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PAPER

From isoxazolidines to tetrahydro-1,3-oxazines for the synthesis of chiral pyrrolidines†‡

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A novel approach for the synthesis of chiral tetrasubstituted pyrrolidines has been developed. The rearrangement of isoxazolidines into tetrahydro-1,3-oxazines using reactive organic bromides is herein described for the first time. The subsequent opening reaction of these tetrahydro-1,3-oxazines with nucleophiles probes the usefulness of the method for the synthesis of biologically active compounds.

Introduction

Nitrones and sulfones are two of the most important functional groups in organic chemistry due to their versatility.[1] Nitrones undergo several synthetically useful reactions such as 1,3-dipolar cycloadditions and nucleophilic additions, which make them ideal tools for the construction of highly functionalized nitrogen heterocycles.[2] Especially important are the cyclic nitrones, as they have been applied to the synthesis of many biologically active natural products.[3] The excellent properties of the sulfone group as well as its being easily removable, have made it increasingly important in synthetic chemistry, for example in the synthesis of demanding and sophisticated complex molecules such as peptide-based inhibitors.[4] Although there is very extensive literature dedicated to the study of cyclic nitrones[5] and vinyl sulfones,[6] studies of the reactivity of both together are scarce.[7] Recently, we studied the reactivity of several cyclic nitrones with phenylvinylsulfone (Scheme 1).[8]

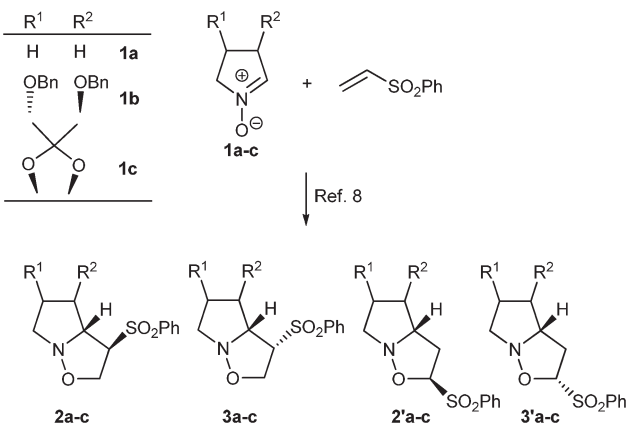
This study started with the aim of obtaining pyrrolidine-based organocatalysts with a phenylsulfone group. In order to synthesize the required organocatalysts it was necessary to open the isoxazolidine ring. This step has usually been achieved by cleavage of the N–O bond, mainly by reduction,[9] oxidation[10] with *m*-CPBA or alkylation of the nitrogen atom followed by treatment with base.[11]

Results and discussion

We initially focused our attention on the ring opening reaction of compounds **2a–c** and **3a–c** (Scheme 2), as they are the straightforward precursors for the organocatalysts.

Treatment of isoxazolidines **2a**,**2b** and **3a**,**3b** with $Mo(CO)_6$, for the reductive cleavage of the N–O bond[9c] (Table 1, entries 1, 3, 5 and 7) gave the expected products, **4a**,**4b** and **5a**,**5b**, respectively. Surprisingly, when compounds **2c** and **3c** were submitted to these conditions, not only were the corresponding pyrrolidines **4c** and **5c** obtained, but two other rearranged products, identified as the corresponding bicyclic tetrahydro-1,3-oxazines **10** and **11** respectively (entries 9 and 11), were obtained.

As we were aware of the importance of this rearrangement, we focused our attention on the alkylation conditions, in order to see if this rearrangement takes place with alkylating agents (Table 1). When isoxazolidines **2a–c** and **3a–c** were submitted to



Scheme 1 Reaction of cyclic nitrones with phenylvinylsulfone.

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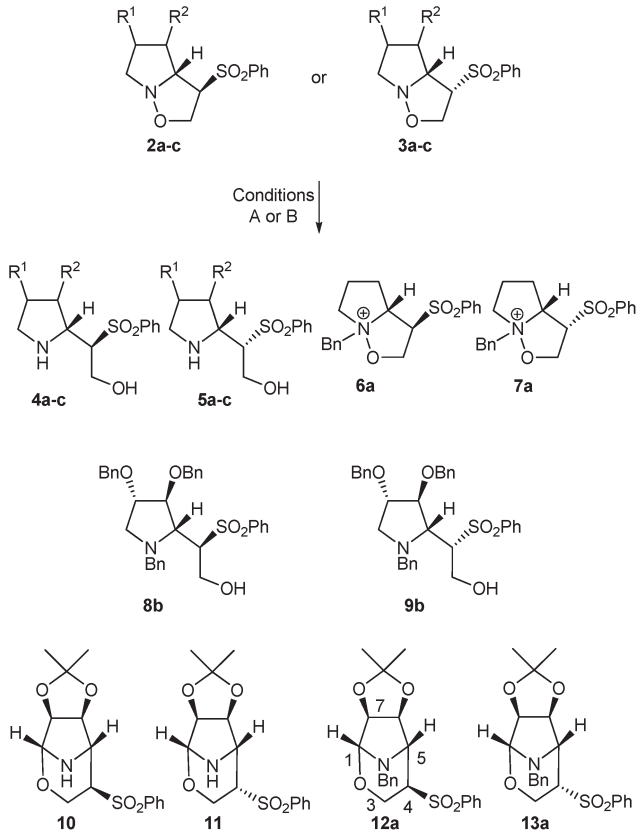
† Electronic supplementary information (ESI) available: Detailed experimental procedures, optimization studies, complete characterization of products, NMR spectra, IR spectra, CCDC 888605. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ra22110a

‡ This manuscript is dedicated to Prof. Arturo San Feliciano on the occasion of his 65th birthday.



Scheme 2 Ring opening reaction of isoxazolidines **2a–c** and **3a–c** (details of reaction conditions A or B are given in Table 1).

treatment with benzyl bromide it was observed that pyrrolidines with no substituents in the 3 or 4 positions (entries 2 and 4) undergo alkylation of the nitrogen atom with neither ring opening nor rearrangement. Pyrrolidines **2b** and **3b**, protected with benzyl groups (entries 6 and 8), gave products resulting from alkylation, followed by ring opening (**8b** and **9b** respectively) in low yield by transformation in the work up or chromatography. To our delight, for compounds with an acetonide group (entries 10 and 12) the rearrangement was the only reaction, producing tetrahydro-1,3-oxazines **12a** and **13a** in moderate and good yields respectively. The stereochemistry of the rearranged compounds was easily established by the

Table 1 Ring opening reaction of isoxazolidines **2a–c** and **3a–c**

Entry	Compound	Conditions[a]	Product (% yield)[b]
1	**2a**	A	**4a**(35)
2	**2a**	B	**6a** (24)
3	**3a**	A	**5a** (35)
4	**3a**	B	**7a** (55)
5	**2b**	A	**4b** (20)
6	**2b**	B	**8b** (10)
7	**3b**	A	**5b** (—)
8	**3b**	B	**9b** (10)
9	**2c**	A	**4c** (50), **10** (50)
10	**2c**	B	**12a** (46)
11	**3c**	A	**5c** (20), **11** (53)
12	**3c**	B	**13a** (67)

[a] Conditions A: $Mo(CO)_6$, H_2O–MeCN, reflux, 24 h; conditions B: BnBr, $CHCl_3$, reflux, 20 h. [b] Yield of isolated product.

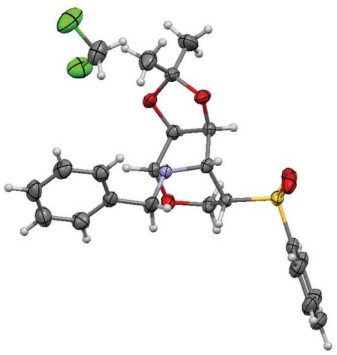


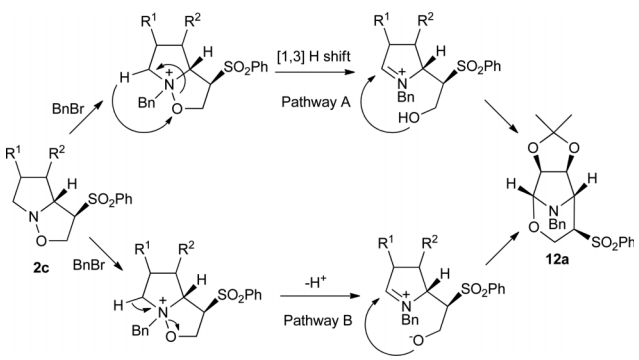
Fig. 1 X-ray crystal structure of compound **13a**. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are shown as spheres of arbitrary radius.

observation of no coupling between the H-5 and H-4 hydrogens in the ^{1}H NMR spectra and corroborated by X-ray analysis for compound **13a** (Fig. 1).[12]

This rearrangement could be understood as a 1,3-hydride shift from the C–H in the α-position with regard to the tertiary amine (*tert*-amino effect) to the oxygen of the isoxazolidine (Pathway A in Scheme 3). The structural rigidity of the tricyclic derivatives **2c** and **3c** could be responsible for their unique reactivity, forcing the topology required in the transition state. Therefore, this could represent a nice example of a 1,3-hydride shift triggered reaction cascade involving ring opening–ring closure sequences which, to the best of our knowledge, are quite uncommon. Related intramolecular hydride shift–ring closure transformations are known, including some recent advances through catalytic approaches.[13] It could also be considered a deprotonation–ring opening followed by the cyclization step (Pathway B in Scheme 3). More synthetic studies to better understand the mechanism are being conducted.

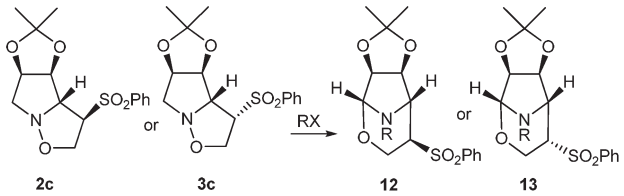
This kind of behaviour of the isoxazolidine moiety for these kinds of compounds has rarely been observed. The related formation of oxazines from isoxazolidines has been observed by Uccella and co-workers through alkylation of the isoxazolidines to give isoxazolidinium salts, followed by treatment with a base.[14]

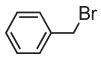
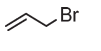
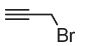
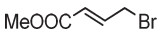
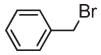
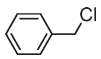
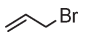
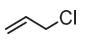
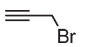
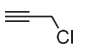
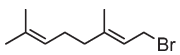
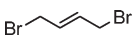
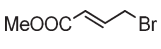
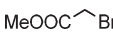
The novelty of the reactions reported herein rests in their occurrence under thermal conditions with no reagent added, which would further support a 1,3-hydride shift mechanism.



Scheme 3 Suggested mechanisms for the synthesis of tetrahydro-1,3-oxazines.

Table 2 Isoxazolidine to oxazine rearrangement[a]



Entry	S. M.	RX	Product	Yield (%)
1	**2c**		**12a**	46
2	**2c**		**12b**	60
3	**2c**		[b]	30
4	**2c**		**12d**	25
5	**3c**		**13a**	67
6	**3c**		**13a**	20
7	**3c**		**13b**	74
8	**3c**		**13b**	—
9	**3c**		**13c**	25
10	**3c**		**13c**	—
11	**3c**		**13d**	30
12	**3c**		**13e**	80
13	**3c**		**13f**	35
14	**3c**		**13g**	20

[a] Isoxazolidine (1 mmol) in $CHCl_3$ (0.06 M); RX (1 mmol), 60 °C for 20 h. [b] In this case, only the alkylation product was isolated in 30% yield.

Formation of tetrahydro-1,3-oxazines from tertiary amines bearing an OH group able to trap the intermediate iminium ion is a well established process occurring usually by oxidation or under photochemical conditions.[15] The particular structure of adducts **2c** and **3c** seems to suggest kinetic lability of the C–H α to N for stereoelectronic reasons, according to similar observations reported for the oxidation of the parent hydroxylamines to the corresponding nitrones.[16]

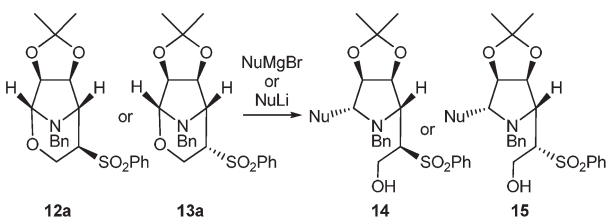
Having obtained bicyclic aminals **12** and **13**, and taking into account the importance of nitrones such as **1c**, which has been used in the synthesis of many natural and biologically active compounds,[3b,3c] we decided to explore the scope of the reaction using different alkylating agents (Table 2). The rearrangement of isoxazolidines **2c** and **3c** to the bicyclic system only works with very effective alkylating agents such as allylic or benzylic species, and in higher yields with bromides than with chlorides (entries 5–8 and 9, 10). When geranyl bromide was employed, no reaction with **2c** occurred due to the steric hinderence of the sulfonyl group; the yield was low with **3c** (entry 11). Moreover, no reaction occurred in any case with either saturated alkyl bromides or acyl compounds.

To demonstrate the importance of this reaction, we decided to open the bicyclic system with different nucleophiles as has been done with other aminals, in particular by Bosch and Amat.[17] Compounds **12a** and **13a** were chosen as starting materials. First of all, **12a** and **13a** were treated with methylmagnesium bromide. When the reaction was performed using 1, 3 or even 5 equivalents of the Grignard reagent, ring opening either did not occur or only occurred in poor yield. The desired products (**14a** and **15a**) were formed in high yield only when using at least 10 equivalents of the nucleophile (Table 3, entries 1 and 2). Moreover, lithium nucleophiles resulted in quite poor yields or no reaction, irrespective of the number of equivalents used (entries 3 and 4). Other Grignard reagents led to the opening of the aminal in high yields when 10 equivalents were used (entries 5–10). In this manner, pyrrolidines with four chiral centers were obtained in high yield in a simple way.

It can be observed that the configuration of the sulfone group does not influence the stereochemistry of the incoming nucleophile; in all cases, the same α-Nu were obtained independently of the starting material **12a** or **13a**. The stereochemistry of the ring opened product was established by analysis of the NMR experiments (bidimensional and NOE, see ESI†) and confirmed by transformation of **14a** and **15a** into pyrrolidine **16** by treatment with Na(Hg) amalgam as shown in Scheme 4. Since the stereochemistry of **16** is known,[18] it could be established that the nucleophile had entered through the α side. The stereochemistry was also corroborated by transformation of compound **15h** in the same manner to form *meso* diolefin **17**.

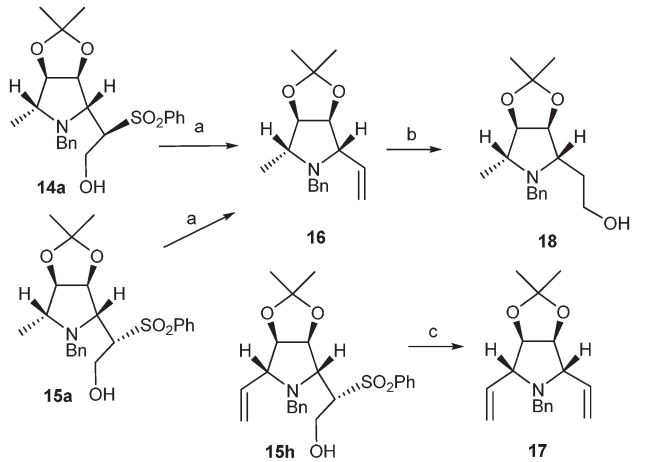
In order to further extend the applicability of this methodology, compound **16**, which had previously been transformed by Palmer and Jäger into biologically active pyrrolidines,[18] was submitted to hydroboration and oxidation affording pyrrolidine

Table 3 Opening of aminals[a]



Entry	S. M.	Nucleophile	Product	Yield (%)
1	**12a**	MeMgBr	**14a** Nu = Me	85
2	**13a**	MeMgBr	**15a** Nu = Me	98
3	**13a**	MeLi	**15a** Nu = Me	40
4	**13a**	*n*-BuLi	**15b** Nu = Bu	—
5	**13a**	EtMgBr	**15c** Nu = Et	98
6	**13a**	PhMgBr	**15d** Nu = Ph	70
7	**13a**	AllylMgBr	**15e** Nu = Allyl	85
8	**13a**	2-NaphCH_2MgBr	**15f** Nu = 2-NaphCH_2-	80
9	**13a**	*c*-hexCH_2MgBr	**15g** Nu = *c*-hexCH_2-	90
10	**13a**	VinylMgBr	**15h** Nu = Vinyl	54

[a] **12a** or **13a** (1 mmol) , Et_2O (0.08 M); NuMgBr (10 mmol) or NuLi (10 mmol), −60 °C for 2 h.



Scheme 4 a. Na(Hg) 5%, MeOH, r.t., 2 h, 100%; b. 9-BBN, THF, $NaBO_3$, r.t., 30%; c. Na(Hg) 5%, MeOH, r.t., 2 h, 100%.

18, the C-5 epimer of which has been previously transformed into a fucosidase inhibitor by Defoin *et al.*.[19]

As depicted in Scheme 4, both compounds **14a** and **15a** led to the same olefin **16**, which increased the yield of the final product (**18**).

Conclusions

A new method for the synthesis of chiral pyrrolidines is described. This approach is based on the rearrangement of chiral isoxazolidines into tetrahydro-1,3-oxazines by treatment with reactive organic bromides. Opening of the obtained tetrahydro-1,3-oxazines with different nucleophiles affords the corresponding chiral pyrrolidines in a diastereoselective manner. These compounds can be used for diversity oriented synthesis of biologically active compounds.

Experimental section

N–O cleavage of isoxazolidines using $Mo(CO)_6$: standard procedure

To a stirred solution of isoxazolidine (1 mmol) in 1 mL of H_2O and 15 mL of MeCN was added 0.7 mmol of $Mo(CO)_6$ and the mixture was heated at reflux. The solution was stirred for 24 h then concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane–EtOAc 1 : 1) to obtain rearranged compound.

(1′*R,2*R**)-2-(1-Phenylsulfonyl-2-hydroxyethyl)pyrrolidine 4a.** IR (film): 3299, 29589, 2924, 1447, 1304, 1144, 691 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.99–7.58 (5H, m, H_{Ar}), 4.11–4.04 (1H, m, H_A-2′), 3.89–3.84 (1H, m, H_B-2′), 3.50–47 (1H, m, H-1′), 3.00–2.93 (3H, m, H-2 and H-5), 2.10–1.74 (4H, m, H-3 and H-4); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.0, 134.2, 129.5, 128.7, 67.3, 59.1, 56.1, 45.8, 31.3, 25.5; HRMS (EI) calcd for $C_{12}H_{17}NO_3S$ $(M + H)^+$ 256.0929; found 256.1017.

(1′*R*,2*R*,4*S*,5*S*)-2-(1-Phenylsulfonyl-2-hydroxyethyl)-4,5-bis (benzyloxy)pyrrolidine 4b. $[\alpha]_D^{20}$ −22.0 (*c* 0.4, MeOH); IR (film): 3431, 2922, 2851, 1628, 1449, 1148, 1086, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87–7.22 (15H, m, H_{Ar}), 4.56–4.34 (4H, m, CH_2–Bn), 4.34 (1H, d, *J* = 2.2 Hz, H-3), 4.03–3.87 (3H, m, H-2 and H-2′), 3.88 (1H, t, *J* = 5.8 Hz, H-4), 3.57–3.43 (1H, m, H-1′), 3.89–3.84 (1H, m, H_B-2′), 3.50–47 (1H, m, H-1′), 3.25 (1H, dd, *J* = 5.6 and 12.0 Hz, H_B-5), 3.07 (1H, dd, *J* = 1.8 and 12.0 Hz, H_A-5), 2.07 (2H, bs, NH and OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4, 137.9, 137.8, 134.1, 129.5, 128.8, 128.7, 128.5, 128.2, 128.1, 128.0, 127.9, 85.5, 82.5, 71.9, 71.6, 61.9, 60.2, 50.4; HRMS (EI) calcd for $C_{26}H_{30}NO_5S$ $(M + H)^+$ 468.1815; found 468.1819.

(1′*R*,2*R*,3*S*,4*R*)-2-(1-Phenylsulfonyl-2-hydroxyethyl)-3,4-isopropylidenedioxypyrrolidine 4c. $[\alpha]_D^{20}$ = +2.1 (*c* = 2.5, $CHCl_3$); IR (film): 3481, 3334, 2987, 2909, 2840, 1434, 1144, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 8.2 Hz, H*ortho*), 7.69 (1H, t, *J* = 7.4 Hz, H*para*), 7.59 (2H, d, *J* = 7.4 Hz, H*meta*), 5.15 (1H, d, *J* = 5.6 Hz, H-3), 4.75 (1H, t, *J* = 4.7 Hz, H-4), 3.90 (1H, dd, *J* = 3.4 and 11.8 Hz, H_A-2′), 3.80 (1H, dd, *J* = 7.7 and 13.2 Hz, H_B-2′), 3.69 (1H, d, *J* = 10.0 Hz, H-2), 3.15–3.06 (1H, m, H-1′), 3.08 (1H, d, *J* = 13.6 Hz, H_B-5), 2.97 (1H, dd, *J* = 13.6 Hz, H_A-5), 1.45 (3H, s, Me-acetonide), 1.33 (3H, s, Me-acetonide); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 134.2, 129.3, 128.9, 111.4, 84.8, 81.0, 65.4, 63.4, 61.6, 51.6, 26.3, 24.1; HRMS (EI) calcd for $C_{15}H_{22}NO_5S$ $(M + H)^+$ 328.1213; found 328.1218.

(1′*S,2*R**)-2-(1-Phenylsulfonyl-2-hydroxyethyl)pyrrolidine 5a.** IR (film): 3343, 3065, 2961, 2874, 1304, 1144, 1049, 760, 691, 565 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.99–7.58 (5H, m, H_{Ar}), 4.13–3.95 (1H, m, H_A-2′), 3.87–3.81 (1H, m, H_B-2′), 3.50–3.47 (1H, m, H-1′), 3.02–2.85 (3H, m, H-2 and H-5), 2.13–1.74 (4H, m, H-3 and H-4); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.0, 134.3, 129.6, 128.7, 68.2, 59.7, 56.2, 46.5, 31.3, 25.4; HRMS (EI) calcd for $C_{12}H_{17}NO_3S$ $(M + H)^+$ 256.0929; found 256.1017.

(1′*S*,2*R*,3*S*,4*R*)-2-(1-Phenylsulfonyl-2-hydroxyethyl)-3,4-isopropylidenedioxypyrrolidine 5c. $[\alpha]_D^{20}$ −32.0 (*c* 1.5, $CHCl_3$); IR (film): 3501, 3326, 2983, 2913, 1446, 1283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 7.4 Hz, H*ortho*), 7.65 (1H, t, *J* = 7.4 Hz, H*para*), 7.58 (2H, d, *J* = 7.4 Hz, H*meta*), 4.75–4.70 (2H, m, H-3 and H-4), 4.06 (1H, dd, *J* = 4.9 and 13.2 Hz, H_B-2′), 3.99 (1H, dd, *J* = 3.5 and 13.2 Hz, H_A-2′), 3.52 (1H, dd, *J* = 2.5 and 8.4 Hz, H-2), 3.19–3.18 (1H, m, H-1′), 3.02 (1H, dd, *J* = 4.6 and 11.8 Hz, H_A-5), 2.97 (1H, d, *J* = 11.8 Hz, H_B-5), 2.82 (1H, s, N–H), 1.44 (3H, s, Me-acetonide), 1.30 (3H, s, Me acetonide); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 133.4, 129.1, 128.9, 112.7, 83.6, 80.8, 67.9, 62.3, 59.4, 51.8, 26.8, 24.6; HRMS (EI) calcd for $C_{15}H_{22}NO_5S$ $(M + H)^+$ 328.1213; found 328.1202.

(1*R*,4*R*,5*R*,6*S*,7*S*)-4-Phenylsulfonyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 10. $[\alpha]_D^{20}$ −2.7 (*c* 0.7, $CHCl_3$); IR (film): 2982, 2934, 2882, 1301, 1148, 733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.70–7.56 (3H, m, H*meta* and H*para*), 4.86 (1H, s, H-1), 4.75 (1H, dd, *J* = 1.2 and 5.4 Hz, H-6), 4.55, 4.48 (2H, m, H-7 and H_B-3), 3.87 (1H, dd, *J* = 5.8 and 14.2 Hz, H_A-3), 3.77 (1H, bs, H-5), 2.73 (1H, dd, *J* = 3.0 and 5.8 Hz, H-4), 1.45 (3H, s, Me-acetonide), 1.31 (3H, s, Me acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.5, 134.6, 129.8, 128.9, 112.9, 88.8, 81.9, 78.7, 59.1, 57.9, 56.5, 26.1, 24.9; HRMS (EI) calcd for $C_{15}H_{20}NO_5S$ $(M + H)^+$ 326.1056; found 326.1067.

(1*R*,4*S*,5*R*,6*S*,7*S*)-4-Phenylsulfonyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 11. $[\alpha]_D^{20}$ = +20.0 (*c* = 0.9, $CHCl_3$); IR (film): 3412, 3338, 2974, 2929, 1373, 1140, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.70 (1H, t, *J* = 7.6 Hz, H*para*), 7.60 (2H, d, *J* = 7.6 Hz, H*meta*), 5.32 (1H, d, *J* = 5.4 Hz, H-6), 4.77 (1H, s, H-1), 4.72 (1H, d, *J* = 5.4 Hz, H-7), 4.01 (1H, dd, *J* = 5.8 and 11.8 Hz, H_B-3), 3.87 (1H, t, *J* = 11.8 Hz, H_A-3), 3.77 (1H, sa, H-5), 3.50 (1H, ddd, *J* = 2.6, 5.8 and 8.4 Hz, H-4), 1.45 (3H, s, Me-acetonide), 1.38 (3H, s, Me acetonide); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 134.4, 129.6, 128.2, 111.7, 88.8, 81.8, 78.7, 61.3, 59.6, 57.9, 25.7, 24.4; HRMS (EI) calcd for $C_{15}H_{20}NO_5S$ $(M + H)^+$ 326.1056; found 326.1068.

Alkylation of heterocycles: standard procedure

To a stirred solution of isoxazolidine (1 mmol) in $CHCl_3$ (0.06 M) was added dropwise RBr (1 mmol) and the solution heated at 60 °C. The solution was stirred at 60 °C for 20 h. Then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane–EtOAc 8 : 2) to obtain the rearranged compound.

(3*R,3a*R**)-*N*-Benzyl-3-phenylsulfonylhexahydropyrrolo[1,2-*b*]-isoxazole 6a.** IR (film): 3314, 2928, 2872, 1447, 1306, 1049, 916, 691, 600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.89–7.15 (10H, m, H*Ar*), 4.23–3.96 (1H, m, H_A-2), 3.90–3.88 (1H, m, H_B-2 and H-3), 3.60–3.24 (3H, m, H-3a, H_A-6 and H_A–CH_2Bn), 3.03–2.95 (1H, m, H_B-6), 2.95 (1H, d, *J* = 12.3 Hz, H_B–CH_2Bn), 2.33–2.05 (2H, m, H-4), 1.95–1.87 (1H, m, H_A-5), 1.78-1.13 (1H, m, H_B-5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 134.3, 129.5, 129.4, 129.2, 128.9, 128.2, 127.9, 63.3, 62.1, 59.4, 58.6, 53.7, 26.0, 24.5; HRMS (EI) calcd for $C_{19}H_{22}NO_5S$ $(M + H)^+$ 344.1314;

(3*S,3a*R**)-*N*-Benzyl-3-phenylsulfonylhexahydropyrrolo[1,2-*b*]-isoxazole 7a.** IR (film): 3397, 2993, 2882, 1449, 1152, 723, 602 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.08–7.26 (10H, m, H*Ar*), 5.90 (1H, d, *J* = 12.8 Hz, H_B–CH_2Bn), 5.45–5.42 (1H, m, H-3a), 5.29–4.99 (3H, m, H-2 and H_A–CH_2Bn), 4.72–4.64 (1H, m, H-3), 4.39–4.28 (1H, m, H_B-6), 3.66–3.62 (1H, m, H_A-6), 3.46–3.38 (1H, m, H_B-4), 2.98–2.94 (1H, m, H_A-5), 2.27–2.11 (2H, m, H_A-4 and H_B-5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.6, 135.6, 132.7, 131.1, 130.4, 129.3, 129.0, 127.8, 79.3, 71.2, 10.8, 66.7, 66.0, 31.7, 23.9; HRMS (EI) calcd for $C_{19}H_{22}NO_5S$ $(M + H)^+$ 344.1314; found 344.1328.

(1′*R*,2*R*,4*S*,5*S*)-*N*-Benzyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-4,5-bis(benzyloxy)pyrrolidine 8b. $[\alpha]_D^{20}$ −35.7 (*c* 0.4, MeOH); IR (film): 3422, 2955, 2922, 2851, 1701, 1609, 1497, 1364, 1146, 1086, 802, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85–7.12 (20H, m, H*Ar*), 4.46–4.39 (6H, m, H-3, H-4 and CH_2–Bn), 4.05 (1H, dd, *J* = 8.8 and 11.8 Hz, H_A-2′), 3.99 (1H, dd, *J* = 3.8 and 11.8 Hz, H_B-2′), 3.87–3.79(1H, m, H-2), 3.85 (1H, d, *J* = 12.8 Hz, H_A–NCH_2), 3.68–3.58 (1H, m, H-1′), 3.58 (1H, d, *J* = 12.8 Hz, H_B–NCH_2), 3.05 (1H, d, *J* = 11.4 Hz, H_A-5), 2.70 (1H, dd, *J* = 4.4 and 11.4 Hz, H_B-5), 1.50 (1H, bs, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 138.5, 138.2, 137.6, 134.1, 129.6, 129.1, 128.7, 128.1, 127.9, 127.8, 127.6, 87.7, 81.8, 77.3, 71.5, 71.3, 66.9, 61.9, 59.7, 57.1; HRMS (EI) calcd for $C_{33}H_{36}NO_5S$ $(M + H)^+$ 558.2308; found 558.2296.

(1′*S*,2*R*,4*S*,5*S*)-*N*-Benzyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-4,5-bis(benzyloxy)pyrrolidine 9b. $[\alpha]_D^{20}$ −15.7 (*c* 0.2, MeOH); IR (film): 3404, 3059, 2916, 1603, 1560, 1306, 1084, 689, 573 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91–7.12 (10H, m, H*Ar*), 4.78–4.41 (6H, m, H-3, H-4 and CH_2–Bn), 4.26 (1H, dd, *J* = 8.0 and 11.8 Hz, H_A-2′), 4.12 (1H, dd, *J* = 3.8 and 11.8 Hz, H_B-2′), 4.07–3.87(1H, m, H-2), 3.82 (1H, d, *J* = 12.8 Hz, H_A–NCH_2), 3.49–3.45 (1H, m, H-1′), 3.30 (1H, d, *J* = 12.8 Hz, H_B–NCH_2), 3.05 (1H, d, *J* = 10.2 Hz, H_A-5), 2.46 (1H, dd, *J* = 3.6 and 10.2 Hz, H_B-5) 1.56 (1H, bs, OH); HRMS (EI) calcd for $C_{33}H_{36}NO_5S$ $(M + H)^+$ 558.2308; found 558.2296.

(1*R*,4*R*,5*R*,6*S*,7*S*)-8-Benzyl-4-phenylsulfonyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 12a. $[\alpha]_D^{20}$ −31.7 (*c* 0.6, $CHCl_3$); IR (film): 3391, 3060, 2970, 2921, 1446, 1385, 1152 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85–7.30 (10H, m, H*Ar*), 4.71 (1H, s, H-1), 4.62 (1H, d, *J* = 5.0 Hz, H-7), 4.52 (1H, d, *J* = 5.0 Hz, H-6), 4.38 (1H, d, *J* = 12.0 Hz, H_A–CH_2Bn), 4.26–4.23 (1H, m, H_A-3), 4.20 (1H, d, *J* = 12.0 Hz, H_B–CH_2Bn), 4.13 (1H, s, H-5), 3.85–3.75 (1H, m, H_B-3), 3.10 (1H, t, *J* = 6.2 Hz, H-4), 1.52 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.9, 138.5, 134.4, 129.8, 128.7, 128.4, 127.3, 113.3, 90.1, 84.6, 83.1, 61.8, 59.6, 58.4, 52.6, 25.9, 24.8; HRMS (EI) calcd for $C_{22}H_{25}NO_5S$ $(M + H)^+$ 416.1526; found 416.1538.

(1*R*,4*R*,5*R*,6*S*,7*S*)-4-Phenylsulfonyl-8-propenyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 12b. $[\alpha]_D^{20}$ −31.7 (*c* 0.6, $CHCl_3$); IR (film): 3069, 2982, 2932, 2860, 1447, 1306, 1209, 1450, 1072, 731, 606 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.2 Hz, H*ortho*), 7.70–7.52 (3H, m, H*para* and H*meta*), 5.75–5.58 (1H, m, H-2′), 5.31 (1H, dd, *J* = 1.8 and 13.6 Hz, H_A-3′), 5.14 (1H, dd, *J* = 1.8 and 13.6 Hz, H_B-3′), 4.70 (1H, s, H-1), 4.62 (1H, d, *J* = 5.4 Hz, H-6), 4.51 (1H, d, *J* = 5.4 Hz, H-7), 4.20–4.09 (2H, m, 2*H*-3), 4.05 (1H, s, H-5), 3.80–3.55 (2H, m, H-4 and H_A-1′), 3.07–3.01 (1H, m, H_B-1′), 1.48 (3H, s, Me-acetonide), 1.26 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 135.3, 134.3, 129.7, 128.8, 117.3, 113.4, 90.3, 84.7, 83.5, 62.3, 59.8, 58.4, 51.9, 26.1, 25.0; HRMS (EI) calcd for $C_{18}H_{24}NO_5S$ $(M + H)^+$ 366.1369; found 366.1351.

(3*R*,3a*R*,4*S*,5*R*)-3-Phenylsulfonyl-*N*-propargyl-4,5-isopropylidenedioxyhexahydropyrrolo[1,2-*b*]isoxazole 12c. $[\alpha]_D^{20}$ = +5.5 (*c* = 0.2, $CHCl_3$); IR (film): 3275, 2955, 2924, 2851, 1260, 1145, 758, 689, 584 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* = 7.8 Hz, H*ortho*), 7.66–7.53 (3H, m, H*para* and H*meta*), 5.08 (1H, dd, *J* = 3.0 and 6.6 Hz, H-4), 4.76–4.72 (1H, m, H-5), 4.12 (1H, dd, *J* = 5.4 and 12.4 Hz, H_B-2), 3.98 (1H, dd, *J* = 6.6 and 12.4 Hz, H_A-2), 3.57–3.31 (1H, m, H-3a, H-3, 2*H*-1′), 3.08 (1H, dd, *J* = 3.0 and 13.2 Hz, H_B-5), 2.98 (1H, dd, *J* = 5.6 and 13.2 Hz, H_A-5), 2.18 (1H, t, *J* = 2.4 Hz, H-3′), 1.47 (3H, s, Me-acetonide), 1.31 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.1, 134.2, 129.3, 129.2, 112.4, 84.2, 79.4, 77.8, 73.9,

67.3, 65.0, 60.6, 56.7, 43.4, 27.4, 24.9; HRMS (EI) calcd for $C_{18}H_{23}NO_5NaS$ (M + Na) 388.1189; found 388.1195.

(1*R*,4*R*,5*R*,6*S*,7*S*)-8-Methylcrotonate-4-phenylsulfonyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 12d. $[\alpha]_D^{20}$ −23.6 (*c* 1.4, $CHCl_3$); IR (film): 3429, 2980, 2851, 1719, 1447, 1152, 978, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.67 (1H, m, H*para*), 7.57 (H, m, H*meta*), 6.80 (1H, dt, *J* = 4.8 and 16.0 Hz, H-3′), 6.15 (1H, dt, *J* = 1.8 and 16.0 Hz, H-2′), 4.67 (1H, s, H-1), 4.63 (1H, d, *J* = 5.4 Hz, H-7), 4.51 (1H, d, *J* = 5.4 Hz, H-6), 4.14 (1H, dd, *J* = 5.4 and 12.6 Hz, H_B-3), 4.10 (1H, s, H-5), 4.03 (1H, ddd, *J* = 1.9, 4.8 and 6.4 Hz, H_B-1′), 3.88 (1H, ddd, *J* = 1.9, 4.8 and 6.4 Hz, H_A-1′), 3.76 (1H, dd, *J* = 6.5 and 12.6 Hz, H_A-3), 3.04–3.01 (1H, m, H-4), 3.75 (3H, s, CO_2CH_3), 1.49 (3H, s, Me-acetonide), 1.26 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.2, 145.6, 138.6, 134.4, 129.8, 128.7, 121.9, 113.4, 90.0, 84.3, 83.0, 61.7, 60.0, 58.5, 51.7, 49.4, 25.9, 24.8; HRMS (EI) calcd for $C_{20}H_{26}NO_7S$ $(M + H)^+$ 424.1424.; found 424.1434.

(1*R*,4*S*,5*R*,6*S*,7*S*)-8-Benzyl-4-phenylsulfonyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 13a. $[\alpha]_D^{20}$ −28.3 (*c* 0.7, $CHCl_3$); IR (film): 3387, 2978, 2864, 1589, 1397, 1140 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.84–7.52 (10H, m, H*Ar*), 5.34 (1H, d, *J* = 5.8 Hz, H-6), 4.72 (1H, d, *J* = 5.8 Hz, H-7), 4.50 (1H, s, H-1), 4.14–3.97 (3H, m, CH_2Bn and 1H-3), 3.84 (1H, t, *J* = 14.8 Hz, H-3), 3.73 (1H, ddd, *J* = 2.6, 6.2 and 8.8 Hz, H-4), 3.56 (1H, s, H-5), 1.52 (3H, s, Me-acetonide), 1.37 (3H, s, Me acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.1, 137.3, 134.4, 129.8, 128.7, 128.3, 127.5, 112.5, 89.6, 81.4, 77.4, 59.9, 59.8, 54.1, 48.3, 26.4, 25.4; HRMS (EI) calcd for $C_{22}H_{25}NO_5NaS$ (M + Na) 438.1345; found 438.1349.

(1*R*,4*S*,5*R*,6*S*,7*S*)-4-Phenylsulfonyl-8-propenyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 13b. $[\alpha]_D^{20}$ −13.7 (*c* 0.6, $CHCl_3$); IR (film): 3067, 2982, 2936, 1310, 1246, 1101, 903, 866, 731, 604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.72–7.52 (3H, m, H*para* and H*meta*), 5.71–5.63 (1H, m, H-2′), 5.33 (1H, d, *J* = 5.4 Hz, H-6), 5.20 (1H, dd, *J* = 1.8 and 7.2 Hz, H_A-3′), 5.02 (1H, dd, *J* = 1.8 and 7.2 Hz, H_B-3′), 4.70 (1H, d, *J* = 5.4 Hz, H-7), 4.51 (1H, s, H-1), 4.02–3.87 (2H, m, 2*H*-3), 3.60 (1H, s, H-5), 3.59–3.42 (2H, m, H-4 and H_A-1′), 3.29–3.19 (1H, m, H_B-1′), 1.45 (3H, s, Me-acetonide), 1.36 (3H, s, Me-acetonide).); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.1, 134.5, 134.3, 129.9, 128.4, 117.6, 112.6, 89.5, 81.5, 77.9, 59.9, 59.8, 53.9, 46.9, 26.4, 25.5; HRMS (EI) calcd for $C_{18}H_{24}NO_5S$ $(M + H)^+$ 366.1369; found 366.1372.

(1*R*,4*S*,5*R*,6*S*,7*S*)-4-Phenylsulfonyl-8-propargyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 13c. $[\alpha]_D^{20}$ = +8.4 (*c* = 1.6, $CHCl_3$); IR (film): 3275, 2957, 2924, 2853, 1381, 1319, 885, 727, 604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.70–7.57 (3H, m, H*para* and H*meta*), 5.36 (1H, d, *J* = 6.0 Hz, H-6), 4.72 (1H, d, *J* = 6.0 Hz, H-7), 4.56 (1H, s, H-1), 4.02 (1H, dd, *J* = 1.8 and 11.6 Hz, H_B-3), 3.91 (1H, d, *J* = 11.6 Hz, H_A-3), 3.81 (1H, s, H-5), 3.66 (1H, ddd, *J* = 1.8, 6.6 and 9.6 Hz, H-4), 2.05 (1H, t, *J* = 2.6 Hz, H-3′), 1.46 (3H, s, Me-acetonide), 1.37 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.0, 134.5, 129.9, 128.5, 112.9, 89.6, 81.6, 78.2, 77.9, 59.8, 59.7, 53.8, 34.3, 26.4, 25.7; HRMS (EI) calcd for $C_{18}H_{22}NO_5S$ $(M + H)^+$ 364.1210; found 364.1211.

(1*R*,4*S*,5*R*,6*S*,7*S*)-8-Geranyl-4-phenylsulfonyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 13d. $[\alpha]_D^{20}$ −7.3 (*c* 0.5, $CHCl_3$); IR (film): 2963, 2926, 2855, 1458, 1375, 1153, 885, 604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.69–7.55 (3H, m, H*para* and H*meta*), 5.32 (1H, d, *J* = 5.8 Hz, H-6), 5.09–5.02 (2H, m, H-2′′ and H-6′′), 4.68 (1H, d, *J* = 5.8 Hz, H-7), 4.48 (1H, s, H-1), 4.02–3.87 (2H, m, H-3), 3.64–3.59 (2H, m, H-4 and H-5), 3.36 (1H, dd, *J* = 6.2 and 12.8 Hz, H_A-1′′), 3.25 (1H, dd, *J* = 7.2 and 12.8 Hz, H_B-1′′), 2.03–1.28 (13H, m, geranyl), 1.45 (3H, s, Me-acetonide), 1.36 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6, 138.3, 134.4, 131.9, 129.8, 128.4, 120.2, 112.7, 89.6, 81.6, 78.4, 59.8, 59.7, 41.7, 39.7, 34.5, 26.6, 26.4, 25.9, 25.7, 17.9, 16.8; HRMS (EI) calcd for $C_{25}H_{36}NO_5S$ $(M + H)^+$ 462.2308; found 462.2318.

(1*R*,4*S*,5*R*,6*S*,7*S*)-4-Phenylsulfonyl-8-((*E*)-4-bromobut-2-en-1-yl)-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 13e. $[\alpha]_D^{20}$ −8.0 (*c* 0.3, $CHCl_3$); IR (film): 3348, 2984, 2928, 2853, 1447, 1373, 1207, 725, 604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.72–7.57 (3H, m, H*para* and H*meta*), 5.97–5.93 (2H, m, H-3′), 5.90–5.57 (1H, m, H-2′), 5.33 (1H, d, *J* = 6.0 Hz, H-6), 4.84 (1H, s, H-1), 4.69 (1H, d, *J* = 6.0 Hz, H-7), 3.97–3.82 (3H, m, H-4 and 2*H*-3), 3.58 (1H, s, H-5), 3.57–3.20 (4H, m, 2*H*-1′ and 2*H*-4′), 1.44 (3H, s, Me-acetonide), 1.21 (3H, s, Me-acetonide). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.1, 134.6, 131.3, 129.4, 128.4, 128.2, 112.6, 89.5, 81.4, 78.3, 60.1, 59.8, 54.1, 45.3, 32.1, 26.3, 25.5; HRMS (EI) calcd for $C_{19}H_{26}NO_5SBr$ $(M + H)^+$ 458.0631; found 458.0644.

(1*R*,4*S*,5*R*,6*S*,7*S*)-8-Methylcrotonate-4-phenylsulfonyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 13f. $[\alpha]_D^{20}$ −13.1 (*c* 0.9, $CHCl_3$); IR (film): 3412, 2988, 2951, 1719, 1375, 1319, 1308, 1086, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.0 Hz, H*ortho*), 7.64 (1H, m, H*para*), 7.55 (H, m, H*meta*), 6.74 (1H, dt, *J* = 1.8 and 15.0 Hz, H-3′), 6.04 (1H, dt, *J* = 5.0 and 15.0 Hz, H-2′), 5.29 (1H, d, *J* = 5.8 Hz, H-6), 4.66 (1H, d, *J* = 5.8 Hz, H-7), 4.45 (1H, s, H-1), 3.91–3.88 (2H, m, H-3), 3.66 (3H, s, CO_2CH_3), 3.63 (1H, ddd, *J* = 1.8, 5.0 and 16.0 Hz, H_B-1′), 3.62 (1H, s, H-5), 3.59–3.54 (1H, m, H-4), 3.35 (1H, ddd, *J* = 1.8, 5.0 and 16.0 Hz, H_A-1′), 1.44 (3H, s, Me-acetonide), 1.21 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.7, 144.2, 137.9, 134.6, 129.9, 128.3, 122.7, 112.6, 89.6, 81.3, 78.3, 60.4, 59.8, 54.3, 51.7, 44.7, 26.2, 25.3; HRMS (EI) calcd for $C_{20}H_{25}NO_7NaS$ (M + Na) 446.1243; found 446.1249.

(1*R*,4*S*,5*R*,6*S*,7*S*)-8-Methylacetate-4-phenylsulfonyl-6,7-isopropylidendioxy-2-oxa-8-azabicyclo[3.2.1]octane 13g. $[\alpha]_D^{20}$ −11.0 (*c* 0.5, $CHCl_3$); IR (film): 2980, 2955, 2918, 2872, 2849, 1751, 1431, 1379, 1287, 1086, 885, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 7.8 Hz, H*ortho*), 7.71–7.61 (3H, m, H*para* and H*meta*), 5.35 (1H, d, *J* = 6.0 Hz, H-6), 4.72 (1H, d, *J* = 6.0 Hz, H-7), 4.63 (1H, s, H-1), 3.91–3.79 (2H, m, H-3), 3.79 (1H, s, H-5), 3.75 (1H, d, *J* = 16.4 Hz, H_A-1′), 3.65 (3H, s, CO_2CH_3), 3.56–3.45 (1H, m, H-4), 3.41 (1H, d, *J* = 16.4 Hz, H_B-1′), 1.48 (3H, s, Me-acetonide), 1.37 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 138.1, 134.6, 129.9, 128.4,

113.2, 90.6, 81.6, 78.6, 61.5, 59.8, 54.8, 52.2, 46.6, 26.4, 25.9; HRMS (EI) calcd for $C_{18}H_{24}NO_7S$ $(M + H)^+$ 398.1268; found 398.1261.

Addition of organometallic reagents: standard procedure

To a stirred solution of rearranged compound (1 mmol) in Et_2O (0.08 M) was added dropwise RMgBr or RLi (10 mmol) at −60 °C. The solution was stirred at −60 °C for 2 h. Then the mixture was allowed to warm slowly to room temperature. It was quenched with a saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane–EtOAc 1 : 1) to obtain the pyrrolidine product.

(1′*R*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-5-methyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-3,4-isopropylidenedioxypyrrolidine 14a. $[\alpha]_D^{20}$ −4.3 (*c* 0.4, $CHCl_3$); IR (film): 2959, 2920, 2851, 1144, 1051, 800, 584 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.92–7.25 (10H, m, H*Ar*), 5.04 (1H, dd, *J* = 2.6 and 6.0 Hz, H-3), 4.35 (1H, dd, *J* = 3.2 and 6.0 Hz, H-4), 4.01 (1H, dd, *J* = 4.4 and 12.0 Hz, H_A-2′), 3.89 (1H, d, *J* = 13.2 Hz, H_A-CH_2Bn), 3.66–3.56 (2H, m, H-2 and H_B-2′), 3.64 (1H, d, *J* = 13.2 Hz, H_B- CH_2Bn), 3.42–3.36 (1H, m, H-1′), 3.12 (1H, dq, *J* = 3.2 and 7.0 Hz, H-5), 1.45 (3H, s, Me-acetonide), 1.30 (3H, s, Me-acetonide), 1.20 (3H, d, *J* = 7.0 Hz, Me–C-5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0, 135.7, 134.2, 129.8, 129.4, 128.8, 128.7, 127.8, 112.5, 86.4, 84.2, 69.0, 66.9, 64.1, 60.0, 59.4, 27.6, 25.3, 19.8; HRMS (EI) calcd for $C_{23}H_{30}NO_5NaS$ (M + Na) 454.1658; found 454.1640.

(1′*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-5-methyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-3,4-isopropylidenedioxypyrrolidine 15a. $[\alpha]_D^{20}$ = +5.8 (*c* = 0.7, $CHCl_3$); IR (film): 3474, 2986, 2965, 2934, 1449, 1381, 1308, 1043, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.55 (10H, m, H*Ar*), 4.76 (1H, d, *J* = 6.0 Hz, H-3), 4.09 (1H, t, *J* = 6.5 Hz, H-4), 4.06 (1H, ddd, *J* = 1.0, 4.7 and 11.6 Hz, H_A-2′), 3.96 (1H, dd, *J* = 7.5 and 11.6 Hz, H_B-2′), 3.82 (1H, d, *J* = 13.6 Hz, H_A–CH_2Bn), 3.59 (1H, s, H-2), 3.49 (1H, d, *J* = 13.6 Hz, H_B–CH_2Bn), 3.03–2.99 (1H, m, H-1′), 2.70–2.67 (1H, m, H-5), 1.41 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide), 1.20 (3H, d, *J* = 6.0 Hz, Me–C-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 135.7, 133.9, 129.5, 129.2, 128.8, 128.6, 127.7, 112.5, 84.6, 78.6, 65.7, 63.5, 63.3, 58.4, 56.3, 27.9, 25.8, 17.6; HRMS (EI) calcd for $C_{23}H_{30}NO_5S$ $(M + H)^+$ 432.1815; found 432.1824.

(1′*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-5-ethyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-3,4-isopropylidenedioxypyrrolidine 15c. $[\alpha]_D^{20}$ = +4.4 (*c* = 0.9, $CHCl_3$); IR (film): 3412, 2963, 2932, 2876, 1449, 1308, 1065, 733, 689 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.79–6.98 (10H, m, *Ar*), 4.79 (1H, dd, *J* = 1.8 and 6.2 Hz, H-3), 4.26 (1H, t, *J* = 6.2 Hz, H-4), 4.09–3.95 (2H, m, H-2′), 3.87 (1H, d, *J* = 13.6 Hz, H_A–CH_2Bn), 3.58 (1H, bs, H-2), 3.50 (1H, d, *J* = 13.6 Hz, H_B–CH_2Bn), 2.95–2.92 (1H, m, H-1′), 2.69–2.60 (1H, m, H-5), 1.77–1.67 (2H, m, –CH_2–C-5), 1.41 (3H, s, Me-acetonide), 1.30 (3H, s, Me-acetonide), 0.97 (3H, t, *J* = 7.8 Hz, CH_3–CH_3CH_2–C-5). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.3, 136.3, 134.2, 129.7, 129.4, 128.9, 128.0, 112.6, 83.3, 79.1, 69.2, 66.1, 63.8, 58.5, 57.3, 23.5, 26.1, 25.3, 9.4; HRMS (EI) calcd for $C_{24}H_{31}NO_5NaS$ $(M + Na)^+$ 468.1815; found 468.1805.

(1′*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-5-phenyl-3,4-isopropylidenedioxypyrrolidine 15d. $[\alpha]_D^{20}$ = +6.2 (*c* = 0.3, $CHCl_3$); IR (film): 3497, 3063, 3030, 2988, 2934, 2872, 2857, 1493, 1308, 1217, 1030, 596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–6.81 (15H, m, *Ar*), 4.81 (1H, dd, *J* = 1.6 and 6.0 Hz, H-3), 4.31 (1H, t, *J* = 6.7 Hz, H-4), 4.25 (1H, dd, *J* = 5.6 and 11.9 Hz, H_A-2′), 4.14 (1H, dd, *J* = 5.6 and 11.9 Hz, H_B-2′), 3.73 (1H, d, *J* = 13.7 Hz, H_A–CH_2Bn), 3.60–3.58 (2H, m, H-2 and H-5), 3.34 (1H, d, *J* = 13.7 Hz, H_B–CH_2Bn), 3.11–3.07 (1H, m, H-1′), 1.50 (3H, s, Me-acetonide), 1.28 (3H, s, Me-acetonide); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.0, 135.1, 134.1, 129.6, 129.2, 128.5, 128.1, 127.7, 127.3, 112.7, 85.3, 78.9, 72.1, 64.3, 58.0, 55.4, 27.9, 25.8; HRMS (EI) calcd for $C_{28}H_{31}NO_5NaS$ $(M + Na)^+$ 516.1833; found 516.1805.

(1′*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-5-propenyl-3,4-isopropylidenedioxypyrrolidine 15e. $[\alpha]_D^{20}$ = +4.3 (*c* = 0.5, $CHCl_3$); IR (film): 3503, 2982, 2916, 2848, 1449, 1150, 1070, 737, 590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91–7.24 (10H, m, *Ar*), 5.90–5.76 (1H, m, H-2′′), 5.20–5.03 (2H, m, H-3′′), 4.78 (1H, dd, *J* = 2.0 and 6.2 Hz, H-3), 4.31 (1H, t, *J* = 6.2 Hz, H-4), 4.09–3.98 (2H, m, H-2′), 3.91 (1H, d, *J* = 13.2 Hz, H_A–CH_2Bn), 3.58 (1H, s, H-2), 3.56 (1H, d, *J* = 13.2 Hz, H_B–CH_2Bn), 3.09–2.95 (1H, m, H-1′), 2.48–2.16 (3H, m, H-5, H-1′′), 1.42 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.8, 138.3, 136.2, 135.7, 134.3, 129.7, 129.4, 129.3, 128.5, 127.3, 118.4, 112.7, 82.4, 79.0, 67.6, 65.4, 64.1, 58.4, 57.1, 36.2, 28.1, 26.0; HRMS (EI) calcd for $C_{25}H_{32}NO_5S$ $(M + H)^+$ 458.1995; found 458.1978.

(1′*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-5-naphthalenylmethyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-3,4-isopropylidenedioxypyrrolidine 15f. $[\alpha]_D^{20}$ = +30.4 (*c* = 2.6, $CHCl_3$); IR (film): 3449, 2986, 2932, 1449, 1306, 1148, 752, 689 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81–7.09 (17H, m, *Ar*), 4.78 (1H, dd, *J* = 1.8 and 5.4 Hz, H-3), 4.38 (1H, t, *J* = 5.4 Hz, H-4), 3.99–3.86 (2H, m, H-2′), 3.80 (1H, d, *J* = 13.2 Hz, H_A–CH_2Bn), 3.77 (1H, bs, H-2), 3.50 (1H, d, *J* = 13.2 Hz, H_B–CH_2Bn), 3.20–3.26 (2H, m, H-1′′), 3.09–3.04 (1H, m, H-1′), 2.85–2.80 (1H, m, H-5), 1.36 (3H, s, Me-acetonide), 1.26 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.3, 136.5, 135.4, 133.7, 129.8, 129.4, 129.1, 128.3, 127.9, 127.7, 126.4, 125.7, 112.5, 83.3, 79.4, 69.4, 66.5, 64.5, 58.5, 39.5, 28.2, 26.1; HRMS (EI) calcd for $C_{33}H_{35}NO_5NaS$ $(M + Na)^+$ 580.2128; found 580.2131.

(1′*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-5-cyclohexylmethyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-3,4-isopropylidenedioxypyrrolidine 15g. $[\alpha]_D^{20}$ = +7.8 (*c* = 0.4, $CHCl_3$); IR (film): 3462, 2986, 2851, 1449, 1308, 1063, 754, 592 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77–7.02 (10H, m, *Ar*), 4.82 (1H, dd, *J* = 1.8 and 6.0 Hz, H-3), 4.23 (1H, t, *J* = 6.0 Hz, H-4), 4.05–3.92 (2H, m, H-2′), 3.85 (1H, d, *J* = 13.2 Hz, H_A–CH_2Bn), 3.53 (1H, bs, H-2), 3.48 (1H, d, *J* = 13.2 Hz, H_B–CH_2Bn), 3.46 (2H, d, *J* = 6.6 Hz, H-1′′), 2.95–2.79 (2H, m, H-5 and H-1′), 1.86–1.53 (11H, m, cyclohexyl), 1.31 (3H, s, Me-acetonide), 1.41 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.3, 136.3, 134.2, 129.9, 129.4, 129.1,

128.1, 112.5, 84.9, 79.4, 69.1, 66.0, 65.4, 63.5, 58.7, 57.4, 41.9, 40.7, 34.9, 34.3, 32.9, 28.1, 26.8, 26.4, 26.1; HRMS (EI) calcd for $C_{29}H_{39}NO_5NaS$ $(M + Na)^+$ 536.2440; found 536.2441.

(1′*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-2-(1-phenylsulfonyl-2-hydroxyethyl)-5-vinyl-3,4-isopropylidenedioxypyrrolidine 15h. $[\alpha]_D^{20}$ = +40.0 (*c* = 0.3, $CHCl_3$); IR (film): 2984, 2920, 2849, 1449, 1215, 1070, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.97–6.95 (10H, m, *Ar*), 5.79–5.61 (1H, m, H-1′′), 5.40–5.29 (2H, m, H-2′′), 4.79 (1H, dd, *J* = 1.2 and 5.6 Hz, H-3), 4.26 (1H, t, *J* = 7.0 Hz, H-4), 4.07 (1H, dd, *J* = 4.2 and 11.8 Hz, H_A-2′), 3.93 (1H, dd, *J* = 5.8 and 11.8 Hz, H_B-2′), 3.89 (1H, d, *J* = 13.2 Hz, H_A–CH_2Bn), 3.60 (1H, s, H-2), 3.35 (1H, d, *J* = 13.2 Hz, H_B–CH_2Bn), 3.08 (1H, t, *J* = 7.8 Hz, H-1′′), 2.93–2.95 (1H, m, H-1′), 1.46 (3H, s, Me-acetonide), 1.30 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 137.3, 135.8, 134.4, 129.9, 129.5, 129.2, 128.8, 128.1, 120.1 112.8, 83.2, 79.3, 72.4 64.9, 63.7, 58.5, 56.1, 28.2, 26.1; HRMS (EI) calcd for $C_{25}H_{32}NO_5NaS$ (M + Na), 466.1658; found 466.1660.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-5-methyl-2-vinylpyrrolidine 16

a) To a solution of pyrrolidine **15a** (40 mg, 0.09 mmol) in MeOH (1.5 mL) was added 128 mg (0.28 mmol) of 5% Na (Hg) amalgam at r.t. The mixture was stirred for 2 h at this temperature under an argon atmosphere. Next, it was filtered to remove the Hg residue and diluted with DCM (30 mL). The mixture was 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 obtain **16** (25 mg, 100%). $[\alpha]_D^{20}$ −5.0 (*c* 0.5, CH_2Cl_2); IR (film): 2980, 2965, 2930, 1449, 1246, 1148, 1070, 866 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31–7.21 (5H, m, H*Ar*), 5.84–5.66 (1H, m, H-1′), 5.39–5.20 (2H, m, H-2′), 4.29 (1H, dd, *J* = 5.0 and 6.8 Hz, H-3), 4.16 (1H, dd, *J* = 4.8 and 6.8 Hz, H-4), 3.84 (1H, d, *J* = 14.6 Hz, H_A–CH_2Bn), 3.49 (1H, d, *J* = 14.6 Hz, H_B–CH_2Bn), 3.09 (1H, dd, *J* = 5.0 and 8.4 Hz, H-2), 2.70–2.64 (1H, m, H-5), 1.43 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide), 1.22 (3H, d, *J* = 5.6 Hz, Me–C-5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.8, 137.6, 129.5, 128.2, 127.1, 118.9, 113.5, 85.4, 83.5, 72.9, 63.9, 53.4, 27.5, 25.6, 18.5; HRMS (EI) calcd for $C_{17}H_{24}NO_2$ $(M + H)^+$ 274.1801; found 274.1800.

b) To a solution of pyrrolidine **14a** (10 mg, 0.02 mmol) in MeOH (1 mL) was added 48 mg (0.06 mmol) of 5% Na (Hg) amalgam at r.t. The mixture was stirred for 2 h at this temperature under an argon atmosphere. Next, it was filtered to eliminate the Hg residue and diluted with DCM (30 mL). The mixture was 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 obtain **16** (6 mg, 100%).

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-2,5-divinyl-3,4-isopropylidenedioxypyrrolidine 17

To a solution of pyrrolidine **15h** (24 mg, 0.06 mmol) in MeOH (1 mL) was added 75 mg (0.16 mmol) of 5% Na (Hg) amalgam at r.t. The mixture was stirred for 2 h at this temperature under an argon atmosphere. Next, it was filtered to remove the Hg residue and diluted with DCM (30 mL). The mixture was 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 obtain **17** (17 mg, 100%). IR (film): 2982, 2924, 1375, 1267, 1072, 922, 866, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.26–7.21 (5H, m, H*Ar*), 5.82–5.84 (2H, m, H-1′), 5.38 (2H, d, *J* = 1.8 Hz, H_A-2′), 5.20 (2H, dd, *J* = 5.0 and 6.8 Hz, H_B-2′), 4.30 (2H, dd, *J* = 1.2 and 3.0 Hz, H-3 and H-4), 3.70 (2H, bs, CH_2Bn), 3.12 (2H, dd, *J* = 1.8 and 7.8 Hz, H-2 and H-5), 1.42 (3H, s, Me-acetonide), 1.27 (3H, s, Me-acetonide); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5, 136.5, 130.1, 128.1, 127.1, 118.9, 113.7, 83.7, 77.3, 71.7, 52.6, 27.4, 25.6; HRMS (EI) calcd for $C_{18}H_{24}NO_2$ $(M + H)^+$ 286.1803; found 286.1801.

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-5-methylpyrrolidine-2-ethanol 18

9-BBN (1.8 ml, 0.9 mmol) was added to a solution of vinylpyrrolidine **16** (50 mg, 0.18 mmol) in THF (1.50 mL) at 0 °C. The reaction mixture was stirred at r.t. for 4 h. A saturated aqueous solution of $NaBO_3$ was added and the resulting mixture was stirred at r.t. for 18 h. 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 obtain **18** (15 mg, 30%). $[\alpha]_D^{20}$ −12.8 (*c* 0.8, CH_3Cl); IR (film): 3397, 2980, 2932, 2866, 1452, 1341, 1028, 733, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33–7.17 (5H, m, H*Ar*), 4.29 (1H, dd, *J* = 5.0 and 6.8 Hz, H-3), 4.16 (1H, dd, *J* = 4.6 and 6.8 Hz, H-4), 4.05–3.99 (1H, m, H_A-2′), 3.84 (1H, d, *J* = 14.3 Hz, H_A–CH_2Bn), 3.54–3.40 (1H, m, H_B-2′), 3.49 (1H, d, *J* = 14.3 Hz, H_B–CH_2Bn), 3.12–3.05 (1H, m, H-2), 2.70–2.64 (1H, m, H-5), 1.95–1.85 (1H, m, H_A-1′), 1.83–1.75 (1H, m, H_B-1′), 1.44 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide), 1.17 (3H, d, *J* = 5.6 Hz, Me–C-5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.2, 132.3, 130.4, 128.6, 113.2, 83.5, 81.2, 72.7, 68.663.5, 54.4, 27.6, 24.3, 17.6; HRMS (EI) calcd for $C_{17}H_{26}NO_3$ $(M + H)^+$ 292.1907; found 292.1911.

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12 Crystal data for **13a**: $C_{22}H_{25}NO_5S$, CH_2Cl_2, M = 500.42, monoclinic, space group $P2_1$, a = 6.0659(2) Å, b = 15.5656(6) Å, c = 12.9608(5) Å, $\alpha = \gamma = 90°$, β = 99.791(3)°, V = 1205.93(8) Å^3, Z = 2, D_c = 1.378 Mg m^{-3}, μ(Cu-Kα) = 3.521 mm^{-1}, F(000) = 524. 6938 reflections were collected at $4.48 \leqslant 2\theta \leqslant 67.01$ and merged to give 3318 unique reflections (R_{int} = 0.0254), of which 3132 with $I > 2\sigma(I)$ were considered to be observed. Final values are R_1 = 0.0379, wR_2 = 0.1017, GOF = 1.039, max/min residual electron density 0.355 and −0.352 e. Å^{-3}. A suitable single crystal of the **13a** compound was mounted on a glass fibre for data collection on a Bruker Kappa APEX II CCD (charge coupled device) diffractometer. Data were collected at 298 K using Cu-Kα 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^{TM} program package. The structure was 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. Hydrogen atom positions were calculated by geometrical methods and refined as a riding model. CCDC 888605.

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