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THE TOTAL SYNTHESIS OF RIFAMYCIN W#

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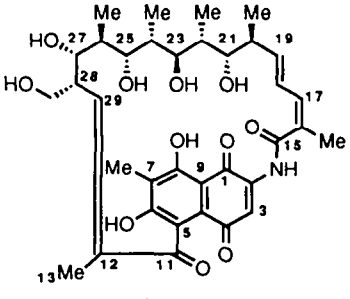
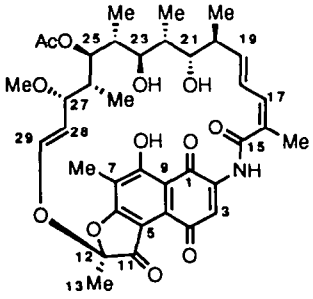
Summary: The first total synthesis of rifamycin W (**1**) has been accomplished by coupling two segments of the aliphatic ansa-chain **40** and the aromatic chromophore **12**. The totally enantiospecific sequence elucidates the configurations of the C28 position and the C12 - C29 double bond to be *R* and *E*, respectively.

Rifamycins,[1] isolated in 1957 by Sensi et al.[2] from the fermentation broths of a strain of *Nocardia mediterranei*, are the first family of ansamycin antibiotics characterized by an aromatic ring system spanned by a long aliphatic bridge, called the "ansa-chain". Among many rifamycins, rifampicin,[3] the hydrazone derivative of 3-formylrifamycin SV, has been discovered as a broad-spectrum antibiotic and is mainly used for the treatment of tuberculosis.

Only the total synthesis of rifamycin S has been accomplished by Kishi and co-workers.[4] During the course of our synthetic studies of rifamycins,[5] we have been interested in rifamycin W (**1**).[6] Rifamycin W (**1**) was isolated from a mutant strain of *Nocardia mediterranei*[6a] and its structure was estimated[6b] on the basis of spectroscopic studies in comparison with rifamycin S. Although the configurations of the C28 position and the C12 - C29 double bond were so far unknown, the isolation of **1** promoted the biosynthetic studies of ansamycins. Rifamycin W (**1**) is transformed by the parent *Nocardia* strain into rifamycin S and is therefore thought to be the biosynthetic intermediate of all the rifamycins.[6a] We wish to describe in this full account[5] the details of the first total synthesis of rifamycin W (**1**) and elucidate the whole stereochemistry of **1** as depicted below.



1 : rifamycin W



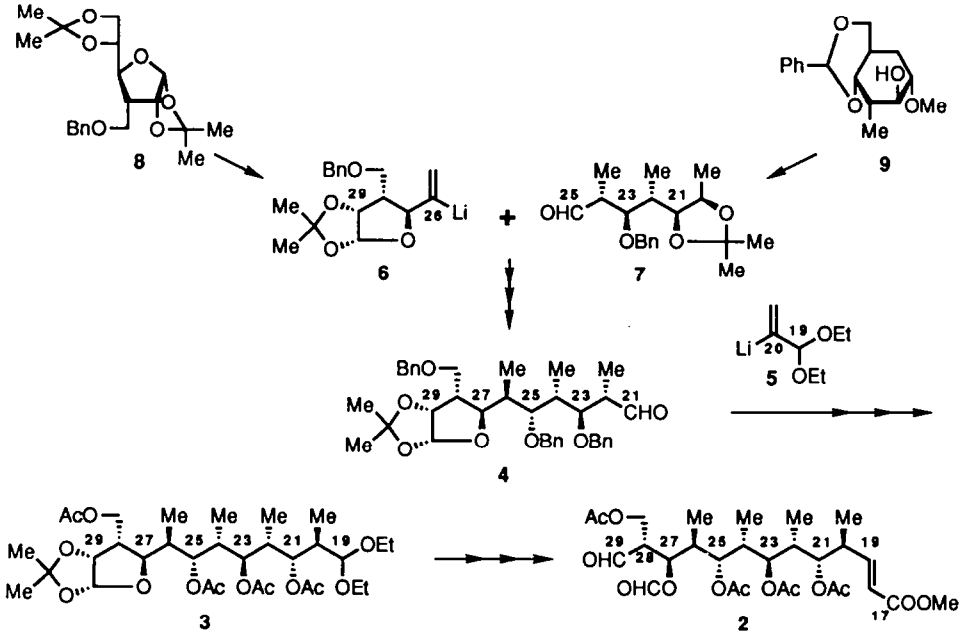
rifamycin S

Dedicated to Professor David Ollis on the occasion of his 65th birthday.

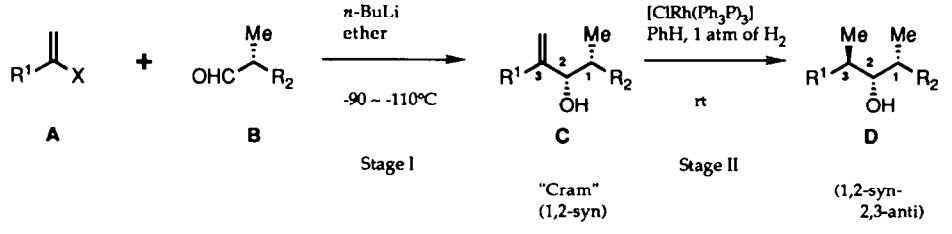
Preliminary Studies

The first crucial step for the synthesis of **1** should be the effectively stereocontrolled enantiospecific construction of the ansa-chain compound. We assumed conveniently the C28-hydroxylmethyl configuration in **1** to be *R* by considering the facility of the synthesis. When the opposite stereochemistry is required, the chemical interchange of the C28-hydroxylmethyl and the C29-aldehydic functionalities in **40** could be considered to be feasible. The selected ansa-chain compound **2** having (28*R*)-configuration was previously synthesized from the sugar derivatives **8** and **9** in our laboratories (Scheme 1).[7] In that synthesis, our developed "two-stage coupling

Scheme 1



Scheme 2

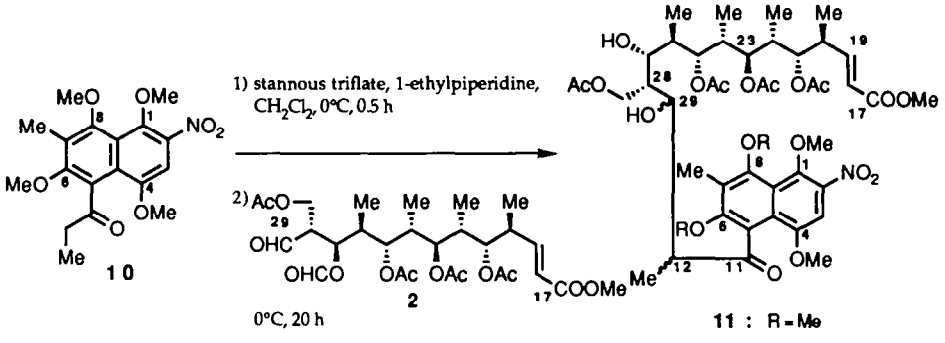


process" played a key role. This new coupling process consists of two consecutive reaction stages (Scheme 2). The first stage is the "Cram (1,2-syn)" selective coupling reaction of a chiral vinyl halide **A** with a chiral α-methyl aldehyde **B** and the second one is the highly 2,3-anti-selective homogeneous hydrogenation of the major Cram type intermediary coupling product **C** with Wilkinson's catalyst. Consequently, the coupling of **A** and **B** by this process affords preferentially the final product **D** having 1,2-syn-2,3-anti configuration. Over the last decade, remarkable progress has been made in the development of stereocontrolled aldol-type reaction.[8] Nevertheless, there have been only a limited number of reports[9] of the aldol reaction which constructs this type of three contiguous stereogenic centers because of the difficulty of effective preparation of *E*-enolate which is indispensable for this purpose. The addition reaction of Hiyama reagent[10a] ($MeCH{=}CHCH_2Br$ - $CrCl_2$) or crotylborane reagents[10b,10c,10d] to the chiral α-methyl aldehydes is one of the alternatives. The another characteristic of our "two-stage coupling process" distinguished from others is that five contiguous stereogenic centers are built up when chiral vinyllithium reagents like **6** are used.[11] Therefore, "two-stage coupling process" is one of the convergent synthetic methods which are the most attractive for the synthesis of the stereochemically complex natural products.

In practice (Scheme 1), the ansa-chain compound **3**, that is the precursor of **2**, was efficiently prepared by sequential coupling of the intermediates **6**,**7**, and **5**.[7]

The next crucial step should be the effective connection between the aliphatic ansa-chain and the aromatic chromophore. We previously succeeded[12] in the coupling between the ansa-chain aldehyde **2** derived from **3** and the Mukaiyama's tin enolate[13] of the aromatic segment **10** to obtain the aldol product **11** as a diastereomeric mixture in 87% yield (Scheme 3). Therefore, an

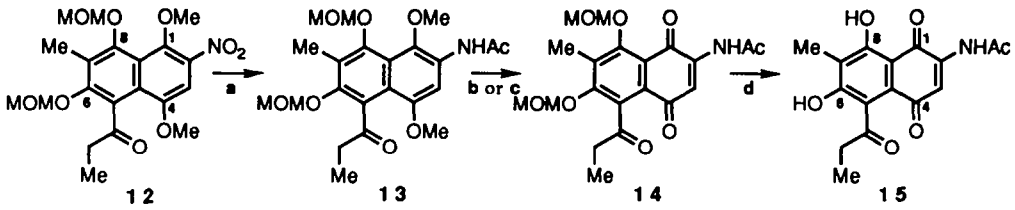
Scheme 3



aldol reaction for construction of the C12 - C29 bond seemed to be an attractive connection method. Although the methoxyl groups at C6[14] and C8 of **10** or **11** are quite stable during the elaboration of **10** or **11** toward the total synthesis of rifamycin W (**1**), the effective ether bond

cleavage (de-O-methylation) of these methoxyl groups would be the crucial problem at the final stage of the conquest of **1**. On the other hand, 1,4-dimethoxyl portions in **10** or **11** could be transformed into the 1,4-naphtoquinone form present in **1** by oxidative demethylation. In this respect, we chose the preparation of **12**[15] having more acid-labile protecting groups at the C6 and C8 portions. However, before carrying out the coupling between the ansa-chain aldehyde and the aromatic chromophore **12**, it might be profitable to investigate whether this aromatic segment **12** could really be transformed into the 6,8-dihydroxy-1,4-naphthoquinone derivative (Scheme 4). The acetamide **13**, prepared from **12** by reduction of nitro group and usual acetylation, was oxidized with ammonium cerium(IV) nitrate (CAN)[16] in aqueous acetonitrile

Scheme 4[a]



[a] (a) H_2, 5% Pd-C, MeOH, 25°C, 15 min; Ac_2O, pyridine, 25°C, 12 h (100%); (b) CAN (2.5 equiv), aq. MeCN, -20°C, 5 min (90%); (c) AgO (4 equiv), 1N aq. HNO_3 (4 equiv), dioxane, 25°C, 1.5 h (92%); (d) 1:1 1N aq. HCl-THF, 25°C, 2 d (100%).

or with silver(II) oxide[17] and nitric acid in dioxane to produce the quinone **14** in 90% or 92% yield, respectively. The methoxymethyl protecting groups in **14** was cleanly cleaved with 1N HCl-THF at room temperature for 2 days to give the desired hydroxyquinone **15** quantitatively. Since rifamycin W itself[18] survived under these conditions, these results encouraged us to pursue the experiments under this strategy.

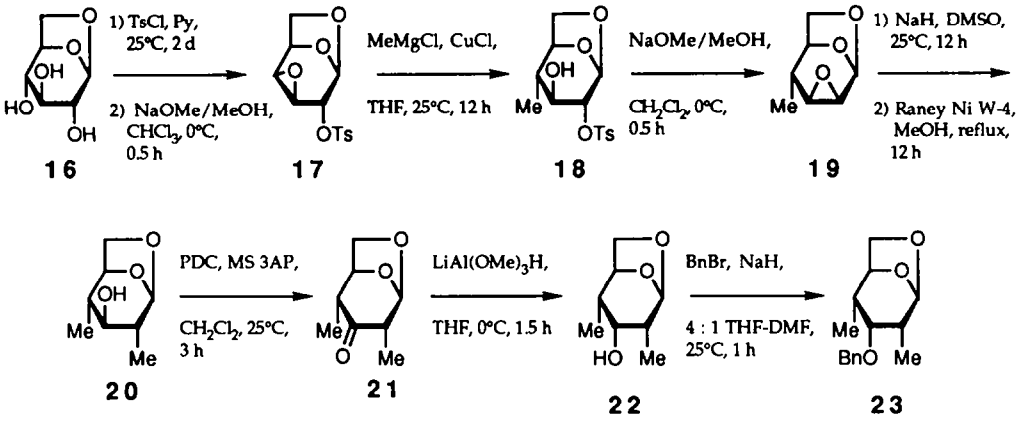
The aldol coupling between **2** and the tin enolate of **12**, unfortunately, gave the coupling products contaminated with the partial de-O-methoxymethylated by-products. At this stage, the other metal enolates were required and, consequently, the other ansa-chain aldehydes were also required to match with the selected metal enolate and to minimize the reaction steps after the coupling of these two segments.

Preparation of the Ansa-chain Compound

As described above, we previously prepared[7] the ansa-chain aldehyde **7**, corresponding to the C21 ~ C25 portion of the ansa-chain of **1**, from methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-altropyranoside **9**.[19] We developed the much more effective new route to the same portion of **1** starting from levoglucosan (**16**).

Readily available levoglucosan (**16**)[20~23] was transformed into **23** by the literature procedures with slight modifications (Scheme 5). Levoglucosan (**16**) was converted via the 2,3-di-

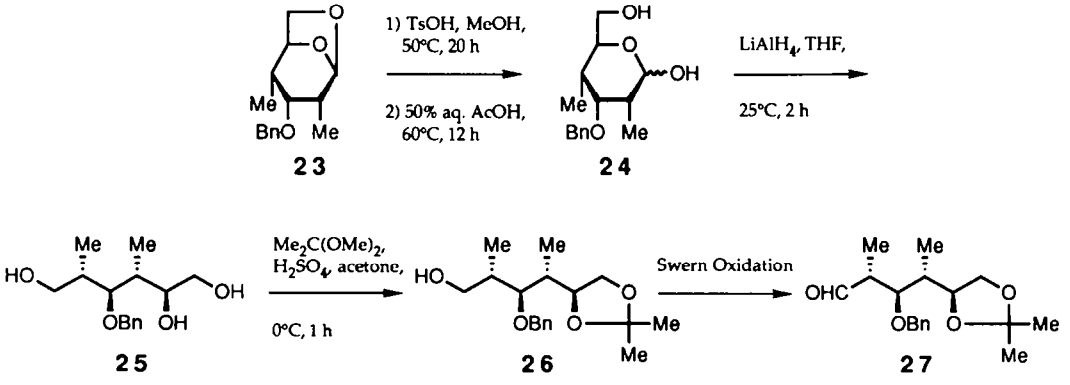
Scheme 5



O-tosylate into the epoxy tosylate **17**.[24] The epoxide ring in **17** was opened stereospecifically by reaction with methylmagnesium chloride-copper(I) chloride[25] in THF to give **18**.[25,26] After base-treatment of **18**, the resultant epoxide **19**[25,26b,26c,26d] was treated[27] with DMSO anion prepared from NaH and DMSO at room temperature for 12 h followed by reductive desulfurization with Raney Ni W-4 in methanol under reflux for 12 h to afford **20**.[26c,26d,27,28] Oxidation of **20** with PDC in the presence of molecular sieves 3A powder (MS 3AP) in CH_2Cl_2 to give the ketone **21**.[26c] Clean reduction[29] of **21** with lithium trimethoxyaluminohydride[30] in THF furnished **22**[26c] as a sole product in 97% yield from **20**. Benzylation of **22** with NaH and benzyl bromide in THF-DMF afforded **23**[31] in quantitative yield.

The 1,6-ether bond in **23** was most effectively cleaved by successive treatment with *p*-toluenesulfonic acid in methanol and 50% aqueous acetic acid at 60°C for 12 h to afford **24** in 93% yield (Scheme 6). $LiAlH_4$ reduction of **24** in THF at 0°C gave the triol **25** in 92% yield, which was

Scheme 6

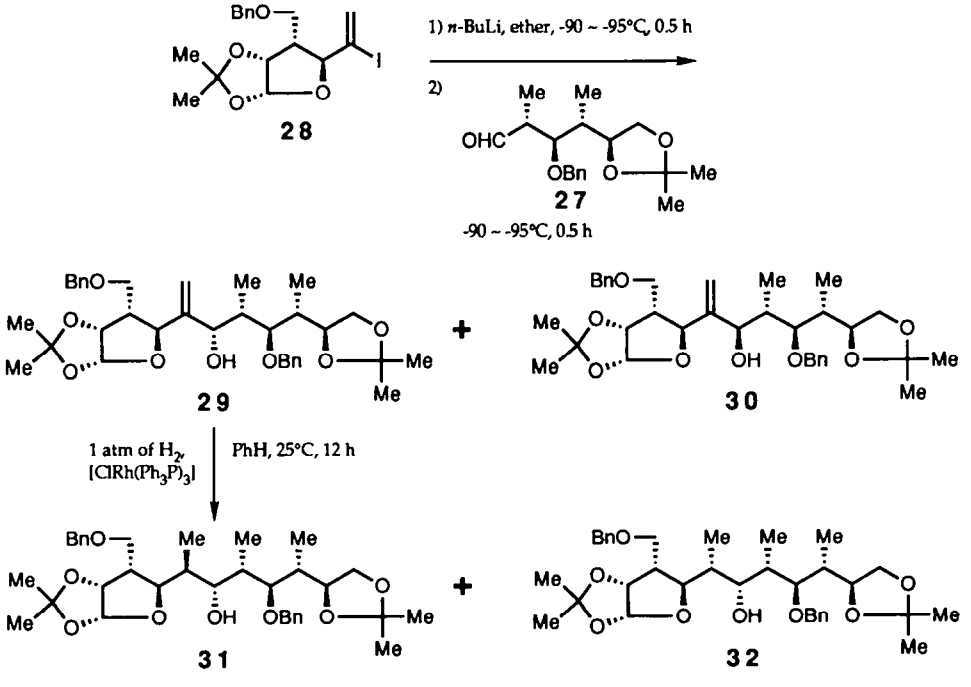


acetonized with 2,2-dimethoxypropane and a catalytic amount of sulfuric acid in acetone to give **26** in 97% yield. Swern oxidation of **26** furnished the desired aldehyde **27** in quantitative yield.

With the aldehyde **27** corresponding to the C21 ~ C25 portion of rifamycin W (**1**) now in hand, the next stage was its elaboration to the key intermediate **3** using our "two-stage coupling process". This was accomplished by conceptually similar route to the previous synthesis of **3**.[7]

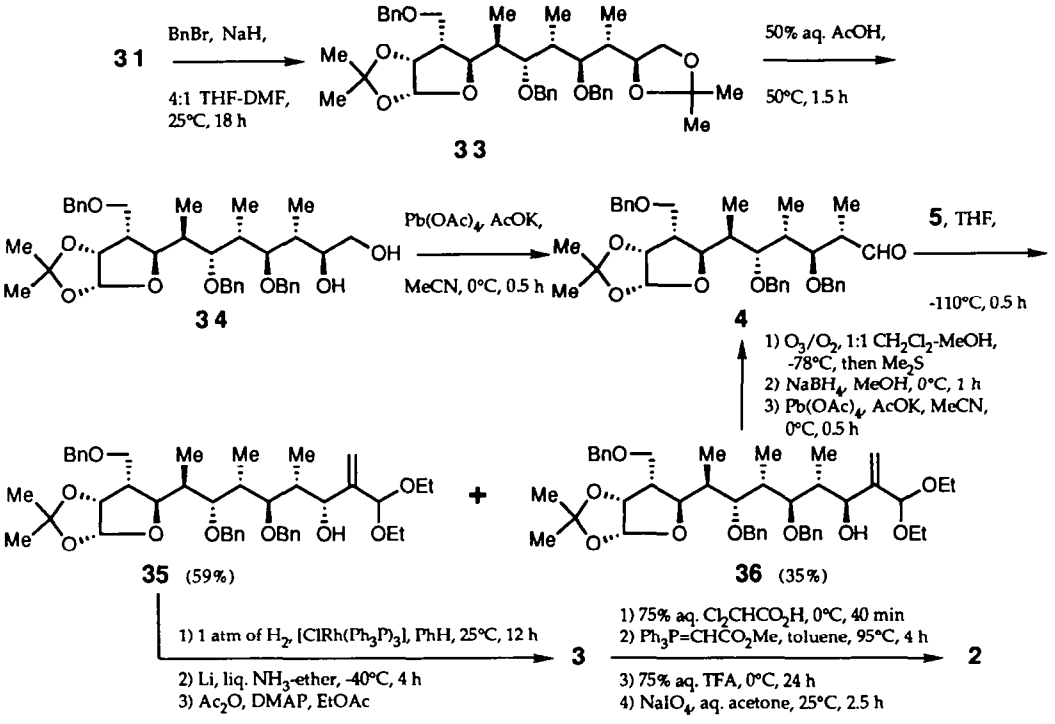
A 1.9M ethereal solution of **28**[7] (3 equiv) was lithiated with 3 equiv of *n*-butyllithium at -90 ~ -95°C for 0.5 h under argon. To this was added a 0.3M ethereal solution of **27** (1 equiv) and stirred at -90 ~ -95°C for 0.5 h. Quenching with saturated aqueous NH_4Cl followed by chromatographic isolation afforded the major coupling product **29** (61% yield from **27**) and the minor one **30** (2.65% yield from **27**). The homogeneous hydrogenation of **29** with 0.25 equimolar amount of chlorotris(triphenylphosphine)rhodium(I) in benzene under an atmospheric pressure of hydrogen gave the hydrogenated product **31** and **32** in 90% and 3.6% yield, respectively. We could confidently predict the structures of **29**, **30**, **31**, and **32** as depicted in Scheme 7 by considering generality of our "two-stage coupling process". This prediction was confirmed in the later stage of this synthesis.

Scheme 7



Benzylation of **31** followed by the selective deacetonization of the resultant benzyl ether **33** afforded **34** in 78% yield (two steps) (Scheme 8). Oxidative cleavage of the glycol function of **34** with lead tetraacetate provided the aldehyde **4** in 98% yield. The ^1H NMR spectrum and TLC

Scheme 8



mobilities of **4** were identical with those of the authentic sample.[7] This result established the structures of **29** ~ **32**. The aldehyde **4** could be transformed into the key intermediate **2** by the same procedure as previously reported.[7,32] In these transformations, we found that the undesired minor product **36** obtained from the coupling between **4** and **5** could be transformed to **4** by a three-step sequence in 78% yield. This aldehyde **4** was again subjected to the coupling with **5**, raising the yield of **35** from **4** to 75%.

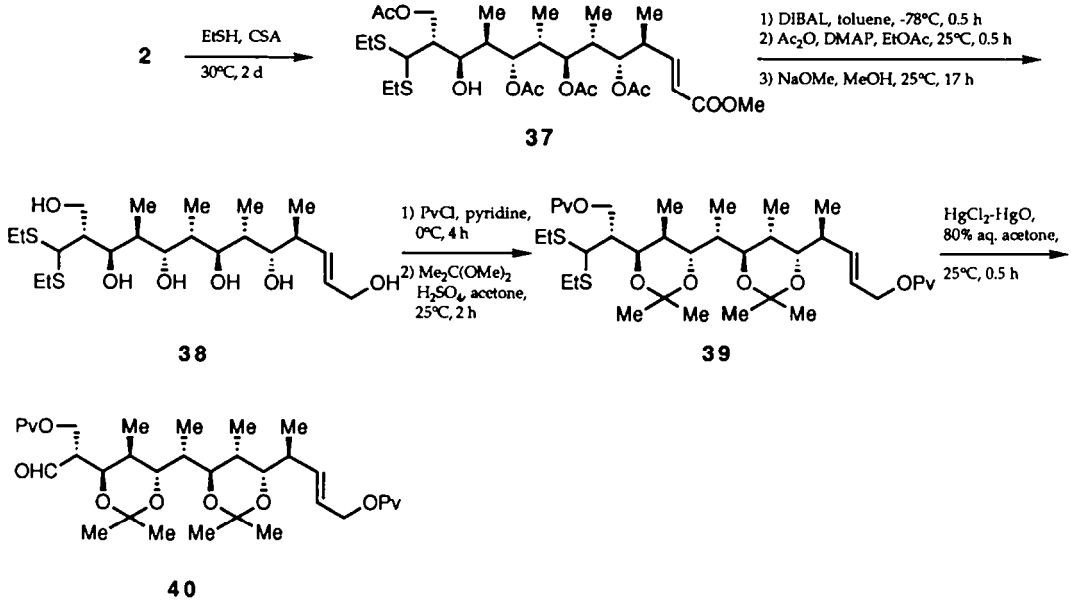
Coupling of the Ansa-chain Compound and the Aromatic Chromophore

With the aldehyde **2** in hand, we turned our attention to the elaboration to the ansa-chain aldehyde suitable for the coupling with the new aromatic chromophore **12**.

Treatment of **2** with ethanethiol and a catalytic amount of camphorsulfonic acid gave the de-O-formylated dithioacetal **37** in 70% yield (Scheme 9). Reduction of **37** with excess diisobutylaluminum hydride in toluene at -78°C gave, with partial de-O-acetylation, the crude allylic alcohol, which was totally acetylated for the convenient isolation and purification.

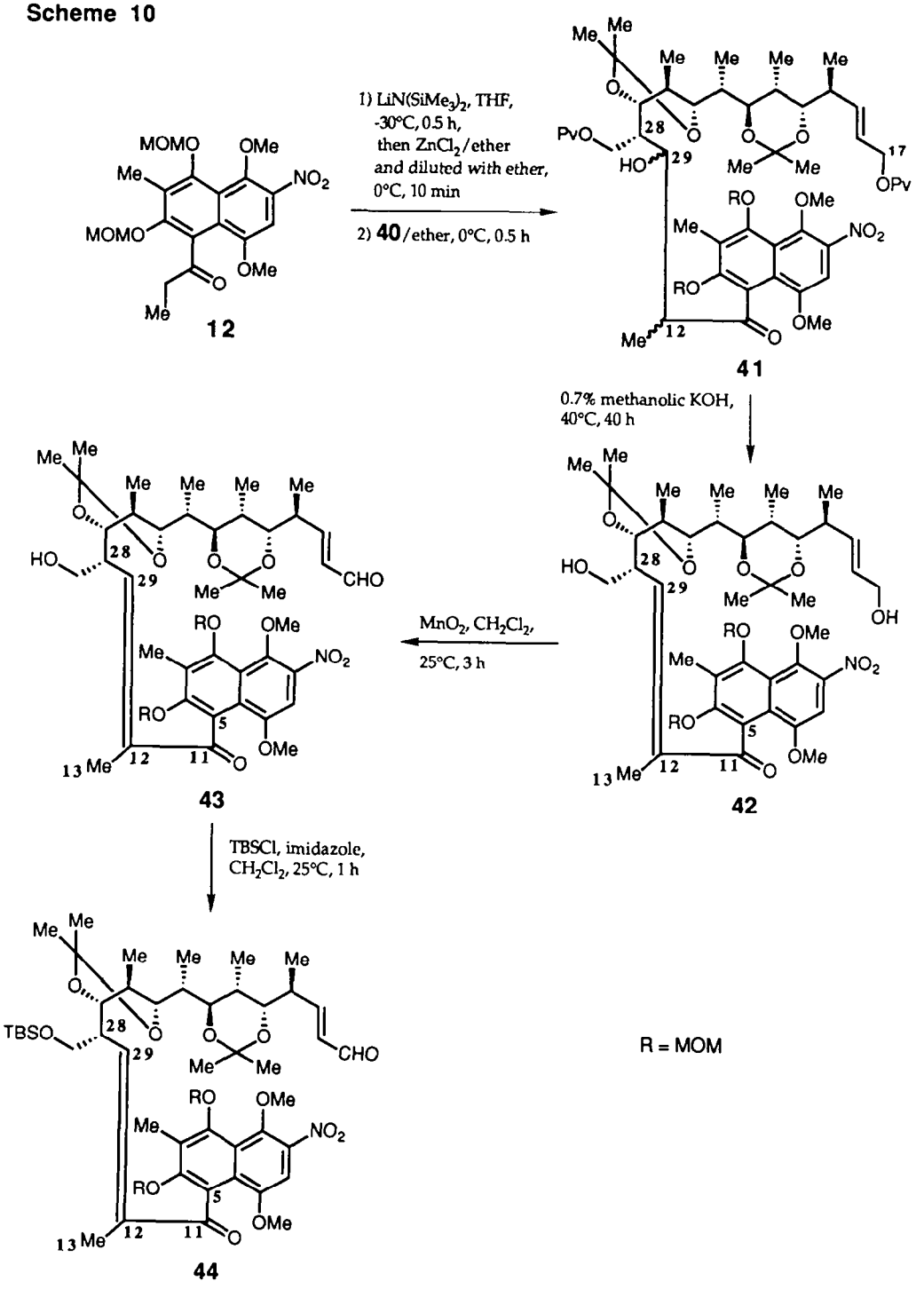
Hydrolysis of the acetate groups gave the pure hexaol **38** in 95% yield from **37**. After pivaloylation of the two primary hydroxyl groups in **38** with pivaloyl chloride in pyridine at 0°C, the resultant tetraol was acetonized with 2,2-dimethoxypropane in acetone containing a catalytic amount of sulfuric acid afforded **39** in 81% yield. Dethioacetalization of **39** with $HgCl_2$-HgO in aqueous acetone furnished the new ansa-chain aldehyde **40** in quantitative yield.

Scheme 9

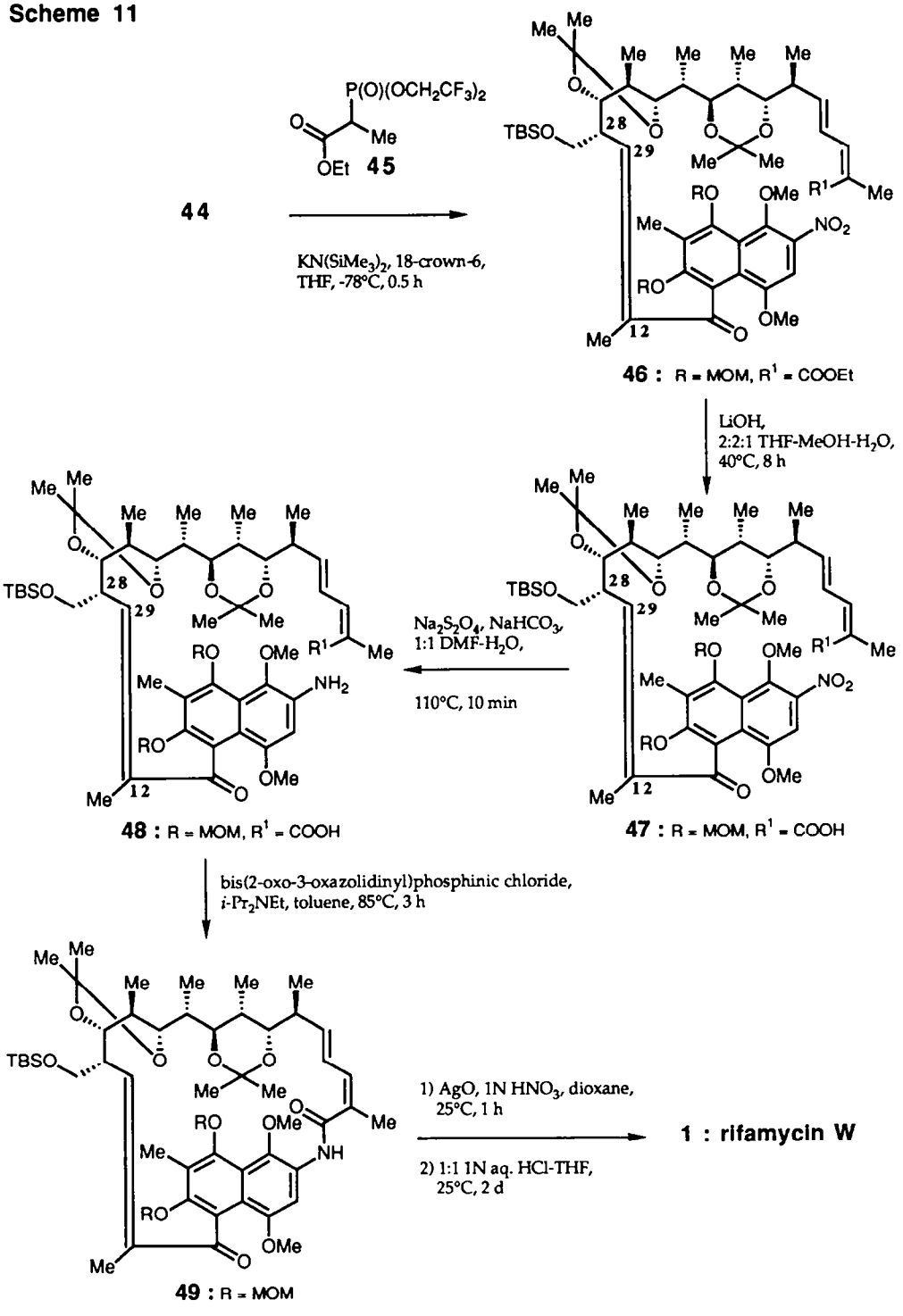


The stage was now set for us to examine the coupling reaction between the ansa-chain aldehyde and the aromatic chromophore (Scheme 10). Originally, the coupling was conducted under the conditions including a lithium enolate, which was prepared from **12** and lithium bis(trimethylsilyl)amide in THF, and the aldehyde **40** to give the product **41**. However, the yield of **41** was varied and low (20 ~ 45%). After many unsuccessful trials, we found that the House's aldol conditions[33] gave the satisfactory results with good reproducibility. Namely, anhydrous zinc chloride (3 equiv) in ether was added at -30°C to a THF solution of a lithium enolate of **12**, which was prepared from **12** (3 equiv) and lithium bis(trimethylsilyl)amide (3 equiv) at -30°C for 0.5 h. After dilution with ether[34] and 10 min stirring at 0°C, the aldehyde **40** (1 equiv) in ether was added to the resultant zinc enolate of **12**. After 0.5 h at 0°C, usual work-up and silica-gel chromatographical purification gave a mixture of the two separable adducts **41** in a ratio of 7 : 1 in 86% combined yield. The major adduct was still a 1.2 : 1 inseparable mixture, whereas the minor one was a 3 : 1 inseparable mixture. The stereochemistry of these four isomers has not been determined. Both the separated adducts were independently dehydrated with 0.7% methanolic KOH at 40°C for 40 h to afford the same α,β-unsaturated ketone **42** in 85% yield. The

Scheme 10


1) LiN(SiMe3)2, THF, -30°C, 0.5 h, then ZnCl2/ether and diluted with ether, 0°C, 10 min
2) 40/ether, 0°C, 0.5 h
12
41
0.7% methanolic KOH, 40°C, 40 h
42
MnO2, CH2Cl2, 25°C, 3 h
43
TBSCl, imidazole, CH2Cl2, 25°C, 1 h
44
R = MOM

Scheme 11


P(O)(OCH2CF3)2
OEt 45
44
KN(SiMe3)2, 18-crown-6,
THF, -78°C, 0.5 h
46 : R = MOM, R1 = COOEt
LiOH,
2:2:1 THF-MeOH-H2O,
40°C, 8 h
47 : R = MOM, R1 = COOH
Na2S2O4, NaHCO3,
1:1 DMF-H2O,
110°C, 10 min
48 : R = MOM, R1 = COOH
bis(2-oxo-3-oxazolidinyl)phosphinic chloride,
i-Pr2NEt, toluene, 85°C, 3 h
49 : R = MOM
1) AgO, 1N HNO3, dioxane,
25°C, 1 h
2) 1:1 1N aq. HCl-THF,
25°C, 2 d
1 : rifamycin W

^{1}H NMR spectrum, however, showed that **42** consisted of a 3 : 1 inseparable mixture. In order to determine the stereochemistry of the C12 - C29 double bond in **42**, NOE experiments were conducted. Thus, irradiation of the singlets at 2.05 and 2.09 ppm, corresponding to the methyl-13 groups of the major and the minor **42**, respectively, caused no NOE enhancement of the olefinic region at 5.60 ~ 6.00 ppm. This implies that the configuration of the C12 - C29 double bond in **42** is *E*. The ^{1}H NMR studies of natural rifamycin W (**1**) in our hands revealed no NOE between Me-13 and H-29 resonances, showing the *E*-configuration of the C12 - C29 double bond in **1**. Therefore, it is reasonable to assume that this inseparable mixture should be due to the atropisomers because of hindered rotation around the C5 -C11 bond.[35] On the basis of molecular model studies, we expected that the free rotation about the C5 - C11 bond would be possible after the aromatic portion was transformed into the intact structure present in **1**.

Final Stage

Oxidation of allylic alcohol **42** with MnO_2 in CH_2Cl_2 at room temperature followed by silylation of the resultant allylic aldehyde **43** with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in CH_2Cl_2 gave **44** in 86% yield from **42**. Still's olefination[36] of **44** using **45** and potassium bis(trimethylsilyl)amide with 18-crown-6 in THF at -78°C gave the desired (*Z*,*E*)-diene ester **46** in 82% yield as a sole product (Scheme 11). Hydrolysis of **46** with LiOH in 2 : 2 : 1 THF-MeOH-H_2O at 40°C for 8 h afforded the carboxylic acid **47** in 98% yield. Selective reduction of the nitro group in **47** was a troublesome step. Of a variety of conditions, sodium dithionite reduction[37] in DMF-H_2O at 110°C gave the best result (quantitative yield). The resultant unstable aminocarboxylic acid **48** was readily cyclized under the Baker's conditions[38] using bis(2-oxo-3-oxazolidinyl)phosphinic chloride and diisopropylethylamine in toluene at 85°C for 3 h to afford the labile product, which was immediately oxidized with AgO[17] in dioxane using nitric acid as a initiator followed by deprotection with 1N aqueous HCl in THF at 25°C for 2 days to afford rifamycin W (**1**) in 30% yield from **47**. As expected, both atropisomers of **42** were converged into the single isomer **1**. All data including ^{1}H NMR, IR, UV spectra and TLC mobility were identical with those of natural rifamycin W.[6b,18] This goal indicates that the configurations of the C28 position having a hydroxylmethyl group and the C12 - C29 double bond are *R* and *E*, respectively.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 photoelectric polarimeter in chloroform unless otherwise noted. IR spectra were recorded on a BIO RAD DIGILAB FTS-65 spectrometer and ^{1}H NMR spectra were on either a JEOL GSX270 or a JEOL GSX400 spectrometer in $CDCl_3$ using TMS as internal standard unless otherwise noted. Mass spectra were recorded on a JEOL JMS-DX302 mass spectrometer. Silica-gel TLC and column chromatography were performed on Merck TLC 60F-254 and Merck Kieselgel 60 or 100, 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.

1,6-Anhydro-2,4-dideoxy-2,4-di-*C*-methyl-β-D-allopyranose (22).[26c] To a stirred solution of lithium trimethoxyaluminohydride in dry THF [prepared from 13.1 g (345 mmol) of $LiAlH_4$ and 41.8 ml (1.03 mol) of MeOH in 512 ml of dry THF][30] at 0°C was added a solution of **21**[26c] (10.8 g, 69.2 mmol; prepared from **20** by PDC oxidation in CH_2Cl_2 in the presence of MS 3AP) in dry THF (54 ml). After 1.5 h at 0°C, water (13.2 ml), 10% aqueous NaOH (20 ml), and water (34 ml) were carefully added to the ice-cooled reaction mixture. The insoluble materials were filtered with Celite and washed with ethyl acetate. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (160 g) with 1:1 hexane-ethyl acetate to afford **22** (10.6 g, 97%) as a colorless syrup: Rf = 0.46 (10:1 chloroform-MeOH); ^{1}H NMR δ 1.02 (3H, d, 2-Me, J=7.3Hz), 1.16 (3H, d, 4-Me, J=7.3Hz), 1.50 (1H, d, 3-OH, J=6.8Hz), 1.97 (1H, ddq, H-4, $J_{3,4}$=6.8, $J_{4,5}$=1.0, and $J_{4,Me}$=7.3Hz), 2.11 (1H, ddq, H-2, $J_{1,2}$=2.0 and $J_{2,3}$=$J_{2,Me}$=7.3Hz), 3.74 (1H, dd, H-6, $J_{5,6}$=5.4 and $J_{6,6'}$=7.3Hz), 3.80 (1H, dd, H-6', $J_{5,6'}$<1.0 and $J_{6,6'}$=7.3Hz), 4.19 (1H, ddd, H-3, $J_{2,3}$=$J_{3,4}$=$J_{3,OH}$=6.8Hz), 4.35 (1H, br d, H-5, J=5.4Hz), and 5.33 (1H, d, H-1, $J_{1,2}$=2.0Hz).

1,6-Anhydro-3-*O*-benzyl-2,4-dideoxy-2,4-di-*C*-methyl-β-D-allopyranose (23).[31] To a stirred solution of **22** (8.81 g, 55.7 mmol), benzyl bromide (13.2 ml, 111 mmol) in dry THF (53 ml) and dry DMF (13 ml) at 0°C was added portionwise NaH (4.01 g, 167 mmol). After 1 h at 25°C, ethanol (7.43 ml) was added carefully to the ice-cooled reaction mixture. The mixture was poured into water (200 ml) and extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (400 g) with 24:1 chloroform-ethyl acetate to afford **23** (13.8 g, 100%) as a coloress syrup: Rf = 0.86 (1:1 hexane-ethyl acetate); ^{1}H NMR δ 1.06 (3H, d, 2-Me, J=7.3Hz), 1.21 (3H, d, 4-Me, J=7.3Hz), 2.07 (1H, ddq, H-4, $J_{3,4}$=6.5, $J_{4,5}$=1.0, and $J_{4,Me}$=7.3Hz), 2.25 (1H, ddq, H-2, $J_{1,2}$=2.0, $J_{2,3}$=6.5, and $J_{2,Me}$=7.3Hz), 3.73 (1H, dd, H-6, $J_{5,6}$=5.0 and $J_{6,6'}$=7.0Hz), 3.78 (1H, dd, H-6', $J_{5,6'}$=2.0 and $J_{6,6'}$=7.0Hz), 3.89 (1H, dd, H-3, $J_{2,3}$=$J_{3,4}$=6.5Hz), 4.36 (1H, br d, H-5, $J_{5,6}$=5.0Hz), 4.48 and 4.49 (each 1H, ABq, OCH_2Ph, J=10.0Hz), 5.36 (1H, d, H-1, $J_{1,2}$=2.0Hz), and 7.25 ~ 7.40 (5H, m, Ph).

3-*O*-Benzyl-2,4-dideoxy-2,4-di-*C*-methyl-D-allopyranose (24). To a solution of **23** (21.2 g, 85.4 mmol) in dry MeOH (210 ml) was added *p*-toluenesulfonic acid (646 mg, 3.75 mmol) and the mixture was stirred at 50°C for 20 h. The reaction mixture was neutralized with Amberlite IRA-400 and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel (300 g) with 2:1 hexane-ethyl acetate to afford methyl glycoside (22.7 g, 95%; α:β = 1:2.5) as a colorless syrup [Rf = 0.41 (2:1 hexane-ethyl acetate); ^{1}H NMR δ 0.90 and 1.02 (each d, 2- and 4-Me (α), J=7.0Hz), 0.96 and 1.06 (each d, 2- and 4-Me (β), J=7.0Hz), 3.44 (s, OMe (α)), and 3.49 (s, OMe (β)); Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.57; H, 8.42]. A mixture of this syrup (12.3 g, 43.9 mmol) and 50% aqueous acetic acid (246 ml) was stirred at 60°C for 12 h. After concentration, the residue was chromatographed on silica gel (300 g) with ethyl acetate to afford **24** (11.5 g, 98%; α:β = 1:2.5) as colorless crystals: Rf = 0.32 (α-anomer), 0.26 (β-anomer) (ethyl acetate); mp 103 ~ 104.5°C (colorless needles; ethyl acetate); ^{1}H NMR δ 0.96 (d, Me (β), J=7.0Hz), 1.02 (d, Me (α), J=7.0Hz), 1.12 (d, Me (β), J=7.0Hz), 1.14 (d, Me (α), J=7.0Hz), 2.04 (dd, 6-OH (α), J=6.0 and 6.0Hz), 2.15 (dd, 6-OH (β), J=6.0 and 6.0Hz), 2.84 (d, 1-OH (β), J=6.4Hz), 4.61 and 4.64 (ABq, OC*H*$_2$Ph (β), J=11.2Hz), 4.63 and 4.67 (ABq, OC*H*$_2$Ph (α), J=11.2Hz), 4.87 (dd, H-1 (β), $J_{1,OH}$=6.4 and $J_{1,2}$=9.0Hz), 4.96 (dd, H-1 (α), $J_{1,2}$=3.0 and $J_{1,OH}$=11.2Hz), 5.06 (d, 1-OH (α), J=11.2Hz), and 7.25 ~ 7.40 (m, Ph); Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.38; H, 7.98.

3-*O*-Benzyl-2,4-dideoxy-2,4-di-*C*-methyl-D-allitol (25). To a stirred solution of **24** (9.20 g, 34.5 mmol) in dry THF (184 ml) at 0°C was added portionwise $LiAlH_4$ (5.24 g, 138 mmol). After 2 h at 25°C, water (5.24 ml), 10% aqueous NaOH (5.24 ml), and water (15.7 ml) were carefully added to the ice-cooled reaction mixture. The insoluble materials were filtered with Celite and washed with chloroform. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (1 kg) with 15:1 chloroform-MeOH to afford **25** (8.54 g, 92%) as colorless crystals: Rf = 0.39 (10:1 chloroform-MeOH); $[\alpha]_D^{28}$ -10.5° (c 1.32, MeOH); mp 48.0 - 49.5°C (colorless needles; ethyl acetate-hexane); ^{1}H NMR δ 0.96 and 1.08 (each 3H, each d, 2- and 4-Me, J=6.8Hz), 1.65 ~ 1.80 (1H, br, OH), 2.00 ~ 2.15 (2H, m, H-2 and 4), 2.35 ~ 2.50 (2H, m, 1- and 6-OH), 3.45 ~ 3.80 (6H, m, H-1, 1', 3, 5, 6, and 6'), 4.64 and 4.67 (each 1H, ABq, OC*H*$_2$Ph, J=11.0Hz), and 7.30 ~ 7.40 (5H, m, Ph); Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.13; H, 8.87.

3-*O*-Benzyl-2,4-dideoxy-5,6-*O*-isopropylidene-2,4-di-*C*-methyl-D-allitol (26). To a stirred solution of **25** (5.51 g, 20.5 mmol) and 2,2-dimethoxypropane (2.52 ml, 20.5 mmol) in dry acetone (110 ml) at 0°C was added concd H_2SO_4 (0.0055 ml). After 1 h at 0°C, the reaction mixture was neutralized with solid $NaHCO_3$. The insoluble materials were filtered and washed with acetone. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (200 g) with 30:1 toluene-ethyl acetate to afford **26** (6.14g, 97%) as a colorless syrup: Rf = 0.57 (1:1 hexane-ethyl acetate); $[\alpha]_D^{29}$ -5.1°, $[\alpha]_{435}^{29}$ -11.4° (c 1.61); ^{1}H NMR δ 0.99 (3H, d, Me, J=6.8Hz), 1.00 (3H, d, Me, J=7.3Hz), 1.34 and 1.41 (each 3H, each s, CMe_2), 2.06 (1H, m), 2.19 (1H, m), 2.59 (1H, dd, OH, J=5.6 and 5.6Hz), 3.49 (1H, dd, J=3.4 and 7.6Hz), 3.60 ~ 3.70 (3H, m), 3.98 (1H, dd, J=5.9 and 8.3Hz), 4.15 (1H, ddd, H-5, J=5.9, 8.3, and 8.3Hz), 4.56 and 4.62 (each 1H, ABq,

OC*H*$_2$Ph, J=11.0Hz), and 7.25 ~ 7.40 (5H, m, Ph); Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.91; H, 8.79.

3-*O*-Benzyl-2,4-dideoxy-5,6-*O*-isopropylidene-2,4-di-*C*-methyl-D-allose (27). A solution of DMSO (2.75 ml, 38.8 mmol) in dry CH_2Cl_2 (42.3 ml) was added to a stirred solution of oxalyl chloride (1.86 ml, 19.4 mmol) in dry CH_2Cl_2 (42.3 ml) at -78°C. After 20 min at -78°C, a solution of **26** (2.99 g, 9.69 mmol) in dry CH_2Cl_2 (18 ml) was added dropwise and the resultant suspension was stirred at -78°C for 15 min. After addition of triethylamine (8.10 ml, 58.1 mmol), the mixture was gradually warmed to 0°C. Saturated aqueous NH_4Cl was added to the reaction mixture and phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (60 g) with 5:1 hexane-ethyl acetate to afford **27** (2.97 g, 100%) as a colorless syrup: Rf = 0.51 (3:1 hexane-ethyl acetate); IR ($CHCl_3$) 1721 cm^{-1}; ^1H NMR δ 0.93 (3H, d, Me, J=7.3Hz), 1.16 (3H, d, Me, J=6.8Hz), 1.34 and 1.40 (each 3H, each s, CMe_2), 2.16 (1H, m), 2.82 (1H, m), 3.62 (1H, dd, H-6, $J_{5,6}$=$J_{6,6'}$=7.8Hz), 3.76 (1H, dd, H-3, J=3.9 and 5.9Hz), 3.98 (1H, dd, H-6', $J_{5,6'}$=5.9 and $J_{6,6'}$=7.8Hz), 4.13 (1H, ddd, H-5, $J_{5,6'}$=5.9 and $J_{4,5}$=$J_{5,6}$=7.8Hz), 4.53 and 4.57 (each 1H, ABq, OC*H*$_2$Ph, J=11.0Hz), 7.25 ~ 7.40 (5H, m, Ph), and 9.78 (1H, d, CHO, J=3.0Hz).

8-*O*-Benzyl-3-*C*-(benzyloxymethyl)-3,5,7,9-tetradeoxy-1,2:10,11-di-*O*-isopropylidene-7,9-di-*C*-methyl-5-*C*-methylene-α-D-*allo*-L-*talo*-undecofuranose-(1,4) (29) and Its D-*allo*-D-*allo* Epimer 30. To a cooled (-90 ~ -95°C), stirred solution of **28**[7] (12.9 g, 31.0 mmol) in dry ether (290 ml) was added 1.59M butyllithium in hexane (19.5 ml, 31.0 mmol) and the mixture was stirred at -90 ~ -95°C for 0.5 h. To this was added a solution of the aldehyde **27** (3.40 g, 11.1 mmol) in dry ether (6.8 ml) and stirring was continued at -90 ~ -95°C for 0.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (500 g) with toluene-ethyl acetate (15:1 to 8:1) to afford the coupling products (6.23 g) contaminated with impurities. This was re-chromatographed on silica gel (500 g) with 2.5:1 hexane-ethyl acetate to afford the pure **29** (4.00 g, 61%) and **30** (174 mg, 2.65%) as colorless syrups: **29**, Rf = 0.30 (5:1 benzene-ethyl acetate); $[\alpha]_D^{32}$ +30.9° (c 1.14); ^1H NMR δ 0.92 (3H, d, Me, J=6.7Hz), 0.98 (3H, d, Me, J=6.7Hz), 1.32, 1.33, 1.39, and 1.49 (each 3H, each s, 2xCMe_2), 2.05 ~ 2.15 (1H, m), 2.20 ~ 2.35 (2H, m), 2.80 (1H, d, 6-OH, J=3.0Hz), 3.44 (1H, dd, H-3', J=5.4 and 9.3Hz), 3.50 (1H, dd, H-8, J=4.9 and 6.4Hz), 3.65 ~ 3.75 (2H, m, H-3' and 11), 3.91 (1H, dd, H-11', $J_{10,11'}$=6.4 and $J_{11,11'}$=8.3Hz), 4.11 (1H, d, H-4, $J_{3,4}$=10.3Hz), 4.24 (1H, ddd, H-10, J=6.4, 6.4, and 8.3Hz), 4.40 and 4.45 (each 1H, ABq, OC*H*$_2$Ph, J=12.0Hz), 4.51 (1H, br s, H-6), 4.62 and 4.63 (each 1H, ABq, OC*H*$_2$Ph, J=12.0Hz), 4.73 (1H, dd, H-2, $J_{1,2}$=$J_{2,3}$=3.9Hz), 5.30 and 5.33 (each 1H, each s, C=CH_2), 5.79 (1H, d, H-1, $J_{1,2}$=3.9Hz), and 7.25 ~ 7.35 (10H, m, 2xPh); Anal. Calcd for $C_{35}H_{48}O_8$: C, 70.44; H, 8.11. Found: C, 70.31; H, 7.88. **30**, Rf = 0.35 (5:1 benzene-ethyl acetate), ^1H NMR δ 0.85 (3H, d, Me, J=6.8Hz), 1.01 (3H, d, Me, J=7.3Hz), 1.32, 1.34, 1.40, and 1.59 (each 3H, each s, 2xCMe_2), 2.15 ~ 2.35 (3H, m, H-3,7, and 9), 3.58 (1H, dd, H-3', J=6.2 and 9.8Hz), 3.60 ~ 3.70 (2H, m, H-8 and 11), 3.76 (1H, dd, H-3', J=8.2

and 9.8Hz), 3.89 (1H, dd, H-11', J=6.4 and 8.2Hz), 3.98 (1H, br s, 6-OH), 4.05 (1H, d, H-6, J=9.6Hz), 4.26 (1H, ddd, H-10, J=6.4, 6.4, and 7.8Hz), 4.39 (1H, d, H-4, J=10.2Hz), 4.51 (2H, s, OCH_2Ph), 4.54 and 4.62 (each 1H, ABq, OCH_2Ph, J=11.2Hz), 4.76 (1H, dd, H-2, $J_{1,2}=J_{2,3}$=3.9Hz), 5.27 and 5.30 (each 1H, each s, $C=CH_2$), 5.83 (1H, d, H-1, J=3.9Hz), and 7.25 ~ 7.40 (10H, m, 2xPh).

8-*O*-Benzyl-3-*C*-(benzyloxymethyl)-3,5,7,9-tetradeoxy-1,2:10,11-di-*O*-isopropylidene-5,7,9-tri-*C*-methyl-α-D-*glycero*-D-*altro*-L-*talo*-undecofuranose-(1,4) (31) and Its D-*glycero*-D-*altro*-D-*allo* Epimer 32. A solution of **29** (8.20 g, 13.7 mmol) and chlorotris(triphenylphosphine)rhodium(I) (2.10 g, 2.27 mmol) in benzene (138 ml) was stirred under an atmospheric pressure of hydrogen at 25°C for 12 h. The reaction mixture was then concentrated and the residue was passed through Florisil (100 ~ 200 mesh, 150 g) with ether and again concentrated. The residue was chromatographed on silica gel (1.1 kg) with 5:1 toluene-ethyl acetate to afford **31** (7.40 g, 90%) and **32** (296 mg, 3.6 %) as colorless syrups: **31**, Rf = 0.29 (5:1 toluene-ethyl acetate); $[\alpha]_D^{24}$ +25.3° (c 1.17); ^{1}H NMR δ 0.77 (3H, d, Me, J=6.8Hz), 0.94 (3H, d, Me, J=6.8Hz), 0.97 (3H, d, Me, J=7.3Hz), 1.32, 1.32, 1.40, and 1.49 (each 3H, each s, 2xCMe_2), 1.71 ~ 1.84 (1H, m), 1.90 ~ 2.03 (1H, m), 2.16 ~ 2.35 (2H, m), 3.05 (1H, d, 6-OH, J=2.4Hz), 3.40 ~ 3.50 (2H, m), 3.66 (1H, dd, J=8.0 and 8.0Hz), 3.78 (1H, dd, J=8.0 and 9.8Hz), 3.91 (1H, dd, J=6.2 and 8.0Hz), 3.95 (1H, br d, H-6, J=9.2Hz), 4.20 (1H, ddd, H-10, J=6.0, 6.0, and 9.8Hz), 4.34 (1H, dd, J=2.0 and 11.0Hz), 4.51 (2H, s, OCH_2Ph), 4.58 (2H, s, OCH_2Ph), 4.70 (1H, dd, H-2, $J_{1,2}=J_{2,3}$=3.9Hz), 5.75 (1H, d, H-1 $J_{1,2}$=3.9Hz), and 7.25 ~ 7.40 (10H, m, 2xPh); Anal. Calcd for $C_{35}H_{50}O_8$: C,70.21; H, 8.42. Found: C, 70.34; H, 8.17. **32**, Rf = 0.23 (5:1 toluene-ethyl acetate); ^{1}H NMR δ 0.97 (3H, d, Me, J=7.3Hz), 1.02 (3H, d, Me, J=7.3Hz), 1.05 (3H, d, Me, J=7.3Hz), 1.30, 1.31, 1.37, and 1.46 (each 3H, each s, 2xCMe_2), 1.85 ~ 2.00 (2H, m), 2.10 ~ 2.30 (2H, m), 2.60 (1H, d, 6-OH, J=3.2Hz), 3.38 (1H, dd, J=3.8 and 7.0Hz), 3.46 (1H, dd, J=6.2 and 9.8Hz), 3.65 ~ 3.75 (2H, m), 3.80 ~ 3.95 (3H, m), 4.27 (1H, ddd, H-10, J=5.9, 5.9, and 7.8Hz), 4.42 (2H, s, OCH_2Ph), 4.56 and 4.60 (each 1H, ABq, OCH_2Ph, J=12.0Hz), 4.59 (1H, dd, H-2, $J_{1,2}=J_{2,3}$=3.9Hz), 5.64 (1H, d, H-1, $J_{1,2}$=3.9Hz), and 7.25 ~ 7.40 (10H, m, 2xPh).

6,8-Di-*O*-benzyl-3-*C*-(benzyloxymethyl)-3,5,7,9-tetradeoxy-1,2:10,11-di-*O*-isopropylidene-5,7,9-tri-*C*-methyl-α-D-*glycero*-D-*altro*-L-*talo*-undecofuranose-(1,4) (33). By the procedure described in the preparation of **23**, a sample of **31** (7.22 g, 12.1 mmol) afforded, after silica-gel column chromatography with 10:1 hexane-acetone, **33** (7.50 g, 90%) as a colorless syrup: Rf = 0.83 (4:1 toluene-ethyl acetate); $[\alpha]_D^{24}$ -23.4° (c 1.07); ^{1}H NMR δ 0.84 (3H, d, Me, J=6.8Hz), 0.97 (3H, d, Me, J=6.8Hz), 0.99 (3H, d, Me, J=6.8Hz), 1.27, 1.28, 1.35, and 1.38 (each 3H, each s, 2xCMe_2), 1.90 ~ 2.10 (2H, m), 2.20 ~ 2.40 (2H, m), 3.44 (1H, dd, J=6.3 and 9.8Hz), 3.48 (1H, dd, J=2.5 and 9.8Hz), 3.63 (1H, dd, J=8.0 and 8.0Hz), 3.70 ~ 3.80 (2H, m), 3.95 (1H, dd, J=5.9 and 8.2 Hz), 4.15 ~ 4.30 (2H, m), 4.45 ~ 4.60 (4H, m, 2xOCH_2Ph), 4.57 and 4.83 (each 1H, ABq, OCH_2Ph, J=11.7Hz), 4.68 (1H, dd, H-2, $J_{1,2}=J_{2,3}$=3.9Hz), 5.79 (1H, d, H-1, $J_{1,2}$=3.9Hz), and 7.20 ~ 7.40 (15H, m, 3xPh); Anal. Calcd for $C_{42}H_{56}O_8$: C, 73.23; H, 8.19. Found: C, 73.41; H, 8.17.

6,8-Di-*O*-benzyl-3-*C*-(benzyloxymethyl)-3,5,7,9-tetradeoxy-1,2-*O*-isopropylidene-5,7,9-tri-*C*-methyl-α-D-*glycero*-D-*altro*-L-*talo*-undecofuranose-(1,4) (34). A solution of **33** (7.50 g, 10.9 mmol) in 50% aqueous acetic acid (150 ml) was stirred at 50°C for 1.5 h, then concentrated. The residue was chromatographed on silica gel (375 g) with 1:1 toluene-ethyl acetate to afford **34** (6.17 g, 87%) as a colorless syrup: Rf = 0.47 (2:1 toluene-ethyl acetate); $[\alpha]_D^{27}$ -22.2° (c 1.26); ^{1}H NMR δ 0.85 (3H, d, Me, J=6.8Hz), 0.97 (3H, d, Me, J=7.3Hz), 1.05 (3H, d, Me, J=6.8Hz), 1.22 and 1.27 (each 3H, each s, CMe_2), 1.95 ~ 2.30 (4H, m, H-3, 5, 7,and 9), 2.41 (1H, br t, OH), 3.33 ~ 3.55 (4H, m), 3.70 ~ 3.85 (4H, m), 4.19 (1H, dd, J=1.0 and 10.8Hz), 4.45 ~ 4.65 (5H, m, 2xOCH_2Ph and one of OCH_2Ph), 4.67 (1H, d, H-2, $J_{1,2}$=$J_{2,3}$=3.9Hz), 4.78 (1H, d, one of OCH_2Ph, J=12.2Hz), 5.78 (1H, d, H-1 $J_{1,2}$=3.9Hz), and 7.20 ~ 7.35 (15H, m, 3xPh); Anal. Calcd for $C_{39}H_{52}O_8$: C, 72.20; H, 8.08. Found: C, 72.54; H, 8.46.

6,8-Di-*O*-benzyl-3-*C*-(benzyloxymethyl)-3,5,7,9-tetradeoxy-1,2-*O*-isopropylidene-5,7,9-tri-*C*-methyl-α-D-*altro*-L-*talo*-decodialdofuranose-(1,4) (4). To a stirred solution of **34** (1.80 g, 2.77 mmol) in acetonitrile (45 ml) at 0°C were added potassium acetate (1.52 g, 15.5 mmol) and lead tetraacetate (1.35 g, 3.05 mmol). After 0.5 h at 0°C, the reaction mixture was filtered with Celite and washed with acetonitrile. The combined filtrate and washings were concentrated and the residue was chromotographed on silica gel (25 g) with 5:1 toluene-ethyl acetate to affford **4** (1.68g, 98%) as a colorless syrup. The ^{1}H NMR and TLC mobilities of this sample were identical with those of the authentic **4**.[7]

Transformation of 36 into 4. A stirred solution of **36**[7] (586 mg, 0.784 mmol) in 1:1 (v/v) MeOH-CH_2Cl_2 (23.4 ml) at -78°C was bubbled with O_3/O_2 gas. After 9 min at -78°C, nitrogen gas was bubbled for a few min and Me_2S (0.575 ml, 7.83 mmol) and MeOH (11.7 ml) were added and the mixture was warmed to 0°C. To this was added $NaBH_4$ (29.6 mg, 0.782 mmol) and the mixture was stirred for 1 h at 0°C. The reaction mixture was neutralized with solid CO_2 and concentrated. The residue was dissolved in ethyl acetate and washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (20 g) with 5:1 toluene-ethyl acetate to afford a colorless syrup (563 mg). By the procedure described in the preparation of **4** from **34**, a sample of this syrup (563 mg) afforded, after silica-gel column chromatography (20 g) with 6:1 toluene-ethyl acetate, **4** (375 mg, 78% from **36**) as a colorless syrup. The ^{1}H NMR and TLC mobilities of this sample were identical with those of the authentic **4**.[7]

Methyl 5,7,9-tri-*O*-acetyl-2-*C*-(acetoxymethyl)-2,4,6,8,10,11,12-heptadeoxy-4,6,8,10-tetra-*C*-methyl-*aldehydo*-L-*glycero*-L-*talo*-L-*manno*-(*E*)-11-tridecenuronate 1-(Diethyl dithioacetal) (37). A mixture of **2** (788 mg, 1.34 mmol), *dl*-10-camphorsulfonic acid (62.4 mg, 0.269 mmol), and dry ethanethiol (23.7 ml) was stirred at 25°C for 2 d. The reaction mixture was neutralized with triethylamine and concentrated. The residue was chromatographed on silica gel (8.9 g) with 3:2 hexane-ethyl acetate to afford **37** (869 mg, 97%) as a colorless syrup: Rf = 0.45 (3:2 hexane-ethyl acetate); $[\alpha]_D^{27}$ -8.3°, $[\alpha]_{435}^{27}$ -16.7° (c 0.12); IR ($CHCl_3$) 1731 cm^{-1}; ^{1}H NMR δ 0.90 (3H, d, Me, J=7.0Hz), 0.92 (3H, d, Me, J=7.0Hz), 0.95 (3H, d, Me, J=7.0Hz), 1.06 (3H, d, Me, J=7.0Hz), 1.20 ~ 1.30

(6H, m, 2xSCH$_2$*Me*), 1.65 ~ 1.80 (1H, m), 1.97, 1.99, 2.06, and 2.10 (each 3H, each s, 4xOAc), 2.10 ~ 2.25 (1H, m), 2.25 ~ 2.45 (2H, m), 2.50 ~ 2.70 (5H, m), 3.18 (1H, d, OH, J=4.6Hz), 3.72 (3H, s, CO_2Me), 4.15 (1H, dd, J=6.0 and 12.0Hz), 4.25 (1H, dd, J=4.0 and 12.0Hz), 4.42 (1H, d, J=2.4Hz), 4.80 ~ 4.90 (2H, m), 5.03 (1H, dd, J=2.0 and 9.8Hz), 5.80 (1H, d, H-12, $J_{11,12}$=15.2Hz), and 6.75 (1H, dd, H-11, $J_{10,11}$=9.0 and $J_{11,12}$=15.2Hz); Anal. Calcd for $C_{31}H_{52}O_{11}S_2$: C, 55.99; H, 7.88. Found: C, 55.76; H, 7.74; MS *m/e* 664 (M^+).

2,4,6,8,10,11,12-Heptadeoxy-3,5:7,9-di-*O*-isopropylidene-4,6,8,10-tetra-*C*-methyl-13-*O*-pivaloyl-2-C-(pivaloyloxymethyl)-*aldehydo*-L-*glycero*-L-*talo*-L-*manno*-(*E*)-11-tridecose 1-(Diethyl dithioacetal) (39). To a stirred solution of **37** (1.49 g, 2.24 mmol) in dry toluene (30 ml) at -78°C was added dropwise 1.0M diisobutylaluminum hydride (20.3 ml, 20.3 mmol). After 0.5 h at -78°C, 50% aqueous acetic acid (2.28 ml) was added to the reaction mixture and the new mixture was warmed to room temperature and concentrated. The thoroughly dried powder was dissolved in dry ethyl acetate (60 ml), and 4-dimethylaminopyridine (4.09 g, 33.5 mmol) and acetic anhydride (2.12 ml, 22.5 mmol) were added. After 0.5 h at 25°C, the insoluble materials were filtered with Celite and washed with ethyl acetate. The combined filtrate and washings were concentrated. The residue was chromatographed on silica gel (81 g) with 2:1 hexane-ethyl acetate to afford the hexaacetate. This was dissolved in 15.6 ml of MeOH and to this was added 28% NaOMe in MeOH (0.416 ml). The mixture was stirred at 25°C for 17 h, then neutralized with Dowex 50W-X8 and filtered. The filtrate was concentrated to afford almost pure **38** (998 mg, 95%) as a colorless foam [Rf = 0.20 (10:1 chloroform-MeOH)]. This hexaol **38** (208 mg, 0.444 mmol) was dissolved in dry pyridine (2 ml) and cooled to 0°C. To this was added pivaloyl chloride (0.120 ml, 0.974 mmol). After 4 h at 0°C, the reaction mixture was diluted with ethyl acetate and washed with water, saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (3 g) with toluene-ethyl acetate (4:1 to 2:1) to afford tetraol (240 mg, 85%) as a colorless syrup [Rf = 0.41 (1:1 toluene-ethyl acetate)]. To a stirred mixture of this tetraol (180 mg, 0.283 mmol) and 2,2-dimethoxypropane (0.348 ml, 2.83 mmol) in dry acetone (3.6 ml) at 0°C was added 10 % (v/v) concd H_2SO_4 in acetone (2 ml). After 3 h at 25°C, the reaction mixture was neutralized with 0.1N aqueous NaOH and concentrated. The residue was chromatographed on silica gel (3 g) with 10:1 toluene-ethyl acetate to afford **39** (193 mg, 81% from **38**) as a colorless syrup: Rf = 0.93 (2:1 toluene-ethyl acetate); $[\alpha]_D^{27}$ -15.5° (c 0.66); IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR δ 0.88 (3H, d, Me, J=7.0Hz), 0.90 (3H, d, Me, J=7.0Hz), 0.92 (3H, d, Me, J=7.0Hz), 0.93 (3H, d, Me, J=7.0Hz), 1.20 (9H, s, Pv), 1.23 (9H, s, Pv), 1.20 ~ 1.40 (18H, m, 2xCMe$_2$ and 2xSCH$_2$*Me*), 1.40 ~ 1.55 (1H, m), 1.70 ~ 1.85 (2H, m), 2.20 ~ 2.40 (2H, m), 2.57 and 2.70 (each 2H, each q, 2xSC*H*$_2$Me, J=7.8Hz), 3.19 (1H, dd, J=6.2 and 10.0Hz), 3.45 (1H, dd, J=4.0 and 10.4Hz), 3.62 (1H, dd, J=1.0 and 7.8Hz), 4.01 (1H, dd, J=4.0 and 11.2Hz), 4.18 (1H, dd, J=5.8 and 12.0Hz), 4.32 (1H, d, J=3.0Hz), 4.37 (1H, dd, J=3.0 and 12.0Hz), 4.52 (2H, d, J=6.2Hz), 5.59 (1H, ddd, H-12, J=6.2, 6.2, and 16.0Hz), and 5.80 (1H, dd, H-11, J=6.8 and 16.0Hz); MS *m/e* 717 (M^+).

2,4,6,8,10,11,12-Heptadeoxy-3,5:7,9-di-*O*-isopropylidene-4,6,8,10-tetra-*C*-methyl-13-*O*-pivaloyl-2-*C*-(pivaloyloxymethyl)-L-*glycero*-L-*talo*-L-*manno*-(*E*)-11-tridecose (40). To a vigorously stirred solution of **39** (205 mg, 0.286 mmol) in 4:1 (v/v) acetone-water (12.3 ml) at 25°C were added HgO (248 mg, 1.15 mmol) and $HgCl_2$ (311 mg, 1.15 mmol). After 50 min at 25°C, the insoluble materials were filtered with Celite into 10% aqueous KI (15 ml) and washed with acetone. The filtrate and washings were combined. After subsequent removal of acetone by concentration, the aqueous layer was extracted with $CHCl_3$. The extracts were washed with 10% aqueous KI, saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (9 g) with 15:1 toluene-ethyl acetate to afford **40** (167 mg, 96%) as a colorless syrup: Rf = 0.26 (15:1 toluene-ethyl acetate); IR ($CHCl_3$) 1724 cm^{-1}; ^1H NMR δ 0.89 ~ 0.95 (12H, m, 4xMe), 1.81 and 1.20 (each 9H, each s, 2xPv), 1.24, 1.26, 1.28, and 1.28 (each 3H, each s, 2xCMe_2), 1.52 (1H, m), 1.74 (1H, m), 1.84 (1H, m) 2.29 (1H, m), 2.73 (1H, m), 3.19 (1H, dd, J=6.6 and 9.9Hz), 3.46 (1H, dd, J=3.3 and 10.4Hz), 3.70 (1H, dd, J=1.1 and 7.7Hz), 4.13 (1H, dd, J=4.4 and 10.4Hz), 4.20 ~ 4.30 (2H, m), 4.51 (2H, d, H-13, J=6.0Hz), 5.59 (1H, ddd, H-12, J=6.0, 6.0, and 16.0Hz), 5.81 (1H, dd, H-11, J=6.6 and 16.0Hz), and 9.72 (1H, d, CHO, J=3.3Hz).

Coupling of 12 and 40. To a stirred solution of **12** (366 mg, 0.864 mmol) in dry THF (0.91 ml) at -30°C was added a 1.0M $LiN(SiMe_3)_2$ in THF (0.864 ml, 0.864 mmol). After 0.5 h at -30°C, 1.0M $ZnCl_2$ in ether (0.864 ml, 0.864 mmol) was added to the above solution. After 5 min at -30°C, dry ether (2.6 ml) was added and the mixture was warmed to 0°C. After 10 min at 0°C, a solution of **40** (176 mg, 0.288 mmol) in dry ether (0.88 ml) was added and the new mixture was stirred at 0°C for 0.5 h. The reaction mixture was quenched by adding phosphate buffer solution (pH 7.41; 10 ml) and extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (70 g) with 3:1:0.5 chloroform-hexane-ethyl acetate to afford the **major 41** (224 mg, 75%) and the **minor 41** (37 mg, 11%) as yellow foam: **major 41**, Rf = 0.18 (3:1:0.5 chloroform-hexane-ethyl acetate); ^1H NMR δ 0.80 ~ 1.40 (45H, m), 1.45 ~ 1.60 (1H, m), 1.70 ~ 1.80 (1H, m), 1.80 ~ 1.95 (1H, m), 2.00 ~ 2.15 (1H, m), 2.20 ~ 2.35 (1H, m), 2.48 (3Hx1.0/2.2, s, ArMe), 2.51 (3Hx1.2/2.2, s, ArMe), 3.09 (1Hx1.2/2.2, dq, H-12, J=7.5 and 10.0Hz), 3.22 [1H, dd, J=7.0 and 8.7Hz (contaminated with 1Hx1.0/2.2 of H-12)], 3.58 and 3.62 (each 3Hx1.0/2.2, each s, OMe), 3.60 and 3.61 (each 3Hx1.2/2.2, each s, OMe), 3.91 and 3.93 (each 3Hx1.0/2.2, each s, OMe), 3.92 and 3.93 (each 3Hx1.2/2.2, each s, OMe), 4.52 (2H, d, H-17, J=6.0Hz), 4.90 ~ 5.10 (4H, m, 2xOCH_2O), 5.60 (1H, dt, H-18, J=6.0 and 15.0Hz), 5.81 (1H, dd, H-19, J=6.9 and 15.0Hz), 7.04 (1Hx1.2/2.2, s, H-3), and 7.07 (1Hx1.0/2.2, s, H-3). **minor 41**: Rf = 0.12 (3:1:0.5 chloroform-hexane-ethyl acetate); ^1H NMR δ 0.40 ~ 1.30 (45H, m), 2.49 (3Hx3/4, s, ArMe), 2.51 (3Hx1/4, s, ArMe), 3.60 and 3.62 (each 3H, each s, OMe), 3.90 (6H, s, 2xOMe), 4.475 ~ 4.55 (2H, m, 2xH-17), 4.95 ~ 5.05 (4H, m, 2xOCH_2O), 5.58 [1Hx3/4, dt, H-18, J=6.0 and 15.8Hz (contaminated with minor H-18)], 5.78 [1Hx3/4, dd, H-19, J=6.2 and 15.8Hz (comtaminated with minor H-19)], 7.07 (1Hx3/4, s, H-3), and 7.09 (1Hx1/4, s, H-3).

Dehydration of 41: **(a)** The **major 41** (207 mg, 0.200 mmol) was dissolved in 0.7% methanolic KOH (4.1 ml) and the mixture was stirred at 40°C for 44 h. The reaction mixture was neutralized with Dowex 50W-X8 and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel (16 g) with 1:1 hexane-ethyl acetate to afford **42** (144 mg, 85%) as yellow foam: Rf = 0.65 (10:1 chloroform-MeOH); ^{1}H NMR δ 0.38, 0.99, 1.22, and 1.23 (each 3Hx3/4, each s, 2xCMe_2), 0.78, 0.79, 0.87, and 0.90 (each 3Hx3/4, each d, 4xMe), 1.35 ~ 1.50 (1H, m), 1.60 ~ 1.80 (2H, m), 2.05 (3Hx1/4, d, H-13, J=1.0Hz), 2.09 (3Hx3/4, d, H-13, J=1.0Hz), 2.15 ~ 2.35 (1H, m), 2.44 (3Hx3/4, s, ArMe), 2.46 (3Hx1/4, s, ArMe), 2.70 ~ 2.95 (1H, m), 3.08 (1Hx3/4, dd, J=6.2 and 9.2Hz), 3.14 (1Hx1/4, dd, J=6.2 and 9.2Hz), 3.50, 3.61, 3.79, and 3.88 (each 3Hx3/4, each s, 4xOMe), 3.53, 3.62, 3.80, and 3.94 (each 3Hx1/4, each s, 4xOMe), 4.05 ~ 4.15 (2H, m, 2xH-17), 4.90 ~ 5.10 (4H, m, 2xOCH_2O), 5.60 ~ 5.80 (2H+1Hx3/4, m, H-18, 19, and 29), 5.95 (1Hx1/4, dq, H-29, J=1.0 and 9.2Hz), 7.01 (1Hx3/4, s, H-3), and 7.05 (1Hx1/4, s, H-3); Anal. Calcd for $C_{44}H_{65}NO_{15}$: C, 62.32; H, 7.73; N, 1.65. Found: C, 62.25; H, 7.75; N, 1.65; MS *m/e* 847 (M^+).

(b) The **minor 41** was dehydrated as in the case of (a) to afford **42** (85%). The ^{1}H NMR and TLC mobilities were identical with those of **42** derived from the **major 41**.

Preparation of 46. To a stirred solution of **42** (37.3 mg, 0.0440 mmol) in dry CH_2Cl_2 (0.56 ml) was added MnO_2 (373 mg). After 3 h at 25°C, the reaction mixture was filtered with Celite and the filtrate was washed with ethyl acetate. The combined filtrate and washings were concentrated to afford the crude **43** (37.2 mg, 100%) as yellow foam [Rf = 0.36 (2:1 hexane-acetone); ^{1}H NMR δ 0.38, 0.98, 1.21, and 1.23 (each 3Hx3/4, each s, 2xCMe_2), 0.78, 0.80, 0.89, and 1.00 (each 3Hx3/4, each d, 4xMe, J=6.5Hz), 0.84, 0.85, 0.93, and 1.02 (each 3Hx1/4, each d, 4xMe, J=6.5Hz), 1.00, 1.03, 1.15, and 1.27 (each 3Hx1/4, each s, 2xCMe_2), 1.35 ~ 1.55 (1H,m), 1.65 ~ 1.80 (2H, m), 2.05 (3Hx1/4, d, H-13, J=1.5Hz), 2.09 (3Hx3/4, d, H-13, J=1.5Hz), 2.44 (3Hx3/4, s, ArMe), 2.46 (3Hx1/4, s, ArMe), 2.45 ~ 2.55 (1H, m), 2.70 and 2.95 (1H, m), 3.12 (1Hx3/4, dd, J=6.3 and 9.2Hz), 3.18 (1Hx1/4, dd, J=6.3 and 9.2Hz), 3.50, 3.60, 3.78, and 3.89 (each 3Hx3/4, each s, 4xOMe), 3.52, 3.62, 3.80, and 3.93 (each 3Hx1/4, each s, 4xOMe), 4.85 ~ 5.10 (4H, m, OCH_2O), 5.70 (1Hx3/4, dd, H-29, J=1.5 and 9.0Hz), 5.95 (1Hx1/4, dd, H-29, J=1.5 and 9.0Hz), 6.13 (1Hx3/4, ddd, H-18, J=1.5, 7.5, and 15.9Hz), 6.14 (1Hx1/4, ddd, H-18, J=1.5, 7.5, and 15.9Hz), 6.92 (1H, dd, H-19, J=6.8 and 15.9Hz), 7.00 (1Hx3/4, s, H-3), 7.05 (1Hx1/4, s, H-3), 9.49 (1Hx3/4, d, CHO, J=7.5Hz), and 9.50 (1Hx1/4, d, CHO, J=7.5Hz)]. This aldehyde **43** was dissolved in dry CH_2Cl_2 (0.74 ml) and to this were added imidazole (9.0 mg, 0.132 mmol) and TBSCl (13.3 mg, 0.0882 mmol) . After 1 h at 25°C, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1 g) with 4:1 hexane-acetone to afford **44** (40.4 mg, 95%) as yellow foam [Rf = 0.41 (3:1 hexane-acetone); ^{1}H NMR δ -0.27 and -0.13 (each 3Hx1.0/2.2, each s, $SiMe_2$), -0.02 and -0.01 (each 3Hx1.2/2.2, each s, $SiMe_2$), 0.37, 0.96, 1.22, and 1.24 (each 3Hx1.2/2.2, each s, 2xCMe_2), 1.06, 1.18, 1.22, and 1.28 (each 3Hx1.0/2.2, each s, 2xCMe_2), 0.65 (9Hx1.0/2.2, s, *t*-Bu), 0.82 (9Hx1.2/2.2, s, *t*-Bu), 0.70 ~ 1.10 (12H, m, Me), 1.40 ~ 1.60 (1H, m), 1.65 ~ 1.80 (2H, m), 2.01 (3H, s, H-13), 2.46 (3Hx1.0/2.2, s, ArMe), 2.49 (3Hx1.2/2.2, s, ArMe), 2.45 ~ 2.60 (1H, m), 2.65 ~ 2.75 (1H, m), 3.12 (1Hx1.2/2.2, dd,

J=6.3 and 9.5Hz), 3.20 (1Hx1.0/2.2, dd, J=6.3 and 9.5Hz), 3.51, 3.53, 3.77, and 3.78 (each 3Hx1.2/2.2, each s, 4xOMe), 3.61, 3.61, 3.88, and 3.92 (each 3Hx1.0/2.2, each s, 4xOMe), 4.90 ~ 5.10 (4H, m, 2xOCH_2O), 5.71 (1Hx1.2/2.2, dd, H-29, J=1.5 and 9.3Hz), 5.94 (1Hx1.0/2.2, dd, H-29, J=1.5 and 9.3Hz), 6.14 (1Hx1.2/2.2, ddd, H-18, J=1.0, 7.7, and 15.8Hz), 6.15 (1Hx1.0/2.2, ddd, H-18, J=1.0, 7.7, and 15.8Hz), 6.93 (1Hx1.2/2.2, dd, H-19, J=6.9 and 15.8Hz), 6.94 (1Hx1.0/2.2, dd, H-19, J=6.9 and 15.8Hz), 6.98 (1Hx1.2/2.2, s, H-3), 6.99 (1Hx1.0/2.2, s, H-3), 9.49 (1Hx1.2/2.2, d, CHO, J=7.7Hz), and 9.50 (1Hx1.0/2.2, d, CHO, J=7.7Hz)]. To a solution of Still's reagent **45** (55.2 mg, 0.159 mmol) and 18-crown-6 (211 mg, 0.798 mmol) in dry THF (3.3 ml) at -78°C was added 0.5M $KN(SiMe_3)_2$ (0.320 ml, 0.160 mmol). After 10 min at -78°C, the sample of **44** (30.6 mg, 0.0319 mmol) in dry THF (0.61 ml) was added to the reaction mixture. After 0.5 h at -78°C, saturated aqueous NH_4Cl was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (5.4 g) with 4:1 benzene-ethyl acetate to afford **46** (27.3 mg, 82%) as yellow foam: Rf = 0.44 (3:1 hexane-acetone); IR ($CHCl_3$) 1694 and 1658 cm^{-1}; ^1H NMR δ ($CHCl_3$=7.26) -0.27 and -0.13 (each 3Hx1.0/2.2, each s, $SiMe_2$), -0.02 and -0.01 (each 3Hx1.2/2.2, each s, $SiMe_2$), 0.35 ~ 1.35 (27H, m, Me), 0.65 (9Hx1.0/2.2, s, *t*-Bu), 0.82 (9Hx1.2/2.2, s, *t*-Bu), 1.35 ~ 1.50 (1H, m), 1.60 ~ 1.80 (2H, m), 1.94 and 2.02 (each 3H, each br s, H-13 and 15-Me), 2.30 ~ 2.45 (1H, m), 2.47 (3Hx1.0/2.2, s, ArMe), 2.49 (3Hx1.2/2.2, s, ArMe), 2.60 ~ 2.75 (1H, m), 3.09 (1Hx1.2/2.2, dd, J=6.0 and 9.5Hz), 3.17 (1Hx1.0/2.2, dd, J=6.0 and 9.5Hz), 3.52, 3.53, 3.61, 3.61, 3.77, 3.78, 3.89, and 3.92 (total 12H, each s, 4xOMe), 4.21 (2H, q, CO_2CH_2Me, J=7.5Hz), 4.85 ~ 5.05 (4H, m, OCH_2O), 5.72 (1Hx1.2/2.2, dd, H-29, J=1.5 and 9.0Hz), 5.95 (1Hx1.0/2.2, dd, H-29, J=1.5 and 9.0Hz), 5.99 (1H, dd, H-19, J=7.4 and 16.0Hz), 6.40 (1H, d, H-17, J=11.0Hz), 6.98 (1Hx1.2/2.2, s, H-3), 6.99 (1Hx1.0/2.2, s, H-3), and 7.14 (1H, dd, H-18, J=11.0 and 16.0Hz); MS *m/e* 1043 (M^+).

Hydrolysis of 46. A solution of **46** (9.1 mg, 0.00871 mmol) and LiOH (2.1 mg) in 2:2:1 THF-MeOH-H_2O was stirred at 40°C for 8 h. The reaction mixture was neutralized with solid NH_4Cl and extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1 g) with 3:1 hexane-acetone to afford **47** (8.7 mg, 98%) as yellow foam: Rf = 0.22 (3:1 hexane-acetone); IR ($CHCl_3$) 1658 cm^{-1} ; ^1H NMR δ ($CHCl_3$=7.26) -0.27 and -0.13 (each 3Hx1.0/2.2, each s, $SiMe_2$), -0.02 and -0.01 (each 3Hx1.2/2.2, each s, $SiMe_2$), 0.35 ~ 1.30 (24H, m), 0.65 (9Hx1.0/2.2, s, *t*-Bu), 0.81 (9Hx1.2/2.2, s, *t*-Bu), 1.35 ~ 1.50 (1H, m), 1.60 ~ 1.85 (2H, m), 1.97 and 2.01 (each 3H, each br s, H-13 and 15-Me), 2.30 ~ 2.45 (1H, m), 2.46 (3Hx1.0/2.2, s, ArMe), 2.49 (3Hx1.2/2.2, s, ArMe), 2.60 ~ 2.80 (1H, m), 3.09 (1Hx1.2/2.2, dd, J=6.4 and 9.8Hz), 3.16 (1Hx1.0/2.2, dd, J=6.4 and 9.8Hz), 3.52, 3.54, 3.61, 3.61, 3.72, 3.73, 3.89, and 3.92 (total 12H, each s, 4xOMe), 4.85 ~ 5.05 (4H, m, 2xOCH_2O), 5.71 (1Hx1.2/2.2, dd, H-29 J=1.0 and 9.0Hz), 5.95 (1Hx1.0/2.2, dd, H-29, J=1.0 and 9.0Hz), 6.01 (1H, dd, H-19, J=7.4 and 16.0Hz), 6.52 (1H, d, H-17, J=11.0Hz), 6.98 (1Hx1.2/2.2, s, H-3), 6.99 (1Hx1.0/2.2, s, H-3), and 7.18 (1H, dd, H-18, J=11.0 and 16.0Hz); Anal. Calcd for $C_{53}H_{81}NO_{16}Si$: C, 62.64; H, 8.03; N, 1.38. Found: C,62.91; H, 7.76; N, 1.27.

Preparation of rifamycin W (1). A mixture of **47** (11.3 mg, 0.0111 mmol), $NaHCO_3$ (6.6 mg, 0.0786 mmol), and sodium dithionite (3.9 mg, 0.0224 mmol) in 1:1 (v/v) DMF-H_2O (0.45 ml) was stirred at 110°C for 10 min. The reaction mixture was poured into saturated aqueous NH_4Cl. Solid NH_4Cl was added to adjust pH to 4 and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated to afford the crude **48** (11.0 mg, 100%) as a brown syrup [Rf = 0.32 (2:1 hexane-acetone); ^1H NMR δ ($CHCl_3$=7.26) -0.26 and -0.13 (each 3Hx1.0/2.2, each s, $SiMe_2$), -0.02 and -0.01 (each 3Hx1.2/2.2, each s, $SiMe_2$), 0.69 (9Hx1.0/2.2, s, *t*-Bu), 0.82 (9Hx1.2/2.2, s, *t*-Bu), 1.97 and 1.99 (each 3H, each br s, H-13 and 15-Me), 2.41 (3Hx1.0/2.2, s, ArMe), 2.44 (3Hx1.2/2.2, s, ArMe), 3.49, 3.52, 3.61, 3.61, 3.67, 3.67, 3.67, and 3.70 (total 12H, each s, 4xOMe), 4.80 ~ 5.05 (4H, m, OCH_2O), 6.29 (1Hx1.0/2.2, s, H-3), and 6.30 (1Hx1.2/2.2, s, H-3)]. To a solution of the above crude **48** (11.0 mg) in dry toluene (8.51 ml) were added diisopropylethylamine (0.0223 ml, 0.125 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride[38] (13.0 mg, 0.0511 mmol) at 25°C. After 3 h at 85°C, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and NaCl solutions. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried and concentrated to afford the crude **49** (10.8 mg, 100%) as a brown syrup [Rf = 0.43 (3:1 hexane-acetone)]. To a vigorously stirred mixture of the above **49** (10.8 mg), AgO(II) (6.4 mg, 0.052 mmol) in dioxane (1.1 ml) was added 1N aqueous HNO_3 (0.0512 ml, 0.0512 mmol) at 25°C. After 1 h at 25°C, the reaction mixture was poured into 1:1 (v/v) mixture of saturated aqueous NaCl and $NaHCO_3$ and extracted with ethyl acetate. The extracts were dried and concentrated to afford crude yellow foam (10.4 mg). This sample was dissolved in 1:1 (v/v) 1N aqueous HCl-THF (0.3 ml). After 2 d at 25°C, the reaction mixture was diluted ethyl acetate and washed with saturated aqueous NaCl, dried, and concentrated. The residue was purified by HPTLC (Merck Art 5628, 10 cm x 10 cm) with 3:1 chloroform-MeOH to afford rifamycin W (**1**) (2.2 mg, 30% from **47**): Rf = 0.52 (3:1 chloroform-MeOH); UV (H_2O) λmax nm (log ε) 245 (4.41) and 350 (3.81); IR (KBr) 3427, 1636, 1605, 1545, and 1492 cm^{-1}; ^1H NMR (CD_3OD) δ 0.44 (3H, d, 22-Me, J=7.0Hz), 0.71 (3H, d, 24- or 26-Me, J=7.0Hz), 0.91 (3H, d, 20-Me, J=7.0Hz), 1.05 (3H, d, 24- or 26-Me, J=7.0Hz), 1.25 ~ 1.45 (1H, m, H-22), 1.75 ~ 1.90 (2H, m, H-24 and 26), 1.99 (3H, s, ArMe), 2.04 (3H, d, Me-13, J=0.8Hz), 2.08 (3H, br s, 16-Me), 2.25 ~ 2.40 (1H, m, H-20), 2.55 ~ 2.675 (1H, m, H-28), 3.45 (1H, dd, H-25, J=2.0 and 10.2Hz), 3.56 (1H, dd, one of CH_2OH, J=7.4 and 11.2Hz), 3.61 (1H, dd, one of CH_2OH, J=6.4 and 11.2Hz), 3.99 (1H, dd, H-23, $J_{22,23}$=9.8 and $J_{23,24}$<1.0Hz), 4.05 (1H, dd, H-21, $J_{20,21}$=10.0 and $J_{21,22}$<1.0Hz), 4.29 (1H, s, H-27, $J_{26,27}$=$J_{27,28}$=0Hz), 6.09 (1H, dd, H-19, $J_{18,19}$=16.0 and $J_{19,20}$=6.8Hz), 6.23 (1H, d, H-17, $J_{17,18}$=11.0Hz), 6.52 (1H, br d, H-29, $J_{28,29}$=10.0 and $J_{29,Me\text{-}13}$=0.8Hz), 6.54 (1H, dd, H-18, $J_{17,18}$=11.0 and $J_{18,19}$=16.0Hz), and 7.37 (1H, s, H-3). The synthetic sample of rifamycin W (**1**) was identical spectroscopically and chromatographically with natural rifamycin W.[6b,18]

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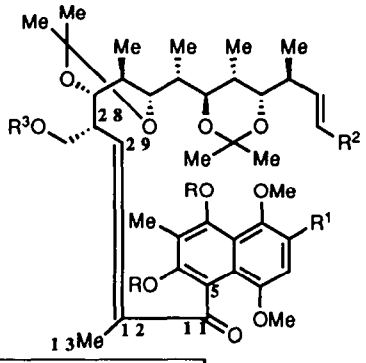
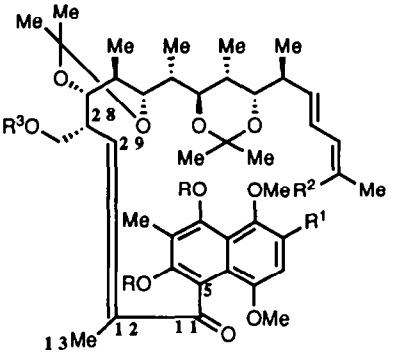
34. Ether appeared to be the best solvent.[33] Lithium enolate of **12**, however, could not be produced in ether because of the low solubility of **12** in ether. This ether dilution process after the litium enolate generatiuon in THF could not be omitted in order to obtain the satisfactory result.

35. The ratios of atropisomers in the compounds derived from **42** and some compounds prepared during a period of this synthetic study depend on whether the C28-hydroxymethyl group is protected or not. The ratios are shown below.



2.5 ~ 3.0 : 1 ratio group

42 : R = MOM, R^1 = NO_2, R^2 = CH_2OH, R^3 = H
43 : R = MOM, R^1 = NO_2, R^2 = CHO, R^3 = H
50 : R = MOM, R^1 = NHAc, R^2 = CH_2OH, R^3 = H



51 : R = MOM, R^1 = NO_2, R^2 = CO_2Et, R^3 = H
52 : R = MOM, R^1 = NO_2, R^2 = CO_2H, R^3 = H

1.1 ~ 1.3 : 1 ratio group

44 : R = MOM, R^1 = NO_2, R^2 = CHO, R^3 = TBS
53 : R = MOM, R^1 = NO_2, R^2 = CH_2OAc, R^3 = Ac
54 : R = MOM, R^1 = NHAc, R^2 = CH_2OPv, R^3 = Pv

46 : R = MOM, R^1 = NO_2, R^2 = CO_2Et, R^3 = TBS
47 : R = MOM, R^1 = NO_2, R^2 = CO_2H, R^3 = TBS
48 : R = MOM, R^1 = NH_2, R^2 = CO_2H, R^3 = TBS
55 : R = MOM, R^1 = NO_2, R^2 = CO_2Et, R^3 = MOM
56 : R = MOM, R^1 = NHAc, R^2 = CO_2Et, R^3 = TBS

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