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Access to Enantiopure Ribosyl-Diazepanone Core of Liposidomycins

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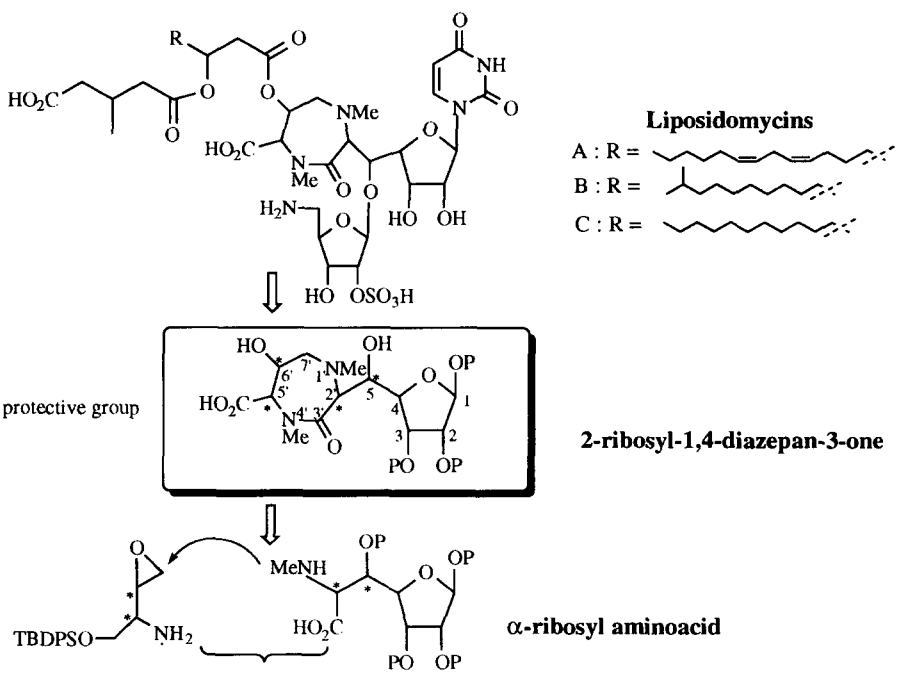
Abstract : A convergent synthesis of the ribosyl-diazepanone core of liposidomycins, new nucleoside antibiotics, has been carried out *via* enantiomerically pure epoxide and α-ribosyl aminoacid, chiral key intermediates obtained from L-ascorbic acid and D-ribose, respectively.

After our preliminary results[1] concerning the synthesis of the diazepanone core of liposidomycins, new nucleoside antibiotics involved in inhibition of bacterial peptidoglycan synthesis,[2] which demonstrated the relevance of our synthetic approach, we next turned our attention to the access to enantiopure ribosyl-diazepanone:



The two proposed key steps are the regiospecific nucleophilic opening of a chiral epoxide by the amino group of an α-ribosyl aminoacid for the $N_{1'}$-$C_{7'}$ bond creation and cyclization by a peptidic coupling reaction at the origin of the lactam ($C_{3'}$-$N_{4'}$ bond).

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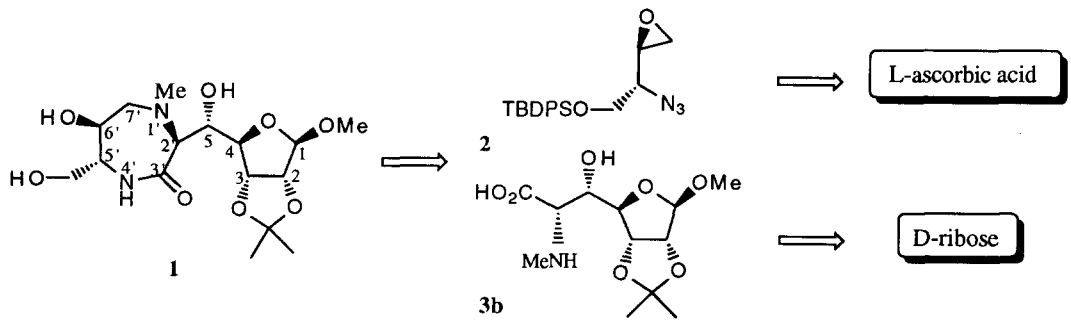
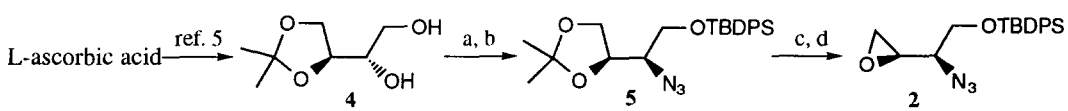
If a few approaches to the 1,4-diazepan-3-one ring have been described,[1,3] only one stereoselective synthesis of a 2-ribosyl-3,4,5,6-tetrahydro-2*H*-1,4-diazepin-3-one was carried out.[4] The absolute and relative configurations at C_5, $C_{2'}$, $C_{5'}$ and $C_{6'}$ are still unkown. However according to Ubukata and coll.,[4] NMR data suggested a 5*S*,2'*S* configuration. Furthermore, concerning $C_{5'}$ and $C_{6'}$, comparison of coupling constants obtained by Knapp and coll.[3a] for *cis* and *trans* 5,6-disubstituted-1,4-diazepan-3-ones (J = 2.2 and 5.2 Hz, respectively) with that mentioned for the uridinyl-diazepanone (J = 4.8 Hz),[2c] obtained by methanolysis of liposidomycins B and C, seems to be in favor of a *trans* relative configuration for the natural product. In the light of these stereochemical considerations and taking the hypothesis that the biosynthetic route to liposidomycins involves naturally occurring aminoacids, we postulated that the absolute configuration of chiral centers of the target molecule and that of the key synthons was as indicated below :



Enantiomerically pure (2*R*,3*R*)-3-azido-4-*tert*-butyldiphenylsilyloxy-1,2-epoxybutane **2** was prepared from L-ascorbic acid (Scheme 1). Selective protection of the primary alcohol function of the diol **4**[5] as its TBDPS derivative cleanly occurred and was followed by introduction of the azido group with total inversion of configuration in two steps: first, activation of the secondary alcohol as its triflate derivative and then nucleophilic substitution by tetramethylguanidinium azide (TMGA)[6] which afforded the azide **5** (81% yield). Acidic hydrolysis of the acetonide was followed by Mitsunobu reaction (triphenylphosphine-diisopropyl azodicarboxylate) on the resulting diol to yield the azido epoxide **2** (51%).

Scheme 1

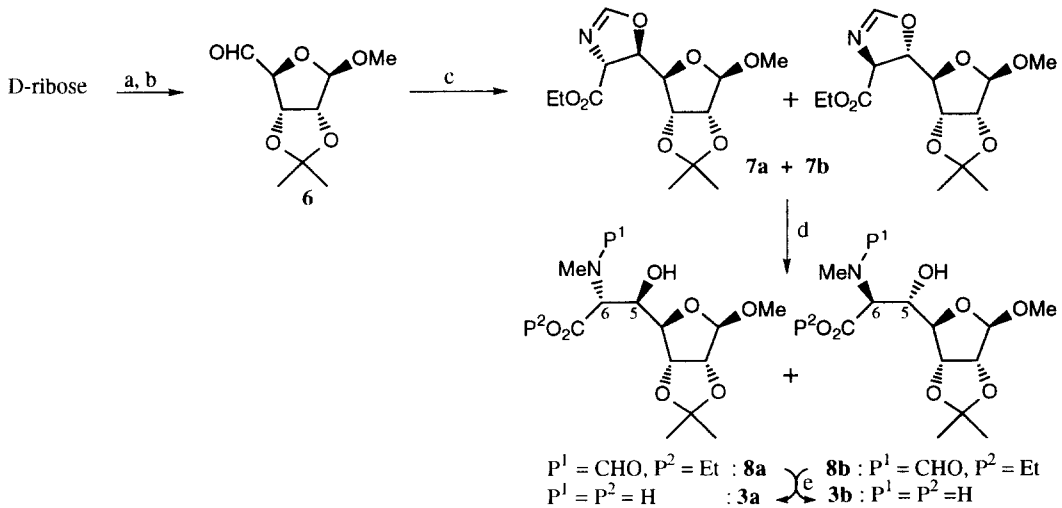


a) TBDPSCl, ImH, DMF, 97%. b) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78°C then TMGA excess -78°C to 20°C, 81%. c) TFA, H_2O,THF, 0°C, 65%. d) PPh_3, DIAD, 130°C, 0.01 mmHg, 79%.

The key step of the α-ribosyl aminoacid synthesis (Scheme 2) was the diastereoselective condensation of ethyl isocyanoacetate on enantiomerically pure aldehyde **6** obtained from D-ribose. The obtention of the oxazoline intermediates which can be isomerized into the thermodynamically more stable *trans* isomers should ensure the major formation of the *threo* isomers.[7] Thus, the hygroscopic aldehyde **6** was prepared in 48% overall yield through the protection of both anomeric hydroxyl and secondary alcohol functions according to Leonard and coll.[8] followed by oxidation of the primary alcohol function under Moffat conditions.[9] As expected, condensation of ethyl isocyanoacetate on aldehyde **6** in THF in the presence of triethylamine led to a 7:3 mixture of *trans* oxazolines **7a** and **7b** ($^3J_{4,5}$ = 5.2 and 7.2 Hz, respectively).[10] The corresponding *N*-methyl formamides **8a** and

8b (*ratio* 7:3, respect.) were then obtained in 76% overall yield by successive treatment with a solution of trimethyloxonium tetrafluoroborate in dichloromethane and hydrolysis with an aqueous solution of sodium hydrogenocarbonate.[11] Basic hydrolysis with 2N aqueous KOH afforded α-ribosyl aminoacids **3a** and **3b**[12] in 50% yield after purification and separation by silica gel flash chromatography. Absolute configuration at the newly created chiral center C_6 of both diastereomeric aminoacids was determined by the Cotton effect,[13] and that of C_5 was then deduced from the *trans* relation observed in oxazolines **7a** and **7b**. Thus the major isomer **3a** was revealed to be 5*R*,6*R* and the minor one, **3b**, 5*S*,6*S* which corresponds to that of the supposed natural product.

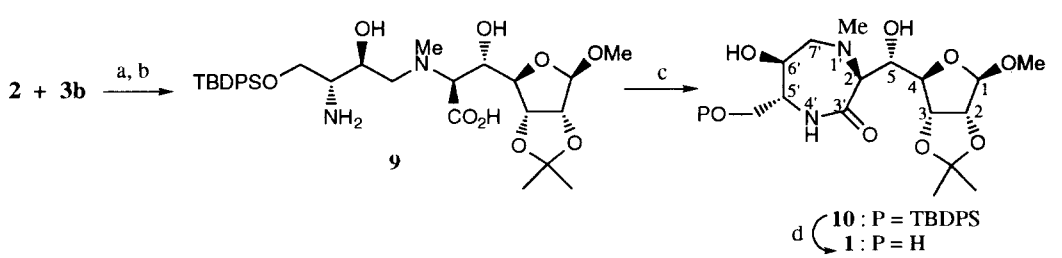
Scheme 2



a) $Me_2C(OMe)_2$, Me_2CO, MeOH, HCl_g, 75%. b) *i*. DMSO, DCC, pyridine, H_3PO_4, *ii*. $(CO_2H)_2$, 60%. c) $CNCH_2CO_2Et$, Et_3N, THF. d) *i*. Me_3OBF_4,CH_2Cl_2, *ii*. $NaHCO_3$aq., 76% from **6**. e) 2N aqueous KOH, 80°C, 50%.

Access to the ribosyl diazepanone **1** (Scheme 3) required first condensation of the ribosyl aminoacid **3b** on to the epoxide **2** which cleanly occurred in the presence of sodium *tert*-butanolate at 100°C for 48 h and was followed by reduction of the azide in the presence of palladium on charcoal in methanol to afford the amine **9** (65% overall yield). Intramolecular peptidic coupling with an excess of DCC[3c] in CH_2Cl_2 at 0°C led to the expected lactam **10** (35% isolated yield) which was then desilylated to give the target ribosyl diazepanone **1**.[14]

Scheme 3



a) *t*BuOH, NaH, 48h, 100°C. b) H_2, Pd/C 10%, MeOH, 65%. c) DCC excess, CH_2Cl_2, 0°C, 15h, 35%. d) TBAF, THF.

In conclusion, this convergent synthesis offers a rapid access to the 2-ribosyl-1,4-diazepan-3-one encountered in liposidomycins through regiospecific opening of an homochiral epoxide obtained from L-ascorbic acid by an enantiopure ribosyl aminoacid prepared from D-ribose. Work is in progress to improve the reaction conditions of the ribosyl aminoacid preparation, as well as to disclose other strategies for its synthesis.

An interesting feature of the way proposed is that starting from either L-ascorbic or D-isoascorbic acids, various configurations are easily available for the epoxide synthon, in case the retained configuration for the diazepanone moiety did not happen to be the natural one, other absolute configurations at $C_{5'}$,$C_{6'}$ could be readily accessible.

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10 (a) Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn* **1973**, *46*, 3308-3310. (b) Schmidt, U.; Siegel, W. *Tetrahedron Lett.* **1983**, *28*, 2849-2852.
11 Togni, A.; Pastor, S.D.; Rihs, G. *Helv. Chim. Acta* **1989**, *72*, 1471-1478.
12 Selected physical data of **3b** : $[\alpha]_D$ -14 (c 1.0, NaOH 0.1N); ^1H NMR (250 MHz, D_2O) 5.17(s, 1H, H_1), 5.03(d, 1H, $J_{3,2}$ 6.0, H_3), 4.84(d, 1H, $J_{2,3}$ 6.0, H_2), 4.25(d, 1H, $J_{4,5}$ 10.1, H_4), 4.17(dd, 1H, $J_{5,4}$ 10.1, $J_{5,6}$ 2.3, H_5), 3.76(d, 1H, $J_{6,5}$ 2.3, H_6), 3.49(s, 3H, OMe), 2.85(s, 3H, NMe), 1.58, 1.44(2s, 6H, CMe_2); ^{13}C NMR (63 MHz, D_2O) 172.5(C_7), 116.1(CMe_2), 112.2(C_1), 88.7, 87.1, 84.6(C_{2-4}), 71.5(C_5), 67.4(C_6), 58.8(OMe), 34.5(NMe), 28.2, 26.7(CMe_2); c.d. data (c 3.10^{-3} M, 20°C, H_2O) : $\Delta\varepsilon$ (235) 0, (215) +0.37, (210) +0.90, (196) +2.17, (190) +1.50; HRMS (FAB$^+$) calcd for $C_{12}H_{22}O_7N$: 292.1396, found : 292.1394.
13 Legrand, M.; Viennet, R. *Bull. Soc. Chim. Fr.* **1965**, 679-681. **3a** and **3b** respectively exhibited a positive[12] and a negative Cotton effect (**3b** : c.d. data (c 3.10^{-3} M, 20°C, H_2O) : $\Delta\varepsilon$ (235) 0, (215) -1.16, (210) -1.64, (196) -2.65, (190) -2.47).
14 Selected physical data of **1** : $[\alpha]_D$ -3 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, CD_3OD) 4.92(s, 1H, H_1), 4.90(d, 1H, $J_{3,2}$ 6.2, H_3), 4.59(d, 1H, $J_{2,3}$ 6.2, H_2), 4.23(d, 1H, $J_{4,5}$ 9.2, H_4), 4.10(ddd, 1H, $J_{5',6'}$ 9, $J_{5',CHOH}$ 5, $J_{5',CH'OH}$ 3.3, $H_{5'}$), 3.93(dd, 1H, $J_{5,4}$ 9.2, $J_{5,2'}$ 2.2, H_5), 3.81-3.70(m, 3H, J_{CHOH} -11, $J_{CHOH,5'}$ 5, $J_{CH'OH,5'}$ 3.3, CH_2OH, $H_{6'}$), 3.44(d, 1H, $J_{2',5}$ 2.2, $H_{2'}$), 3.37(s, 3H, OMe), 3.01(dd, 1H, $J_{7'b,7'a}$ -15, $J_{7'b,6'}$ 3.3, $H_{7'b}$), 2.90(dd, 1H, $J_{7'a,7'b}$ -15, $J_{7'a,6'}$ 3.5, $H_{7'a}$), 2.46(s, 3H, NMe), 1.43,1.30(2s, 6H, CMe_2); ^{13}C NMR (126 MHz, CD_3OD) 175.7 ($C_{3'}$), 113.3(CMe_2), 111.6(C_1), 88.5(C_4), 86.6(C_2), 83.3(C_3), 75.9($C_{2'}$), 72.7(C_5), 69.7($C_{6'}$), 61.4(CH_2OH), 61.3($C_{7'}$), 56.9($C_{5'}$), 56.5(OMe), 44.6(NMe), 26.8, 25.2(CMe_2); HRMS (FAB$^+$) calcd for $C_{16}H_{29}O_8N_2$: 377.1924, found : 377.1933.