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Synthetic Studies of Pyridomycin. IV.[1] Syntheses of Some Twelve-membered Ring Compounds Designed for Construction of Intact Ring System with Exocyclic (*Z*)-*s*-Butylidene Side Chain in Pyridomycin

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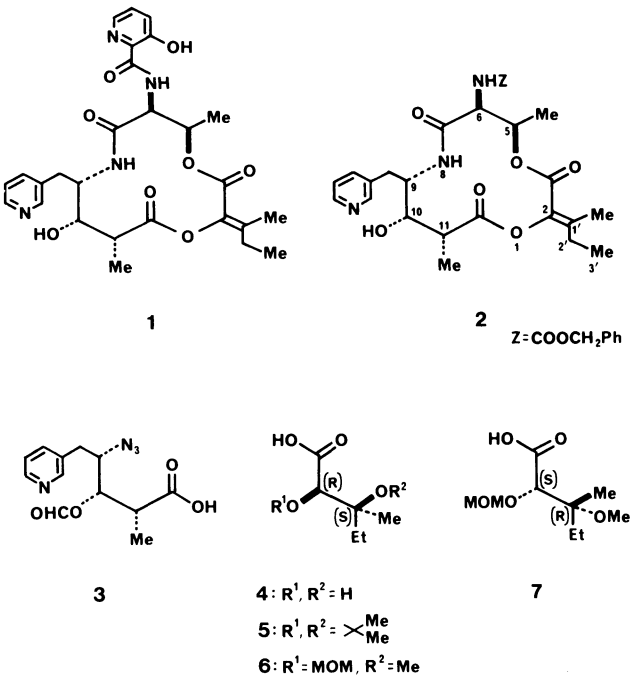
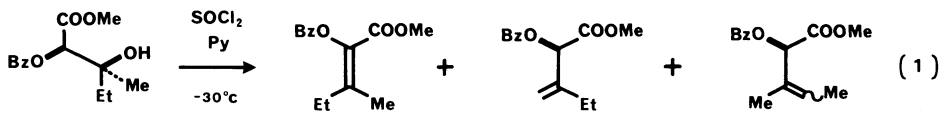
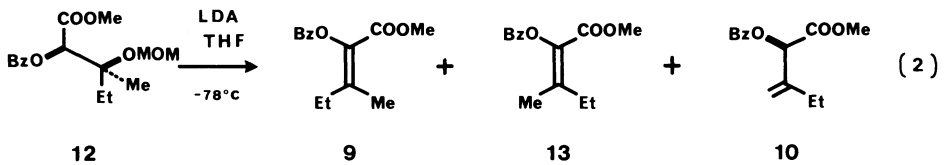
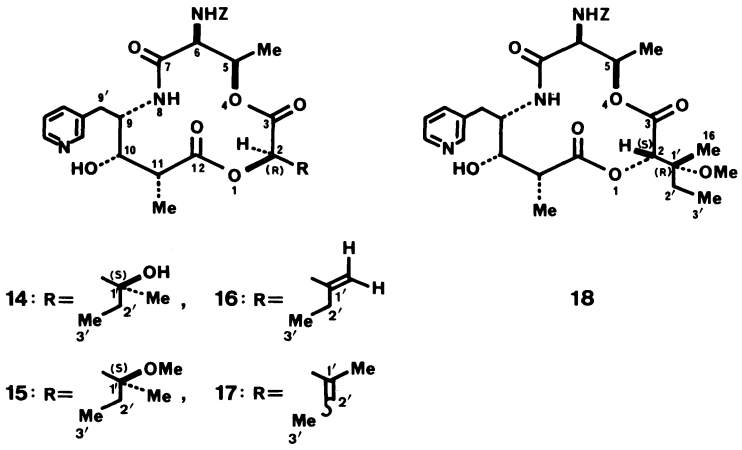
(2*R*,5*R*,6*S*,9*S*,10*S*,11*R*)-10-Hydroxy-2-[(1′*S*)-1′-hydroxy-1′-methylpropyl]-5,11-dimethyl-9-(3-pyridylmethyl)-6-(benzyloxycarbonylamino)-8-aza-1,4-dioxacyclododecane-3,7,12-trione and its 1′-*O*-methyl derivative, and (2*S*,1′*R*)-diastereomer of the latter have been enantiospecifically synthesized from sugar and L-threonine derivatives. The attempts to convert them into a pyridomycin precursor with the 2-(*Z*)-*s*-butylidene side chain were unsuccessful.

Pyridomycin(**1**) is an antimycobacterial antibiotic[2] produced by *Streptomyces pyridomyceticus*.[3] The most striking characteristic in its structure[4] is a novel heterocyclododecane system with unique exocyclic *s*-butylidene and 3-pyridylmethyl side chains. In the studies directed towerd the total synthesis of pyridomycin, it was first considered[1] that the cyclic compound **14** could serve as a synthetic precursor of **2** which was an intermediate of **1**, if the regiospecific dehydration[5] from **14** proceeded through an *anti*-elimination mechanism to generate the corresponding exocyclic (*Z*)-*s*-butylidene side chain in **2**. The synthetic segments, **3**[6] and **4** (or **5**),[1] utilizable to construct **14** together with L-threonine derivatives have already been enantiospecifically synthesized from D-glucose in our laboratories. Recently, an open chain model compound **8** prepared from **4** was treated with thionyl chloride in pyridine at −30 °C for 1 h to yield, in a 40% yield, a mixture[7] consisting of 16% methyl (*Z*)-2-benzyloxy-3-methyl-2-pentenoate **9** and each 42% of its regioisomers, **10** and **11** (Eq. 1). This fact indicated that the dehydration of **8** procceded through a concerted *anti*-elimination

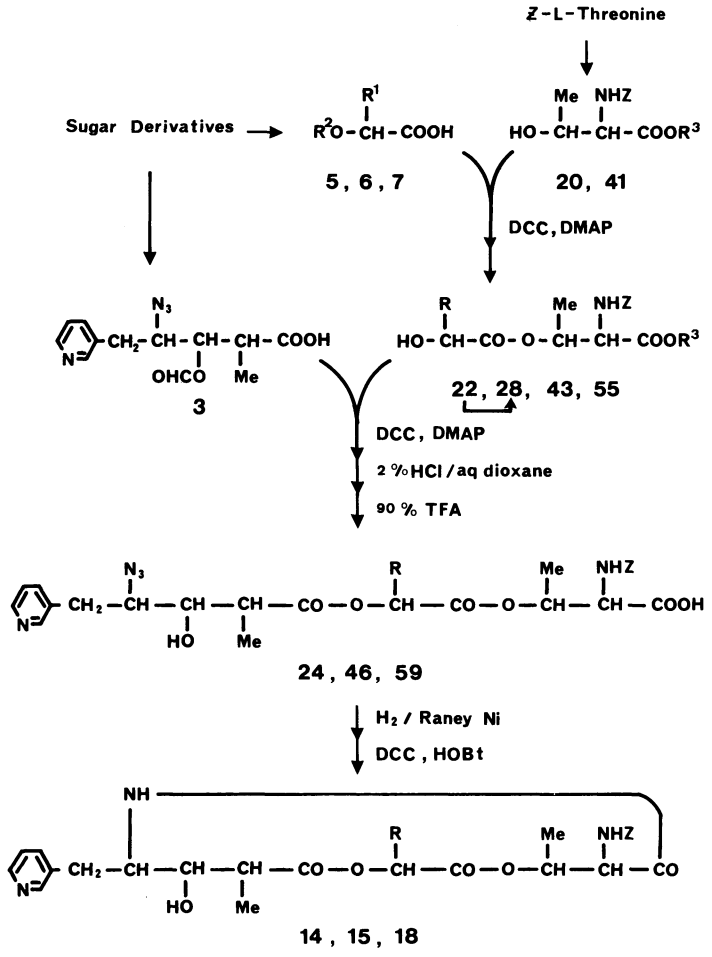








mechanism[5] to yield exclusively the *Z*-isomer **9**. In order to improve the regioselectivity in the formation of **9**, the treatment of **12** derived from **8** with 1.2 equivalents of lithium diisopropylamide (LDA) in THF at −78 °C for 30 min gave a 1:1:1 mixture[7] of **9**, **13**, and **10** in a 40% yield (Eq. 2). This reaction appeared to proceed by an ElcB like mechanism where competitive abstractions of the H-2 proton and the 3-methyl proton are followed by expulsion of the 3-methoxymethoxyl group. These observations suggested that the 12-membered cyclic substrates, **14** and **15** (or **18**) would be a key intermediate for the total synthesis of pyridomycin **1**. Herein we describe the enantiospecific syntheses of **14**, **15**, and its diastereomer **18**, along with the attempts made to convert them into **2** by β-elimination.



Scheme 1.

The synthetic routes are summarized in Scheme 1 accompanied by Charts 1, 2, and 3. *O-t*-Butyl-*N*-benzyloxycarbonyl-L-threonine[8] was converted, in a 92% yield, into the 2,2,2-trichloroethyl ester **19** by treatment with 2,2,2-trichloroethanol, dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP)[9] in ethyl acetate. De-*O-t*-butylation of **19** with trifluoroacetic acid (TFA) afforded a 95% yield of **20**, which was condensed with **5**[1] in the presence of DCC and DMAP to give **21** in an 85% yield. Deisopropylidenation of **21** with 80% TFA followed by condensation of the resulting **22** with **3**[5] in the presence of DCC and DMAP afforded a 73% yield of **23**. One-step conversion of **23** into the seco amino acid **26** of the lactam **14** by treatment with Zn-dust in acetic acid was unsuccessful because of formation of many complex products. Treatment of **23** with Zn-dust in 1 M† aqueous ammonium acetate gave the azido acid **24** (53% yield) and the 5-membered lactam **25** (17.6% yield). De-*O*-formylation of **23** with 2% hydrogen chloride in 50% aqueous dioxane followed by treatment with Zn-dust in 1 M† aqueous ammonium acetate afforded a crude product, whose TLC showed the presence of **26** and **25**, indicating the absence of **24**. However, only the lactam **25** was isolated on the preparative TLC [silica-gel(Merck 5715), 3:1:1 *n*-BuOH–AcOH–H_2O] of the crude product.

On the other hand, treatment of **22** with Zn-dust in acetic acid provided a 98% yield of **27**, which was converted into the benzhydryl ester **28** in an 89% yield by treatment with diphenyldiazomethane in ethyl acetate. Coupling reaction of **28** and **3** with DCC and DMAP proceeded smoothly to afford **29** in an 86% yield. De-*O*-formylation of **29** with 2% hydrogen chloride in 50% aqueous dioxane followed by treatment with 90% TFA gave **24** in an 84% yield. The azido acid **24** was selectively hydrogenolized with Raney Ni in methanol to provide the seco amino acid **26** in good yield. Cyclization of **26** was performed according to the modified Okawa's method in 10^{-3} M DMF solution with DCC (20 equiv) and 1-hydroxybenzotriazole (HOBt, 5 equiv)[10] at 5 °C for 60 h to afford the intramolecular cyclization product **14** in a 37% yield. The cyclization of **26** which was carried out with Woodward's reagent *K* according to the procedure described in the previous paper,[11] gave a 1.5% yield of **14**.

Another route to **14** from **27** was also investigated. Treatment of **27** with *t*-butyl carbazate and DCC in ethyl acetate afforded the *N*-Boc-hydrazide **30** in an 82% yield. Condensation of **30** and **3** with DCC and DMAP gave a 91% yield of product **31**. De-*O*-formylation of **31** by treatment with 2 equivalents of hydrazine hydrate in ethanol afforded a 63% yield of **32**. Hydrogenolysis of **32** with Raney Ni in 50% acetic acid followed by exposure of the resulting amino acid *N*-Boc-hydrazide to 90% TFA gave the crude seco amino acid hydrazide trifluoroacetate, which was then cyclized by the azide method using HOBt as a catalyst according to the procedure described by Veber *et al.*[12] to yield a 2.9% yield of **14**. The structure of **14** thus obtained was confirmed by 250 MHz ^{1}H-NMR and MS.

Dehydration of **14** with thionyl chloride in pyridine was carried out in the same way as in the case of the model compound **8** to give a 79% yield of dehydration product (EIMS, *m/z* 553 (M^+)) after silica-gel column chromatography. The 250 MHz ^{1}H-NMR spectrum of this product revealed that it consisted mostly of a *ca.* 1:1 mixture of the undesired regioisomers, **16** and **17** (a mixture of geometrical isomers), being contaminated by a trace amount of **2** (see Expl.). Moreover, all attempts to separate these isomers on TLC were unsuccessful. Furthermore, though attempts to isomerize the mixture of **16** and

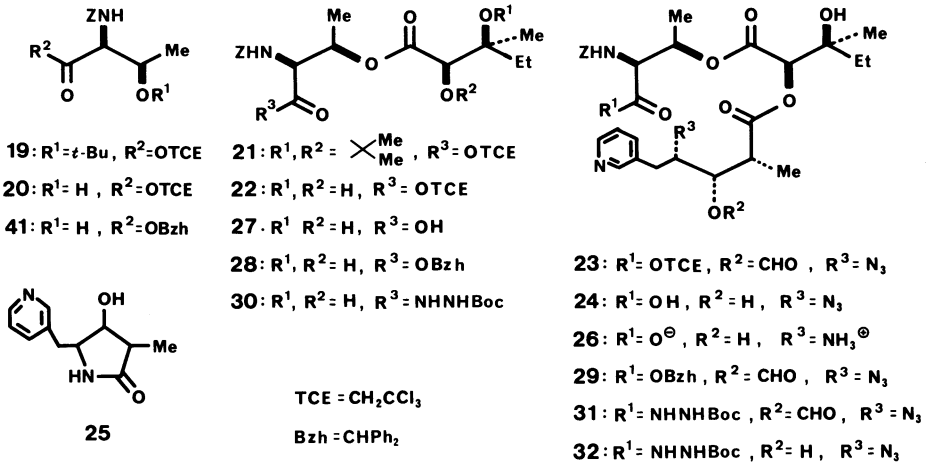


Chart 1.

† 1 M=1 mol dm^{-3}.

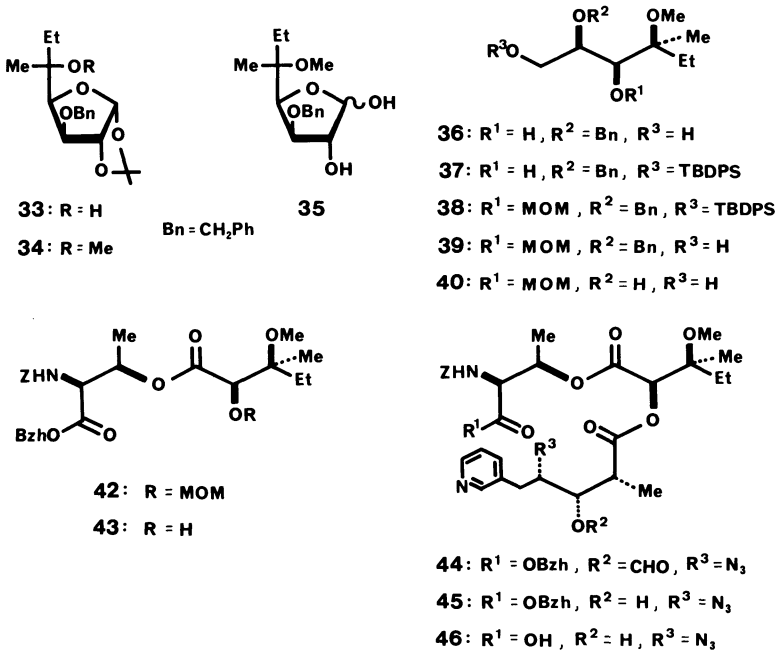


Chart 2.

17 to **2** were made under the following conditions; (a) triethylamine, DMF, 11—15 °C, 20 h, (b) LDA, THF, −75 °C, 1 h, (c) [RhCl(Ph$_3$P)$_3$],[13] ethanol, 100 °C, 3 h, (d) DBU, dioxane, 35 °C, 1.5 h, no appreciable change in the constitutional ratio of the starting olefins could be observed, with the exception of the condition (d) in which **16** was completely isomerized to **17**.

The second key intermediate **15** was next synthesized. The starting material **6** was derived from **33** which was previously prepared from D-glucose.[6] *O*-Methylation of **33** with sodium hydride and methyl iodide in DMF afforded a 77% yield of **34**, which was deisopropylidenated with boiling 50% aqueous acetic acid to give the lactol **35** in a 65% yield. Periodate oxidation of **35** followed by lithium aluminium hydride reduction afforded the diol **36** in a 67% yield. Selective *t*-butyldiphenylsilylation of **36** followed by methoxymethylation of the resulting silyl derivative **37** yielded **38**, which was then desilylated with tetrabutylammonium fluoride in THF to afford **39** in a 42% yield from **36**. Hydrogenolysis of **39** on Pd-black, followed by periodate oxidation of the resulting diol **40** gave the crude aldehyde, which was immediately oxidized with pyridine dichromate (PDC) in DMF to provide the carboxylic acid **6** in a 74% overall yield from **39**. *N*-Benzyloxycarbonyl-L-threonine was treated with diphenyldiazomethane to afford the benzhydryl ester **41** in an 80% yield. Condensation of **6** and **41** with DCC and DMAP followed by the sequential treatments of the resulting linear ester **42** with 90% TFA and with diphenyldiazomethane gave **43** in a 42% overall yield from **6**. Condensation of **43** and **3** with DCC and DMAP followed by the sequential treatments of the resulting linear ester **44** with 2% hydrogen chloride in 50% aqueous dioxane and with 90% TFA gave the azido acid **46** in a 57% overall yield from **43**. Selective hydrogenolysis of the azide group of **46** with Raney Ni in methanol followed by cyclization of the resulting seco amino acid with DCC (20 equiv) and HOBt (5 equiv) in 10^{-3} M DMF solution afforded the intramolecular cyclization product **15** in a 15% yield after sillica-gel column chromatography. The structure of **15** was also confirmed by ^{1}H-NMR and MS.

The elimination reaction of **15** was carried out with 2.2 equivalents of LDA in THF at −78 °C for 1 h. However, from the resulting light yellow solution, only the starting **15** was recovered in *ca.* 70% yield after silica-gel chromatography. This result showed that there occurred no base-promoted elimination from **15** through an ElcB like mechanism in contrast to the case of the acyclic model substrate **12**. This might be explained as follows. The ^{1}H-NMR spectrum of **15** revealed that **15** had a preferred rigid conformation. Unfortunately, because of this conformation, the base catalized enolization of the C-3 carbonyl group of **15** may be hardly stereoelectronically[14,15] or stereochemically assisted. In this respect, we were interested in the base-promoted elimination from the third cyclic substrate **18** which was the (2*S*, 1′*R*)-diastereomer of **15** and therefore might exist in a conformation different from **15**.

The preparation of **18** was started from **7**, the

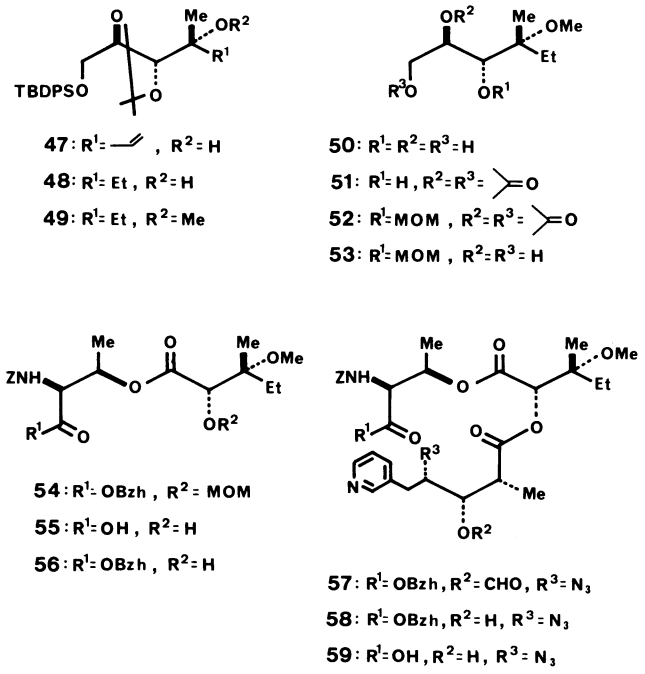


Chart 3.

enantiomer of **6**, in the same manner as that described in the preparation of **15**. The vinyl compound **47**[16] whose stereochemistry had been well confirmed, was hydrogenated on Pd–carbon to yield **48** in a 99% yield. *O*-Methylation of **48** with sodium hydride and methyl iodide in DMF afforded **49** in a 76% yield. The successive treatments with tetrabutylammonium fluoride and with 80% TFA gave **50** in a 67% yield. Reaction of **50** with *N,N'*-carbonyldiimidazole in benzene afforded the cyclic carbonate **51** as a sole product in a 61% yield. The *O*-methoxymethylated product **52** derived from **51** was decarbonated with sodium hydroxide in methanol to afford the crude diol **53**, which was subjected to the two-stage oxidation with sodium periodate in aqueous acetone and with PDC in DMF to provide **7** in a 51% overall yield from **52**. Condensation of **7** and **41** afforded an 85% yield of **54**, which was transformed, in a 65% yield, into the hydroxy benzhydryl ester **56** *via* **55** by the procedure described in the preparation of the diastereomer **43**. Condensation of **56** and **3** gave the linear ester **57** in a 72% yield, which was converted into the azido acid **59** *via* **58** in an 80% yield. Hydrogenolysis of **59** followed by cyclization with DCC and HOBt to afford **18** in a 15% yield after silica-gel column chromatography. The structure of **18** was confirmed by ^{1}H-NMR and MS. The elimination reaction of **18** was carried out in the same condition as in the case of **15** and no elimination reaction occurred. The starting **18** was recovered from the reaction mixture in *ca.* 60% yield.

Experimental

The melting points were determined on a micro hot-stage Yanaco MP-S3 and are uncorrected. The optical rotations were measured with a Carl Zeiss photoelectric polarimeter and a JASCO DIP-360 photoelectric polarimeter in chloroform unless stated otherwise. The ^{1}H-NMR spectra were recorded with either a Varian EM-390 or a Bruker WM 250 spectrometer in $CDCl_3$ using TMS as the internal standard. The IR spectra, EIMS, and SIMS were measured with a Hitachi Perkin-Elmer 225 spectrophotometer, a Hitach RMU-6M mass spectrometer, and Hitachi M-80 mass spectrometer, respectively. The TLC was carried out on Merck TLC plates (60F-254, 0.25 mm). The column chromatography was performed on silica-gel, Wakogel C-200. In general, the evaporation and concentration were carried out under reduced pressure below 30 °C unless otherwise noted.

N-Benzyloxycarbonyl-O-t-butyl-L-threonine 2,2,2-Trichloroethyl Ester (19). DCC (1.56 g, 7.573 mmol) was added at a time to an ice-cooled solution of *N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonine (2.23 g, 7.212 mmol), 2,2,2-trichloroethanol (0.696 ml, 7.212 mmol), and DMAP (59 mg, 0.48 mmol) in dry ethyl acetate (36 ml) and the mixture was stirred at 0 °C for 1.5 h. After the *N,N'*-dicyclohexylurea (DCU) had been filtered off, a small amount of acetic acid was added to the filtrate and the mixture (pH 3—4) was stirred under ice-cooling until unchanged DCC was destroyed. The DCU formed was filtered and the filtrate was evaporated to a white solid (3.41 g), which was chromatographed on silica-gel (200 g) with 12:2:1 benzene–hexane–ethyl acetate to afford **19** (2.91 g, 92%) as colorless needles. Recrystallization from pentane gave a pure sample: Mp 89—90 °C; $[\alpha]_D^{19}$ −5° (*c* 1.00); ^{1}H-NMR (90 MHz) δ=1.15 (9H, s), 1.28 (3H, d, J=6.5 Hz), 4.62 and 4.82 (2H, each d), 5.17 (2H, s), and 7.39 (5H, s).

Found: C, 48.76; H, 5.50; N, 3.01; Cl, 23.86%. Calcd for $C_{18}H_{24}NO_5Cl_3$: C, 49.05; H, 5.49; N, 3.18; Cl, 24.13%.

N-Benzyloxycarbonyl-L-threonine 2,2,2-Trichloroethyl Ester (20). A solution of **19** (1.89 g) in TFA (6.0 ml) was kept at room temperature for 5 min and then evaporated. The residue was repeatedly co-evaporated with ether and then dried over NaOH pellets under reduced pressure to give a crystalline solid (1.66 g), which was recrystallized from ether–pentane to afford **20** (1.56 g, 95%) as colorless needles: Mp 90—91 °C; $[\alpha]_D^{23}$ −21° (*c* 0.79); ^{1}H-NMR (90 MHz) δ=1.31 (3H, d, J=6.4 Hz); 4.77 and 4.88 (2H, each d), 5.17 (2H, s), and 7.40 (5H, s).

Found: C, 43.43; H, 4.13; N, 3.60; Cl, 27.58%. Calcd for $C_{14}H_{16}NO_5Cl_3$: C, 43.71; H, 4.19; N, 3.64; Cl, 27.58%.

N-Benzyloxycarbonyl-O-[(2R,3S)-2,3-dihydroxy-2,3-O-isopropylidene-3-methylpentanoyl]-L-threonine 2,2,2-Trichloroethyl Ester (21). To an ice-cooled solution of **5** (445 mg, 2.36 mmol), **20** (909 mg, 2.363 mmol), and DMAP (29 mg, 0.236 mmol) in dry ethyl acetate (8.4 ml) was added DCC (488 mg, 2.385 mmol) at a time and the mixture was stirred at 0 °C for 2 h. The DCU resulted was filtered off and the filtrate was evaporated to a pale yellow solid (1.43 g), which was chromatographed on silica-gel (100 g) with 10:1 benzene–ethyl acetate to afford **21** (1.12 g, 85%) as colorless needles. Recrystallization from ethyl acetate–

pentane gave a pure sample: Mp 108—109 °C; $[\alpha]_D^{23}$ +16° (*c* 0.55); IR (CCl_4) 3390 and 1720 cm^{-1}; ^{1}H-NMR (90 MHz) δ=0.99 (3H, t, *J*=6.5, 8.0 Hz), 1.12 (3H, s), 1.39 and 1.56 (each 3H, each s), 1.45 (3H, d, *J*=6.5 Hz), 1.5—2.0 (2H, m), 4.33 (1H, s), 4.67 (1H, dd, *J*=4.0, 11.0 Hz), 4.75 and 4.81 (2H, each d), 5.21 (2H, s), 5.53 (1H, dq), 5.3—5.7 (1H, br), and 7.43 (5H, s).

Found: C, 50.03; H, 5.55; N, 2.45; Cl, 19.37%. Calcd for $C_{23}H_{30}NO_8Cl_3$: C, 49.78; H, 5.45; N, 2.52; Cl, 19.17%.

N-*Benzyloxycarbonyl*-O-*[(2*R,*3*S)-*2,3-dihydroxy-3-methylpentanoyl]*-L-*threonine 2,2,2-Trichloroethyl Ester (22).* A solution of **21** (856 mg) in 80% aqueous TFA (10 ml) was allowed to stand at room temperature for 1 h and then evaporated. The residue (792 mg) was chromatographed on silica-gel (30 g) with 3:1 benzene–ethyl acetate to afford **22** (743 mg, 94%) as colorless needles: Mp 76—77 °C, $[\alpha]_D^{21}$ −41° (*c* 0.97); IR (CCl_4) 3440 and 1725 cm^{-1}; ^{1}H-NMR (90 MHz) δ=0.91 (3H, t, *J*=6.9, 7.9 Hz), 1.17 (3H, s), 1.42 (3H, d, *J*=6.5 Hz), 1.3—1.8 (2H, m), 2.78 (2H, br-s), 3.97 (1H, s), 4.5—4.8 (1H, m), 4.76 (2H, s), 5.18 (2H, s), 5.52 (1H, dq, *J*=3.5 Hz), 5.3—4.9 (1H, br), and 7.39 (5H, s).

Found: C, 46.82; H, 5.14; N, 2.52; Cl, 20.32%. Calcd for $C_{20}H_{26}NO_8Cl_3$: C, 46.66; H, 5.09; N, 2.72; Cl, 20.66%.

N-*Benzyloxycarbonyl*-O-*[(2*R,*3*S)-*2-((2*R,*3*S,*4*S)-*4-azido-3-formyloxy-2-methyl-5-(3-pyridyl)pentanoyloxy)-3-hydroxy-3-methylpentanoyl]*-L-*threonine 2,2,2-Trichloroethyl Ester (23).* To an ice-cooled solution of **22** (213 mg, 0.414 mmol), **3** (115 mg, 0.414 mmol), and DMAP (5.1 mg, 0.041 mmol) in dry ethyl acetate (2.9 ml) was added DCC (89.7 mg, 0.435 mmol) and the mixture was stirred at 0 °C for about 24 h. After the DCU had been filtered off, a small amount of acetic acid was added to the filtrate and the mixture was stirred at room temperature for 1 h. The DCU was removed by filtration and the filtrate was evaporated to a yellow syrup (447 mg), which was chromatographed on silica-gel (30 g) with 2:1 benzene–ethyl acetate to afford **23** (235 mg, 73%) as colorless syrup: $[\alpha]_D^{26}$ −8° (*c* 1.0); IR (CCl_4) 3440, 2110, and 1735 cm^{-1}; ^{1}H-NMR (90 MHz) δ=0.93 (3H, t, *J*=7.5 Hz), 1.23 (3H, s), 1.28 (3H, d, *J*=4.0 Hz), 1.40 (3H, d, *J*=9.0 Hz), 1.5—1.7 (2H, m), 2.5—3.3 (3H, m), 3.5—3.8 (1H, m), 4.0—4.3 (1H, br), 4.5—4.7 (1H, m), 4.76 (3H, s), 5.16 (2H, s), 5.2—6.0 (3H, m), 7.06 (5H, s), 7.2—7.4 (1H, m), 7.5—7.7 (2H, m), 8.20 (1H, s), and 8.4—8.6 (2H, m).

Found: C, 49.77; H, 5.06; N, 8.81%. Calcd for $C_{32}H_{38}N_5O_{11}Cl_3$: C, 49.59; H, 4.94; N, 9.04%.

N-*Benzyloxycarbonyl*-O-*[(2*R,*3*S)-*2-((2*R,*3*S,*4*S)-*4-azido-3-hydroxy-2-methyl-5-(3-pyridyl)pentanoyloxy)-3-hydroxy-3-methylpentanoyl]*-L-*threonine (24).* *(a) Preparation from 23.* To a stirred solution of **23** (25.5 mg, 0.033 mmol) in dry THF (0.25 ml) was added an aqueous 1 M ammonium acetate solution (0.022 ml) and then Zn-dust (21.5 mg, 3.3 mmol) at room temperature. After being stirred for 20 h at room temperature, the reaction mixture was filtered through a Celite and the filter cake was washed with chloroform. The filtrate and washings were evaporated and the residue was chromatographed on silica-gel (5 g) with 80:15:1 chloroform–methanol–acetic acid to give **24** (10.8 mg, 53%) and **25** (1.2 mg, 18%), whose R_f-values in the same solvent system were 0.37 and 0.13, respectively. **24**: Colorless syrup; IR ($CHCl_3$) 2100 cm^{-1}; ^{1}H-NMR (250 MHz) δ=0.88 (3H, t, *J*=8.0 Hz), 1.03 (3H, d, *J*=6.0 Hz), 1.24 (3H, s), 1.26 (3H, d, *J*=7.5 Hz), 1.53 (1H, dq, *J*=8.0 Hz), 1.66 (1H, dq), 2.9—3.2 (3H, m), 3.35 (1H, m), 3.68 (1H, d-like), 4.32 (1H, d, *J*=7.0 Hz), 4.73 (1H, s), 5.14 (2H, s), 5.4—5.8 (3H, m), 6.08 (1H, d, 10.0 Hz), 7.14—7.21 (1H, m), 7.2—7.4 (5H, m), 7.56—7.64 (1H, m), 8.47 (1H, m), and 8.56 (1H, d-like); SIMS, *m/z* 616 (M^+ +1). **25**: Colorless crystal, IR (KBr) 3300, 3180, 1700, and 1660 cm^{-1}; ^{1}H-NMR (250 MHz) δ=1.12 (3H, d, *J*=8.0 Hz), 2.54 (1H, dq, *J*=5.0 Hz), 2.91 (1H, dd, *J*=15.0, 8.0 Hz), 3.08 (1H, dd, *J*=10.0 Hz), 3.88 (1H, m), 4.07 (1H, m), 4.70 (1H, m), 7.85 (1H, d, *J*=8.0 Hz), 8.41 (1H, d, *J*=4.0 Hz), and 8.52 (1H, s).

(b) Preparation from 29. A solution of **29** (246 mg) in 25 ml of 2% HCl [in 50% (v/v) aqueous dioxane] was kept at 20 °C for 8 h and was concentrated to a syrup (250 mg), which was dissolved in 90% TFA (2.5 ml). The solution was kept at 20 °C for 0.5 h and then evaporated. The residue was co-evaporated with ether repeatedly to remove TFA and the final residue was chromatographed on silica-gel (20 g) with 90:10:1 chloroform–methanol–acetic acid to afford **24** (169 mg, 84% yield from **28**). This product was proved to be identical with the sample of **24** obtained in (a) by TLC and ^{1}H-NMR.

N-*Benzyloxycarbonyl*-O-*[(2*R,*3*S)-*2,3-dihydroxy-3-methylpentanoyl]*-L-*threonine (27).* To a solution of **22** (494 mg, 0.96 mmol) in acetic acid (5 ml) was added Zn-dust (2.2 g, 33.6 mmol) portionwise over a period of 1 h. After being stirred at 20 °C for 4 h, the reaction mixture was filtered through a Celite and the filter cake was washed with chloroform. The filtrate and washings were evaporated to a syrup (450 mg), which was chromatographed on silica-gel (25 g) with 80:5:1 chloroform–methanol–acetic acid to give **27** as a colorless glass (365 mg, 98%): ^{1}H-NMR (90 MHz, $CDCl_3$+D_2O) δ=0.88 (3H, t, *J*=7.5 Hz), 1.13 (3H, s), 1.33 (3H, d, *J*=6.0 Hz), 1.4—1.7 (2H, m) 3.90 (1H, s), 4.3—4.6 (1H, m), 5.08 (2H, s), 5.3—5.6 (1H, m), and 7.38 (5H, s).

N-*Benzyloxycarbonyl*-O-*[(2*R,*3*S)-*2,3-dihydroxy-3-methylpentanoyl]*-L-*threonine Benzhydryl Ester (28).* A mixture of benzophenone hydrazone (214 mg, 1.09 mmol), HgO (yellow) (239 mg, 1.10 mmol) and petroleum ether (0.3 ml) were stirred at room temperature for 5 h. The reaction mixture was filtered and the filtrate was evaporated to give a red-purple colored syrup of diphenyldiazomethane, which was dissolved in ethyl acetate (1.6 ml). To a solution of **27** (167 mg, 0.53 mmol) in ethyl acetate (1.6 ml) was added dropwise the above prepared solution of diphenyldiazomethane. After violent foaming had been settled, the reaction mixture was stirred at room temperature for 2 h, and then the excess diphenyldiazomethane was decomposed by addition of concd HCl under ice-cooling. The resulting mixture was washed with cold saturated aqueous $NaHCO_3$ and NaCl solutions, dried, and evaporated to a yellow syrup (359 mg), which was chromatographed on silica-gel (15 g) with 5:1 toluene–ethyl acetate to afford **28** (250 mg, 89%) as a syrup: $[\alpha]_D^{19}$ −4°, $[\alpha]_{365}^{19}$ −8° (*c* 1.81); ^{1}H-NMR (90 MHz) δ=0.83 (3H, t, *J*=6.0 Hz), 0.95 (3H, s), 1.33 (3H, d, *J*=6.0 Hz), 1.0—1.5 (2H, m), 1.6—2.0 (1H, br), 2.9—3.2 (1H, br), 3.81 (1H, br-d, *J*=10 Hz), 4.5—4.8 (1H, m), 5.13 (2H, s), 5.4—5.9 (2H, m), 6.80 (1H, s), and 7.2—7.6 (15H, m).

Found: C, 67.57; H, 6.46; N, 2.45%. Calcd for $C_{31}H_{35}NO_8$: C, 67.75; H, 6.41; N, 2.55%.

N-*Benzyloxycarbonyl*-O-*[(2*R,*3*S)-*2-((2*R,*3*S,*4*S)-*4-azido-3-formyloxy-2-methyl-5-(3-pyridyl)pentanoyloxy)-3-hydroxy-3-

methylpentanoyl]-L-threonine Benzhydryl Ester (29). To a solution of **28** (952 mg, 1.79 mmol), **3** (497 mg, 1.79 mmol), and DMAP (20 mg, 0.16 mmol) in dry ethyl acetate (15 ml) was added DCC (442 mg, 3.14 mmol) at a time and the mixture was stirred at room temperature for 48 h. The formed DCU was filtered off and the filtrate was concentrated and chromatographed on silica-gel (100 g) with 1:1 toluene–ethyl acetate to give **29** (1.23 g, 86%) as a glassy solid: ^{1}H-NMR (90 MHz) δ=0.85 (3H, t, J=7.5 Hz), 1.06 (3H, s), 1.20 (3H, d, J=9.0 Hz), 1.36 (3H, d, J=6.0 Hz), 1.2—1.5 (2H, m), 2.6—3.3 (3H, m), 3.5—3.8 (1H, m), 4.0—4.3 (1H, br), 4.5—4.8 (1H, m), 4.70 (1H, s), 5.3—5.8 (3H, m), 6.86 (1H, s), 7.1—7.4 (15H, m), 7.5—7.7 (1H, m), 8.16 (1H, s, CHO), and 8.4—8.6 (2H, m).

N-Benzyloxycarbonyl-O-[(2R,3S)-2,3-dihydroxy-3-methylpentanoyl]-L-threonine t-Butoxycarbonylhydrazide (30). To a solution of **27** (253 mg, 0.66 mmol) and Boc-NHNH$_2$ (105 mg, 0.79 mmol) in dry ethyl acetate (2.6 ml) was added DCC (143 mg, 0.69 mmol) and the mixture was stirred at room temperature for 2 h. The formed DCU was filtered off and the filtrate was concentrated and chromatographed on silica-gel (50 g) with 1:1 chloroform–ethyl acetate to give a glassy solid, which was again chromatographed on silica-gel (50 g) with 5:1 toluene–acetone to afford pure sample of **30** (286 mg, 82%) as a colorless glassy solid: $[\alpha]_D^{20}$ +50° (c 1.00); IR ($CHCl_3$) 3425, 3340, 1765, 1720, and 1685 cm^{-1}; ^{1}H-NMR (250 MHz) δ=0.86 (3H, t, J=7.0 Hz), 1.16 (3H, s), 1.24 (3H, d, J=6.0 Hz), 1.44 (9H, s), 1.40—1.60 (2H, m), 4.06 (1H, d, J=4.0 Hz), 4.50 (1H, dd, J=3.0, 10 Hz), 4.91 (1H, br-s), 5.10 (2H, s), 5.30—5.45 (2H, m), 6.45 (1H, d, J=2.0 Hz), 6.84 (1H, d, J=10 Hz), 7.36 (5H, s), and 8.80 (1H, d, J=2.0 Hz).

Found: C, 55.49, H, 7.10; N, 8.54%. Calcd for $C_{23}H_{35}N_3O_9$: C, 55.52; H, 7.09; N, 8.45%.

N-Benzyloxycarbonyl-O-[(2R,3S)-2-((2R,3S,4S)-4-azido-3-formyloxy-2-methyl-5-(3-pyridyl)pentanoyloxy)-3-hydroxy-3-methylpentanoyl]-L-threonine t-Butoxycarbonylhydrazide (31). To an ice-cooled solution of **30** (72.9 mg, 0.146 mmol), **3** (40.7 mg, 0.146 mmol), and DMAP (1.8 mg, 0.015 mmol) in dry ethyl acetate (0.8 ml) was added DCC (31.8 mg, 0.154 mmol) and the mixture was stirred at room temperature for 5 h. The DCU formed was filtered off and the filtrate was concentrated and chromatographed on silica-gel (10 g) with 1:3 chloroform–ethyl acetate to give **31** (100 mg, 91%) as a glassy solid: IR ($CHCl_3$) 2100 cm^{-1}; $[\alpha]_D^{17}$ 0°, $[\alpha]_{436}^{17}$ −39°, $[\alpha]_{365}^{17}$ −71° (c 0.84); ^{1}H-NMR (250 MHz) δ=0.93 (3H, t, J=7.0 Hz), 1.28 (3H, s), 1.29 (3H, d, J=8.0 Hz), 1.33 (3H, d, J=7.0 Hz), 1.5—1.65 (2H, m), 2.84 (1H, dd, J=11.0, 15 Hz), 3.04 (1H, dd, J=6.0 Hz), 3.16 (1H, dq, J=7.0 Hz), 3.65 (1H, br), 3.83 (1H, ddd, J=4.0 Hz), 4.48 (1H, d, J=10 Hz), 4.78 (1H, s), 5.12 (2H, ABq), 5.39 (1H, dd), 5.48 (1H, dq), 5.86 (1H, d, J=10 Hz), 7.2—7.35 (1H, m), 7.35 (5H, s), 7.63 (1H, d, J=10 Hz), 8.22 (1H, s), 8.53 (1H, d, J=4.0 Hz), 8.60 (1H, d, 2.0 Hz), and 8.74 (1H, br).

Found: C, 55.65; H, 6.35; N, 12.80%. Calcd for $C_{35}H_{47}N_7O_{12}$: C, 55.47; H, 6.25; N, 12.94%.

N-Benzyloxycarbonyl-O-[(2R,3S)-2-((2R,3S,4S)-4-azido-3-hydroxy-2-methyl-5-(3-pyridyl)pentanoyloxy)-3-hydroxy-3-methylpentanoyl]-L-threonine t-Butoxycarbonylhydrazide (32). A mixture of **31** (208 mg, 0.274 mmol), hydrazine hydrate (0.027 ml, 0.56 mmol), and ethanol (2 ml) was stirred at room temperature for 5 h. The reaction mixture was then concentrated and chromatographed on silica-gel (20 g) with 20:1 chloroform–methanol to afford a syrup of **32**. This syrup was again chromatographed on silica-gel (15 g) with 1:3 chloroform–ethyl acetate to give a pure sample of **32** (125 mg, 62.5%): IR ($CHCl_3$) 2100 cm^{-1}; $[\alpha]_D^{17}$ +9° (c 1.66).

Found: C, 56.18; H, 6.62; N, 13.17%. Calcd for $C_{34}H_{47}N_7O_{11}$: C, 55.96; H, 6.49; N, 13.44%.

(2R,5R,6S,9S,10S,11R)-10-Hydroxy-2-[(1'S)-1'-hydroxy-1'-methylpropyl]-5,11-dimethyl-9-(3-pyridylmethyl)-6-(benzyloxycarbonylamino)-8-aza-1,4-dioxacyclododecane-3,7,12-trione (14). (a) *By HOBt-DCC Method:*[11] A solution of **24** (336 mg, 0.546 mmol) in methanol (30 ml) was stirred with a catalytic amount of Raney Ni (Nikko R-100) for 1 h under bubbling with hydrogen gas. The reaction mixture was filtered through a Celite and the catalyst was washed with a 1:1 methanol–dioxane. The combined filtrate and washings were evaporated to a glassy solid of crude **26**, To a solution of this residue in dry DMF (540 ml) was added HOBt (370 mg, 2.73 mmol) and then DCC (2.27 g, 11 mmol) portionwise at 0 °C with stirring. The mixture was kept at 5 °C for 60 h, after which time acetic acid (2 ml) was added to the mixture to decompose the unchanged DCC. The resulting mixture was then evaporated and the residue was taken with chloroform. The DCU undissolved was filtered and washed with chloroform twice. The combined filtrate and washings were washed with saturated aqueous $NaHCO_3$ and NaCl solutions successively, dried, and evaporated. The residue was chromatographed on silica-gel (20 g) with 15:1 chloroform–methanol to afford **14** (118 mg, 37%) as an amorphous powder: $[\alpha]_D^{18}$ −21° (c 0.96); EIMS, m/z 571 (M^+); ^{1}H-NMR (250 MHz) δ=0.93 (3H, t, J=7.5 Hz), 1.25 (3H, s), 1.31 (3H, d, J=6.5 Hz), 1.42 (3H, d, J=7.5 Hz), 1.52 and 1.65 (each 1H, each dq, J_{gem}=7.5 Hz), 2.55 (1H, q, J=0, 7.5 Hz), 2.6—2.8 (2H, m), 3.59 (1H, br-s), 4.03 (1H, q-like), 4.25—4.45 (2H, m), 4.96 (1H, s, H-2), 5.14 (2H, s), 5.34 (1H, dq, J=6.5, 7.0 Hz), 5.49 (1H, d, J=9 Hz), 6.26 (1H, d, J=9 Hz), 7.17 (1H, dd, J=5.0, 8.0 Hz), 7.37 (5H, s), 7.61 (1H, ddd, J=1.5, 1.8, 8.0 Hz), 8.46 (1H, dd, J=1.5, 5.0 Hz), and 8.54 (1H, d, J=1.8 Hz).

Found: C, 60.22; H, 6.69; N, 7,13%. Calcd for $C_{29}H_{37}N_3O_9$: C, 60.93; H, 6.52; N, 7.35%.

(b) By Azide Method Using HOBt:[12] A solution of **32** (87 mg, 0.119 mmol) in 50% aqueous acetic acid (8.7 ml) was stirred with Raney Ni for 3 h under bubbling with hydrogen gas. The mixture was filtered through a Celite and the filter cake was washed with methanol. The combined filtrate and washings were concentrated to a green syrup (250 mg), which was dissolved in 90% aqueous TFA (3 ml). The resulting solution was kept at room temperature for 1 h and then evaporated. The residue was co-evaporated with ether repeatedly to afford amorphous powder. A solution of this powder (250 mg) in dry DMF (3 ml) was acidified by addition of 6.53 M HCl in THF (0.109 ml, 0.715 mmol) at −25 °C. Isopentyl nitrite (0.020 ml, 0.145 mmol) was added and the solution stirred at −25 °C for 2 h. The resulting solution of the acyl azide was added to 100 ml of cold (−40 °C) DMF containing HOBt (81.1 mg, 0.6 mmol). The solution was neutralized by addition of triethylamine (0.150 ml, 1.062 mmol) and stored at −30 °C for 18 h and −5 °C for 24 h. The solvent was evaporated and the residue was partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer

separated was extracted with ethyl acetate (10 ml×5). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and NaCl solutions, dried, and evaporated. The residue was chromatographed on silica-gel (20 g) with 10:1 chloroform–methanol to afford a syrup (3.5 mg). It was preparatively thin-layer chromatographed on PLC plate (Merck 5715) with 10:1 chloroform–methanol to give a pure sample of **14** (2 mg, 2.9%).

*Dehydration Product (**16**+**17**) from **14**.* To a cold (−30 °C) solution of **14** (9 mg, 0.016 mmol) in dry pyridine (0.2 ml) was added freshly distilled $SOCl_2$ (0.012 ml, 0.16 mmol) under stirring. After being stirred at −20—−30 °C for 45 min, cold water was added and the mixture was extracted with chloroform (5×1 ml). The combined extracts were washed with saturated aqueous NaCl, dried, and evaporated to give a brown syrup (10 mg). It was chromatographed on silica-gel (2 g) with 30:1 chloroform–methanol to afford a colorless syrup of dehydration product (7 mg, 79%): EIMS, *m/z* 553 (M^+); ^{1}H-NMR (250 MHz) δ=1.08 (t, 3×H-3′ (**16**, **2**)), 1.31 (d, 5-Me, J=7.0 Hz), 1.38 (d, 11-Me (**16**, **17**), J=7.0 Hz), 1.39(d, H-5 (**2**), J=7.0 Hz), 1.50 (d, 11-Me (**2**), J=7.5 Hz), 1.63 (s, 1′-Me (**17**)), 1.67 (d, 3×H-3′ (**17**), J=7.0 Hz), 1.9—2.2 (2H, m, H-2′ (**16**, **2**)), 2.28 (*ca.* 0.5H, s, 1′-Me (**2**)), 2.50 (1H, dq, H-11, $J_{10,11}$=1.0 Hz), 2.60 (0.2H, dq, H-11 (**2**)), 2.90—3.05 (2H, m, 2×H-9′), 3.50—3.60 (1H, m, H-10), 4.02 (1H, q-like, H-9, $J\fallingdotseq$8 Hz), 4.29 (1H, t-like, H-6, $J\fallingdotseq$7 Hz), 4.35—4.50 (1H, br, OH), 5.14 (2H, s, $OC\underline{H}_2Ph$), 5.18 and 5.38 (each 0.5H, each s, H-2 (**16**, **17**)), 5.26 and 5.32 (each *ca.* 0.5H, each s, $\underline{H}_2C$=(**16**)), 5.38 (1H, dq, H-5, $J_{5,6}$=7.0 Hz), 5.40—5.50 (1H, br, 6-NH), 5.77 (*ca.* 0.5H, m, H-2′ (**17**)), 6.04 (1H, br-d, H—N(8), J=8 Hz), 7.18 (1H, dd, J=8.0, 4.5 Hz), 7.38 (5H, s, Ph), 7.62 (1H, ddd, J=2.0, 2.0 Hz), 8.46 (1H, dd), and 8.54 (1H, d).

*Isomerization of Dehydration Products with DBU (**16**→**17**).* A sample of the dehydration product (**16**+**17**) (7.9 mg) was dissolved in DBU (0.006 ml) and dry dioxane (0.01 ml), and then dioxane was removed by evaporation under reduced pressure. The residue was stored at 35 °C for 1.5 h. The reaction mixture was neutralized with aqueous 0.5 M HCl and then extracted thoroughly with chloroform. The combined extracts were washed with saturated aqueous NaCl, dried, and evaporated to give a yellow syrup, which was chromatographed on silica-gel (2 g) with 15:1 chloroform–methanol to afford a colorless syrup (2.7 mg) of **17** whose R_f-value was identical with the starting dehydration product: ^{1}H-NMR (250 MHz) δ=1.30 (3H, d, 5-Me, J=7.0 Hz), 1.39 (3H, 11-Me, J=7.5 Hz), 1.63 (3H, s, 1′-Me), 1.67 and 1.68 (each 1.5H, each d, 3×H-3′, J=7.0 Hz), 2.50 (1H, dq, H-11, $J_{10,11}$=1.0 Hz), 2.90—3.05 (2H, m, 2×H-9′), 3.50—3.60 (1H, m, H-10), 4.02 (1H, q-like, H-9, $J\fallingdotseq$8 Hz), 4.29 (1H, t-like, H-6, $J\fallingdotseq$7 Hz), 4.35—4.50 (1H, br, OH), 5.15 (2H, s, $OC\underline{H}_2Ph$), 5.18 and 5.38 (each 0.5H, each s, H-2), 5.38 (1H, dq, H-5, $J_{5,6}$=7.0 Hz), 5.40—5.50 (1H, br, 6-NH), 5.77 (1H, m, H-2′), 6.04 (1H, br-d, H-N(8), $J\fallingdotseq$8 Hz), 7.18 (1H, dd, J=8.0, 4.5 Hz), 7.38 (5H, s, Ph), 7.62 (1H, ddd, J=2.0, 2.0 Hz), 8.46 (1H, dd), and 8.54 (1H, d).

*3-O-Benzyl-6-deoxy-5-C-ethyl-1,2-O-isopropylidene-5-O-methyl-α-D-glucofuranose (**34**).* To a solution of **33** (5.37 g, 0.017 mol) in dry DMF (26 ml) was added 55% NaH (2.27 g, 0.052 mol) under ice-cooling. After the mixture had been stirred at room temperature for 0.5 h, methyl iodide (2.12 ml, 0.034 mol) was added to the mixture and stirring was continued for 1 h. The resulting mixture was poured into cold water and extracted with ethyl acetate. The extract was dried and evaporated to a brown syrup (8 g), which was chromatographed on silica-gel (200 g) with 5:1 toluene–ethyl acetate to afford **34** (4.38 g, 77%): A colorless syrup, $[\alpha]_D^{31}$ −68° (*c* 1.44); ^{1}H-NMR (90 MHz) δ=0.86 (3H, t, J=6.0 Hz), 1.30 (3H, s), 1.35 and 1.51 (each 3H, each s), 3.30 (3H, s), 3.90 and 4.15 (each 1H, each d, J=0, 3.0 Hz), 4.55 (1H, d, J=4.5 Hz), and 5.96 (1H, d).

Found: C, 67.55; H, 8.30%. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39%.

*3-O-Benzyl-6-deoxy-5-C-ethyl-5-O-methyl-D-glucofuranose (**35**).* A mixture of **34** (4.3 g) and 50% aqueous acetic acid (40 ml) was boiled under reflux for 5 h, and evaporated to a brown syrup, which was chromatographed on silica-gel (200 g) with 1:2 toluene–ethyl acetate to afford **35** (2.45 g, 65%).

Found: C, 64.73; H, 8.10%. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16%.

*2-O-Benzyl-5-deoxy-4-C-ethyl-4-O-methyl-D-arabinitol (**36**).* To a solution of **35** (2.35 g) in acetone (60 ml) was added a solution of sodium periodate (3.4 g) in water (40 ml). After the mixture had been stirred at room temperature for 3 h, a solution of the periodate (1.7 g) in water (20 ml) was added to the reaction mixture. The mixture was stirred in a dark place at room temperature for 1 h and filtered. Acetone was removed from the filtrate by concentration and the aqueous residue was extracted with chloroform. The extract was washed with saturated aqueous NaCl, dried, and evaporated. The residual syrup (1.74 g) was dissolved in dry THF (34 ml) and cooled in an ice-bath. Powdered $LiAlH_4$ (0.6 g, 155 mmol) was added slowly to the stirred solution and then stirred at room temperature for 2 h. Wet ether was added to the ice-cold reaction mixture to decompose the excess $LiAlH_4$. The mixture was filtered and the filter cake was washed with chloroform. The filtrate and washings were combined and evaporated to a yellow syrup (2 g), which was chromatographed on silica-gel (50 g) with 2:1 benzene–ethyl acetate to give **36** (1.4 g, 67%): a colorless syrup, $[\alpha]_D^{34}$ −25° (*c*, 1.00); ^{1}H-NMR (90 MHz) δ=0.88 (3H, t, J=7.5 Hz), 1.23 (3H, s), and 3.25 (3H, s).

Found: C, 67.06; H, 8.74%. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02%.

*2-O-Benzyl-5-deoxy-4-C-ethyl-3-O-methoxymethyl-4-O-methyl-D-arabinitol (**39**).* To a solution of **36** (1.43 g, 8.1 mmol) in dry DMF (14 ml) was added imidazole (817 mg, 12 mmol) and *t*-butyldiphenylsilyl chloride (TBDPSCl) (3.12 ml, 12 mmol), and the mixture was stirred at room temperature for 2 h. The resulting mixture was poured into cold water, and extracted with ethyl acetate. The extract was washed with a saturated aqueous NaCl solution, dried, and evaporated to a syrup, which was chromatographed on silica-gel (100 g) with 10:1 toluene–ethyl acetate to give a practically pure sample of **37** (a yellow syrup, 4.0 g, 97%). To an ice-cooled solution of this sample of **37** (4.0 g) in dry DMF (40 ml) was added methoxymethyl chloride (0.9 ml, 11.9 mmol) and diisopropylamine (2 ml, 11.5 mmol), and then the mixture was stirred at 60 °C for 2 h. The reaction mixture was poured into a cold water and extracted with ethyl acetate. The extract was washed with a saturated aqueous NaCl

solution, dried and evaporated to a crude syrup of **38** (4.0 g). To a solution of this syrup (4.0 g) in dry THF (20 ml) was added tetrabutylammonium, fluoride (1 M THF solution, 10 ml) dropwise under ice-cooling. After being stand at 0 °C for 2 h, the mixture was poured into an icewater and extracted with chloroform. The extract was washed with a saturated NaCl solution, dried, and evaporated to a syrup (4 g), which was chromatographed on silica-gel with 1:1 toluene–ethyl acetate to afford **39** (1.03 g, 42% from **36**): A colorless syrup; $[\alpha]_D^{33}$ −15° (*c* 1.00); ^{1}H-NMR (90 MHz) δ=0.87 (3H, t, *J*=7.2 Hz), 1.29 (3H, s), 1.57 (2H, q), 3.22 and 3.46 (each 3H, each s), 4.62 and 4.79 (each 2H, each s), and 7.38 (5H, s).

Found: C, 65.58; H, 8.87%. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03%.

(2R,3S)-(+)-3-Methoxy-2-(methoxymetoxy)-3-methylpentanoic Acid (6). A solution of **39** (740 mg) in methanol (7 ml) was stirred with Pd-black for 1 h under bubbling with hydrogen gas. The filtered solution was evaporated to a colorless syrup of **40** (700 mg), which was dissolved in acetone (7 ml) and to the solution a solution of sodium periodate (1.5 g, 7 mmol) in water (15 ml) was added dropwise under ice-cooling. After being stirred in a dark place at room temperature for 4 h, the reaction mixture was filtered, and acetone was removed by concentration. The resulting aqueous residue was extracted with chloroform. The extract was washed with saturated aqueous NaCl, dried, and evaporated to give 4-deoxy-3-*C*-ethyl-2-*O*-(methoxymethyl)-3-*O*-methyl-D-erythrose (colorless liquid, 780 mg). The crude aldehyde was dissolved in DME (1.8 ml) and to the solution PDC (5.4 g) was added. After being stirred at room temperature for 2 d, the mixture was filtered through silica-gel (10 g) with ether to remove the chromate. The filtrate was then evaporated to a syrup, which was chromatographed on silica-gel (30 g) with 80:5:1 chloroform–methanol–acetic acid to afford **6** (a colorless syrup, 480 mg, 74%): $bp_{0.1}$ 130 °C (bath temp); IR ($CHCl_3$) 1723 cm^{-1}; $[\alpha]_D^{29}$ +64° (*c* 1.09); ^{1}H-NMR (90 MHz) δ=0.92 (3H, t, *J*=7.5 Hz), 1.30 (3H, s), 1.73 (2H, q), 3.35 and 3.44 (each 3H, each s), 4.11 (1H, s) 4.60 and 4.85 (2H, m), and 7.79 (1H, br-s, COOH).

Found: C, 52.70; H, 8.69%. Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80%.

N-Benzyloxycarbonyl-L-threonine Benzhydryl Ester (41). To a solution of *N*-benzyloxycarbonyl-L-threonine (500 mg, 1.97 mmol) in ethyl acetate (5 ml) was added dropwise a solution of diphenyldiazomethane in petroleum ether prepared from benzophenone hydrazone (580 mg, 2.95 mmol) and HgO (yellow) (640 mg, 2.95 mmol) in petroleum ether (0.3 ml) at room temperature for 5 h. After violent foaming had been settled, the reaction mixture was stirred at room temperature for 2 h and then excess diphenyldiazomethane was decomposed by addition of concd HCl. Water was added to the reaction mixture and extracted with ethyl acetate four times. The combined extracts were evaporated to a yellow syrup, which was chromatographed on silica-gel with 3:1 toluene–ethyl acetate to afford a pale yellow crystalline solid (662 mg, 80%). Recrystallization from hexane–ethyl acetate gave a pure sample of **41**: Colorless needles, mp 94—95 °C; $[\alpha]_D^{29}$ −19° (*c* 1,03); ^{1}H-NMR (90 MHz) δ=1.20 (3H, d, *J*=6.0 Hz), 1.8—2.1 (1H, br-s), 4.2—4.5 (2H, m), 5.10 (2H, s), 5.61 (1H, br-d, *J*=10 Hz), 6.90 (1H, s), and 7.36 (15H, s).

Found: C, 70.90; H, 6.07; N, 3.40%. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34%.

N-Benzyloxycarbonyl-O-[(2R,3S)-2-(methoxymethoxy)-3-methoxy-3-methylpentanoyl]-L-threonine Benzhydryl Ester (42). By the procedure described in the preparation of **21**, the mixture of **41** (712 mg, 1.7 mmol), **6** (350 mg, 1.69 mmol), ethyl acetate (8 ml), DMAP (20 mg, 0.16 mmol), and DCC (520 mg, 2.55 mmol) afforded **42** (650 mg, 65%) after silica-gel chromatography with 5:1 benzene–ethyl acetate: A colorless syrup, ^{1}H-NMR (90 MHz) δ=0.83 (3H, t, *J*=7.5 Hz), 1.12 (3H, s), 1.32 (3H, d, *J*=6.6 Hz), 1.53 (2H, q,), 3.18 and 3.28 (each 3H, each s), 4.00 (1H, s), 4.3—4.65 (1H, m), 4.39 and 4.48 (each 1H, ABq, J_{gem}=7.5 Hz), 5.13 (2H, s), 5.3—5.8 (2H, m), 6.86 (1H, s), and 7.10—7.50 (15H, m).

N-Benzyloxycarbonyl-O-[(2R,3S)-2-hydroxy-3-methoxy-3-methylpentanoyl]-L-threonine Benzhydryl Ester (43). A solution of **42** (650 mg) in 90% aqueous TFA (6 ml) was kept at room temperature for 1 h. Evaporation of the reaction mixture followed by co-evaporation with ether yielded a brown syrup (750 mg), which was chromatographed on silica-gel (30 g) with 80:5:1 chloroform–methanol–acetic acid to afford a colorless syrup (370 mg, 89%) of the hydroxy acid. By the same procedure as described in the preparation of **41**, the syrup (113 mg) was treated with diphenyldiazomethane to give a crude syrup (300 mg) of **43**, which was chromatographed on silica-gel (10 g) with 5:1 benzene–ethyl acetate to afford a pure sample of **43** (115 mg, 72%): A colorless syrup; $[\alpha]_D^{30}$ −2°, $[\alpha]_{365}^{30}$ −5° (*c* 2.24); ^{1}H-NMR (90 MHz) δ=0.86 (3H, t, *J*=7.5 Hz), 1.00 (3H, s), 1.31 (3H, d, *J*=7.5 Hz), 1.50 (2H, q), 2,83 (1H, br-s), 3.03 (3H, s), 3.96 (1H, s), 4.60 (1H, dd, *J*=3.0, 9.0 Hz), 5.10 (2H, s), 5.53 (1H, dq), 5.73 (1H, br-s), 6.86 (1H, s), and 7.07—7.47 (15H, m).

Found: C, 68.28; H, 6.62; N, 2.70%. Calcd for $C_{32}H_{37}NO_8$: C, 68.19; H, 6.62; N, 2.49%.

N-Benzyloxycarbonyl-O-[(2R,3S)-2-((2R,3S,4S)-4-azido-3-hydroxy-2-methyl-5-(3-pyridyl)pentanoyloxy)-3-methoxy-3-methylpentanoyl]-L-threonine (46). By the procedure described in the preparation of **29**, a mixture of **43** (117 mg, 0.207 mmol), ethyl acetate (2 ml), DMAP (2.5 mg, 0.02 mmol), and DCC (105 mg, 0.5 mmol) afforded **44** (105 mg, 63%) after purification through silica-gel (20 g) column with 3:1 toluene–ethyl acetate. A solution of **44** (105 mg) in 22 ml of a 2% HCl (in 50% (v/v) aqueous dioxane) was stirred at 35 °C for 10 h, and then evaporated to afford a syrup of **45**, which was dissolved in a 90% TFA (1 ml) and kept at room temperature for 30 min. The reaction mixture was evaporated and co-evaporated with ether. The final residue was chromatographed on silica-gel (10 g) with 80:5:1 chloroform–methanol–acetic acid to give **46** (70 mg, 57% from **43**) as a colorless glassy solid.

(2R,5R,6S,9S,10S,11R)-10-Hydroxy-2-[(1'S)-1'-methoxy-1'-methylpropyl]-5,11-dimethyl-9-(3-pyridylmethyl)-6-(benzyloxycarbonylamino)-8-aza-1,4-dioxacyclododecane-3,7,12-trione (15). By the procedure described in the preparation (a) of **14**, the azido acid **46** (110 mg) afforded a crude syrup of **15** which was purified through silica-gel column chromatography with 30:1 chloroform–methanol to provide a pure sample of **15** (16 mg, 15%) as a colorless glass: $[\alpha]_D^{27}$ −17° (*c* 0.53); ^{1}H-NMR (250 MHz) δ=0.85 (3H, t, *J*=6.2 Hz), 1.29 (3H, s), 1.30 (3H, d, *J*=7.5 Hz), 1.41 (3H, d, *J*=6.3 Hz), 1.71 (2H, q,

J=6.2 Hz), 2.59 (1H, q, J=6.3 Hz), 2.86—3.05 (2H, m), 3.21 (1H, s), 3.58 (1H, s-like), 3.93—4.10 (1H, m), 4.1—4.5 (2H, m), 5.00 (1H, s, H-2), 5.15 (2H, s), 5.40 (1H, dq, J=5.4, 7.5 Hz), 5.3—5.5 (1H, br), 6.25 (1H, br-d), 7.17 (1H, dd, J=5.0, 8.0 Hz), 7.38 (5H, s), 7.61 (1H, ddd, J=1.5, 1.8, 8.0 Hz), 8.46 (1H, dd, J=1.5, 5.0 Hz), and 8.53 (1H, d, J=1.8 Hz).

Found: m/z 585.2692. Calcd for $C_{30}H_{39}N_3O_9$: M, 585.2684.

5-O-(t-Butyldiphenylsilyl)-1-deoxy-2-C-ethyl-3,4-O-isopropylidene-D-ribitol (48). A solution of **47**[16] (3.0 g, 6.8 mmol) in methanol (30 ml) was stirred with 5% Pd–carbon (*ca.* 0.5 g) for 0.5 h under bubbling with hydrogen gas. The filtered solution was evaporated to a syrup of **48** (3.0 g, 99%). An analytical sample was obtained by silica-gel column chromatography with 10:1 toluene–ethyl acetate; colorless syrup, $[\alpha]_D^{31}$ +28° (c 1.09).

Found: C, 70.65; H, 8.40%. Calcd for $C_{26}H_{37}O_4Si$: C, 70.55; H, 8.64%.

5-O-(t-Butyldiphenylsilyl)-1-deoxy-2-C-ethyl-3,4-O-isopropylidene-2-O-methyl-D-ribitol (49). By the procedure described in the *O*-methylation of **33**, the sample of **48** (2.85 g) was *O*-methylated to afford a crude syrup of **49** (5 g), which was chromatographed on silica-gel (100 g) with 20:1 toluene–ethyl acetate to give a pure sample of **49** (2.24 g, 76%); a colorless syrup, $[\alpha]_D^{30}$ +35° (c 1.16); ^{1}H-NMR δ=0.86 (3H, t, J=7.5 Hz), 1.08 (9H, s), 1.12 (3H, s), 1.33 and 1.38 (each 3H, each s), 1.5—1.8 (2H, m), 3.15 (3H, s), and 3.5—3.8 (2H, m).

Found: C, 71.29; H, 8.62%. Calcd for $C_{27}H_{40}O_4Si$: C, 71.02; H, 8.82%.

1-Deoxy-2-C-ethyl-2-O-methyl-D-ribitol (50). To a cold solution of **49** (2.24 g) in dry THF (12 ml) was added (n-Bu)$_4$NF (7.75 ml of 1 M THF solution) dropwise. After being stirred at 5 °C for 3 h, the mixture was poured into a cold water and extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl, dried, and evaporated to afford a syrup, which was dissolved in an 80% aqueous TFA (25 ml). After being kept at room temperature for 1 h, the mixture was evaporated. The residue (2.5 g) was chromatographed on silica-gel (100 g) with 15:1 chloroform–methanol to give a pure sample of **50** (5.8 g, 67%); a colorless syrup, $[\alpha]_D^{31}$ +9° (c 1.00); ^{1}H-NMR (90 MHz) δ=0.91 (3H, t, J=6.0 Hz), 1.21 (3H, s), 1.73 (2H, q), 2.7—3.1 (3H, br), and 3.23 (3H, s).

Found: C, 53.81; H, 9.90%. Calcd for $C_8H_{18}O_4$: C, 53.91; H, 10.18%.

1-Deoxy-2-C-ethyl-2-O-methyl-D-ribitol 4,5-carbonate (51). A solution of **50** (65 mg, 0.37 mmol) and *N,N'*-carbonyldiimidazole (72 mg, 0.444 mmol) in dry benzene (1.3 ml) was stirred at room temperature for 2 h, and the reaction mixture was then poured into a cold water and extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl, dried, and evaporated. The residual syrup (80 mg) was chromatographed with 3:1 benzene–ethyl acetate to afford **17** (46 mg, 61%) as colorless crystals; mp 77—79 °C (hexane–ethyl acetate); $[\alpha]_D^{33}$ +17° (c 1.00); ^{1}H-NMR (90 MHz) δ=0.93 (3H, t, J=7.0 Hz), 1.18 (3H, s), 1.6—1.85 (2H, m), 2.9—3.1 (1H, br-s), 3.25 (3H, s), 3.88 (1H, d, J=4.5 Hz), and 4.4—5.0 (3H, m).

Found: C, 52.85; H, 7.75%. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90%.

1-Deoxy-2-C-ethyl-3-O-methoxymethyl-2-O-methyl-D-ribitol 4,5-carbonate (52). By the procedure described in the *O*-methoxymethylation of **47**, the sample of **51** (251 mg) was *O*-methyoxymethylated to afford a crude syrup of **52** (251 mg), which was chromatographed on silica-gel (25 g) with 5:1 benzene–ethyl acetate to give a pure sample of **52** (252 mg, 93%); a colorless syrup, $[\alpha]_D^{33}$ +30° (c 1.00); IR ($CHCl_3$) 1803 cm^{-1}: ^{1}H-NMR (90 MHz) δ=0.91 (3H, t, J=7.5 Hz), 1.20 (3H, s), 1.5—1.7 (2H, m), 3.23 and 3.43 (each 3H, each s), 3.91 (1H, d, J=1.0 Hz), and 4.3—5.1 (5H, m).

Found: C, 53.28; H, 7.97%. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12%.

(2S,3R)-(−)-3-Methoxy-2-(methoxymethoxy)3-methylpentanoic Acid (7). To a solution of **52** (251 mg, 1.08 mmol) in methanol (3 ml) was added an aqueous 1 M NaOH solution (2.2 ml). After being stirred at room temperature for 20 min, the reaction mixture was neutralized with CG-50 resin (H$^+$ type) to pH 6—8 under ice-cooling, and filtered. The filtrate and methanolic washings were combined and evaporated to give a crude syrup of **53**. The two-stage oxidation of the crude **53** was carried out by the same procedure described in the preparation of **6** from **40** to afford the enantiomeric **7** (114 mg, 51% yield from **52**). This sample of **7** was purified by bulb to bulb distillation; colorless syrup, $bp_{0.1}$ 130 °C (bath temp.); IR ($CHCl_3$) 1723 cm^{-1}; $[\alpha]_D^{28}$ −61° (c 0.96); the ^{1}H-NMR (90 MHz) and IR spectra were identical with those of **6**.

Found: C, 52.52; H, 8.61%. Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80%.

N-Benzyloxycarbonyl-O-[(2S,3R)-2-(methoxymethoxy)-3-methoxy-3-methylpentanoyl]-L-threonine Benzhydryl Ester (54). The title compound **54** was prepared from **7** and **41** by the procedure described in the preparation of **42**. **54**: A colorless syrup, ^{1}H-NMR (90 MHz) δ=0.81 (3H, t, J=7.5 Hz), 1.13 (3H, s), 1.36 (3H, d, J=6.6 Hz), 1.2—1.5 (2H, m), 3.18 (3H, s), 3.31 (3H, s), 4.00 (1H, s), 4.36 and 4.53 (each 1H, ABq, J=7.5 Hz), 4.63 (1H, dd, J=2.5, 12 Hz), 5.15 (2H, s), 5.61 (1H, dq), 5.78 (1H, br-d), 6.90 (1H, s), and 7.13—7.58 (15H, m).

N-Benzyloxycarbonyl-O-[(2S,3R)-2-hydroxy-3-methoxy-3-methylpentanoyl]-L-threonine (55). **55**: Colorless needles, mp 120—121 °C; $[\alpha]_D^{28}$ +39° (c 1.25); ^{1}H-NMR (90 MHz) δ=0.83 (3H, t, J=7.5 Hz), 1.10 (3H, s), 1.30 (3H, d, J=6.0 Hz), 1.60 (2H, q), 3.15 (3H, s), 3.88 (1H, br), 4.08 (1H, s), 4.56 (2H, dd, J=1.0, 10 Hz), 5.08 (2H, s), 5.53 (1H, dq), 5.5—6.2 (2H, br), and 7.40 (5H, s).

N-Benzyloxycarbonyl-O-[(2S,3R)-2-hydroxy-3-methoxy-3-methylpentanoyl]-L-threonine Benzhydryl Ester (56). **56**: A colorless syrup, $[\alpha]_D^{30}$ +3°, $[\alpha]_{365}^{30}$ +16° (c 1.49); ^{1}H-NMR (90 MHz) δ=0.81 (3H, t, 7.5 Hz), 1.00 (3H, s), 1.33 (3H, d, J=6.6 Hz), 1.26—1.70 (2H, m), 2.8—3.0 (1H, m), 3.16 (3H, s), 3.73 (1H, s), 4.50—4.76 (1H, m), 5.15 (2H, s), 5.4—5.8 (2H, m), 6.83 (1H, s), and 7.13—7.58 (15H, m).

Found: C, 68.17; H, 6.61; N, 2.48%. Calcd for $C_{32}H_{37}NO_8$: C, 68.19; H, 6.62; N, 2.49%.

N-Benzyloxycarbonyl-O-[(2S,3R)-2-((2R,3S,4S)-4-azido-3-formyloxy-2-methyl-5-(3-pyridyl)pentanoyloxy)-3-methoxy-3-methylpentanoyl]-L-threonine Benzhydryl Ester (57). The compound **57** was prepard from **3** (118 mg) and **56** (232 mg) by the same procedure as described in the preparation of **44**. A practically pure sample of **57** (281 mg, 72%) was obtained

by silica-gel (25 g) column chromatography of the crude product with 1:1 toluene–ethyl acetate.

N-Benzyloxycarbonyl-O-[(2S,3R)-2-((2R,3S,4S)-4-azido-3-hydroxy-2-methyl-5-(3-pyridyl)pentanoyloxy)-3-methyoxy-3-methylpentanoyl]-L-threonine Benzhydryl Ester (58). A practically pure sample of **57** (281 mg) was dissolved in a 2% HCl solution in 50% aqueous dioxane (5 ml). After being stirred at 35 °C for 7 h, the reaction mixture was evaporated to a syrup of **58** which was used for the next preparation without further purification. A pure sample of **58** was obtained by silica-gel column chromatography with 40:1 chloroform–methanol; a colorless syrup, $[\alpha]_D^{31}$ +8°, $[\alpha]_{365}^{31}$ +17° (*c* 0.90).

Found: C, 64.91; H, 6.35; N, 8.75%. Calcd for $C_{43}H_{49}N_5O_{10}$: C, 64.90; H, 6.20; N, 8.80%.

(2S,5R,6S,9S,10S,11R)-10-Hydroxy-2-[(1'R)-1'-methoxy-1'-methylpropyl]-5,11-dimethyl-9-(3-pyridylmethyl)-6-(benzyloxycarbonylamino)-8-aza-1,4-dioxacyclododecane-3,7,12-trione (18). By the procedure described in the preparation of **15**, the title compound **18** was obtained in a 12% yield from **58** *via* the azido acid **59** as a colorless syrup: $[\alpha]_D^{29}$ −48° (*c* 0.89); ^{1}H-NMR (250 MHz) δ=0.88 (3H, t, *J*=8.3 Hz), 1.17 (3H, d, *J*=5.0 Hz), 1.33 (3H, d, *J*=8.0 Hz), 1.43 (3H, s), 1.65—1.90 (2H, m), 2.44 (2H, dq, *J*=1.5, 8.0 Hz), 2.9—3.2 (2H, m), 3.26 (3H, s), 3.60 (1H, br), 4.00—4.13 (1H, m), 4.0—4.5 (1H, br), 4.45 (1H, dd, *J*=5.0 Hz), 4.71 (1H, s, H-2), 5.00 (1H, dq), 5.13 (2H, s), 5.86 (1H, br-d), 6.76 (1H, br-d), 7.25 (1H, dd, *J*=5.0, 8.0 Hz), 7.36 (5H, s), 7.69 (1H, ddd, *J*=1.5, 1.8, 8.0 Hz), 8.51 (1H, dd, *J*=1.5, 5.0 Hz), and 8.59 (1H, d, *J*=1.8 Hz).

Found: *m/z* 585.2678. Calcd for $C_{30}H_{39}N_3O_9$: M, 585.2683.

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