. Found: C, 57.79; H, 5.78.

Cyclohexyl 3-*O*-Acetyl-2,6-anhydro-4-*O*-benzyl-2-thio-β-D-altropyranoside (27), To a stirred solution of **23** (32.7 mg, 0.0927 mmol) and cyclohexanol (**25**) (0.019 mL, 0.185 mmol) in CH_2Cl_2 (0.930 mL) was added TMSOTf (0.0197 mL, 0.102 mmol) at −40 °C under argon. After the resulting solution was allowed to warm to −20 °C for 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and then the mixture was extracted with $CHCl_3$ (1 mL × 3). The extracts were washed with saturated aqueous NaCl (3 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (3 g of silica gel, 3:1 hexane−ethyl acetate) gave **27** (32.9 mg, 90%) as a colorless oil: R_f 0.55 (3:1 hexane−ethyl acetate); $[\alpha]^{24}_D$ −18.1° (*c* 0.31, $CHCl_3$); ^{1}H-NMR δ 1.1−2.1 (10H), 2.10 (3H, s), 2.49 (1H, dd, J = 11.9 and 3.4 Hz), 2.92 (1H, dd, J = 3.9 and 3.6 Hz), 3.29 (1H, dd, J = 11.9 and 2.6 Hz), 3.73 (1H, m), 3.90 (1H, d, J = 8.0 Hz), 4.21 (1H, dd, J = 3.4 and 2.6 Hz), 4.51 and 4.58 (each 1H, ABq, J = 11.6 Hz), 5.39 (1H, d, J = 3.6 Hz), 5.59 (1H, dd, J = 8.0 and 3.9 Hz), 7.24−7.4 (5H, m). Anal. Calcd for $C_{21}H_{28}O_5S$: C, 64.26; H, 7.19. Found: C, 64.09; H, 6.92.

Cyclohexyl 2,6-Anhydro-4-*O*-benzyl-2-thio-β-D-altropyranoside (28), To a solution of **27** (240 mg, 0.611 mmol) in dry MeOH (4.8 mL) was added 5 M NaOMe−MeOH (0.183 mL, 0.917 mmol) under ice-cooling. After the resulting solution was stirred at 25 °C for 1 h, the reaction was quenched with solid CO_2 and then the mixture was concentrated. The residue was dissolved in $CHCl_3$ (10 mL) and washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash column chromatography (10 g of silica gel, 3:1 hexane−ethyl acetate) gave **28** (213 mg, 99%) as white crystals: R_f 0.49 (3:1 hexane−ethyl acetate); $[\alpha]^{29}_D$ −23.5° (*c* 0.79, $CHCl_3$); mp 153.0 ~ 153.5 °C (ethyl acetate, needles); ^{1}H-NMR δ 1.1−2.1 (10H), 2.47 (1H, dd, J = 11.9 and 3.4 Hz), 2.99 (1H, dd, J = 4.1 and 3.6 Hz), 3.30 (1H, dd, J = 11.9 and 2.8 Hz), 3.60 (1H, d, J = 4.1 Hz), 3.70 (1H, m), 3.84 (1H, d, J = 8.4 Hz), 4.22 (1H, dd, J = 3.4 and 2.8 Hz), 4.43 (1H, ddd, J = 8.4, 4.1, and 4.1 Hz), 4.69 (2H, s), 5.42 (1H, d, J = 3.6 Hz), 7.25−7.45 (5H, m). Anal. Calcd for $C_{19}H_{26}O_4S$: C, 65.11; H, 7.48. Found: C, 64.93; H, 7.22.

Cyclohexyl 2,6-Anhydro-4-*O*-benzyl-2-thio-β-D-altropyranoside-3-ulose (29), To a stirred solution of **28** (184.2 mg, 0.526 mmol) in CH_2Cl_2 (7.4 mL) was added Dess−Martin periodinane (0.89 g, 2.10 mmol). After the mixture was stirred at 25 °C for 1 h, ether (7.4 mL) and a mixture (7.4 mL) of 7:1 saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ was added to the mixture. The resulting mixture was stirred for 10 min and then extracted with ether (10 mL × 3). The extracts were washed with saturated aqueous NaCl (30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (30 g of silica gel, 3:1 hexane−ethyl acetate) gave **29** (181.3 mg, 99%) as white crystals: R_f 0.40 (3:1 hexane−ethyl acetate); $[\alpha]^{28}_D$ −163° (*c* 1.01, $CHCl_3$); mp 113.5 ~ 114.2 °C (ethyl acetate−hexane, flakes); ^{1}H-NMR δ 1.1−2.1 (10H), 2.72 (1H, ddd, J = 11.9, 3.4, and 0.8 Hz), 3.25 (1H, dd, J = 3.6 and 0.8 Hz), 3.43 (1H, dd, J = 11.9 and 2.4 Hz), 3.76 (1H, m), 4.15 (1H, d, J = 1.4 Hz), 4.43 (1H, ddd, J = 3.4, 2.4, and 1.4 Hz), 4.85 and 5.00 (each 1H, ABq, J = 12.0 Hz), 5.46 (1H, d, J = 3.6 Hz), 7.24−7.4 (5H, m). Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.49; H, 6.94. Found: C, 65.33; H, 6.54.

Cyclohexyl 2,6-Anhydro-4-*O*-benzyl-2-thio-β-D-mannopyranoside (30), To a stirred solution of **29** (188 mg, 0.538 mmol) in dry toluene (1.9 mL) was added 1 M DIBALH−toluene (1.63 mL, 0.163 mmol) at −78 °C. After the resulting solution was stirred at −78 °C for 75 min, the reaction was quenched with saturated aqueous NH_4Cl (2 mL) and then the mixture was allowed to warm to room temperature. The resulting mixture was filtered, and the filter cake was washed with $CHCl_3$. The filtrate and washings were combined and concentrated *in vacuo*. Purification of the residue by flash column chromatography (20 g of silica gel, 3:1 hexane−ethyl acetate) gave **30** (161 mg, 86%) and its C3 epimer **28** (11.3 mg, 6.0%) as white crystals, respectively. **30**: R_f 0.35 (3:1 hexane−ethyl acetate); $[\alpha]^{29}_D$ −42.8° (*c* 0.87, $CHCl_3$); mp 115.5 ~ 116.0 °C (ethyl acetate−hexane, needles); ^{1}H-NMR δ 1.1−2.1 (10H), 2.55 (1H, dd, J = 11.9 and 3.2 Hz), 2.92 (1H, dd, J = 3.2 and 3.0 Hz), 3.03 (1H, d, J = 12.0 Hz), 3.30 (1H, dd, J = 11.9 and 3.0 Hz), 3.46 (1H, d, J = 3.0 Hz), 4.74 (1H, m), 4.08 (1H, ddd, J = 12.0, 3.0, and 3.0 Hz), 4.16 (1H, dd, J = 3.2 and 3.0 Hz), 4.68 and 4.76 (each 1H, ABq, J = 12.1 hz), 5.25 (1H, d, J = 3.2 Hz), 7.24−7.4 (5H, m). Anal. Calcd for $C_{19}H_{26}O_4S$: C, 65.11; H, 7.48. Found: C, 64.78; H, 7.44.

Cyclohexyl 2,6-Anhydro-4-*O*-benzyl-2-sulfinyl-β-D-mannopyranoside (31), To an ice-cold solution of **30** (46.6 mg, 0.133 mmol) in dry CH_2Cl_2 (1 mL) was added *m*-chloroperoxybenzoic acid (22.9 mg, 0.133 mmol) with stirring. After the resulting mixture was stirred under ice-cooling for 75 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and then the mixture was extracted with $CHCl_3$ (1 mL × 3). The extracts were washed with saturated aqueous NaCl (3 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (1 g of silica gel, 2:1 hexane−ethyl acetate) gave **31** (48.7 mg, 100%) as white crystals: R_f 0.22 (2:1 hexane−ethyl acetate); $[\alpha]^{28}_D$ −62.3° (*c* 1.50, $CHCl_3$); mp 104.0 ~ 105.0 °C (ethyl acetate, needles); IR ($CHCl_3$) 1042 cm^{-1} (S=O); ^{1}H-NMR δ 1.1−2.1 (10H), 2.78 (1H, ddd, J = 14.5, 3.0, and 1.6 Hz), 3.64 (1H, m), 3.78 (1H, dd, J = 14.5 and 3.2 Hz), 4.08 (1H, m), 4.22−4.32 (3H, m), 4.44 (1H, dd, J = 3.2 and 3.0 Hz), 4.73 and 4.87 (each 1H, ABq, J = 12.0 Hz), 5.23 (1H, d, J = 4.1 Hz), 7.24−7.4 (5H, m). Anal. Calcd for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15. Found: C, 62.25; H, 7.01.

Cyclohexyl 3-*O*-(3-*O*-Acetyl-2,6-anhydro-4-*O*-benzyl-2-thio-β-D-altropyranosyl)-2,6-anhydro-4-*O*-benzyl-2-sulfinyl-β-D-mannopyranoside (32), To a stirred solution of **31** (107.0 mg, 0.292 mmol) and

23 (206.0 mg, 0.584 mmol) in dry CH_2Cl_2 (5.8 mL) was added TMSOTf (0.113 mL, 0.584 mmol) at −30 °C under argon. After the resulting solution was allowed to warm to 0 °C for 90 min, the reaction was then quenched with saturated aqueous $NaHCO_3$ (6 mL) and then the mixture was extracted with $CHCl_3$ (5 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (30 g of silica gel, 1:2 hexane−ethyl acetate) gave **32** (171.0 mg, 89%) as a colorless oil: R_f 0.40 (1:2 hexane−ethyl acetate); $[\alpha]^{30}_D$ −67.7° (*c* 0.47, $CHCl_3$); IR ($CHCl_3$) 1020 cm^{-1} (S=O); ^{1}H-NMR δ 1.1−1.85 (10H), 2.12 (3H, s), 2.47 (1H, dd, J = 11.9 and 3.0 Hz), 2.68 (1H, dd, J = 14.2 and 2.8 Hz), 3.06 (1H, dd, J = 3.8 and 3.8 Hz), 3.24 (1H, dd, J = 11.9 and 3.0 Hz), 3.62 (1H, m), 3.82 (1H, dd, J = 14.2 and 3.2 Hz), 3.93 (1H, d, J = 8.2 Hz), 4.2−4.25 (2H, m), 4.45 (1H, dd, J = 3.2 and 2.8 Hz), 4.51 and 4.60 (each 1H, ABq, J = 11.8 Hz), 4.53 (1H, d, J = 5.2 Hz), 4.67 (1H, dd, J = 5.2 and 2.0 Hz), 4.77 and 4.89 (each 1H, ABq, J = 11.6 Hz), 5.19 (1H, d, J = 3.8 Hz), 5.6−5.68 (2H, m), 7.2−7.5 (10H, m). Anal. Calcd for $C_{34}H_{42}O_9S_2$: C, 61.99; H, 6.43. Found: C, 61.77; H, 6.29.

Cyclohexyl 2,6-Anhydro-3-*O*-(2,6-anhydro-4-*O*-benzyl-2-thio-β-D-altropyranosyl)-4-*O*-benzyl-2-thio-β-D-mannopyranoside (33), To a stirred solution of **32** (162 mg, 0.246 mmol) in dry THF (3.2 mL) was added 1 M LAH−THF (0.370 mL, 0.370 mmol) under ice-cooling. After the resulting mixture was stirred under ice-cooling for 90 min, the reaction was quenched with water (3 mL). The resulting mixture was filtered, and the filter cake was washed with $CHCl_3$. The filtrate and washings were combined and concentrated *in vacuo*. Purification of the residue by flash column chromatography (5 g of silica gel, 3:1 hexane−ethyl acetate) gave **33** (142.5 mg, 96%) as a white foam: R_f 0.50 (3:1 hexane−ethyl acetate); $[\alpha]^{30}_D$ −76.3° (*c* 0.54, $CHCl_3$); ^{1}H-NMR δ 1.1−2.05 (10H), 2.51 (1H, dd, J = 11.9 and 3.0 Hz), 2.63 (1H, dd, J = 11.4 and 3.0 Hz), 3.05 (1H, dd, J = 3.6 and 2.6 Hz), 3.08 (1H, dd, J = 4.0 and 3.6 Hz), 3.28 (1H, dd, J = 11.9 and 2.8 Hz), 3.29 (1H, dd, J = 11.4 and 2.8 Hz), 3.58 (1H, d, J = 4.0 Hz), 3.72 (1H, m), 3.87 (1H, d, J = 8.0 Hz), 3.89 (1H, d, J = 3.9 Hz), 4.16 (1H, dd, J = 3.0 and 2.8 Hz), 4.26 (1H, dd, J = 3.0 and 2.8 Hz), 4.43 (1H, dd, J = 3.9 and 2.6 Hz), 4.47 (1H, dd, J = 8.0 and 4.0 Hz), 4.70 (2H, s), 4.77 and 4.80 (each 1H, ABq, J = 12.0 Hz), 5.18 (1H, d, J = 3.6 Hz), 5.46 (1H, d, J = 3.6 Hz), 7.2−7.5 (10H, m). Anal. Calcd for $C_{32}H_{40}O_7S_2$: C, 63.98; H, 6.71. Found: C, 64.05; H, 6.36.

Cyclohexyl 2,6-Anhydro-3-*O*-(2,6-anhydro-4-*O*-benzyl-2-thio-β-D-altropyranoside-3-ulosyl)-4-*O*-benzyl-2-thio-β-D-mannopyranoside (34), To a stirred solution of **33** (117.8 mg, 0.196 mmol) in CH_2Cl_2 (4.7 mL) was added Dess−Martin periodinane (0.13 g, 0.295 mmol). After the mixture was stirred at 25 °C for 1 h, ether (4.7 mL) and a mixture (4.7 mL) of 7:1 saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ were added to the mixture. The resulting mixture was stirred for 10 min and then extracted with ether (5 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (10 g of silica gel, 10:1 toluene−ethyl acetate) gave **34** (117.3 mg, 99%) as a white foam: R_f 0.52 (2:1 hexane−ethyl acetate); $[\alpha]^{29}_D$ −136° (*c* 1.38, $CHCl_3$); ^{1}H-NMR δ 1.1−2.1 (10H), 2.63 (1H, dd, J = 11.8 and 3.0 Hz), 2.73 (1H, dd, J = 11.9 and 3.0 Hz), 3.03 (1H, dd, J = 3.6 and 3.6 Hz), 3.31 (1H, dd, J = 11.8 and 2.8 Hz), 3.38 (1H, d, J = 3.6 Hz), 3.41 (1H, dd, J = 11.9 and 2.8 Hz), 3.72 (1H, m), 3.89 (1H, d, J = 4.0 Hz), 4.13 (1H, d, J = 0.8 Hz), 4.20 (1H, dd, J = 3.0 and 2.8 Hz), 4.42−4.5 (2H, m), 4.71 and 4.75 (each 1H, ABq, J = 12.2 Hz), 4.86 and 5.02 (each 1H, ABq, J = 12.0 Hz), 5.17 (1H, d, J = 3.6 Hz), 5.50 (1H, d, J = 3.6 Hz), 7.2−7.5 (10H, m). Anal. Calcd for $C_{32}H_{38}O_7S_2$: C, 64.19; H, 6.40. Found: C, 64.24; H, 6.25.

Cyclohexyl 2,6-Anhydro-3-*O*-(2,6-anhydro-4-*O*-benzyl-2-thio-β-D-mannopyranosyl)-4-*O*-benzyl-2-thio-β-D-mannopyranoside (35), To a stirred solution of **34** (87.8 mg, 0.147 mmol) in dry toluene (1 mL) was added 1 M DIBALH−toluene (0.29 mL, 0.290 mmol) at −78 °C. After the resulting solution was stirred at −78 °C for 60 min, the reaction was quenched with saturated aqueous NH_4Cl (1 mL) and then the mixture was allowed to warm to room temperature. The resulting mixture was filtered, and the filter cake was washed with $CHCl_3$. The filtrate and washings were combined and concentrated *in vacuo*. Purification of the residue by flash column chromatography (5 g of silica gel, 1:1 hexane−ethyl acetate) gave **35** (69.7 mg, 79%) and its C3′ epimer **33** (6.7 mg, 7.6%) as a white foam, respectively. **35**: R_f 0.39 (1:1 hexane−ethyl acetate); $[\alpha]^{29}_D$ −55.0° (*c* 1.05, $CHCl_3$); ^{1}H-NMR δ 1.1−2.1 (10H), 2.60 (1H, dd, J = 11.9 and 3.0 Hz), 2.63 (1H, dd, J = 11.8 and 3.0 Hz), 3.02−3.1 (2H, m), 3.06 (1H, d, J = 12.0 Hz), 3.27 (1H, dd, J = 11.9 and 2.9 Hz), 3.30 (1H, dd, J = 11.8 and 2.9 Hz), 3.49 (1H, d, J = 2.6 Hz), 3.72 (1H, m), 3.87 (1H, d, J = 3.9 Hz), 4.11 (1H, ddd, J = 12.0, 2.8, and 2.6 Hz), 4.18 (1H, dd, J = 3.0 and 2.9 Hz), 4.21 (1H, dd, J = 3.0 and 2.9 Hz), 4.51 (1H, dd, J = 3.9 and 3.0 Hz), 4.68 and 4.78 (each 1H, ABq, J = 12.1 Hz), 4.74 and 4.81 (each 1H, ABq, J = 12.2 Hz), 5.18 (1H, d, J = 3.2 Hz), 5.28 (1H, d, J = 3.0 Hz), 7.2−7.5 (10H, m). Anal. Calcd for $C_{32}H_{40}O_7S_2$: C, 63.98; H, 6.71. Found: C, 63.80; H, 6.76.

Methyl 2,6-Anhydro-3-*C*-methyl-2-thio-β-L-mannopyranoside (37), To a solution of **36** (49.5 mg, 0.167 mmol) in MeOH (1.5 mL) was added 20% $Pd(OH)_2$ on carbon (25 mg). Then the mixture was stirred vigorously at 40 °C for 1 h under H_2 and filtered. The filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography (3 g of silica gel, 7:1 chloroform−methanol) gave **37** (25.8 mg, 75%) as white crystals: R_f 0.14 (1:2 hexane−ethyl acetate); $[\alpha]^{28}_D$ +92.6° (*c* 1.03, $CHCl_3$); mp 115.5 ~ 116.0 °C (ethyl acetate−hexane, needles); ^{1}H-NMR δ 1.43 (3H, s), 2.32 (1H, d, J = 7.4 Hz), 2.71 (1H, dd, J = 11.9 and 2.9 Hz), 2.80 (1H, d, J = 3.2 Hz), 3.28 (1H, dd, J = 11.9 and 2.8 Hz), 3.57 (3H, s), 3.80 (1H, d, J = 7.4 Hz), 3.84 (1H, br s), 4.10 (1H, dd, J = 2.9 and 2.8 Hz), 5.02 (1H, d, J = 3.2 Hz). Anal. Calcd for $C_8H_{14}O_4S$: C, 46.59; H, 6.84. Found: C, 46.59; H, 6.87.

Methyl 2,6-Anhydro-4-*O*-isobutyryl-3-*C*-methyl-2-thio-β-L-mannopyranoside (38), To an ice-cold solution of **37** (57.6 mg, 0.279 mmol) in dry pyridine (1.2 mL) was added isobutyryl chloride (0.0324 mL, 0.307 mmol) and 4-(dimethylamino)pyridine (3.4 mg, 0.0279 mmol). After, the resulting solution was stirred at 25 °C for 90 min and then poured into water (1 mL). The mixture was extracted with $CHCl_3$ (1 mL × 3). The extracts were washed with saturated aqueous NaCl (3 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (1 g of silica gel, 1:1 hexane−ethyl acetate) gave **38** (77.2 mg, 100%) as a colorless oil: R_f 0.48 (1:1 hexane−ethyl acetate); $[\alpha]^{30}_D$ +82.0° (*c* 0.89, $CHCl_3$); ^{1}H-NMR δ 1.21 (3H, d, J = 6.8 Hz), 1.23 (3H, d, J = 6.8 Hz), 1.42 (3H, s), 2.65 (1H, septet, J = 6.8 Hz), 2.79 (1H, dd, J = 11.9 and 3.0 Hz), 2.84 (1H, d, J = 3.5 Hz), 3.27 (1H, dd, J = 11.9 and 2.6 Hz), 3.84 (1H, br s), 4.11 (1H, dd, J = 3.0 and 2.6 Hz), 4.85 (1H, s), 5.04 (1H, d, J = 3.5 Hz). Anal. Calcd for $C_{12}H_{20}O_5S$: C, 52.16; H, 7.29. Found: C, 52.39; H, 7.24.

Phenyl 2,6-Anhydro-4-*O*-isobutyryl-3-*C*-methyl-1,2-dithio-L-mannopyranoside (39). To a stirred solution of **38** (70.4 mg, 0.255 mmol) in dry CH_2Cl_2 (0.8 mL) was added Me_3SiSPh (0.235 mL, 1.28 mmol) and TMSOTf (0.054 mL, 0.281 mmol). After the resulting solution was stirred at 25 °C for 90 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and then the mixture was extracted with $CHCl_3$ (1 mL × 3). The extracts were washed with saturated aqueous NaCl (4 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (5 g of silica gel, 3:1 hexane−ethyl acetate) gave **39** (79.0 mg, 87%, α/β = 1/3) as a colorless oil: R_f 0.43 (3:1 hexane−ethyl acetate); ^{1}H-NMR δ 1.20 (3 × $^3/_4$H, d, J = 6.8 Hz), 1.22 (3 × $^3/_4$H, d, J = 6.8 Hz), 1.23 (3 × $^1/_4$H, d, J = 7.0 Hz), 1.26 (3 × $^1/_4$H, d, J = 7.0 Hz), 1.41 (3 × $^3/_4$H, s), 1.60 (3 × $^1/_4$H, s), 2.55−2.75 (1H, m), 2.91 ($^3/_4$H, dd, J = 11.9 and 3.2 Hz), 2.96 ($^1/_4$H, dd, J = 11.9 and 2.8 Hz), 3.06 ($^1/_4$H, s), 3.08 ($^3/_4$H, d, J = 3.6 Hz), 3.21 ($^1/_4$H, dd, J = 11.9 and 3.0 Hz), 3.65 ($^3/_4$H, dd, J = 11.9 and 3.0 Hz), 3.72 ($^1/_4$H, br s), 3.75 ($^3/_4$H, br s), 4.23 ($^3/_4$H, dd, J = 3.2 and 3.0 Hz), 4.27 ($^1/_4$H, dd, J = 3.0 and 2.8 Hz), 4.78 ($^1/_4$H, s), 4.84 ($^3/_4$H, s), 5.77 ($^3/_4$H, d, J = 3.6 Hz), 5.88 ($^1/_4$H, s), 7.25−7.38 (3H, m), 7.68−7.57 (2H, m). Anal. Calcd for $C_{17}H_{22}O_4S_2$: C, 57.60; H, 6.26. Found: C, 57.50; H, 5.99.

Phenyl 2,6-Anhydro-3-*O*-(diethylisopropylsilyl)-4-*O*-isobutyryl-3-*C*-methyl-1,2-dithio-L-mannopyranoside (24), To a solution of **39** (78.0 mg, 0.220 mmol, α/β = 1/3) in dry CH_2Cl_2 (1.6 mL) were added 2,6-lutidine (0.090 mL, 0.770 mmol) and diethylisopropylsilyl triflate (0.137 mL, 0.0660 mmol). After the resulting mixture was stirred at 25° C for 3 h, the mixture was poured into water (1.5 mL) and then extracted with $CHCl_3$ (1 mL × 3). The extracts were washed with

saturated aqueous NaCl (4 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (5 g of silica gel, 5:1 hexane−ethyl acetate) gave **24** (106 mg, 100%, α/β = 1/3) as a colorless oil: R_f 0.62 (5:1 hexane−ethyl acetate); ^{1}H-NMR δ 0.58 (4H, m), 0.86−1.05 (13H, m), 1.19 (3 × $^3/_4$H, d, J = 6.6 Hz), 1.21 (3 × $^3/_4$H, d, J = 6.6 Hz), 1.22 (3 × $^1/_4$H, d, J = 6.8 Hz), 1.24 (3 × $^1/_4$H, d, J = 6.8 Hz), 1.54 (3 × $^1/_4$H, s), 1.71 (3 × $^3/_4$H, s), 2.55−2.75 (1H, m), 2.96 ($^3/_4$H, dd, J = 11.9 and 3.0 Hz), 2.97 ($^3/_4$H, d, J = 3.6 Hz), 2.97 ($^1/_4$H, s), 3.01 ($^1/_4$H, dd, J = 11.9 and 2.8 Hz), 3.17 (^{1}4H, dd, J = 11.9 and 3.0 Hz), 3.60 ($^3/_4$H, dd, J = 11.9 and 2.9 Hz), 4.17 ($^3/_4$H, dd, J = 3.0 and 2.9 Hz), 4.22 ($^1/_4$H, dd, J = 3.0 and 2.8 Hz), 4.86 ($^1/_4$H, s), 4.92 ($^3/_4$H, s), 5.75 ($^3/_4$H, d, J = 3.6 hz), 5.84 ($^1/_4$H, s), 7.2−7.35 (3H, m), 7.45−7.55 (2H, m). Anal. Calcd for $C_{24}H_{38}O_4S_2Si$: C, 59.71; H, 7.93. Found: C, 59.60; H, 7.78.

Cyclohexyl 2,6-Anhydro-3-*O*-[2,6-anhydro-3-*O*-(2,6-anhydro-3-*O*-(diethylisopropylsilyl)-4-*O*-isobutyryl-3-*C*-methyl-2-thio-β-L-mannopyranosyl)-4-*O*-benzyl-2-thio-β-D-mannosyl]-4-*O*-benzyl-2-thio-β-D-mannopyranoside (22). To a stirred suspension of **35** (27.4 mg, 0.0456 mmol), **24** (38.2 mg, 0.0791 mmol), and powdered 4A molecular sieves (40 mg) in dry CH_2Cl_2 (0.8 mL) was added NBS (15.5 mg, 0.087 mmol) at −30 °C. After the resulting mixture was allowed to warm to −20 °C for 30 min with stirring, the reaction was quenched with aqueous $NaHCO_3$ (1 mL) and then the mixture was extracted with $CHCl_3$ (1 mL × 3). The extracts were washed with saturated aqueous NaCl (4 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (5 g of silica gel, 5:1 hexane−ether) gave **22** (39.0 mg, 89%) as a white foam: R_f 0.60 (1:1 hexane−ether); $[\alpha]^{28}_D$ −54.9° (*c* 0.79, $CHCl_3$); ^{1}H-NMR δ 0.63 (4H, q, J = 7.8 Hz), 0.9−1.05 (13H, m), 1.12 (3H, d, J = 7.0 Hz), 1.17 (3H, d, J = 7.0 Hz), 1.1−2.05 (10H, m), 1.67 (3H, s), 2.54 (1H, septet, J = 7.0 Hz), 2.6−2.7 (3H, m), 2.88 (1H, dd, J = 11.9 and 2.0 Hz), 3.02 (1H, dd, J = 11.9 and 4.0 Hz), 3.07 (1H, dd, J = 3.0 and 3.0 Hz), 3.14 (1H, dd, J = 3.2 and 3.0 Hz), 3.28 (1H, dd, J = 11.9 and 2.8 Hz), 3.30 (1H, dd, J = 11.9 and 2.8 Hz), 3.65−3.75 (1H, m), 3.79 (1H, d, J = 3.2 Hz), 3.87 (1H, d, J = 3.4 Hz), 4.15−4.25 (3H, m), 4.27 (1H, dd, J = 3.0 and 2.8 Hz), 4.49 (1H, dd, J = 3.0 and 2.8 Hz), 4.63 and 4.78 (each 1H, ABq, J = 11.6 Hz), 4.74 and 4.82 (each 1H, ABq, J = 12.1 Hz), 4.75 (1H, br s), 5.18 (1H, d, J = 3.2 Hz), 5.23 (1H, d, J = 3.0 Hz), 5.58 (1H, br s), 7.25−7.5 (10H, m). Anal. Calcd for $C_{50}H_{72}O_{11}S_3Si$: C, 61.70; H, 7.46. Found: C, 61.53; H, 7.10.

Cyclohexyl 2,6-Dideoxy-3-*O*-[2,6-dideoxy-3-*O*-(2,6-dideoxy-3-*O*-(diethylisopropylsilyl)-4-*O*-isobutyryl-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-β-D-*arabino*-hexopyranosyl]-β-D-*arabino*-hexopyranoside (40). To a solution of **22** (30.0 mg, 0.0308 mmol) in EtOH−dioxane (3:1) (0.9 mL) was added a catalytic amount of Raney Ni (W4) under H_2. After the reaction mixture was vigorously stirred at 50 °C for 24 h, the mixture was filtered and the catalyst was washed with EtOH. The combined filtrate and washings were concentrated *in vacuo*. Purification of the residue by flash column chromatography (1 g of silica gel, 3:1 hexane−ethyl acetate) gave **40** (16.5 mg, 76%) as a white foam: R_f 0.46 (3:1 hexane−ethyl acetate); $[\alpha]^{29}_D$ −63.8° (*c* 0.47, $CHCl_3$); ^{1}H-NMR δ 0.60 (4H, q, J = 7.8 Hz), 0.75−1.05 (13H, m), 1.15−2.05 (14H, m), 1.18 (3H, d, J = 6.4 Hz), 1.19 (6H, d, J = 7.0 Hz), 1.35 (3H, d, J = 6.0 Hz), 1.37 (3H, d, J = 6.4 Hz), 1.39 (3H, s), 2.07 (1H, ddd, J = 12.4, 5.4, and 1.8 Hz), 2.22 (1H, ddd, J = 13.0, 5.2, and 1.8 Hz), 2.57 (1H, septet, J = 7.0 Hz), 3.08 (1H, dd, J = 9.0 Hz), 3.10 (1H, dd, J = 9.0 Hz), 3.23 (1H, dq, J = 9.0 and 6.0 Hz), 3.35 (1H, dq, J = 9.0 and 6.4 Hz), 3.35−3.55 (2H, m), 3.57−3.72 (1H, m), 3.92 (1H, dq, J = 9.2 and 6.4 Hz), 4.17 (1H, s), 4.43 (1H, s), 4.52 (1H, dd, J = 9.8 and 1.8 Hz), 4.56 (1H, dd, J = 9.4 and 1.8 Hz), 4.75 (1H, d, J = 9.2 Hz), 4.92 (1H, dd, J = 2.8 and 2.8 Hz). Anal. Calcd for $C_{36}H_{66}O_{11}Si$: C, 61.51; H, 9.46. Found: C, 61.22; H, 9.72.

Cyclohexyl 2,6-Dideoxy-3-*O*-[2,6-dideoxy-3-*O*-(2,6-dideoxy-4-*O*-isobutyryl-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-β-D-*arabino*-hexopyranosyl]-β-D-*arabino*-hexopyranoside (3). To a stirred solution of **40** (24.0 mg, 0.0342 mmol) in dry THF (0.8 mL) was added 1 M *n*-Bu_4NF−THF (0.103 mL, 0.103 mmol). After the resulting solution was stirred at 25 °C for 90 min, the mixture was poured into H_2O (0.6 mL) and then extracted with $CHCl_3$ (1 mL × 3). The extracts were washed with saturated aqueous NaCl (2 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (2 g of silica gel, 1:2 hexane−ethyl acetate) gave **3** (16.6 mg, 85%) as white crystals: R_f 0.42 (1:2 hexane−ethyl acetate); $[\alpha]^{28}_D$ −84.1° (*c* 0.44, $CHCl_3$); mp 181.0 ~ 182.0 °C (hexane, needles); ^{1}H-NMR δ 1.15−2.15 (15H, m), 1.22 (3H, d, J = 7.0 Hz), 1.23 (3H, d, J = 7.0 Hz), 1.24 (3H, d, J = 6.2 Hz), 1.34 (3H, s), 1.36 (3H, d, J = 6.2 Hz), 1.37 (3H, d, J = 6.0 Hz), 2.24 (1H, ddd, J = 12.8, 5.4, and 1.8 Hz), 2.39 (1H, s), 2.64 (1H, septet, J = 7.0 Hz), 3.10 (1H, dd, J = 9.0 and 9.0 Hz), 3.11 (1H, ddd, J = 9.0, 9.0, and 1.4 Hz), 3.23 (1H, dq, J = 9.0 and 6.2 Hz), 3.35 (1H, dq, J = 9.0 and 6.0 Hz), 3.4−3.55 (2H, m), 3.58−3.7 (1H, m), 3.99 (1H, dq, J = 9.4 and 6.2 Hz), 4.04 (1H, d, J = 1.4 Hz), 4.42 (1H, s), 4.52 (1H, dd, J = 10.0 and 2.0 Hz), 4.56 (1H, dd, J = 9.8 and 1.8 Hz), 4.60 (1H, d, J = 9.4 Hz), 5.01 (1H, dd, J = 3.6 and 2.4 Hz). Anal. Calcd for $C_{29}H_{50}O_{11}$: C, 60.61; H, 8.77. Found: C, 60.31; H, 8.53.

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