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Synthesis of the diazepanone-nucleoside portion of liposidomycins by aldol reaction of the enolate of diazepanone with a nucleoside 5′-aldehyde

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Abstract

The diazepanone-nucleoside part of liposidomycins has been synthesized by the aldol reaction between the enolate of a stereochemically defined diazepanone and a uridine 5′-aldehyde. The configurations of two new stereocenters in the aldol product have been assigned on the basis of the ^{1}H NMR coupling constants and NOE of its derivative.

1. Introduction

The liposidomycins are a family of novel lipid-containing nucleoside antibiotics of unusual complexity, recently found in the culture filtrate and mycelia of *Streptomyces griseosporeus*.[1] These antibiotics strongly inhibit the formation of the lipid intermediate in bacterial peptidoglycan synthesis with three orders of magnitude greater activity than that of tunicamycins and with extremely high specificity.[2,3] The structures of liposidomycin A,[4] B **1**,[2] and C proposed on the basis of degradation and spectroscopic studies are identical except for slight variations in the lipid portion. However, six stereogenic centers including two in the junction between the diazepanone and the nucleoside moieties remained unassigned. Because of a renewed interest in the development of new antibacterial drugs which inhibit the enzymes of bacterial peptidoglycan biosynthesis[5] and because of their unique structural features, the liposidomycins merit serious consideration as the synthetic target. There have been a few endeavors to synthesize liposidomycins.[6–9] We have also completed the synthesis of the diazepanone moiety **2**,[10] the aminopentose moiety,[11,12] and the lipid portion[13] of liposidomycins. Although ribosyl-substituted diazepanones have been synthesized by Spada et al.[6] and by Le Merrer et al.,[9] the diazepanone-nucleoside moiety of

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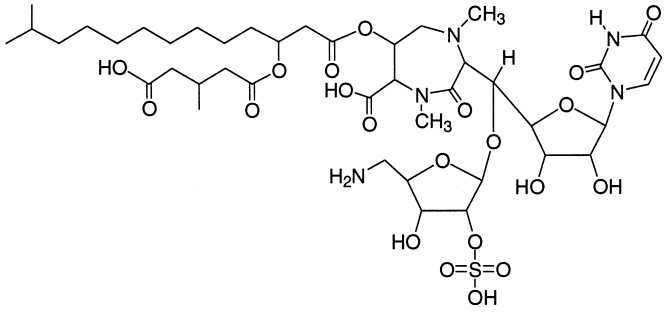
liposidomycins has not been constructed yet. Here we report the synthesis of the diazepanone-nucleoside part of liposidomycins that is the crucial step for the eventual total synthesis of liposidomycins.



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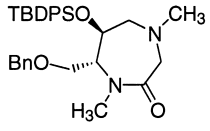

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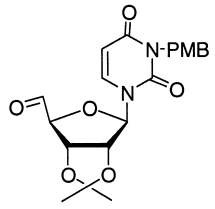

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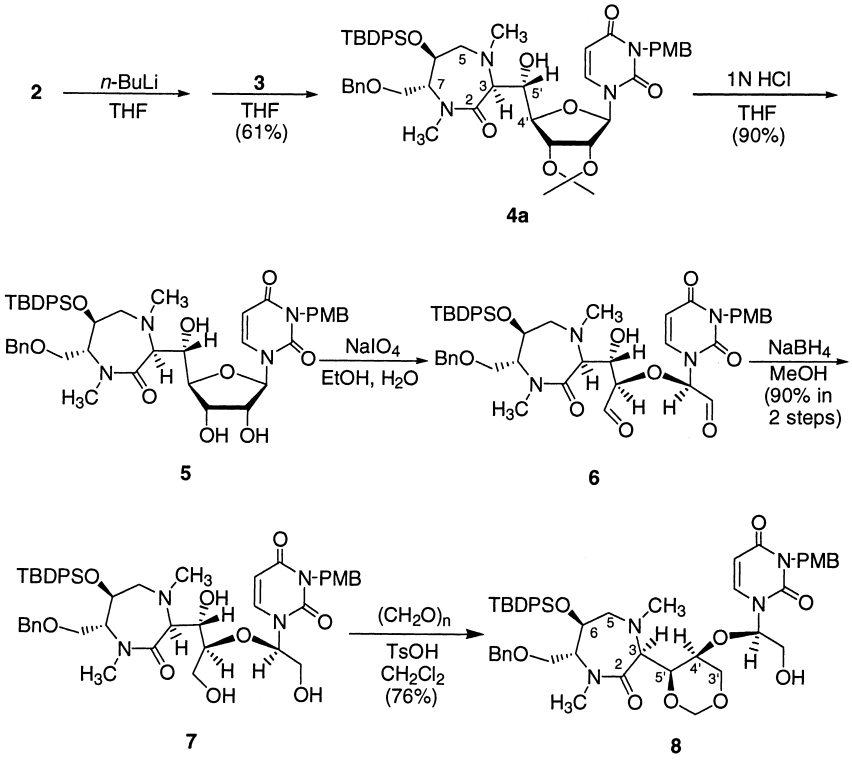
Either of two strategies can be utilized for the synthesis of the diazepanone-nucleoside moiety: (i) the elaboration of the diazepanone ring after chain extension of the ribose moiety of uridine; or (ii) the direct coupling of the diazepanone ring and uridine 5′-aldehyde. Our attempt at the synthesis of the diazepanone-nucleoside moiety based on the first strategy resulted in a complete failure. Thus, the reaction of the properly protected uridine 5′-aldehyde (**3**)[14] and the enolate of the protected glycin or sarcosine did not provide any aldol adducts probably because of the facile retro-aldol reaction. Although the reaction of the protected uridine 5′-aldehyde **3** and the nitronate of methyl nitroacetate gave adducts of which the retro-aldol was slower, the further elaboration of the adduct toward the diazepanone-nucleoside part was unsuccessful. We, therefore, carried out the direct coupling between the 1,4-dimethyl-1,4-diazepanone ring **2**[10] and the properly protected uridine 5′-aldehyde (**3**).

The stereochemically defined diazepanone **2** in THF was treated with n-butyllithium and the solution was stirred at −78°C for 30 min. To the resulting orange solution of the enolate was added the THF solution of aldehyde **3** and the reaction mixture was stirred for a further 1.5 h at −78°C. After usual workup, the reaction mixture was chromatographed to afford a mixture of four diastereomeric adducts in 61% yield. Repeated chromatography of the diastereomeric mixture afforded pure **4a** and three other pure diastereomers, **4b**, **4c**, and **4d**, in the ratio of 70:21:5:4.[15] We carried out the aldol reaction of **2** and **3** under various different conditions in the hope of improving the diastereoselectivity and the yield. However, addition of the Lewis acid such as $TiCl_4$, $BF_3 \cdot Et_2O$, or $ZnBr_2$ only retarded the aldol reaction. The reaction of the boron enolate of **2** with the aldehyde **3** was also very sluggish and a Mukaiyma type aldol reaction of silyl enol ether of **2** with aldehyde **3** did not occur. The stereochemistry of the newly generated stereogenic centers, C-3 and C-5′, of the major isomer **4a** was determined by the 600 MHz ^{1}H NMR study of its derivative **8**. The isopropylidene group in **4a** was hydrolyzed with 1 N HCl at 50–60°C without affecting the TBDPS group to give triol **5** in 90% yield. The reaction of **5** with sodium metaperiodate in aqueous ethanol gave the crude dialdehyde **6** which, without purification, was reduced

to triol **7** with sodium borohydride in methanol (90% yield in two steps). Reaction of compound **7** and paraformaldehyde in the presence of a catalytic amount of p-toluenesulfonic acid and copper sulfate at room temperature overnight afforded the methylene acetal **8**[16] in 76% yield (see Scheme 1).



Scheme 1.

The absolute configuration at C-4′ of compound **8** must be *S* since C-4′ of **8** originated from C-4′ of uridine. The vicinal coupling constants J(H-4′, H-3$_a$′)=10.2 Hz and J(H-4′, H-3$_b$′)=2.3 Hz of **8** are consistent with a chair form of the dioxane ring with the nucleoside portion in the equatorial position at C-4′ of compound **8** as shown in Fig. 1 (A). The coupling constant J(H-4′, H-5′)=2.7 Hz of **8** indicates that two hydrogens are in a *gauche* relationship and the diazepanone ring is located in an axial position at C-5′ of the dioxane ring in compound **8**. Therefore, the (*S*)-configuration can be assigned to C-5′ of compound **8** and of compound **4a** as well. Vicinal coupling constants and NOE interactions suggest that the preferred conformation of the diazepanone ring of compound **8** is the chair form with the OTBDPS at C-6 and CH_2OBn at C-7 in pseudo-diaxial positions as shown in Fig. 1. Thus, small coupling constants, J(H-5$_a$, H-6)=1.2 Hz and J(H-5$_b$, H-6)=1.6 Hz and NOE interactions between H-6 and H-5$_a$, between H-6 and H-5$_b$, and between *t*-butyl protons of TBDPS group and H-5$_a$ indicate that the OTBDPS group of the diazepanone ring is in the pseudo-axial position. The fact that the CH_2OBn group must have a *trans* relationship with the OTBDPS group, and that NOE interactions exist between C-8 methylene protons of CH_2OBn group and other protons such as H-5$_b$ and H-3 also suggests that the CH_2OBn group is in a pseudo-axial position in the diazepanone ring. The CH_2OBn group in the pseudo-axial orientation avoids an unfavorable interaction with the N-1 methyl group as observed by Knapp.[7] With these results in mind, the absolute configuration at C-3 of the diazepanone ring of **8** and **4a** could be assigned to be *S* on the basis of the NOE interactions between H-3 and H-5$_b$ and between H-3 and H-8s. Therefore, it is quite

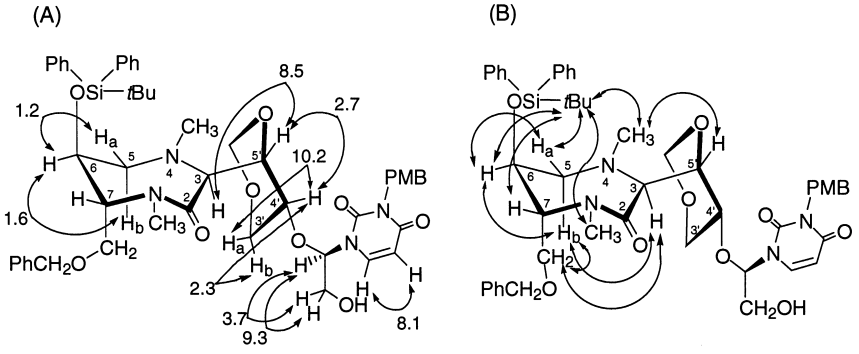


Fig. 1. (A) Vicinal $J_{(H,H)}$ coupling constants (Hz) measured for **8**; (B) average conformation of **8** with indication of NOE interactions

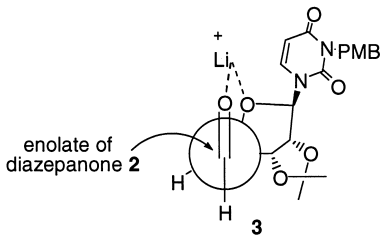


Fig. 2. The *si* face attack of the enolate of the diazepanone **2** to the carbonyl group of the nucleoside **3** in the chelation model

reasonable that the bulky group at C-3 of compound **8** is in the pseudo-equatorial position in this chair conformation. The NOE interactions between the *t*-butyl protons of the TBDPS group and protons of both N-1 and N-4 methyl groups further confirm that the chair form shown in Fig. 1 is a more favorable conformation than another possible chair form of the diazepanone ring. Consequently, C-3 and C-5′ configurations both in **4a** and **8** were determined to be *S* and *S*, respectively. The relative stereochemistry between C-3 and C-5′ of aldol adduct 4a, therefore, is *syn*.

The (*S*)-configuration at C-5′ in **4a** generated in the aldol reaction of **2** and **3** could be interpreted by the chelation model in which lithium is coordinated to both the ribose ring oxygen and the carbonyl oxygen of the nucleoside **3** and thus the enolate of **2** attacks the *si* face of the carbonyl group as shown in Fig. 2. The preference for the formation of *syn* aldol **4a** in the reaction of *E*-enolate of **2** with aldehyde **3** is not unusual. Although the aldol reaction of chiral enolates with nucleoside 5′-aldehydes or even with ribose 5-aldehydes is not well documented, it is known that the reaction of the *E*-enolate derived from cyclohexanone with benzaldehyde afforded almost a 1:1 mixture of *syn* and *anti* aldols under kinetically controlled reaction conditions.[17]

Acknowledgements

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15. Compound **4a**: $[\alpha]_D$ +3.1 (*c* 0.36; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.26 (s, 3H), 1.52 (s, 3H), 2.59 (s, 3H), 3.04 (brs, 5H), 3.30–3.50 (m, 4H), 3.77 (s, 3H), 3.88 (brs, 1H), 4.03 (m, 1H), 4.29 (s, 2H), 4.39 (d, 1H, *J*=9.1 Hz), 4.55 (m, 2H), 4.67 (m, 1H), 5.00 and 5.10 (ABq, 2H, *J*=13.5 Hz), 5.75 (d, 1H, *J*=8.3 Hz), 6.02 (d, 1H, *J*=2.1 Hz), 6.82 (d, 2H, *J*=8.7 Hz), 7.14 (m, 2H), 7.20–7.55 (m, 11H), 7.55–7.72 (m, 4H), 7.80 (d, 1H, *J*=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 18.8, 22.4, 25.4, 26.7, 26.8, 27.1, 31.4, 38.1, 38.8, 43.3, 55.1, 59.0, 65.0, 66.8, 68.6, 68.9, 70.9, 72.8, 77.2, 78.2, 85.7, 86.2, 91.6, 101.7, 113.7, 113.9, 127.4, 127.9, 128.0, 128.1, 128.6, 129.3, 130.3, 130.4, 131.0, 133.1, 133.4, 136.0, 136.1, 137.5, 138.5, 151.2, 159.3, 163.1, 174.3. HMRS (FAB) calcd for $C_{51}H_{63}O_{10}N_4Si$ (MH^+) 919.4313; found 919.4334. Compound **4b**: $[\alpha]_D$ +56.3 (*c* 0.08; $CHCl_3$). Compound **4d**: $[\alpha]_D$ +24.0 (*c* 0.10; $CHCl_3$).
16. Compound **8**: $[\alpha]_D$ −5.0 (*c* 0.08; $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 1.13 (s, 9H), 2.53 (s, 3H), 2.95 (dd, 1H, *J*=1.6, 15.0 Hz), 3.03 (s, 3H), 3.07 (dd, 1H, *J*=1.2, 15.0 Hz), 3.31 (d, 1H, *J*=8.5 Hz), 3.32 (1H, m), 3.42 (2H, m), 3.58 (dd, 1H, *J*=9.3, 12.3 Hz), 3.62 (brs, 1H), 3.71 (dd, 1H, 2.3, 12.6 Hz), 3.79 (s, 3H), 3.83 (dd, 1H, *J*=3.7, 12.3 Hz), 3.89 (dd, 1H, *J*=10.2, 12.6 Hz), 4.07 (m, 1H), 4.10 (ddd, 1H, *J*=2.3, 2.7, 10.2 Hz), 4.23 and 4.30 (ABq, 2H, *J*=12.1 Hz), 4.28 (m, 1H), 4.76 (d, 1H, *J*=6.4 Hz), 4.91 (d, 1H, *J*=6.4 Hz), 5.05 (s, 2H), 5.79 (d, 1H, *J*=8.1 Hz) 6.15 (dd, 1H, *J*=3.7, 9.3 Hz), 6.84 (d, 2H, *J*=8.7 Hz), 7.14 (d, 2H, *J*=6.9 Hz), 7.30–7.50 (m, 12H), 7.64–7.75 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.5, 27.4, 32.0, 39.0, 39.3, 44.1, 55.6, 59.5, 66.0, 67.0, 69.2, 69.7, 70.1, 71.3, 73.3, 82.8, 85.6, 97.0, 102.7, 114.1, 127.9, 128.3, 128.4, 128.9, 129.4, 130.6, 131.2, 133.3, 133.6, 136.2, 136.3, 137.6, 137.9, 151.1, 159.5, 162.9, 174.4. HMRS (FAB) calcd for $C_{49}H_{61}O_{10}N_4Si$ (MH^+) 893.4157; found 893.4147.
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