A CONVENIENT SYNTHESIS OF THE FIVE-MEMBERED LACTAMS FROM D-ARABINOSE

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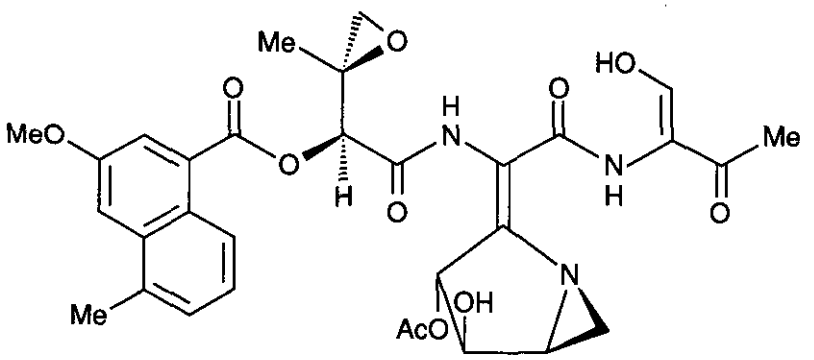
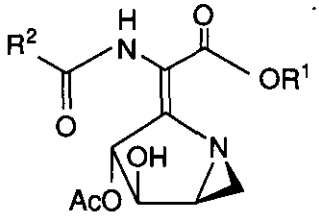
Abstract--- Synthesis of the five-membered lactams, (3*S*, 4*R*, 5*S*)-1-benzoyl- and (3*S*, 4*R*, 5*S*)-1-benzyloxycarbonyl-5-benzyloxymethyl-3, 4-dibenzyloxy-pyrrolidin-2-ones (**3a** and **3b**) which are the important intermediates for the unsaturated five membered amino acid moiety (**2**) in carzinophilin (**1**) was described. Lactams (**3a** and **3b**) were synthesized from 2, 3, 5-tri-*O*-benzyl-D-arabinitol (**6**) by a convenient method in seven steps.

Carzinophilin (**1**)[1] (Azinomycin B)[2] is well known due to its potent antitumor activities resulting from its strand cross-link formation with DNA. The unique structure of **1** involving an epoxide moiety and an unsaturated five-membered amino acid with an aziridine ring, is attractive to most synthetic chemists as a target of total synthesis. Our group has also examined the synthesis of **1** for the purpose to decide its structure by chemical method, and has already reported the synthesis of the epoxide containing moiety.[3] Recently, we started the project directed at the synthesis of the unsaturated five-membered amino acid moiety (**2**).

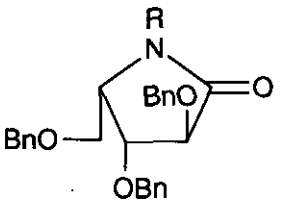
In this paper, we wish to report a synthetic method for the five membered lactam (**3**), an important intermediate for the synthesis of **2**, using D-arabinose as a starting material. Recently, various synthetic studies of the sugar-like *N*-containing five-membered ring from corresponding furanose in related to



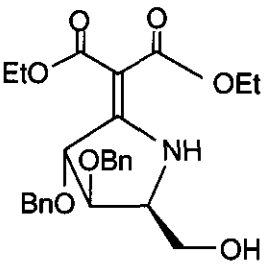
1 carzinophilin (azinomycin B)



2



3a R=Bz
3b R=CBz

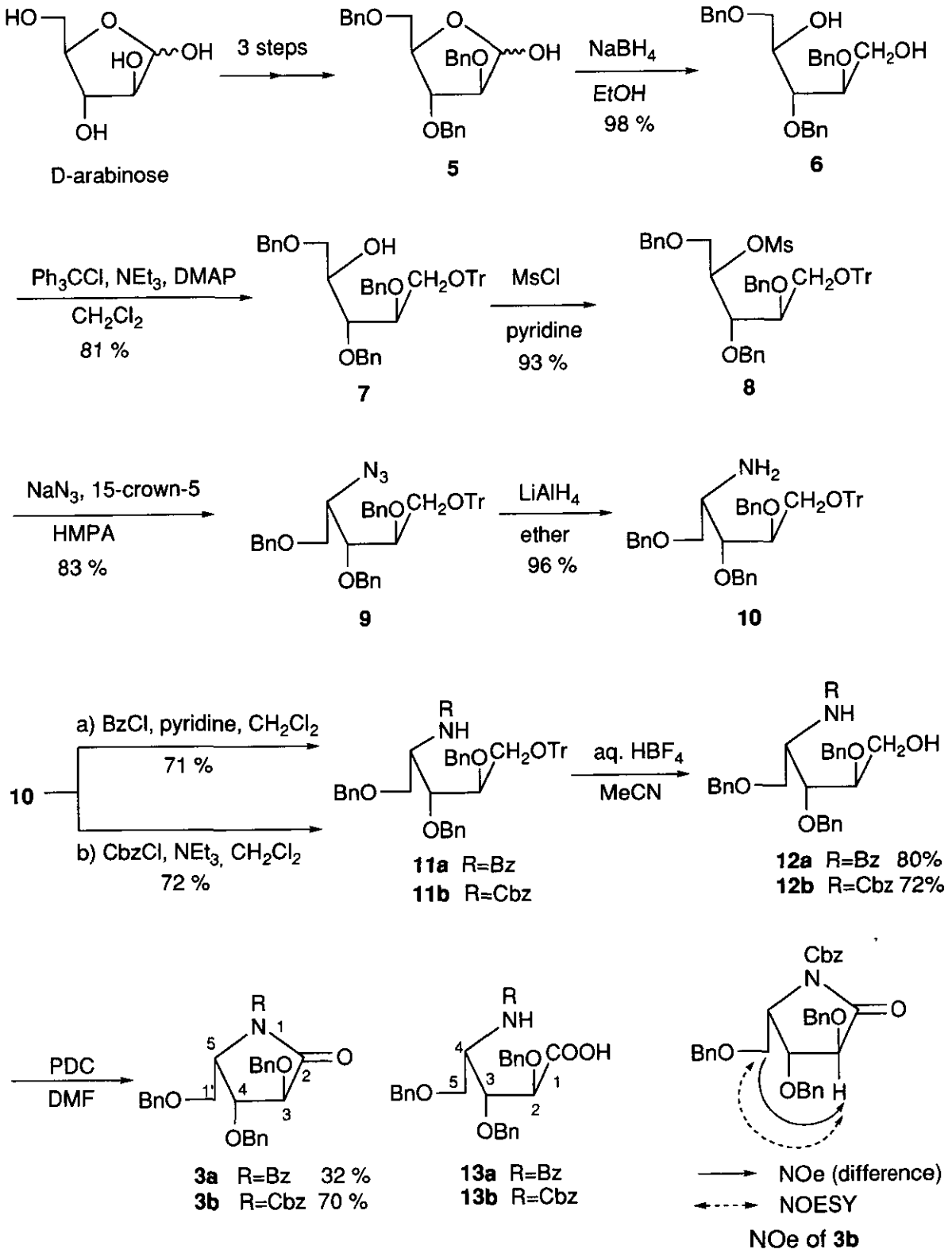


4

Figure 1

azasugars have been reported [4, 5] due to their potent glycosidase inhibitors which have potential anti AIDS-virus activity. Among them, a few reports[5] concern with the synthetic method for the five-membered lactam which is easily converted to azasugars by reduction of carbonyl group. M. Hashimoto *et al.*[6] have reported an efficient synthesis of the five-membered lactam (**4**) in related to carzinophilin from D-arabinose using Luigi's method.[6] We have also chosen D-arabinose as a chiral block to construct **3**.

For the synthesis of 2, 3, 5-tri-*O*-benzyl-α– and β–D-arabinofuranose (**5**), we applied the procedure described by Fleetcher.[7] Thus, treatment of D-arabinose with MeOH-HCl afforded methyl arabinofuranoside. This was benzylated with benzyl bromide and sodium hydride, and subsequently treated with acetic acid-HCl to give **5** in 29% total yield from D-arabinose. Compound (**5**) was converted to the arabinitol (**6**) by reduction with $NaBH_4$ in 98% yield. The primary hydroxyl group of **6** was selectively protected using trityl chloride to afford **7** in 81% yield. The secondary hydroxyl group of **7** was mesylated with methanesulfonyl chloride, giving **8** in 93% yield. Treatment of **8** with sodium azide and 15-crown-5[8] produced azide (**9**) in 83% yield. Azide (**9**) was converted to amine (**10**) by reduction with


HO
O
HO
OH
OH
3 steps
BnO
O
BnO
OH
OBn
NaBH4
EtOH
98 %
BnO
OH
BnO
CH2OH
OBn
D-arabinose
5
6
Ph3CCl, NEt3, DMAP
CH2Cl2
81 %
BnO
OH
BnO
CH2OTr
OBn
MsCl
pyridine
93 %
BnO
OMs
BnO
CH2OTr
OBn
7
8
NaN3, 15-crown-5
HMPA
83 %
N3
BnO
CH2OTr
BnO
OBn
LiAlH4
ether
96 %
NH2
BnO
CH2OTr
BnO
OBn
9
10
10
a) BzCl, pyridine, CH2Cl2
71 %
b) CbzCl, NEt3, CH2Cl2
72 %
R
NH
BnO
CH2OTr
BnO
OBn
aq. HBF4
MeCN
R
NH
BnO
CH2OH
BnO
OBn
11a R=Bz
11b R=Cbz
12a R=Bz 80%
12b R=Cbz 72%
PDC
DMF
R
N
1
5
BnO
2
O
BnO
1'
4
3
OBn
R
NH
4
BnO
COOH
BnO
5
3
1
2
OBn
Cbz
N
BnO
O
BnO
OBn
H
3a R=Bz 32 %
3b R=Cbz 70 %
13a R=Bz
13b R=Cbz
NOe (difference)
NOESY
NOe of 3b

Scheme 1

$LiAlH_4$[9] in 96% yield. The amino group of **10** was protected with a benzoyl or a benzyloxycarbonyl group by treating with benzoyl chloride or carbobenzyloxy chloride to give **11a** or **11b** in 71% or 72% yield, respectively. Trityl ethers (**11a** and **11b**) were detritylated by treatment with HBF_4[10] to afford **12a** and **12b** in 80 and 72% yields, respectively. Oxidation of each **12a** and **12b** with PDC[11] successively afforded the five-membered lactams (**3a**) and (**3b**) in 34% and 70% yields, respectively after spontaneous ring closure. Oxidative ring closure reactions of **12a** to **3a** were carried out two times, but the yields were not improved and each reaction gave **3a** in 22% and 34% yields, respectively. Furthermore, relative amount of **13a** (22% yield) was produced together with **3a**, whereas **12b** did not gave intermediate (**13b**) and afforded only single product (**3b**). It can be assumed the oxidative ring closure of **12** to **3** occurs through **13** as intermediates. It is considered that the electron density of nitrogen in **13a** having benzoyl group is more poor than in **13b** having benzyloxycarbonyl group and we assumed that this fact caused ring closure of **13a** to **3a** to occur somewhat difficulty and ring closure of **13b** to occur easily to afford single product of **3b**. In conclusion, it is clarified the benzyloxycarbonyl group is more suitable than the benzoyl group as a *N*-protective group for conversion of **12** to **3.**

Generally, introduction of an azide group by replacing a mesyl group with sodium azide causes inversion of the configuration by S_N2 reaction as shown in Scheme 1. We assigned the chirality at C-4 in **3b** by nOe measurement. NOes between H-3 and Ha-1' were observed in both difference and NOESY spectra. These data show that H-3 and Ha-1' are located in *cis* position.

Thus, we achieved the synthesis of the five membered lactam (**3b**) in seven steps and in 19% total yield from 2, 3, 5-tri-*O*-benzyl-D-arabinitol (**6**) which is easily available from D-arabinose. Each reaction involved in this procedure is employable in a large scale preparation and applicable to the synthesis of other five-membered lactams from a corresponding furanose derivative. Furthermore, the effect of *N*-substituted group was observed in the reactivity of oxidative ring closure reaction of **12** to **3.**

ACKNOWLEDGEMENTS

We are grateful to prof. Dr. C. Shin. (University of Kanagawa) for valuable suggestions concerning the reaction condition to introduce an azide group.

EXPERIMENTAL

Melting points were measured on a Yanagimoto Micro Melting Apparatus and are uncorrected. Measurements of optical rotations were performed with a JASCO model DPI-181 polarimeter. Ir spectra were recorded on a Hitachi 260-230 spectrophotometer. Nmr spectra were taken with a WXR-300 and a XL-400 spectrometers in $CDCl_3$ otherwise described. The nOe spectra were measured on a XL-400 spectrometer using Varian's standard program. Assignments of ^{13}C-nmr signals were performed by HMQC and HMBC spectra. Low resolution mass spectra (LR-ms) were obtained on a JEOL JMS-DX300 mass spectrometer and high resolution mass spectra (HR-ms) were taken on a JEOL JMX-AX505 mass spectrometer. Preparative thin layer chromatography (tlc) was performed on a 60PF254 silica gel plate. Flush colmun chromatography was carried out using 60H silica gel.

2,3,5-Tri-*O*-benzyl-α- and β-D-arabinofuranoses (5)

A solution of D-arabinose (8.0 g, 0.05 mol) and 15% HCl-MeOH (6 ml) in dry MeOH (253 ml) was stirred at room temperature for 18 h. The mixture was neutralized with Ag_2CO_3 under stirring for 0.5 h, then the methanol was evaporated *in vacuo* to give methyl arabinofuranoside as a residue. This was dissolved in DMF (20 ml), and 60% NaH in oil (17.2 g, 0.43 mmol) was added. After stirring for 0.5 h, benzyl bromide (38.3 ml, 0.32 mmol) was added to the mixture at 0 °C and the stirring was continued at room temperature for 16 h. Methanol (2 ml) was added to decompose excess NaH, and the solvent was removed by concentration *in vacuo*. The residue was poured into water (100 ml), and extracted with $CHCl_3$ (100 ml x 5). The combined extracts were washed with water (100 ml), dried over Na_2SO_4, then concentrated *in vacuo*. Resultant methyl 2, 3, 5-tri-*O*-benzylarabinofuranoside was dissolved in acetic acid (107 ml), and 6N HCl (16 ml) was added. The solution was stirred at 65 °C for 22 h. The mixture was concentrated *in vacuo* , and the resultant residue was dissolved in $CHCl_3$ (200 ml). The chloroform solution was washed with saturated $NaHCO_3$ (10 ml x 7), water (10 ml), dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by flush column chromatography (silica gel, hexane/AcOEt=9:1) to give **5** as colorless crystals (4.9 g, 29% from D-arabinose). mp 69-70 °C ($CHCl_3$/hexane) (lit.,[12] mp 74-76°, ethyl acetate-light petroleum). $[\alpha]_D^{25}$ -9.33 ° (c=0.15, $CHCl_3$) (lit.,[12] $[\alpha]_D^{25}$ -25.8°, c=1, dioxane/water=9:1). HR-ms m/z: Calcd for $C_{26}H_{28}O_5Na$ (M+Na) 443.1834. Found 443.1838.

2,3,5-Tri-*O*-benzyl-D-arabinitol (6)

To a solution of **5** (1.6 g, 3.75 mmol) in dry ethanol (20 ml), $NaBH_4$ (179.4 mg, 4.16 mmol) was added at 0 °C. After stirring for 40 min, excess NH_4Cl was added to the mixture and the ethanol was removed by concentration *in vacuo*. The residue was partitioned between $CHCl_3$ (30 ml) and water (12 ml), and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative tlc (hexane/AcOEt=1:1) to afford **6** as a colorless oil (1.5 g, 98%). $[\alpha]_D^{25}$ +2.73 ° (c=1.32, $CHCl_3$) (lit.[13], $[\alpha]_D^{22}$+1.30°, c=4.12, $CHCl_3$). ^{1}H-Nmr δ: 3.64 (1H, dd, J=10.0, 5.0, 5-H_a), 3.67 (1H, dd, J=10.0, 4.0, 5-H_b), 3.72 (1H, dd, J=7.0, 4.0, 3-H), 3.74 (1H, m, 2-H), 3.78 (2H, m, 1-H_2), 4.02 (1H, ddd, J=7.0, 5.0, 4.0, 4-H), 4.51-4.67 (6H, m, 2, 3, 5-OCH_2), 7.23-7.37 (15H, m, Bn x 3). ^{13}C-Nmr δ: 61.48 (t, C-1), 70.52 (d, C-4), 71.01 (t, C-5), 72.78, 73.49, 73.70 (each t, 2, 3, 5-OCH_2), 78.39 (d, C-3), 79.48 (d, C-2). HR-ms: m/z Calcd for $C_{26}H_{31}O_5$ (M+H) 423.2172. Found 423.2170.

2,3,5-Tri-*O*-benzyl-1-*O*-trityl-D-arabinitol (7)

To a solution of **6** (1.4 g, 3.40 mmol) in CH_2Cl_2 (20 ml), 4-dimethylaminopyridine (41.6 mg, 0.34 mmol), triphenylchloromethane (1.1 g, 4.08 mmol), and triethylamine (0.85 ml, 6.06 mmol) were added. After stirring at room temperature for 16 h, the solvent was removed by concentration *in vacuo* and the residue was purified by flush column chromatography (hexane/AcOEt=9:1) to give **7** as a colorless crystals (1.8 g, 81%). Mp 103-104 °C (ether). $[\alpha]_D^{24}$ +0.35 ° (c=2.27, $CHCl_3$). ^{1}H-Nmr δ: 2.74 (1H, d, J=5.0, 4-OH), 3.34, 3.49 (each 1H, dd, J=9.5, 6.0, 5-H_2), 3.54, 3.59 (each 1H, dd, J=10.5, 5.5, 1-H_2), 3.78 (1H, dd, J=7.5, 3.0, 3-H), 3.94 (1H, ddd, J=7.5, 5.5, 4.0, 2-H), 3.95 (1H, dt, J=3.0, 5.5, 4-H), 4.43 (2H, s), 4.48, 4.51 (each 1H, d, J=11.5), 4.57, 4.71 (each 1H, d, J=11.5) (2, 3, 5-OCH_2), 7.22-7.46 (30H, m, Tr x 1, Bn x 3). ^{13}C-Nmr δ: 63.10 (t, C-5), 70.10 (d, C-4), 71.21 (t, C-1), 73.12, 73.31, 73.78, (each t, 2, 3, 5-OCH_2), 77.94 (d, C-2), 78.86 (d, C-3). HR-ms m/z: Calcd for $C_{45}H_{44}O_5Na$ (M+Na) 687.3086. Found 664.3191. *Anal.* Calcd for $C_{45}H_{44}O_5$: C, 81.30; H, 6.67. Found: C, 81.27; H, 6.84.

2,3,5-Tri-*O*-benzyl-4-*O*-methanesulfonyl-1-*O*-trityl-D-arabinitol (8)

To a solution of **7** (1.4 g, 2.11 mmol) in dry pyridine (4 ml, 3.91 mol), mesyl chloride (0.2 ml, 2.53 mmol) was added dropwise at 0 °C under argon. After stirring for 2 h, additional portion of mesyl chloride (0.2 ml, 2.53 mmol) was added, and the mixture was further stirred at 0 °C for 18 h. The pyridine was removed by concentration *in vacuo*, and the residue was dissolved in $CHCl_3$ (100 ml). The

chloroform solution was washed with 5% HCl (5 ml), saturated NaCl (5 ml), and saturated $NaHCO_3$ (5 ml), dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by flush column chromatography (hexane/AcOEt=6:1) to give **8** as a light yellow oil (1.4 g, 93%). $[\alpha]_D^{24}$ + 6.80 ° (c=2.06, $CHCl_3$). ^{1}H-Nmr δ: 2.89 (3H, s, 4-CH_3), 3.30, 3.36 (each 1H, dd, J=10.0, 6.0, 1-H_2), 3.71 (1H, dd, J=11.0, 7.0, 5-H_a), 3.72 (1H, dt, J=3.5, 6.0, 2-H), 3.82 (1H, dd, J=11.0, 3.5, 5-H_b), 4.08 (1H, t, J=3.5, 3-H), 4.40 4.43 (each 1H, d, J=12.0), 4.52, 4.60 (each 1H, d, J=12.0), 4.53, 4.64 (each 1H, d, J=11.0) (2, 3, 5-OCH_2), 4.96 (1H, dt, J=3.5, 7.0, 4-H), 7.14-7.45 (30H, m, Tr x 1, Bn x 3). ^{13}C-Nmr δ: 38.43 (q, 4-CH_3), 63.01 (t, C-1), 69.06 (t, C-5), 73.19 (t, OCH_2 x 2), 74.69 (t, OCH_2), 78.05 (d, C-2), 79.41 (d, C-3), 82.43 (d, C-4). HR-ms m/z: Calcd for $C_{46}H_{46}O_7SNa$ (M+Na) 765.2862. The data of elemental analysis could not been obtained because of the lability of **8**.

4-Azido-2,3,5-tri-*O*-benzyl-4-deoxy-1-*O*-trityl-D-arabinitol (9)

To a solution of **8** (1.4 g, 1.83 mmol) in HMPA (2.3 ml), sodium azide (0.26 g, 3.66 mmol) and 15-crown-5 (0.73 ml, 3.66 mmol) were added, and the mixture was stirred at 80-90 °C for 6 h. Additional amounts of sodium azide (0.26 g, 3.66 mmol) and 15-crown-5 (0.73 ml, 3.66 mmol) were added, and the stirring was continued at 80-90 °C for 42 h. The HMPA was removed by concentration *in vacuo*, and the residue was dissolved in $CHCl_3$ (80 ml). The chloroform solution was washed with saturated NaCl (6 ml x 6), and the aqueous layer was further extracted with $CHCl_3$ (12 ml). The combined $CHCl_3$ layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flush column chromatography (hexane/AcOEt=10:1) to give **9** as a colorless oil (1.0 g, 83%). $[\alpha]_D^{25}$ +3.69 ° (c=1.41, $CHCl_3$). Ir ($CHCl_3$) ν_{max} cm^{-1}: 2110 (N_3). ^{1}H Nmr δ: 3.22 (1H, dd, J=10.0, 5.0, 1-H_a), 3.45, 3.50 (each 1H, dd, J=10.0, 7.0, 5-H_2), 3.50 (1H, dd, J=10.0, 4.5, 1-H_b), 3.57 (1H, dt, J=4.5, 7.0, 4-H), 3.76 (1H, ddd, J=5.5, 5.0, 4.5, 2-H), 3.95 (1H, dd, J=5.5, 4.5, 3-H), 4.41-4.74 (6H, m, 2, 3, 5-OCH_2), 7.19-7.49 (30H, m, Tr x 1, Bn x 3). ^{13}C-Nmr δ: 61.31 (δ, C-4), 62.62 (t, C-1), 69.42 (t, C-5), 72.77, 73,14, 74.93 (each t, 2, 3, 5-OCH_2), 78.29 (d, C-3), 79.21 (d, C-2). HR-ms m/z: $C_{45}H_{43}N_3O_4Na$ (M+Na) 712.3151. Found 712.3170. *Anal.* Calcd for $C_{45}H_{43}N_3O_4$: C, 78.35; H, 6.28; N, 6.09. Found: C, 78.36; H, 6.34; N, 5.76.

4-Amino-2,3,5-tri-*O*-benzyl-4-deoxy-1-*O*-trityl-D-arabinitol (10).

To a solution of **9** (1.0 g, 1.50 mmol) in dry ether (10 ml), $LiAlH_4$ (142.2 mg, 3.74 mmol) was added at room temperature under argon, and the mixture was stirred for 6.5 h. A mixture of ether and water (1:1) was added to decompose excess $LiAlH_4$, and the resultant precipitates were filtered off. The ethereal filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to give crude **10** as a colorless oil (0.95 g, 96%). $[\alpha]_D^{26}$ +0.44 ° (c=2.26, $CHCl_3$). ^{1}H-Nmr δ: 2.99 (1H, dt, J=6.0, 4.0, 4-H), 3.27, 3.36 (each 1H, dd, J=9.0, 6.0, 5-H_2), 3.31 (1H, dd, J=10.0, 4.5, 1-H_a), 3.46 (1H, dd, J=10.0, 4.0, 1-H_b), 3.70 (2H, s, 4-NH_2), 3.83 (1H, ddd, J=6.0, 4.5, 4.0, 2-H), 3.87 (1H, dd, J=6.0, 4.0, 3-H), 4.41-4.76 (6H, m, 2, 3, 5-OCH_2), 7.18-7.50 (30H, m, Tr x 1, Bn x 3). ^{13}C-Nmr δ: 51.53 (d, C-4), 62.88 (t, C-1), 72.77 (t x 2, C-5, OCH_2), 72.96, 74.92 (each t, OCH_2 x 2), 79.50, 79.97 (each d, C-2, C-3). HR-ms m/z: Calcd for $C_{45}H_{45}NO_4Na$ (M+Na) 686.3246. Found 686.3258. *Anal.* Calcd for $C_{45}H_{45}NO_4$: C, 81.42; H, 6.83; N, 2.11. Found: C, 81.41; H, 6.83; N, 1.78.

4-Benzoylamino-2,3,5-tri-*O*-benzyl-4-deoxy-1-*O*-trityl-D-arabinitol (11a)

To a solution of **10** (33.2 mg, 0.05 mmol) in dry CH_2Cl_2 (0.5 ml), dry pyridine (0.05 ml, 0.62 mmol) and benzoyl chloride (17.7 mg, 0.13 mmol) were added, and the mixture was stirred at 0 °C for 1.5 h. The mixture was diluted with $CHCl_3$ (30 ml), and the chloroform solution was washed with 5% HCl (2 ml x 2), saturated $NaHCO_3$ (2 ml), and saturated NaCl (2ml), dried over Na_2SO_4, then concentrated *in vacuo*. The residue was purified by preparative tlc (hexane/AcOEt=3:2) to give **11a** as a colorless oil (29.3 mg, 71%). $[\alpha]_D^{26}$ -39.99 ° (c=0.10, $CHCl_3$). Ir ($CHCl_3$) ν_{max} cm^{-1}: 3430 (NH), 1660 (NHCO). ^{1}H-Nmr δ: 3.32 (1H, dd, J=10.0, 5.5, 1-H_a), 3.41 (1H, t, J=9.0, 5-H_a), 3.41 (1H, dd, J=10.0, 4.0, 1-H_b), 3.54 (1H, dd, J=9.0, 5.0, 5-H_b), 3.74 (1H, dt, J=4.0, 5.5, 2-H), 4.26 (1H, dd, J=5.5, 1.5, 3-H), 4.39 , 4.49 (each 1H, d, J=12.0), 4.50, 4.73 (each 1H, d, J=11.0), 4.52, 4.64 (each 1H, d, J=12.0) (2, 3, 5-OCH_2), 4.45-4.53 (1H, m, 4-H), 6.46 (1H, d, J=8.5, 4-NH), 7.15-7.55 (35H, m, Tr x 1, Bz x 1, Bn x 3). HR-ms m/z: Calcd for $C_{52}H_{49}NO_5Na$ (M+Na) 790.3508. Found 790.3504. *Anal.* Calcd for $C_{52}H_{49}NO_5$: C, 81.33; H, 6.43; N, 1.82. Found: C, 81.16; H, 6.50; N, 1.81.

2,3,5-Tri-*O*-benzyl-4-carbobenzyloxyamino-4-deoxy-1-*O*-trityl-D-arabinitol (11b)

To a solution of **10** (38.5 mg, 0.06 mmol) in dry CH_2Cl_2 (1 ml), triethylamine (0.03 ml, 0.17 mmol) and benzyloxycarbonyl chloride (0.05 ml, 0.09 mmol) were added under argon, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo*, and the residue was dissolved in

$CHCl_3$ (20 ml). The chloroform solution was washed with 5% HCl (2 ml x 2), saturated $NaHCO_3$ (2ml x 2), and saturated NaCl (2 ml x 2), dried over Na_2SO_4, then concentrated *in vacuo*.. The residue was purified by preparative tlc (hexane/AcOEt=3:2) to give **11b** as a colorless oil (46.3 mg, 72%). $[\alpha]_D^{25}$ -6.00 ° (c=0.10, $CHCl_3$). Ir ($CHCl_3$): ν_{max} cm^{-1} 3450 (NH), 1720 (COO). ^{1}H-Nmr δ: 3.23-3.47 (4H, m, 1-H_2, 5-H_2), 3.73 (1H, dd, J=9.0, 5.5, 2-H), 4.06 (1H, q, J=7.0, 4-H), 4.16 (1H, dd, J=9.0, 7.0, 3-H), 4.32-4.78 (6H, m, 2, 3, 5-OCH_2), 4.93, 5.02 (each 1H, d, J=12.0, CO_2CH_2Ph), 5.08 (1H, d, J=7.0, 4-NH), 7.15-7.63 (35H, m, Tr x 1, Cbz x 1, Bn x 3). ^{13}C-Nmr δ: 50.66 (d, C-4), 62.93 (t, C-1), 66.58 (t, $CO_2\underline{C}H_2Ph$), 69.26 (t, C-5), 72.81, 72.90, 74.87 (each t, 2, 3, 5-OCH_2), 76.58 (d, C-3), 79.98 (d, C-2), 155.63 (s, $\underline{C}O_2CH_2Ph$). HR-ms m/z: Calcd for $C_{53}H_{51}NO_6Na$ (M+Na) 820.3614. Found 820.3611. *Anal.* Calcd for $C_{53}H_{51}NO_6$: C, 79.77; H, 6.44; N, 1.75. Found: C, 79.61; H, 6.45; N, 1.75.

4-Benzoylamino-2,3,5-tri-*O*-benzyl-4-deoxy-D-arabinitol (12a)

To a solution of **11a** (8.4 mg, 0.01 mmol) in acetonitrile (0.2 ml), 42% aqueous HBF_4 (0.004 ml, 0.01 mmol) was added, and the mixture was stirred at room temperature for 2 h. The mixture was neutralized with triethylamine (0.01 ml, 0.07 mmol), then concentrated *in vacuo*. The residue was purified by preparative tlc (hexane/AcOEt=3:2) to give **12a** as a colorless oil (4.6 mg, 80%). $[\alpha]_D^{25}$ -19.43 ° (c=0.35, $CHCl_3$). Ir ($CHCl_3$) ν_{max} cm^{-1}: 3450 (NH), 1660 (NHCO). ^{1}H-Nmr δ: 2.17 (1H, br, 1-OH), 3.50 (1H, t, J=9.0, 5-H_a), 3.58 (1H, dd, J=9.0, 5.0, 5-H_b), 3.66 (1H, ddd, J=7.0, 5.0, 4.0, 2-H), 3.74 (1H, dt, J=12.0, 5.0, 1-H_a), 3.84 (1H, dt, J=12.0, 4.0, 1-H_b), 4.09 (1H, dd, J=7.0, 1.5, 3-H), 4.44-4.85 (6H, m, 2, 3, 5-OCH_2), 4.60-4.67 (1H, m, 4-H), 6.56 (1H, d, J=9.0, 4-NH), 7.21-7.52 (20H, m, Bz x 1, Bn x 3). HR-ms m/z: Calcd for $C_{33}H_{35}NO_5Na$ (M+Na) 548.2413. Found 548.2437. *Anal.* Calcd for $C_{33}H_{35}NO_5$: C, 75.41; H, 6.71; N, 2.66. Found: C, 75.19; H, 6.75; N, 2.62.

2,3,5-Tri-*O*-benzyl-4-carbobenzyloxyamino-4-deoxy-D-arabinitol (12b)

The reaction was carried out in the same procedure as described for the preparation of **12a** using **11b** (28.9 mg, 0.04 mmol), 42% aqueous HBF_4 (0.003 ml, 0.07 mmol), and triethylamine (0.01 ml, 0.07 mmol), to give **12b** as a colorless oil (14.7 mg, 72%). Ir ($CHCl_3$) ν_{max} cm^{-1}: 3440 (NH), 1720 (NHCOO). ^{1}H-Nmr δ: 2.05 (1H, br, 1-OH), 3.42 (1H, t, J=9.0, 5-H_a), 3.48 (1H, dd, J=9.0, 5.5, 5-H_b), 3.68 (2H, m, 1-Ha, 2-H), 3.81 (1H, dt, J=5.0, 9.0, 1-H_b), 3.97 (1H, dd, J=9.0, 2.0, 3-H), 4.15 (1H, dt, J=5.5, 9.0, 4-H), 4.43, 4.51 (each 1H, d, J=12.0), 4.48, 4.78 (each 1H, d, J=11.0), 4.60, 4.69 (each 1H, d,

J=11.5) (2, 3, 5-OCH_2), 5.06, 5.10 (each 1H, d, J=12.0, $CO_2C\underline{H}_2Ph$), 5.16 (1H, d, J=9.0, 4-NH), 7.19-7.36 (20H, m, Cbz x 1, Bn x 3). ^{13}C-Nmr δ: 50.28 (d, C-4), 61.67 (t, C-1), 66.93 (t, $CO_2\underline{C}H_2Ph$), 69.42 (t, C-5), 72.99, 73.18, 79.95 (each t, 2, 3, 5-OCH_2), 76.79 (d, C-3), 80.89 (d, C-2), 156.00 (s, $\underline{C}O_2CH_2Ph$). HR-ms m/z: Calcd for $C_{34}H_{37}NO_6Na$ (M+Na) 578.2623. Found 578.2558. *Anal.* Calcd for $C_{34}H_{37}NO_6$: C, 73.49; H, 6.71; N, 2.52. Found: C, 73.23; H, 6.78; N, 2.66.

(3*S*,4*R*,5*S*)-1-Benzoyl-5-benzyloxymethyl-3,4-dibenzyloxypyrrolidin-2-one (3a)

To a solution of **12a** (46.0 mg, 0.10 mmol) in dry DMF (0.4 ml), PDC (386.1 mg, 0.30 mmol) was added. The mixture was stirred at room temperature for 8 h. The mixture was diluted with ether (10 ml), and the ethereal solution was filtered through a pad of celite. The filtrate was concentrated *in vacuo*. The residue was pertitioned between $CHCl_3$ (20 ml) and water (16 ml), and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative tlc (hexane/AcOEt=3:2) to afford **3a** (16 mg, 34%) and **13a** (10 mg, 22%) as colorless oil. **3a**: $[\alpha]_D^{25}$ -31.25 ° (c=0.16, $CHCl_3$). Ir ($CHCl_3$) ν_{max} cm^{-1}: 1760 (lactam carbonyl), 1685 (CONH). ^{1}H-Nmr δ: 3.85 (1H, dd, J=10.0, 2.0, 1'-H_a), 3.88 (1H, dd, J=10.0, 3.0, 1'-H_b), 4.32 (1H, t, J=8.5, 4-H), 4.68 (1H, ddd, J=8.5, 3.0, 2.0, 5-H), 4.54 (2H, s), 4.68, 4.73 (each 1H, d, J=12.0), 4.70, 5.06 (each 1H, d, J=11.5) (3, 4, 1'-$OC\underline{H}_2$), 4.79 (1H, d, J=8.5, 3-H), 7.10-7.45 (20H, m, Bz x 1, Bn x 3). ^{13}C-Nmr δ: 55.33 (d, C-5), 65.48 (t, C-1'), 72.65, 73.02, 73.47 (each t, 3, 4, 1'-$O\underline{C}H_2$), 77.69 (d, C-4), 80.86 (d, C-3), 169.96, 171.66 (each s, C-2, $\underline{C}OPh$). HR-ms m/z: Calcd for $C_{33}H_{31}NO_5Na$ (M+Na) 544.2100. Found 544.2109. *Anal.* Calcd for $C_{33}H_{31}NO_5$: C, 75.99; H, 5.99; N, 2.69. Found: C, 75.69; H, 6.26; N, 2.82. **13a:** ^{1}H-Nmr (pyridine-d_5) δ:3.55 (1H, t, J=7.0, 5-Ha), 3.60 (1H, br t, J=7.0, 5-Hb), 3.74 (1H, m, 2-H), 3.78 (1H, m, 4-H), 3.97 (1H, t, J=4.9 , 3-H), 4.62, 4.69 (each 1H, d, J=11.0), 4.66, 5.70 (each 1H, d, J=10.0), 4.84, 5.26 (each 1H, d, J=11.0) (2, 3, 5-OCH_2). HR-ms m/z: Calcd for $C_{33}H_{31}NO_6$ (M-1) 538.2230. Found 538.2232.

(3*S*,4*R*,5*S*)-1-Benzyloxycarbonyl-5-benzyloxymethyl-3,4-dibenzyloxypyrrolidin-2-one (3b)

The reaction was carried out in the same procedure as described for the preparation of **3a** using **12b** (39.1 mg, 0.06 mmol) and PDC (242.6 mg, 0.64 mmol), to give **3b** as a colorless oil (27 mg, 70%). $[\alpha]_D^{25}$ -32.07 ° (c=0.58, $CHCl_3$). Ir ($CHCl_3$) ν_{max} cm^{-1}: 1800, 1770 (CONCOO), 1720 (COO). ^{1}H-Nmr δ: 3.72, 3.74 (each 1H, dd, J=10.0, 2.0, 1'-H_2), 4.20 (1H, t, J=8.0, 4-H), 4.24 (1H, dt, J=2.0, 8.0, 5-H),

4.44 (2H, s), 4.62, 4.67 (each 1H, d, J=12.0), 4.76, 5.14 (each 1H, d, J=11.5) (3, 4, 1'-OC<u>H</u>2), 4.67 (1H, d, J=8.0, 3-H), 5.23, 5.25 (each 1H, d, J=12.0, CO2C<u>H</u>2Ph), 7.18-7.40 (20H, m, Cbz x 1, Bn x 3). ^{13}C-Nmr δ: 56.19 (d, C-5), 65.01 (t, C-1'), 68.32 (t, $CO_2\underline{C}H_2Ph$), 72.61, 73.06, 73.31 (each t, 3, 4, 1'-OCH_2), 77.63 (d, C-4), 80.20 (d, C-3), 151.02 (s, $\underline{C}O_2CH_2Ph$), 170.72 (s, C-2). HR-ms m/z Calcd for $C_{34}H_{33}NO_6Na$ (M+Na) 574.2208. Found 574.2242. *Anal.* Calcd for $C_{34}H_{33}NO_6$: C, 74.03; H, 6.03; N, 2.54. Found: C, 73.75; H, 6.04; N, 2.56.

REFERENCES

1. a) T. Hatter, F. Koga, Y. Sano, K. Kanamori, A. Matsumae, R. Sugawara, T. Shima, S. Ito, and S. Tomizawa, *J. Antibiot. Ser A*, 1954, **7**, 107. b) M. Onda, Y. Konda, A. Noguchi, S. Omura, and T. Hata, *J. Antibiot. Ser A*, 1969, **22**, 42. c) M. Onda, Y. Konda, S. Omura, and T. Hata, *Chem. Pharm. Bull.*, 1971, **19**, 2013. d) R.W. Armstrong, M. E. Salvati, and M. Nguyen, *J. Am. Chem. Soc.*, 1992, **114**, 3144.
2. a) K. Nagaoka, M. Matsumoto, J. Ono, K. Yokoi, S. Ishizaki, and T. Nakashima, *J. Antibiot.*, 986, **30**, 1527. b) S. Ishizaki, M. Otsuka, K. Kikuta, K. Nagaoka, and T. Nakashima, *J. Antibiot.*, 1987, **40**, 60. c) K. Yokoi, K. Nagaoka, and T. Nakashima, *Chem. Pharm. Bull.*, 1986, **34**, 4554. d) E. J. Moran and R. W. Armstrong, *Tetrahedron Lett.*, 1991, **32**, 3807.
3. Y. Konda, T. Machida, T. Sasaki, K. Takeda, and Y. Harigaya, *Chem. Pharm. Bull.*, 1995, **42**, 285.
4. a) G. W. J. Fleet and P. W. Smith, *Tetrahedron*, 1986, **42**, 5685.
   b) Q. Meng and M. Hesse, *Helv. Chim. Acta*, 1991, **74**, 445.
5. a) S. A. Miller and A. R. Chamberlin, *J. Am. Chem. Soc.*, 1990, **112**, 8100.
   b) L. Luigi, N. Francesco, P. Angelo, P.Cristina, and P. Luigi, *Tetrahedron Lett.*, 1993, **34**, 4555.
6. M. Hashimoto and S. Terashima, *Chem. Lett.*, 1994, 1001.
7. S. Tejima and H. G. Fleetcher, Jr., *J. Org. Chem.*, 1963, **28**, 2999.
8. Y. Nakamura and C. Shin., *Chem. Lett.*, 1992, 49.
9. J. H. Borer, *J. Am. Chem. Soc.*, 1951, **73**, 5865.
10. R. Albert, K. Dax, R. Pleschko, and A. E. Stutz, *Carbohydrate Res.*, 1985, **137**, 282.
11. E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, **5**, 399.
12. P. A. Gent and R. Gigg, *Carbohydrate Res.*, 1976, **49** 325.
13. Y. Rabinsohn and H. G. Fletcher, JR., *J. Org. Chem.*, 1967, **32**, 3452

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