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Stereocontrolled Entry to Negamycin from D-Glucose

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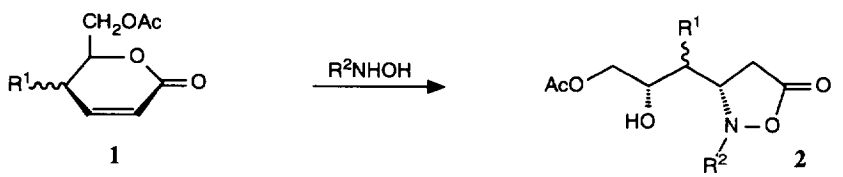
Abstract: Conjugate addition-rearrangement of N-benzylhydroxy-lamine to lactone **6** provides isoxazolidin-5-one **7** which was in turn mesylated at the hydroxy group and subjected to the next skeleton rearrangement to afford 3,5-disubstituted isoxazolidine **10**. Standard transformation of **10** gave negamycin lactone **4**.

Recently we have reported that conjugate addition-rearrangement of *N*-substituted hydroxylamines to enlactones **1** proceeded exclusively *anti* to the terminal acetoxymethyl group, while axial location of the entering hydroxylamine caused opening of the six-membered lactone ring by the *N*-hydroxy group to afford isoxazolidin-5-one derivatives **2**[1,2] (Scheme). Rapid formation of the isoxazolidin-5-one ring eliminates the problem of easy retro-addition which has limited the use of azide anion or *O*-benzyl-hydroxylamine in these reactions.[3] Compounds **2** have been shown to be attractive substrates for the synthesis of carbapenem antibiotics.[2,4]

Scheme



1 **2**

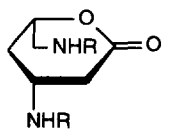
R^1= H, OAc R^2= Alkyl, Benzyl

Liberation of the 5-OH group of the sugar chain, while all other groups remain protected, is a consequence of the isoxazolidin-5-one ring formation. This creates a unique possibility to switch from the D-configurational series of sugars to those of the L-series. The stereochemistry of the conjugate addition-rearrangement, together with inversion of configuration at the C-5 carbon atom, provides a very attractive entry to important 3-amino-3-deoxy sugars which have the amino function and the terminal C-6 carbon atom *cis* - located, such as components of anthracycline antibiotic daunosamine and acosamine,[5] or negamycin

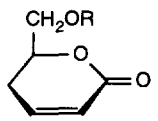
lactone **3**, the latter being the main - fragment of the antibiotic negamycin.[6]

In the present studies we exemplified this idea by synthesis of *N*, *N*-diacetyl-negamycin lactone **4**. The significant activity of negamycin has stimulated considerable interest in the synthesis of this antibiotic in both racemic[7,8] and enantiomerically pure form.[8,9]

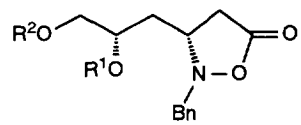
Lactone **5**[2,10] was hydrolyzed[10] and subsequently silylated to afford **6**.[11] Treatment of **6** with *N*-benzylhydroxylamine (1.1 equiv.) in anhydrous ethanol at room temp. for 1 h furnished D-erythro compound **7** which was mesylated (standard conditions) to give **8** in 70% yield. The structure and configuration of **9**[11], obtained from **5** by sequential desilylation and acetylation, was proved by X-ray analysis.[12]



3: R= H
4: R= Ac



5: R= Ac
6: R= *t*-$BuPh_2Si$

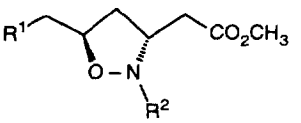


7: R^1= H, R^2= *t*-$BuPh_2Si$
8: R^1= Ms, R^2= *t*-$BuPh_2Si$
9: R^1= Ms, R^2= Ac

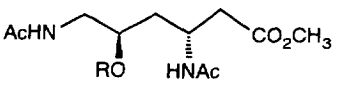
Compound **8** (1 mmol) dissolved in anhydrous methanol was slowly treated at room temp. with anhydrous K_2CO_3 (1 equiv.). After disappearance of the substrate (TLC), the solution was filtered through Florisil, evaporated and purified by chromatography to afford the methyl ester **10**[11] in 59% yield. The silyl protecting group was subsequently removed with tetrabutylammonium fluoride and the liberated hydroxyl group was mesylated to afford **11**. The mesyl group in **11**[11] was displaced using sodium azide in DMF at 60°C for 24 h, affording **12**[11] in 77% yield. Esters **10-12** thus prepared, displayed similar analytical and spectroscopic data to related izoxazolidine derivatives obtained in another way.[8] The L-threo (trans) configuration of **14**[11] was proved by NOE measurements.

Catalytic hydrogenation of **12** [H_2, 10% Pd/C, acetic acid-acetic anhydride (4:1) mixture, 2 h, 41%] resulted in reduction of the azide group, *N*-deprotection of the isoxazolidine ring and acetylation of both nitrogen atoms to give **13**.[11]

Hydrogenolysis of **13**[11] (Ni/Ra, MeOH, 0.5 h) resulted in N-O bond cleavage to give the (3R, 5R) δ-hydroxy-β-lysine derivative **15**, characterized as triacetate **16**.[11] Lactonization of **15** in acetic acid in the presence of catalytic amounts of p-TsOH afforded negamycin lactone *N*,*N*-diacetate **4**[11].



10: R^1= O*t*-BuPh$_2$Si, R^2= Bn
11: R^1= OMs, R^2= Bn
12: R^1= N_3, R^2= Bn
13: R^1= NHAc, R^2= Ac
14: R^1= OAc, R^2= Bn



15: R= H
16: R= Ac

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11. Selected spectral and analytical data:
6: $[\alpha]_D$ -49.5° (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 1.07 (s, 9H, *t*-Bu), 2.33-2.69 (m, 2H, H-5, 5'), 3.84 (d, 2H, CH_2O-), 4.01 (m, 1H, H-6), 6.01 (m, 1H, H-3), 6.89 (m, 1H, H-4). Found: C, 71.9; H, 7.2. $C_{22}H_{26}O_3Si$ requires C, 72.09; H, 7.15.

8: $[\alpha]_D$ -71.8° (*c* 1.7, CH_2Cl_2); ^1H NMR ($CDCl_3$): 1.06 (s, 9H, *t*-Bu), 1.78-2.12 (m, 2H, H-4,4'), 2.45, 2.74 (2 dd, 2H, H-2, 2'), 2.93 (s, 3H, Ms), 3.55 (m, 1H, H-3), 3.70 (d, 2H, H-6,6'), 4.09 (s, 2H, Bn), 4.65 (m, 1H, H-5). Found: C, 63.2; H, 6.8; N, 2.6. $C_{30}H_{37}NO_6SSi$ requires C, 63.46; H, 6.57; N, 2.47.

9: mp. 89-90°C; $[\alpha]_D$ -74.5° (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$): 1.84, 2.07 (2 x ddd, 2H, H-4,4'), 2.09 (s, 3H, Ac), 2.50, 3.02 (2 x dd, 2H, H-2,2'), 3.03 (s, 3H, Ms), 3.65 (m, 1H, H-3), 4.02, 4.21 (2 x dd, 2H, H-6,6'), 4.17 (2 x d, 2H, Bn), 4.85 (m, 1H, H-5). Found: C, 51.7; H, 5.9; N, 3.8. $C_{16}H_{21}NO_7S$ requires C, 51.74; H, 5.70; N, 3.77.

10: $[\alpha]_D$ +43.0° (*c* 0.6, CH_2Cl_2); ^1H NMR ($CDCl_3$): 1.07 (s, 9H, *t*-Bu), 2.08 (m, 1H, H-4), 2.37-2.67 (m, 3H, H-2,2'4'), 3.44 (m, 1H, H-3), 3.66 (s, 3H, OCH_3), 3.62-3.82 (m, 2H, H-6,6'), 3.90, 3.97 (2d, 2H, Bn), 4.21 (m, 1H, H-5). Found: C, 71.3; H, 7.6; N, 2.6. $C_{30}H_{37}NO_4Si$ requires C, 71.53; H, 7.40; N, 2.78.

11: $[\alpha]$ +66.5° (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): 2.21, 2.38 (2 m, 2H, H-3,3'), 2.47, 2.61 (2 dd, 2H, H-2,2'), 2.91 (s, 3H, Ms), 3.44 (bs, 1H, H-3), 3.67 (s, 3H, OCH_3), 3.92, 3.98 (2 d, 2H, Bn), 4.25-4.36 (m, 3H, H-5,6,6'). Found: C, 52.6; H, 6.3; N, 3.9. $C_{15}H_{21}NO_6S$ requires C, 52.47; H, 6.16; N, 4.08.

12: $[\alpha]_D$ +51.8° (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$): 2.15, 2.38 (2 m, 2H, H-3,3'), 2.45, 2.59 (2 dd, 2H, H-2,2'), 3.27, 3.42 (2 dd, 2H, H-6,6'), 3.40 (m, 1H, H-3), 3.67 (s, 3H, OCH_3), 3.94, 3.99 (2d, 2H, Bn), 4.23 (m, 1H, H-5). Found: C, 58.2; H, 6.0; N, 19.2. $C_{14}H_{18}N_4O_3$ requires C, 57.92; H, 6.25; N, 19.30.

13: mp. 110-112°C; $[\alpha]_D$ +32.5 (*c* 0.5, CH_2Cl_2); ^1H NMR ($CDCl_3$): 2.02, 2.13 (2 s, 6H, 2 Ac), 2.25 (m, 2H, H-4,4'), 2.50, 2.93 (2 m, 2H, H-2,2'), 3.18, 3.55 (2 bm, 2H, H-6,6'), 4.44 (m, 1H, H-3), 4.67 (m, 1H, H-5). Found: C, 51.2; H, 7.1; N, 11.0. $C_{11}H_{18}N_2O_5$ requires C, 51.15; N, 7.02; N, 10.85.

14: $[\alpha]_D$ +62.0° (*c* 1, CH_2Cl_2), ^1H NMR ($CDCl_3$): 2.08 (s, 3H, Ac), 2.16, 2.32 (2m, 2H, H-4,4'), 2.44, 2.55, (2 x dd, 2H, H-2,2'), 3.41 (m, 1H, H-3), 3.65 (s, 3H, OMe), 3.94, 3.99 (2 x d, 2H, Bn), 4.11, 4.21 (2 x dd, 2H, H-6,6'Z), 4.29 (m, 1H, H-5). Found: C, 62.2; H, 7.0; N, 4.5. $C_{16}H_{21}NO_5$ requires C, 62.53; H, 6.89; N, 4.56.

16: $[\alpha]_D$ -5.3° (*c* 1.0, MeOH); ^1H NMR (D_2O): 1.73, 1.90 (2 m, 2H, H-4,4'), 1.93, 1.96, 2.09 (3 s, 9H, 3 Ac), 2.50, 2.64 (2 dd, 2H, H-2,2'), 3.27, 3.41 (2 dd, 2H, H-6,6'), 3.69 (s, 3H, OCH_3), 4.27 (m, 1H, H-3), 5.03 (m, 1H, H-5). Found: C, 51.4; H, 7.5; N, 9.1. $C_{13}H_{22}N_2O_6$ requires C, 51.63; H, 7.33; N, 9.27.

4: mp. 182-185°C, lit.[9a] 183-185°C; $[\alpha]_D$ -6.2° (*c* 1.2, H_2O), lit.[9a] -5.8° (*c* 1.0, H_2O); ^1H NMR (pyridine -d_5, 90°C): 1.77 (ddd, 1H, *J* 10.9, 11.5, 13.6 Hz, H-4), 2.00, 2.02 (2s, 6H, 2 Ac), 2.43 (m, 1H, *J* 1.3, 2.8, 5.2, 13.6 Hz, H-4'), 2.66 (dd, 1H, *J* 8.6, 17.1 Hz, H-2), 3.15 (ddd, 1H, *J* 1.3, 6.6, 17.1 Hz, H-2'), 3.56 (dt, 1H, *J* 6.0, 6.0, 14.0 Hz, H-6), 3.69 (ddd, 1H, 4.3, 6.0, 14.0 Hz, H-6'), 4.53-4.66 (m, 2H, H-3.5), 8.23, 8.33 (2bs, 2H, 2NH). Found: C, 52.5; H, 7.3; N, 11.95. $C_{10}H_{16}N_2O_4$ requires C, 52.62; N, 7.07; N, 12.27.

12. Jurczak, M.; Socha, D.; Urbańczyk-Lipkowska, Z.; Chmielewski, M. unpublished results.

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