The Total Synthesis of AB3217-A, a Novel Anti-mite Substance, via Intermolecular Etherification and Intramolecular Glycosylation

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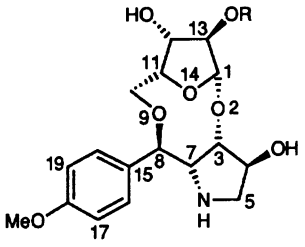
(Received May 17, 1994)

The first total synthesis of AB3217-A has been achieved. The deacetylanisomycin unit, (3*S*,4*S*,5*R*)-3-benzyloxy-1-(benzyloxycarbonyl)-5-[(1*R*)-1-hydroxy-1-(4-methoxyphenyl)methyl]-4-(2-tetrahydropyranyloxy)-pyrrolidine (**18**), was prepared from dimethyl L-tartrate by a stereoselective pyrrolidine-ring formation and a stereoselective reduction of phenyl ketone as the key steps. The lithium alkoxide of **18** was coupled with the D-xylofuranose unit, phenyl 2,3-di-*O*-benzyl-5-*O*-trifluoromethanesulfonyl-1-thio-α-D-xylofuranoside which was prepared from 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose, via an intermolecular etherificaiton. The resulting coupling product was subjected to de-*O*-tetrahydropyranylation and an intramolecular glycosylation to afford 4,12,13-tribenzyl-6-(benzyloxycarbonyl)AB3217-A (**30**). Final deprotection of **30** furnished AB3217-A.

AB3217-A (**1a**) was isolated in 1989 from the fermentation broth of the strain of *Streptomyces platensis* AB3217.[1] Two new substances, AB3217-B (**1b**) and AB3217-C (**1c**), the C13-ester derivatives of **1a**, were also isolated from the same strain.[1a,2] They showed marked activity against the two spotted spider mite, *Tetranychus urticae*.[1,2] The structure of **1a** was determined by spectroscopic means and its absolute configuration was determined by X-ray crystallographic analysis.[1] The structures of **1b** and **1c** were determined on the basis of spectroscopic studies in comparison with **1a**.[1a,2] The characteristic structure is a novel nine-membered ring built of deacetylanisomycin and β-D-xylofuranose, which are linked through glycosidic and ether bonds. We wish to describe in this full account[3] the details of the first total synthesis of AB3217-A (**1a**). It was divided into the deacetylanisomycin unit and the D-xylofuranose unit. On the basis of molecular model studies, we anticipated that the glycosidic bond could be formed in a β-fashion by an intramolecular glycosylation after connecting two units by an intermolecular etherification (Fig. 1). Although glycosylations are among the most widely-used reactions in the synthesis of biologically active substances,[4] intramolecular glycosylations have been rarely used in the synthesis of natural products.[5]



AB3217-A (1a): R = H
AB3217-B (1b): R = C(O)(CH$_2$)$_4$C(OH)Me$_2$
AB3217-C (1c): R = C(O)(CH$_2$)$_2$CHMe$_2$

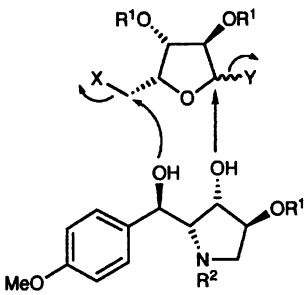


Fig. 1.

Results and Discussion

Synthesis of Deacetylanisomycin Unit. Synthesis of the pyrrolidine subunit began with the known diol **2**,[6] which was prepared from dimethyl L-tartrate in two steps, by the modified Seebach procedures (Scheme 1).[6] Mono-methoxybenzylation of **2** with 4-methoxybenzyl chloride (MPMCl) and NaH in DMF gave **3** in 76% yield. Tosylation of **3** followed by one-pot transformation of the resulting tosylate with *dl*-10-camphorsulfonic acid (CSA) and sodium methoxide in MeOH afforded epoxide **4** in 55% yield. Protection of **4** with 3,4-dihydro-2*H*-pyran (DHP) and CSA in CH_2Cl_2 provided **5** in 76% yield. All compounds having tetrahydropyranyl (THP) ether in this account consist of a 3 : 2—2 : 1 anomeric mixture, which were not separated. The epoxide-opening of **5** with NaN_3–NH_4Cl[7] in 8 : 1 MeOH–H_2O gave azido alcohol as a single isomer, which was benzylated with benzyl bromide and NaH in DMF to afford **6** in 95% yield. The epoxide-opening of other derivatives, having the benzoyl or *t*-butyldimethylsilyl (TBS) protecting group instead of the THP protecting group in **5**, resulted in a concomitant migration of these protecting groups. Reduction of the azido function of **6** with triphenylphosphine in aqueous THF and the resulting amine was protected with the *t*-butoxycar-

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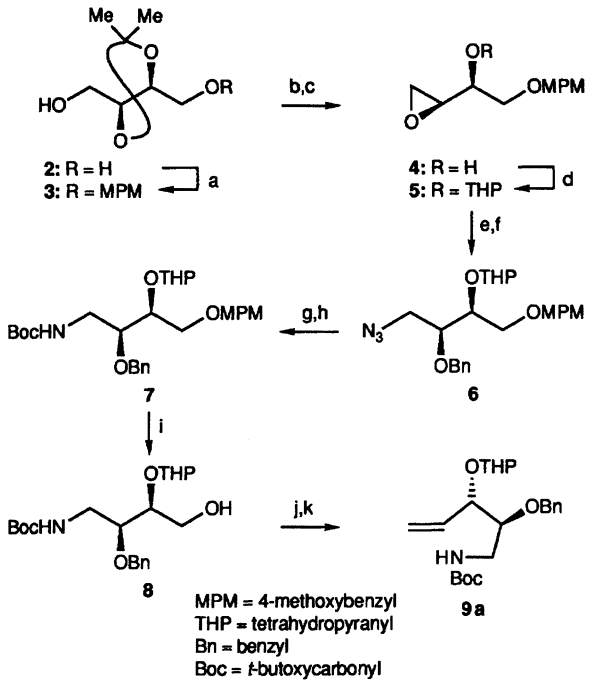
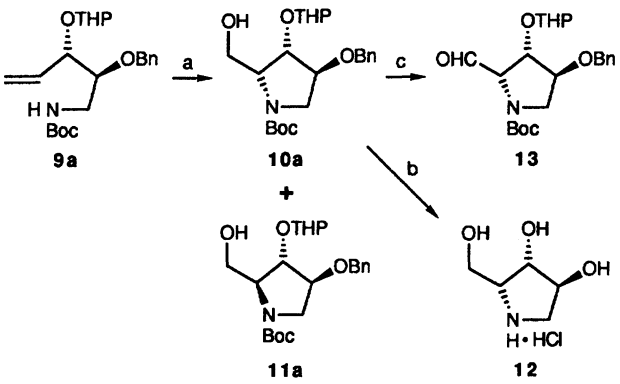


(a) MPMCl, NaH, DMF, -20 to 25 °C, 1 h, 76%; (b) TsCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 2 h, 91%; (c) CSA, MeOH, 25 °C, 7 h, then NaOMe, 25 °C, 1 h, 60%; (d) DHP, CSA, CH_2Cl_2, 25 °C, 0.5 h, 76%; (e) NaN_3, NH_4Cl, 8:1 MeOH-H_2O, 75 °C, 2 h; (f) BnBr, NaH, DMF, 25 °C, 1 h, 95% (2 steps); (g) Ph_3P, THF, 50 °C, 2 h, then H_2O, 50 °C, 2 h; (h) $(Boc)_2O$, $NaHCO_3$, CH_2Cl_2-H_2O, 25 °C, 1 h, 94% (2 steps); (i) DDQ, 18:1 CH_2Cl_2-H_2O, 25 °C, 0.5 h, 95%; (j) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 0.5 h, then Et_3N, -78 to 0 °C, 0.5 h; (k) $Ph_3P{=}CH_2$, benzene, 0 to 25 °C, 15 min, 68% (2 steps).

Scheme 1.

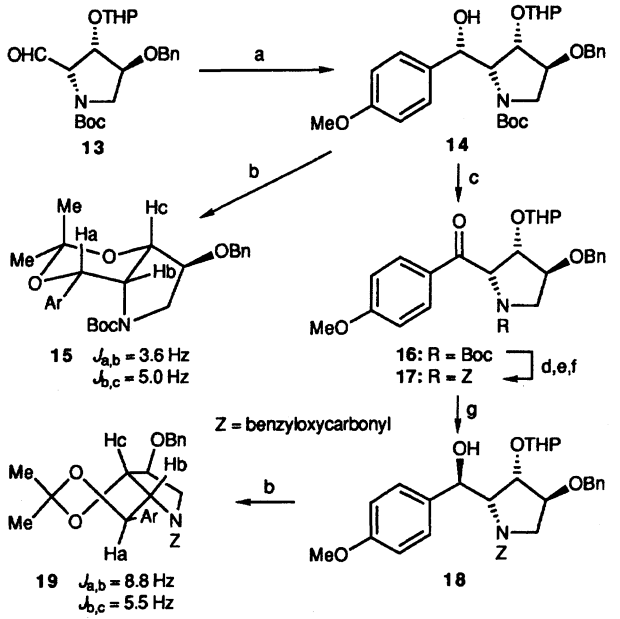
bonyl (Boc) group to afford **7** in 94% yield. Deprotection of **7** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) gave alcohol **8** in 95% yield, which was subjected to Swern oxidation and Wittig olefination with methylidenetriphenylphosphorane to give **9a** in 68% yield. The first crucial step for the synthesis of the deacetylanisomycin unit was the pyrrolidine-ring formation, which was realized by a method conceptually similar to those of Joullié[8] or Takahata-Momose[9] (Scheme 2). Namely, epoxidation of **9a** with MCPBA followed by $BF_3{\cdot}OEt_2$ treatment gave pyrrolidines **10a** and **11a** in 45 and 15% yields, respectively. A nonstereoselective pyrrolidine-ring formation or no reaction was observed when other amino olefins **9b**—**9d** were subjected to the conditions summarized in Table 1. Although the identical isolated yield of **10** was obtained in Entries 1—3, **9a** was the best choice because of total efficiency of the synthesis. The newly generated stereocenter in the major pyrrolidine **10a** was confirmed by its conversion to the known hydrochloride of 1,4-dideoxy-1,4-imino-D-xylitol (**12**)[10] by hydrogenolysis and acidic hydrolysis. Swern oxidation of **10a** gave aldehyde **13** in 82% yield.

The above aldehyde **13** was coupled with 4-anisyllithium prepared from 4-bromoanisole and *n*-BuLi in THF[9] to afford **14** in 80% yield as a single isomer (Scheme 3). The configuration at the benzylic stereo-



(a) (1) MCPBA, $NaHCO_3$, CH_2Cl_2, 25 °C, 2 d; (2) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C, 10 min, 45% (for **10a**), 15% (for **11a**); (b) (1) H_2, $Pd(OH)_2$, MeOH, 25 °C, 0.5 h; (2) 1:1 THF-2M aq HCl, 50 °C, 0.5 h, 95% (2 steps); (c) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 0.5 h, then Et_3N, -78 to 0 °C, 0.5 h, 82%.

Scheme 2.



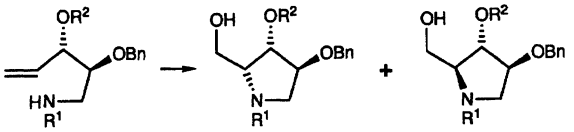
(a) 4-bromoanisole, *n*-BuLi, THF, -78 °C, 0.5 h, then **13** in THF, -78 °C, 0.5 h, 80%; (b) (1) CSA, MeOH, 25 °C, 0.5 h, 90%: (2) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, 25 °C, 1 d, 90%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 0.5 h, then Et_3N, -78 to 0 °C, 0.5 h, 88%; (d) 1:3 TFA-CH_2Cl_2, 25 °C, 0.25 h; (e) ZCl, K_2CO_3, aq THF, 25 °C, 0.5 h; (f) DHP, CSA, CH_2Cl_2, 25 °C, 0.5 h, 85% (3 steps); (g) DIBAL, toluene, -78 °C, 0.5 h, 91%.

Scheme 3.

center was determined by the coupling constants of the ^1H NMR spectrum of acetonide **15** obtained from **14** by acidic treatment and acetonization. This remarkable, but undesirable, facial selectivity may arise from NBoc-assisted addition of anisyllithium to the aldehyde.[8,9,11]

To invert the benzylic configuration, **14** underwent Swern oxidation to give **16** in 88% yield. Acidic treatment of **16** followed by successive *N*-benzyloxycarbonylation and *O*-protection provided **17** in 85% yield. It was necessary to alter the *N*-protecting group from Boc to benzyloxycarbonyl (Z) group because final deprotection of **30** (R^2=Boc, vide infra) under acidic conditions resulted in failure. Finally, diisobutylaluminum hydride

Table 1. Pyrrolidine-Ring Formation



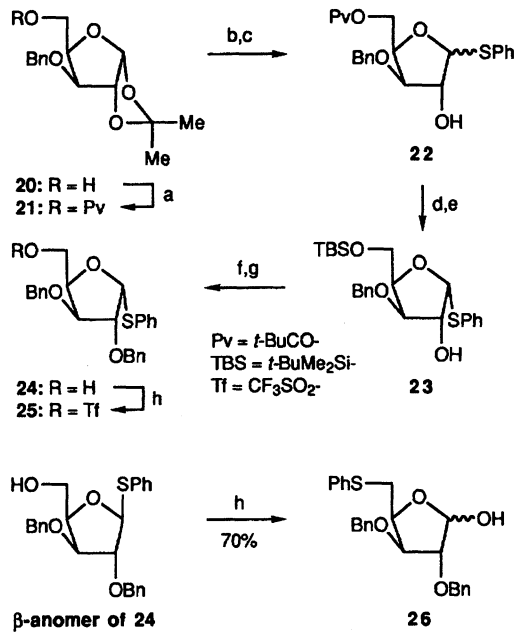
9a~9d 10a~10d 11a~11d

Entry	9			Conditions[a]	Isolated yield 10	Isolated yield 11
1	**9a**:[b]	R^1=Boc,	R^2=THP	A	45%	15%
2	**9b**:[b]	R^1=Boc,	R^2=TBS	A	45%	47%
3	**9c**:[b]	R^1=Boc,	R^2=H	A	45%	47%
4	**9c**			B	Almost no reaction	
5	**9d**	R^1=Z,	R^2=H	B	Almost no reaction	

a) (A) (1) MCPBA (3 equiv), $NaHCO_3$ (1.5 equiv), CH_2Cl_2, 25 °C, 2 d; (2)BF_3·OEt_2 (1.2 equiv), CH_2Cl_2, −78 °C, 10 min (see Ref. 8). (B) D-(−)-Diisopropyl tartrate, *t*-butyl hydroperoxide, Ti(O-*i*-Pr)$_4$, MS3AP, CH_2Cl_2, −20 °C, 15 d (see Ref. 9). b) The corresponding Z-derivatives (R^1=Z) gave low yields of **10** and **11**.

(DIBAL) reduction of **17** afforded **18** in 91% yield as a single isomer. This desirable facial selectivity may arise from NZ-assisted addition of hydride to the ketone.[12] The newly created stereocenter in **18** was confirmed by the coupling constants of the ^{1}H NMR spectrum of acetonide **19** derived from **18**.[13]

Synthesis of D-Xylofuranose Unit. Synthesis of the D-xylofuranose unit was initiated from **20**, which was derived from 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose in four steps (Scheme 4).[14] Pivaloylation of **20** with pivaloyl chloride (PvCl) and triethylamine in CH_2Cl_2 afforded **21**. Although the acetyl derivative of **20** (R=Ac) was used in the initial studies,[3] the pivaloate **21** was selected for the large scale preparation because the pivaloyl group was more stable than the acetyl group on the next deacetoinzation. After deacetonization of the crude **21** in 50% aqueous acetic acid at 100 °C for 5 h, the resulting free sugar (92% yield from **20**) was treated with diphenyl disulfide and tributylphosphine in THF[15,16] to afford a 1 : 2 mixture of α : β anomers **22** in 94% combined yield. Since this mixture could not be separated, it was subjected to de-*O*-pivaloylation with methyllithium in ether and the subsequent silylation with TBSCl to afford the separable phenyl α-thioglycoside **23** and its β-anomer in 30 and 59% yields, respectively. Benzylation and subsequent de-*O*-silylation of **23** gave **24** in 95% yield. The anomeric configurations of **24** and its β-anomer (and hence **23** and its β-anomer) were determined by their ^{1}H NMR NOE experiments: for **24**, H-1→H-2, 9.7%. For β-anomer, H-1→H-2, 4.0%; H-1→H-3, 2.1%; H-1→H-4, 2.3%. Finally, introduction of a leaving group to **24** was realized by treatment of **24** with trifluoromethanesulfonic anhydride (Tf_2O) and triethylamine in CH_2Cl_2 at −78 °C for 5 min to afford the extremely labile triflate **25**, which was immediately subjected to the next reaction. Etherification of other derivatives

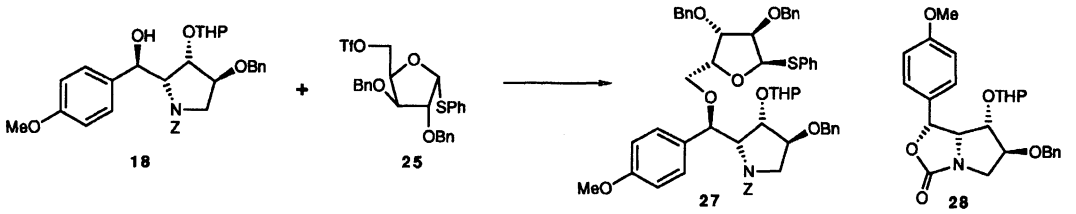


(a) PvCl, Et_3N, CH_2Cl_2, 25 °C, 15 h; (b) 50% aq AcOH, 100 °C, 5 h, 92% (2 steps); (c) $(PhS)_2$, *n*-Bu_3P, THF, 25 °C, 0.5 h, 94%; (d) MeLi, ether, 0 to 25 °C, 15 min; (e) TBSCl, imidazole, DMF, 0 °C, 0.5 h, 30% (for **23**) (2 steps); (f) BnBr, NaH, *n*-Bu_4NI, THF, 25 °C, 2 h; (g) *n*-Bu_4NF, THF, 25 °C, 0.5 h, 95% (2 steps); (h) Tf_2O, Et_3N, CH_2Cl_2, -78 °C, 5 min.

Scheme 4.

of **24** (R=Ms or Ts, or OR=I) with the model alkoxide, which was derived from 4-methoxybenzyl alcohol or 1-(4-methoxyphenyl)-2-methyl-1-propanol, under a variety of conditions was unsuccessful, giving either the recovered starting materials or decomposition depending on the conditions employed. Triflation of the corresponding β-anomer of **24** was also unsuccessful, giving **26** via 1,5-SPh group migration.[17] The structure of **26** was confirmed by the ^{1}H NMR and mass spectra. Al-

Table 2. Intermolecular Etherification of the Deacetylanisomycin Unit and the D-Xylofuranose Unit



Entry	Base[a]	Solvent	Equiv of **25**[b]	Conditions[c]	Isolated yield/%		
					27	**18**	**28**
1	$KN(SiMe_3)_2$	DMF	1.5	A	Trace	82	Trace
2	$NaN(SiMe_3)_2$	DMF	1.5	A	20	0	50
3	$LiN(i\text{-}Pr)_2$	DMF	1.5	A	33	57	0
4	*n*-BuLi	DMF	1.5	A	35	51	0
5	$LiN(i\text{-}Pr)_2$	HMPA	1.1	A	30	0	56
6	$LiN(i\text{-}Pr)_2$	HMPA	1.5	A	31	42	0
7	$LiN(i\text{-}Pr)_2$	HMPA	2.1	A	30	60	0
8	*n*-BuLi	DMF	1.5	B	55	Trace	33
9	*n*-BuLi	DMF	3.0	B	37	57	Trace
10	*n*-BuLi	DMF	1.5	C	64	20	Trace
11	*n*-BuLi	DMF	2.0	C	75	Trace	Trace

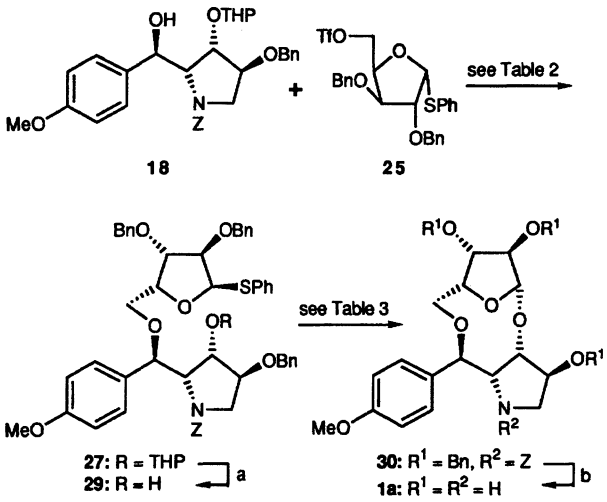
a) 1.5 equiv (for **18**) of base was used. b) Equiv of **25** for **18**. c) (A) Base was added at 0 °C to a mixture of **18**, **25**, MS4AP, and solvent. The reaction mixture was stirred at 25 °C for 0.5 h. (B) Base was added at 0°C to a mixture of **18**, MS4AP, and DMF. After 5 min at 0 °C, **25** in DMF was added and the mixture was stirred at 25 °C for 0.5 h. (C) After washing a hexane solution of the crude **25** with water, the residual **25** was subjected to the conditions B.

Table 3. Intramolecular Glycosylation of **29** with NBS

Entry	Solvent	Temp/°C	Time/h	Yield of **30**
1	CH_2Cl_2	25	1	Decomp
2	CH_3CN	25	24	30%
3	CH_3NO_2	25	30	**29**+Decomp
4	THF	25	20	Decomp
5	Toluene	60	6d	40%
6	Toluene	90	24	64%
7	Toluene	110	2	46%

though it was disappointing not to be able to utilize the β-anomer of **24**, it was decided to investigate the intermolecular etherification of the deacetylanisomycin and D-xylofuranose units.

Intermolecular Etherification. We examined a number of conditions to achieve this connection; the relevant data are summarized in Table 2. Since the cyclic urethane **28** was formed in 89% yield when **18** was treated with lithium diisopropylamide (LDA) in DMF at 0 to 25 °C for 0.5 h, the base was added after mixing **18**, **25**, molecular sieves 4A powder (MS 4AP), and solvent. It was necessary to add MS 4AP to the reaction mixture because triflate **25** was very unstable in DMF without MS 4AP. Among the bases employed, lithium bases were better than potassium and sodium bases (Entries 1—4). Hexamethylphosphoric triamide (HMPA) could be also used as a solvent (Entries 5—7). It was found that the work-up procedure in the preparation of triflate **25** was important to obtain a good



Scheme 5.

yield of the coupling product (Entries 8—11; see footnote c of Table 2 and Experimental), giving 75% yield of **27** reproducibly (Entry 11). Acidic treatment of **27** afforded **29** in 90% yield (Scheme 5).

Intramolecular Glycosylation, Final Stage. The ultimate intramolecular glycosylation of **29** was accomplished by *N*-bromosuccinimide (NBS)[16] in several solvents (Table 3). The stability of the oxonium ion derived from **29** and NBS depended on the solvent employed. Toluene proved to be the best solvent, providing

30 in 64% yield. A final deprotection of **30** by hydrogenolysis in a mixture of 1:2 dioxane–0.01 M (1 M=1 mol dm^{-3}) aqueous HCl and resin purification furnished AB3217-A (**1a**) in 80% yield. The synthetic **1a** was identical in all respects (^{1}H NMR, IR, UV, mp, $[\alpha]_D$, and TLC mobilities) with the natural AB3217-A.[1)]

Experimental

The 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 a JEOL GSX270 spectrometer in $CDCl_3$ at 25 °C using TMS as internal standard or in DMSO-d_6 at 80 °C (DMSO=2.50) unless otherwise noted. Mass spectra (EI) were recorded on a JEOL JMS-DX302 mass spectrometer. Silica-gel TLC and column chromatography were performed on a Merck TLC 60F-254 and a 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, the organic solvents were purified and dried by appropriate procedures, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

(2*S*,3*S*)-2,3-Isopropylidenedioxy-4-(4-methoxybenzyloxy)-1-butanol (3). To a stirred suspension of NaH (2.41g, 100 mmol) in dry DMF (750 ml) was added at −20 °C a solution of **2** (15.1 g, 93.1 mmol) in dry DMF (75 ml). After 0.5 h at −20 °C, MPMCl (13.2 ml, 97.4 mmol) was added and the mixture was warmed to 25 °C during 1 h. The reaction mixture was concentrated at 45 °C and to the residue were added ether and saturated aqueous NH_4Cl. The aqueous layer was extracted with ether and the combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1 kg) with 2:1 hexane–ethyl acetate to afford **3** (20.0 g, 76%) as a colorless syrup: R_f=0.50 (3:2 hexane–ethyl acetate); $[\alpha]_D^{30}$+10.6° (*c* 1.06); IR ($CHCl_3$) 3599, 3459, 3019, 2877, 1613, 1514, 1373, 1249, 1172, 1081, and 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.41 (6H, s, CMe_2), 2.25 (1H, dd, *J*=8.0 and 4.5 Hz, OH), 3.52 (1H, dd, $J_{3,4}$=5.9 Hz, J_{gem}=9.9 Hz, H-4), 3.62—3.80 (3H, m, H-1, H-1′, and H-4′), 3.81 (3H, s, OMe), 3.92 (1H, dt, $J_{1,2}=J_{1',2}$=4.3 Hz, $J_{2,3}$=8.2 Hz, H-2), 4.03 (1H, ddd, $J_{2,3}$=8.2 Hz, $J_{3,4}$=5.9 Hz, $J_{3,4'}$=4.9 Hz, H-3), 4.52 (2H, s, OCH_2Ar), 6.88 and 7.24 (each 2H, each d, *J*=8.5 Hz, aromatic protons). Found: *m/z* 283.1559 (M+H)$^+$. Calcd for $C_{15}H_{23}O_5$: M+1, 283.1546.

(2*S*,3*S*)-3,4-Epoxy-1-(4-methoxybenzyloxy)-2-butanol (4). To a stirred solution of **3** (33.1 g, 117 mmol) in dry CH_2Cl_2 (500 ml) were added at 0 °C *p*-toluenesulfonyl chloride (24.6 g, 129 mmol), triethylamine (24.5 ml, 176 mmol), and 4-dimethylaminopyridine (DMAP) (2.86 g, 23.4 mmol). After 2 h at 25 °C, the reaction mixture was poured into cold saturated aqueous NH_4Cl and the new mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1.2 kg) with 3:1 hexane–ethyl acetate to afford a colorless syrup (46.7 g, 91%). This was dissolved in dry MeOH (935 ml) and to this was added CSA (4.97 g, 21.4 mmol). After 7 h at 25 °C, the reaction mixture was cooled to 0 °C and to this was added NaOMe (6.94 g, 128 mmol); the new mixture was stirred at 25 °C for 1 h. The reaction mixture was treated with CG-50 in MeOH and the insoluble materials were filtered and washed with MeOH. The combined filtrate and washings were concentrated. The residue was dissolved in ethyl acetate and this was washed with water and saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1.2 kg) with 3:1 and then 1:1 hexane–ethyl acetate to afford **4** (14.5 g, 60%) as a colorless syrup: R_f=0.35 (1:1 hexane–ethyl acetate); $[\alpha]_D^{23}$+13.6° (*c* 1.03); IR ($CHCl_3$) 3564, 3019, 1613, 1514, 1250, 1175, 1101, and 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.25 (1H, d, *J*=6.3 Hz, OH), 2.74—2.81 (2H, m, 2×H−4), 3.10 (1H, dt, *J*=2.9, 7.8, and 7.8 Hz, H-3), 3.54 (1H, dd, J_{gem}=10.0 Hz, $J_{1,2}$=6.0 Hz, H-1), 3.59 (1H, dd, J_{gem}=10.0 Hz, $J_{1',2}$=5.0 Hz, H-1′), 3.76 (1H, m, H-2), 3.81 (3H, s, OMe), 4.50 (2H, s, OCH_2Ar), 6.89 and 7.26 (each 2H, each d, *J*=8.5 Hz, aromatic protons). Found: *m/z* 224.1061 (M$^+$). Calcd for $C_{12}H_{16}O_4$: M, 224.1048.

(2*S*,3*S*)-1,2-Epoxy-4-(4-methoxybenzyloxy)-3-(2-tetrahydropyranyloxy)butane (5). To a stirred solution of **4** (21.4 g, 95.4 mmol) in dry CH_2Cl_2 (430 ml) were added at 25 °C DHP (16.6 ml, 182 mmol) and CSA (4.43 g, 19.1 mmol). After 0.5 h at 25 °C, triethylamine (2.66ml, 19.1 mmol) was added and the mixture was concentrated. The residue was chromatographed on silica gel (800 g) with 4:1 hexane–ethyl acetate to afford **5** (22.3 g, 76%) as a colorless syrup: R_f=0.60 (2:1 hexane–ethyl acetate); IR ($CHCl_3$) 3012, 2948, 1613, 1513, 1249, 1175, 1120, 1076, 1034, and 984 cm^{-1}; ^{1}H NMR ($CDCl_3$, 3:2 mixture) δ=1.40—1.95 (6H,m). 2.58 (3/5H, dd, *J*=5.0 and 3.0 Hz, H-1), 2.73 — 2.82 (7/5H, m, H-1 and H-1′), 3.11 (2/5H, ddd, *J*=7.0, 5.0, and 3.0 Hz, H-2), 3.16 (3/5H, ddd, *J*=5.0, 4.0, and 3.0 Hz, H-2), 3.43—3.74 (4H, m), 3.81 (3H, s, OMe), 3.84—4.01 (1H, m), 4.47 and 4.50 (each 2/5H, ABq, *J*=12.0 Hz, OCH_2Ar), 4.49 and 4.53 (each 3/5H, ABq, *J*=12.0 Hz, OCH_2Ar), 4.81 (2/5H, br t, *J*=4.0 Hz, OCHO), 4.91 (3/5H, dd, *J*=4.0 and 2.6 Hz, OCHO), 6.88 (2H, d, *J*=9.0 Hz, aromatic protons), 7.23 and 7.25 (4/5H and 6/5H, each d, *J*=9.0 Hz, aromatic protons). Found: *m/z* 308.1624 (M$^+$). Calcd for $C_{17}H_{24}O_5$: M, 308.1623.

(2*S*,3*S*)-1-Azido-2-benzyloxy-4-(4-methoxybenzyloxy)-3-(2-tetrahydropyranyloxy)butane (6). A mixture of **5** (20.6 g, 66.8 mmol), NH_4Cl (7.86 g, 147 mmol), NaN_3 (21.7 g, 334 mmol), and 8:1 MeOH–water (372 ml) was heated at 75 °C for 2 h. The reaction mixture was concentrated and to the residue were added ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated aqueous NaCl, dried and concentrated. The residue (23.5 g) was dissolved in dry DMF (340 ml) and to this was added benzyl bromide (11.9 ml, 100 mmol). To this was added at 0 °C NaH (2.57 g, 107 mmol) and the mixture was stirred at 25 °C for 1 h. MeOH (8 ml) was added at 0 °C and the mixture was stirred at 25 °C for 0.5 h. Saturated aqueous NH_4Cl was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (800 g) with 7:1 hexane–ethyl acetate to afford **6** (28.0 g, 95%) as a colorless syrup: R_f=0.50 (4:1 hexane–

acetone); IR ($CHCl_3$) 3011, 2946, 2103, 1612, 1514, 1249, 1117, 1075, and 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 3:2 mixture) δ=1.40—1.90 (6H, m), 3.23—4.07 (8H, m), 3.80 and 3.81 (total 3H, each s, OMe), 4.39—4.52 (2H, m), 4.61—4.75 (3H, m), 6.86 (2H, d, J=8.0 Hz, aromatic protons), and 7.19—7.36 (7H, m, aromatic protons). Found: m/z 441.2272 (M^+). Calcd for $C_{24}H_{31}N_3O_5$: M, 441.2264.

(2*S*,3*S*)-2-Benzyloxy-1-(*t*-butoxycarbonylamino)-4-(4-methoxybenzyloxy)-3-(2-tetrahydropyranyloxy)butane (7). To a stirred solution of **6** (11.7 g, 26.5 mmol) in dry THF (117 ml) was added at 25 °C triphenylphosphine (7.65 g, 29.2 mmol). After 2 h at 50 °C, water (2.4 ml) was added and the mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2 (234 ml) and water (89 ml). To this were added at 0 °C $NaHCO_3$ (8.91 g, 106 mmol) and $(Boc)_2O$ (12.2 ml, 53.1 mmol). After 1 h at 25 °C, the reaction mixture was concentrated and the residue was dissolved in ethyl acetate. This was washed with water, saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (500 g) with 4:1 and then 3:1 hexane–ethyl acetate to afford **7** (12.9 g, 94%) as a colorless syrup: R_f=0.40 (4:1 hexane–ethyl acetate); IR ($CHCl_3$) 3449, 3011, 2945, 1706, 1512, 1367, 1249, 1173, 1074, and 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 3:2 mixture) δ=1.42 and 1.43 (total 9H, each, s, *t*-Bu), 1.40—1.95 (6H, m), 3.10—4.10 (8H, m), 3.79 and 3.80 (total 3H, each s, OMe), 4.38, 4.40 and 4.45, 4.48 (total 2H, each ABq, J=11.0 Hz, OCH_2Ar), 4.50—4.75 (3H, m, OCH_2Ar and OCHO), 4.84 and 5.51 (total 1H, each br, NH), 6.86 and 6.87 (total 2H, each d, J=8.6 Hz, aromatic protons), and 7.18—7.37 (7H, m, aromatic protons). Found: m/z 515.2875 (M^+). Calcd for $C_{29}H_{41}NO_7$: M, 515.2883.

(2*S*,3*S*)-3-Benzyloxy-4-(*t*-butoxycarbonylamino)-2-(2-tetrahydropyranyloxy)-1-butanol (8). To a stirred solution of **7** (12.6 g, 24.4 mmol) in 18:1 CH_2Cl_2–water (240 ml) was added at 0 °C DDQ (6.10 g, 26.9 mmol). After 0.5 h at 25 °C, the reaction mixture was passed through Florisil (480 g) and eluted with CH_2Cl_2. The eluate was concentrated and the residue was chromatographed on silica gel (500 g) with 3:2 hexane–ethyl acetate to afford **8** (9.18g, 95%) as a colorless syrup: R_f=0.20 (2:1 hexane–ethyl acetate); IR ($CHCl_3$) 3452, 1707, 1506, 1455, 1393, 1368, 1274, 1248, 1163, 1135, 1074, 1028, and 981 cm^{-1}; ^1H NMR ($CDCl_3$, 3:2 mixture) δ=1.43 and 1.44 (total 9H, each s, *t*-Bu), 1.45—1.90 (6H, m), 3.14 (1H, dt, J=13.8 and 5.8 Hz), 3.30—4.05 (8H, m), 4.50—4.75 (3H, m), 4.82 and 5.35 (total 1H, each br, NH), and 7.28—7.38 (5H, m, Ph). Found: C, 63.26; H, 8.88; N, 3.43%. Calcd for $C_{21}H_{33}NO_6$: C, 63.78; H, 8.41; N, 3.54%.

(3*S*,4*S*)-4-Benzyloxy-5-(*t*-butoxycarbonylamino)-3-(2-tetrahydropyranyloxy)-1-pentene (9a). A solution of DMSO (6.90 ml, 97.2 mmol) in dry CH_2Cl_2 (17 ml) was added at −78 °C to a stirred solution of oxalyl dichloride (4.24 ml, 48.6 mmol) in dry CH_2Cl_2 (117 ml). After 20 min at −78 °C, a solution of **8** (16.0 g, 40.5 mmol) in dry CH_2Cl_2 (96 ml) was added dropwise and the resulting suspension was stirred at −78 °C for 0.5 h. After addition of triethylamine (22.6 ml, 162 mmol), the mixture was gradually warmed to 0 °C during 0.5 h. The reaction mixture was quenched with water and extracted with 4:1 benzene–ether. The extracts were washed with saturated aqueous NaCl, dried and concentrated. The residue (15.9 g) was dissolved in dry benzene (470 ml) and to this was added at 0 °C $Ph_3P{=}CH_2$ (33.5 g, 121 mmol). After 15 min at 25 °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 (750 g) with 6:1 hexane–ethyl acetate to afford **9a** (10.8 g, 68%) as a colorless syrup: R_f=0.70 (3:1 hexane–ethyl acetate); IR ($CHCl_3$) 3453, 1708, 1506, 1455, 1393, 1368, 1272, 1248, 1168, 1118, 1076, 1023, and 971 cm^{-1}; ^1H NMR ($CDCl_3$, 2:1 mixture) δ=1.43 (9H, s, *t*-Bu), 1.45—1.95 (6H, m), 3.11 and 3.24 (total 1H, dt, J=13.4 and 6.2 Hz), 3.30–3.65 (3H, m), 3.82—3.95 (1H, m), 4.24 and 4.29 (total 1H, dd, J=6.2 and 6.2 Hz), 4.61, 4.72 and 4.65, 4.75 (total 2H, each AB_q, J=11.6 Hz, OCH_2Ph), 4.60—5.10 (2H, m), 5.20—5.43 (2H, m, 2×H-1), 5.79 and 5.94 (total 1H, each ddd, J=17.0, 10.0, and 6.4 Hz, H-2), and 7.28—7.38 (5H, m, Ph). Found: C, 67.13; H, 9.02; N, 3.52%. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50; N, 3.58%.

(3*S*, 4*S*, 5*R*)-3-Benzyloxy-1-(*t*-butoxycarbonyl)-5-hydroxymethyl-4-(2-tetrahydropyranyloxy)pyrrolidine (10a) and Its 5*S*-Epimer 11a. To a stirred mixture of **9a** (3.85 g, 9.83 mmol) and $NaHCO_3$ (1.24 g, 14.8 mmol) in dry CH_2Cl_2 (77 ml) was added at 0 °C MCPBA (5.09 g, 29.5 mmol). After 2 d at 25 °C, a 7:1 mixture of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ was added and the new mixture was extracted with CH_2Cl_2. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was dissolved in dry CH_2Cl_2 (80 ml) and to this was added at −78 °C $BF_3{\cdot}OEt_2$ (1.45 ml, 11.8 mmol). After 10 min at −78 °C, saturated aqueous NH_4Cl was added and the mixture was extraxted with CH_2Cl_2. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (400 g) with 5:1 chloroform–ethyl acetate to afford **10a** (1.80 g, 45%) and **11a** (601 mg, 15%) as colorless syrups.

10a: R_f = 0.39 (5:1 chloroform–ethyl acetate); IR ($CHCl_3$) 3445, 1688, 1455, 1398, 1368, 1255, 1169, 1130, 1076, 1035, and 979 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.42 (9H, s, *t*-Bu), 1.35—1.85 (6H, m), 3.27 (1H, dd, J=11.6 and 4.2 Hz), 3.47 (1H, dd, J=11.6 and 5.8 Hz), 3.41—3.52 (1H, m), 3.60—3.75 (2H, m), 3.75—3.92 (2H, m), 4.09 (1H, br t, J=5.8 Hz), 4.13—4.22 (1H, m), 4.23 (1H, dd, J=6.8 and 5.2 Hz), 4.55 (2H, s, OCH_2Ph), 4.72 (1H, br), and 7.25—7.40 (5H, m, Ph). Found: C, 64.64; H, 8.76; N, 3.21%. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44%.

11a: R_f=0.25 (5:1 chloroform–ethyl acetate); ^1H NMR (DMSO-d_6) δ=1.30—1.80 (6H, m), 1.42 (9H, s, *t*-Bu), 3.20—3.90 (7H, m), 3.96—4.65 (5H, m), 4.70—4.78 (1H, br), and 7.25—7.40 (5H, m, Ph).

1,4-Dideoxy-1,4-imino-D-xylitol Hydrochloride (12). A mixture of **10a** (48.3 mg, 0.119 mmol), $Pd(OH)_2$(10 mg), and MeOH (1 ml) was stirrled under an atmosphere of hydrogen (1 atm) at 25 °C for 0.5 h. The insoluble materials were filtered and washed with MeOH. The combined filtrate and washings were concentrated and the residue was dissolved in 1:1 THF–2 M aqueous HCl (1 ml). After 0.5 h at 50 °C, the mixture was concentrated to afford **12** (19.1 mg, 95%) as a colorless syrup. The ^{13}C NMR spectrum was identical with the reported one:[10] ^{13}C NMR

(67 MHz, D_2O, dioxane=69.3 ppm) δ=77.1, 65.7, 60.0, and 53.3 [lit,[10] 77.1, 65.7, 60.0, and 53.3].

(3*S*,4*S*,5*S*)-3-Benzyloxy-1-(*t*-butoxycarbonyl)-5-formyl-4-(2-tetrahydropyranyloxy)pyrrolidine (13). A solution of DMSO (0.352 ml, 4.96 mmol) in dry CH_2Cl_2 (0.88 ml) was added at −78 °C to a stirred solution of oxalyl dichloride (0.216 ml, 2.48 mmol) in dry CH_2Cl_2 (5.8 ml). After 20 min at −78 °C, a solution of **10a** (504 mg, 1.24 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise and the resulting suspension was stirred at −78 °C for 0.5 h. After addition of triethylamine (1.04 ml, 7.44 mmol), the mixture was gradually warmed to 0 °C during 0.5 h. The reaction mixture was quenched with water and extracted with 4:1 benzene–ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (30 g) with 5:1 and then 4:1 hexane–ethyl acetate to afford **13** (412 mg, 82%) as a colorless syrup: R_f=0.57 (2:1 hexane–ethyl acetate); ^{1}H NMR (DMSO-d_6, 2:1 mixture) δ=1.39 (9H, s, *t*-Bu), 1.30—1.65 (6H, m), 3.40—3.70 (4H, m), 4.07—4.16 (1H, m), 4.25 (1H, dd, J=6.0 and 2.0 Hz), 4.50—4.75 (4H, m), 7.27—7.39 (5H, m, Ph), 9.44 and 9.48 (total 1H, each d, J=2.0 Hz, CHO).

(3*S*,4*S*,5*R*)-3-Benzyloxy-1-(*t*-butoxycarbonyl)-5-[(1*S*)-1-hydroxyl-1-(4-methoxyphenyl)methyl]-4-(2-tetrahydropyranyloxy)pyrrolidine (14). To a stirred solution of 4-bromoanisole (0.507 ml, 4.05 mmol) in dry THF (8.1 ml) was added at −78 °C 1.61 M *n*-BuLi in hexane (2.38 ml, 3.84 mmol). After 0.5 h at −78 °C, a solution of **13** (410 mg, 1.01 mml) in dry THF (2.1 ml) was added and the mixture was stirred at −78 °C for 0.5 h. 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 (50 g) with 4:1 and then 3:1 hexane–ethyl acetate to afford **14** (420 mg, 80%) as a colorless syrup: R_f=0.20 (3:1 hexane–ethyl acetate); IR ($CHCl_3$) 3499, 3011, 2950, 1687, 1513, 1397, 1368, 1248, 1175, 1079, and 1035 cm^{-1}; ^{1}H NMR (DMSO-d_6, 2:1 mixture) δ=1.00—1.85 (15H, m), 3.20 (1H, dd, J=11.0 and 5.0 Hz), 3.63 (1H, dd, J=11.0 and 7.2 Hz), 3.73 and 3.74 (total 3H, each s, OMe), 4.05—4.20 (2H, m), 4.55 (2H, s, OC*H*$_2$Ph), 4.76 and 5.00 (total 1H, each m), 4.83 (1H, d, J=5.6 Hz), 6.83 and 7.16 (each 2H, ABq, J=8.4 Hz, aromatic protons), and 7.26—7.40 (5H, m, Ph). Found: C, 67.62; H, 7.63; N, 3.09%. Calcd for $C_{29}H_{39}NO_7$: C, 67.82; H, 7.65; N, 2.73%.

Preparation of 15. A mixture of **14** (15.3 mg, 0.0279 mmol), CSA (1.3 mg, 0.0056 mmol), and MeOH (0.31 ml) was stirred at 25 °C for 0.5 h. Triethylamine (0.002 ml, 0.01 mmol) was added and the mixture was concentrated. The residue was chromatographed on silica gel (2 g) with 2:1 hexane–ethyl acetate to afford a syrup (11.6 mg, 90%). This was dissolved in dry CH_2Cl_2 (0.2 ml) and to this were added 2,2-dimethoxypropane (0.006 ml, 0.05 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (0.3 mg, 0.001 mmol). After 1 d at 25 °C, triethylamine (0.003 ml, 0.02 mmol) was added and the mixture was concentrated. The residue was chromatographed on silica gel (2 g) with 6:1 hexane–ethyl acetate to afford **15** (11.3 mg, 90%) as a colorless syrup: R_f=0.90 (2:1 hexane–ethyl acetate); ^{1}H NMR (DMSO-d_6, 60 °C) δ=1.32 and 1.49 (each 3H, each s, CMe_2), 3.40 (1H, dd, J_{gem}=11.6 Hz, J=2.4 Hz, one of CH_2N), 3.71 (3H, s, OMe), 3.84—3.93 (2H, m, one of CH_2N and C*H*OBn), 3.91 (1H, dd, J=3.6 and 5.0 Hz, CHN), 4.47 (2H, s, OC*H*$_2$Ph), 4.60 (1H, d, J=5.0 and 0 Hz, C*H*OCMe$_2$), 5.12 (1H, d, J=3.6 Hz, C*H*OCMe$_2$), 6.80 (2H, d, J=9.0 Hz, aromatic protons), and 7.15—7.35 (7H, m, aromatic protons).

(3*S*, 4*S*, 5*S*)-3-Benzyloxy-1-(*t*-butoxycarbonyl)-5-(4-methoxybenzoyl)-4-(2-tetrahydropyranyloxy)pyrrolidine (16). A solution of DMSO (0.232 ml, 3.27 mmol) in dry CH_2Cl_2 (0.582 ml) was added at −78 °C to a stirred solution of oxalyl dichloride (0.143 ml, 1.64 mmol) in dry CH_2Cl_2 (3.86 ml). After 20 min at −78 °C, a solution of **14** (420 mg, 0.818 mmol) in dry CH_2Cl_2 (2.5 ml) was added dropwise and the resulting suspension was stirred at −78 °C for 0.5 h. After addition of triethylamine (0.684 ml, 4.91 mmol), the mixture was gradually warmed to 0 °C during 0.5 h. The reaction mixture was quenched with water and extracted with 4:1 benzene–ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (35 g) with 3:1 hexane–ethyl acetate to afford **16** (366 mg, 88%) as a colorless syrup: R_f=0.40 (2:1 hexane–ethyl acetate); IR ($CHCl_3$) 1697, 1602, 1402, 1368, 1257, 1232, 1173, 1126, 1034, and 974 cm^{-1}; ^{1}H NMR (DMSO-d_6, 2:1 mixture) δ=1.00—1.55 (15H, m), 3.10—3.20 (2H, m), 3.50 (1H, dd, J=11.0 and 3.4 Hz), 3.64 and 3.66 (total 1H, each dd, J=11.0 and 5.0 Hz), 3.84 and 3.86 (total 3H, each s, OMe), 4.15 (1H, m), 4.50—4.77 (4H, m), 5.36—5.50 (1H, m, H-5), 7.02 and 7.95 (each 2H, ABq, J=8.6 Hz, aromatic protons), and 7.26—7.40 (5H, m, Ph). Found: C, 67.61; H, 7.44, N; 2.95%. Calcd for $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N. 2.74%.

(3*S*, 4*S*, 5*S*)-3-Benzyloxy-1-(benzyloxycarbonyl)-5-(4-methoxybenzoyl)-4-(2-tetrahydropyranyloxy)pyrrolidine (17). To a stirred solution of **16** (366 mg, 0.715 mmol) in CH_2Cl_2 (3.66 ml) was added at 25 °C 1:1 trifluoroacetic acid (TFA)–CH_2Cl_2 (3.66 ml). After 15 min at 25 °C, the mixture was concentrated and the residue was dissolved in 2:1 THF–water (10.5 ml). To this were added at 0 °C K_2CO_3 (148 mg, 1.07 mmol) and benzyl chloroformate (0.122 ml, 0.858 mmol). After 0.5 h at 25 °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 (330 mg) was dissolved in dry CH_2Cl_2 (5 ml) and to this were added at 25 °C DHP (0.130 ml, 1.43 mmol) and CSA (33.2 mg, 0.143 mmol). After 0.5 h at 25 °C, triethylamine (0.020 ml, 0.14 mmol) was added and the mixture was concentrated. The residue was chromatographed on silica gel (20 g) with 2:1 hexane–ethyl acetate to afford **17** (332 mg, 85%) as a colorless syrup: R_f=0.80 (1:1 hexane–ethyl acetate); IR ($CHCl_3$) 1703, 1602, 1422, 1354, 1261, 1229, 1172, 1126, 1033, and 980 cm^{-1}; ^{1}H NMR (DMSO-d_6, 3:2 mixture) δ=1.10—1.60 (6H, m), 3.00—4.30 (6H, m), 3.85 and 3.87 (total 3H, each s, OMe), 4.55—4.80 (4H, m), 4.90—5.15 (2H, m, COOC*H*$_2$Ph), 5.50—5.65 (1H, m, H-5), 7.00 and 7.95 (each 2H, each br, aromatic protons), and 7.05—7.40 (10H, m, 2×Ph). Found: C, 69.86; H, 6.88; N, 2.20%. Calcd for $C_{32}H_{35}NO_7$: C, 70.44; H, 6.47; N, 2.59%.

(3*S*,4*S*,5*R*)-3-Benzyloxy-1-(benzyloxycarbonyl)-5-[(1*R*)-1-hydroxy-1-(4-methoxyphenyl)methyl]-4-(2-tetrahydropyranyloxy)pyrrolidine (18). To a stirred solution of **17** (225 mg, 0.412 mmol) in dry toluene (4.5 ml) was added at −78 °C 1.02 M DIBAL in toluene (0.810 ml,

0.826 mmol). After 0.5 h at −78 °C, MeOH (0.06 ml) and water (0.1 ml) were added and the mixture was warmed to 25 °C. To this were added potassium sodium tartrate tetrahydrate (1.16 g, 4.11 mmol) in water (5 ml) and the new mixture was stirred at 25 °C for 5 h. The mixture was extracted with ethyl acetate and the extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (20 g) with 3:1 and then 2:1 hexane–ethyl acetate to afford **18** (206 mg, 91%) as a colorless syrup: R_f=0.50 (2:1 hexane–ethyl acetate); IR ($CHCl_3$) 1675, 1510, 1420, 1240, 1210, 1110, 1035, and 965 cm^{-1}; ^1H NMR (DMSO-d_6, 2:1 mixture) δ=1.20—1.75 (6H, m), 3.20—4.00 (6H, m), 3.73 and 3.74 (total 3H, each s, OMe), 4.15—4.60 (4H, m), 4.70—5.15 (4H, m), 6.78 and 6.82 (total 2H, each d, J=8.4 Hz, aromatic protons), and 7.20—7.40 (12H, m, aromatic protons). Found: C, 70.04; H, 6.91; N, 2.86%. Calcd for $C_{32}H_{37}NO_7$: C, 70.18; H, 6.81; N, 2.56%.

Preparation of 19. A mixture of **18** (17.6 mg, 0.0343 mmol), CSA (1.6 mg, 0.0069 mmol), and MeOH (0.35 ml) was stirred at 25 °C for 0.5 h. Triethylamine (0.003 ml, 0.02 mmol) was added and the mixture was concentrated. The residue was chromatographed on silica gel (2 g) with 2:1 hexane–ehtyl acetate to afford a syrup (13.2 mg, 90%). This was dissolved in dry CH_2Cl_2 (0.3 ml) and to this were added 2,2-dimethoxypropane (0.0076 ml, 0.062 mmol) and PPTS (0.4 mg, 0.002 mmol). After 1 d at 25 °C, triethylamine (0.003 ml) was added and the mixture was concentrated. The residue was chromatographed on silica gel (2 g) with 6:1 hexane–ethyl acetate to afford **19** (13.0 mg, 90%) as a colorless syrup: R_f=0.90 (2:1 hexane–ethyl acetate); ^1H NMR (DMSO-d_6) δ=1.36 and 1.39 (each 3H, each s, CMe_2), 3.48 (1H, dd, J=12.5 and 2.5 Hz, one of CH_2N), 3.73 (3H, s, OMe), 3.99 (1H, d, J=2.5 and 0 Hz, C*H*OBn), 4.03 (1H, d, J=12.5 and 0 Hz, one of CH_2N), 4.34 (1H, dd, J=8.8 and 5.5 Hz, CHN), 4.46 (1H, d, J=8.8 Hz, C*H*OCMe$_2$), 4.47 (1H, d, J_{gem}=12.5 Hz, one of OC*H*$_2$Ph), 4.48 (1H, d, d=5.5 and 0 Hz, C*H*OCMe$_2$), 4.53 (2H, s, OC*H*$_2$Ph), 4.86 (1H, d, J_{gem}=12.5 Hz, one of OC*H*$_2$Ph), 6.82 (2H, d, J=9.0 Hz, aromatic protons), and 7.20—7.40 (12H, m, aromatic protons).

Phenyl 3-*O*-Benzyl-5-*O*-(*t*-butyldimethylsilyl)-1-thio-α-D-xylofuranoside (23). To a stirred solution of **20** (5.53 g, 19.7 mmol) in dry CH_2Cl_2 (110 ml) were added at 25 °C triethylamine (5.49 ml, 39.4 mmol) and PvCl (4.37 ml, 35.5 mmol). After 15 h at 25 °C, water was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue (7.19 g) was dissolved in 50% aqueous acetic acid (90 ml) and the mixture was heated at 100 °C for 5h. The reaction mixture was concentrated and the residue was chromatographed on silica gel (300 g) with 3:2 and then 1:1 hexane–ethyl acetate to afford a free sugar (5.86 g, 92%) as a colorless syrup. To a stirred solution of this sample (4.60 g, 14.2 mmol) in dry THF (46 ml) were added at 25 °C diphenyl disulfide (4.64 g, 21.3 mmol) and (n-Bu)$_3$P (5.31 ml, 21.3 mmol). After 0.5 h at 25 °C, the mixture was concentrated. The residue was chromatographed on silica gel (300 g) with 8:1 and then 4:1 hexane–ethyl acetate to afford thioglycoside **22** (5.53 g, 94%) as a colorless syrup. To a stirred solution of this sample (5.53 g, 13.3 mmol) in dry ether (55 ml) was added at 0 °C 1.15 M MeLi in ether (115 ml, 133 mmol). After 15 min at 25 °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 (4.42 g) was dissolved in dry DMF (88 ml) and to this was added at 0 °C TBSCl (2.20g, 14.6 mmol) and imidazole (1.09 g, 16.0 mmol). After 0.5 h at 25 °C, water was added and the mixture was extraxted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (600 g) with 40:1 chloroform–ethyl acetate to afford **23** (1.78 g, 30%) as colorless crystals and its β-anomer (3.52 g, 59%) as a colorless syrup.

23: R_f=0.30 (40:1 chloroform–ethyl acetate); mp 76—77 °C (not recrystallized); $[\alpha]_D^{25}$+70.0° (c 1.02); IR ($CHCl_3$) 2955, 2932, 1472, 1257, 1095, 1054, 1007, and 840 cm^{-1}; ^1H NMR ($CDCl_3$, $CHCl_3$=7.26) δ=0.06 and 0.07 (each 3H, each s, $SiMe_2$), 0.90 (9H, s, t-Bu), 2.43 (1H, d, J=4.2 Hz, OH), 3.84 (1H, dd, J_{gem}=10.0 Hz, $J_{4,5}$=5.8 Hz, H-5), 3.90 (1H, dd, J=10.0 Hz, $J_{4,5'}$=7.0 Hz, H-5′), 4.06 (1H, dd, $J_{3,4}$=4.2 Hz, $J_{2,3}$=2.0 Hz, H-3), 4.37 (1H, ddd, $J_{3,4}$=4.2 Hz, $J_{4,5}$=5.8 Hz, $J_{4,5'}$=7.0 Hz, H-4), 4.43 (1H, ddd, $J_{1,2}$=4.2 Hz, $J_{2,3}$=2.0 Hz, $J_{2,OH}$=4.2 Hz, H-2), 4.64 and 4.66 (each 1H, ABq, J_{gem}=11.8 Hz, OC*H*$_2$Ph), 5.66 (1H, d, $J_{1,2}$=4.2 Hz, H-1), 7.24—7.36 and 7.48—7.54 (8H and 2H, each m, 2×Ph). Found: C, 64.19; H, 7.48; S, 6.90%. Calcd for $C_{24}H_{34}O_4SSi$: C, 64.53: H, 7.67; S, 7.18%.

β-Anomer of 23: R_f=0.25 (40:1 chloroform–ethyl acetate); ^1H NMR ($CDCl_3$, $CHCl_3$=7.26) δ=0.07 (6H, s, $SiMe_2$), 0.91 (9H, s, t-Bu), 2.03 (1H, d, $J_{2,OH}$=4.0 Hz, OH), 3.85 (1H, dd, J_{gem}=10.4 Hz, $J_{4,5}$=5.4 Hz, H-5), 3.94 (1H, dd, J_{gem}=10.4 Hz, $J_{4,5'}$=5.4 Hz, H-5′), 4.02 (1H, dd, $J_{2,3}$=3.2 Hz, $J_{3,4}$=5.4 Hz, H-3), 4.26 (1H, dt, $J_{3,4}$=$J_{4,5}$=$J_{4,5'}$=5.4 Hz, H-4), 4.36 (1H, ddd, $J_{1,2}$=4.0 Hz, $J_{2,3}$=3.2 Hz, $J_{2,OH}$=4.0 Hz, H-2), 4.64 and 4.69 (each 1H, ABq, J_{gem}=12.0 Hz, OC*H*$_2$Ph), 5.16 (1H, d, $J_{1,2}$=4.0 Hz, H-1), 7.20—7.40 and 7.48—7.54 (8H and 2H, each m, 2×Ph).

Phenyl 2,3-Di-*O*-benzyl-1-thio-α-D-xylofuranoside (24). To a solution of **23** (1.50 g, 3.36 mmol), benzyl bromide (0.599 ml, 5.04 mmol), and tetrabutylammonium iodide (62.1 mg, 0.168 mmol) in dry THF (18 ml) was added at 0 °C NaH (129 mg, 5.38 mmol). After 2 h at 25 °C, ethanol (0.7 ml) was added and the mixture was stirred at 25 °C for 0.5 h. 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 dissolved in dry THF (30 ml) and to this was added at 25 °C 1.00 M (n-Bu)$_4$NF in THF (3.70 ml, 3.70 mmol). After 0.5 h at 25 °C, the reaction mixture was concentrated and the residue was chromatographed on silica gel (50 g) with 4:1 and then 3:1 hexane–ethyl acetate to afford **24** (1.35 g, 95%) as a colorless syrup: R_f=0.25 (3:1 hexane–ethyl acetate); IR ($CHCl_3$) 3552, 3014, 1455, 1358, 1107, 1056, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.28 (1H, dd, J=9.0 and 4.0 Hz, OH), 3.81 (1H, ddd, J_{gem}=12.0 Hz, $J_{4.5}$=4.0 Hz, $J_{5,OH}$=9.0 Hz, H-5), 3.88 (1H, ddd, J_{gem}=12.0 Hz, $J_{4,5'}$=4.0 Hz, $J_{5',OH}$=4.0 Hz, H-5′), 4.29 (1H, dd, $J_{2,3}$=4.0 Hz, $J_{3,4}$=6.0 Hz, H-3), 4.33 (1H, dd, $J_{1,2}$=5.8 Hz, $J_{2,3}$=4.0 Hz, H-2), 4.45 (1H, ddd, $J_{3,4}$=6.0 Hz, $J_{4,5}$=$J_{4,5'}$=4.0 Hz, H-4), 4.48, 4.54, 4.63, and 4.78 (each 1H, 2×ABq, J=12.0 Hz, 2×OC*H*$_2$Ph), 5.88 (1H, d, $J_{1,2}$=5.8 Hz, H-1), and 7.20—7.55 (15H, m, 3×Ph). Found: C, 71.12;

H, 6.07; S, 7.66%. Calcd for $C_{25}H_{26}O_4S$: C, 71.07; H, 6.20; S, 7.59%

Triflation of the β-Anomer of 24. The β-anomer of **24** [R_f=0.28 (3:1 hexane–ethyl acetate); ^{1}H NMR ($CDCl_3$) δ=2.20 (1H, br, OH), 3.80—3.93 (2H, br m, 2×H-5), 4.17 (1H, dd, $J_{2,3}$=2.8 Hz, $J_{3,4}$=5.8 Hz, H-3), 4.20 (1H, dd, $J_{1,2}$=4.0 Hz, $J_{2,3}$=2.8 Hz, H-2), 4.27 (1H, ddd, $J_{3,4}=J_{4,5}=J_{4,5'}$=5.8 Hz, H-4), 4.44, 4.58, 4.60, and 4.69 (each 1H, 2×ABq, J=12.0 Hz, 2×OCH_2Ph), 5.38 (1H, d, $J_{1,2}$=4.0 Hz, H-1), and 7.22—7.53 (15H, m, 3×Ph)] was obtained from the β-anomer of **23** as described above for the preparation of **24** from **23**. To a stirred solution of the β-anomer of **24** (10.7 mg, 0.0253 mmol) and triethylamine (0.0106 ml, 0.0759 mmol) in dry CH_2Cl_2 (0.13 ml) was added at −78 °C Tf_2O (0.0040 ml, 0.024 mmol). After 5 min at −78 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (2 g) with 4:1 hexane–ethyl acetate to afford **26** (7.5 mg, 70%, α:β=1:1.3) as a colorless syrup: R_f=0.56 (3:1 hexane–ethyl acetate);

^{1}H NMR ($CDCl_3$) of α-isomer: δ=3.21 (2H, d, $J_{4,5}$=7.2 Hz, 2×H-5), 3.89 (1H, dd, $J_{1,2}$=4.0 Hz, H-2), 3.91 (1H, d, $J_{1,OH}$=10.0 Hz, OH), 4.00 (1H, dd, $J_{2,3}$=1.4 Hz, $J_{3,4}$=4.0 Hz, H-3), 4.34 (1H, ddd, $J_{4,5}$=7.2 Hz, $J_{3,4}$=4.0 Hz, H-4), 4.45—4.61 (4H, m, 2×OCH_2Ph), 5.48 (1H, dd, $J_{1,2}$=4.0 Hz, $J_{1,OH}$=10.0 Hz, H-1), and 7.15—7.40 (15H, m, 3×Ph);

^{1}H NMR ($CDCl_3$) of β-isomer: δ=3.29 (1H, dd, J_{gem}=13.8 Hz, $J_{4,5}$=8.2 Hz, H-5), 3.34 (1H, dd, J_{gem}=13.8 Hz, $J_{4,5'}$=6.2 Hz, H-5′), 3.38 (1H, d, $J_{1,OH}$=11.2 Hz, OH), 3.94 (1H, br s, H-2), 4.03 (1H, br d, $J_{2,3}$=0 Hz, $J_{3,4}$=4.0 Hz, H-3), 4.40 (1H, ddd, $J_{4,5}$=8.2 Hz, $J_{3,4}$=4.0 Hz, $J_{4,5'}$=6.2 Hz, H-4), 4.45—4.61 (4H, m, 2×OCH_2Ph), 5.25 (1H, d, $J_{1.2}$=0 Hz, $J_{1,OH}$=11.2 Hz, H-1), and 7.15—7.40 (15H, m, 3×Ph); M^+ (αβ mixture), 422.

Intermolecular Etherification. To a stirred solution of **24** (383 mg, 0.906 mmol) and triethylamine (0.379 ml, 2.72 mmol) in dry CH_2Cl_2 (4.53 ml) was added at −78 °C Tf_2O (0.152 ml, 0.906 mmol). After 5 min at −78 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The extracts were concentrated and the residue was dissolved in hexane. The organic layer was washed with water and saturated aqueous NaCl, dried, and concentrated. The residue was dried under vacuum for 0.5 h. To a stirred suspension of **18** (248 mg, 0.453 mmol) and MS 4AP (906 mg) in dry DMF (4.53 ml) was added at 0 °C 1.63 M *n*-BuLi in hexane (0.417 ml, 0.680 mmol). After 5 min at 0 °C, a solution of the above triflate in dry DMF (2.27 ml) was added and the mixture was stirred at 25 °C for 0.5 h. Saturated aqueous NH_4Cl was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (40 g) with 12:1 toluene–ethyl acetate to afford **27** (323 mg, 75%) as a colorless syrup: R_f=0.60 (8:1 chloroform–ethyl acetate); IR ($CHCl_3$) 1690, 1510, 1450, 1350, 1240, 1210, 1085, 1050, and 1035 cm^{-1}; ^{1}H NMR (DMSO-d_6, 2:1 mixture) δ=1.20—1.70 (6H, m), 3.72 (3H, s, OMe), 4.08 (1H, dd, J=4.0 and 2.0 Hz), 4.98 and 5.05 (each 1H, ABq, J=12.0 Hz, COOCH_2Ph), 5.84 and 5.85 (total 1H, each d, J=5.6 Hz, C*H*SPh), 6.74 (2H, d, J=8.8 Hz, aromatic protons), and 7.10—7.50 (27H, m, aromatic protons). Found: C, 71.45; H, 6.59; N, 1.29%. Calcd for $C_{57}H_{61}NO_{10}S$: C, 71.90; H, 6.46; N, 1.47%.

Preparation of 28. To a stirred solution of **18** (20.0 mg, 0.0365 mmol) in dry DMF (0.2 ml) was added at 0 °C 1 M LDA in THF (0.0365 ml, 0.0365 mmol). After 0.5 h at 25 °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 (2 g) with 10:1 chloroform–ethyl acetate to afford **28** (14.2 mg, 89%) as a colorless syrup: R_f=0.29 (10:1 chloroform–ethyl acetate); ^{1}H NMR (DMSO-d_6) δ=0.80—1.60 (6H, m), 3.15 and 3.18 (total 1H, each d, J=0 and 12.6 Hz), 3.18—3.30 (1H, m), 3.51 (0.5H, dd, J=2.8 and 5.2 Hz) 3.53—3.65 (1H, m), 3.75 and 3.77 (total 3H, each s, OMe), 3.78 (0.5H, dd, J=5.0 and 12.6 Hz), 3.87 and 4.02 (total 1H, each d, J=0 and 2.0 Hz), 4.23 and 4.31 (total 1H, each d, J=0, 0, and 5.0 Hz), 4.47 and 4.51 (total 1H, each dd, J=2.0 and 7.8 Hz), 4.55 and 4.56 (total 2H each s, OCH_2Ph), 5.92 (1H, d,J=7.8 Hz), 6.94 and 6.95 (total 2H, each d, J=9.0 Hz), and 7.26—7.39 (7H, m); M^+, 439.

Acid-Hydrolysis of 27. To a stirred solution of **27** (132 mg, 0.139 mmol) in dioxane (0.66 ml) and MeOH (1.98 ml) was added at 0 °C CSA (6.5 mg, 0.028 mmol). After 2 h at 25 °C, triethylamine (0.005 ml) was added and the mixture was concentrated. The residue was chromatographed on silica gel (12 g) with 4:1 hexane–ethyl acetate to afford **29** (109 mg, 90%) as a colorless syrup: R_f=0.38 (3:1 hexane–ethyl acetate); $[\alpha]_D^{25}$+50.6° (*c* 1.25); IR ($CHCl_3$) 3444, 3012, 1694, 1513, 1455, 1414, 1354, 1249, 1110, 1060, and 1030 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=3.32—3.37 (2H, m), 3.41 (1H, dd, J=10.6 and 6.0 Hz), 3.63 (1H, dd, J=10.6 and 5.0 Hz), 3.73 (3H, s, OMe), 3.89 (1H, m), 4.07—4.23 (3H, m), 4.35—5.05 (13H, m), 5.83 (1H, d, $J_{1,13}$=5.0 Hz, H-1), 6.76 (2H, d, J=8.0 Hz, H-17 and H-19), and 7.17—7.51 (27H, m, aromatic protons). Found: C, 71.76; H, 6.33; N, 1.77; S, 3.93%. Calcd for $C_{52}H_{53}NO_9S$: C, 71.95; H, 6.15; N, 1.61; S, 3.69%.

Intramolecular Glycosylation. To a stirred suspension of **29** (109 mg. 0.126 mmol) and MS 4AP (1.26 g) in dry toluene (12.6 ml) was added at 25 °C NBS (33.5 mg, 0.188 mmol). After 1 h at 25 °C, the mixture was heated at 90 °C for 24 h. The reaction mixture was cooled to ambient temperature and the insoluble materials were filtered out. The filtrate was washed with toluene and the combiend filtrate and washings were concentrated. The residue was chromatographed on silica gel (15 g) with 35:2 and then 10:1 chloroform–ethyl acetate to afford **30** (61.1 mg, 64%) as a colorless foam: R_f=0.42 (10:1 chloroform–ethyl acetate); $[\alpha]_D^{25}$+30.4° (*c* 1.02); IR ($CHCl_3$) 1696, 1513, 1454, 1419, 1356, 1248, 1096, 1058, 1030, and 979 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=3.16 (1H, dd, J=11.8 and 6.0 Hz), 3.31 (1H, dd, J=11.8 and 7.8 Hz), 3.71 (3H, s, OMe), 3.87 (1H, dd, J=13.0 and 11.4 Hz), 3.99 (1H, dd, J=13.0 and 6.0 Hz), 4.15—4.85 (15H, m), 5.31 (1H, s, H-1), 6.72 (2H, d, J=9.0 Hz, H-17 and H-19), 7.13 (2H, d, J=9.0 Hz, H-16 and H-20), and 7.20—7.40 (20H, m, 4×Ph). Found: C, 72.71; H, 6.24; N, 2.17%. Calcd for $C_{46}H_{47}NO_9$: C, 72.90; H, 6.25; N, 1.85%.

AB3217-A (1a). A mixture of **30** (53 mg, 0.0699 mmol), $Pd(OH)_2$ (159 mg), dioxane (3.71 ml), and 0.01 M aqueous HCl (7.42 ml) was stirred under an atomosphere of hydrogen (1 atm) at 25 °C for 12 h. The insoluble materi-

als were filtered and thoroughly washed with MeOH. The combined filtrate and washings were concentrated and the residue was dissolved in 0.1 M aqueous NaOH (0.74 ml) and this was stirred at 25 °C for 0.5 h. This was passed through CM-Sephadex (C-25) with 50% aqueous MeOH and then triethylamine–CO_2 buffer in 50% aqueous MeOH. The latter eluate was concentrated to afford **1a** (19.8 mg, 80%) as colorless crystals. The analytical sample of **1a** was obtained by recrystallization from MeOH: $R_f=0.32$ (1 : 1 ethyl acetate–MeOH); mp 238—239 °C [mp of natural AB3217-A: 241 °C, lit,[1] 241 °C]; mixed mp 238—239 °C; $[\alpha]_D^{26}-61.3°$ (c 0.46, H_2O) [$[\alpha]_D^{26}$ of natural AB3217-A:−61.0° (c 0.41, H_2O), lit,[1] $[\alpha]_D^{24}-52.5$ °C (c 1.0, H_2O)]; UV (H_2O) λ_{max} nm (ε) 226 (9200) and 272 (1160) [lit,[1] λ_{max} nm (ε) 226 (11400), 272 (1100), and 278 (900)]; IR (KBr) 3511, 3416, 3339, 2940, 2920, 2890, 1610, 1510, 1455, 1390, 1370, 1300, 1250, 1240, 1175, 1120, 1100, 1080, 1065, 1020, 1010, 1000, and 890 cm^{-1}. IR (KBr) of natural AB3217-A: 3510, 3416, 3339, 2945, 2920, 2890, 1610, 1510, 1455, 1390, 1370, 1305, 1250, 1240, 1170, 1120, 1105, 1080, 1065, 1025, 1015, 1000, and 890 cm^{-1}; ^1H NMR (DMSO-d_6, 25 °C) $\delta=1.50$ (1H, br, NH), 2.42 (1H, dd, $J=11.0$ and 4.0 Hz, H-5), 2.85 (1H, dd, $J=11.0$ and 5.7 Hz, H-5′), 3.41 (1H, m, H-7), 3.65—3.75 (2H, m, 2×H-10), 3.73 (3H, s, OMe), 3.94 (1H, m, H-4), 4.00 (2H, m, H-12 and H-13), 4.09 (1H, dd, $J=6.4$ and 3.6 Hz, H-3), 4.18 (1H, m, H-11), 4.40 (1H, d, $J=9.6$ Hz, H-8), 4.87 (1H, br, OH), 4.90 (1H, s, H-1), 5.40 (2H, br, 2×OH), 6.85 (2H, d, $J=8.6$ Hz, H-17 and H-19), and 7.21 (2H, d, $J=8.6$ Hz, H-16 and H-20).

We would like to thank the Institute of Microbial Chemistry and Hokko Chemical Industry CO., Ltd. for a generous gift of AB3217-A (**1a**). We also thank Dr. Kenji Kanbe, Hokko Chemical Industry Co., Ltd., for his useful advice on the isolation procedure of **1a** and for kindly providing spectroscopic charts of **1a**. We are grateful to the Institute of Microbial Chemistry for the generous support of our program.

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