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Stereoselective synthesis of 3-alkylsulfinylmethylisoxazolines and their use as chiral nucleophiles in the chain elongation of 2,3-*O*-isopropylidene-D-glyceraldehyde

J. A. López-Sastre,[a] J. D. Martín-Ramos,[b] J. F. Rodríguez-Amo,[a,*] M. Santos-García[a] and M. A. Sanz-Tejedor[a,*]

[a]*Departamento de Química Orgánica (E.T.S.I.I.), Paseo del Cauce s/n, 47011 Valladolid, Spain*
[b]*Departamento de Mineralogía y Petrología, Facultad de Ciencias, C/Fuentenueva s/n, 18002 Granada, Spain*

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Abstract

The reaction of racemic 3-methylisoxazolines and enantiomerically pure (R_S)- and (S_S)-methanesulfinates and (R_S)- and (S_S)-ethanesulfinates of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose allows enantiomerically pure 3-alkylsulfinylmethylisoxazolines with both absolute configurations at sulfur to be obtained. One of these has been used as a chiral nucleophile in the four carbon homologation of 2,3-*O*-isopropylidene-D-glyceraldehyde **17**.

1. Introduction

The rational construction of substances with multiple stereogenic centres is a leading subject in the modern organic synthesis panorama. Among the various techniques with which a densely functionalized homochiral compound can be constructed,[1] one of the more viable methodologies exploits, as a key operation, carbon–carbon bond forming homologation of readily available sugar derived templates (incorporating suitable stereogenic centres) by means of *n*-carbon synthons.[2] Towards this end, versatile five-membered heterocycles as functional elongation reagents have been frequently used in reactions with enantiopure aldehydo or imino sugars. For example, Casiraghi et al. have shown the utility of 2-siloxy-furan, pyrrole and thiophene derivatives as four-carbon building blocks for the construction of complex molecules bearing multiple contiguous stereogenic centres.[3] Likewise, several 2-substituted thiazoles have been exploited by Dondoni et al. in *n*-carbon chain extension of aldehydes and aldonitrones[4] and, recently, 4-substituted isoxazoles have also been used.[5]

* Corresponding author.

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For this purpose, the isoxazoline ring is another especially valuable heterocycle. As distinguished from other heterocycles that have been used to date, they can bear two stereogenic centres (C4 and C5) in their structure and, moreover, they are versatile intermediates in organic synthesis.[6] Isoxazoline ring reductive cleavage can be controlled to give either γ-amino alcohols or β-hydroxyketones.[7] The latter transformation stands as a very interesting alternative to the aldol reaction.

In connection with our research devoted to asymmetric synthesis using the sulfinyl group as a chiral auxiliary,[8] and to the iterative chain elongation of 2,3-*O*-isopropylidene-D-glyceraldehyde **17** using ethyl ethylthiomethyl sulfoxide[9] and (R_S)-methyl *p*-tolyl sulfoxide[10] as formyl anion equivalents, we thought to study the chain elongation of aldehyde **17** in four-carbon atoms, in one synthetic step, by using enantiomerically pure 3-alkylsulfinylmethylisoxazolines as chiral nucleophiles. The sulfinyl group in alkylsulfinylmethylisoxazolines offers the advantage of providing a handle for the resolution and increasing the acidity of the hydrogens α to this sulfinyl group; in this way, these intermediates can be exploited for further synthetic transformations, before unmasking the functionalities latent in the heterocyclic ring.

Herein we provide a simple approach to enantiomerically pure 3-alkylsulfinylmethylisoxazolines, and the synthesis of β,γ,δ-trihydroxymethylisoxazolines according to a four-carbon homologative protocol exploiting the aforementioned sulfinylisoxazolines as functional elongation reagents.

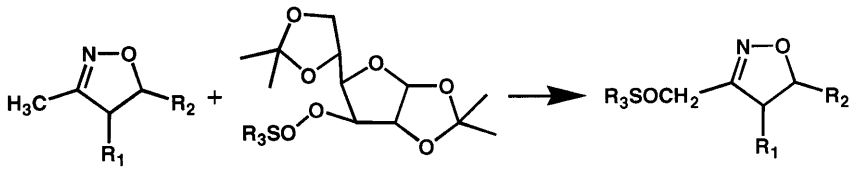
2. Results and discussion

Preparation of 3-alkylsulfinylmethylisoxazolines, compounds **9a**,**b**–**15a**,**b** (Table 1), has been carried out using the methodology developed by Cinquini et al.,[11] that consists of the *exo*-metallation of racemic 3-methylisoxazolines and subsequent reaction with a chiral non-racemic sulfinic ester.

The starting racemic 3-methylisoxazolines (compounds **1**–**4**) were synthesized by 1,3-dipolar cycloaddition between ethanonitrile oxide[12] and different monosubstituted and symmetric 1,2-disubstituted alkenes. The sulfinic esters employed in this study are (R_S)- and (S_S)-methanesulfinates[13] and (R_S)- and (S_S)-ethanesulfinates[14] of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (compounds **5**, **6**, **7** and **8**, respectively). They have been synthesized according to Llera's procedure[15] by addition of the corresponding methyl or ethylsulfinylchloride to 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (DAG) in the presence of a suitable base (pyridine for the (R_S) epimer or ^{i}Pr$_2$EtN for the (S_S) epimer).

3-Alkylsulfinylmethylisoxazolines (compounds **9a**,**b**–**15a**,**b**, Table 1) were easily prepared by *exo*-deprotonation of isoxazolines **1**–**4** with the appropriate lithium amide[16] and subsequent Andersen reaction with enantiomerically and diastereomerically pure methane or ethanesulfinates of DAG (compounds **5**–**8**). As is shown in Table 1, the base employed for metallation of 4,5-disubstituted isoxazolines, compounds **1** and **2**, was lithium diisopropylamide (LDA) (entries 1–6). When metallation was carried out on 4-unsubstituted isoxazolines, compounds **3** and **4**, which might be deprotonated at unsubstituted C4 position, a more hindered base such as lithium tetramethylpiperidide (LTMP) was used in order to minimize the *endo*-deprotonation. In the case of isoxazoline **3** (entry 7) the *endo*-metallation reaction is not overridden completely, yielding 20% of the corresponding *endo*-metallated product (**16**).

Table 1
Synthesis of 3-sulfinylmethylisoxazolines **9a**,**b**–**15a**,**b**



1a,b; $R_1=R_2=-(CH_2)_3-$
2a,b; $R_1=R_2=-C_6H_5$ [iii]
3a,b; $R_1=H$; $R_2=-C_5H_{11}$
4a,b; $R_1=H$; $R_2=-C_6H_5$

5; $R_3=CH_3$ [i]
6; $R_3=CH_3$ [ii]
7; $R_3=CH_3CH_2$ [i]
8; $R_3=CH_3CH_2$ [ii]

i: (R) configuration at sulfur; **ii:** (S) configuration at sulfur; **iii:** *trans*-arrangement of substituents.

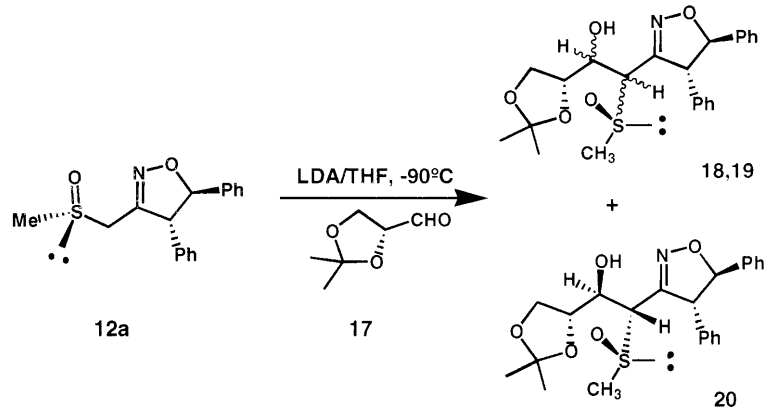
Entry	Isoxazoline	Base	Sulfinate	Product (% yield)[a]	d.r./a:b
1	**1a**,**b**	LDA	**6**	**9a**,**b** (70)	48:52
2	**1a**,**b**	LDA	**8**	**10a**,**b** (65)	48:52
4	**2a**,**b**	LDA	**5**	**11a**,**b** (65)	53:47
5	**2a**,**b**	LDA	**6**	**12a**,**b** (55)	50:50
6	**2a**,**b**	LDA	**7**	**13a**,**b** (56)	48:52
7	**3a**,**b**	LTMP	**6**	**14a**,**b** (47)[b]	55:45
8	**4a**,**b**	LTMP	**6**	**15a**,**b** (32)	52:48

[a] Isolated yield.
[b] A 20% yield of 3-methyl-4-methylsulfinyl-5-*n*-pentyl-isoxazoline (**16**) was also obtained.

In each reaction, mixtures of two diastereoisomeric sulfinylmethylisoxazolines (a,b) in almost equal proportions, were generated because the diastereoselection in the process, as expected, was low. However, in every case, column chromatography or, in one instance (entry 1, compounds **9a**,**b**), fractional crystallization allowed a clean separation of the diastereoisomeric mixtures into diastereomerically and enantiomerically pure derivatives (Table 1). Compounds **11a** and **11b** are enantiomers of compounds **12a** and **12b**, respectively, as confirmed by their having the same spectroscopic data and only differing in the sign of their optical rotation. This result is in agreement with both the suggested concerted mechanism for 1,3-dipolar cycloadditions[17,18] (synthesis of isoxazolines **1**–**4**) and with the inversion of sulfur atom configuration that occurs in these Andersen reactions, employed to obtain compounds **9a**,**b**–**15a**,**b**.

Next, we studied the four carbon chain elongation of aldehyde **17** using enantiomerically pure 3-methylsulfinylmethylisoxazoline **12a** as the homologating reactant (Scheme 1). Metallation of compound **12a** with LDA (at −90°C) gave rise to the corresponding *exo*-azaenolate, whose aldol-type reaction with compound **17** afforded hydroxysulfoxides **18**, **19** and **20** in high yield, and in a high level of diastereoselectivity (12:4:84, **18**:**19**:**20**, ratio). These compounds were isolated as pure diastereoisomers by flash chromatography.

The absolute configuration of major compound **20** was unequivocally assigned by X-ray analysis as (4*R*,5*R*,1′*S*,2′*R*) (Fig. 1).



Scheme 1.

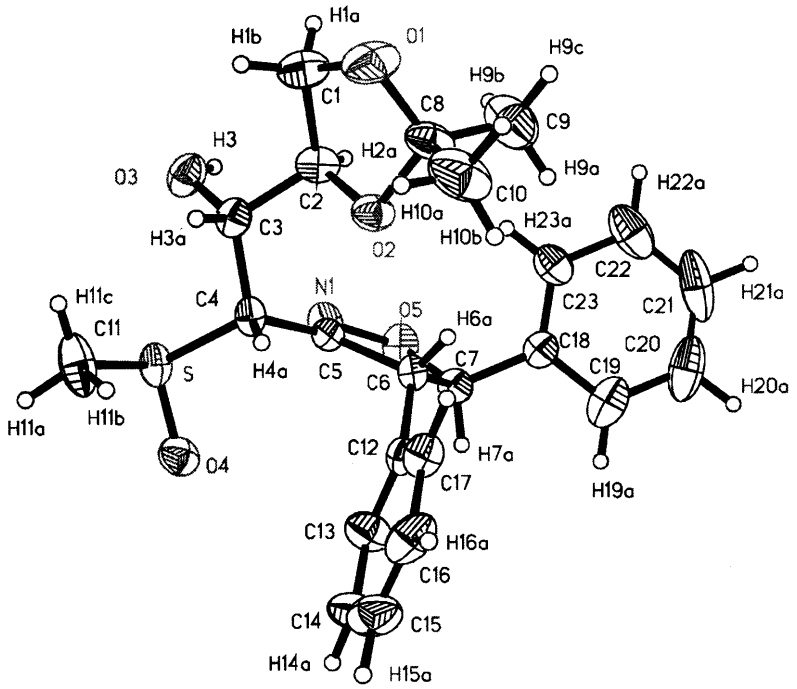


Figure 1. X-Ray structure of compound **20**

The observed (2*R*) stereochemistry at the HO-bearing carbon in compound **20**, which is the predominant isomer obtained from reaction of compounds **12a** and **17**, is in accord with a non-chelation controlled addition (Felkin–Anh–Houk model).[19] To account for the stereochemistry at C1′ in the major product **20**, we propose that this aldol reaction derives from the transition state shown in Fig. 2, in which the chelation of the lithium cation by the azaenolate and the oxygen of the sulfinyl group causes the chiral azaenolate to have a distinct facial bias, with the '*si*' face shielded by the phenyl group at C4 and the methyl group at sulfur. So, as can be seen in Fig. 2, the aldehyde approaches the azaenolate from the less hindered face ('*re*' face). This is in agreement with previous results obtained in related systems.[11b,20]

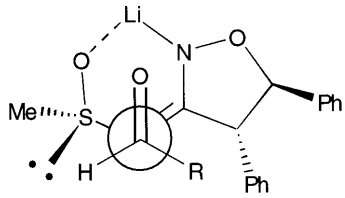


Figure 2.

On the basis of the structural assignment of compound **20**,[21] we can establish the same absolute configuration at sulfur, C4 and C5 for the other products (compounds **18** and **19**) obtained in the same process, and for the starting isoxazoline **12a**. Furthermore, compound **12b** has the same absolute configuration at sulfur but the opposite at the centres in the ring to compound **12a**. In the same way, the absolute configurations of compounds **11a** and **11b** could be established as (R_S,4*S*,5*S*) and (R_S,4*R*,5*R*), respectively, because they are enantiomers of **12a** and **12b**.

In summary, several enantiomerically pure 3-alkylsulfinylmethylisoxazolines with both absolute configurations at sulfur have been prepared. Although the present synthesis employs a conventional diastereoisomeric separation, it can provide an efficient and short route to all possible enantiomers of 3-alkylsulfinylmethylisoxazolines. Furthermore, the wide range of substituents available in the dipolarophile should allow the synthesis of a considerable number of isoxazoline derivatives capable of being exploited as chiral homologous reactants.

The reaction of isoxazoline **12a** with 2,3-*O*-isopropylidene-D-glyceraldehyde **17** takes place with high diastereoselectivity and allows access to complex molecules bearing multiple contiguous stereogenic centres capable of different transformations due to the isoxazoline ring versatility. The study of the reductive ring cleavage that is able to provide optically pure β-hydroxyketones, γ-aminoalcohols or α,β-unsaturated ketones is currently in progress.

3. Experimental

3.1. General methods

Dry solvents and liquid reagents were distilled under argon just prior to use: THF and diethyl ether were distilled from sodium and benzophenone ketyl, benzene over sodium, and triethylamine and diisopropylamine over calcium hydride. Alkenes, nitroethane and phenylisocyanate were commercially available from Aldrich Chemical Co. and used without further purification. All reaction vessels, after being flame-dried, were kept under argon. Organic solutions were dried over anhydrous sodium or magnesium sulfate, and the solvent was evaporated at reduced pressure below 40°C.

TLC was performed on glass plates coated with silica gel G (Merck) or SI-F-254 (Scharlau), spots being developed either with sulfuric acid in ethanol (10%) or with phosphomolybdic acid in ethanol. Column chromatographic separations were performed by using silica gel Merck 60 (70–230 mesh, ASTM, for gravity chromatography) or 230–400 mesh (for flash chromatography).

Optical rotations were measured with a 141 Perkin–Elmer polarimeter. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (80 MHz, $CDCl_3$) spectra were performed with a Bruker AC-300 spectrometer. Chemical shifts were measured in ppm (δ), relative to $SiMe_4$ as the internal reference; signal multiplicities are quoted as s, singlet; d, doublet; dd, double doublet; ddd, doubled double doublet; dq, double quartet; t, triplet; q, quartet, and m, multiplet. *J* values are given in Hz. Diastereoisomeric ratios were determined by integration of well separated signals at ^{1}H NMR spectra. IR spectra were measured on a Nicolet FTIR-20-SX spectrometer. Mass spectra were recorded by the direct insertion technique by electronic impact (ei) or chemical ionization (ci), using a HP-588-A spectrometer at 70 eV with a temperature source of 200°C. Elemental analyses were performed in a Carlo Erba Elemental Analyzer 1106. 2,3-*O*-Isopropylidene-D-glyceraldehyde **17** was synthesized from 1,2:5,6-di-*O*-isopropylidene-D-mannitol by oxidation with sodium periodate.[22]

3.2. Synthesis of 3-alkylsulfinylmethylisoxazolines. General procedure

To a stirred solution of the base (LDA[23] or LTMP[24]) (15 mmol) in THF (10 ml) cooled at −95°C, 3-methylisoxazoline (10 mmol) in THF (20 ml) was added over 10 min. The mixture was stirred for an additional 4 hour period at −80°C or at −95°C (depending on the 3-methylisoxazoline), and the sulfinate (5 mmol) in THF (20 ml) was then added. After being stirred for 30 minutes, the reaction mixture was quenched with a saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous phase extracted twice with dichloromethane. The combined organic layers were dried, concentrated under reduced pressure and the residue was purified by column chromatography.

*3.2.1. 3-(Methylsulfinyl)methyl-4,5-trimethyleneisoxazoline **9a**,**b***

3-Methyl-4,5-trimethyleneisoxazoline **1a**,**b**, (4.25 g, 34 mmol) was treated with (*S*)-methylsulfinate of DAG, **6** (7.35 g, 25 mmol) and LDA (41 mmol) at −80°C, following the general procedure. The work-up led to a mixture containing compounds **9a** and **9b** in a 48:52 ratio (estimated by integration of the signals corresponding to CH_3SO in the ^{1}H NMR spectrum of the crude reaction). Column chromatography using diethyl ether:hexane (2:1) as the eluent afforded a mixture of diastereoisomers **9a** and **9b** (3.25 g, 17.4 mmol, 70%). Separation of both diastereoisomers by crystallization (diethyl ether:hexane 10:1) afforded pure **9a** as a yellow syrup and pure **9b** as a white solid (mp 98–99°C).

*3.2.1.1. 3-(Methylsulfinyl)methyl-4,5-trimethyleneisoxazoline **9a**.* R_f=0.17 (isopropanol:diethyl ether, 1:10); $[\alpha]_D^{20}$=+377.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.36–1.46 (m, 1H, -**CH$_2$**-cyclopent.), 1.64–1.81 (m, 3H, -**CH$_2$**-cyclopent.), 1.88–1.97 (m, 1H, -**CH$_2$**-cyclopent.), 2.08–2.15 (m, 1H, -**CH$_2$**-cyclopent.), 2.67 (s, 3H, **CH$_3$**-SO-), 3.52 (d, 1H, J_{gem} 13.9, SO-**CH$_2$**-CCN), 3.84 (d, 1H, J_{gem} 13.9, SO-**CH$_2$**-CCN), 3.83 (m, 1H, **H**-C4), 5.16 (dd, 1H, $J_{5,4}$ 8.9, J_{vic} 5.0, **H**-C5); ^{13}C NMR δ 23.2, 30.1 and 35.7 (-**C**H$_2$-cyclopent.), 37.9 (**C**H$_3$-SO-), 49.0 (SO**C**H$_2$CCN), 54.7 (**C**4), 87.3 (**C**5) and 151.9 (**C**3). IR (KBr, liquid film): 2975, 2890, 1610, 1455, 1440, 1415, 1405, 1345, 1320, 1050, 1025, 920 and 760 cm^{-1}; MS (*m*/*e*) (ei): 187 (M$^+$, 11), 172 (3), 124 (100), 107 (4), 94 (37), 79 (87), 67 (26), 41 (18). Anal. calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48. Found: C, 51.21; H, 7.02; N, 7.51.

3.2.1.2. 3-(Methylsulfinyl)methyl-4,5-trimethyleneisoxazoline ***9b***. R_f=0.12 (isopropanol:diethyl ether, 1:10); $[\alpha]_D^{20}$=−158.3 (*c* 0.67, $CHCl_3$); ^{1}H NMR δ 1.38–1.48 (m, 1H, -**CH$_2$**-cyclopent.), 1.65–1.81 (m, 3H, -**CH$_2$**-cyclopent.), 1.91–2.00 (m, 1H, -**CH$_2$**-cyclopent.), 2.09–2.18 (m, 1H, -**CH$_2$**-cyclopent.), 2.72 (s, 3H, **CH$_3$**-SO-), 3.65 (d, 1H, J_{gem} 13.3, SO-**CH$_2$**-CCN), 3.73 (dd, 1H, J_{vic} 8.5, $J_{4,5}$ 8.9, **H**-C4), 3.80 (d, 1H, J_{gem} 13.3, SO-**CH$_2$**-CCN), 5.13 (dd, 1H, $J_{5,4}$ 0.9, J_{vic} 5.0, **H**-C5); ^{13}C NMR δ 23.3, 30.3 and 35.8 (-**C**H$_2$-cyclopent.), 39.6 (**C**H$_3$-SO-), 52.0 (SO**C**H$_2$CCN), 54.1 (**C**4), 87.5 (**C**5) and 152.6 (**C**3); IR (KBr, liquid film): 2975, 2890, 1615, 1460, 1450, 1415, 1405, 1345, 1320, 1040, 970, 915 and 760 cm^{-1}; MS (*m*/*e*) (ei): 187 (M$^+$, 6), 172 (2), 124 (100), 107 (5), 94 (44), 79 (98), 63 (40), 41 (34). Anal. calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48. Found: C, 51.47; H, 7.03; N, 7.46.

3.2.2. 3-(Ethylsulfinyl)methyl-4,5-trimethyleneisoxazoline ***10a,b***

3-Methyl-4,5-trimethyleneisoxazoline **1a**,**b** (2.82 g, 22.6 mmol) was treated with (*S*)-ethylsulfinate of DAG, **8** (3.79 g, 11.3 mmol) and LDA (31.64 mmol) at −80°C, as described in the general procedure. The work-up led to a mixture containing compounds **10a** and **10b** in a 48:52 ratio (estimated by integration of the signals corresponding to SO-**CH$_2$**-CCN in the ^{1}H NMR spectrum of the crude reaction).[9c]

3.2.3. 4,5-Diphenyl-3-(methylsulfinyl)methylisoxazoline ***11a,b***

4,5-Diphenyl-3-methylisoxazoline **2a**,**b** (4.94 g, 36 mmol) was treated with (*R*)-methylsulfinate of DAG, **5** (5.80 g, 18 mmol) and LDA (44 mmol) at −80°C, according to the general procedure. The work-up led to a mixture containing compounds **11a** and **11b** in a 53:47 ratio (estimated by integration of the signals corresponding to **H**C-4 in the ^{1}H NMR spectrum of the crude reaction). Column chromatography using diethyl ether:hexane (2:1) as the eluent afforded a mixture of diastereoisomers **11a** and **11b** (3.50 g, 11.7 mmol, 65%), which were separated by successive chromatographies (diethyl ether:hexane, 4:1) to yield pure **11a** and pure **11b** as yellow syrups.

3.2.3.1. 4,5-Diphenyl-3(methylsulfinyl)methylisoxazoline ***11a***. R_f=0.08 (diethyl ether:hexane, 4:1); $[\alpha]_D^{20}$=+222.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 2.60 (s, 3H, **CH$_3$**-SO-), 3.42 (d, 1H, J_{gem} 13.9, SO-**CH$_2$**-CCN), 3.64 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 4.64 (d, 1H, J_{trans} 7.1, **H**-C4), 5.60 (d, 1H, J_{trans} 7.1, **H**-C5) and 7.24–7.41 (m, 10H, **H**-arom.); ^{13}C NMR δ 37.7 (**C**H$_3$-SO-), 47.7 (SO-**C**H$_2$-CCN), 64.8 (**C4**), 91.0 (**C5**), 125.5, 128.0, 128.2, 128.4, 128.8 and 129.4 (**C**H-arom.), 137.1 (C4-**C**-arom.), 139.6 (C5-**C**-arom.) and 152.6 (**C3**); IR (KBr, liquid film): 3075, 3050, 2975, 2925, 1605, 1495, 1460, 1425, 1410, 1315, 1310, 1055, 910, 760 and 700 cm^{-1}; MS (*m*/*e*) (ci): 340 (M$^+$+41, 4), 328 (M$^+$+29, 12), 300 (M$^+$+1, 100), 284 (2), 265 (5), 237 (13), 222 (4), 197 (14), 160 (2), 132 (7), 107 (51). Anal. calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.19; H, 5.70; N, 4.70.

3.2.3.2. 4,5-Diphenyl-3-(methylsulfinyl)methylisoxazoline ***11b***. R_f=0.05 (diethyl ether:hexane, 4:1); $[\alpha]_D^{20}$=−221.4 (*c* 1.04, $CHCl_3$); ^{1}H NMR δ 2.64 (s, 3H, **CH$_3$**-SO-), 3.51 (d, 1H, J_{gem} 13.1, SO-**CH$_2$**-CCN), 3.71 (d, 1H, J_{gem} 13.1, SO-**CH$_2$**-CCN), 4.40 (d, 1H, J_{trans} 7.1, **H**-C4), 5.57 (d, 1H, J_{trans} 7.1, **H**-C5) and 7.22–7.43 (m, 10H, **H**-arom.); ^{13}C NMR δ 39.5 (**C**H$_3$-SO-), 51.3 (SO-**C**H$_2$-CCN), 64.5 (**C**4), 91.0 (**C**5), 125.3, 127.9, 128.5, 128.9 and 129.6 (**C**H-arom.), 136.8 (C4-**C**-arom.), 139.6 (C5-**C**-arom.) and 153.0 (**C**3); IR (KBr, liquid film): 3075, 3050, 2975, 2925, 1605, 1495, 1460, 1425, 1410, 1315, 1050, 915, 760 and 700 cm^{-1}; MS (*m*/*e*) (ci): 340 (M$^+$+41, 5), 328

(M^++29, 16), 300 (M^++1, 100), 284 (2), 265 (8), 237 (12), 222 (4), 197 (8), 132 (3), 130 (4), 107 (17). Anal. calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.31; H, 5.70; N, 4.66.

3.2.4. 4,5-Diphenyl-3-(methylsulfinyl)methylisoxazoline ***12a,b***

4,5-Diphenyl-3-methylisoxazoline **2a,b** (4.94 g, 36 mmol) was treated with (*S*)-methylsulfinate of DAG, **6** (5.80 g, 18 mmol) and LDA (40 mmol) at −80°C, as in previous experiments. The work-up led to a mixture containing compounds **12a** and **12b** in an equimolar ratio (estimated by integration of the signals corresponding to H-C4 in the ^{1}H NMR spectrum of the crude reaction). Column chromatography using diethyl ether:hexane (2:1) as the eluent afforded a mixture of diastereoisomers **12a** and **12b** (2.88 g, 9.6 mmol, 55%), which were separated by successive chromatographies (diethyl ether:hexane, 10:1) to yield pure **12a** and pure **12b** as yellow syrups.

3.2.4.1. 4,5-Diphenyl-3-(methylsulfinyl)methylisoxazoline ***12a***. R_f=0.12 (diethyl ether:hexane, 10:1); $[\alpha]_D^{20}$=−221.7 (*c* 1.05, $CHCl_3$); ^{1}H NMR δ 2.60 (s, 3H, **CH$_3$**-SO-), 3.42 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 3.64 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 4.64 (d, 1H, J_{trans} 7.1, **H**-C4), 5.60 (d, 1H, J_{trans} 7.1, **H**-C5) and 7.24–7.41 (m, 10H, **H**-arom.); ^{13}C NMR δ 37.8 (**CH$_3$**-SO-), 47.8 (SO-**CH$_2$**-CCN), 64.9 (**C4**), 91.1 (**C5**), 125.6, 128.1, 128.3, 128.5, 128.9 and 129.5 (**C**H-arom.), 137.2 (C4-**C**-arom.), 139.7 (C5-**C**-arom.) and 152.6 (**C3**); IR (KBr, liquid film): 3075, 3050, 2975, 2925, 1605, 1500, 1460, 1425, 1410, 1315, 1310, 1055, 910, 760 and 700 cm^{-1}. MS (*m*/*e*) (ci): 340 (M^++41, 6), 328 (M^++29, 14), 300 (M^++1, 100), 284 (2), 265 (4), 237 (14), 230 (3), 222 (4), 197 (13), 160 (2), 132 (6), 107 (47). Anal. calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.19; H, 5.75; N, 4.66.

3.2.4.2. 4,5-Diphenyl-3-(methylsulfinyl)methylisoxazoline ***12b***. R_f=0.06 (diethyl ether:hexane, 10:1); $[\alpha]_D^{20}$=+227.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 2.64 (s, 3H, **CH$_3$**-SO-), 3.51 (d, 1H, J_{gem} 13.1, SO-**CH$_2$**-CCN), 3.71 (d, 1H, J_{gem} 13.1, SO-**CH$_2$**-CCN), 4.40 (d, 1H, J_{trans} 7.1, **H**-C4), 5.57 (d, 1H, J_{trans} 7.1, **H**-C5) and 7.22–7.43 (m, 10H, **H**-arom.); ^{13}C NMR δ 39.5 (**CH$_3$**-SO-), 51.3 (SO-**CH$_2$**-CCN), 64.5 (**C4**), 91.0 (**C5**), 125.3, 127.9, 128.5, 128.9 and 129.6 (**C**H-arom.), 136.8 (C4-**C**-arom.), 139.6 (C5-**C**-arom.) and 153.0 (**C3**); IR (KBr, liquid film): 3075, 3050, 2975, 2925, 1605, 1495, 1460, 1425, 1410, 1315, 1055, 915, 760 and 700 cm^{-1}; MS (*m*/*e*) (ci): 340 (M^++41, 6), 328 (M^++29, 10), 300 (M^++1, 100), 284 (2), 265 (6), 237 (12), 230 (3), 222 (4), 197 (12), 160 (2), 132 (5), 107 (39). Anal. calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.27; H, 5.71; N, 4.69.

3.2.5. 4,5-Diphenyl-3-(ethylsulfinyl)methylisoxazoline ***13a,b***

4,5-Diphenyl-3-methylisoxazoline **2a,b** (2.08 g, 15.2 mmol) was treated with (*R*)-ethylsulfinate of DAG, **7** (2.57 g, 7.6 mmol) and LDA (22.8 mmol) at −80°C, as in the previous experiments. The work-up led to a mixture containing compounds **13a** and **13b** in a 48:52 ratio (estimated by integration of the signals corresponding to H-C4 in the ^{1}H NMR spectrum of the crude reaction).[9c]

*3.2.6. 3-(Methylsulfinyl)methyl-5-*n*-pentylisoxazoline* ***14a,b***

3-Methyl-4-*n*-pentylisoxazoline **3a,b** (2.17 g, 14 mmol) was treated with (*S*)-methylsulfinate of DAG, **6** (2.25 g, 7 mmol) and LTMP (21 mmol) at −95°C, as in previous preparations. The work-up led to a mixture containing compounds **14a** and **14b** in a 55:45 ratio (estimated by

integration of the signals corresponding to H-C4 in the ^{1}H NMR spectrum of the crude reaction). Column chromatography using diethyl ether:hexane (1:1) as the eluent afforded a mixture of diastereoisomers **14a** and **14b** (715 mg, 3.30 mmol, 47%) and pure *3-methyl-4-methylsulfinyl-5-n-pentylisoxazoline*, **16** (304 mg, 1.40 mmol, 20%). The mixture of compounds **14a** and **14b** was successively chromatographed (diethyl ether:hexane 2:1) to produce pure **14a** as a white solid from diethyl ether–hexane (mp 43–45°C) and pure **14b** as a white solid from diethyl ether–hexane (mp 63–64°C).

*3.2.6.1. 3-(Methylsulfinyl)methyl-5-*n*-pentylisoxazoline **14a**.* R_f=0.20 (isopropanol:diethyl ether, 1:10); $[\alpha]_D^{20}$=−91.2 (*c* 0.60, $CHCl_3$); ^{1}H NMR δ 0.89 (t, 3H, J_{vic} 6.6, **CH$_3$**-alk), 1.25–1.39 (m, 6H, -**CH$_2$**-), 1.41–1.63 (m, 1H, C5-**CH$_2$**-), 1.69–1.79 (m, 1H, C5-**CH$_2$**-), 2.67 (s, 3H, **CH$_3$**-SO-), 2.86 (dd, 1H, J_{trans} 8.5, J_{gem} 17.4, **H**-C4), 3.14 (dd, 1H, J_{cis} 10.4, J_{gem} 17.4, **H**-C4), 3.57 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 3.88 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN) and 4.60–4.71 (m, 1H, **H**-C5); ^{13}C NMR δ 13.9 (**CH$_3$**-alk), 22.5 (**C4′**), 25.1 (**C3′**), 31.5 (**C2′**), 34.8 (**C1′**), 38.3 (**CH$_3$**-SO-), 42.8 (**C4**), 50.9 (SO-**CH$_2$**-CCN), 81.9 (**C5**) and 150.8 (**C3**); IR (KBr, liquid film): 2975, 2925, 2875, 1615, 1470, 1425, 1415, 1400, 1350, 1340, 1040, 1030, 915, 815 and 730 cm^{-1}; MS (*m*/*e*) (ei): 217 (M$^+$, 16), 200 (2), 154 (15), 146 (100), 122 (4), 98 (24), 83 (58), 67 (32), 41 (52). Anal. calcd for $C_{10}H_{19}NO_2S$: C, 55.28; H, 8.81; N, 6.44: Found: C, 55.65; H, 8.92; N, 6.25.

*3.2.6.2. 3-(Methylsulfinyl)methyl-5-*n*-pentylisoxazoline **14b**.* R_f=0.15 (isopropanol:diethyl ether, 1:10); $[\alpha]_D^{20}$=+108.2 (*c* 0.60, $CHCl_3$); ^{1}H NMR δ 0.89 (t, 3H, J_{vic} 6.6, **CH$_3$**-alk), 1.31–1.43 (m, 6H, -**CH$_2$**-), 1.51–1.62 (m, 1H, C5-**CH$_2$**-), 1.67–1.76 (m, 1H, C5-**CH$_2$**-), 2.67 (s, 3H, **CH$_3$**-SO-), 2.71 (dd, 1H, J_{trans} 8.7, J_{gem} 17.4, **H**-C4), 3.25 (dd, 1H, J_{cis} 10.4, J_{gem} 17.4, **H**-C4), 3.58 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 3.87 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN) and 4.62–4.71 (m, 1H, **H**-C5); ^{13}C NMR δ 13.9 (**CH$_3$**-alk), 22.5 (**C4′**), 25.0 (**C3′**), 31.5 (**C2′**), 34.9 (**C1′**), 38.3 (**CH$_3$**-SO-), 42.7 (**C4**), 51.0 (SO-**CH$_2$**-CCN), 81.9 (**C5**) and 150.8 (**C3**); IR (KBr, liquid film): 2975, 2925, 2875, 1615, 1480, 1435, 1420, 1405, 1355, 1340, 1040, 1030, 915, 730 and 690 cm^{-1}; MS (*m*/*e*) (ei): 217 (M$^+$, 13), 154 (12), 146 (78), 112 (26), 98 (33), 83 (46), 63 (58), 41 (100). Anal. calcd for $C_{10}H_{19}NO_2S$: C, 55.28; H, 8.81; N, 6.44. Found: C, 55.65; H, 8.92; N, 6.25.

*3.2.6.3. 3-Methyl-4-methylsulfinyl-5-*n*-pentylisoxazoline **16**.* R_f=0.22 (diethyl ether:hexane, 10:1); ^{1}H NMR δ 0.90 (t, 3H, J_{vic} 6.5, **CH$_3$**-C_4H_8-); 1.30–1.72 (m, 8H, -(**CH$_2$**)$_4$-); 2.12 (s, 3H, **CH$_3$**-CNC); 2.48 (s, 3H, **CH$_3$**-SO-); 3.98 (d, 1H, $J_{4,5}$ 4.2, **H**-C4) and 4.35 (m, 1H, **H**-C5).

*3.2.7. 5-Phenyl-3-(methylsulfinyl)methylisoxazoline **15a**,**b***

5-Phenyl-3-methylisoxazoline **4a**,**b** (1.51 g, 9.4 mmol) was treated with (*S*)-methylsulfinate of DAG, **6** (1.50 g, 4.7 mmol) and LTMP (14 mmol) at −95°C, as in previous experiments. The work-up led to a mixture containing compounds **15a** and **15b** in a 52:48 ratio (estimated by integration of the signals corresponding to H-C4 in the ^{1}H NMR spectrum of the crude reaction). Column chromatography using diethyl ether:hexane (4:1) as the eluent afforded a mixture of diastereoisomers **15a** and **15b** (335 mg, 1.50 mmol, 32%), which were separated by successive chromatographies (diethyl ether:hexane, 1:1) to yield pure **15a** and pure **15b** as yellow syrups.

*3.2.7.1. 5-Phenyl-3-(methylsulfinyl)methylisoxazoline **15a**.* R_f=0.32 (isopropanol:diethyl ether, 1:3); $[\alpha]_D^{20}$=−227.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 2.66 (s, 3H, **CH$_3$**-SO-), 3.26 (dd, 1H, J_{trans} 8.6,

J_{gem} 17.8, **H**-C4), 3.53 (dd, 1H, J_{cis} 11.1, J_{gem} 17.8, **H**-C4), 3.63 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 3.92 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 5.68 (dd, 1H, J_{trans} 8.6, J_{cis} 11.1, **H**-C5) and 7.32–7.40 (m, 5H, **H**-arom.); ^{13}C NMR δ 38.4 (**CH$_3$**-SO-), 45.4 (**C4**), 50.8 (SO-**CH$_2$**-CCN), 82.8 (**C5**), 125.8, 128.4 and 128.8 (**C**H-arom.), 140.0 (**C**-arom.) and 150.7 (**C3**); IR (KBr, liquid film): 3050, 3025, 2975, 2950, 1610, 1475, 1460, 1430, 1410, 1335, 1305, 1210, 1030, 910, 760 and 700 cm^{-1}; MS (*m*/*e*) (ei): 223 (M$^+$, 23), 206 (4), 175 (2), 160 (78), 142 (16), 129 (72), 115 (100), 91 (24), 77 (38) and 51 (23). Anal. calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.52; H, 6.06; N, 6.31.

3.2.7.2. 5-Phenyl-3-(methylsulfinyl)methylisoxazoline ***15b***. R_f=0.27 (isopropanol:diethyl ether, 1:3); $[\alpha]_D^{20}$=+229.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 2.68 (s, 3H, **CH$_3$**-SO-), 3.07 (dd, 1H, J_{trans} 8.4, J_{gem} 17.4, **H**-C4), 3.63 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 3.66 (dd, 1H, J_{cis} 11.0, J_{gem} 17.4, **H**-C4), 3.91 (d, 1H, J_{gem} 13.5, SO-**CH$_2$**-CCN), 5.68 (dd, 1H, J_{trans} 8.4, J_{cis} 11.0, **H**-C5) and 7.27–7.41 (m, 5H, **H**-arom.); ^{13}C NMR δ 38.2 (**CH$_3$**-SO-), 45.6 (**C4**), 50.4 (SO-**CH$_2$**-CCN), 82.8 (**C5**), 125.7, 128.4 and 128.8 (**C**H-arom.), 140.0 (**C**-arom.) and 150.6 (**C3**); IR (KBr, liquid film): 3050, 3025, 2975, 2925, 1610, 1475, 1460, 1430, 1415, 1340, 1305, 1210, 1115, 1080, 1030, 905, 760, 735 and 700 cm^{-1}; MS (*m*/*e*) (ei): 223 (M$^+$, 18), 160 (57), 142 (16), 129 (72), 115 (160), 91 (26), 77 (40) and 51 (33). Anal. calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.52; H, 6.06; N, 6.23.

3.3. Addition of 4,5-diphenyl-3-(methylsulfinyl)methylisoxazoline ***12a*** *to 2,3-*O*-isopropylidene-*D*-glyceraldehyde* ***17***

To a stirred solution of compound **12a** (1 g, 3.34 mmol) in THF (70 ml) cooled at −90°C, LDA (5 mmol) as a solution in THF was added dropwise. After two hours at −90°C, freshly distilled aldehyde **17** (1.3 g, 10.03 mmol) was added at once and the reaction mixture was stirred for an additional hour, then quenched by addition of a saturated aqueous ammonium chloride solution and warmed to room temperature. The organic layer was separated and the aqueous phase extracted twice with dichloromethane; the combined organic layers were dried and concentrated under reduced pressure. The work-up led to a mixture containing compounds **18**, **19** and **20** in a 12:4:84 ratio (estimated by integration of the signals corresponding to H-C5 in the ^{1}H NMR spectrum of the crude reaction). Column chromatography using diethyl ether:hexane (1:1) as the eluent afforded a fraction (145 mg, 20% yield) containing a mixture of compounds **18** and **19**, and pure **20** (664 mg, 48% yield) as a white solid. After subsequent flash chromatography (diethyl ether:hexane, 1:2) pure **18** and pure **19** were obtained as clear syrups.

*3.3.1. (4*R*,5*R*)-Diphenyl-3-(2′-hydroxy-(3′*R*)-4′-isopropylidendioxy-1′-(*S$_S$*)-methylsulfinyl)-butylisoxazoline* ***18***

R_f=0.20 (diethyl ether:hexane, 10:1); $[\alpha]_D^{20}$=−301.3 (*c* 0.31, $CHCl_3$); ^{1}H NMR δ 1.10 and 1.24 (2s, each 3H, C(CH$_3$)$_2$), 2.63 (s, 3H, **CH$_3$**-SO-), 3.30 (d, 1H, $J_{2',OH}$ 2.1, **H**O-C2′, exchanges with D_2O), 3.67 (dd, 1H, J_{gem} 8.6, $J_{4',3'}$ 5.7, **H**-C4′), 3.81 (dd, 1H, J_{gem} 8.6, $J_{4',3'}$ 3.7, **H**′-C4′), 4.01–4.07 (m, 3H, **H**-C1′, **H**-C2′ and **H**-C3′), 4.76 (d, 1H, $J_{4,5}$ 6.4, **H**-C4), 5.66 (d, 1H, $J_{5,4}$ 6.4, **H**-C5) and 7.29–7.45 (m, 10H, **H**-arom.); ^{13}C NMR δ 24.9 and 26.6 (C(**C**H$_3$)$_2$), 36.2 (**CH$_3$**-SO-), 58.8 (**C**2′), 65.7 (**C**4), 66.0 (**C**4′), 71.8 (**C**3′), 75.1 (**C**1′), 90.3 (**C**5), 109.7 (**C**(CH$_3$)$_2$), 125.7, 128.2, 128.4,

128.6, 129.0 and 129.6 (**C**H-arom.), 137.4 (**C**arom-C4), 139.6 (**C**arom-C5) and 156.6 (**C**3); IR (KBr, liquid film): 3250, 3010, 2950, 2900, 1610, 1495, 1460, 1380, 1375, 1245, 1220, 1070, 1020, 905 and 705 cm^{-1}; MS (m/z) (ei) (relative intensity): 431 (1, M^++2), 430 (3, M^++1), 429 (12, M^+), 414 (3, M^+−15), 366 (11, M^+-CH_3SO), 351 (9, $M^+-(CH_3SO+CH_3)$), 266 (100, $C_{17}H_{16}NO_2^+$), 101 (84, $C_5H_9O_2^+$), 43 (77, $C_2H_3O^+$). Anal. calcd for $C_{23}H_{27}O_5NS$: C, 64.32; H, 6.34, N, 3.26. Found: C, 64.25; H, 6.33; N, 3.31.

*3.3.2. (4*R,*5*R*)-Diphenyl-3-(2′-hydroxy-(3′*R*),4′-isopropylidendioxy-1′-(*S_S*)-methylsulfinyl)-butylisoxazoline* **19**

R_f=0.12 (diethyl ether:hexane, 10:1); $[\alpha]_D^{20}$=+164.0 (*c* 0.45, $CHCl_3$); ^{1}H NMR δ 1.19 and 1.32 (2s, each 3H, C(CH_3)$_2$), 2.83 (s, 3H, **CH$_3$**-SO-), 3.54 (d, 1H, $J_{1',2'}$ 8.4, **H**-C1′), 3.89–3.94 (m, 1H, **H**-C3′), 3.94 (dd, 1H, J_{gem} 7.9, $J_{4',3'}$ 2.5, **H**-C4′), 4.04 (dd, 1H, J_{gem} 7.9, $J_{4',3'}$ 2.8, **H**-C4′), 4.22 (ddd, 1H, $J_{2',1'}$ 8.4, $J_{2'OH}$ 2.9, $J_{2',3'}$ 6.8, **H**-C2′, collapses to dd on exchange with D_2O, $J_{2',1'}$ 8.4, $J_{2',3'}$ 6.8), 4.46 (d, 1H, $J_{2',OH}$ 2.9, **H**O-C2′, exchanges with D_2O), 4.74 (d, 1H, $J_{4,5}$ 7.5, **H**-C4), 5.60 (d, 1H, $J_{5,4}$ 7.5, **H**-C5) and 7.28–7.49 (m, 10H, **H**-arom.); ^{13}C NMR δ 25.3 and 26.4 (C(**C**H$_3$)$_2$), 35.3 (**C**H$_3$-SO-), 57.9 (**C**2′), 64.6 (**C**4), 66.1 (**C**4′), 72.4 (**C**3′), 77.2 (**C**1′), 91.0 (**C**5), 110.0 (**C**(CH$_3$)$_2$), 125.5, 128.2, 128.4, 128.8 and 129.8 (**CH**-arom.), 137.2 (**C**arom.-C4), 139.6 (**C**arom.-C5) and 153.7 (**C**3); IR (KBr, liquid film): 3300, 3010, 2950, 2900, 1605, 1495, 1460, 1385, 1375, 1260, 1220, 1070, 1030 and 705 cm^{-1}; MS (m/z) (ei) (relative intensity): 430 (1, M^++1), 429 (3, M^+), 414 (2, M^+−15), 366 (7, M^+-CH_3SO), 351 (4, $M^+-(CH_3SO+CH_3)$), 299 (11, $C_{17}H_{17}NO_2S^+$), 266 (90, $C_{17}H_{16}NO_2^+$), 101 (100, $C_5H_9O_2^+$), 43 (76, $C_2H_3O^+$). Anal. calcd for $C_{23}H_{27}O_5NS$: C, 64.32; H, 6.34, N, 3.26. Found: C, 64.37; H, 6.40; N, 3.29.

*3.3.3. (4*R,*5*R*)-Diphenyl-3-(2′*R*)-hydroxy-(3′*R*),4′-isopropylidendioxy-(1′*S*)-methyl-(*S_S*)-sulfinyl)butylisoxazoline* **20**

A white solid was recrystallized from isopropanol–diethyl ether to give crystals and its structure was determined by X-ray diffraction: mp 137.5–138.5°C. R_f=0.31 (ethyl acetate:diethyl ether, 1:1.5); $[\alpha]_D^{20}$=−228.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.20 and 1.32 (2s, each 3H, C(CH_3)$_2$), 2.62 (s, 3H, **CH$_3$**-SO-), 3.62 (d, 1H, $J_{2',OH}$ 8.7, **H**O-C2′, exchanges with D_2O), 3.80 (d, 1H, $J_{1',2'}$ 2.3, **H**-C1′), 3.75–3.82 (m, 1H, **H**-C3′), 3.93 (dd, 1H, J_{gem} 8.7, $J_{4',3'}$ 5.1, **H**-C4′), 4.06 (dd, 1H, J_{gem} 8.7, $J_{4',3'}$ 6.2, **H**-C4′), 4.40 (ddd, 1H, $J_{2',1'}$ 2.3, $J_{2'OH}$ 8.7, $J_{2',3'}$ 8.8, **H**-C2′, collapses to dd on exchange with D_2O, $J_{2',1'}$ 2.3, $J_{2',3'}$ 8.8), 4.36 (d, 1H, $J_{4,5}$ 6.2, **H**-C4), 5.64 (d, 1H, $J_{5,4}$ 6.2, **H**-C5) and 7.24–7.46 (m, 10H, **H**-arom.); ^{13}C NMR δ 25.0 and 26.7 (C(**C**H$_3$)$_2$)), 35.5 (**C**H$_3$-SO-), 57.4 (**C**2′), 66.2 (**C**4), 67.6 (**C**4′), 69.0 (**C**3′), 76.1 (**C**1′), 89.6 (**C**5), 109.9 (**C**(CH$_3$)$_2$), 125.2, 128.0, 128.5, 128.8, 128.9 and 129.5 (**CH**-arom.), 136.3 (**C**arom.-C4), 139.8 (**C**arom.-C5) and 154.4 (**C**3); IR (KBr, liquid film): 3150, 3050, 3010, 2950, 2900, 1605, 1495, 1460, 1385, 1370, 1295, 1215, 1060, 1025, 915, 860 and 705 cm^{-1}; MS (m/z) (ci) (relative intensity): 328 (2), 300 (12), 197 (5), 180 (6), 147 (2), 131 (66) 107 (100). Anal. calcd for $C_{23}H_{27}NO_5S$: C, 64.32; H, 6.34, N, 3.26. Found: C, 64.02; H, 6.31; N, 3.13.

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