Pergamon

Tetrahedron Letters 42 (2001) 4401–4404

TETRAHEDRON LETTERS

Stereoselective synthesis of the 5′-aminofuranoside part of polyoxins via (3,3)-sigmatropic rearrangement of allylic thiocyanates

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Received 5 February 2001; accepted 2 May 2001

Abstract—A new and stereoselective route for the synthesis of the benzyl 5-(*R*)-*N*-Cbz-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-6-enfuranoside **5e** and 5-(*R*)-*N*-acetyl-5,6-dideoxy-1,3-*O*-isopropylidene-β-D-*ribo*-hept-6-enfuranoside **12** as useful protected precursors of the 5′-aminofuranoside part of polyoxins is presented. The key-step involves diastereoselective introduction of the amino group at C-5 of the ribose and xylose by (3,3)-sigmatropic rearrangements of the corresponding allylic thiocyanates.

The polyoxins are a class of pyrimidine nucleoside peptide antibiotics that were first isolated from *Streptomyces cacaoi* var *asoensis* over 30 years ago.[1] Polyoxins and closely related compounds such as nikkomycins (Fig. 1), display significant activity against phytopathogenic fungi[2] and are ineffective against other microorganisms, plants or animals.[3] Since 1970, with the first published synthesis[4] of the sugar component of the nucleoside portion of the polyoxins, the synthesis of polyoxin C,[5] polyoxin L,[6] polyoxin J,[7] and/or fragments of the polyoxins[8] have been undertaken by various groups.

This paper concerns a simple approach to the stereoselective introduction of a nitrogen atom at C-5 of ribose and xylose via aza-Claisen rearrangements of thiocyanates leading to benzyl 5-(*R*)-*N*-Cbz-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-6-enfuranoside **5e** and 5-(*R*)-*N*-acetyl-5,6-dideoxy-1,3-*O*-isopropylidene-β-D-*ribo*-hept-6-enfuranoside **12**, useful protected precursors of the 5′-aminofuranoside part of polyoxins. Analogous methodology was previously used for the stereoselective synthesis of thymine polyoxin C,[9] polyoxamic acid,[10] lincosamine precursors[11] and branched-chain amino sugars.[12] Overman's thermal rearrangement of trichloro- and trifluoroacetimidates derived from uridine led only to an inseparable mixture of isomers.[13]

The starting thiocyanates **2a–e** were prepared by S_N2 displacement of the *O*-mesyl group of the corresponding mesylates derived from *trans*-allylic alcohols[13,14] **1a–e** by thiocyanate ($KSCN/CH_3CN$) (Scheme 1). The thermal rearrangements of the thiocyanates **2a–e** were carried out at 70–80°C in benzene under N_2 for 1.5–5 h to give good yields of the isothiocyanates **3a–e** and **4a–e** (61–80%). Excellent stereoselectivity was observed for the rearrangement of **2e** (**4e**:**3e** = 98:2) (Scheme 1, Table 1). The absolute configuration at C-5 in **4e** was unambiguously determined by chemical tranformations. Thus, reaction of the isothiocyanate **4e** with toluene-3,4-dithiol[15] in $MeOH/H_2O$ led to the corresponding

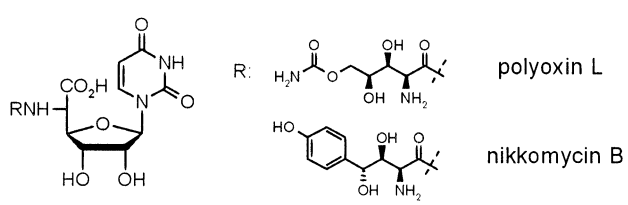

Figure 1.

Keywords: rearrangements; polyoxins; diastereoselection; thiocyanates.
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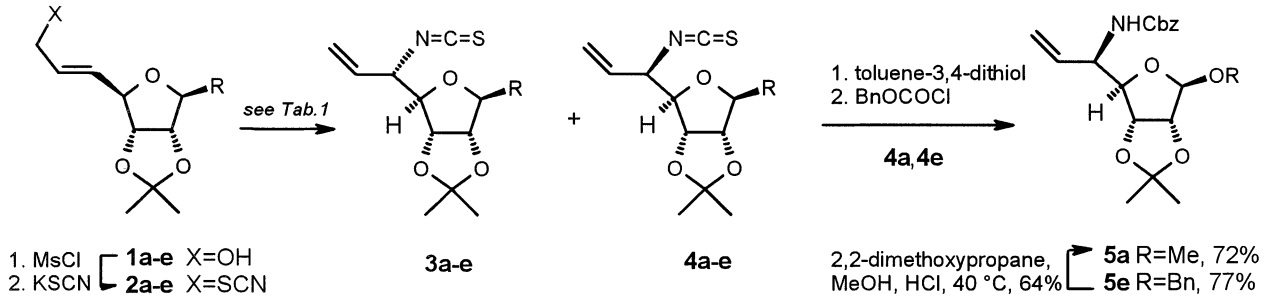
PII: S0040-4039(01)00735-3

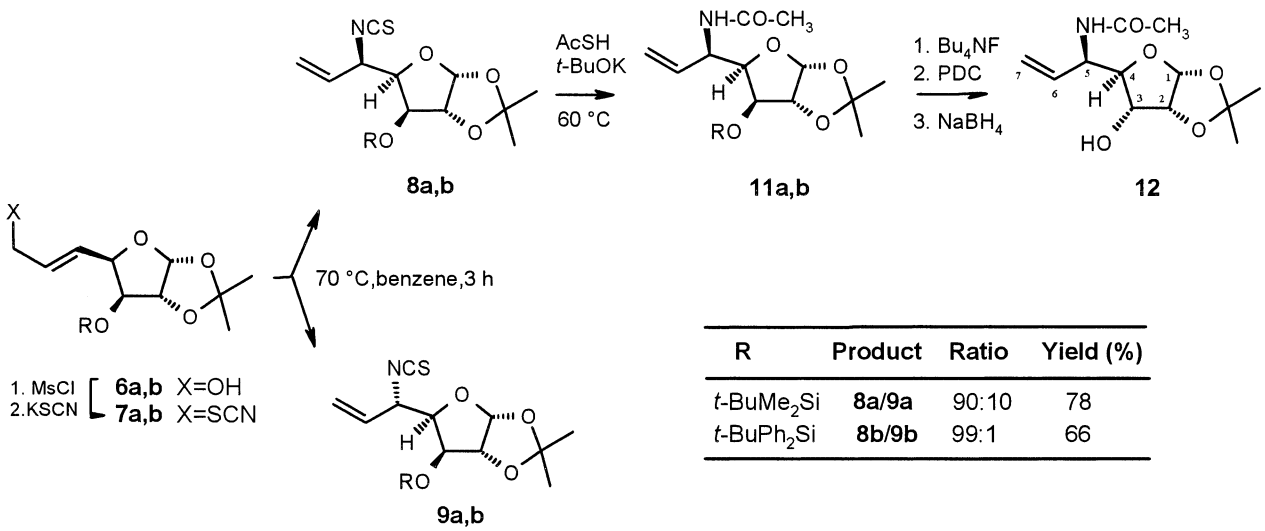


Scheme 1.

Table 1. Isothiocyanates **3a**–**e** and **4a**–**e** produced via Scheme 1

Entry	Educt	Products	R	Conditions (°C, h)	Ratio[a]	Yield (%)
1	**2a**	**4a**/**3a**	OCH_3	Benzene (80, 1.5)	72:28	68
2	**2b**	**4b**/**3b**	$OCH_2{=}CH_2$	Benzene (70, 2)	75:25	71
3	**2c**[b]	**4c**/**3c**	O-2-THP	Benzene (70, 4)	81:19	78
4	**2d**	**4d**/**3d**	1-Uridyl	Xylene (70, 5)	60:40	61
5	**2e**	**4e**/**3e**	OBn	Xylene (70, 4)	98:2	80

[a] Determined by ^{1}H NMR.
[b] Mixture of the diastereoisomers.



R	Product	Ratio	Yield (%)
t-$BuMe_2Si$	**8a**/**9a**	90:10	78
t-$BuPh_2Si$	**8b**/**9b**	99:1	66

Scheme 2.

amine which, after reaction with BnOCOCl in CH_2Cl_2, afforded the amide **5e** (77%). Heating **5e** with 2,2-dimethoxypropane/HCl in acetone/MeOH at 60°C for 24 h gave **5a** (64% from **4e**). Spectroscopic data for **5a**[†] (having the 5-(*R*) configuration) are identical with recently published results.[14]

A second approach was examined simultaneously and was based on the stereoselective introduction of an amino group at C-5 of xylose with a bulky substituent at C-3 as chiral selector. The allylic alcohols[13,16] **6a**,**b** were converted to thiocyanates **7a**,**b** in an analogous manner to **1a**–**e** (Scheme 2). The thermal rearrangement of thiocyanates **7a**,**b** was carried out at 70°C in benzene under N_2 for 3 h to give a mixture of isothiocyanates **8a**/**9a** and **8b**/**9b** with very good stereoselectivities (Scheme 2). Reaction of **9a** and **9b** with thioacetic acid (1.3 mol) and *t*-BuOK (0.2 mol) in the presence of 18-crown-6 in THF at 60°C (4 h) gave **11a** (76%) and **11b** (82%). The configuration of the newly introduced stereocenter at C-5 in **11a** was established by X-ray analysis[17] (Fig. 2), thus confirming the configuration at C-5 as (*R*). Inversion of the *xylo*-configuration at C-3

[†] All compounds showed ^{1}H, ^{13}C, IR and HRMS spectra consistent with the reported structures. Spectroscopic data of **5e**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.45 (s, 3H), 3.33 (s, 3H), 3.99 (dd, 1H, J=1.1, 9.4 Hz), 4.29 (dd, 1H, J=5.6, 9.8 Hz), 4.59 (d, 1H, J=4.9 Hz), 4.74 (d, 1H, J=4.9 Hz), 4.97 (br s, 1H), 4.99 (s, 1H), 5.11 (dd, 1H, J=4.7, 17 Hz), 5.24 (dd, 1H, J=1, 4.7 Hz), 5.27 (d, 1H, J=11.4 Hz), 5.95 (m, 1H), 7.25–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 25.0, 26.4, 55.0, 55.4, 66.9, 88.8, 109.7, 112.6, 116.8, 126.9, 12765, 128.0, 128.1, 128.4, 135.3, 136.2, 155.9. $[\alpha]_D^{22}=-12$ (*c* 0.19, $CHCl_3$). Mp 80–82°C.

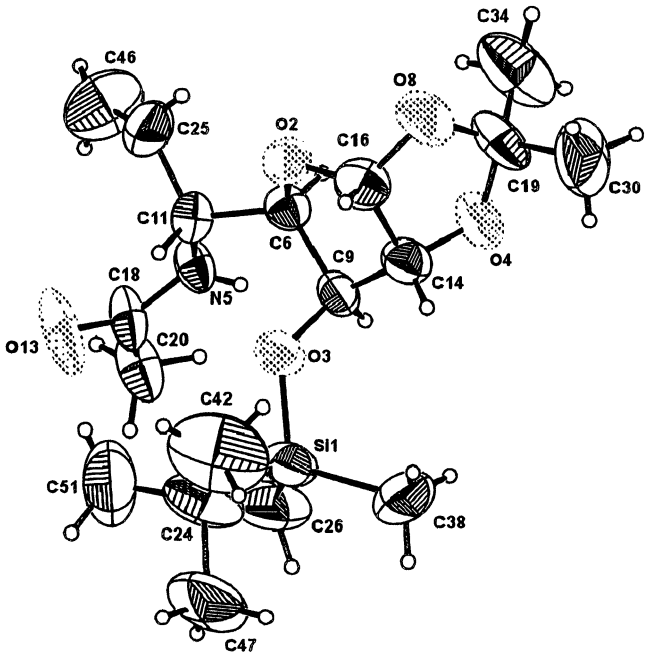


Figure 2. ORTEP diagram of **11a** showing crystallographic numbering.

in **11a**,**b** to the *ribo*-configuration in **12**‡ was accomplished by a series of functional group manipulations: (1) selective removal TBDMS group with Bu_4NF in MeCN (93 and 94%); (2) oxidation of the 3-OH group with PDC (Ac_2O, CH_2Cl_2, 76%); (3) $NaBH_4$ reduction in CH_3OH (90%).

In conclusion, a stereoselective synthesis of the 5′-aminofuranoside part of polyoxins has been accomplished via (3,3)-sigmatropic rearrangement of ribose- and xylose-derived allylic thiocyanates.

Acknowledgements

The present work was supported by a Grant Agency (1/6080/99) from the Ministry of Education, Slovak Republic.

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‡ Spectroscopic data of **12**: ^1H NMR (500 MHz, $CDCl_3$): 1.37, 1.57 (6H, 2×s, 2×CH_3), 2.01 (3H, s, NHCOCH_3), 3.83 (1H, dd, H-4, $J_{3,4}=8.7$ Hz, $J_{4,5}=3.6$ Hz), 3.86 (1H, bdd, H-3, $J_{3,4}=8.7$ Hz, $J_{2,3}=4.7$ Hz), 4.55 (1H, dd, H-2, $J_{1,2}=3.9$ Hz, $J_{2,3}=4.7$ Hz), 4.74 (1H, m, H-5), 5.28 (1H, dt, H-7a, $J_{5,7a}=1.2$ Hz, $J_{6,7a}=10.3$ Hz, $J_{7a,7b}=1.2$ Hz), 5.35 (1H, dt, H-7b, $J_{5,7b}=1.3$ Hz, $J_{6,7b}=17.3$ Hz, $J_{7a,7b}=1.2$ Hz), 5.77 (1H, ddd, H-6, $J_{5,6}=7.4$ Hz, $J_{6,7a}=10.3$ Hz, $J_{6,7b}=17.3$ Hz), 5.78 (1H, d, H-1, $J_{1,2}=3.9$ Hz), 5.88 (1H, bd, N*H*COCH$_3$, $J_{5,NH}=8.5$ Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta=$ 23.23 (NHCO*C*H$_3$), 26.11, 26.80 (-C(*C*H$_3$)$_2$), 49.80 (C-5), 73.91, 82.71, 84.27 (C-2, C-3, C-4), 105.12 (C-1), 111.55 (*C*(CH$_3$)$_2$), 117.41 (C-7), 134.81 (C-6), 171.80 (NH*C*OCH$_3$).

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17. Single-crystal X-ray diffraction: **11a**: Empirical formula $C_{18}H_{33}NO_5Si$, Mw 371.55, orthorhombic, space group $P2_12_12_1$ (no. 19), $a=9.069(7)$, $b=9.376(11)$, $c=28.140(9)$ Å, $V=2392.7(2)$ Å^3, $Z=4$, $D_c=1.026$ cm^{-3}, $F(000)=800$. A colorless plate-like crystal of the dimensions 0.5×0.3×0.15 mm (from acetone/hexane) was measured at 293(2) K on CAD4 diffractometer with graphite-monochromated Mo Kα radiation ($\lambda=0.71073$ Å). Absorption was neglected ($\mu=0.124$ mm^{-1}). The cell parameters were determined from 23 reflections in the 12–13° θ range. The intensities variation of 3%. Of 3363 measured reflections, 3354 were unique ($R_{int}=0.026$) and 2932 were regarded as 'observed' according to the $I\geq 2\delta$ (I) criterion. Data treatment: the structure was solved by direct methods (SHELX-86) and refined by SHELXL-93 using a full-matrix least-squares procedure based on F^2. Hydrogen atoms were refined isotropically, all other atoms anisotropically. Convergence for observed reflections and 332 parameters was achieved at $R=0.0312$, $R_w=0.0831$, GOF = 1.040, $(\Delta/\delta)_{max}=\pm 0.001$. The final difference electron density map was featureless with extreme values of 0.30; −0.16 e Å^{-3}.