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SYNTHETIC STUDIES OF LIPOSIDOMYCIN DEGRADATION PRODUCT: ATTEMPT FOR INTRODUCTION OF AN URACIL GROUP

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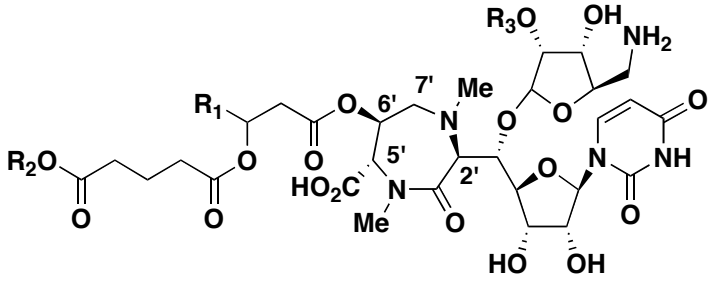
Abstract- Toward the synthesis of liposidomycin degradation product, the introduction of a uracil group was studied. In the presence of an *N*-methyl group on the diazepanone ring, the introduction of a uracil group failed. The *O*-nitrobenzenesulfonyl (Ns) protecting group played an important role for the introduction of a uracil group.

Liposidomycins (**1a**) are a family of novel lipid-containing nucleoside antibiotics of unusual complexity, found in the culture filtrate and mycelia of *Streptomyces griseosporeus*.[1] Liposidomycins inhibit 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 effect is about 1000 times that of tunicamycins that have the same action, and indicates very high selectivity. The structure of liposidomycins was proposed on the basis of degradation and spectroscopic studies.[3] However, the stereogenic centers in the lipid and diazepanone moieties remained unassigned. The synthetic studies of liposidomycin and diazepanone ring model compounds have been executed for the assignment of stereochemistry by Spada-Ubukata,[4] Knapp,[5] Kim,[6] and Gravier-Pelletier.[7] In 2004, the stereochemistry of diazepanone moieties was revealed by X-Ray crystallography analysis of caprazamycin (**1b**).[8] In 2005, Matsuda *et al*. succeeded in the total synthesis of Caprazol (**2b**), a core structure of the Caprazamycin antituberculosis antibiotics.[9]

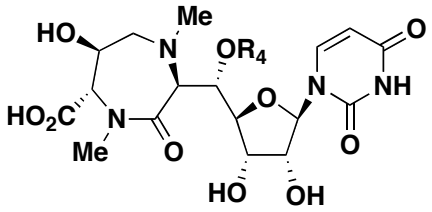
We already studied the assignment of liposidomycin stereochemistry, and the synthesis of 1,4-diazepane-3-one analogue (**3**) was reported.[10] This paper describes the synthesis of triacetate (**9**) from the coupling of the amine part (**4**) and carboxylic acid part (**5**), and further attempt for the introduction of a uracil moiety into **9** as shown in Scheme 1. The carboxylic acid (**5**) was prepared from the

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

corresponding alcohol (**11**)[4] by oxidation. PDC oxidation of **11** required long reaction time and over-oxidation occurred.



1a: Liposidomycins: R_1= alkyl chain, R_2 = H, R_3 = SO_3H
1b: Caprazamycins : R_1= alkyl chain, R_2 = sugar unit, R_3 = H



2a: Liposidomycins degradation product: R_4= H
2b: Caprazol: R_4= aminosugar

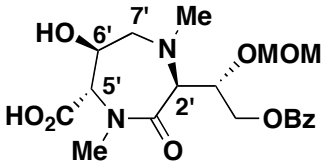


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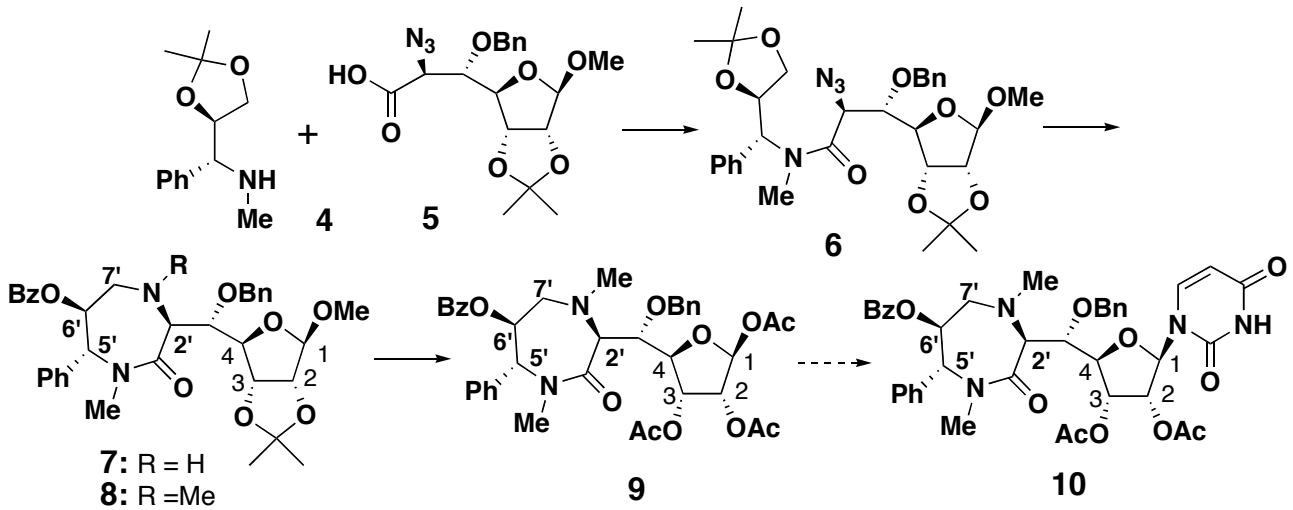
Figure 1



7: R = H
8: R =Me

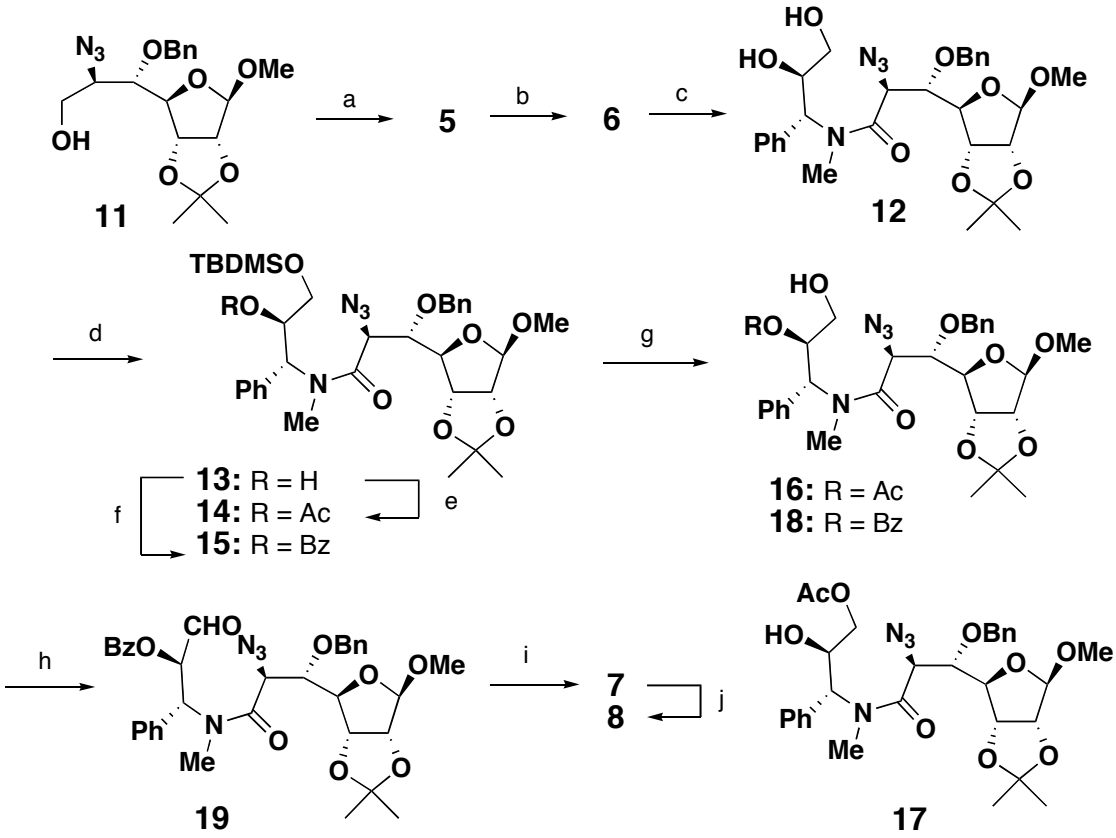
4 **5** **6** **9** **10**

Scheme 1

The following coupling reaction with amine part (**4**)[11] under DCC conditions gave amide (**6**) in only 38% yield (2 steps). To improve the low yield of the coupling reaction, 2, 2, 6, 6-tetramethyl-1-piperidinyloxy free radical (TEMPO)[12] was used as an oxidation reagent. The obtained crude **5** was coupled with **4** *via* acid chloride to afford **6** in 76 % yield (2 steps).

Selective acid hydrolysis of the acetonide group of **6** readily gave 1,2-diol (**12**) in 76 % yield. Sequential protection of the primary hydroxy group with the TBDMS group and the secondary hydroxy group of **13**

with the Ac and Bz groups afforded **14** and **15**, respectively. Careful acid and/or fluoride treatment of acetate (**14**) gave a mixture of primary alcohol (**16**) and Ac group migrated secondary alcohol (**17**) in moderate yields. The TBDMS deprotection of benzoate (**15**) by HF-pyridine gave the desired **18** in 95% yield. Swern oxidation and following reductive amination of **19** on 10% Pd-C in EtOAc in the presence of AcOH produced 1,4-diazepanan-3-one (**7**) in 63 % yield. *N*-1 Methylation by HCHO, AcOH and $NaBH_3CN$ in MeCN afforded 1,4-diazepanon-3-one compound (**8**) in 85 % yield (Scheme 2).



a) NaBr, TEMPO, $NaHCO_3$aq, trichloroisocyanuric acid, acetone, 0˚C to rt; b) $(COCl)_2$, and 4, DIPEA, CH_2Cl_2, rt, (2 steps 76%); c) 1N HCl, THF, 45˚C, 76%; d) TBDMSCl, imidazole, CH_2Cl_2, 89%; e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 96%; f) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 95%; g) HF-pyridine, THF, 95%; h) DMSO-$(COCl)_2$, Et_3N, CH_2Cl_2, 63%; i) 10% Pd-C/ H_2, EtOAc, AcOH, 63%; j) 37 wt%-HCHO, $NaBH_3CN$, AcOH, MeCN, 85%.

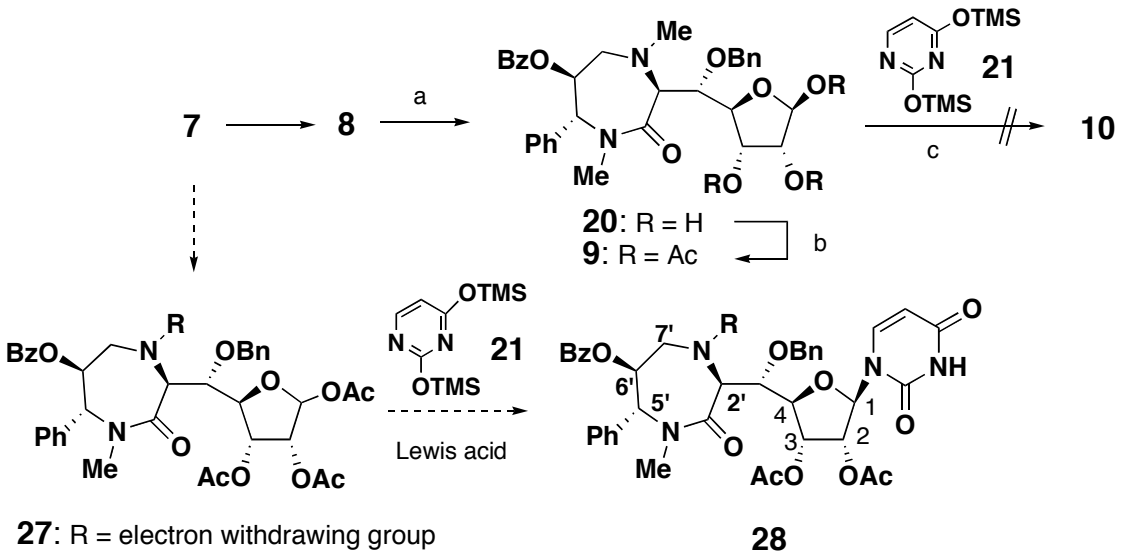
Scheme 2

When the ^{1}H-NMR spectrum of **8** was compared with that of **2a**, the *J* values for **8** closely matched those of **2a** (Table 1). Therefore, the stereochemistry of **8** was expected to be the same at the degradation product of liposidomycin.

Table 1. ^{1}H-NMR spectral data of 1,4-diazepan-3-one compounds

position	**2a** (in D_2O)	**8**
2’	3.68, d, *J* = 10 Hz	3.62, d, *J* = 8.0 Hz
5’	4.22, d, *J* = 4.8 Hz	5.03, d, *J* = 4.4 Hz
6’	4.46, dt, *J* = 4.8, 2.7 Hz	5.98, dt, *J* = 4.4, 2.2 Hz
7’	3.16, dd, *J* = 2.7, 15.3 Hz	3.30, dd, *J* = 2.2, 16.0 Hz
7’	3.21, dd, *J* = 2.7, 15.3 Hz	3.45, dd, *J* = 2.2, 16.0 Hz

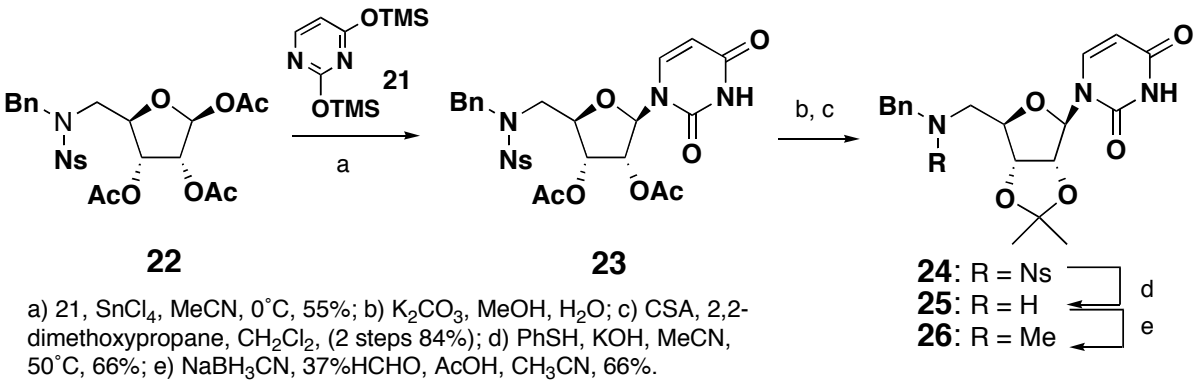
After the deprotection of the C1-methyl acetal and 2, 3-acetonide group of **8** under acidic conditions, all of the hydroxyl groups of **20** were protected with an acetyl group to provide triacetate (**9**).[13] Unfortunately, all attempts for glycosidation with a uracil group using bistrimethylsilyluracil (**21**) promoted by Lewis acid were unsuccessful (Scheme 3). The uracil group did not react with **9** due to the presence of an unshared electron pair of *N*-1' nitrogen at the diazepanone ring due to the trapping of Lewis acid.[5]



a) 1N HCl, THF, 56˚C; b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 48% (2 steps); c) $SnCl_4$, MeCN.

Scheme 3

We prepared the nitrogen group masked model compound (**22**)[14] with an *O*-nitrobenzenesulfonyl (Ns) group[15,16] for the glycosidation of a uracil group (Scheme 4). The glycosilation of **22** with **21** in the presence of $SnCl_4$ in CH_2Cl_2 proceeded smoothly; the target compound (**23**) was obtained in 55 % yield. After the acetyl group conversion into the 2,3-acetonide group, the Ns group was removed by PhSH. The following reductive methylation of **25** provided *N*-methyl compound (**26**)[17] in 44 % yield (2 steps).



a) 21, $SnCl_4$, MeCN, 0˚C, 55%; b) K_2CO_3, MeOH, H_2O; c) CSA, 2,2-dimethoxypropane, CH_2Cl_2, (2 steps 84%); d) PhSH, KOH, MeCN, 50˚C, 66%; e) $NaBH_3CN$, 37%HCHO, AcOH, CH_3CN, 66%.

Scheme 4

On these studies, we found the Ns protecting group played an important role for the introduction of a uracil group. Therefore, the introduction of a uracil for **27** having an electron-withdrawing group on the amino group is an ongoing project.

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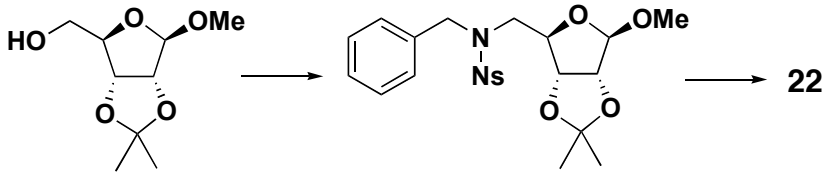
13. Data for triacetate (**9**): $[\alpha]_D^{23}$ = +26.3° (*c* 0.24, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (2H, d, *J* = 7.1 Hz), 7.72-7.22 (13H, m), 6.23 (1H, d, *J* = 4.6 Hz), 5.93 (1H, dt, *J* = 4.4, 2.2 Hz), 5.33 (1H, dd, *J* = 2.0, 6.3 Hz), 5.12 (1H, dd, *J* = 4.6, 6.3 Hz), 5.05 (1H, d, *J* = 4.4 Hz), 4.93 (1H, t, *J* = 2.0 Hz), 4.78 (1H, d, *J* = 10.4 Hz), 4.61 (1H, d, *J* = 10.4 Hz), 4.11 (1H, dd, *J* = 2.0, 9.3 Hz), 3.70 (1H, d, *J* = 9.3 Hz), 3.40 (1H, dd, *J* = 2.2, 15.7 Hz), 3.35 (1H, dd, *J* = 2.2, 15.7 Hz), 3.22 (3H, s), 2.67 (3H, s), 2.16 (3H, s), 2.11 (3H, s), 2.04 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.4, 170.3, 170.0, 169.3,

165.9, 137.9, 134.8, 133.6, 130.9, 129.8, 129.5, 129.4, 128.82, 128.77, 128.70, 128.5, 128.1, 127.9, 125.6, 112.7, 93.9, 85.4, 75.9, 74.9, 74.2, 71.0, 70.5, 68.2, 65.7, 56.3, 38.7, 38.4, 30.4, 28.9, 23.0, 21.3, 20.8 (Cx2); IR (neat, cm^{-1}) 2926 (m), 2855 (w), 1748 (s), 1646 (m), 1603 (w), 1497 (w), 1451 (w), 1397 (w), 1372 (w), 1314 (w), 1258 (s), 1225 (s), 1177 (w), 1109 (m), 1096 (m), 1071 (m), 1026 (m), 1011 (m), 939 (w), 914 (w), 756 (s), 714 (m), 698 (m), 660 (w); FAB-HRMS calcd for $C_{38}H_{43}N_2O_{11}$ $(M+H)^+$, 703.2867; found 703.2851.

14. Compound **22** was made from the methyl 2,3-isopropylidene-β-D-ribofuranoside (**29**) *via* **30** in following three step sequences: the coupling with *O*-nitrobenzenesulfonyl benzyl amine under Mitsunobu conditions, deprotection of methyl acetal and acetonide by 1N HCl, and the acetyl protection.



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17. Data for (**26**): $[\alpha]_D^{22}$ = +16.9°(*c* 0.21, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (5H, m), 7.03 (1H, d, *J* = 7.7 Hz), 6.60 (1H, s), 5.49 (1H, d, *J* = 7.7 Hz), 5.01 (1H, d, *J* = 6.3 Hz), 4.72 (1H, dd, *J* = 4.4, 6.3 Hz), 4.25 (1H, ddd, *J* = 3.7, 4.4, 10.2 Hz), 3.73 (1H, d, *J* = 12.9 Hz), 3.53 (1H, d, *J* = 12.9 Hz), 3.07 (1H, dd, *J* = 9.3, 10.2 Hz), 2.57 (1H, dd, *J* = 3.7, 9.3 Hz), 2.27 (3H, s), 1.55 (3H, s), 1.32 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.2, 150.9, 140.4, 136.5, 129.9 (Cx2), 128.3 (Cx2), 127.4 (Cx2), 113.7, 91.8, 84.8, 84.5, 84.0, 61.0, 59.0, 41.2, 27.3, 25.4; IR (neat, cm^{-1}) 3904 (w), 3854 (w), 3839 (w), 3821 (w), 3737 (w), 3712 (w), 3690 (w), 3650 (w), 3629 (w), 3567 (w), 2926 (w), 2361 (m), 1717 (m), 1653 (s), 1559 (w), 1541 (w), 1522 (w), 1507 (w), 1489 (w), 1456 (w), 1375 (m), 1213 (m), 1159 (w), 1094 (w), 1065 (m), 868 (w), 806 (w), 749 (m), 702 (w); FAB-MS (*m/z*) 388 (MH^+, 100), 276 (39), 119 (25), 112 (13), 91 (100); FAB-HRMS calcd for $C_{20}H_{26}N_3O_5$ $(M+H]^+$, 388.1872; found 388.1862.