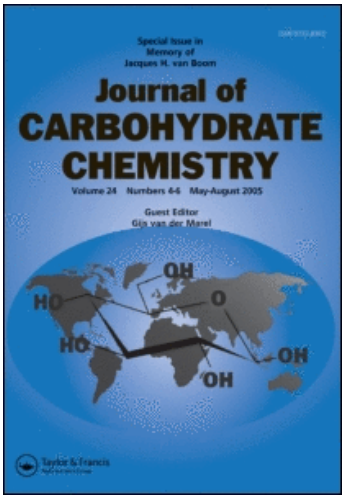

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A Totally Synthetic Route to Enantiomerically Pure D and L-Aminooctoses: Stereocontrolled Synthesis of Methyl α-D-Lincosaminide

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COMMUNICATION

A TOTALLY SYNTHETIC ROUTE TO ENANTIOMERICALLY PURE D AND L-AMINOOCTOSES: STEREOCONTROLLED SYNTHESIS OF METHYL α-D-LINCOSAMINIDE[1]

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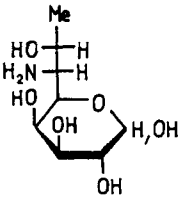
A general method for the stereoselective synthesis of monosaccharides from furan compounds has provided a route to higher-carbon sugars with defined relative configuration of the side chain and the pyranose ring.[2] For the synthesis of enantiomerically pure 6-amino-6,8-dideoxy-octoses, of which an antibiotic sugar lincosamine[3] (1) is a notable representative, substituted furans of the type 2 with defined absolute configu-



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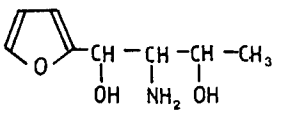

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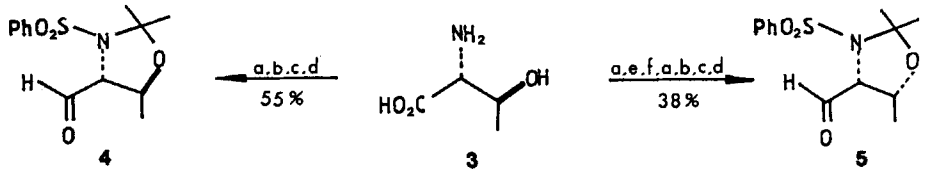
ration are required. Compounds 2 could be obtained by the addition of furan to the appropriate four-carbon chiral synthons,[4] e.g., α-aminoaldehydes. Various *N*-protected α-aminoaldehydes prepared[5] from natural amino acids are extensively used[6] as chiral building blocks for the asymmetric synthesis of

Scheme 1. a. MeOH, SOCl2, reflux; b. PhSO2Cl, NEt3; c. Me2C(OMe)2, Me2CO, *p*-toluenesulfonic acid; d. DIBAL, toluene, -70 °C; e. PhCOCl, NEt3; f. SOCl2, room temp., then 10% HCl, reflux.

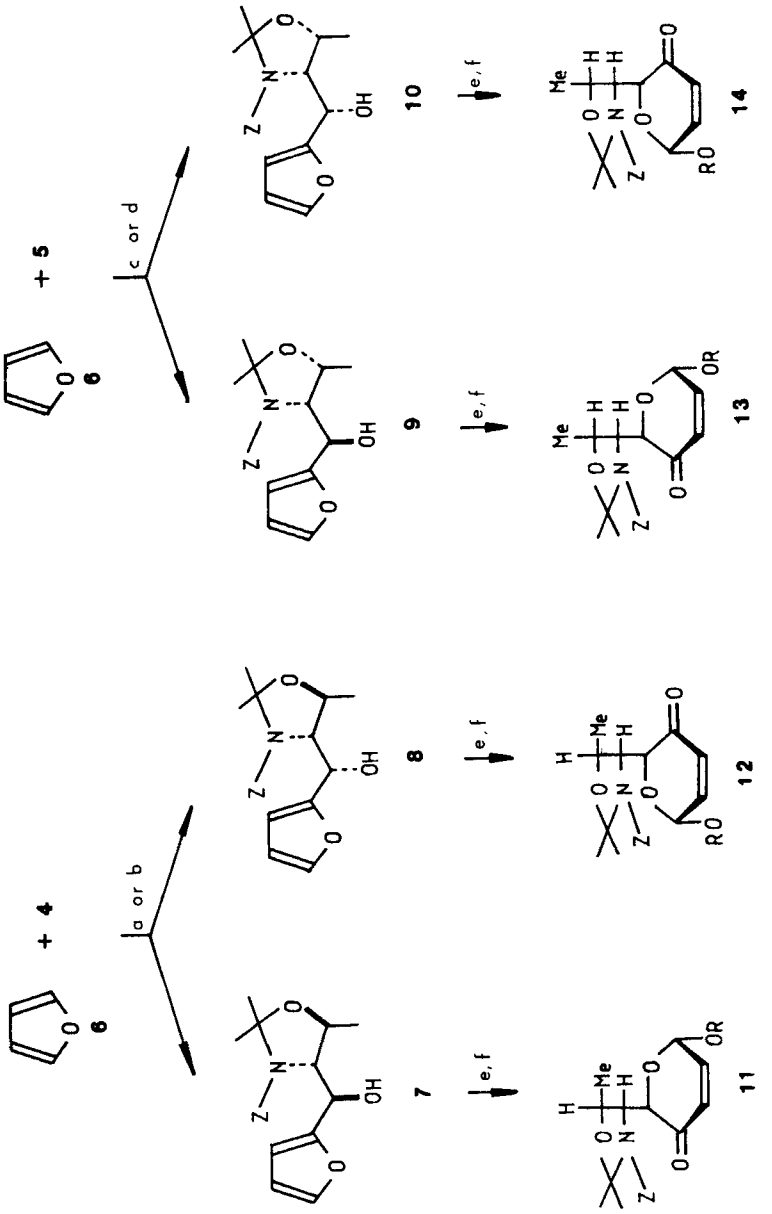


complex molecules. Recently, high diastereoselectivities have been reported for the reactions of *N*- or *N,O*-protected alaninals and serinals with different reagents,[7] including 2-trimethylsilyloxyfuran[8] and furyllithium.[9] From these studies it appeared that the diastereoselectivity of the addition depended mostly on the protecting groups of the α-aminoaldehyde. Now we report on the addition of furyllithium to *N*-benzenesulfonyl-*N,O*-isopropylidene derivatives of D-threoninal 4 and D-allothreoninal 5 which provides an access to enantiomerically pure 2-amino-1-(2-furyl)butan-1,3-diols 7 - 10 (Scheme 2). Availability of these compounds opens a route to the synthesis of aminooctoses of the D or L series in optically pure form.[2] The method is demonstrated by the total synthesis of methyl α-D-lincosaminide, the sugar moiety of the commercial antibiotic lincomycin.[3]

N-Benzenesulfonyl-*N,O*-isopropylidene-D-threoninal (4) and D-allothreoninal (5) were obtained from D-threonine (3) (Scheme 1) as stable solids which could be stored in the refrigerator for months without epimerization or decomposition.

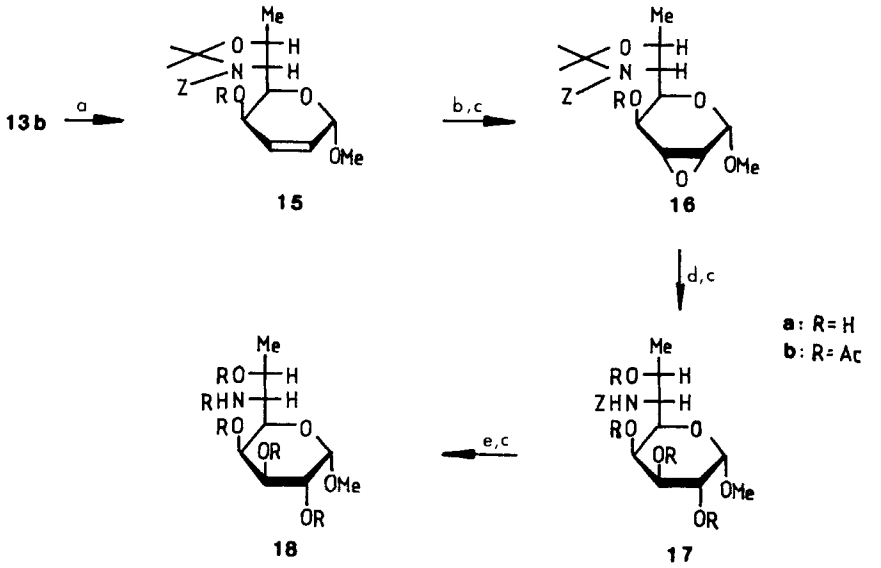
In the reaction of D-threoninal 4 with furyllithium (6) (Scheme 2) a fair diastereocontrol was achieved. In ether solution *anti*-addition product 7 predominated, presumably due to the nonchelation control of the reaction,[10] whereas in the presence of chelating agent ($ZnBr_2$) the direction of asymmetric induction was reversed, resulting in predominance of the *syn*-addition product 8.

Addition of 6 to D-allothreoninal (5) was less amenable to stereocontrol manipulation. Whereas reaction conditions for high selectivity of *syn*-addition (10) were worked out successfully (9:10 = 7:93), the *anti*-addition product 9 was obtained in only slight excess (9:10 = 55:45). The configuration of the new stereogenic centre (C-1) in compounds 7 - 10 was established from the ^1H NMR spectra of the respective 1,3-dioxanes.



Scheme 2. a. $ZnBr_2$ (1 eq), ether, 0 °C to room temp., 78%, 7:8 = 15:85; b. ether, -70 °C, 90%, 7:8 = 80:20; c. THF/hexane, ether, -70 °C, 85%, 9:10 = 55:45; d. glyme, -70 °C, 89%, 9:10 = 7:93; e. m-Cl-C_6H_4-CO_3H, CH_2Cl_2, room temp., 98%; f. MeI, Ag_2O, ether, room temp., 79%.

Scheme 3. a. $NaBH_4$ (1.5 eq.), $CeCl_3$ (1.5 eq.), room temp., 15 min., 65%; b. 60% H_2O_2, MeCN, room temp., 45 h, 95%; c. acetic anhyd. - pyridine, DMAP; d. $HClO_4$, H_2O/THF, 40 °C, 24 h; e. Na/NH_3, -70 °C to room temp., 89% (from **16b**).



Flash column chromatography afforded pure 2-amino-1-(2-furyl)butan-1,3-diols **7** - **10** which were oxidized and then methylated to give the methyl *α*-ulosides **11b** - **14b**, respectively, (small quantities of *β*-anomers were removed by crystallization), the immediate chiral substrates for the synthesis of enantiomerically pure aminooctoses of the D and L-series. The feasibility of the method and the effect of the *N*-benzenesulfonyl and *N,O*-isopropylidene protecting groups on the steric course of the functional groups manipulation in the dihydropyran moiety is shown by the transformation of **13b** into methyl *α*-D-lincosaminide (**18a**) (Scheme 3).

Reduction of the carbonyl group in **13b** with sodium borohydride gave, in sharp contrast to the chemo- and stereoselectivity observed for other methyl *α*-ulosides[11] the *threo* alcohol **15** as a major product (65%) accompanied (26 %) by the saturated alcohol, also with the *threo* configuration. The steric course of the reduction, fortuitously suitable for the elaboration of the lincosamine moiety, resulted from the steric hindrance exerted by the *N*-benzenesulfonyl group. This group prevented the approach of the hydride from the stereoelectronically favoured *β*-side (axial attack, prevailing for other *α*-ulosides[11]) of the dihydropyran ring. The shielding of

the β-face of the C-4 carbonyl group not only reversed the steric course of the reduction but also affected chemoselectivity. The rate of the 1,4-addition became comparable to that of the 1,2-addition leading to a substantial amount of the double bond reduction product. Steric shielding of the dihydropyran β-side was advantageous also in the next step of the synthesis. Thus, epoxidation of alcohol 15 gave exclusively the *gulo* epoxide 16a. Acetylation and then acidic opening of the oxirane ring with concomitant removal of the isopropylidene group led to 17a which was characterized as its tetraacetate 17b. Removal of the *O*-acetyl and *N*-benzenesulfonyl groups gave methyl α-D-lincosaminide (18a), which on acetylation afforded methyl *N*,2,3,4,7-pentaacetyl-α-D-lincosaminide (18b), in 20% overall yield from 5,[12] m p 193-194.5 ^{0}C, $[\alpha]_{D}$ +151.2^{0}. The ^{1}H NMR spectral data from 18b was in full accord with the published data.[13]

Since the synthesis of D-allothreonine by means of asymmetric Sharpless epoxidation has been recently reported[14] the present contribution describes the first totally synthetic route to the enantiomerically pure lincosamine (1) as well as a general approach to D- and L-aminooctoses.

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12. All new compounds were chromatographically homogeneous and gave elemental analyses and/or high resolution mass spectra as well as IR and ^{1}H NMR spectroscopic data in accord with the assigned structures. Selected ^{1}H NMR data (500 MHz, $CDCl_3$) are given below:
13: 6.90 (dd, 1H, $J_{1,2}$ = 3.58 Hz, $J_{2,3}$ = 10.23 Hz, H-2); 6.10 (d, 1H, H-3); 5.25 (d, 1H, H-1); 5.10 (d, 1H, $J_{5,6}$ = 2.39 Hz, H-5); 4.47 (dd, $J_{6,7}$ = 5.72 Hz, H-6); 4.00 (m, 1H, H-7); 3.60 (s, 3H, OCH_3); 1.84 and 1.53 (2*x*s, 2*x*3H, 2*x*CH_3); 1.16 (d, 3H, $J_{7,8}$ = 6.41 Hz, H-8).
15a: 6.32 (ddd, 1H, $J_{2,3}$ = 9.92 Hz, $J_{3,4}$ = 6.44 Hz, $J_{1,3}$ = 1.45 Hz, H-3); 5.87 (dd, 1H, $J_{1,2}$ = 2.60 Hz, H-2); 5.03 (dd, 1H, H-1); 4.76 (bd, 1H, $J_{4,OH}$ = 4.75 Hz, OH); 4.31 (m, 1H, H-4); 4.15 (d, 1H, $J_{5,6}$ = 10.39 Hz, H-5); 4.12 (dd, 1H, $J_{6,7}$ = 3.17 Hz, H-6); 3.78 (dq, 1H, $J_{7,8}$ = 6.54 Hz, H-7); 3.49 (s, 3H, OCH_3); 1.56 and 1.46 (2*x*s, 2*x*3H, 2*x*CH_3); 1.43 (d, 3H, H-8).
16a: 5.00 (dd, 1H, $J_{1,2}$ = 2.79 Hz, $J_{1,3}$ = 0.41 Hz, H-1); 4.82 (bd, 1H, $J_{4,OH}$ = 4.50, OH); 4.51 (m, 1H, H-4); 4.17 (d, 1H, $J_{5,6}$ = 9.85 Hz, H-5); 3.96 (dd, 1H, $J_{6,7}$ = 3.86 Hz, H-6); 3.75 (dq, $J_{7,8}$ = 6.52 Hz, H-7); 3.57 (dd, 1H, $J_{2,3}$ = 3.76 Hz, $J_{3,4}$ = 2.92 Hz, H-3), 3.53 (s, 3H, OCH_3); 3.43 (dd, 1H, H-2), 1.54 and 1.42 (2*x*s, 2*x*3H, 2*x*CH_3); 1.34 (d, 3H, H-8).

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