HETEROCYCLES, Vol. 69, 2006, pp. 487 - 495. © The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2006, Accepted, 17th August, 2006, Published online, 22nd August, 2006. COM-06-S(O)35

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SUGAR ANALOGS OF MYCALAMIDE A

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Abstract – Several new artificial sugar analogs (**3**-**6**) of mycalamide A (**1**), a potent antiviral and antitumor agent, were synthesized through a coupling reaction of glycosyl amines (**10**), (**11**), (**15**), and (**16**) with pederic acid (**12**), and their cytotoxity and antiviral activity were tested.

INTRODUCTION

Mycalamide A (**1**) was isolated from a marine sponge of the *Mycale* genus found in New Zealand.[1] The structurally related compounds, onnamides[2] and theopederins,[3] have been also isolated from a Japanese marine sponge of the genus *Theonella*. The mycalamides exhibit potent *in vitro* cytotoxicity and *in vivo* antitumor activity as well as potent antiviral activity.[1-4] In addition, mycalamide A (**1**) is reported to have immunosuppressive activity *via* inhibition of T-cell activation and to be 10-fold more potent than FK-506.[5] As a result, the mycalamides have attracted much attention of synthetic organic chemists.[6-13] The structure-activity relationship studies of several analogs prepared from natural mycalamides and their simple model compounds have been also reported.[14]

After completion of total syntheses of mycalamide A (**1**),[7] we continued chemical studies in order to clarify the requisite small part of **1** for its biological function. The results revealed that their cytotoxity and antiviral activity didn't decrease by removing the C-3 methyl and/or C-4-exo-methylene group on the left half segment of **1**.[15] Furthermore, the analog (**2**) replaced the right half by glucose derivative showed almost the same cytotoxicity against HeLa cells as that of 5-fluorouracil and good antiviral activity (MIC 3.125 μg/mL, IC_{50} >50 μg/mL) against VZV. However, 3-demethyl and/or demethylene

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This paper is dedicated to Prof. Satoshi Omura on occasion of his 70th birthday.

derivatives of **2** showed no cytotoxicity and anti-viral activity.[16] These interesting results prompted us to investigate the effect of the right half segment to the inhibitory activities. In order to gain the further insight, we have planned to synthesize more simplified analogs. Here, we describe synthesis of several new sugar analogs (**3**-**6**) and their biological activities (Figure 1).

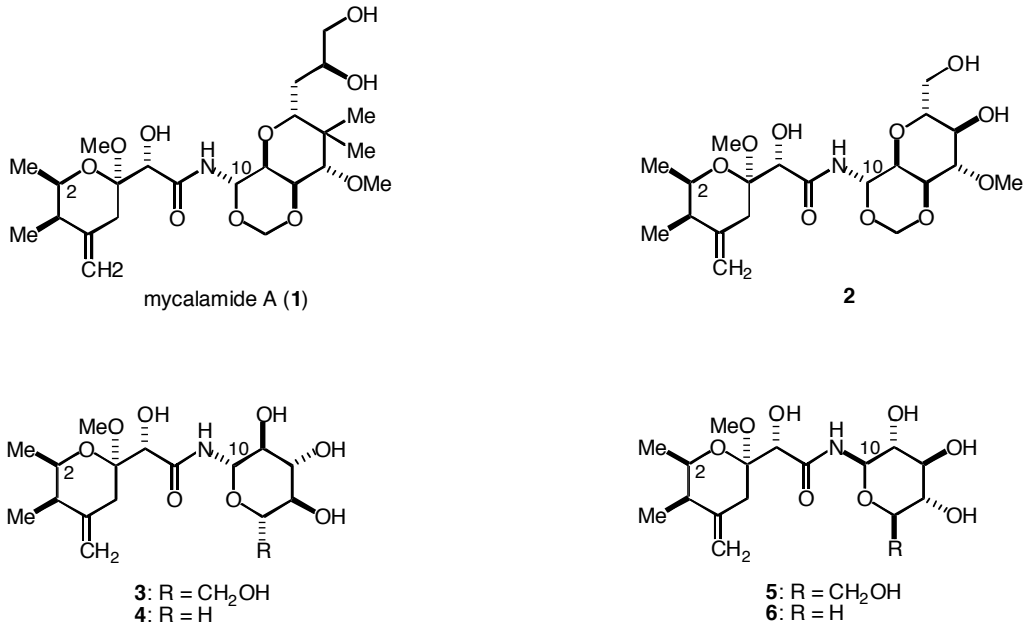
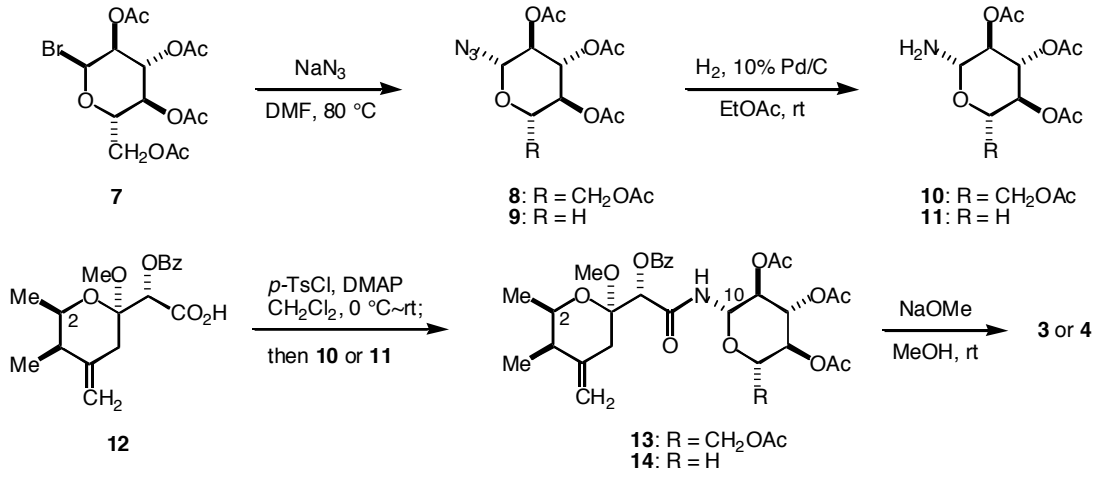


Figure 1

RESULTS AND DISCUSSION

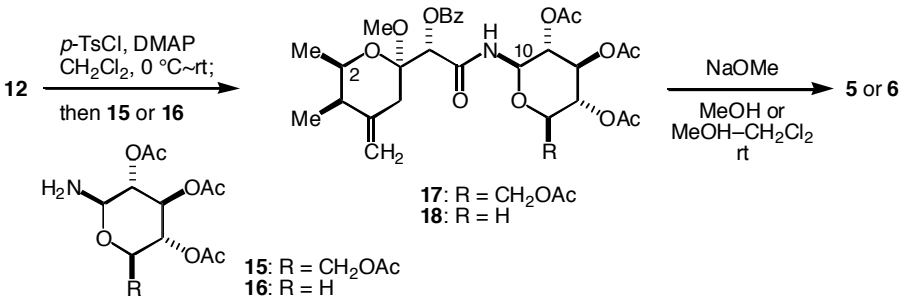
Synthesis of a series of sugar analogs involved a coupling reaction between L- or D-glycosylamines and pederic acid (**12**) as a key step. Initially, an azide (**8**) was prepared from the known bromide (**7**)[17] by the action of NaN_3 in 83% yield (Scheme 1). After hydrogenation, the resulting amine (**10**) was, without purification, submitted to the next coupling reaction under Kishi's conditions.[6] The acid (**12**) was activated with *p*-TsCl and DMAP in CH_2Cl_2 at 0 °C–room temperature followed by addition of **10** to



Scheme 1

afford an amide (**13**) in 63% yield. The large coupling constant value (J = 9.8 Hz) of H-10 shows the 10, 11-*trans* relationship of **13**. All acyl protective groups in **13** were simultaneously removed by NaOMe in methanol to give the L-glycosyl analog (**3**) in 87% yield. Similarly, the known azide (**9**)[18] was hydrogenated, and the resulting amine (**11**) was coupled with **12** to provide an amide (**14**) in 20% yield.[19] Treatment of **14** with NaOMe gave the corresponding L-xylosyl analog (**4**) in 59% yield.

According to the procedure described above, the D-sugar analog (**5**) or (**6**) was synthesized from the antipode (**15**)[20] or (**16**),[21] respectively (Scheme 2).



Scheme 2

The cytotoxicity and anti-viral activity of **3**-**6** were tested according to the method previously reported.[15] In a cytotoxicity test, the L-glycosyl analog (**3**) showed a moderate antitumor activity against HeLa cell (IC_{50} = 7 μg/mL), and the L-xylosyl analog (**4**) was also found to have an antitumor activity to the same extent (IC_{50} = 9 μg/mL). In contrast, the activity of diastereomers (**5**) and (**6**) carrying a D-sugar residue was very poor. Similar results were also obtained in the case of an antiviral activity test, although no compound showed the antiviral activity against HSV-1, and VZV at less than 50 μg/mL (Figure 2). Although explanation about the marked difference of the inhibitory activities between the L- and D-sugar analogs might be interesting, the conformational flexibility of these compounds interfered simple

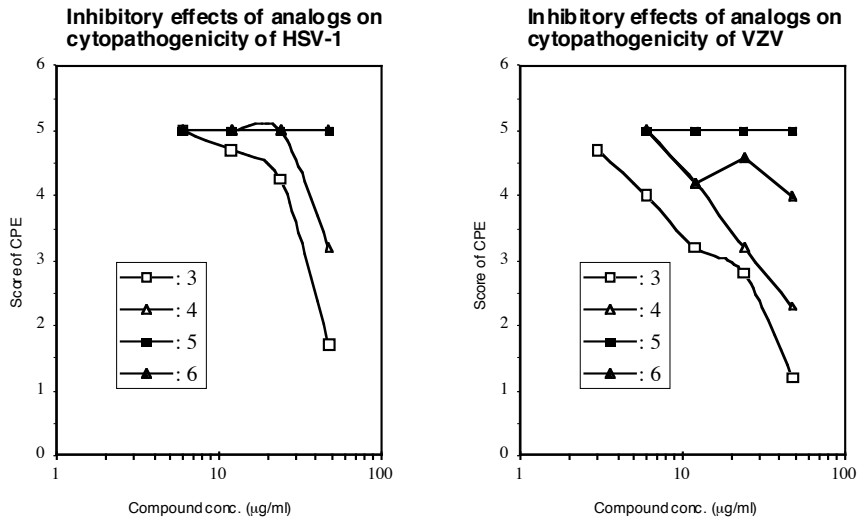


Figure 2

rationalization of the mechanism.[22] In any case, the results obtained here suggest that the stereochemistry around the amide moiety is important for such biological activities. In summary, we have synthesized several new mycalamide analogs (**3**-**6**) carrying a glucose or xylose residue and their cytotoxity and antiviral activity were tested.

EXPERIMENTAL

2,3,4,6-Tetra-*O*-acetyl-α-L-glucopyranosyl azide (8). To a stirred solution of **7** (2.06 g, 5.0 mmol) in DMF (40 mL) was added NaN_3 (0.95 g, 14.6 mmol) at rt. The mixture was stirred at 80 °C for 4 h, cooled, then poured into ice-water and extracted with chloroform. The extracts were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo to give a white solid. Recrystalization from EtOH–CH_2Cl_2 gave **8** (1.55 g, 83%) as colorless needles. mp 129–130 °C; $[\alpha]_D^{20}$ + 29.2° (*c* = 0.97, $CHCl_3$); IR (KBr) cm^{-1}: 2118, 1754, 1748, 1242, 1213; ^{1}H-NMR ($CDCl_3$) δ: 2.02, 2.04, 2.09, 2.11 (12H, each s, Ac), 3.80 (1H, ddd, $J_{4,5}$ = 9.6 Hz, $J_{5,6b}$ = 4.6 Hz, $J_{5,6a}$ = 2.3 Hz, H-5), 4.18 (1H, dd, $J_{6a,6b}$ = 13.0 Hz, $J_{5,6a}$ = 2.3 Hz, H-6a), 4.27 (1H, dd, $J_{5,6b}$ = 4.6 Hz, $J_{6a,6b}$ = 13.0 Hz, H-6b), 4.65 (1H, d, $J_{1,2}$ = 8.9 Hz, H-1), 4.96 (1H, dd, $J_{2,3}$ = 9.2 Hz, $J_{1,2}$ = 8.9 Hz, H-2), 5.11 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 5.23 (1H, dd, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 9.6 Hz, H-3); Anal. Calcd. for $C_{14}H_{19}O_9N$: C, 45.04; H, 5.13; N, 11.26. Found: C, 45.00; H, 5.12; N, 11.06.

Coupling reaction of 10 and 12. The azide (**8**) (114 mg, 0.31 mmol) was hydrogenated over 10% Pd/C (40 mg) in EtOAc (10 mL) under H_2 at rt for 2.5 h to give an unstable amine (**10**) (116 mg), which was immediately diluted with CH_2Cl_2 (2 mL). To a stirred solution of **12** (50.8 mg, 0.15 mmol) in CH_2Cl_2 (15 mL) were added *p*-TsCl (45.7 mg, 0.24 mmol) and DMAP (57.3 mg, 0.47 mmol) at 0 °C and the mixture was stirred at 0 °C for 15 min and rt for 40 min. To this solution was added the above solution of **10** and the mixture was stirred at rt for 5 h. After quenching with MeOH followed by addition of sat. aq. $NaHCO_3$ solution, the resulting mixture was extracted with ether. The extracts were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel with hexane-EtOAc (2:1) → ether and then $CHCl_3$-MeOH (50:1) as the eluent yielded **13** (63.5 mg, 63%) as an amorphous solid. $[\alpha]_D^{27}$ + 41.0° (*c* = 0.18, $CHCl_3$); IR (KBr) cm^{-1}: 1755, 1734, 1717, 1655, 1516, 1073; ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, *J* = 7.3 Hz, 3-Me), 1.18 (3H, d, *J* = 6.3 Hz, 2-Me), 1.86, 1.96, 2.02, 2.06 (12H, each s, AcO), 2.24 (1H, qd, $J_{3,Me}$ = 7.3 Hz, $J_{2,3}$ = 2.4 Hz, H-3), 2.46, 2.65 (2H, each d, $J_{5a,5b}$ = 14.0 Hz, H-5), 3.24 (3H, s, OMe), 3.80 (1H, ddd, $J_{13,14}$ = 9.8 Hz, $J_{14,15a}$ = 4.4 Hz, $J_{14,15b}$ = 2.0 Hz, H-14), 3.95 (1H, qd, $J_{2,Me}$ = 6.3 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.04 (1H, dd, $J_{15a,15b}$ = 12.0 Hz, $J_{14,15a}$ = 2.0 Hz, H-15a), 4.28 (1H, dd, $J_{15a,15b}$ = 12.0 Hz, $J_{14,15b}$ = 4.4 Hz, H-15b), 4.80, 4.88 (2H, each brs, =CH_2-4), 4.91 (1H, t, $J_{12,13}$ = $J_{13,14}$ = 9.8 Hz, H-13), 5.05 (1H, t, $J_{11,12}$ = $J_{10,11}$ = 9.8 Hz, H-11), 5.27 (1H, t, $J_{11,12}$ = $J_{12,13}$ = 9.8 Hz, H-12), 5.29 (1H, dd, $J_{10,11}$ = 9.8 Hz, $J_{10,NH}$ = 9.3 Hz, H-10), 5.51 (1H, s, H-7), 6.97 (1H, d, $J_{10,NH}$ = 9.3 Hz, NH), 7.49 (2H, t, *J* = 7.3 Hz, Ph), 7.62 (1H, t, *J* = 7.3 Hz, Ph), 8.09 (2H, d, *J* = 7.3 Hz, Ph). FAB-MS (m/z): Calcd for $C_{31}H_{38}O_{13}N$ (M^+-OMe) 632.2337, Found 632.2343.

Methanolysis of 13. To a stirred solution of **13** (30.2 mg, 45.5 μmol) in MeOH (0.5 mL) was added NaOMe (2.5 mg, 45.5 μmol) at rt. The mixture was stirred at rt for 1.5 h, and then treated with Dowex 50W X-8 (H^+) resin. The suspension was filtered, and then concentrated in vacuo. The residue was passed through a short column of silica gel with CH_2Cl_2-MeOH (20:1→15:1→10:1) to give **3** (15.4 mg, 87%) as a white powder. $[\alpha]_D^{25}$ + 68.4° (*c* = 0.21, MeOH); IR (KBr) cm^{-1}: 3412, 1684, 1559, 1076; ^{1}H-NMR (CD_3OD) δ: 0.94 (3H, d, J = 6.8 Hz, 3-Me), 1.13 (3H, d, J = 6.8 Hz, 2-Me), 2.14 (1H, qd, $J_{3,Me}$ = 6.8 Hz, $J_{2,3}$ = 2.4 Hz, H-3), 2.21 (1H, d, $J_{5a,5b}$ = 14 Hz, H-5a), 2.42 (1H, ddd, $J_{5a,5b}$ = 14 Hz, $J_{5b,CHH}$ = $J_{5b,CHH}$ = 2.0 Hz, H-5b), 3.20 (3H, s, OMe), 3.23-3.33 (2H, m, H-13,14), 3.26 (1H, t, $J_{10,11}$ = 9.3 Hz, $J_{11,12}$ = 8.8 Hz, H-11), 3.37 (1H, t, $J_{11,12}$ = $J_{12,13}$ = 8.8 Hz, H-12), 3.62 (1H, dd, $J_{15a,15b}$ = 12.0 Hz, $J_{14,15a}$ = 4.9 Hz, H-15a), 3.75 (1H, dd, $J_{15a,15b}$ = 12.0 Hz, $J_{14,15b}$ = 2.0 Hz, H-15b), 3.83 (1H, qd, $J_{2,Me}$ = 6.8 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.21 (1H, s, H-7), 4.58, 4.74 (2H, each t, J = 2.0 Hz, =CH_2-4), 4.88 (1H, d, $J_{10,11}$ = 9.3 Hz, H-10); ^{13}C-NMR (CD_3OD) δ: 12.5 (3-Me), 18.1 (2-Me), 34.1 (C-5), 43.1 (C-3), 48.4 (OMe), 62.6 (C-15), 70.9 (C-2), 71.3 (C-13), 73.0 (C-7), 73.9 (C-11), 79.1 (C-12), 79.6 (C-14), 81.1 (C-10), 101.3 (C-6), 109.9 (CH_2), 148.8 (C-4), 174.6 (C=O); FAB-MS (m/z): Calcd for $C_{17}H_{30}O_9N$ ($M+H^+$) 392.1921, Found 392.1924.

Coupling reaction of 11 and 12. The azide (**9**) (86.2 mg, 0.29 mmol) was hydrogenated over 10% Pd/C (35 mg) in EtOAc (5 mL) under H_2 at rt for 2.5 h to give an unstable amine (**11**) (80.1 mg), which was immediately diluted with CH_2Cl_2 (2 mL). To a stirred solution of **12** (47.1 mg, 0.14 mmol) in CH_2Cl_2 (14 mL) were added *p*-TsCl (43.9 mg, 0.23 mmol) and DMAP (54.2 mg, 0.44 mmol) at 0 °C and the mixture was stirred at 0 °C for 15 min and rt for 30 min. To this solution was added the above solution of **11** and the mixture was stirred at rt for 4 h. After quenching with MeOH followed by addition of sat. aq. $NaHCO_3$ solution, the resulting mixture was extracted with ether. The extracts were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel with hexane-EtOAc (1:1) and then toluene-acetone (40:1→30:1) as the eluent yielded **14** (16.7 mg, 20%) as an amorphous solid. $[\alpha]_D^{25}$ + 49.8° (*c* = 0.24, $CHCl_3$); IR (KBr) cm^{-1}: 1752, 1709, 1655, 1526, 1250, 1227, 1073; ^{1}H-NMR ($CDCl_3$) δ : 1.00 (3H, d, J = 7.3 Hz, 3-Me), 1.18 (3H, d, J = 6.3 Hz, 2-Me), 1.87, 2.00, 2.03 (9H, each s, AcO), 2.24 (1H, qd, $J_{3,Me}$ = 6.8 Hz, $J_{2,3}$ = 2.4 Hz, H-3), 2.46, 2.66 (2H, each d, $J_{5a,5b}$ = 14.0 Hz, H-5), 3.25 (3H, s, OMe), 3.42 (1H, dd, $J_{14a,14b}$ = 12.0 Hz, $J_{13,14a}$ = 11.0 Hz, H-14a), 3.95 (1H, qd, $J_{2,Me}$ = 6.3 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.07 (1H, dd, $J_{14a,14b}$ = 12.0 Hz, $J_{13,14b}$ = 5.9 Hz, H-14b), 4.79, 4.88 (2H, each brs, =CH_2-4), 4.85 (1H, t, $J_{10,11}$ = $J_{11,12}$ = 9.3 Hz, H-11), 4.95 (1H, ddd, $J_{13,14a}$ = 11.0 Hz, $J_{12,13}$ = 9.3 Hz, $J_{13,14b}$ = 5.9 Hz, H-13), 5.19 (1H, t, $J_{11,12}$ = $J_{12,13}$ = 9.3 Hz, H-12), 5.26 (1H, dd, $J_{10,NH}$ = 8.8 Hz, $J_{10,11}$ = 9.3 Hz, H-10), 5.46 (1H, s, H-7), 6.98 (1H, d, $J_{10,NH}$ = 8.8 Hz, NH), 7.49 (2H, t, J = 7.3 Hz, Ph), 7.62 (1H, t, J = 7.3 Hz, Ph), 8.10 (2H, d, J = 7.3 Hz, Ph); FAB-MS (m/z): Calcd for $C_{28}H_{34}O_{11}N$ (M^+-OMe) 560.2132, Found 560.2131.

Methanolysis of 14. To a stirred solution of **14** (9.2 mg, 15.6 μmol) in MeOH (0.8 mL) was added NaOMe (1.2 mg, 22.2 μmol) at rt. The mixture was stirred at rt for 3 h, and then treated with Dowex

50W X-8 (H^+) resin. The suspension was filtered, and then concentrated in vacuo. The residue was passed through a short column of silica gel (CH_2Cl_2) to give **4** (3.3 mg, 59%) as a white powder. $[\alpha]_D^{26}$ + 86.0° (*c* = 0.12, MeOH); IR (KBr) cm^{-1}: 3412, 1684, 1539, 1075; ^{1}H-NMR (CD_3OD) δ: 0.91 (3H, d, *J* = 6.8 Hz, 3-Me), 1.11 (3H, d, *J* = 6.3 Hz, 2-Me), 2.12 (1H, qd, $J_{3,Me}$ = 6.8 Hz, $J_{2,3}$ = 2.4 Hz, H-3), 2.19 (1H, d, $J_{5a,5b}$ = 14.0 Hz, H-5a), 2.38 (1H, ddd, $J_{5a,5b}$ = 14.0 Hz, $J_{5b,CHH}$ = $J_{5b,CHH}$ = 2.0 Hz, H-5b), 3.18 (3H, s, OMe), 3.24 (1H, dd, $J_{14a,14b}$ = 11.0 Hz, $J_{13,14a}$ = 1.4 Hz, H-14a), 3.27 (1H, t, $J_{10,11}$ = $J_{11,12}$ = 8.3 Hz, H-11), 3.33 (1H, t, $J_{11,12}$ = $J_{12,13}$ = 8.3 Hz, H-12), 3.40-3.46 (1H, m, H-13), 3.78 (1H, dd, $J_{14a,14b}$ = 11.0 Hz, $J_{13,14b}$ = 4.9 Hz, H-14b), 3.81 (1H, qd, $J_{2,Me}$ = 6.3 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.18 (1H, s, H-7), 4.57, 4.72 (2H, each brt, *J* = 2.0 Hz, =CH_2-4), 4.82 (1H, d, $J_{10,11}$ = 8.3 Hz, H-10); ^{13}C-NMR (CD_3OD) δ: 12.5 (3-Me), 18.1 (2-Me), 34.1 (C-5), 43.1 (C-3), 48.4 (OMe), 68.2 (C-14), 70.9 (C-2), 71.1 (C-13), 73.1 (C-7), 73.5 (C-11), 78.3 (C-12), 81.5 (C-10), 101.3 (C-6), 109.9 (CH_2), 148.4 (C-4), 174.6 (C=O); FAB-MS (m/z): Calcd for $C_{16}H_{28}O_8N$ ($M+H^+$) 362.1815, Found 362.1863.

Preparation of 5. Treatment of **12** (52.6 mg, 0.14 mmol) and **15** (108 mg, 0.31 mmol) as described for preparation of **13** from **10** and **12** afforded **17** (72.4 mg, 76%) as an amorphous solid. $[\alpha]_D^{25}$ + 63.2° (*c* = 0.13, $CHCl_3$); IR (KBr) cm^{-1}: 1749, 1734, 1717, 1224, 1037; ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, *J* = 7.3 Hz, 3-Me), 1.23 (3H, d, *J* = 6.4 Hz, 2-Me), 2.02, 2.14 (12H, each s, AcO), 2.25 (1H, m, $J_{3,Me}$ = 7.3 Hz, $J_{2,3}$ = 2.4 Hz, H-3), 2.44, 2.54 (2H, each d, $J_{5a,5b}$ = 14.2 Hz, H-5), 3.19 (3H, s, OMe), 3.79 (1H, m, $J_{13,14}$ = 9.8 Hz, $J_{14,15b}$ = 4.4 Hz, $J_{14,15a}$ = 2.5 Hz, H-14), 4.02 (1H, qd, $J_{2,Me}$ = 6.4 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.04 (1H, dd, $J_{15a,15b}$ = 12.2 Hz, $J_{14,15a}$ = 2.5 Hz, H-15a), 4.19 (1H, dd, $J_{15a,15b}$ = 12.2 Hz, $J_{14,15b}$ = 4.4 Hz, H-15b), 4.79, 4.87 (2H, each brt, *J* = 2.0 Hz, =CH_2-4), 4.97 (1H, t, $J_{12,13}$ = $J_{13,14}$ = 9.8 Hz, H-13), 5.07 (1H, dd, $J_{11,12}$ = $J_{10,11}$ = 9.8 Hz, H-11), 5.27 (1H, t, $J_{11,12}$ = $J_{12,13}$ = 9.8 Hz, H-12), 5.29 (1H, dd, $J_{10,NH}$ = 9.7 Hz, $J_{10,11}$ = 9.8 Hz, H-10), 5.31 (1H, s, H-7), 7.15 (1H, d, $J_{10,NH}$ = 9.7 Hz, NH), 7.44 (2H, t, *J* = 7.3 Hz, Ph), 7.58 (1H, t, *J* = 7.3 Hz, Ph), 8.08 (2H, d, *J* = 7.3 Hz, Ph).

Treatment of **17** (9.2 mg, 15.6 mmol) as described for preparation of **3** from **13** afforded **5** (8.3 mg, 73%) as an amorphous solid. $[\alpha]_D^{26}$ + 75.3° (*c* = 0.53, MeOH); IR (KBr) cm^{-1}: 3400, 1682, 1543, 1076; ^{1}H-NMR (CD_3OD) δ: 1.00 (3H, d, *J* = 7.0 Hz, 3-Me), 1.18 (3H, d, *J* = 6.4 Hz, 2-Me), 2.20 (1H, qd, $J_{3,Me}$ = 7.0 Hz, $J_{2,3}$ = 2.1 Hz, H-3), 2.23, 2.42 (2H, each d, $J_{5a,5b}$ = 14 Hz, H-5), 3.25 (3H, s, OMe), 3.24 (1H, t, $J_{10,11}$ = $J_{11,12}$ = 9.2 Hz, H-11), 3.28 (1H, t, $J_{12,13}$ = $J_{13,14}$ = 9.2 Hz, H-13), 3.36 (1H, m, H-14), 3.40 (1H, t, $J_{11,12}$ = $J_{12,13}$ = 9.2 Hz, H-12), 3.62 (1H, dd, $J_{15a,15b}$ = 11.9 Hz, $J_{14,15a}$ = 5.5 Hz, H-15a), 3.80 (1H, dd, $J_{15a,15b}$ = 11.9 Hz, $J_{14,15b}$ = 2.4 Hz, H-15b), 3.91 (1H, qd, $J_{2,Me}$ = 6.4 Hz, $J_{2,3}$ = 2.1 Hz, H-2), 4.30 (1H, s, H-7), 4.63, 4.79 (2H, each t, *J* = 1.8 Hz, =CH_2-4), 4.93 (1H, d, $J_{10,11}$ = 9.2 Hz, H-10); ^{13}C-NMR (CD_3OD) δ: 12.5 (3-Me), 18.1 (2-Me), 34.0 (C-5), 43.1 (C-3), 48.4 (OMe), 63.0 (C-15), 71.0 (C-2), 71.7 (C-13), 72.5 (C-7), 74.3 (C-11), 78.8 (C-12), 79.7 (C-14), 81.0 (C-10), 101.3 (C-6), 110.1 (CH_2), 148.2 (C-4), 174.6 (C=O); FAB-MS (m/z): Calcd for $C_{17}H_{30}O_9N$ ($M+H^+$) 392.1921, Found 392.1915.

Preparation of 6. Treatment of **12** (21.9 mg, 65.5 μmol) and **16** (36.2 mg, 131 μmol) as described for preparation of **14** from **11** and **12** afforded **18** (31.2 mg, 81%) as an amorphous solid. $[\alpha]_D^{25}$ + 91.0° (*c* =

0.10, $CHCl_3$); IR (KBr) cm^{-1}: 1734, 1705, 1224, 1078; ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J = 6.8 Hz, 3-Me), 1.26 (3H, d, J = 6.3 Hz, 2-Me), 2.03, 2.05, 2.15 (9H, each s, AcO), 2.23 (1H, qd, $J_{3,Me}$ = 6.8 Hz, $J_{2,3}$ = 2.7 Hz, H-3), 2.44, 2.52 (2H, each d, $J_{5a,5b}$ = 14.7 Hz, H-5), 3.19 (3H, s, OMe), 3.40 (1H, t, $J_{14a,14b}$ = $J_{13,14a}$ = 11.2 Hz, H-14a), 4.01-4.18 (2H, m, H-2, 14b), 4.80, 4.88 (2H, each brs, =CH_2-4), 4.90 (1H, t, $J_{10,11}$ = $J_{11,12}$ = 9.6 Hz, H-11), 4.95 (1H, m, H-13), 5.15 (1H, dd, $J_{11,12}$ = 9.6 Hz, $J_{12,13}$ = 9.2 Hz, H-12), 5.30 (1H, dd, $J_{10,NH}$ = $J_{10,11}$ = 9.2 Hz, H-10), 5.34 (1H, s, H-7), 7.25 (1H, d, $J_{10,NH}$ = 9.6 Hz, NH), 7.45 (2H, t, J = 6.9 Hz, Ph), 7.58 (1H, t, J = 6.9 Hz, Ph), 8.10 (2H, d, J = 7.3 Hz, Ph).

Treatment of **18** (18.8 mg, 31.8 μmol) as described for preparation of **4** from **14** afforded **6** (9.8 mg, 85%) as an amorphous solid. **6**. $[\alpha]_D^{25}$ + 88.8° (c = 0.43, MeOH); IR (KBr) cm^{-1}: 3400, 1686, 1543, 1078; ^{1}H-NMR (CD_3OD) δ: 0.98 (3H, d, J = 7.3 Hz, 3-Me), 1.17 (3H, d, J = 6.3 Hz, 2-Me), 2.20 (1H, qd, $J_{3,Me}$ = 7.3 Hz, $J_{2,3}$ = 2.9 Hz, H-3), 2.21, 2.35 (2H, each d, $J_{5a,5b}$ = 14.1 Hz, H-5), 3.21 (1H, t, $J_{10,11}$ = $J_{11,12}$ = 8.8 Hz, H-11), 3.25 (3H, s, OMe), 3.26 (1H, dd, $J_{14a,14b}$ = 11.7 Hz, $J_{13,14a}$ = 1.0 Hz, H-14a), 3.36 (1H, t, $J_{11,12}$ = $J_{12,13}$ = 8.8 Hz, H-12), 3.46 (1H, ddd, $J_{12,13}$ = 8.8 Hz, $J_{13,14b}$ = 4.9 Hz, $J_{13,14a}$ = 1.0 Hz, H-13), 3.81 (1H, dd, $J_{14a,14b}$ = 11.7 Hz, $J_{13,14b}$ = 4.9 Hz, H-14b), 3.91 (1H, qd, $J_{2,Me}$ = 6.3 Hz, $J_{2,3}$ = 2.9 Hz, H-2), 4.29 (1H, s, H-7), 4.63, 4.79 (2H, each brt, J = 2.0 Hz, =CH_2-4), 4.86 (1H, d, $J_{10,11}$ = 8.8 Hz, H-10); ^{13}C-NMR (CD_3OD) δ: 12.4 (3-Me), 18.1 (2-Me), 33.9 (C-5), 43.0 (C-3), 48.4 (OMe), 68.6 (C-14), 70.9 (C-2), 71.2 (C-13), 72.3 (C-7), 74.1 (C-11), 78.5 (C-12), 81.7 (C-10), 101.3 (C-6), 110.2 (CH_2), 148.0 (C-4), 174.5 (C=O); FAB-MS (m/z): Calcd for $C_{16}H_{28}O_8N$ ($M+H^+$) 362.1815, Found 362.1812.

ACKNOWLEDGEMENTS

We are grateful to Drs. H. Fukui, Y. Tsuchiya, and K. Fujita (Kaken Pharm. Co., Ltd.) for bioassay. We also thank Ms. K. Harata for mass spectral measurements, and Dr. T. Chihara and his staff in RIKEN for the elemental analyses.

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