Tetrahedron: *Asymmetry* 22 (2011) 1467–1472

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Sulfone chemistry for the synthesis of *C*-branched pyrrolidines

Mari F. Flores [a], Pilar García [a], Narciso M. Garrido [a], Isidro S. Marcos [a], Francisca Sanz [b], David Díez [a,*]

[a] *Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caidos 1-5, 37008 Salamanca, Spain*
[b] *Servicio General de Rayos X, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caidos 1-5, 37008 Salamanca, Spain*

ARTICLE INFO

Article history:
Received 12 July 2011
Accepted 20 July 2011
Available online 6 September 2011

Dedicated to Professor Pilar Basabe on the occasion of her 65th birthday

ABSTRACT

The synthesis of a *C*-branched homopyrrolidinol has been achieved by making use of the reactivity of the sulfone group in four different ways. The stereochemistry of the two compounds has been established by X-ray diffraction analysis.

1. Introduction

The sulfone group is one of the most versatile functional groups in organic chemistry.[1]

From a methodological point of view, sulfones have been employed in the synthesis of many of the most demanding and sophisticated complex molecules.[2] The excellent properties of this group, both as a powerful electron withdrawing group and as an easily removed substituent,[3] have made it increasingly important in synthetic chemistry; for example in the synthesis of peptide-based inhibitors.[4]

In our research group we are interested in the chemistry of this functionality in the form of allyl sulfones such as **I** (Fig. 1), which can be transformed into dienyl sulfone **II** by treatment with *n*-BuLi.[5] This compound is very useful in organic synthesis because it can be transformed into isosorbide analogues **III**, and generates four stereocenters in one step.[6] Allyl sulfone **I** was used as the starting material for the synthesis of vinylcyclopropanols **IV**,[7] which allowed us to obtain aminoacids **V**[8] and **VI**[9] (Fig. 1).

The Sharpless epoxidation of **II** led to both enantiomers of **VII**.[10] One of these chiral epoxides was easily transformed into vinyl sulfone **VIII**, which can also be obtained without difficulty from D-erithronolactol.[11] Compound **VIII** proved to be the most versatile of all, since it could be cyclisized into sulfone **IX**[10] (Fig. 1). Recently, our attention was focused on the synthesis of chiral organocatalysts. Thus, we decided to use vinyl sulfone **VIII** for the synthesis of organocatalysts, synthons, and biologically active compounds (Fig. 2).

Vinyl sulfone **VIII** was transformed into chiral catalyst **X** (Fig. 2).[12] The diastereoselective epoxidation of **VIII** gave epoxide **XI**,[13] which was transformed into vinylbromides such as **XIII**[13] or biologically active iminosugars such as **DIM XII**,[14] or organocatalysts such as **XIV** (Fig. 2).[15]

Herein we have employed step by step the reactivity of the sulfone group for the synthesis of *C*-branched homoprolinols, that is, the stabilization of an anion at the α-position of the sulfone and the addition to a nitrone,[16] the 1,3 dipolar cycloaddition of a vinyl sulfone and a nitrone,[17] and the formation and reduction of the aldehyde formed[18] by the opening of the isoxazolidine and a desulfonylation reaction.[2]

2. Results and discussion

It is well known that proline and proline derivatives play unique and important roles in the conformation of peptides and proteins. As a result, many analogues of these compounds have been synthesized.

Moreover, *C*-branched proline derivatives have attracted much attention since the substitution at C-2 can change the properties of the aminoacid or their derivatives.[19] Recently, the synthesis of the Me-C2 of proline **1**, or tetrazol analogues **2**, which increased the output as organocatalysts,[20] has been described. Barker and co-workers have studied the influence of α-methyl substitution of proline-based organocatalysts on the asymmetric α-oxidation of aldehydes[21] while Fleet and co-workers have described the synthesis of *C*-branched iminosugars, **3**, with interesting biological activities[22] (Fig. 3).

Due to the importance of the *C*-branched pyrrolidine skeleton, we decided to develop a new methodology to obtain these kinds of compounds in a simple manner using the reactivity of the sulfone group.

Nitrone **4** was chosen as the starting material, as it is a known compound used in the synthesis of many natural and biologically active compounds, such as polyhydroxypyrrolidines or polyhydroxypyrrolizidines, and we were able to obtain an X-ray structure.[23]

* Corresponding author. Tel.: +34 923 294474; fax: +34 923 294574.
E-mail address: ddm@usal.es (D. Díez).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.08.001

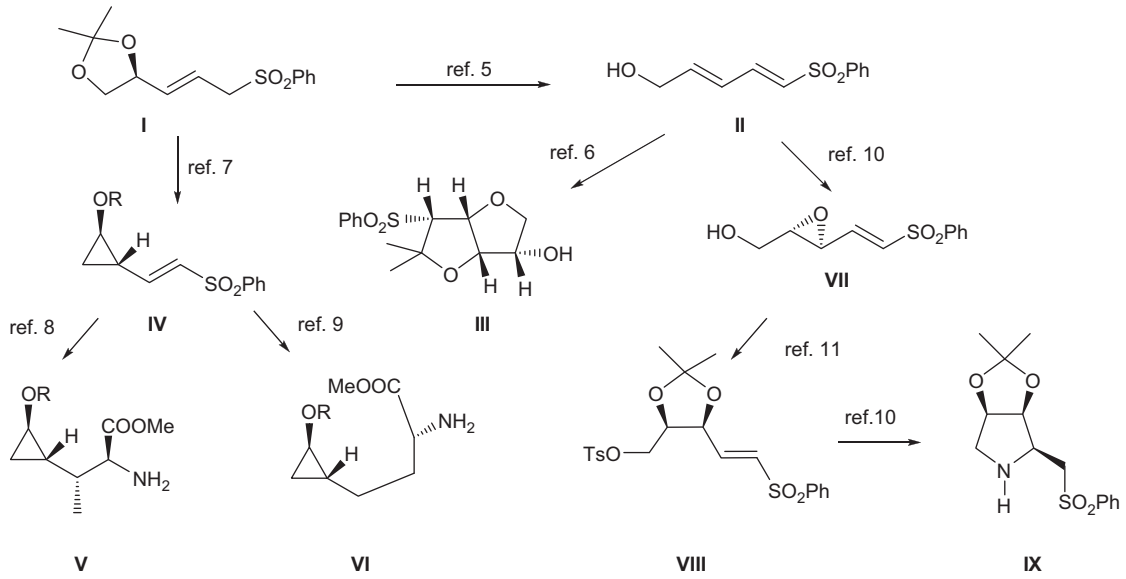


Figure 1. The use of allyl **I** and dienyl sulfones **II** as synthons.

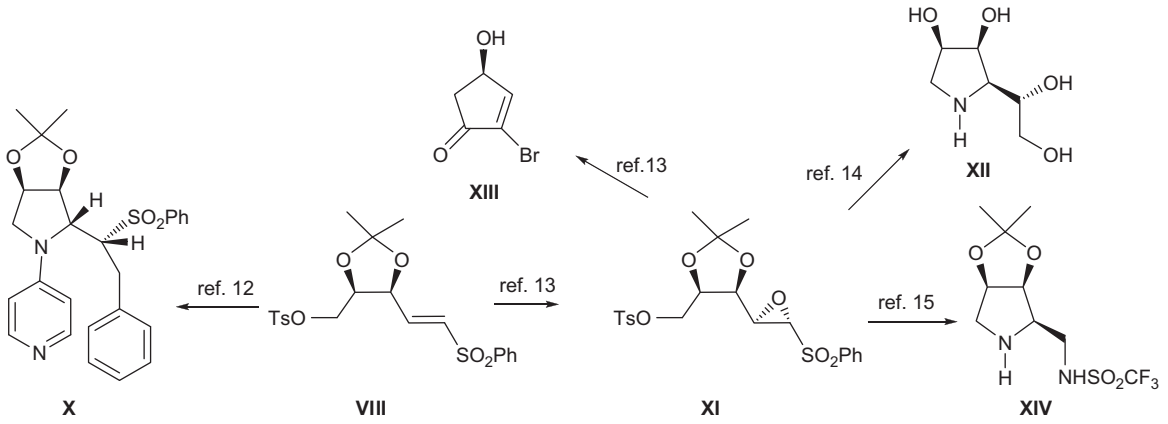


Figure 2. Vinyl sulfone **VIII** used as a starting material in the synthesis of useful synthons.

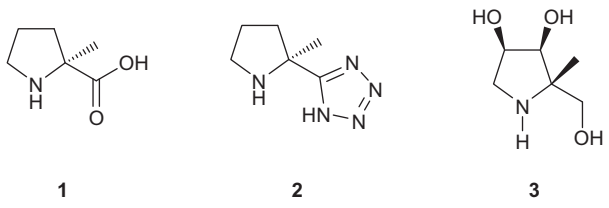
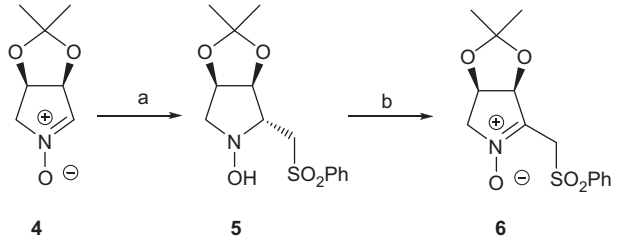


Figure 3. Me-branched pyrrolidines.



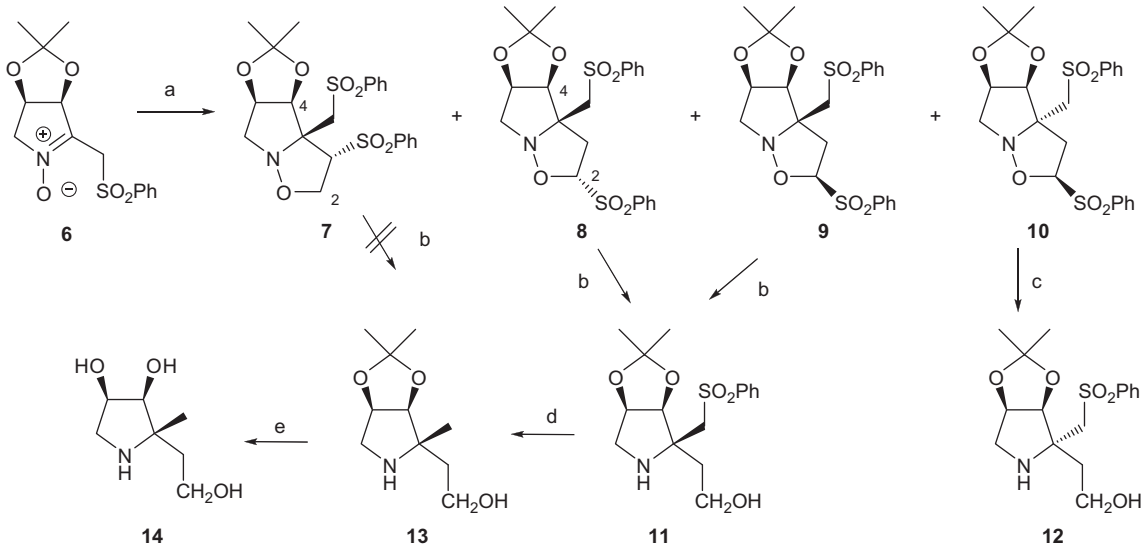
Scheme 1. Reagents and conditions: (a) $MeSO_2Ph$, *n*-BuLi, THF, −78 °C, (48%); (b) MnO_2, DCM, 0 °C, 2 h, (98%).

The addition of the lithium derivative of methyl phenyl sulfone to nitrone **4** under the usual conditions stereoselectively led to hydroxylamine **5** (Scheme 1). We had previously used this reaction in the synthesis of an organocatalyst.[24] Hydroxylamine **5** was subjected to air oxidation and gave nitrone **6** in low yield. In order to increase the yield, hydroxylamine **5** was oxidised to the required nitrone by treatment with manganese dioxide[25] in nearly quantitative yield (Scheme 1). The structure of nitrone **6** was established by X-ray determination.[26]

We were able to obtain nitrone **6** in sufficient yield, to tackle the synthesis of a *C*-branched substituted pyrrolidine. First, we studied the 1,3-dipolar cycloaddition of nitrone **6** and phenyl vinyl sulfone. Several solvents were tested but no reaction took place. Using toluene at reflux gave a mixture of isoxazolidines, which were obtained in 70% yield, as depicted in Scheme 2.

After chromatographic separation of isomers **7**–**10**, the stereochemical assignment of each of the products was determined by NMR spectroscopy. Fortunately, we were able to crystallize isoxazolidines **8** and **9**, and determine their structures by X-ray analysis[27] (Fig. 4).

The stereochemistry of compounds **7** and **10** were established by NMR studies; particularly the ^{13}C NMR resonances of C-3



Scheme 2. Reagents and conditions: (a) phenyl vinyl sulfone, toluene, reflux 110 °C, 24 h (70%), ratio 1.0/3.5/1.4/1.0. (b) Na(Hg) 5%, MeOH, rt, 2 h, (40%). (c) Na(Hg) 5%, MeOH, rt, 2 h, (15%). (d) Na(Hg) 5%, MeOH, 35° C, 20 h, (57%). (e) HCl 6 M, MeOH, rt, 1.5 h, (65%).

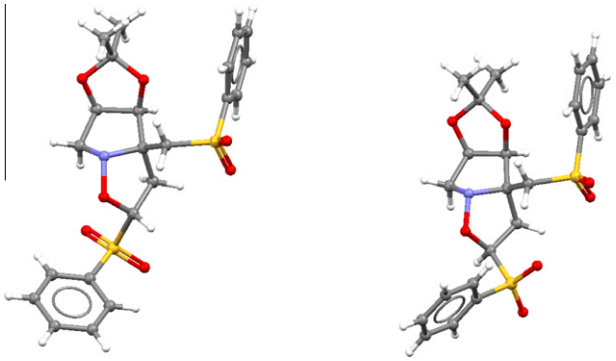


Figure 4. X-ray structures of isoxazolidines **8** and **9**.

(79.2 ppm) for **7** and C-2 (96.2 ppm) in **10** and the NOEs observed for both compounds as shown in Figure 5.

Further reduction of the phenyl sulfonyl group present in the isoxazolidines afforded the desired *C*-branched proline derivative. Compounds **7**, **8, 9,** and **10** were thus submitted to desulfonylation under the usual conditions.[28]

When compounds **8** and **9** were treated with an Na(Hg) amalgam, only pyrrolidine **11** was obtained in moderate yield. Under these reaction conditions, only one sulfone was removed. Similar results were also observed for isoxazolidine **10**, providing pyrrolidine **12**, although in low yield. On the other hand, isoxazolidine **7** did not give any product.

It is worth mentioning that when the sulfonyl group at C-2 was removed, we managed the cleavage of the N–O bond and the reduction of the aldehyde intermediate formed.

Several conditions using a Na(Hg) amalgam were tested to eliminate both sulfonyl groups in one step; however the reaction did not take place in any case. We also attempted alternative methods for the desulfonylation, such as Mg–MeOH–$NiBr_2$, which had been successfully used in obtaining dideoxyaminosugars,[29] but this was unsuccessful in giving the desired product.

Finally, slightly heating the pyrrolidine in MeOH at 35 °C and using 6 equiv of the Na(Hg) amalgam gave the desired pyrrolidine **13**. With compound **13** in hand, our final step was its deprotection under the usual conditions,[6] employing HCl 6 M in MeOH to afford a *C*-branched homopyrrolidinol **14** in a moderate yield. We have thus provided a new route to obtain *C*-branched homopyrrolidines starting from easily available nitrones using the sulfone reactivity.

3. Conclusions

In conclusion, the synthesis of a *C*-branched homoprolinol derivative has been achieved from chiral nitrone **1,** in only five steps. The synthesis was carried out using only sulfone chemistry, which corroborates the versatility of the sulfone group. Moreover, the structures of two compounds have been determined by X-ray

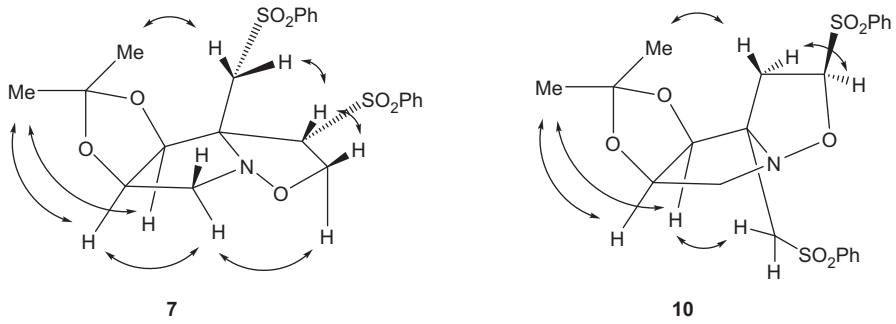


Figure 5. Main NOEs for the structure determination of **7** and **10**.

analysis, which gives more value to the sulfone group and its capability to form crystals easily.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased with the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C NMR, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ ppm and coupling constants (J) are given in Hertz. Mass spectra were performed at a VG-TS 250 spectrometer at 70 eV ionizing voltage. Mass spectra are presented as m/z (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionization (ammonia as gas) or the Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin-Elmer 241 polarimeter in 1 dm cells. THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

4.2. Cycloaddition of nitrone 6 to phenyl vinyl sulfone

Phenyl vinyl sulfone (850 mg, 5.04 mmol) was added to a solution of nitrone **6** (1.26 g, 4.06 mmol) in toluene (13.5 mL) at rt. The resulting mixture was heated at reflux for 24 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **7**, **8**, **9,** and **10** in 70% yield (ratio 1.0/3.5/1.4/1.0).

4.2.1. (3*S*,3a*S*,4*S*,5*R*)-3-Phenylsulfonyl-3a-phenylsulfonylmethyl-4,5-isopropylidenedioxy-hexahydropyrrolo[1,2-*b*]-isoxazole 7

$[\alpha]_D^{20} = +8.2$ (c 0.22, $CHCl_3$). IR (film) ν (cm^{-1}) 3412, 2921, 1638, 1446, 1381; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.06–7.99 (4H, m, H *ortho*′ and H *ortho*), 7.65–7.54 (6H, m, H*Ar*), 5.52 (1H, dd, J = 7.4 and 9.3 Hz, H-3), 5.48 (1H, d, J = 6.4 Hz, H-4), 4.93 (1H, dt, J = 1.8 and 6.4 Hz, H-5), 4.26 (1H, dd, J = 7.4 and 9.4 Hz, H_A-2), 3.97 (1H, t, J = 9.4 Hz, H_B-2), 3.96 (1H, d, J = 15 Hz, H_A-1′), 3.38 (1H, dd, J = 6.4 and 12.7 Hz, H_A-6), 3.30 (1H, d, J = 15 Hz, H_B-1′), 3.15 (1H, dd, J = 1.8 and 12.7 Hz, H_B-6), 1.33 (3H, s, Me-acetonide), 1.26 (3H, s, Me-acetonide).^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.3, 139.5, 134.5, 133.8, 129.7, 129.2, 128.8, 128.0, 112.1, 79.2, 78.9, 77.7, 77.3, 67.2, 58.1, 55.9, 25.7, 24.0; HRMS (ESI): calcd for $C_{22}H_{25}NO_7S_2Na$, $[M+Na]^+$: 502.0964; found 502.0983.

4.2.2. (2*S*,3a*S*,4*S*,5*R*)-2-Phenylsulfonyl-3a-phenylsulfonylmethyl-4,5-isopropylidenedioxy-hexahydropyrrolo[1,2-*b*]-isoxazole 8

$[\alpha]_D^{20} = -104.7$ (c 0.46, $CHCl_3$). IR (film) ν (cm^{-1}) 3375, 3048, 2983, 2925, 1450, 1381, 1315, 1148; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.94–7.87 (4H, m, H *ortho*′ and H *ortho*), 7.68–7.54 (6H, m, H*Ar*), 5.18 (1H, dd, J = 6.9 and 9.7 Hz, H-2), 4.96 (1H, bt, J = 6.2 Hz, H-5), 4.80 (1H, d, J = 6.2 Hz, H-4), 3.92 (1H, dd, J = 1.2 and 14.4 Hz, H_A-1′), 3.77 (1H, dd, J = 6.2 and 12.4 Hz, H_A-6), 3.61 (1H, dd, J = 9.7 and 14 Hz, H_B-3), 3.58 (1H, d, J = 12.4 Hz, H_B-6), 3.22 (1H, d, J = 14.4 Hz, H_B-1′), 2.65 (1H, dd, J = 6.9 and 14 Hz, H_A-3), 1.33 (3H, s, Me-acetonide), 1.26 (3H, s, Me-acetonide).^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.6, 137.0, 134.5, 133.1, 129.4, 129.1, 128.0, 127.8, 111.4, 95.7, 79.1, 77.7, 76.4, 59.3, 57.5, 34.4, 25.8, 24.6.; HRMS (ESI): calcd for $C_{22}H_{25}NO_7S_2Na$, $[M+Na]^+$: 502.0964; found 502.0940.

4.2.3. (2*R*,3a*S*,4*S*,5*R*)-2-Phenylsulfonyl-3a-phenylsulfonylmethyl-4,5-isopropylidenedioxy-hexahydropyrrolo[1,2-*b*]isoxazole 9

$[\alpha]_D^{20} = -45.2$ (c 0.46, $CHCl_3$). IR (film) ν (cm^{-1}) 3424, 3060, 2974, 2917, 1626, 1581, 1458, 1311, 1140; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.02 (2H, d, J = 8.1 Hz, H *ortho*′), 7.94 (2H, d, J = 8.3 Hz, H *ortho*), 7.68–7.54 (6H, m, H*Ar*), 5.14 (1H, dd, J = 4.2 and 9.8 Hz, H-2), 4.94 (1H, d, J = 6.2 Hz, H-4), 4.85 (1H, dt, J = 1.7 and 6.2 Hz, H-5), 3.97 (1H, d, J = 13.2 Hz, H_B-1′), 3.88 (1H, dd, J = 4.2 and 15 Hz, H_B-3), 3.82 (1H, d, J = 13.2 Hz, H_A-1′), 3.38 (1H, dd, J = 1.7 and 12.6 Hz, H_B-6), 2.88 (1H, dd, J = 6.2 and 12.6 Hz, H_A-6), 2.48 (1H, dd, J = 9.8 and 15 Hz, H_A-3), 1.36 (3H, s, Me-acetonide), 1.28 (3H, s, Me-acetonide).^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 141.7, 136.3, 134.3, 133.5, 129.5, 129.4, 128.9, 127.9, 112.1, 92.5, 82.0, 77.3, 75.6, 58.8, 58.1, 35.9, 27.2, 24.8.; HRMS (ESI): calcd for $C_{22}H_{25}NO_7S_2Na$, $[M+Na]^+$: 502.0964; found 502.0984.

4.2.4. (2*R*,3a*R*,4*S*,5*R*)-2-Phenylsulfonyl-3a-phenylsulfonylmethyl-4,5-isopropylidenedioxy-hexahydropyrrolo[1,2-*b*]-isoxazole 10

$[\alpha]_D^{20} = -55.7$ (c 1.24, $CHCl_3$). IR (film) ν (cm^{-1}) 3383, 3068, 2983, 2938, 1446, 1368, 1303, 1148, 1074; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.93 (2H, s, H *ortho*′), 7.91 (2H, s, H *ortho*), 7.68–7.51 (6H, m, H*Ar*), 5.11 (1H, dd, J = 7.4 and 9.4 Hz, H-2), 4.94 (1H, d, J = 7 Hz, H-4), 4.66 (1H, dd, J = 6.4 and 11.5 Hz, H-5), 3.62 (1H, dd, J = 6.4 and 10.5 Hz, H_A-6), 3.54 (1H, dd, J = 6.4 and 10.5 Hz, H_B-6), 3.37 (1H, dd, J = 9.4 and 14.2 Hz, H_A-3), 3.33 (1H, d, J = 14.4 Hz, H_A-1), 3.25 (1H, d, J = 14.4 Hz, H_B-1), 3.08 (1H, dd, J = 7.4 and 14.2 Hz, H_B-3), 1.63 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide).^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.4, 136.9, 134.3, 134.1, 129.3, 129.3, 129.2, 128.1, 114.9, 96.2, 80.4, 76.9, 74.9, 60.9, 58.5, 33.4, 26.5, 24.8.; HRMS (ESI): calcd for $C_{22}H_{25}NO_7S_2Na$, $[M+Na]^+$: 502.0964; found 502.0964.

4.3. Desulfonylation of 8 to yield 11

To a solution of isoxazolidine **8** (66 mg, 0.14 mmol) in MeOH (1.5 mL) was added 200 mg (0.42 mmol) of 5% Na (Hg) amalgam at rt. The mixture was stirred for 2 h at this temperature under an argon atmosphere. Next, it was filtered to eliminate the Hg residue and concentrated under pressure. The reaction product was then extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, *n*-hexane/EtOAc 6:4) to give pyrrolidine **11** (19 mg, 40%).

4.3.1. (2*S*,3*S*,4*R*)-2-Hydroxyethyl-2-phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine 11

$[\alpha]_D^{20} = -11.0$ (c 0.59, MeOH). IR (film) ν (cm^{-1}) 3318, 2917, 2848, 1638, 1446, 1385, 1303, 1144, 1078; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.94 (2H, d, J = 8.0 Hz, H *ortho*), 7.68–7.54 (3H, m, H*para* and H*meta*), 4.80 (1H, dd, J = 4.5 and 5.6 Hz, H-4), 4.48 (1H, d, J = 5.6 Hz, H-3), 4.05 (1H, dt, J = 2.2 and 10 Hz, H_A-2′), 3.78–3.81 (1H, m, H_B-2′), 3.68 (1H, d, J = 7.8 Hz, H_A-1″), 3.60 (1H, d, J = 7.8 Hz, H_B-1″), 3.12 (1H, dd, J = 4.5 and 13.8 Hz, H_A-5), 2.95 (1H, d, J = 13.8 Hz, H_B-5), 2.15- 2.03 (2H, m, CH_2-1′), 1.39 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide).^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 141.9, 133.8, 129.3, 128.0, 111.4, 85.6, 82.4,

67.4, 59.9, 57.8, 50.7, 31.6, 26.2, 24.2.; HRMS (ESI): calcd for $C_{16}H_{24}NO_5S$, $[M+H]^+$: 342.1369; found 342.1361.

4.4. Desulfonylation of 10 to yield 12

To a solution of isoxazolidine **10** (97.4 mg, 0.20 mmol) in MeOH (2.5 mL) was added 290 mg (0.60 mmol) of 5% Na (Hg) amalgam at rt. The mixture was stirred for 2 h at this temperature under an argon atmosphere. Next, it was filtered to eliminate the Hg residue and concentrated under reduced pressure. The reaction product was then extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, *n*-hexane/EtOAc 6:4) to give pyrrolidine **12** (10 mg, 15%).

4.4.1. (2*R*,3*S*,4*R*)-2-Hydroxyethyl-2-phenylsulfonylmethyl-3,4-isopropylidenedioxypyrrolidine 12

$[\alpha]_D^{20} = -22.5$ (*c* 1.03, MeOH). IR (film) ν (cm^{-1}) 3412, 2983, 2929, 2864, 1389, 1213, 1144, 1086; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.94 (2H, d, J = 8.0 Hz, H *ortho*), 7.62–7.58 (3H, m, H*para* and H*meta*), 4.72 (1H, dd, J = 4.4 and 5.8 Hz, H-4), 4.55 (1H, d, J = 5.8 Hz, H-3), 3.80–3.70 (2H, m, CH_2-2″), 3.32 (1H, d, J = 14.6 Hz, H_A-1″), 3.20 (1H, d, J = 14.6 Hz, H_B-1″), 3.02 (1H, d, J = 13.4 Hz, H_B-5), 2.83 (1H, dd, J = 4.4 and 13.4 Hz, H_A-5), 2.35–2.22 (2H, m, CH_2-1′), 1.48 (3H, s, Me-acetonide), 1.30 (3H, s, Me-acetonide).^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 141.5, 134.0, 129.5, 127.9, 111.9, 85.5, 81.8, 67.5, 56.7, 50.6, 35.0, 26.2, 24.5.; HRMS (ESI): calcd for $C_{16}H_{24}NO_5S$, $[M+H]^+$: 342.1369; found 342.1372

4.5. Desulfonylation of 11 to yield 13

To a solution of pyrrolidine **11** (50.0 mg, 0.15 mmol) in MeOH (2.5 mL) was added 460 mg (0.90 mmol) of 5% Na (Hg) amalgam at rt. The mixture was stirred for 20 h at 35 °C under an argon atmosphere. Then, it was filtered to eliminate the Hg residue and concentrated under reduced pressure. The reaction product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, *n*-hexane/EtOAc 2:8) to give the desired pyrrolidine **13** (17 mg, 57%).

4.5.1. (2*S*,3*S*,4*R*)-2-Hydroxyethyl-2-methyl-3,4-isopropylidenedioxypyrrolidine 13

$[\alpha]_D^{20} = -12.3$ (*c* 0.3, MeOH). IR (film) ν (cm^{-1}) 3307, 2925, 2856, 1605, 1381, 1123, 1082, 772; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.75 (1H, dd, J = 4 and 5.4 Hz, H-4), 4.12 (1H, d, J = 5.4 Hz, H-3), 4.10–4.05 (1H, m, H_A-2′), 3.68–3.57 (1H, m, H_B-2″), 3.04 (1H, dd, J = 4 and 14 Hz, H_A-5), 2.97 (1H, d, J = 14 Hz, H_B-5), 1.78–1.65 (1H, m, H_A-1′), 1.47 (3H, s, Me-acetonide), 1.29 (3H, s, CH_3-1″), 1.30 (3H, s, Me-acetonide), 1.15–1.05 (1H, m, H_B-1′).^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 111.1, 87.8, 83.2, 76.6, 66.2, 60.1, 51.0, 34.1, 26.3, 24.1, 18.7.; HRMS (ESI): calcd for $C_{10}H_{20}NO_3$, $[M+H]^+$: 202.1437; found 202.1418.

4.6. Deprotection of 13 to yield 14

To a solution of pyrrolidine **13** (15.0 mg, 0.07 mmol) in MeOH (1.5 mL) was added 2–3 drops of HCl 6 M at rt. The mixture was stirred for 1.5 h under an argon atmosphere. Then, it was diluted with MeOH and concentrated under reduced pressure to give pyrrolidine **13** (7.3 mg, 65%).

4.6.1. (2*S*,3*S*,4*R*)-2-Hydroxyethyl-2-methyl-3,4-dihydroxypyrrolidine 14

$[\alpha]_D^{20} = -32.9$ (*c* 0.4, H_2O). IR (film) ν (cm^{-1}) 3456, 2870, 1431, 1388, 1103, 1052, 772; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 4.40 (1H, m, H-4), 4.10 (1H, t, J = 6.8 Hz, H_A-2′), 3,94 (1H, d, J = 5.0 Hz, H-3), 3.70–3.61 (1H, m, H_B-2′), 3.45 (1H, dd, J = 6.0 and 13.4 Hz, H_A-5), 3.08 (1H, dd, J = 6.0 and 13.4 Hz, H_B-5), 2.08–2.03 (1H, m, H_A-1′), 1.85–1.80 (1H, m, H_B-1′),1.34 (3H, s, CH_3-1″). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 75.9, 69.4, 67.5, 57.2, 48.1, 37.9, 17.3.; HRMS (ESI): calcd for $C_7H_{16}NO_3$, $[M+H]^+$: 162.2068; found 162.2070.

Acknowledgments

The authors thank the Junta de Castilla y León for financial support (GR178, SA001A09 and EUI2008-000173), MICINN (CTQ2009-11172) and for the doctoral fellowship awarded to M.F.F.

References

1. (a) Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulfoxides*; Jonh Wiley and Sons: ChiChester, 1988; (b) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993; (c) Paquette, L. A. *Synlett* **2001**, 1–12; (d) Najera, C.; Sansano, J. M. *Recent Res. Devel. Org. Chem.* **1998**, *2*, 637; (e) Chinchilla, R.; Najera, C. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 437.
2. Ley, S. V.; Armstrong, A.; Díez-Martín, D.; Ford, M. J.; Grice, P.; Knight, J. G.; Kolb, H. C.; Madin, A.; Marby, C. A.; Mukherjee, S.; Shaw, A. N.; Slawin, A. M. Z.; Vile, S.; White, A. D.; Williams, D. J.; Woods, M. J. *Chem. Soc., Perkin Trans. 1* **1991**, 667.
3. Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.
4. Lovejoy, B.; Welch, A. R.; Carr, S.; Luong, C.; Broka, C.; Hendriks, R. T.; Campbell, J. A.; Walker, K. A. M.; Martin, R.; Van Wart, H.; Browner, M. F. *Nat Struct. Biol.* **1999**, *6*, 217.
5. (a) Urones, J. G.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Bastida, A. J.; San Feliciano, S. G.; Diez, D.; Goodman, J. M. *Synlett* **1998**, 1361; (b) Diez Martín, D.; San Feliciano, S. G.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Synthesis* **2001**, 1069.
6. Urones, J. G.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; San Feliciano, S. G.; Coca, R.; Diez, D. *Synlett* **1998**, 1364.
7. (a) Diez, D.; García, P.; Pacheco, M. P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synlett* **2002**, 355; (b) Diez, D.; García, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synthesis* **2003**, 53; (c) Diez, D.; García, P.; Fernández, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synlett* **2005**, 158.
8. Diez, D.; García, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Org. Lett.* **2003**, *5*, 3687.
9. (a) Diez, D.; García, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2005**, *61*, 3687; See too: (b) Diez, D.; García, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2005**, *61*, 11641; (c) Diez, D.; García, P.; Moro, R. F.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synthesis* **2005**, 3327.
10. (a) Diez, D.; Beneitez, M. T.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synlett* **2001**, 655; (b) Diez, D.; Beneitez, M. T.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Tetrahedron: Asymmetry* **2002**, *13*, 639.
11. (a) Diez, D.; Beneitez, M. T.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synlett* **2003**, 729; (b) Diez, D.; Núñez, M. G.; Beneitez, A.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synlett* **2009**, 390.
12. Diez, D.; Gil, M. J.; Moro, R. F.; Garrido, N. M.; Marcos, I. S.; Basabe, P.; Sanz, F.; Broughton, H. B.; Urones, J. G. *Tetrahedron: Asymmetry* **2005**, *16*, 2980.
13. Diez, D.; Beneitez, M. T.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Sanz, F.; Broughton, H. B.; Urones, J. G. *Org. Lett.* **2003**, *5*, 4361.
14. Diez, D.; Beneitez, M. T.; Gil, M. J.; Moro, R. F.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synthesis* **2005**, 565.
15. Diez, D.; Gil, M. J.; Moro, R. F.; Marcos, I. S.; García, P.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2007**, *63*, 740.
16. (a) Merino, P.; Lanaspa, A.; Merchan, F.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2381; (b) Merino, P.; Castillo, E.; Merchan, F.; Tejero, T. *Tetrahedron: Asymmetry* **1725**, *1997*, 8; (c) Murga, J.; Portholes, R.; Falomir, E.; Carda, M.; Marco, A. J. *Tetrahedron: Asymmetry* **1807**, *2005*, 16; (d) Delso, I.; Tejero, T.; Goti, A.; Merino, P. *Tetrahedron* **2010**, *66*, 1220.
17. Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808.
18. (a) Chemla, F. J. *Chem. Soc. Perkin Trans. 1* **2002**, 275. and references cited therein; (b) Wee, A. G. H.; McLeod, D. D. *J. Org. Chem.* **2003**, *68*, 6268; (c) Jackson, R. F. W.; Standen, S. P.; Clegg, W.; McCamley, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 141; (d) see also reference 13.
19. (a) De Poli, M.; Moretto, A.; Crisma, M.; Peggion, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B.; Toniolo, C. *Chem. Eur. J.* **2009**, *15*, 8015. and references cited therein; For the synthesis of iminosugars using nitrone chemistry see (b) Li, Y.-X.; Huan, M.-H.; Yamashita, Y.; Kato, A.; Jia, Y.-M.; Wang, W.-B.; Fleet, G. W. J.;

Nash, R. J.; Yu, C.-Y. *Org. Biomol. Chem.* **2011**, *9*, 3405. and references cited therein.
20. Tong, S.-T.; Harris, P. W.; Brimble, M. A.; Barker, D. *Eur. J. Org. Chem.* **2008**, 164.
21. Tong, S.-T.; Harris, P. W. R.; Brimble, M. A.; Barker, D. *Tetrahedron* **2009**, *65*, 4801.
22. (a) Otero, J. M.; Soengas, R. G.; Estevez, J. C.; Estevez, R. J.; Watkin, D. J.; Evinson, E. L.; Nash, R. J.; Fleet, W. J. *Org. Lett.* **2007**, *9*, 623; (b) da Cruz, F. P.; Horne, G.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 6812.
23. Flores, M. F.; García, P.; Garrido, N. M.; Sanz, F.; Diez, D. *Acta Cryst.* **2011**, *E67*, o1115.
24. (a) Flores, M. F.; Núñez, M. G.; Moro, R. F.; Garrido, N. M.; Marcos, I. S.; Iglesias, E. F.; García, P.; Diez, D. *Molecules* **2010**, *15*, 1501; For the addition of organometallics to nitrones see: (b) Delso, I.; Tejero, T.; Goti, A.; Merino, P. *J. Org. Chem.* **2011**, *76*, 4139. and references cited therein.
25. Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503.
26. Flores, M. F.; García, P.; Garrido, N. M.; Sanz, F.; Diez, D. *Acta Cryst.* **2011**, *E67*, o1116.
27. Suitable single crystals of **8** and **9** were mounted on glass fiber for data collection on a Bruker Kappa APEX II CCD diffractometer. Data were collected at 298(2) K using Cu K_α radiation (λ = 1.54178 Å) and ω scan technique, and were corrected for Lorentz and polarization effects. Structure solution, refinement, and data output were carried out with the SHELXTL™ program package. The structures were solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms.
(a) Crystal data for **8**: $C_{22}H_{25}N_1O_7S_2$, M = 479.55, monoclinic, space group $P2_1$ (n° 4), a = 9.0271(3) Å, b = 14.4516(5) Å, c = 9.4376(4) Å, $\alpha = \gamma$ 90, β = 109.507(3)°, V = 1160.52(7) Å^3, Z = 2, D_c = 1.372 Mg/m^3, m = (Cu–K_α) = 0.790 mm^{-1}, F(0 0 0) = 504. 6864 reflections were collected at 4.97 ⩽ 2θ ⩽ 66.05 and merged to give 3336 unique reflections (R_{int} = 0.0282), of which 3142 with $I > 2\sigma I$ were considered to be observed. Final values are R = 0.0354, wR = 0.0843, GOF = 1.074, max/min residual electron density 0.177 and −0.191 e. Å^{-3}.
(b) Crystal data for **9**: $C_{22}H_{25}N_1O_7S_2$, M = 479.55, orthorhombic, space group $P2_12_12_1$ (n° 19), a = 9.4439(3) Å, b = 11.5345(4) Å, c = 20.6737(7) Å, $\alpha = \beta = \gamma$ 90°, V = 2252.00(13) Å^3, Z = 4, D_c = 1.414 Mg/m^3, m = (Cu-K_α) = 2.528 mm^{-1}, F(0 0 0) = 1008. 11481 reflections were collected at 4.28 ⩽ 2θ ⩽ 67.04 and merged to give 3738 unique reflections (R_{int} = 0.0298), of which 3665 with I > 2 σI were considered to be observed. Final values are R = 0.0275, wR = 0.0713, GOF = 1.054, max/min residual electron density 0.212 and -0.225 e. Å^{-3}.
Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary material numbers CCDC CCDC 824817 and 824818, respectively.
28. (a) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477; (b) López-Perez, A.; Adrio, J.; Carretero, J. C. *Angew. Chem. Int.* **2009**, *48*, 340; (c) Flick, A. C.; Arevalo, M. J.; Lee, H. I.; Padwa, A. *J. Org. Chem.* **2010**, *75*, 1992.
29. Das, I.; Pathak, T. *Org Lett.* **2006**, *8*, 1303.