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Synthesis of α-Azido Aldehydes. Stereoselective Formal Access to the Immunosuppressant Myriocin.

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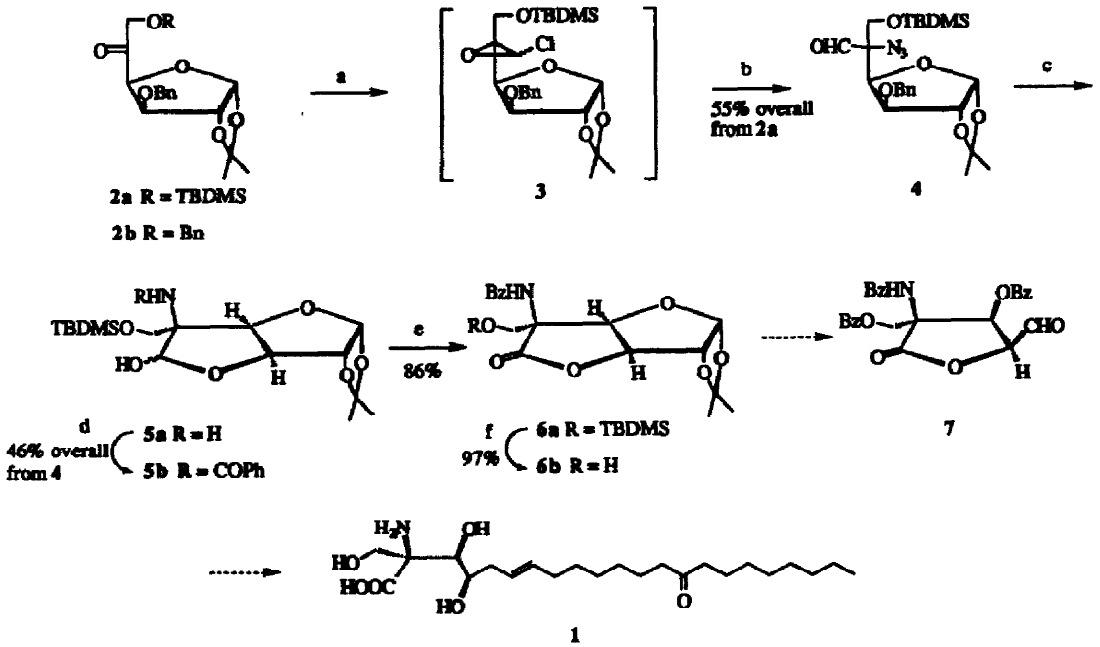
Abstract: *Stereoselective preparation of an acyclic α–azido aldehyde permitted access in a few steps to a key intermediate in a formal synthesis of myriocin.*

The metabolite myriocin, isolated in 1972 from the thermophilic fungus *Myriococcum albomyces*, was shown to exhibit a potent immunosuppressive activity[1]. Very recent biological results revealed that myriocin **1** (thermozymocidin) was almost two order of magnitude more efficient than cyclosporine A[2,3]. In view of these findings, myriocin is being considered as a candidate for clinical applications[4].

The first total synthesis of myriocin, reported more than ten years ago[5,6], was accomplished with poor diastereoselectivity, due to a Strecker reaction-based strategy in forming the crucial α,α-disubstituted amino nitrile precursor. A subsequent, very elegant formal synthesis of myriocin **1**, using Pd(0) catalysed cis-hydroxyamination of a carbohydrate derived vinyl epoxide, as its key step, was also disclosed[7]. However, in this scheme, the transformation of **2a**[8] into the intermediate **6b** required 13 steps[7]. In this letter, we report the stereoselective conversion of **2a** into **6b** in only 6 steps (overall yield 21%) making optically active myriocin synthetically more readily available.

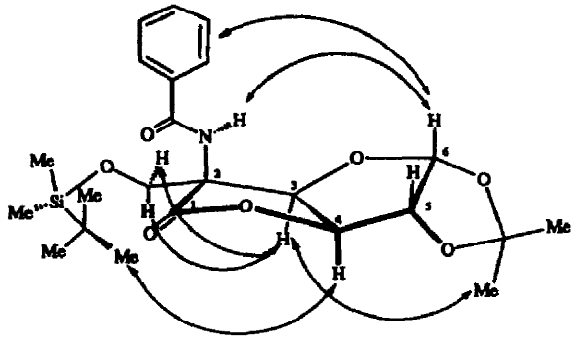
A few years ago, we have shown that Darzens condensation, in the presence of potassium t-butoxide, of some carbohydrate ketones with chloromethyl p-tolylsulfone gave stereospecifically α,β-epoxy sulfones[9]. In the presence of azide ion, the latter afforded branched-chain functionalized azido-sugars[9]. The same reaction sequence on ketones **2a** and **2b** led only to rapid decomposition. However, treatment of **2a** with dichloromethyllithium, as described by Sato and al.[10,11], afforded α,β-epoxy chlorides **3** which, without isolation, in the presence of azide ion furnished cleanly, by SN_2 reaction at the β-carbon relative to the chlorine, the key α-azido aldehyde **4** $[\alpha]_D$ - 25 (c 1.03, $CHCl_3$) of (S)-configuration (55% overall yield)[12]. A similar sequence from ketone **2b**[13] gave two α-azido aldehydes (2 : 1) isomeric at C-5.

Hydrogenolysis of **4** (Pd-C, H_2, EtOH, 3 bars) was followed by benzoylation of the intermediate **5a** leading to **5b** as a mixture of two anomers (46% from **4**). Swern oxidation of **5b** gave the lactone **6a** (86%)



a) LDA/THF, -78°C then CH_2Cl_2 (4 eq.) and 2a (1 eq.)/THF, -78°C to r.t. b) NaN_3 (10 eq.), DMPU (5 eq.), 15 crown-5 ether (0.1 eq.), 70°C; c) H_2 Pd/C (3 bars) /EtOH abs.; d) BzO_2/MeOH, r.t.; e) Swern oxdn; f) TBAF (2 eq.) /THF.

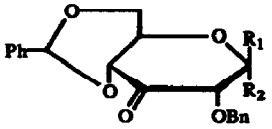
$[\alpha]_D$ + 32 (c 0.72 , $CHCl_3$), whose configuration at C-2 was ascertained by a 400 MHz NOESY experiment[14] (Figure).



FIGURE

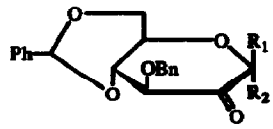
Desilylation ($NBu_4^+ F^-$, 97%) of **6a** afforded **6b**, $[\alpha]_D$ + 33 (c 1.0, $CHCl_3$); lit[7]. $[\alpha]_D$ + 19 (c 0.3, $CHCl_3$)[15]. The ^1H NMR spectrum of **6b** exhibits chemical shifts and coupling constants identical with its reported spectrum[7]. Rama Rao et al.[7] have described the transformation of lactone **6b** into aldehyde **7** which had already been converted into myriocin **1**[6]. Thus, the present work can be considered as a relatively short, stereoselective formal synthesis of myriocin **1** .

In our earlier investigations[9], the method using chloromethyl p-tolylsulfone followed by azide ion treatment revealed far from general in preparing branched-chain azido-sugars. For instance, treatment of ketone **8**[16] led only to decomposition and ketone **11**[17] gave only the elimination product **12** $[\alpha]_D$ + 33 (c 0.74, $CHCl_3$).



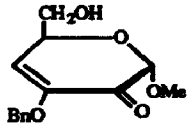
8 R_1 = OMe ; R_2 = H

9 R_1 = H ; R_2 = OMe



10 R_1 = OMe ; R_2 = H

11 R_1 = H ; R_2 = OMe



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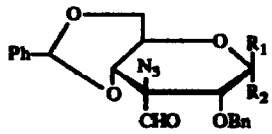
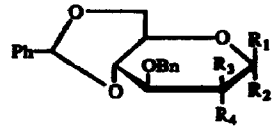


13 R_1 = OMe ; R_2 = H

14 R_1 = H ; R_2 = OMe



15 R_1 = OMe ; R_2 = H; R_3 = CHO ; R_4 = N_3

16 R_1 = H ; R_2 = OMe R_3 = N_3 ; R_4 = CHO

In view of the good results obtained on ulose **2a** when applying Sato's procedure[10,11], four carbohydrate ketones **8**[16], **9**[18], **10**[19] and **11**[17] were reacted with dichloromethyllithium and the crude reaction products were treated with azide nucleophile. The following α-azido aldehydes were obtained, respectively, as the only isomers : **13** (52%) $[\alpha]_D$ - 54 (c 0.98, $CHCl_3$),**14** (50%) $[\alpha]_D$ - 22 (c 1.03, $CHCl_3$), **15** (46%) $[\alpha]_D$ - 119 (c 1.03, $CHCl_3$),**16** (54%) $[\alpha]_D$ + 43 (c 0.95, $CHCl_3$). Compound **15**, whose absolute configuration at C-2 is identical to that in the α,α-disubstituted amino acid **1**, appears to be a further candidate as starting material for an enantioselective synthesis of myriocin and its analogues. The configuration at the quaternary carbon was easy to determine by ^{13}C NMR spectroscopy as described[9], only in case of **14**. For all the branched-chain sugars the structures were unambiguously ascertained by means of nOe results by selective irradiation of the respective aldehyde protons and inspection of the behaviour of the neighboring hydrogen atoms.

The new branched-chain α-azido aldehydes may prove to be highly useful synthons for the enantioselective synthesis of a variety of biologically important α,α-disubstituted amino acids[20].

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12. Compound **4** : ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H, CHO), 7.42-7.28 (m, 5H, Ph), 6.00 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.66 and 4.45 (2d, 2H, J_{gem} = 11.7 Hz, OCH_2Ph), 4.64 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-2), 4.49 and 4.05 (2d, 2H, $J_{3,4}$ = 3.8 Hz, H-3 and H-4), 4.07 and 3.90 (2d, 2H, J_{gem} = 10.8Hz, 2H-6), 1.47 and 1.34 [2s, 6H, $C(CH_3)_2$], 0.86 [s, 9H, $SiC(CH_3)_3$], 0.03 and 0.01 [2s, 6H, $Si(CH_3)_2$]; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.7 (CHO), 136.4, 128.7 128.3 (Ph), 112.5 [$C(CH_3)_2$], 105.1 (C-1), 82.1, 82.1 and 81.0 (C-2, -3, -4), 72.3 OCH_2Ph), 71.6 (C-5), 64.2 (C-6), 27.0 and 26.6 [$C(CH_3)_2$], 25.7 [$SiC(CH_3)_3$], 18.1 [$C(CH_3)_2$], - 5.6 $Si(CH_3)_2$.

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14. It has been reported (Hauser, F. M.; Adams, Jr, T. C. *J. Org. Chem.* **1984**, *49*, 2296-2297.) (see also ref. 7) that Grignard reactions on ketone **2a** proceeds via a stereoselective approach giving alcohols of (S)-configuration in agreement with our findings in the reaction with dichloromethyllithium.

15. No explanation is advanced for the discrepancy between our and the reported $[\alpha]_D$ value for **6b**. The ^{1}H-^{1}H NMR NOESY experiment on our compound **6b** revealed a reversed signal assignment for H-3 and H-4 relative to the signal attribution proposed earlier[7]. Compound **6b** : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.38 (m, 5H, Ph), 6.79 (s, 1H, NH), 5.92 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-6), 5.27 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-3), 5.07 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-4), 4.86 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-5), 4.43 (m, 1H, OH), 4.15 and 3.91 (2d, 2H, J_{gem} = 11.4 Hz, CH_2), 1.50 and 1.33 [2s, 6H, $C(CH_3)_2$]; Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found : C, 58.58; H, 5.43; N, 3.94.

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