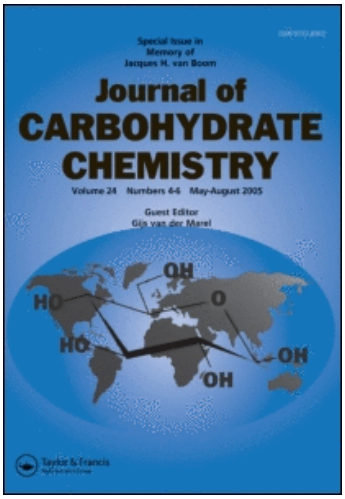

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Synthetic Studies of *N*-demethylossamine and Elaboration of its Glycosylation

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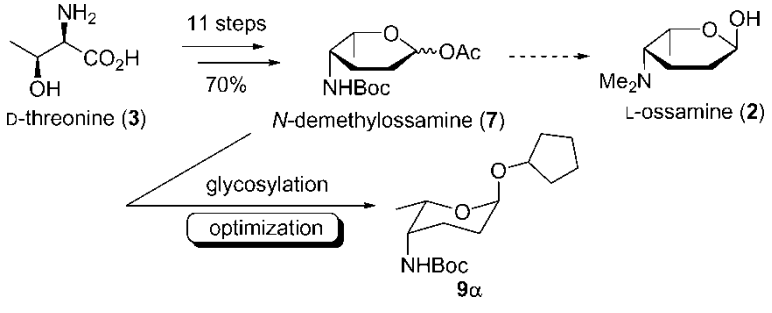
An amino-sugar, *N*-demethylossamine, was efficiently synthesized from D-threonine, two stereogenic centers of which were directly used as those at the C-4 and 5 positions of the target sugar. In addition, the glycosylation study indicated that reaction of the acetate **7** with cyclopentanol under Lewis acid conditions, provided the desired α-L-glycoside **9α**.



Keywords Synthesis, Glycosylation, Ossamine, Ossamycin, D-Threonine

INTRODUCTION

Ossamycin (**1**), a second metabolite of *Streptomyces* sp. isolated in South America,[1] is a 24-membered macrolide antibiotic,[2] carrying remarkable

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antitumor activity (Fig. 1). Its tetradeoxy-4-aminohexose residue, ossamine (**2**),[3] is a component of such natural products as dunaimycin D2S[4] and spinosyn G.[5] The typical synthetic methods[6] of ossamine (**2**) or forosamine (epi-ossamine) usually include one or two successive inversion reactions at the C4 position of the corresponding sugar derivatives to construct the 4-azido-4-deoxy structures. Although these sugar-based syntheses are generally reliable, multistep pathways are required to reach the target substance. Against such background, we elaborated the modified Koskinen pathway,[7] starting from the fully protected threonine derivative **4**. We describe herein our synthetic process, as well as inspection of glycosylation conditions to enable total synthesis of ossamycin (**1**) and its homologs.

RESULTS AND DISCUSSION

The final stage of the synthetic plan of **1** would be condensation of the glycosyl donor **7** with an appropriate glycosyl acceptor, followed by *N*,*N*-dimethylation, because the difficulty of glycosylation of **2** itself as a donor and the facility of the following *N*,*N*-dimethylation are estimated.[6,8] The glycosyl donor **7**, as a precursor of **2**, was produced from the known amino acid derivative **4**[9] (Sch. 1). This fully protected D-threonine **4** was transformed into **5** by successive manipulation involving reduction, the Swern oxidation, the Wittig reaction, and hydrogenation. In the following lactonization, selective cleavage of the aminal protecting group by the Koskinen protocol involving heating in AcOH for 6 days smoothly proceeded without any effect on the Boc group, to afford the desired lactone **6**.[7] In contrast, our successful modification involving desilylation of **5** (PPTS in MeOH at ambient temperature for 12 h), followed by lactonization (heated in AcOH–PhH for 12 h), succeeded effectively to

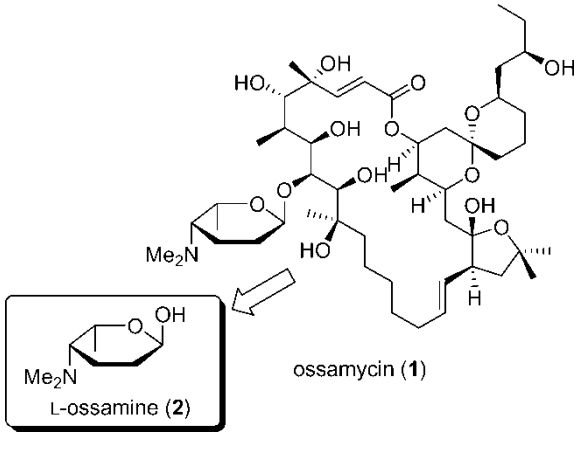
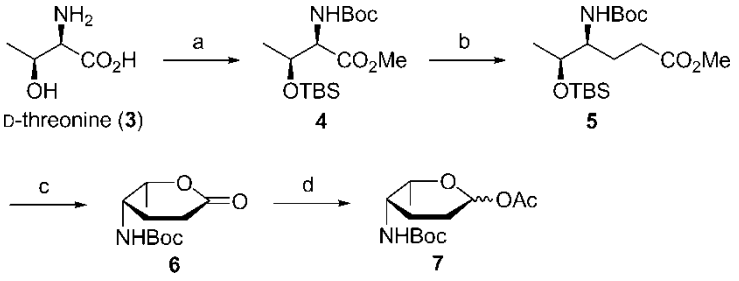


Figure 1: Structures of ossamycin (**1**) and L-ossamine (**2**).

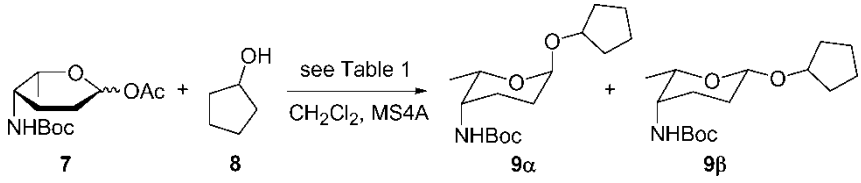


Scheme 1: Synthesis of the intermediate of ossamine **7**: (a) (i) $SOCl_2$, MeOH; (ii) $(Boc)_2O$, $NaHCO_3$/1,4-dioxane-H_2O; (iii) TBSCl, imid, 100% in three steps. (b) (i) $LiBH_4$/EtOH, 99%; (ii) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2; (iii) $Ph_3P{=}CHCO_2Me$/PhH; (iv) Pd-C, H_2/EtOAc, 97% in three steps. (c) (i) PPTS / MeOH; (ii) AcOH / PhH, 79% in two steps. (d) (i) DIBAL-H/$PhCH_3$; (ii) Ac_2O, DMAP/py, 92% in two steps.

reduce the total reaction time, leading to **6**. At the final stage, synthesis of the ossamine intermediate **7** was accomplished by DIBAL-H reduction and the following acetylation.

Glycosylation Study

In the X-ray single crystallographic analysis,[2] ossamycin (**1**) has an equatorial α-L-glycosidic linkage. Rather unstable C1 conformation of the sugar residue might be owing to steric hindrance of the bulky aglycone. We planned to accomplish the total synthesis of **1** by condensation between the glycosyl donor **7** and an aglycone or its equivalent of **1**, and the following dimethylation of the amino function. However, the previous reports[8] suggested that glycosylation of **2** or its homologs was predicted to be accompanied with poor stereoselectivity. To circumvent such difficulty, coupling of **7** with cyclopentanol **8**, as a primitive model-aglycone, was inspected to assess reactivity of **7** and production of the corresponding α-L-product **9α** under various Lewis acid conditions (Sch. 2). Although stereoselectivity of glycosylation generally depends on such parameters, as aglycones or substrates, significant effects of the Lewis acid on the glycosylation were observed (Table 1).



Scheme 2: Condensation between the intermediate of ossamine **7** and cyclopentanol (**8**).

Table 1: Condensation between the *N*-demethylossamine (**7**) and cyclopentanol (**8**).

Entry	Experimental conditions[a]	Yield (%) Products (9α:9β)	Yield (%) s.m. (7)
1	$Et_2O \cdot BF_3$ (0.8 eq.), 0°C to r.t.	29 (3.5:1)	46
2	$Et_2O \cdot BF_3$ (6.0 eq.), 0°C to r.t.	53 (7.0:1)	—
3	$Et_2O \cdot BF_3$ (1.0 eq.), −25°C to r.t.	79 (4.2:1)	10
4	TMSOTf (0.8 eq.), 0°C to r.t.	67 (3.0:1)	19
5	$SnCl_4$ (1.0 eq.), −25°C to r.t.	87 (2.7:1)	—
6	$AgBF_4$ (10 eq.), r.t.	41 (5.0:1)	40

[a]All reactions were stirred overnight. The ratio of **9α** and **9β** was determined by ^{1}H NMR.

Coupling in the presence of $Et_2O \cdot BF_3$ led to the glycosidic products, although the desired **9α** was obtained in poor yield (entry 1). Increase of $Et_2O \cdot BF_3$ effected good anomeric stereoselectivity (entry 2), and the lower reaction temperature contributed to production of **9α** in a better yield than entries 1 and 2 (entry 3). In addition, the optimized coupling conditions using other Lewis acids such as TMSOTf, $SnCl_4$, and $AgBF_4$ were shown (entries 4–6). Unfortunately, 6 eq. or higher amounts of TMSOTf, caused decomposition of **7**. In the synthesis of **1**, the following conditions would be required: The glycosylation might be performed under low-temperature conditions to prevent unexpected side reactions, and even excess amounts of Lewis acids should not affect other functional groups of the corresponding substrates. Comparison of Lewis acids examined above indicated that $Et_2O \cdot BF_3$ might be an applicable reagent to accomplish the purpose.

In conclusion, improvement of the Koskinen protocol successfully attained the synthesis of *N*-demethylossamine derivative. The glycosylation knowledge obtained would be useful for syntheses of ossamycin (**1**), spinocyn G, and their homologs.

EXPERIMENTAL

General

IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL JNM EX-270 and JEOL JNM GX-400 spectrometers in a deuteriochloroform ($CDCl_3$) solution using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained on a Hitachi M-80 B GC-MS spectrometer operating at the ionization energy of 70 eV or JEOL JMS-700 (FAB) spectrometer. Optical rotations were

recorded at the sodium D line and ambient temperatures with a JASCO DIP-360 digital polarimeter. Preparative and analytical TLC were carried out on silica-gel plates (Kieselgel 60 F254, E. Merck AG, Germany) using UV light and/or 5% phosphomolybdic acid in ethanol for detection. Kanto Chemical silica 60N (spherical, neutral, 63–210 μm) was used for column chromatography.

Methyl

(2*R*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy) butanoate (4). To an ice-cooled mixture of $SOCl_2$ (6.1 mL, 0.084 mol) and MeOH (80 mL) was added D-threonine (10.0 g, 0.084 mol); the mixture was refluxed for 1 h. After evaporation, a mixture of $SOCl_2$ – MeOH prepared in the same way was added to the residue, and the mixture was refluxed for another 1 h. Evaporation of the solvent gave D-threonine methyl ester hydrochloride as a yellow oil, which was used in the next step without further purification.

A mixture of the crude, $(Boc)_2O$ (23.1 mL, 0.10 mol), and $NaHCO_3$ (51.8 g, 0.62 mol) in 1,4-dioxane (42 mL)–H_2O (42 mL) was stirred at rt for 2.5 h. The mixture was extracted with EtOAc and washed with 1 M aq. HCl, 1 M aq. $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was dissolved in DMF (84 mL), and then TBSCl (16.5 g, 0.11 mol) and imidazole (28.5 g, 0.42 mol) were added. After being stirred at rt for 10 h, the mixture was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column (hexane/EtOAc 2/1) to give **4** (29.2 g, 100% in three steps). All data of **4** were entirely in accordance with known data.[9]

Methyl

(4*S*,5*S*)-4-(*tert*-butoxycarbonylamino)-5-(*tert*-butyldimethylsilyloxy)-hexanoate (5). To a solution of **4** (29.2 g, 0.084 mol) in EtOH (84 mL) at 0°C was added $LiBH_4$ (5.07 g, 0.23 mol). After being stirred at rt for 30 min, the reaction was quenched by the addition of H_2O and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column (hexane/EtOAc 2/1) to give an alcohol (26.6 g, 99%): $[\alpha]_D^{24}$ +6.0 (*c* 1.00, $CHCl_3$); IR (film) 3448, 2931, 2858, 1695 cm^{-1}; ^1H NMR δ 0.04 (6H, s), 0.85 (9H, s), 1.13 (3H, d, $J = 6.4$ Hz), 1.41 (9H, s), 2.98 (1H, br), 3.47–3.59 (3H, complex), 4.07 (1H, m), 4.90 (1H, m); ^{13}C NMR δ −5.0, −4.3, 14.2, 17.9, 20.8, 25.8, 28.3, 57.3, 60.3, 63.6, 67.3, 79.4, 128.1, 156.6, 170.9. Calcd for $C_{15}H_{33}NO_4Si$: C, 56.39; H, 10.41; N, 4.38%. Found: C, 56.47; H, 10.21; N, 4.28%.

To a solution of $(COCl)_2$ (4.0 mL, 0.045 mol) in CH_2Cl_2 (50 mL) was added DMSO (5.3 mL, 0.075 mmol) in CH_2Cl_2 (10 mL) at −78°C. The mixture was

stirred for 15 min, and then a solution of the alcohol (9.51 g, 0.030 mol) in CH_2Cl_2 (40 mL) was added slowly. After being stirred at the same temperature for 30 min, Et_3N (20.7 mL, 0.15 mol) was added at $-78^\circ C$, and then the mixture was allowed to warm to rt. The reaction mixture was washed with 1 M aq. HCl and 1 M aq. $NaHCO_3$, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on a silica gel column (hexane/EtOAc 2/1) to give an aldehyde (10.0 g, 100%).

A mixture of the aldehyde (10.0 g, 0.031 mol) and $Ph_3P{=}CHCO_2Me$ (16.7 g, 0.050 mol) in PhH (70 mL) was stirred at $90^\circ C$ for 2 h. The mixture was evaporated and chromatographed on a silica gel column (hexane/EtOAc 3/1) to give an *E*-enoate (11.8 g, 100%): $[\alpha]_D^{21}$ +4.9 (*c* 1.00, $CHCl_3$); IR (film) 3450, 3367, 2954, 2931, 2894, 2857, 1724, 1662 cm^{-1}; ^1H NMR δ −0.05 (3H, s), −0.02 (3H, s), 0.80 (9H, s), 1.12 (3H, d, $J = 5.9$ Hz), 1.39 (9H, s), 3.66 (3H, s), 3.93 (1H, m), 4.16 (1H, m), 4.85 (1H, m), 5.88 (1H, d, $J = 15.6$ Hz), 6.85 (1H, dd, $J = 4.9$, 15.6 Hz); ^{13}C NMR δ −5.0, −4.5, 14.1, 17.9, 20.7, 20.9, 25.7, 28.3, 51.4, 57.0, 60.2, 69.6, 77.2, 79.5, 121.0, 147.8, 155.4, 166.3. Calcd for $C_{18}H_{35}NO_5Si$: C, 57.87; H, 9.44; N, 3.75%. Found: C, 57.74; H, 9.33; N, 3.69%.

A solution of the *E*-enoate (11.8 g, 0.032 mol) in EtOAc (100 mL) in the presence of catalytic amounts of 10% Pd-C was stirred at rt for 24 h under hydrogen atmosphere. After filtration through a celite pad, the solvent was evaporated. The residue was chromatographed on a silica gel column (hexane/EtOAc 2/1) to **5** (10.9 g, 97%): $[\alpha]_D^{20}$ −11.4 (*c* 1.00, $CHCl_3$); IR (film) 3373, 2954, 2931, 2858, 1741, 1716 cm^{-1}; ^1H NMR δ 0.04 (6H, s), 0.88 (9H, s), 1.09 (3H, d, $J = 6.4$ Hz), 1.42 (9H, s), 1.72–1.77 (2H, complex), 2.34–2.38 (2H, complex), 3.46 (1H, m), 3.65 (3H, s), 3.81 (1H, m), 4.59 (1H, br); ^{13}C NMR δ −4.8, −4.2, 18.0, 20.8, 25.9, 28.4, 28.5, 30.9, 51.5, 51.6, 55.3, 70.0, 79.0, 156.1, 173.8. Calcd for $C_{18}H_{37}NO_5Si$: C, 57.56; H, 9.93; N, 3.73%. Found: C, 57.63; H, 9.81; N, 3.64%.

(5*S*,6*S*)-3,4,5,6-Tetrahydro-5-(*tert*-butoxycarbonylamino)-6-methyl-2-pyrone (6). A mixture of **5** (8.4 g, 0.022 mol) and PPTS (11.2 g, 0.044 mol) in MeOH (31 mL) was stirred at rt for 12 h. The mixture was extracted with EtOAc, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on silica gel column (hexane/EtOAc 2/1) to give an alcohol (5.7 g, 97%).

The alcohol (5.7 g) was dissolved in PhH (20 mL)–AcOH (10 mL) and heated at $100^\circ C$ for 12 h. The mixture was extracted with EtOAc, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$/MeOH 10/1) to give **6** (4.0 g, 81%): $[\alpha]_D^{21}$ −58.4 (*c* 1.00, EtOH); IR (film) 3348, 2981, 1678 cm^{-1}; ^1H NMR δ 1.31 (3H, d, $J = 6.4$ Hz), 1.40 (9H, s), 1.92 (1H, m), 2.16 (1H, m), 2.53 (2H, t, $J = 7.2$ Hz), 3.98 (1H, m), 4.49 (1H, dq, $J = 2.4$, 6.4 Hz), 5.01 (1H, br); ^{13}C NMR δ 16.9,

25.6, 26.1, 28.3, 46.6, 76.7, 79.8, 155.4, 171.1. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11%. Found: C, 57.43; H, 8.23; N, 6.00%.

1-*O*-Acetyl-2,3,4,6-tetradeoxy-4-(*tert*-butoxycarbonylamino)-*threo*-hexose (7). To a solution of **6** (3.8 g, 0.016 mol) in $PhCH_3$ (20 mL) was added DIBAL-H (1.01 M solution in PhMe, 20 mL, 0.020 mol) at −78°C. After being stirred for 30 min, the reaction was quenched by the addition of sat. aq. NH_4Cl, extracted with EtOAc, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$/MeOH 20/1) to give a mixture of α- and β-lactols (3.8 g, 100%).

A mixture of the lactols (3.8 g) and Ac_2O (5.0 mL, 0.053 mol) in pyridine (20 mL) in the presence of catalytic amounts of DMAP was stirred at rt for 14 h. The reaction mixture was extracted with EtOAc, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on a silica gel column (hexane/EtOAc 3/1) to give **7** (4.0 g, 92%) as a separable mixture of the corresponding α- and β-anomers (the ratio is ca. 2.3:1, determined by ^{1}H NMR spectra). This mixture was used without separation in the next reaction because of no effect of anomeric configuration to the following glycosylation: IR (film) 3585, 3377, 2978, 1710, 1512 cm^{-1}; ^{1}H NMR δ 1.07 (3.0H, d, $J = 6.3$ Hz), 1.14 (7.0H, d, $J = 6.3$ Hz), 1.395 (20.4H, s), 1.402 (8.8H, s), 1.56–2.01 (13.3H, complex), 2.04 (3.2H, s), 2.05 (6.7H, s), 3.57 (2.1H, d, $J = 8.3$ Hz), 3.59 (0.9H, d, $J = 8.3$ Hz), 3.77 (2.3H, m), 4.10 (1.0H, m), 5.00 (2.8H, complex), 5.63 (2.2H, dd, $J = 2.0$, 9.8 Hz), 6.04 (0.9H, m); ^{13}C NMR δ 17.3, 17.4, 21.09, 21.13, 23.1, 23.7, 24.9, 27.7, 28.3, 47.0, 47.6, 68.1, 74.4, 77.2, 79.2, 79.3, 91.7, 94.3, 155.5, 155.6, 168.9, 169.4. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12%. Found: C, 57.05; H, 8.45; N, 5.09%.

Cyclopentyl 2,3,4,6-tetradeoxy-4-(*tert*-butoxycarbonylamino)-*threo*-hexose (9α, 9β). General: A mixture of the amino-sugar **7** and cyclopentanol (**8**, 1.0 eq.) in CH_2Cl_2 (0.1 M concentration) in the presence of molecular sieves 4A powder was stirred at rt for 1 h. To this suspension was added Lewis acid at −78°C—rt (see Table 1). The cooling bath was removed after 2 h, and the reaction was allowed to warm to rt for 10 h. The mixture was then diluted with CH_2Cl_2 (10 mL), extracted with $CHCl_3$, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on a silica gel column (hexane/EtOAc 3/1) to give **9α** and **9β** as an anomeric mixture. A part of the mixture was repeatedly submitted to chromatographic separation using the same solvent as above to give pure **9α** and **9β** **9α**:$[\alpha]_D^{19}$ −102.1 (*c* 0.50, $CHCl_3$); IR (film) 3454, 3338, 2962, 2871, 1716, 1498 1454 cm^{-1}; ^{1}H NMR δ 1.08 (3H, d, $J = 6.8$ Hz), 1.45 (9H, s), 1.43–1.80 (11H, complex), 2.00 (1H. m), 3.61 (1H, br, d, $J = 8.3$ Hz), 4.08 (1H, m), 4.13 (1H, m), 4.82 (1H, br, d, $J = 2.9$ Hz), 5.00 (1H, d, $J = 9.3$ Hz); ^{13}C NMR δ 17.6, 23.3, 23.6, 24.2, 24.9, 28.5, 28.5, 28.5, 31.8, 33.1, 48.2, 65.5, 78.0, 79.1, 95.6, 155.8. Calcd for $C_{16}H_{29}NO_4$: C,

64.18; H, 9.76; N, 4.68%. Found: C, 63.90; H, 9.81; N, 4.50%. **9β**: $[\alpha]_D^{22}$ +85.6 (*c* 0.10, $CHCl_3$); IR (film) 3454, 3338, 2962, 2871, 1716, 1498 1454 cm^{-1}; ^1H NMR δ 1.17 (3H, d, $J = 6.4$ Hz), 1.43 (9H, s), 1.43–1.84 (11H, complex), 1.93 (1H, m), 3.55 (1H, m), 3.64 (1H, dq, $J = 1.5$, 6.4 Hz), 4.34 (1H, m), 4.45 (1H, dd, $J = 1.9$, 9.8 Hz), 5.11 (1H, br, d, $J = 9.3$ Hz); ^{13}C NMR δ 17.6, 23.4, 23.6, 26.8, 28.4, 32.1, 33.3, 47.5, 73.3, 77.2, 79.0, 79.4, 100.6, 155.8. Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68%. Found: C, 63.71; H, 10.24; N, 4.28%.

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