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Stereocontrolled introduction of an amino group at C-6 of D-galactose via (3,3)-sigmatropic rearrangements — novel synthesis of lincosamine and 7-*epi*-lincosamine precursors

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Abstract

A new and stereoselective route to the aminoglycoside components of the antibiotics lincomycin and clindamycin is presented. The key step involves diastereoselective introduction of the amino group at C-6 of D-galactose by (3,3)-sigmatropic rearrangements of the corresponding allylic (*Z*)-trifluoroacetimidate and (*Z*)- and (*E*)-allylic thiocyanates. Epoxidation of the resulting trifluoroacetamide with *m*-CPBA led to the epoxide with high *threo*-selectivity. © 2000 Elsevier Science Ltd. All rights reserved.

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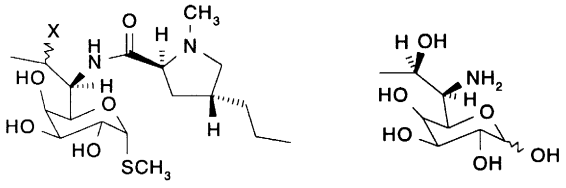
Lincomycin **1** and the semi-synthetic 7-chloro analogue clindamycin **2** are commercial antibiotics used against bacterial infections in humans and animals.[1] Synthetic work on the preparation of **1** and **2** has mainly been focused on lincosamine (**3**), i.e. the carbohydrate moiety of lincomycin (Fig. 1). Synthesis of **3**[2] entailed the stereocontrolled construction of the pyranose ring using furan-based chemistry[3] or hetero Diels–Alder cycloaddition.[4] Syntheses starting from *myo*-inositol[5] or D-threonine[6] have also



1, X = (*R*)-OH
2, X = (*S*)-Cl

3

Fig. 1.

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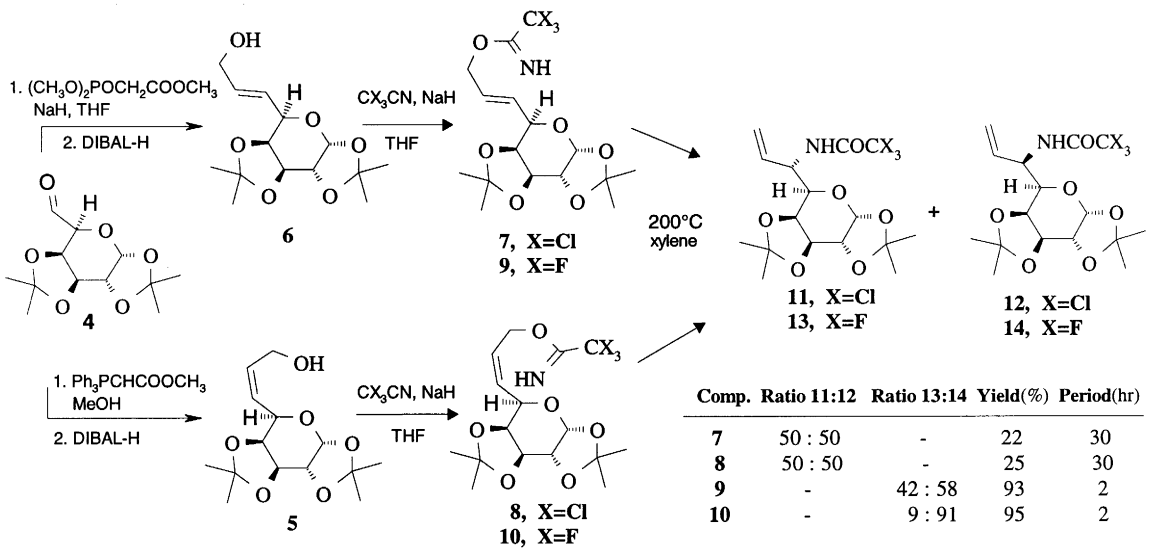
been reported. An alternative approach[7] towards the preparation of **3** comprises a chain-extension of D-galactopyranose, illustrating the very hindered nature of C-6 and the difficulty of introducing the amino group at this position stereoselectively. An elegant solution to this problem has been independently presented by Stick[8] and Knapp[9] and recently by van Delft.[10]

This paper concerns a simple approach to introducing a nitrogen atom at C-6 of galactose, stereoselectively via aza-Claisen rearrangements of trifluoroacetimidates and thiocyanates and subsequent diastereoselective epoxidation of the resulting double-bonds leading to 7,8-anhydro-6-deoxy-6-trifluoroacetamide-1,2:3,4-di-*O*-isopropylidene-D-*threo*-D-*galacto*-octopyranose **18** as a useful lincosamine and 7-*epi*-lincosamine precursor. This methodology was previously used for the stereoselective synthesis of the (+)-polyoxamic acid,[11] thymine polyoxin C[12] and 5′-branched 5′-aminoribonucleoside derivatives.[13]

The starting (*Z*)- and (*E*)-allylic imidates **7**, **8**, **9**, and **10** were synthesized from the 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexaldioaldo-1,5-pyranose **4** by the route shown in Scheme 1. The Wittig olefination of **4** with $Ph_3P{=}CHCOOCH_3$ in MeOH and reduction of the resulting ester with DIBAL-H led selectively to the (*Z*)-allylic alcohol **5**.[14] Side-chain elongation of the dialdose **4** with $(CH_3O)_2POCH_2COOCH_3$/NaH in THF and reaction of the (*E*)-ester using DIBAL-H afforded the (*E*)-allylic alcohol **6**, selectively. Subsequently, **5** was converted to the (*Z*)-trichloroacetimidate **8** and (*Z*)-trifluoroacetimidate **10** by reaction with CCl_3CN/NaH and CF_3CN/NaH (diethyl ether, 0°C), respectively. The imidates (*E*)-**7** and (*E*)-**9** were prepared from (*E*)-allylic alcohol **6** (Scheme 1). The crude imidates were purified by flash chromatography (SiO_2, diethyl ether:hexane=50:50).

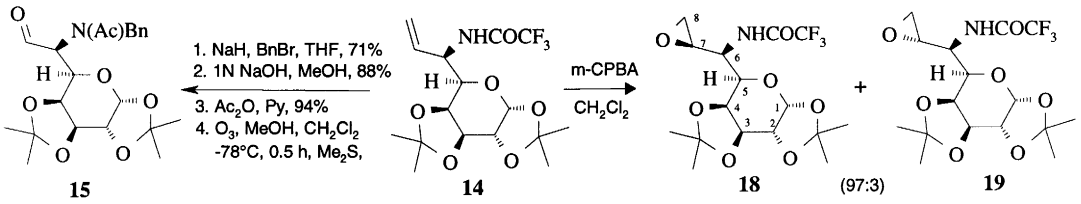


Comp.	Ratio 11:12	Ratio 13:14	Yield(%)	Period(hr)
7	50 : 50	-	22	30
8	50 : 50	-	25	30
9	-	42 : 58	93	2
10	-	9 : 91	95	2

Scheme 1.

Thermal rearrangement of the trichloroacetimidates (*E*)-**7** and (*Z*)-**8** (in xylene at 200°C, 30 h) takes place with decomposition and gave the trichloroacetamides **11** and **12** obtained as a mixture (50:50) in low yields (22 and 25%) (Scheme 1). In contrast, thermolysis (2 h, 200°C) of the (*E*)-trifluoroacetimidate **9** afforded a 42:58 mixture of the trifluoroacetamides **13** and **14** in 93% yield. Finally, rearrangement of the (*Z*)-trifluoroacetimidate **10** gave the trifluoroacetamides **13** and **14** with good stereoselectivity (**13**:**14**=9:91) and yield (95%) (Scheme 1). The (3,3)-sigmatropic rearrangement of allylic imidates can often be accelerated by the use of metal catalysis, particularly by the Hg(II) and Pd(II) species.[15] However, despite repeated attempts, no rearrangement was observed when **7**–**10** were exposed to such

catalysts. These negative results can be compared with literature data.[16] The resulting product **14**† was then transformed into the α-aminoaldehyde **15** (Scheme 2) which is a precursor of lincosamine (**3**).[2] We found that epoxidation of **14** with *m*-CPBA in CH_2Cl_2 (2 days at RT) led to the epoxide **18**‡ with high *threo*-selectivity[17] (**18**:**19**=97:3) (Scheme 2).



Scheme 2.

The configurations of the newly introduced stereocenters at C-6 and C-7 in **18** were established by X-ray analysis (Fig. 2), thus confirming the configurations at C-6 and C-7 as (*R*).

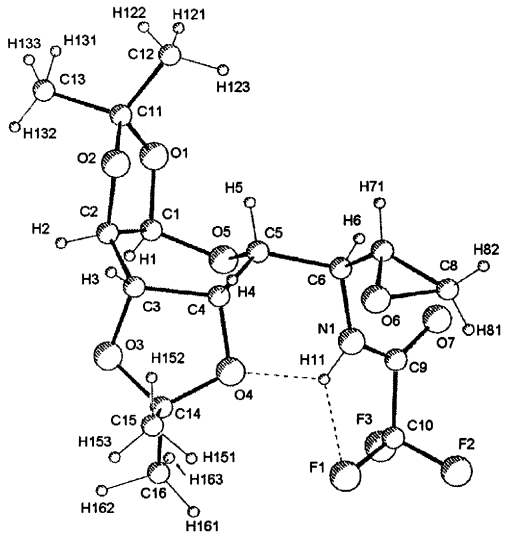
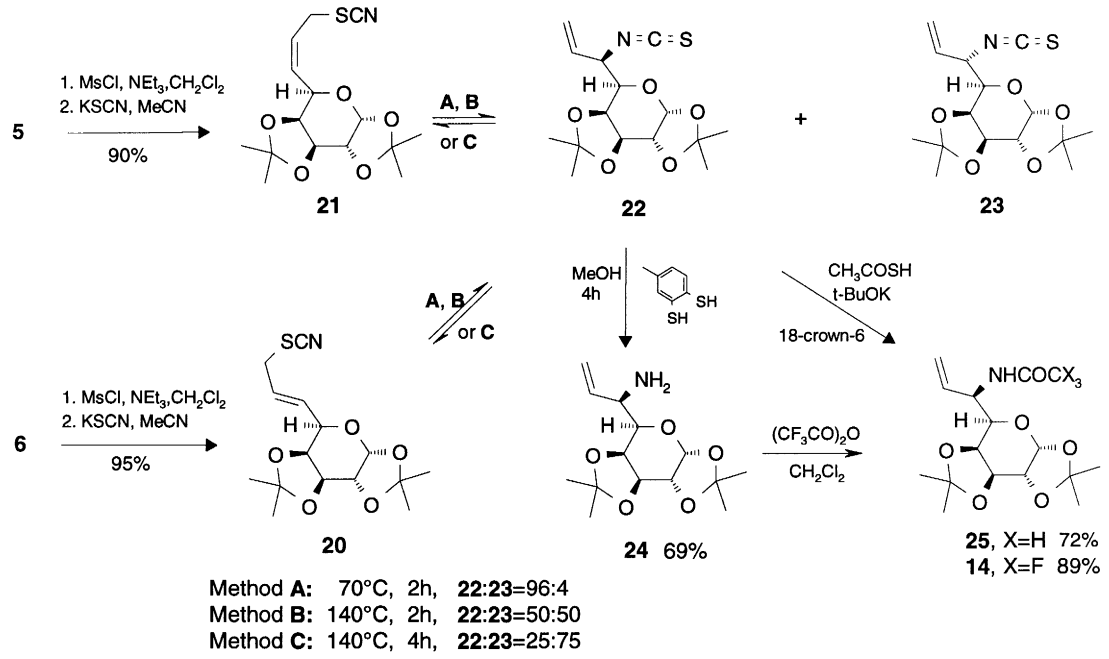


Fig. 2. ORTEP diagram of epoxide **18** showing crystallographic numbering

† All compounds showed ^{1}H, ^{13}C, IR, and HRMS spectra consistent with the reported structures. Spectroscopic data of **14**: ^{1}H NMR data (500 MHz, $CDCl_3$): 1.33 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.86 (1H, dd, H5, $J_{5,4}$=1.8 Hz, $J_{5,6}$=4.7 Hz), 4.32 (1H, dd, H2, $J_{2,1}$=5.1 Hz, $J_{2,3}$=2.3 Hz), 4.42 (1H, dd, H4, $J_{4,3}$=8.1 Hz, $J_{4,5}$=1.8 Hz), 4.61 (1H, dd, H3, $J_{3,2}$=2.3 Hz, $J_{3,4}$=8.1 Hz), 4.79 (1H, m, H6), 5.32 (1H, ddd, H8a, $J_{8a,8b}$=1.7 Hz, $J_{8a,7}$=10.4 Hz, $J_{8a,6}$=0.8 Hz), 5.35 (1H, ddd, H8b, $J_{8b,8a}$=1.7 Hz, $J_{8b,7}$=17.4 Hz, $J_{8b,6}$=0.8 Hz), 5.55 (1H, d, H1, $J_{1,2}$=5.1 Hz), 5.81 (1H, ddd, H7, $J_{7,8a}$=10.4 Hz, $J_{7,8b}$=17.4 Hz, $J_{7,6}$=5.9 Hz), 8.06 (1H, bd, N–H, *J*=0.8); ^{13}C NMR data (125.7 MHz, $CDCl_3$): 23.80 (CH_3), 24.77 (CH_3), 25.45 (CH_3), 26.03 (CH_3), 54.71 (C-6), 65.88 (C-2), 70.28 (C-4), 70.94 (C-4), 71.69 (C-5), 96.64 (C-1), 108.80 ($C(CH_3)_2$), 109.73 ($C(CH_3)_2$), 116.02 (CF_3), 118.39 (C-8), 132.15 (C-7), 156.72 (*C*=O).

‡ Spectroscopic data of **18**: ^{1}H NMR data (500 MHz, $CDCl_3$): 1.34 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.52 (3H, s, CH_3), 2.54 (1H, dd, H8b, $J_{8b,8a}$=4.5 Hz, $J_{8b,7}$=2.6 Hz), 2.80 (1H, dd, H8a, $J_{8a,8b}$=4.5 Hz, $J_{8a,7}$=4.0 Hz), 3.28 (1H, dt, H7, $J_{7,8a}$=4.0 Hz, $J_{7,8b}$=2.6 Hz, $J_{7,6}$=2.4 Hz), 4.04 (1H, dd, H5, $J_{5,6}$=4.7 Hz, $J_{5,4}$=1.7 Hz), 4.34 (1H, dd, H2, $J_{2,1}$=4.9 Hz, $J_{2,3}$=2.3 Hz), 4.52 (1H, dd, H4, $J_{4,3}$=8.1 Hz, $J_{4,5}$=1.7 Hz), 4.55 (1H, ddd, H6, $J_{6,5}$=4.7 Hz, $J_{6,7}$=2.4 Hz, $J_{6,NH}$=8.6 Hz), 4.65 (1H, dd, H3, $J_{3,2}$=2.3 Hz, $J_{3,4}$=8.1 Hz), 5.55 (1H, d, H1, $J_{1,2}$=4.9 Hz), 7.49 (1H, bd, N*H*, *J*=8.6 Hz); ^{13}C NMR data (125.7 MHz, $CDCl_3$): 23.98 (CH_3), 24.80 (CH_3), 25.53 (CH_3), 26.05 (CH_3), 43.80 (C-8), 49.92 (C-7), 51.11 (C-6), 66.42 (C-2), 70.44 (C-3), 70.90 (C-4), 72.23 (C-5), 96.57 (C-1), 108.90 ($C(CH_3)_2$), 109.85 ($C(CH_3)_2$), 116.0 (CF_3), 157.43 (*C*=O).

With the aim of examining similar methodology for the introduction of nitrogen functionality into the 6-position of galactose, we investigated the rearrangement of the allylic thiocyanates **20** and **21** (Scheme 3). The starting thiocyanates **20** and **21** were prepared by S_N2 displacement of the *O*-mesyl group in the corresponding mesylates derived from the (*E*)-allylic alcohol **6** and the (*Z*)-allylic alcohol **5** by the thiocyanate group (KSCN, CH_3CN, rt, 0.5 h). Thermal rearrangement of the thiocyanates **20** and **21** was carried out at 80°C in xylene under N_2 for 2 h to give a high yield of isothiocyanates **22** and **23** (95% for **20**, 90% for **21**) and good stereoselectivity (**16**:**17**=96:4, in both cases) (Scheme 3). The rearrangement thiocyanate→isothiocyanate is reversible and ratios of isothiocyanates **22** and **23** are time and temperature dependent. We found that heating the thiocyanates **20** and **21** in xylene at 140°C for 2 h gave mixtures of the isothiocyanates **22** and **23** in 50:50 ratio; heating for 16 h at the same temperature led to a mixture of **22** and **23** in a 25:75 ratio. Reaction of **22** with thioacetic acid[18] (1.3 mol) and *t*-BuOK (0.2 mol) in the presence 18-crown-6-ether in THF at 60°C (4 h) gave 6-acetamido-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-oct-6-enopyranose **25**. The absolute configuration at C-6 in **22** was unambiguously determined by chemical transformations (Scheme 3). Thus, the reaction of the isothiocyanate **22** with toluene-3,4-dithiol in $MeOH/H_2O$ led to the amine **24** in 69% yield which, after reaction with $(CF_3CO)_2O/NEt_3$ in CH_2Cl_2, afforded trifluoroacetamide **14** in 89% yield. This compound is in all respects identical with **14** prepared from **10** (Scheme 3).



Scheme 3.

Acknowledgements

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