Pergamon

Tetrahedron Vol. 50, No. 25, pp. 7611-7624, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $7.00+0.00

0040-4020(94)00384-X

Synthesis and Absolute Configuration of Four Diastereoisomeric 1-(2-Furyl)-2-aminobutane-1,3-diols

Barbara SZECHNER and Osman ACHMATOWICZ

Pharmaceutical Research Institute, 01-793 Warszawa, Poland

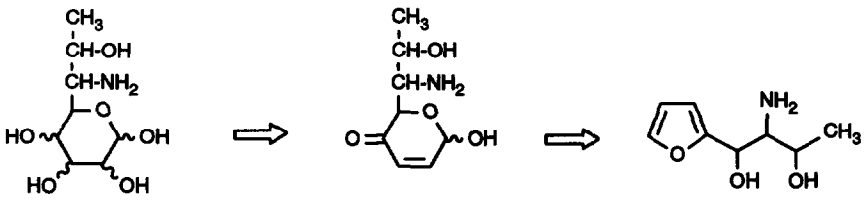
Zdzisław GAŁDECKI and Andrzej FRUZIŃSKI

Institute of General and Ecological Chemistry, Technical University of Łódź, 90-924 Łódź, Poland

Abstract: The synthesis of *N*-benzenesulfonyl-*N,O*-isopropylidene derivatives of (1*R*,2*R*,3*S*)-, (1*S*,2*R*,3*S*)-, (1*R*,2*R*,3*R*)- and (1*S*,2*R*,3*R*)-1-(2-furyl)-2-aminobutane-1,2-diols was accomplished by the addition of furyllithium to the similarly protected D-threoninal and D-allothreoninal, prepared in four steps from D-threonine and D-allothreonine, respectively. The configuration integrity of a β-hydroxy-α-amino aldehydes as well as the structure and the stereochemistry of resultant aminodiols derivatives was established by ^{1}H NMR spectroscopy and single-crystal X-ray analysis.

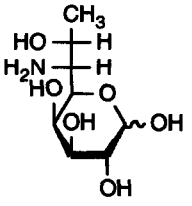
In recent years the increasing interest in the biological role of higher sugars (i.e. monosaccharides containing more then six carbon atoms in the chain) has stimulated numerous efforts to develop their stereoselective and stereocontrolled syntheses[1]. Among general routes to enantiomerically pure higher sugars an approach based on furan compounds[2] offers attractive, not yet fully explored, possibilities. A prerequisite

Scheme 1



1 **2**

for the success of this methodology is the availability of appropriate homochiral furan compounds. For the synthesis of 6-amino-6,8-dideoxyoctoses **1**, a family of higher sugars of which D-lincosamine (**3**) is an outstanding representative[3], 1-(2-furyl)-2-aminobutane-1,3-diols are required (Scheme 1). With the foregoing synthetic goal in mind we have examined addition of furyllithium to the *N*-benzenesulfonyl-*N,O*-isopropylidene derivatives of D-threoninal (**8**) and D-allothreoninal (**13**) which resulted in the formation of four diasteroisomeric 1-(2-furyl)-2-aminobutane-1,3-diols **2** with (1*R*,2*R*,3*S*), (1*S*,2*R*,3*S*), (1*R*,2*R*,3*R*) and (1*S*,2*R*,3*R*) configurations[4]. A preliminary report of this work has been already published[5]. In the present paper we disclose the full details of the synthesis and stereochemistry of the *N*-benzenesulfonyl-*N,O*-isopropylidene derivatives of the above four aminobutanediols **2**.



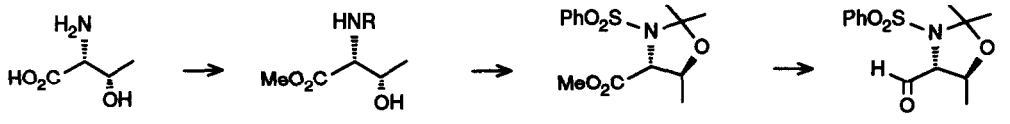
3

RESULTS and DISCUSSION

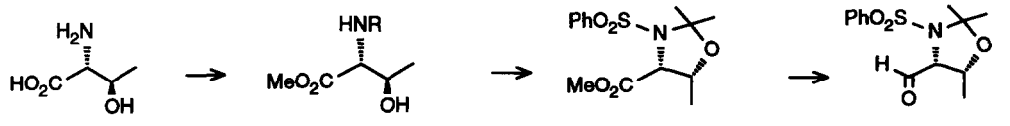
Synthesis of aldehydes **8** *and* **13**

N-Benzenesulfonyl-*N,O*-isopropylidene-D-threoninal (**8**) and the corresponding D-allothreoninal (**13**) were obtained following known procedures[6] as shown in Scheme 2.

Scheme 2



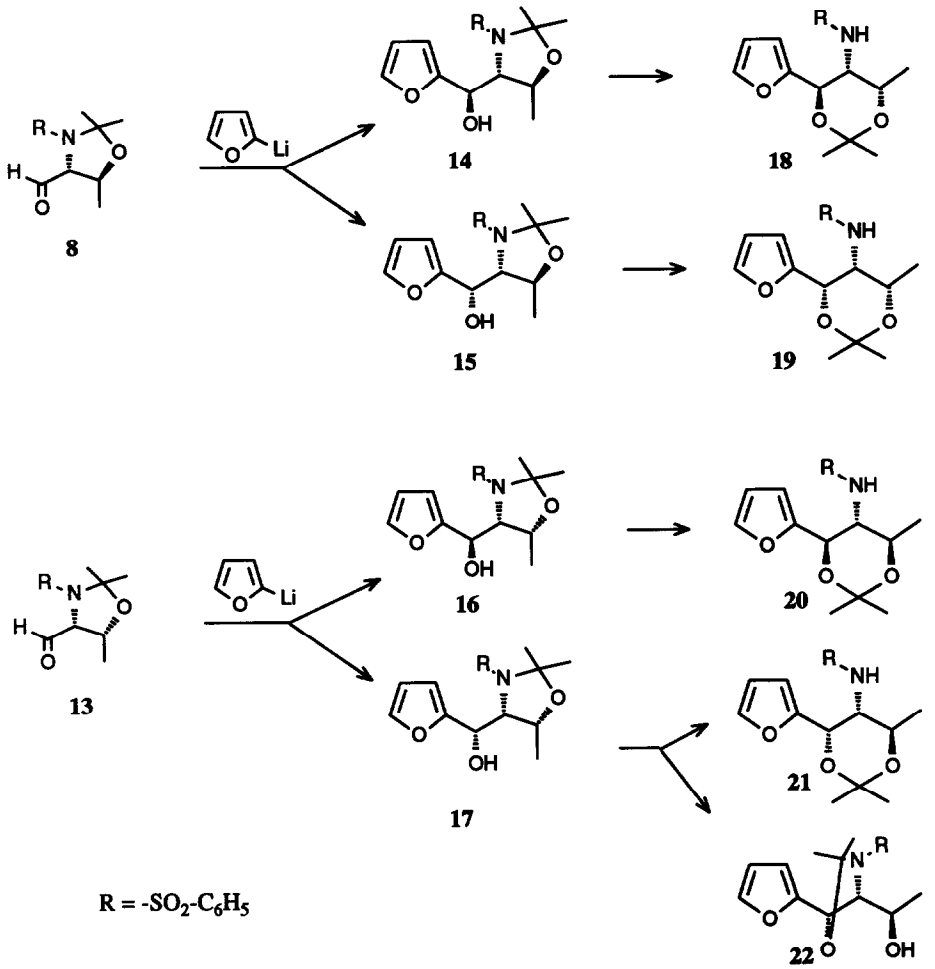
4 **5** R = H; **6** R = SO_2Ph **7** **8**



9 **10** R = H; **11** R = SO_2Ph **12** **13**

Thus D-threonine (**4**) and D-allothreonine (**9**) were treated with thionyl chloride in methanol solution[7] and the resulting esters **5** and **10**, respectively, *N*-acylated with benzenesulfonyl chloride to give the corresponding amides **6** and **11**. After protecting the amido and hydroxy groups as the *N,O*-isopropylidene derivative, the methoxycarbonyl group of esters **7** and **12** was reduced with diisobutylaluminum hydride (DIBAL-H) to give *N,O*-protected D-threoninal **8** and D-allothreoninal **13** in 55% overall yield (calculated on the starting β-hydroxy-α-amino acids **4** and **9**). Aldehydes **8** and **13** are stable, crystalline (**13**) solids which have been stored for months in refrigerator without noticeable (^{1}H NMR, HPLC) decomposition or loss of configuration integrity.

Scheme 3



R = -SO_2-C_6H_5

Addition of furyllithium

Cycloaddition and nucleophilic addition to the carbonyl group of variously protected α-amino aldehydes have been extensively studied[8]. From these studies it has transpired that by the judicious choice of protecting groups and reaction conditions desired *syn* or *anti* addition can be realized with high selectivity. Less information has been accumulated on the nucleophilic addition to the β-hydroxy-α-aminoaldehydes and none of the reported examples referred to their *N,O*-cyclic derivatives. Reaction of furyllithium with aldehydes **8** and **13** gave with good to excellent yield (78 - 90%), in each case, the pairs of alcohols: **14, 15** and **16, 17**, respectively (Scheme 3). The product ratios, as measured by HPLC analysis, varied considerably, depending on the reaction conditions. However, formation of only two products demonstrated the configuration stability of aldehydes **8** and **13** in the course of the C-C bond formation.

From the data in Table 1 it can be seen that the steric outcome of furyllithium addition to aldehydes **8** and **13** is quite different. Whereas for threoninal **8** either *syn* (entry 1) or *anti* (entry 2) addition with satisfactory selectivity has been achieved without optimization, for allothreoninal **13** only *syn* addition has been performed with high selectivity (entry 3 and 4).

The effect of the β-carbon configuration on the nucleophilic addition to the carbonyl group in β-hydroxy-α-amino aldehydes has been noted before[9]. However the observed difference in *syn*:*anti* selectivity between *erythro* and *threo* aldehydes was not as pronounced as in the case of aldehydes **8** and **13**. It appears

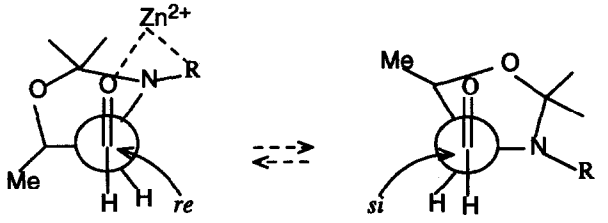
Table 1. Addition of Furyllithium to Aldehydes **8** and **13**.

Entry	Aldehyde	Reaction conditions Solvent. Temp.(°C)	Products	Ratio[a]	Yield[b] (%)
1	**8**	ether, 0 → RT, $ZnBr_2$	**14:15**	14:86	78
2	**8**	ether, -70	**14:15**	81:19	90
3	**13**	THF/ether, RT, $ZnBr_2$	**16:17**	6:94	5
4	**13**	glyme, -70	**16:17**	7:93	89
5	**13**	THF/ether, -70	**16:17**	36:64	*c*
6	**13**	ether, RT	**16:17**	26:74	*c*
7	**13**	ether, RT, 18-crown-6	**16:17**	21:79	*c*
8	**13**	hexane, -70	**16:17**	35:65	*c*
9	**13**	hexane, RT	**16:17**	30:70	*c*
10	**13**	THF/hexane/ether, -70	**16:17**	55:45	85

[a]Determined by HPLC analysis; [b]Yields for isolated products; [c]Not determined.

that the *N,O*-cyclic protecting group has imposed the rigidity on the aldehyde carbon skeleton and as a result has introduced additional steric hindrance of the carbonyl group. Taking this effect into account our results can be rationalized in terms of chelation-controlled conformation A and Felkin-Anh[10] conformation B (Scheme 4). In the presence of a chelating agent ($ZnBr_2$) threoninal **8** has reacted predominantly in conformation A *via* addition to the less hindered *re* face leading to (1*S*,2*R*,3*S*)-aminobutanediol **15**. Under non-chelating conditions conformation B predominates and undergoes *si*-attack to yield (1*R*,2*R*,3*S*)-aminobutenediol **14**. In the case of

Scheme 4



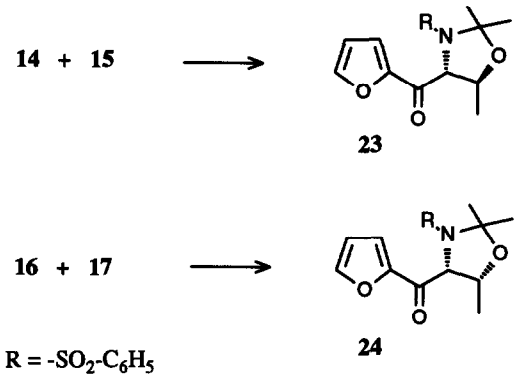
A B

allothreoninal **13** rotamer B, due to the presence of the *N,O*-isopropylidene moiety, has a steric interaction between methyl (C-4) and carbonyl group. Consequently even in the absence of a chelating cation conformation B is not favored and is in equilibrium with rotamer A. Therefor attack on the *re* or *si* face of the carbonyl group is equally probable, leading at best only to modest excess of *anti* addition (entry 10). On the other hand conditions for the *syn* selectivity have been worked out (entry 4).

Reduction of ketones **23** *and* **24**

1-(2-Furyl)-2-aminobutane-1,3-diols **14**, **15** and **17**, as major reaction products, could be readily purified. Isolation of pure aminodiol **16**, available only in the mixture (almost 1:1) with its epimer **17**, required careful column chromatography. To avoid this inconvenience the inversion of configuration at C-1 in alcohol **17** was attempted. A Mitsunobu reaction[12] (dietyl azodicarboxylate-triphenylphosphine-benzoic acid) was unsuccessful. Another possible route to pure alcohol **16** involves the oxidation of alcohols **16** and **17** mixture and subsequent stereoselective reduction of the ketone **24**. Oxidation of the mixtures of alcohols **14** and **15** as well as **16** and **17** with MnO_2 gave good yields of ketones **23** and **24**, respectively. Reduction of ketone **24** with several hydrides (LAH, DIBAL-H, L-Selectride^R, $NaBH_4$) at temperatures from -70°C to ambient failed to give satisfactory results. On the other hand reduction of ketone **23**, which was of no preparative interest and was carried out only for comparison, proved to be stereoselective. Reaction with L-Selectride gave alcohols **14** and **15** in the ratio 99:1 (lithium aluminum hydride: 86:14).

Scheme 5



The structure of 1-(2-furyl)-2-aminobutane-1,3-diols

The gross structure of aminodiols **14**, **15**, **16** and **17** was confirmed by their analytical and spectroscopic data (cf. Experimental). The configuration of their new stereogenic center at C-1 was established using previous methodology[12] i.e. from the ^{1}H NMR coupling constants of the corresponding 1,3-dioxanes. To this end aminodiols were treated with *p*-toluenesulfonic acid in acetone - 2,2-dimethoxypropane (to avoid inadvertent removal of the isopropylidene group) solution. Oxazolidines **14**, **15** and **16** were cleanly (TLC) rearranged into 1,3-dioxanes **18**, **19** and **20**, respectively. Only the reaction of oxazolidine **17** resulted in the mixture comprising 1,3-dioxane **21** and oxazolidine **22**, which were separated by flash chromatography (Scheme 3).

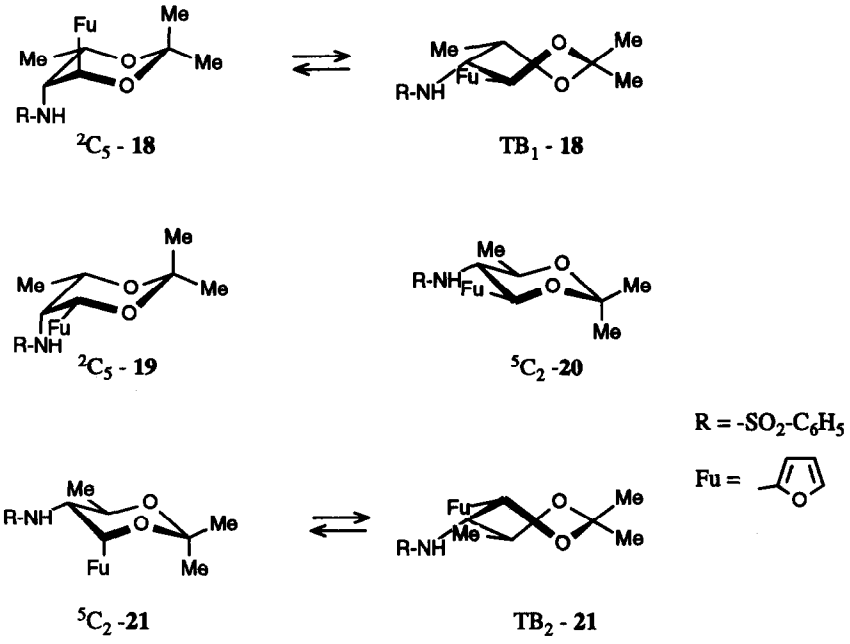
For the 1,3-dioxanes **19** and **20** with both substituents at C-4 and C-6 in equatorial positions the chair conformation $^2C_5$ and $^5C_2$, respectively, can be predicted (Scheme 6). The two other 1,3-dioxanes, **18** and **21**, which have 2,4- or 2,6-diaxial interactions, in either chair conformation should occur in conformational equilibria. Standard molecular mechanics calculations by MMX force field[13] indicated that the chair conformation with 4,6-diaxial interaction of two methyl groups are of high energy. On the other hand local minima have been found for conformations $^5C_2$ and TB_1 in 1,3-dioxane **18** and conformations $^5C_2$ and TB_2 in 1,3-dioxane **21** (Scheme 6).

Comparison of the experimental ^{1}H NMR coupling constants of compounds **18** and **19** as well as **20** and **21** with those calculated for their respective conformations by the PC MODEL routine[13] (Table 2) permitted distinction of the epimers in each pair, thus demonstrating the configuration of the 1,3-dioxanes and at the same time proving the C-1 configuration in the aminobutanediols **14**, **15**, **16** and **17** as shown in Scheme 3. The values of $J_{1,2}$ and $J_{2,3}$ in compounds **19** and **20** show their conformational preference as $^2C_5$ and $^5C_2$, respectively, whereas these values in compounds **18** and **21** confirm the occurrence of a conformational equilibrium between chair and twist-boat forms, (ca 1:1) (Scheme 6).

Because 1-(2-furyl)-2-aminobutane-1,3-diol **16** was intended as a substrate for the enantioselective

synthesis of D-lincosamine (**3**) its absolute configuration, as well as that of its epimer aminodiol **17**, were unambiguously established by single crystal X-ray analyses. This confirmed the assignments based on the ^{1}H NMR as may be seen from the respective ORTEP drawings shown in Figure 1. Most important of all, the results of X-ray analysis rigorously excluded the possibility of epimerization at the C-2 in aldehyde **13** during the furyllithium addition, which in principal could have been overlooked on inspection of the ^{1}H NMR spectra.

Scheme 6

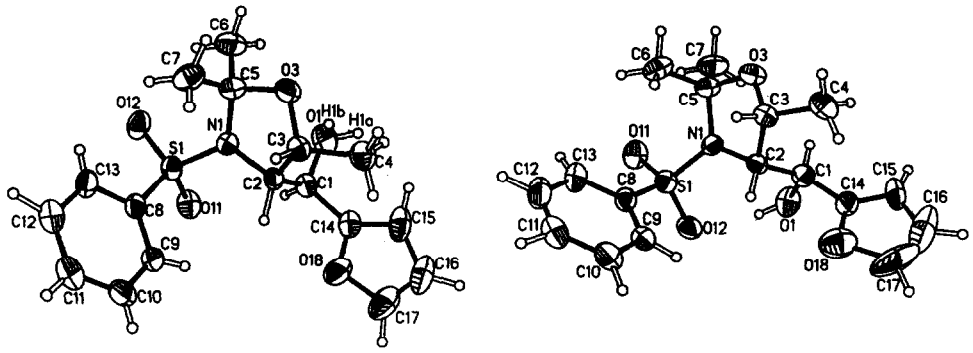


It is apparent from Fig. 1 that the conformation of compounds **16** and **17** in the solid state is analogous. The spatial relationship of their oxazolidine and furan rings is similar as testified by the dihedral angles O18-C14-C1-C2 and C3-C2-C1-C14 (numbering as in **A** and **B** in Fig. 1) which in compound **16** are 42.9° and 70.7° and in compound **17** 37.8° and 78.1°, respectively. Consequently the intramolecular hydrogen bonds exhibited by the hydroxy group in both compounds are different. Alcohol **16** shows hydrogen bonding with the oxygen atom of the oxazolidine ring, O1-H1....O3 (distance 2.63 Å, angle 148.8°), whereas alcohol **17** hydrogen bonds with the oxygen atom of the sulfonyl group, O1-H1....O12 (distance 1.94 Å, angle 166.8°). In **16** the hydroxyl hydrogen atom occupies statistically two positions H1a and H1b with occupancy factors 0.577 and 0.423 respectively (Fig.1 **A**). It may be inferred from the coupling constants ($J_{1,2}$) values of 1.55 Hz and 9.25 Hz respectively for compounds **16** and **17** that their stable conformations (spatial relation of furan and dioxolane moieties) in solution are close to those in crystal, presumably due to the intramolecular

hydrogen bonds.

Table 2. Coupling Constants (Hz) in ^{1}H NMR Spectra of *N*-Benzenesulfonyl-1,3-*O*-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diols **18** - **21**.

Compound	Experimental $J_{1,2}$	Experimental $J_{2,3}$	Conformation	Calculated $J_{1,2}$	Calculated $J_{2,3}$
18	5.49	3.52	$^2C_5$-**18**	1.11	1.50
			TB_1-**18**	10.13	7.76
19	1.98	1.52	$^2C_5$-**19**	1.92	1.93
20	10.28	9.85	$^5C_2$-**20**	10.30	9.69
21	4.54	6.28	$^5C_2$-**21**	5.06	9.80
			TB_2-**21**	0.97	2.63



A **B**

Fig. 1. ORTEP drawings of **16** (**A**) and **17** (**B**) showing numbering of atoms.

EXPERIMENTAL

General procedures

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Boiling points refer to the air-bath temperature. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker MSL 300 or AM 500 spectrometers using TMS as internal reference. Infra-red spectra were recorded with Perkin Elmer FT IR, 1725X or Specord N-60 spectrophotometers. Optical rotations were measured with Perkin Elmer 141 polarimeter. High resolution mass spectra (HRMS) were obtained on AMD 604 and Fimigan MAT 8200 mass spectrometers. HPLC was carried out on Shimadzu Liquid Chromatograph equipped with Beckman Ultrasphere

SI 5 μm column. Column chromatography was carried out on Merck Kieselgel 60 (230-400 Mesh). All reactions and chromatographic separations were monitored in TLC analysis performed on silica gel 60 F_{254} aluminum precoated layer. Yields are reported for chromatographically pure compounds. Solvents and reagents were purified before use according to standard procedures[14].

D-Threonine (**4**) ([α_D] + 27.0° (c 1, H_2O)) was of commercial origin (Aldrich); D-allothreonine (**9**) ([α]$_D$ -9.03°, (c 2, H_2O) was obtained from D-threonine according to the literature procedure[7].

X-Ray structure determination of 16 and 17

Compounds **16** and **17** were crystallized from ether-hexane. Intensity data were collected on a KM-4-diffractometer for compound **16** and on a P3 SIEMENS diffractometer for compound **17**. Data collection and processing parameters are listed in Table 3. The structures were solved with direct methods and refined by anisotropic full-matrix least squares (C bonded H atoms 1.08 Å from C in rigid groups with isotropic temperature factors) using *SHELXTL* program[15]. All H atoms were identified in a difference Fourier synthesis. The geometrical calculations were carried out using *CSU*[16] and *PARST*[17] programs.

Methyl *N*-benzenesulfonyl-D-allothreoninate (11).

To a suspension of D-allothreonine (**9**) hydrochloride (20.0 g, 91 mmol) in methanol (200 mL) was added thionyl chloride (12.2 g, 103 mmol), dropwise, with stirring. After heating to reflux for 3 h solvents were removed in vacuo and evaporation repeated with benzene (2x50 mL). To the glossy residue covered with CH_2Cl_2 (150 mL) triethylamine (31.6 g, 227 mmol) was added slowly with stirring followed by benzenesulfonyl chloride (16.42 g, 93 mmol), the mixture kept for 18 h at 2°C and then poured on ice water. The solid (not soluble in water or CH_2Cl_2) was filtered off, washed with CH_2Cl_2 (150 mL) and combined organic solutions were washed successively with saturated $NaHCO_3$ solution, 5% hydrochloric acid, water and brine, dried ($MgSO_4$), filtered and evaporated to give solid which recrystallized from ethyl acetate afforded 21.1 g (81%) of ester **11**, m.p. 132-133°C, [α]$_D$ 0° (c 1, MeOH), [α]$_D$ -18.9° (c 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3566, 3337, 1741, 1352, 1167 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}NO_5S$: C, 48.34; H, 5.53; N, 5.12%. Found: C, 48,45; H, 5.70; N, 5.37%.

Methyl *N*-benzenesulfonyl-D-threoninate (6).

Prepared according to the procedure described for **11**. Recrystallization from ethyl acetate gave ester **6** (79.5%), m.p. 105-106°C, [α]$_D$ +10.4° (c 1, MeOH), [α]$_D$ +6.7° (c 1, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3360, 1743, 1348, 1166 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}NO_5S$: C, 48.34; H, 5.53; N, 5.12%. Found: C, 48.43; H, 5.54; N, 5.30%.

Methyl *N*-benzenesulfonyl-*N,O*-isopropylidene-D-allothreoninate (12).

To a partially dissolved **11** (20.1 g, 74 mmol) in benzene (250 mL) was added 2,3-dimethoxypropane (15.6 g, 250 mmol) and *p*-toluenesulfonic acid (210 mg). The mixture was heated to gentle boiling and the solvent was slowly distilled off through a Vigreaux column. After 1 h portions of 2,2-dimethoxypropane (6.78 g, 68 mmol) and *p*-toluenesulfonic acid (100 mg) were added and heating was continued. After 4 h (150 mL of solvent was removed) the reaction was completed (TLC), the mixture was diluted with ether (300 mL), washed with saturated $NaHCO_3$ solution, water and brine, dried ($MgSO_4$) and evaporated. The residue was crystallized from ether-hexane to give 20.7 g (90%) of **12**, m.p. 73.5-75.0°C, [α]$_D$ + 55.4° (c 1, $CHCl_3$).
IR($CHCl_3$) ν_{max} 1754, 1736, 1350, 1163 cm^{-1}. ^{1}H NMR (500 MHz) δ 7.88-7.86 (m, 2H, aromatic); 7.59-7.48 (m, 3H, aromatic); 4.37 (apparent quintet, 1H, H-3); 4.30 (d, $J_{2,3}$ = 6.27 Hz, 1H, H-2); 3.50 (s, 3H, OCH_3), 1.81 and 1.66 (2xs, 2xCH_3, >C(CH_3)$_2$), 1.19 (d, J = 6.25 Hz, 3H, -CH_3). IR ($CHCl_3$) ν_{max}: 1754, 1736, 1350, 1163 cm^{-1}.

Table 3. Data Collection* and Processing Parameters of Compounds **16** and **17**.

	16	**17**
Molecular formula	$C_{17}H_{21}N_1O_5S_1$	$C_{17}H_{21}N_1O_5S_1$
Molecular weight	351.42	351.42
Cell constant	*a*= 7.864(2) Å, a=90.0° *b*=11.394(2) Å, b=90.0° *c*=19.551(4) Å, γ=90.0° *V*=1751.7(6) Å^3, *Z*=4	*a*= 7.721(1) Å, α=90.0° *b*=11.587(1) Å, β=90.0° *c*=19.636(4) Å, γ=90.0° *V*=1756.6(4) Å^3, *Z*=4
Density (calcd.)	1.332 g·cm^{-3}	1.329 g·cm-3
Space group	$P2_12_12_1$	$P2_12_12_1$
Radiation	Graphite-monochromated Cu*K*α λ=1.54052 Å	Graphite monochromated Mo*K*α λ=0.71.069 Å
Absorption coefficient	18.3 cm^{-1}	2.0 cm^{-1}
Crystal size	0.11x0.25x0.39 mm	0.11x0.13x0.15 mm
Scan type and speed	2Θ;0.008 ÷ 0.08 deg·s^{-1}	2Θ;4.19 ÷ 29.3 deg·min^{-1}
Scan range	0.7° below $K\alpha_1$ to 0.7° above $K\alpha_2$	0.9° below $K\alpha_1$ to 0.9° above $K\alpha_2$
Background counting	The left and right backgrounds include the same number of outer profile points: s_1=0.25*s where s is the total number of scan points	Stationary counts for one-half of scan time at each end of scan
Collection range	*h,k,l*;$2\Theta_{max}$=75°	*h,k,l*;$2\Theta_{max}$=55°
Unique data measured	1966	2318
Observed data with $\|F_o\| > 4\sigma(\|F_o\|)$, *n*	1700	1636
Number of variables, *p*	306	293
$R_f = \Sigma\|\|F_o\| - \|F_c\|\| / \Sigma\|F_o\|$	0.0395	0.0457
Weighting scheme	$w=1/(\sigma^2(F)+0.0021F^2)$	$w=1/(\sigma^2(F)+0.0013F^2)$
R_w	0.0430	0.0511
$S=[\Sigma w(\|F_o\| - \|F_c\|)^2/(n-p)]^{1/2}$	1.21	1.24
Residual extrema in final difference map	+0.14-0.30 *e*Å^{-3}	+0.21-0.23 *e*Å^{-3}

*The tables containing full experimental data are deposited with Cambridge Crystallographic Data Center (CCDC), UK

Methyl *N*-benzenesulfonyl-*N,O*-isopropylidene-D-threoninate (7).

With the use of the same procedure as for **12**, compound **7** was obtained (90%), m.p. 80.0-80.5°C, $[\alpha]_D$ +125.3° (c 1, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1740, 1345, 1150 cm^{-1}. ^1H NMR (300 MHz) δ 7.92-7.88 (m, 2H, aromatic); 7.60-7.51 (m, 3H, aromatic); 4.32 (dq, $J_{2,3}$ = 7.40, $J_{3,4}$ = 6.08 Hz, H-3); 3.95 (d, 1H, H-2); 3.80 (s, 3H, OCH_3); 1.62 and 1.54 (2xs, 2x3H,>$C(CH_3)_2$); 1.34 (d, 3H, -CH_3).

***N*-Benzenesulfonyl-*N,O*-isopropylidene-D-allothreoninal (13).**

To a cold (-75°C) solution of ester **12** (19.43 g, 62 mmol) in dry toluene (150 mL) was added diisobutylaluminum hydride (DIBAL-H) (11.02 g, 77.5 mmol) in toluene (55 mL) under argon. After stirring at -73°C for 1 h excess of hydride was quenched by addition of methanol (16 mL) and the mixture poured into 1M hydrochloric acid (250 mL). Water layer was extracted with ethyl acetate (3x150 mL), then the combined organic extracts were washed with water, brine, dried ($MgSO_4$), filtered and evaporated. The residue was crystallized from ether-hexane to give 14.26 g (82%) of aldehyde **13**, m.p. 110.5-111.5°C, $[\alpha]_D$ +66° (c 1, $CHCl_3$). IR (CCl_4): ν_{max} 3060, 2810, 1731, 1353, 1157 cm^{-1}. ^1H NMR (500 MHz) δ 9.43 (dd, $J_{1,2}$ = 4.53 Hz, $J_{1,3}$ = 0.78 Hz, 1H, H-1); 7.86 (m, 2H, aromatic); 7.60 (m, 1H, aromatic); 7.53 (m, 2H, aromatic); 4.30 (apparent quintet-d, 1H, H-3); 3.85 (dd, $J_{2,3}$ = 6.64 Hz, H-2); 1.85 and 1.61 (2xs, 2x3H, >$C(CH_3)_2$); 1.23 (d, $J_{3,4}$ = 6.50 Hz, 3H, -CH_3). Anal. Calcd. for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.06; S, 11.29%. Found: C, 55.58; H, 6.49; S, 11.22%.

***N*-Benzenesulfonyl-*N,O*-isopropylidene-D-threoninal (8).**

With the use of the same procedure as for **13** aldehyde **8** was obtained (%). IR($CHCl_3$) ν_{max} 1740, 1340, 1155 cm^{-1}. ^1H NMR (500 MHz) δ 9.61 (d, $J_{1,2}$ = 4.50 Hz, 1H, H-1); 7.82-7.79 (m, 2H, aromatic); 7.64-7.61 (m, 1H, aromatic); 7.57-7.53 (m, 2H, aromatic); 4.24 (dq, $J_{2,3}$ = 8.28 Hz, 1H, H-2); 1.69 and 1.51 (2xs, 2x3H, >$C(CH_3)_2$); 1.28 (d, $J_{3,4}$ = 6.02 Hz, 3H, CH_3). Anal. Calcd. for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.95; S, 11.29%. Found: C, 54.93; H, 5.90; N, 4.92; S, 11.37%.

Addition of furyllithium to aldehydes 8 and 13. Typical procedure.

To a cold (-30°C) solution of furan (1.8 g, 27.5 mmol) in ether (10 mL) under argon the solution of butyllithium in ether (1.27 M, 4.8 mL, 6 mmol) was added. The reaction mixture was allowed to reach room temperature, stirred for 1 h and cooled to 0°C. Then $ZnBr_2$ (1.12 g, 5 mmol) was added at once and the mixture after reaching ambient temperature was stirred for 30 min and cooled again to 0°C. The solution of aldehyde **8** (1.17 g, 4.1 mmol) in ether (20 mL) was added dropwise and the stirring continued at room temperature till completion of the reaction (TLC) (2 h). The reaction mixture was washed with saturated aqueous ammonium chloride solution, water, brine, dried ($MgSO_4$) and evaporated. The oily residue was flash chromatographed affording aminodiols **14** and **15**. Yields and ratios of products obtained in particlular runs are collected in Table 1.

(1*R*,2*R*,3*S*)-*N*-Benzenesulfonyl-*N,O*^{3}-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (14), 73% (Table 1, entry 2), R_f 0.28 (hexane:etyl acetate 7:3), m.p. 160-162°C (ethyl acetate-ether), $[\alpha]_D$ -58.6° (c 0.5, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3384, 1345, 1163, 1091 cm^{-1}. ^1H NMR (300 MHz) δ 7.93-7.89 (m, 2H, aromatic); 7.68-7.52 (m, 3H, aromatic); 7.39 (m, 1H, H-5 furan); 6.41 (m, 1H, H-3 furan); 6.39 (dd, $J_{3,4}$ = 3.23, $J_{4,5}$ = 1.82 Hz, 1H, H-4 furan); 5.39 (m, 1H, H-1); 4.30 (dq, $J_{2,3}$ = 7.50, $J_{3,4}$ = 6.30 Hz, 1H, H-3); 3.53 (dd, $J_{1,2}$ = 2.5 Hz, 1H, H-2); 1.60 and 1.55 (2xs, 2x3H, >$C(CH_3)_2$); 0.76 (d, 3H, -CH_3). Anal. Calcd. for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.03; N, 3.99; S, 9.11%. Found: C, 57.86; H, 6.18; N, 3.95; S, 9.02%. HRMS calcd. for $C_{16}H_{18}NO_5S$ (M - CH_3) 336.0906, found 336.0906.

(1*S*,2*R*,3*S*)-*N*-Benzenesulfonyl-*N,O*^{3}-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (15), 67% (Table 1, entry 1), R_f 0.19

(hexane:ethyl acetate 7:3), m.p. 96.5-98°C (ether-hexane), $[\alpha]_D$ +50.5° (c 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3459, 1344, 1148 cm^{-1}. ^1H NMR (300 MHz) δ 7.96-7.91 (m, 2H, aromatic); 7.66-7.51 (m, 3H, aromatic); 7.43 (dd, $J_{4,5}$ = 2.0, $J_{3,5}$ = 0.96 Hz, 1H, H-5 furan); 6.42 (dd, $J_{3,4}$ = 3.50 Hz, 1H, H-3 furan); 6.39 (dd, 1H, H-4 furan); 4.92 (dd, $J_{1,2}$ = 8.24, $J_{2,OH}$ = 4.10 Hz, 1H, H-1); 4.37 (d, 1H, OH); 4.08 (qd, $J_{3,4}$ = 6.1, $J_{2,3}$ = 3.8 Hz, 1H, H-3); 3.94 (dd, 1H, H-2); 1.58 (2xs, 2x3H, $>C(CH_3)_2$); 0.82 (d, 3H, CH_3). HRMS calcd. for $C_{17}H_{21}NO_5S$ (M^+) 351.1135, found: 351.1140.

(1*R*,2*R*,3*R*)-*N*-Benzenesulfonyl-*N*,O^3-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (16), 48% (Table 1, entry 10), R_f 0.38 (hexane:ether:methylene chloride 10:3:2, developed 4x), m.p. 81.5-82.5°C (ether-hexane), $[\alpha]_D$ +40.5° (c 0.5, $CHCl_3$). IR (KBr) ν_{max} 3580, 3470, 1365, 1160 cm^{-1}. ^1H NMR (500 MHz) δ 7.96-7.93 (m, 2H, aromatic); 7.64-7.60 (m, 1H, aromatic); 7.57-7.53 (m, 2H, aromatic); 7.41 (dd, $J_{4,5}$ = 1.80, $J_{3,5}$ = 0.70 Hz, 1H, H-5 furan); 6.42 (m, 1H, H-3 furan); 6.40 (dd, $J_{3,4}$ = 3.27 Hz, 1H, H-4 furan); 5.04 (bd, $J_{1,OH}$ = 9.34 Hz, 1H, H-1); 4.20 (d, 1H, OH); 4.06 (dd, $J_{2,3}$ = 5.94, $J_{1,2}$ = 1.55 Hz, 1H, H-2); 4.03 (apparent quintet, 1H, H-3); 1.47 and 1.35 (2xs, 2x3H, $>C(CH_3)_2$); 1.38 (d, $J_{3,4}$ = 6.27 Hz, 3H, $-CH_3$). Anal. Calcd. for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.03; N, 3.99%. Found: C, 58.33; H, 6.11; N, 4.11%. HRMS calcd. for $C_{16}H_{18}NO_5S$ ($M-CH_3$) 336.09057, found: 336.09060.

(1*S*,2*R*,3*R*)-*N*-Benzenesulfonyl-*N*,O^3-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (17), 83% (Table 1, entry 4), R_f 0.43 (hexane:ether:methylene chloride 10:3:2, developed 4x), m.p. 120-121.5°C (hexane-ether), $[\alpha]_D$ +75.4° (c 1, $CHCl_3$). IR (KBr) ν_{max} 3500, 1365, 1155 cm^{-1}. ^1H NMR (500 MHz) δ 7.96-7.94 (m, 2H, aromatic); 7.64-7.61 (m, 1H, aromatic); 7.58-7.54 (m, 2H, aromatic); 7.43 (dd, $J_{4,5}$ = 1.82, $J_{3,5}$ = 0.80 Hz, H-5 furan); 6.38 (dd, $J_{3,4}$ = 3.25 Hz, 1H, H-4 furan); 6.36 (m, 1H, H-3 furan); 4.76 (dd, $J_{1,2}$ = 9.25, $J_{1,OH}$ = 7.53 Hz, 1H, H-1); 4.33 (dd, $J_{2,3}$ = 4.58 Hz, 1H, H-2); 3.96 (d, 1H, OH); 3.89 (qd, $J_{3,4}$ = 6.61 Hz, 1H, H-3); 1.70 and 1.49 (2xs, 2x3H, $>C(CH_3)_2$); 0.96 (d, 3H, $-CH_3$). Anal. Calcd. for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.03; N, 3.99%. Found: C, 58.24; H, 6.12; N, 3.90%.

Synthesis of 1,3-dioxanes 18, 19, 20 and 21. Typical procedure.

(1*R*,2*R*,3*S*)-*N*-Benzenesulfonyl-*N*,O^3-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (**14**) (225 mg, 0.64 mmol) was dissolved in acetone (5 mL), 2,2-dimethoxypropane (1 mL) and small crystal of *p*-toluenesulfonic acid were added. The reaction mixture was stirred at ambient temperature for 15 h. After disappearance of the substrate (TLC, hexane - ethyl acetate 6:4) the reaction mixture was neutralized with two drops of triethylamine, solvents were evaporated, the residue dissolved in ether (20 mL), washed with water, brine, dried ($MgSO_4$), filtered and evaporated. Flash chromatography (hexane : ethyl acetate 7:3) of the oily residue afforded 220 mg (98%) of dioxane **18**.

(1*R*,2*R*,3*S*)-*N*-Benzenesulfonyl-1,3-O-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (18), m.p. 146.5-147.5°C, $[\alpha]_D$ -58.6° (c 0.5, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3387, 1385, 1345, 1162 cm^{-1}. ^1H NMR (500 MHz) δ 7.70 (dm, J = 8.5 Hz, 2H, aromatic); 7.48 (m, 1H, aromatic); 7.39 (m, 2H, aromatic); 7.29 (dd, $J_{4,5}$ = 1.82, $J_{3,5}$ = 0.77 Hz, 1H, H-5 furan); 6.22 (dd, $J_{3,4}$ = 3.29 Hz, 1H, H-4 furan); 6.11 (bd, 1H, H-3 furan); 5.10 (d, $J_{NH,2}$ = 10.09 Hz, 1H, NH); 4.47 (d, $J_{1,2}$ = 5.49 Hz, 1H, H-1); 4.35 (qd, $J_{3,4}$ = 6.44, $J_{2,3}$ = 3.54 Hz, 1H, H-3); 3.89 (ddd, 1H, H-3); 1.40 and 1.25 (2xs, 2x3H, $>C(CH_3)_2$); 1.18 (d, $J_{3,4}$ = 6.45 Hz, 3H, $-CH_3$). HRMS calcd. for $C_{16}H_{18}NO_5S$ (M - CH_3): 336.0906. Found: 336.0905.

(1*S*,2*R*,3*S*)-*N*-Benzenesulfonyl-1,3-O-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (19), m.p. 171.5-173°C, $[\alpha]_D$ -36.90° (c 0.5, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3387, 1385, 1338, 1160, 1110 cm^{-1}. ^1H NMR (500 MHz) δ 7.62-87.59 (m, 2H, aromatic); 7.46-7.41 (m, 1H, aromatic); 7.37-7.32 (m, 2H, aromatic); 6.99 (m, 1H, H-5 furan); 6.13 (dd, 1H, H-3 furan); 6.07 (dd, $J_{3,4}$ = 3.27, $J_{4,5}$ = 1.82 Hz, 1H, H-4 furan); 5.09 (d, 1H, NH); 5.08 (d, $J_{1,2}$ = 1.98 Hz, 1H, H-1); 4.19 (qd, $J_{3,4}$ = 6.25, $J_{2,3}$ = 1.52 Hz, 1H, H-3); 3.57 (dt,

$J_{2,NH}$ = 9.67 Hz, 1H, H-2); 1.48 and 1.51 (2xs, 2x3H, >C(CH_3)$_2$); 1.36 (d, 3H, -CH_3). HRMS calcd. for $C_{16}H_{18}NO_5S$ (M - CH_3): 336.0906. Found 336.0904.

(1*R*,2*R*,3*R*)-*N*-Benzenesulfonyl-1,3-O-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (20), m.p. 177.0 - 177.5°C, $[\alpha]_D$ 0 (c 0.3, $CHCl_3$), $[\alpha]_D$ -13.8° (c 0.6, MeOH). IR (KBR) ν_{max} 3450, 3350, 1345, 1165, 1100 cm^{-1}. ^1H NMR (500 MHz) δ 7.60-7.58 (m, 2H, aromatic); 7.48-7.45 (m, 1H, aromatic); 7.39-7.37 (m, 2H, aromatic); 7.09 (dd, $J_{4,5}$ = 1.80, $J_{3,5}$ = 0.78 Hz, 1H, H-5 furan); 6.18 (dd, $J_{3,4}$ = 3.26 Hz, 1H, H-3 furan); 6.09 (dd, 1H, H-4 furan); 4.60 (d, $J_{1,2}$ = 10.26 Hz, 1H, H-1); 4.44 (d, $J_{2,NH}$ = 8.93 Hz, 1H, NH); 3.88 (dq, $J_{2,3}$ = 9.86, $J_{3,4}$ = 6.09 Hz, 1H, H-3); 3.46 (ddd, 1H, H-3); 1.52 and 1.43 (2xs, 2x3H, >C(CH_3)$_2$); 1.25 (d, 3H, -CH_3). HRMS calcd. for $C_{16}H_{18}NO_5S$ 336.09057. Found: 336,09054.

(1*S*,2*R*,3*R*)-*N*-Benzenesulfonyl-1,3-O-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (21), oil, $[\alpha]_D$ -20.1° (c 0.6, $CHCl^3$).IR ($CHCl_3$) ν_{max} 3380, 1343, 1163, 1094 cm^{-1}. ^1H NMR (500 MHz) δ 7.59-7.57 (m, 2H, aromatic); 7.51-7.48 (m, 1H, aromatic); 7.40-7.37 (m, 2H, aromatic); 7.11 (dd, $J_{4,5}$ = 1.83, $J_{3,5}$ = 0.80 Hz, 1H, H-5 furan); 6.16 (dd, J = 3.21 Hz, 1H, H-4 furan); 6.10 (m, 1H, H-3 furan); 5.16 (bd, $J_{2,NH}$ = 8.81 Hz, 1H, NH); 5.03 (d, $J_{1,2}$ = 4.54 Hz; 1H, H-1); 3.95 (quintet, 1H, H-3); 3.41 (ddd, $J_{2,3}$ = 6.27 Hz, 1H, H-2); 1.43 and 1.40 (2xs, 2x3H, >C(CH_3)$_2$); 1.34 (d, $J_{3,4}$ = 6.37 Hz, 3H, -CH_3). HRMS calcd. for $C_{16}H_{18}NO_5S$ (M-CH_3) 336.09057. Found: 336.09021.

(1*S*,2*R*,3*R*)-*N*-Benzenesulfonyl-N,O^1-isopropylidene-1-(2-furyl)-2-aminobutane-1,3-diol (22), oil, $[\alpha]_D$ -31.2° (c 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3509, 1343, 1153, 1092 cm^{-1}. ^1H NMR (500 MHz) δ 7.93-7.91 (m, 2H, aromatic); 7.65-7.62 (m, 1H, aromatic); 7.58-7.55 (m, 2H, aromatic); 7.30 (dd, $J_{4,5}$ = 1.81, $J_{3,5}$ = 0.77 Hz, 1H, H-5 furan); 6.28 (dd, $J_{3,4}$ = 3.29 Hz, 1H, H-4 furan); 6.22 (m, 1H, H-3 furan); 5.17 (d, $J_{1,2}$ = 7.08 Hz, 1H, H-1); 4.36 (qd, $J_{3,4}$ = 6.73, $J_{2,3}$ = 2.10 Hz, H-3); 3.99 (dd, 1H, H-2); 1.73 and 1.60 (2xs, 2x3H, >C(CH_3)$_2$); 1.10 (d, 3H. -CH_3). HRMS calcd. for $C_{16}H_{18}NO_5S$ (M - CH_3): 336.0906. Found: 336.0903.

Oxidation of alcohols 14, 15, and 16, 17. Preparation of ketones 23 and 24. Typical procedure.

To a solution of alcohols **14** and **15** (504 mg, 1.44 mmol) in CH_2Cl_2 (30 mL) was added MnO_2 (2.5 g, 28.7 mmol) and the reaction mixture was allowed to stirr at room temperature. After 18 h the oxidation was completed (TLC), the solution filtered through a Celite pad and taken to dryness. The residue solidified affording 365 mg (73%) of ketone **23**.

(2*R*,3*S*)-*N*-Benzenesulfonyl-*N,O*-isopropylidene-1-(2-furyl)-2-amino-3-hydroxybutan-1-one (23), m.p. 137.5 - 139.5°C (ether), $[\alpha]_D$ +101.9° (c 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 1685, 1570, 1349, 1157 cm^{-1}. ^1H NMR (500 MHz) δ 7.90-7.88 (m, 2H, aromatic); 7.67 (dd, $J_{4,5}$ = 1.68, $J_{3,5}$ = 0.71 Hz, H-5 furan); 7.59-7.56 (m, 1H, aromatic); 7.52-7.48 (m, 2H, aromatic); 7.36 (dd, $J_{3,4}$ = 3.65 Hz, 1H, H-3 furan); 6.61 (dd, 1H, H-4 furan); 4.84 (d, $J_{2,3}$ = 7.35 Hz, 1H, H-2); 4.29 (dq, $J_{3,4}$ = 6.06 Hz, 1H, H-3); 1.63 and 1.61 (2xs, 2x3H, >C(CH_3)$_2$); 1.35 (d, 3H, -CH_3). HRMS Calcd. for $C_{17}H_{19}NO_5S$ (M^+): 349.0983. Found: 349.0979.

(2*R*,3*R*)-*N*-Benzenesulfonyl-*N,O*-isopropylidene-1-(2-furyl)-2-amino-3-hydroxybutan-1-one (24), m.p. 171.5-173.0°C, $[\alpha]_D$ +17.9° (c 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 1688, 1570, 1347, 1158 cm^{-1}. ^1H NMR (500 MHz) δ 7.82-7.80 (m, 2H, aromatic); 7.58 (dd, $J_{4,5}$ = 1.68, $J_{3,5}$ = 0.71 Hz, 1H, H-5 furan); 7.51-7.48 (m, 1H, aromatic); 7.42-7.39 (m, 2H, aromatic); 7.15 (dd, $J_{3,4}$ = 3.62 Hz, H-3 furan); 6.54 (dd, 1H, H-4 furan); 5.24 (d, $J_{2,3}$ = 6.51 Hz, 1H, H-2); 4.54 (quintet, 1H, H-3), 1.86 and 1.71 (2xs, 2x3H, >C(CH_3)$_2$); 1.08 (d, $J_{3,4}$ = 6.41 Hz, 3H, -CH_3). Anal. Calcd. for $C_{17}H_{19}NO_5S$: C, 58.43; H, 5.48; N, 4.01%. Found: C, 58.50; H, 5.35; N, 3.90%.

ACKNOWLEDGMENT

Crystallographic part of this work (ZG and AF) was supported by the Committee for Scientic Research, grant No. 3 0302 91 01.

REFERENCES AND NOTES

1. (a) Secrist, J. A. III; Barnes, K. D.; Wu, S.-R. In *Trends in Synthetic Carbohydrate Chemistry*: *ACS Symposium Series 386*; Horton D., Hawkins, L. D., Mc Garvey, G. J., Eds.; American Chemical Society: Washington, D.C., 1974; pp. 93-106 and references cited therein. (b) Zamojski, A.; Jarosz, S., *Recent Advances in the Synthesis of Higher Sugars, Pol.J.Chem.* **1992**, *66*, 525-585.
2. Achmatowicz, O. In *Organic Synthesis Today and Tomorrow*, Trost, B. M.; Hutchinson, C. R., Eds.; Pergamon Press: New York, 1987, p. 307.
3. Magerlein, B. J. In *Structure Activity Relationships among the Semisynthetic Antibiotics*; Pearlman, D., Ed.; Academic Press: New York, 1977, p. 601.
4. For the sake of simplicity and consistency throughout this paper absolute configuration descriptors (*R*,*S*) refer to unsubstituted 1-(2-furyl)-2-aminobutane-1,3-diols.
5. Szechner, B.; Achmatowicz, O. *J.Carbohydr.Chem.*, **1992**, *11*, 401.
6. (a) Lubell, W. D.; Rapoport, H. *J.Am.Chem.Soc.* **1987**, *109*, 236. (b) Garner, P.; Park, J. M.; *J.Org.Chem.*, **1987**, *52*, 2361.
7. Ibuka, T.; Nishii, S.; Yamamoto, Y. *Chem.Express*, **1988**, *3*, 53.
8. (a) Gołębiowski, A.; Jurczak, J. In *Recent Progress in the Chemical Synthesis of Antibiotics*, Springer Verlag: Berlin, 1990; p. 365. (b) Reetz, M. T. *Pure Appl. Chem.*, **64**, 351 (1992). (c) Dondoni, A., *Carbohydrate Synthesis via Thiazoles* in *Modern Synthetic Reactions*, Verlag Helvetica Chimica Acta, Basel; VCH, Weinheim, 1992, **2**, 377. (d) Gołębiowski, A.; Jurczak, J. *Synlett.* **1993**, 241.
9. Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133.
10. (a) Anh, N. T. *Top.Curr.Chem.* **1980**, *88*, 145. (b) Reetz, M. T. *Angew.Chem.* **1991**, *103*, 1559.
11. Mitsunobu, O. *Synthesis*, **1981**, 1.
12. Szechner, B. *Tetrahedron*, **1981**, *37*, 949.
13. Serena Software, P.O.Box 307, Bloomington, IN 47402-3076.
14. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.
15. Sheldrick, G. M. *SHELXTL PC version 4.1. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data*, Siemens Analytical X-Ray Instruments, Inc.: Madison, USA, 1990.
16. Vickovic, J. *CSU-Crystal Structure Utility. Program for geometrical calculations*. University of Zagreb, Yugoslavia, 1988.
17. Nardelli, M. *Comput.Chem.* **1983**, *7*, 95.

(*Received in UK* 9 *March* 1994; *revised* 25 *April* 1994; *accepted* 29 *April* 1994)