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Diastereoselective syntheses of α-amino-β-hydroxyesters precursors of the ribosyl-diazepanone core of the liposidomycins

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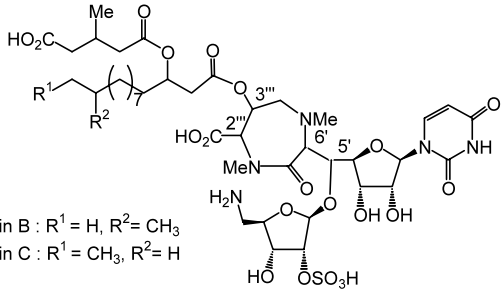
Abstract—The diastereoselective syntheses of the *O*-protected ribosyl-β-hydroxy-α-amino esters **3** and **4**, precursors of α-ribosyl-diazepanone core analogues of the liposidomycins, respectively, from the β-ketoesters **5** and **6** are described. The *anti* relationship between the two adjacent aminated and hydroxylated carbons was controlled by sequential hydrogenation of the β-ketoesters in the presence of chiral ruthenium catalysts and electrophilic amination of the resulting β-hydroxyesters.

The liposidomycins represent a class of complex nucleoside antibiotics isolated from *Streptomyces griseosporeus*.[1] They inhibit the formation of the lipid intermediate in bacterial peptidoglycan synthesis.[2] The structure of the liposidomycin A, B **1** and C **2** are identical except for slight variations in the lipid portion.[3]

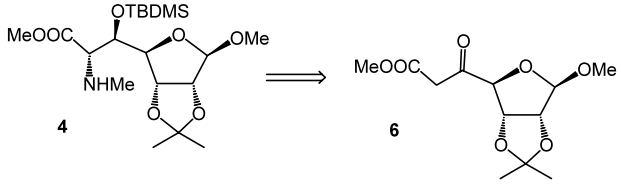


1, Liposidomycin B : $R^1 = H$, $R^2 = CH_3$
2, Liposidomycin C : $R^1 = CH_3$, $R^2 = H$

However, the relative and absolute configurations at C-5′, C-6′, C-2‴ and C-3‴ of the ribosyl-diazepanone core remained unassigned for many years. Very recently the absolute configurations were proposed by Knapp and co-workers[4] for these four stereocentres as 5′*S*, 6′*S*, 2‴*S* and 3‴*S*. Various approaches to the synthesis of derivatives of the common α-ribosyl-diazepanone core of the liposidomycins have been reported.[4–7]

We propose here the diastereoselective syntheses of *O*-protected α-amino-β-hydroxyesters **3** and **4** which could be the key intermediates in a convergent approach to analogues of the ribosyldiazepanone core. The compounds **3** and **4** were obtained with complete *anti* stereoselectivity at C_2–C_3 from the corresponding β-ketoesters **5** and **6** by catalytic hydrogenation followed by electrophilic amination of the resulting β-hydroxyesters. To our knowledge the diastereoselective catalytic hydrogenation of β-ketoester bearing a glycosyl moiety at C_3 has never been reported.

3 **5**



4 **6**

The synthesis of the *O*-protected (2*S*,3*R*)-methyl 2-amino-3-*t*-butyldimethylsilyloxy-4,4-dimethoxybutanoate **3** was performed from **5** in five steps. The synthesis of the enantiomer of the compound **7** was previously described.[8] The use of $RuCl_2$[(*S*)-Binap]–Et_3N[9] as catalyst for the hydrogenation step afforded **7** with comparable yield and stereoselectivity. The

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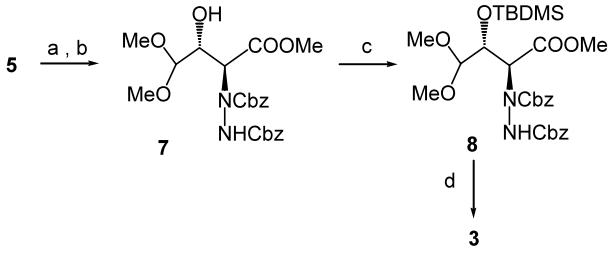
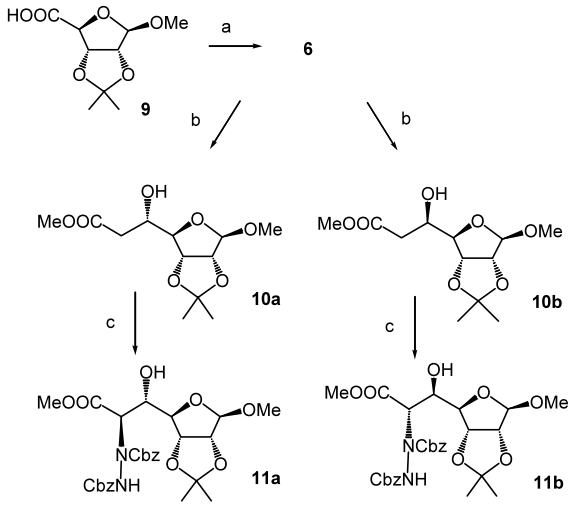
hydroxyl function was protected as a *t*-butyldimethylsilyl ether to give **8** in 88% yield because the cleavage of the N–N bond could not be performed in the presence of an alcohol. The benzylcarbamates were first removed by hydrogenolysis in the presence of Pd/C. The best results for the cleavage of the resulting hydrazine were obtained with H_2 in the presence of Raney-Ni and the *O*-protected α-amino-β-hydroxyester **3**[10] was isolated in 72% yield from **8** (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) H_2 1 atm, $RuCl_2$[(*S*)-Binap]–Et_3N 1%, MeOH, 65°C, 18 h, 91% (ee = 90%); (b) MeZnBr 1.1 equiv., THF, 30 min, 0°C; LDA 2.2 equiv., 1 h, −78°C; CbzN=NCbz 2 equiv., −78°C; satd aq. NH_4Cl, 66% (de >95%); (c) TBDMSOTf 1.5 equiv., 2,6-lutidine 2 equiv., DCM, −78°C, 88%; (d) i. H_2 1 atm, Pd/C 10%, MeOH, 1.5 h, 20°C, ii. H_2 1 atm, Raney-Ni, MeOH, 18 h, 72%.

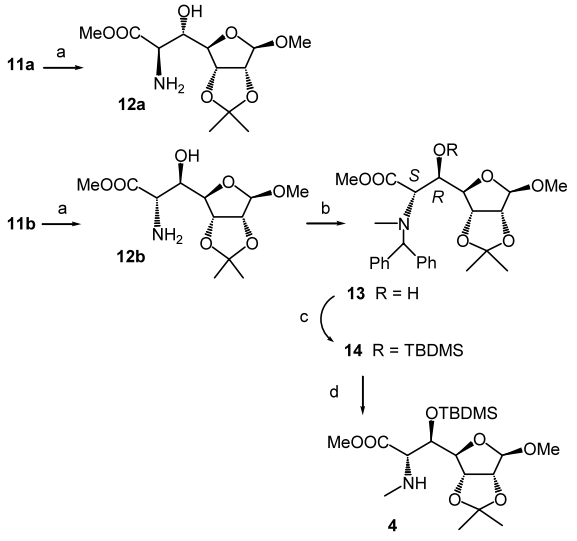
The D-ribose acid derivative **9** was prepared in two steps from D-ribose.[11] The β-ketoester **6** was easily obtained by homologation of the carboxylic acid function of **9** using the Masamune procedure.[12] Partial epimerisation at C_4 was noticed, however optically pure β-ketoester **6** was isolated by recrystallisation from diisopropyl ether. **6** was first reduced with sodium borohydride and a mixture of diastereomers **10a**:**10b** in a 75:25 ratio was obtained. The β-hydroxyesters **10a** and **10b** were easily separated by silica gel chromatography. Catalytic hydrogenations of **6** were conducted in methanol at 40°C under atmospheric pressure in the presence of 2% mol. of chiral ruthenium(II) complexes[13] and afforded the β-hydroxyesters **10** in quantitative yield. With $RuBr_2$[(*R*)-Binap], the diastereomeric ratio was 90:10 in favour of **10a**. The use of $RuBr_2$[(*S*)-Binap] yielded **10b** as the major diastereomer in a **10a**:**10b** ratio of 5:95.[14] The diastereoselectivity of the hydrogenation of the optically pure β-ketoester **6** bearing a ribosyl moiety at C_3, with chiral ruthenium catalysts was completely controlled by the chirality of the diphosphane ligand in the ruthenium complex. The diastereoselective amination step was carried out with dibenzylazodicarboxylate as electrophilic reagent because the conditions of deprotection of benzylcarbamates are compatible with the presence of an acetal function on the ribosyl moiety. The zinc enolates of the β-hydroxyesters **10** were generated using methyl zinc bromide and lithium diisopropylamide,[15] their reaction with the dibenzylazodicarboxylate produced exclusively the *anti* diastereomers **11a** and **11b** with 59 and 56% isolated yield respectively (Scheme 2).

Hydrogenolyses of the benzylcarbamates and of the N–N bond occurred simultaneously under catalysis of

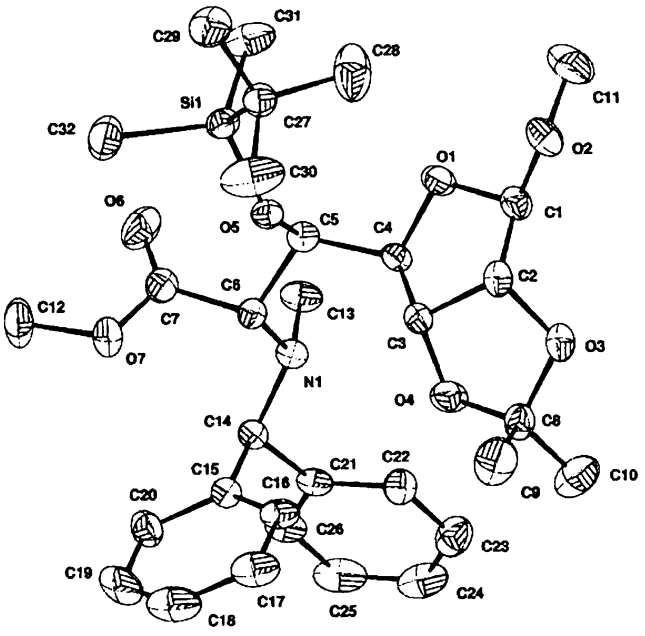


Scheme 2. *Reagents and conditions*: (a) i. Im_2CO 1.3 equiv., THF, 16 h, 20°C, ii. $Mg(MeOOCCH_2COO\text{-})_2$ 1.3 equiv., 16 h, 60%; (b) H_2 1 atm, $RuBr_2L_2$ 0.02 equiv. (for **10a**, L_2: (*S*)-Binap and for **10b**, L_2: (*R*)-Binap), MeOH, 16 h, 40°C, quant. yield; (c) MeZnBr 1.1 equiv., THF, 30 min, 0°C; LDA 2.2 equiv., 1 h, −78°C; CbzN=NCbz 2 equiv., −78°C; satd aq. NH_4Cl, 59% (de >95%) for **11a** and 56% (de >95%) for **11b**.

Raney-Ni. Under these conditions, **11a** and **11b** afforded **12a** and **12b**, respectively, in 75% yield. A synthesis of **12a** based on the aldol condensation of a chiral glycine enolate has been described with a de of 64%.[16] The synthesis of the *N*-methylated α-amino-β-hydroxyester **4** was achieved from **12b**. The reduction of its benzophenone Schiff base derivative followed by reductive *N*-methylation afforded **13** in 74% yield. The hydroxyl function was then silylated and the benzhydril group hydrogenolysed to give **4**[17] in 95% yield from **13** (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) H_2 1 atm, MeOH, Raney-Ni, 24 h; (b) i. Ph_2C=NH 1.05 equiv. DCM, MeOH satd HCl cat., 24 h, ii. $NaBH_3CN$ 3 equiv., MeCN, AcOH cat., 2 h, iii. aq. HCHO 15 equiv., $NaBH_3CN$ 13 equiv., AcOH cat., 24 h; (c) TBDMSOTf 3 equiv., 2,6-lutidine 4 equiv., DCM, 16 h; (d) H_2 1 atm, DCM/MeOH, Pd/C, 16 h.



Scheme 4. X-Ray structure of **14**.

Relative and absolute configurations of the stereocentres were confirmed by crystallographic analysis. The X-ray structure of compound **14**[18] shows an *anti* relationship between the two adjacent aminated and hydroxylated carbons with C_5 (*R*) and C_6 (*S*) absolute configurations, respectively, in 75% yield (Scheme 4).

In conclusion, we propose here the syntheses of the *O*-protected anti-α-amino-β-hydroxyesters **3** and **4** (or **12a**) precursors of 5′-*epi* (or 6′-*epi*) analogues of the ribosyldiazepanone core of the liposidomycins. These compounds were obtained with high enantio and diastereoselectivities. Coupling and cyclisation are under progress in our laboratory. Furthermore, we described the catalytic hydrogenation of the chiral β-ketoester bearing a ribosyl moiety **6** and showed the stereochemistry of the created hydroxyl centre was controlled by the catalyst.

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10. Compound **3** $[\alpha]_D^{25}=+23$ (*c* 0.7, $CHCl_3$).
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14. Compound **10a**: oil; R_f: 0.64 (diethyl ether/pentane 75/25), $[\alpha]_D^{25}=-37$ (*c* 1.7, CH_2Cl_2). Compound **10b**: white solid; mp 31–32°C (*i*Pr_2O); R_f: 0.60 (diethyl ether/pentane 75/25), $[\alpha]_D^{25}=-45$ (*c* 1.0, CH_2Cl_2).
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17. Compound **4** $[\alpha]_D^{25}=-21$ (*c* 1.0, CH_2Cl_2).
18. X-Ray quality crystals of **14** were obtained by slow evaporation from a methanol–water solution. Atomic coordinates, bond distances and angles, and anisotropic displacement parameters have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as deposition No. CCDC 201717. Colourless crystal; mp 120°C, $[\alpha]_D^{25}=-77$ (*c* 1.1, CH_2Cl_2). IR (KBr) 3058, 2956, 2926, 2850, 1734 (C=O), 1492, 1471, 1252, 1092, 741. ^1H NMR (300 MHz, $CDCl_3$): 0.03 (s, 3H), 0.10 (s, 3H), 0.79 (s, 9H), 1.41 (s, 3H), 1.64 (s, 3H), 2.33 (s, 1H), 3.46 (s, 3H), 3.56 (s, 3H), 3.60 (d, 1H, $J=9$ Hz), 4.38 (dd, 1H, $J=3.7$ and 7 Hz), 4.42 (dd, 1H, $J=2$ and 9 Hz), 4.55–4.57 (m, 1H), 4.59 (s, 1H), 4.74 (dd, 1H, $J=3.7$ and 7 Hz), 4.92 (d, 1H, $J=3.7$), 7.18–7.30 (m, 6H), 7.41–7.46 (m, 4H). ^{13}C NMR (75.5 Hz, $CDCl_3$): −5.2, −3.5, 18.2, 25.7, 25.9, 27.2, 35.4, 50.5, 57.0, 65.8, 71.3, 74.6, 77.2, 83.3, 84.4, 109.4, 114.1, 126.8, 127.0, 128.0, 128.1, 128.3, 128.7, 141.6, 142.8, 170.5; Anal. calcd for $C_{32}H_{47}NO_7Si$: C, 65.61; H, 8.09; N, 2.39. Found: C, 65.54; H, 8.23; N, 2.46.