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SYNTHETIC STUDIES OF LIPOSIDOMYCIN DEGRADATION PRODUCT: MODEL STUDIES OF DIAZEPANONE RING CONSTRUCTION

Noriyuki Nakajima,* Taichi Seida, Ai Furuno, Takayuki Asahi, Takao Kishimoto, and Masahiro Hamada

Biotechnology Research Center and Department of Biotechnology, Toyama Prefectural University, 5180 Kurokawa, Imizu, Toyama 939-0398, Japan; E-mail: nori@pu-toyama.ac.jp

Abstract – The model studies of diazepanone ring construction of liposidomycin degradation product was described. A synthesis of the liposidomycin diazepanone ring system using 2-nitrobenzenesulfonamides (*N*-Ns) as an activating and a protecting group has been achieved. Under the intramolecular Mitsunobu reaction conditions, the cyclization reaction proceeded efficiently to give seven-membered ring systems.

INTRODUCTION

Liposidomycin B (**1**) was isolated from *Streptomyces griseosporeus* by Ubukata *et al*. in 1985 and is a liponucleoside characterized by a seven-membered diazepanone ring core with an amino ribose, a uridine, and a fatty-acid side chain (**Figure 1**).[1] Liposidomycins are a specific inhibitor of phospho-*N*-acetylmuramylpentapeptide transferase that is the primary stage of a lipid cycle in bacterial peptideglycan synthesis, and the antibacterial action is expressed.[2]

The synthetic studies of liposidomycins and degradation product (**2**) have been executed for the assignment of stereochemistry by Spada-Ubukata,[3] Knapp,[4] Kim,[5] and Gravier-Pelletier.[6] In 2005, Matsuda, Ichikawa, and co-workers accomplished the first total synthesis of palmitoyl caprazol and caprazol (**3**),[7] a core structure of the caprazamycin antituberculosis antibiotics.[8] The total synthesis of the caprazol and caprazamycin A (**4**) has been achieved by Takemoto and co-workers in 2015.[9] Shibasaki, Watanabe, and co-workers also reported the synthesis of **3** in 2014[10] and caprazamycin B in 2015.[11]

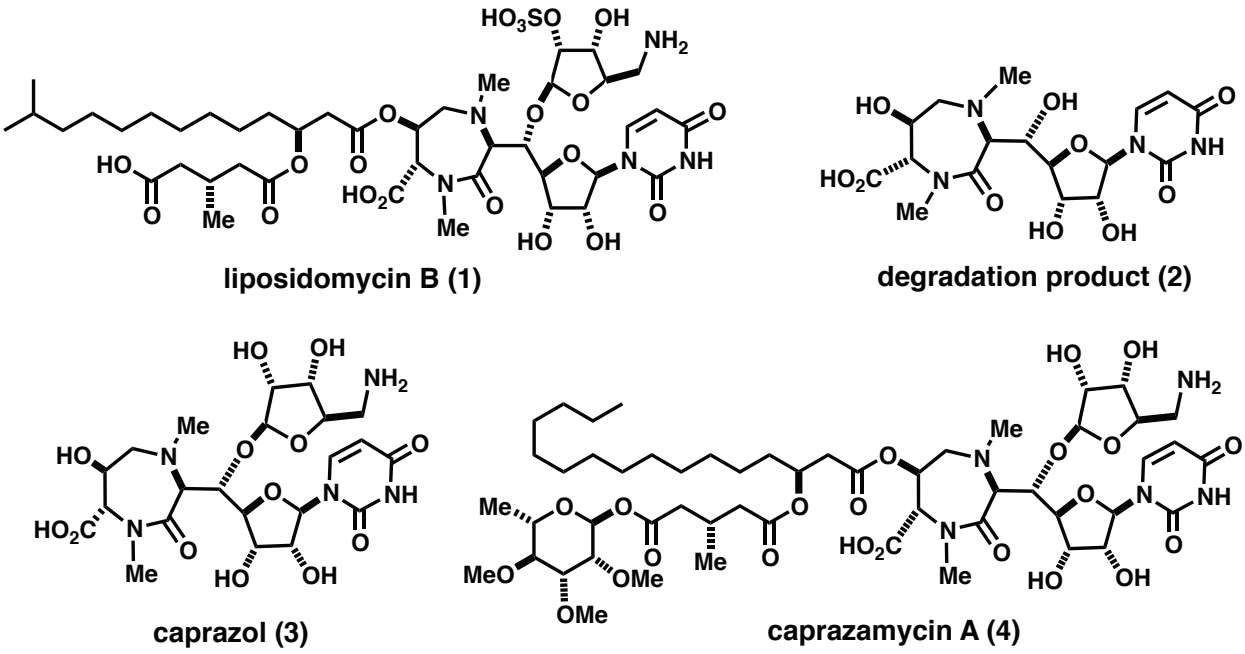
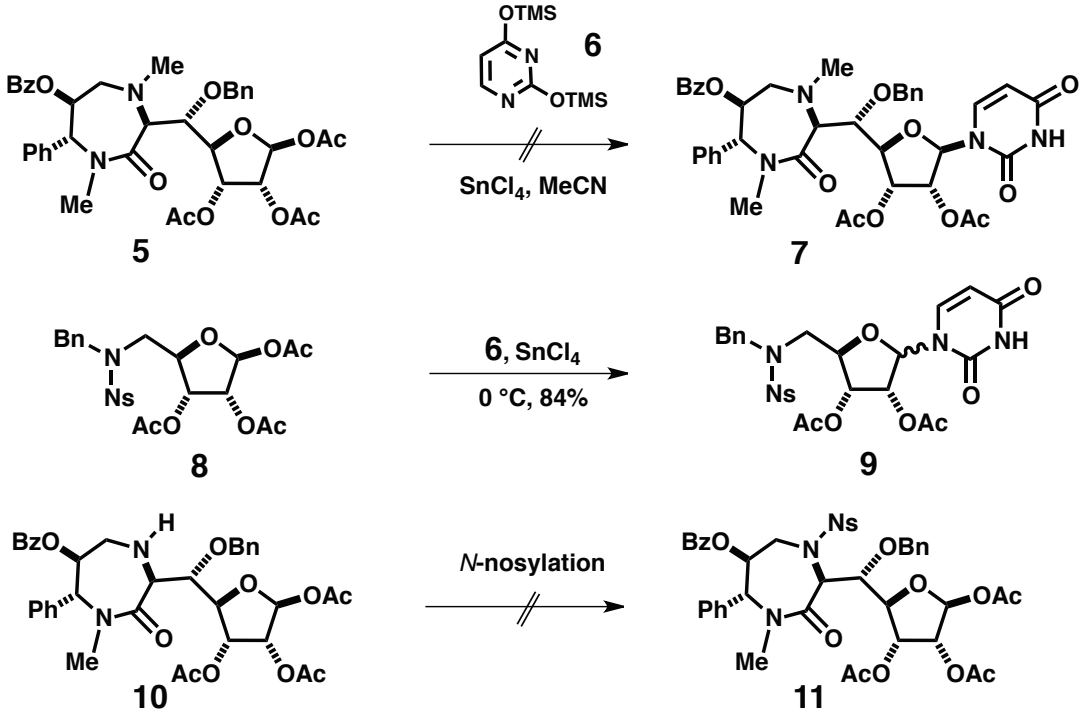


Figure 1. The structure of liposidomycin and caprazol

We previously reported the synthesis of liposidomycin degradation product (**3**). In our synthetic approach, a uracil group will be introduced after the construction of the diazepanone ring part. *N*-Glycosylation of **5** with bistrimethylsilyluracil (**6**) and Lewis acids (TMSOTf, $SnCl_4$, or $BF_3 \cdot OEt_2$) gave no reaction product (**7**),[11] even with use of excess amounts of the glycosyl donor (**Scheme 1**).

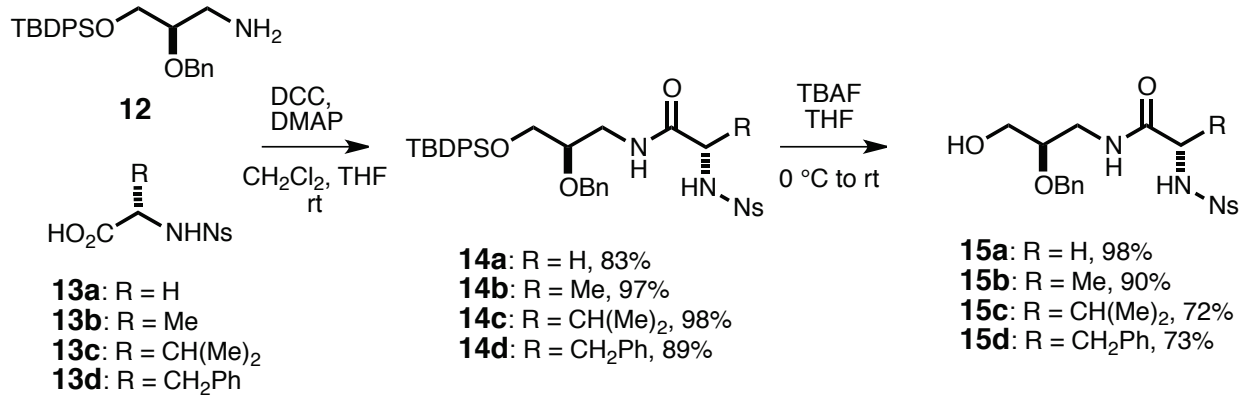


Scheme 1. Study of glycosylation and Ns protection

For the introduction of a uracil group, we prepared the model compound (**8**) having an electron-withdrawing Ns[13] group on the corresponding C1-amino group. The *N*-glycosylation of **8** with **6** in the presence of $SnCl_4$ as a Lewis acid in MeCN proceeded smoothly to obtain the target compound (**9**) in 84% yield.[14] However, all attempt of Ns protection at C-1 amino group of **10** were failed (**Scheme 1**).[15] Therefore, the synthesis of seven-membered ring systems under the intramolecular Mitsunobu reaction conditions using Ns-strategy[13] reported by Fukuyama is studied in this project.

RESULTS AND DISCUSSION

In order to perform the cyclization under Mitsunobu conditions, the precursors **15a-d** were prepared from the coupling of **12** and Ns-amides (**13a-d**). Takemoto group also used Mitsunobu reaction for the diazepanone ring formation.[9] Upon treatment of **12** and **13a-d** with DCC and DMAP in CH_2Cl_2 at room temperature, the reaction smoothly proceeded to give amides (**14a-d**) in 83% to 97% yields. Subsequent TBDPS protecting group deprotection with TBAF treatment in THF provided the cyclization precursors (**15a-d**) in 72% to 98% yields (**Scheme 2**). When Ac protecting group was used instead of benzyl (Bn) protecting group, Ac protecting group was rearranged from secondary position into primary position.



Scheme 2. Synthesis of precursor of cycling product

Diazepanone ring formation was performed under intramolecular Mitsunobu conditions. On the treatment of **15a-d** with triphenylphosphine (PPh_3) and diisopropyl azodicarboxylate (DIAD) in 0.06 M THF solution at room temperature, the desired cyclization reaction proceeded smoothly to afford diazepanone (**16a-d**) in 55% to 76% yields, respectively (**Table 1**).

On these studies, we found the electron-withdrawing group on the amino group played an important role for the diazepanone ring formation and following uracil group introduction. Therefore, the synthesis of **2** by using Ns protecting group at C1-amino group, is an ongoing project.

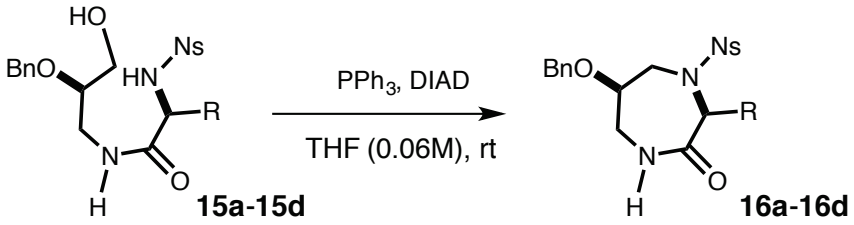


Table 1. Cyclization under intramolecular Mitsunobu reaction conditions

Run	alcohol	PPh3, eq	DIAD, eq	time, h	products	yield, %
1	**15a**	1.5	1.5	4	**16a**	55
2	**15b**	3	3	6	**16b**	76
3	**15c**	1.5	1.5	3	**16c**	57
4	**15d**	3	3	3	**16d**	65

EXPERIMENTAL

General. All reagents used were of commercial quality. Anhydrous THF and CH_2Cl_2 (Kanto Chemical) were used without purification. All air- and moisture-sensitive reactions were performed under an inert gas (Ar or N_2). Analytical TLC was conducted on precoated TLC plates (silica gel $60F_{254}$, Merck) and column chromatography was performed using silica gel 60N (70-230 mesh, Kanto Chemical). ATR-IR spectra were measured using a PerkinElmer Spectrum 100 spectrometer equipped with a Universal ATR accessory. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Biospin AVANCE II 400 spectrometer and a JEOL JNM LA-400 spectrometer using TMS or a solvent peaks as an internal standard (chemical shift in ppm). LR-ESI-MS spectra were recorded on an Agilent Technology 1100 LC-MSD spectrometer using MeOH or MeCN solutions in water or 0.5% HCO_2H as effluents. HR-ESI-MS spectra were acuired on a Bruker Dartonics micrOTOFfocus spectrometer. Specific rotation values were measured with a Horiba polarimeter.

N-[(2*R*)-(2-Benzyloxy-3-*tert*-butyldiphenylsilyloxypropyl)]-(2*S*)-2-(2-nitrobenzenesulfonamido)-propanamide (14b)

To a mixture of amine (**12**, 103.8 mg, 0.25 mmol) and acid (**13b**, 102 mg, 0.37 mg) in CH_2Cl_2 (2.5 mL), THF (1.5 mL) solution of DCC (76.6 mg, 0.37 mmol) and DMAP (6.0 mg, 0.05 mmol) was added at 0 °C. The mixture was stirred for 48 h at room temperature. The precipitated urea was removed by suction filtration, and then diluted with ice water. The mixture was extracted with EtOAc. The combined extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel (hexane: EtOAc = 3 : 2) to give **14b** (166.1 mg, 0.24 mmol, 97%) as a yellow viscous oil; R_f = 0.47 (hexane : EtOAc = 1 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, d, J = 7.6 Hz, Ns), 7.8 (1H, d, J = 7.8 Hz, Ns), 7.71-7.62 (6H, m, Ns, Ar-H),

7.47-7.27 (11H, m, Ar-H, CH_2*Ph*), 6.34 (1H, t, *J* = 5.6 Hz, NH), 5.75 (1H, d, *J* = 7.2 Hz, Ns*NH*), 4.61 (1H, d, *J* = 11.9 Hz, C*H*$_2$Ph), 4.40 (1H, d, *J* = 11.9 Hz, C*H*$_2$Ph), 3.80 (1H, quint, *J* = 7.2 Hz, H-2), 3.72 (1H, one of ABqd, *J* = 10.9 Hz, 4.8 Hz, H-3'), 3.65 (1H, one of ABqd, *J* = 10.9 Hz, 5.1 Hz, H-3'), 3.60-3.54 (1H, ddd, *J* = 13.5 Hz, 4.0 Hz, 2.6 Hz, H-1'), 3.53-3.49 (1H, m, H-2'), 3.24-3.18 (1H, m, H-1'), 1.28 (3H, d, *J* = 7.16 Hz, Me), 1.07 (9H, s, *tert*-Bu); ^{13}C-NMR (100 MHz, $CDCl_3$) δ; 136.1, 135.7, 135.6, 133.9, 132.8, 129.9, 128.7, 128.2, 127.9, 125.7, 71.9, 53.4, 44.2, 26.9, 19.3, 12.2; IR (neat, cm^{-1}) 3319 (w), 3071 (w), 2930 (w), 2856 (w), 1735 (w), 1660 (w), 1589 (w), 1539 (m), 1453 (w), 1427 (w), 1355 (m), 1302 (w), 1260 (w), 1243 (w), 1172 (m), 1142 (m), 1105 (m), 1059 (m), 1027 (m), 937 (w), 853 (w), 822 (m), 783 (m), 738 (m), 699 (s), 654 (m); LSMS-ESI *m/z* 714 $(M+K)^+$, 698 $(M+Na)^+$, 676 $(M+H)^+$; HRMS-ESI *m/z*: calcd for $C_{35}H_{41}N_3O_7SSiNa$, 698.22575; found. 698.23267.

***N*-[(2*R*)-(2-Benzyloxy-3-hydroxypropyl)]-(2*S*)-2-(2-nitrobenzenesulfonamido)propanamide (15b)**

To a mixture of amide (**14b**, 165.0 mg, 0.24 mmol) in THF (2.5 mL) was added TBAF (1.0 M solution in THF, 0.36 mL, 0.36 mmol) at 0 °C. The mixture was stirred for 14 h at room temperature before saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc. The combined extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 1 : 3 to EtOAc) to give **15b** (97.1 mg, 0.21 mmol, 90%) as a yellow viscous oil; R_f = 0.33 (EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.11-8.09 (1H, m, Ns), 7.86-7.83 (1H, m, Ns), 7.78-7.71 (2H, m, Ns), 7.41-7.31 (5H, m, CH_2*Ph*), 6.74 (1H, s, NH), 4.65 (1H, d, *J* = 11.9 Hz, C*H*Ph), 4.59 (1H, d, *J* = 11.9 Hz, C*H*Ph), 3.94 (1H, q, *J* = 7.1 Hz, H-2), 3.59-3.48 (4H, m, H-3', H-2', H-1'), 3.42-3.36 (1H, m, H-1'), 1.32 (3H, d, *J* = 7.2 Hz, Me); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.8, 138.0, 134.1, 133.0, 131.2, 129.1, 128.7, 128.2, 128.1, 128.0, 125.8, 125.3, 71.7, 61.3, 53.4, 39.6, 19.1; IR (neat, cm^{-1}); 3316 (br), 3094 (w), 2925 (w), 1658 (m), 1593 (w), 1537 (s), 1496 (w), 1453 (w), 1441 (w), 1417 (w), 1350 (m), 1301 (w), 1263 (m), 1208 (w), 1169 (m), 1143 (m), 1123 (m), 1088 (m), 1057 (m), 1027 (m), 985 (w), 922 (w), 874 (w), 853 (m), 783 (m), 731 (s), 698 (s), 653 (m); LSMS-ESI *m/z* 476 $(M+K)^+$, 460 $(M+Na)^+$; HRMS-ESI *m/z* $(M+Na)^+$: calcd for $C_{19}H_{23}N_3O_7SNa$, 460.11139; found. 460.11489.

General procedure of diazepanone ring cyclization

To a mixture of amide (1 mmol) in THF (1.6 mL) was added PPh_3 (1.5 mmol) and DIAD (1.5 mmol). The mixture was stirred for 4 h at room temperature before saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc. The combined extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation. The residue was purified by preparative TLC (EtOAc : hexane: 1 : 1 and EtOAc) to give diazepanone compounds.

(6*R*)-6-Benzyloxy-4-(2-nitrobenzenesulfonyl)-1,4-diazepan-2-one (16a)

Yield: 55% as a yellow viscous oil; R_f = 0.66 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04-8.01 (1H, m,

Ns), 7.82-7.80 (1H, m, Ns), 7.67-7.65 (2H, m, Ns), 7.32-7.23 (5H, m, CH_2*Ph*), 6.07 (1H, br, NH), 4.52 (1H, d, *J* = 11.8 Hz, OC*H*$_2$Ph), 4.46 (1H, d, *J* = 11.8 Hz, OC*H*$_2$Ph), 3.66 (2H, d, *J* = 5.3 Hz, H-7), 3.60 (2H, d, *J* = 7.4 Hz, H-5), 3.50-3.45 (1H, m, H-6), 3.37 (2H, s, H-3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.3, 148.0, 137.8, 133.9, 131.1, 129.0, 128.6, 128.2, 128.1, 125.7, 125.3, 75.0, 71.6, 70.9, 70.1, 46.1, 29.7, 22.0, 21.5, 1.0; IR (neat, cm^{-1}); 3303 (w), 2982 (w), 2934 (w), 1704 (m), 1540 (m), 1467(w), 1454 (w), 1411 (w), 1385 (w), 1373 (m), 1353 (m), 1300 (w), 1251 (m), 1166 (m), 1103 (s), 1042 (m), 914 (w), 853 (w), 782 (w), 731 (s), 698 (m), 653 (w); LSMS-ESI *m/z* 406 $(M+H)^+$.

(3*S*,6*R*)-6-Benzyloxy-3-methyl-4-(2-nitrobenzenesulfonyl)-1,4-diazepan-2-one (16b)

Yield: 76% as a yellow viscous oil; R_f = 0.42 (hexane : EtOAc = 1 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, br, Ns), 7.76 (1H, br, Ns), 7.63 (2H, br, Ns), 7.30-7.24 (5H, m, CH_2*Ph*), 6.89 (1H, s, NH), 4.47 (2H, s, OC*H*$_2$Ph), 3.87 (1H, br, H-3), 3.66-3.33 (5H, br, H-7, H-6, H-5), 1.26 (3H, br, Me); ^{1}H-NMR (400 MHz, CD_3OD) δ 7.65 (1H, d, *J* = 8.2 Hz, Ns), 7.71-7.64 (3H, m, Ns), 7.26-7.17 (5H, m, CH_2*Ph*), 4.45 (2H, s, *CH*$_2$Ph), 3.54-3.53 (1H, m, H-3), 3.22-3.15 (5H, m, H-7, H-6, H-5), 1.20 (3H, d, *J* = 5.3 Hz, Me); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.9, 137.8, 133.8, 132.8, 130.9, 129.0, 128.6, 128.2, 128.1, 125.7, 125.3, 71.5, 70.1, 70.0, 53.4, 29.7, 22.0, 21.5, 1.0, 0.0; IR (neat, cm^{-1}); 3297 (w), 2962 (w), 2926 (w), 1708 (m), 1540 (m), 1453 (w), 1413 (w), 1373 (m), 1259 (s), 1171 (m), 1144 (m), 1099 (s), 1026 (s), 916 (w), 853 (w), 796 (s), 732 (m), 698 (m), 653 (w); LSMS-ESI *m/z* 420 $(M+H)^+$.

(3*S*,6*R*)-6-Benzyloxy-3-isopropyl-4-(2-nitrobenzenesulfonyl)-1,4-diazepan-2-one (16c)

Yield: 57% as a colorless viscous oil; R_f = 0.13 (hexane : EtOAc = 1 : 2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 7.4 Hz, Ns), 7.70 (1H, d, *J* = 7.5 Hz, Ns), 7.49-7.40 (2H, m, Ns), 7.29-7.15 (5H, m, *Ph*), 6.06 (1H, d, *J* = 8.1 Hz, NH), 4.34 (2H, s, C*H*$_2$Ph), 3.86 (1H, d, *J* = 9.3 Hz, H-7), 3.65-3.58 (2H, m, H-7, H-3), 3.34 (1H, s, H-6), 3.03 (1H, s, H-5), 2.00-1.91 (1H, m, CH*Me*), 0.91 (6H, dd, *J* = 14.8 Hz, 6.8 Hz, CH*Me*$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.5, 133.0, 132.8, 131.2, 128.0, 127.6, 70.4, 67.1, 65.7, 62.6, 45.7, 31.9, 31.6, 29.7, 29.4, 22.7, 19.1, 17.9, 14.1, 1.0; IR (neat, cm^{-1}) 3343 (w), 2961 (w), 2923 (m), 2853 (w), 1729 (w), 1683 (m), 1540 (s), 1454 (w), 1442 (w), 1428 (m), 1358 (m), 1259 (m), 1172 (s), 1124 (m), 1070 (s), 1027 (m), 909 (w), 868 (w), 853 (w), 798 (m), 784 (m), 732 (s), 698 (m), 653 (m); LSMS-ESI *m/z* 486 $(M+K)^+$, 466 $(M+Na)^+$, 448 $(M+H)^+$; HRMS-ESI *m/z* $(M+H)^+$: calcd for $C_{21}H_{25}N_3O_7SH$, 448.15222; found. 448.15368.

(3*S*,6*R*)-6-Benzyloxy-3-benzyl-4-(2-nitrobenzenesulfonyl)-1,4-diazepan-2-one (16d)

Yield: 65% as a colorless viscous oil; R_f = 0.50 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, br, Ns), 7.74-7.72 (1H, m, Ns), 7.65 (2H, br, Ns), 7.40-7.32 (5H, m, *Ph*), 7.04-6.99 (5H, br, *Ph*), 5.92 (1H, s, NH), 4.54 (2H, s, OC*H*$_2$Ph), 4.03 (1H, br, H-3), 3.66-3.41 (5H, m, H-7, H-6, H-5), 3.18-3.15 (1H, br, C*H*$_2$Ph), 2.79 (1H, br, C*H*$_2$Ph); ^{1}H-NMR (400 MHz, CD_3OD) δ 7.69 (1H, d, *J* = 7.9 Hz, Ns), 7.64-7.57 (2H, m, Ns), 7.52-7.50 (1H, m, Ns), 7.28-7.17 (5H, m, OCH_2*Ph*), 4.48 (2H, dd, *J* = 13.3 Hz, 9.6 Hz, C*H*$_2$Ph), 4.08

(1H, dd, *J* = 9.8 Hz, 4.9 Hz, H-3), 3.21 (5H, m, H-7, H-6, H-5), 2.97 (1H, one of ABqd, *J* = 13.8 Hz, 4.9 Hz, C*H*$_2$Ph), 2.70 (1H, one of ABqd, *J* = 13.6 Hz, 10.1 Hz, C*H*$_2$Ph); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.2, 133.6, 132.9, 128.9, 128.6, 128.1, 128.0, 127.2, 126.0, 71.5, 69.9, 59.8, 55.0, 31.9, 29.7, 22.0, 14.1, 1.9, 1.0, 0.0; IR (neat, cm^{-1}); 3312 (w), 2923 (w), 2852 (w), 1709 (m), 1539 (m), 1497 (w), 1454 (w), 1412 (w), 1373 (m), 1354 (m), 1259 (m), 1102 (s), 1028 (m), 938 (w), 911 (w), 853 (w), 800 (w), 732 (m), 698 (m), 654 (m); LSMS-ESI *m/z* 504 $(M+H)^+$.

REFERENCES AND NOTES

1. K. Isono, M. Uramoto, H. Kusakabe, K. Kimura, K. Izaki, C. C. Nelson, and J. A. McCloskey, *J. Anibiot.*, 1985, **38**, 1617.
2. a) M. Ubukata and K. Isono, *J. Am. Chem. Soc*., 1988, **110**, 4416; b) M. Ubukata, K. Kimura, K. Isono, C. C. Nelson, J. M. Gregson, and J. A. McCloskey, *J. Org. Chem.*, 1992, **57**, 6392.
3. M. R. Spada, M. Ubukata, and K. Isono, *Heterocycles*, 1992, **34**, 1147.
4. S. Knapp, S. Nandan, and L. Resnick, *Tetrahedron Lett.*, 1992, **33**, 5485; S. Knapp, G. J. Morriello, S. R. Nandan, T. J. Emge, G. A. Doss, R. T. Mosley, and L. Chen, *J. Org. Chem.*, 2001, **66**, 5822; S. Knapp, G. J. Morriello, and G. A. Doss, *Org. Lett.*, 2002, **4**, 603.
5. K. S. Kim, J. W. Lim, Y. H. Joo, K. T. Kim, I. H. Cho, and Y. H. Ahn, *J. Carbohydr. Chem.*, 1995, **14**, 439; K. S. Kim and Y. H. Ahn, *Tetrahedron: Asymmetry*, 1998, **9**, 3601.
6. C. Gravier-Pelletier, I. Charvet, Y. L. Merrer, and J.-C. Depezay, *J. Carbohydr. Chem.*, 1997, **16**, 129.
7. S. Hirano, S. Ichikawa, and A. Matsuda, *Angew. Chem. Int. Ed.*, 2005, **44**, 1854; *Angew. Chem.*, 2005, **117**, 1888; S. Hirano, S. Ichikawa, and A. Matsuda, *J. Org. Chem.*, 2007, **72**, 9936; S. Hirano, S. Ichikawa, and A. Matsuda, *J. Org. Chem.*, 2008, **73**, 569.
8. Y. Takahashi, M. Igarashi, T. Miyake, H. Soutome, K. Ishikawa, Y. Komatsuki, Y. Koyama, N. Nakagawa, S. Hattori, K. Inoue, N. Doi, and Y. Akamatsu, *J. Antibiot.*, 2013, **66**, 171; S. N. M. Hanif, A. J. Hickey, and L. Garcia-Contreras, *J. Pharm. Biomed. Anal.*, 2014, **88**, 370.
9. H. Nakamura, C. Tsukano, M. Yasui, Sh. Yokouchi, M. Igarashi, and Y. Takemoto, *Angew. Chem.*, 2015, **54**, 3136.
10. P. Gopinath, L. Wang, H. Abe, G. Ravi, T. Masuda, T. Watanabe, and M. Shibasaki, *Org. Lett.*, 2014, **16**, 3364; P. Gopinath, T. Watanabe, and M. Shibasaki, *J. Org. Chem.*, 2012, **77**, 9260.
11. H. Abe, P. Gopinath, G. Ravi, L. Wang, T. Watanabe, and M. Shibasaki, *Tetrahedron Lett.*, 2015, **56**, 3782.
12. N. Nakajima, T. Isobe, S. Irisa, and M. Ubukata, *Heterocycles*, 2003, **59**, 107.
13. T. Kan and T. Fukuyama, *Chem. Commun*., 2004, 353; A. Fujiwara, T. Kan, and T. Fukuyama,

Synlett, 2000, 1667.

14. S. Fukunishi, M. Ubukata, and N. Nakajima, *Heterocycles*, 2005, **66**, 129.
15. S. Fukunishi, M. Ubukata, and N. Nakajima, *Heterocycles*, 2007, **73**, 627.