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Diastereoselective Diels–Alder cycloaddition of [(1*R*)-10-(*N*,*N*-diethylsulfamoyl) isobornyl] 2*H*-azirine to nucleophilic 1,4-disubstituted 1,3-dienes

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ABSTRACT

Chiral [(1*R*)-10-(*N*,*N*-diethylsulfamoyl)isobornyl] 2*H*-azirine **1** [Timén, A. S.; Somfai, P. *J. Org. Chem.* **2003**, 9958–9963; Timén, A. S.; Fisher, A.; Somfai, P. *Chem. Commun.* **2003**, 1150–1151]. was combined to a number of 1,4-disubstituted-2-aza-1,3-dienes **2a**–**g** [Alves, M. J.; Durães, M. M.; Gil Fortes, A. *Tetrahedron* **2004**, 6541–6553] to give cycloadducts **8a**–**g** as major isomers. High to good diastereofacial differentiation of the two faces of the azirine is observed when R^1,R^2 = Ar **2a**–**e**; diastereoselectivity drops drastically when R^1 = Me or H **2f**,**g**. Cycloaddition of the azirine **1** to *E*,*E*-1,4-diacetoxy-1,3-butadiene shows complete diastereoselectivity giving cycloadduct **11a**.

1. Introduction

Electrophilic 2*H*-azirines are excellent partners in the Diels–Alder cycloaddition yielding fused bicyclic nitrogen-containing compounds with high biological potential.[1] The diastereoselective versions of such reactions have been performed with chiral 2*H*-azirines possessing a chiral ester moiety,[1–4] showing only moderate selectivity, unless twofold equivalents of a Lewis acid was used.[1,2] Unfortunately these conditions turn out to be aggressive in some cases, resulting in extensive decomposition, for example, the aziridine moiety expands thus destroying the first formed six-membered ring structure.[1] Attempts to promote asymmetric Diels–Alder reaction using chiral Lewis acid catalysts have failed, resulting in moderate enantioselectivities. Davis et al. have described two methods[5,6] for installing chirality within the three-membered ring azirine, an electrophilic species capable of acting as a dienophile. One of these methods has reported the synthesis of 2-substituted 3-carboxylic 2*H*-azirines generated and reacted in situ with the diene counterpart in the presence of base. The effectiveness of the facial selectivity in the Diels–Alder approach of reagents was tested with simple dienes; homochiral products were obtained. Even after this success, in our view, interest in a chiral ester azirine auxiliary remains, mainly for the sake of simplicity of the azirine nucleus and of the cycloadduct products formed. We found a high inherent diastereoselectivity in reactions of the 2*H*-azirine **1** bearing the [(1*R*)-10-(*N*,*N*-diethylsulfamoyl)-isobornyl] auxiliary when reacting with 1,4-disubstituted-1,3-dienes. 2-Aza-1,3-dienes **2**, first developed by Ghosez,[7] have been combined in an earlier work with racemic azirine **3** to produce cycloadducts of type **4** and then further transformed into unnatural aminoesters **5**[8,9] (Scheme 1).

Herein we have studied the selectivity control in the cycloaddition of chiral ester azirine **1** to different 1,4-disubstituted 2-aza-butadienes **2**. Commercial 1,4-diacetoxy-1,3-butadiene was added to the diene list to be tested for the product would be an interesting iminosugar precursor **6**. Standard functional group transformation of **6** including hydroxylation of the double bond and reduction of the ester groups would lead to the D-nojirimycin analogue **7**[10] (Scheme 2).

2. Results and discussion

Freshly made azirine **1**, obtained by thermolysis of the respective [(1*R*)-10-(*N*,*N*-diethylsulfamoyl)-isobornyl] 2-azidoacrylate in toluene[3] was combined with dienes **2a**–**g** (0.4–2.2 equiv) and stirred at room temperature under nitrogen for 1–5 days. The crude mixtures were analysed by ^{1}H NMR spectroscopy. Scheme 3 shows the yields and the diastereomeric ratio of isomers obtained. Major cycloadducts were isolated in their hydrolysed forms **8a**–**g** after chromatography. The yields vary from 16% to 65%. Minor isomers were not isolated in pure form in any cases. ^{1}H and ^{13}C NMR spectra of isomeric-enriched samples in the minor isomer showed the very close relationship of the two isomers. In one case, the minor isomer **9c** has shown particularly distinct ^{1}H NMR peaks for the fused aziridine structure. H-7 can be seen as two singlets at δ_H = 2.25 and 2.45 ppm, H-5 as a doublet at δ_H = 4.41 ppm with a small coupling constant J = 1.2 Hz, H-2 as a singlet at δ_H = 5.78 ppm and the NH as a broad singlet at δ_H = 6.20 ppm. Chemical shifts and peak multiplicities of compound **9c** are replicas of the major isomer **8c**. Also H-1′ signals are closely related in both compounds (see Experimental **8c** /**9c**).

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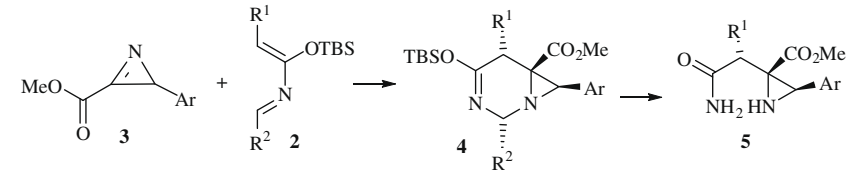
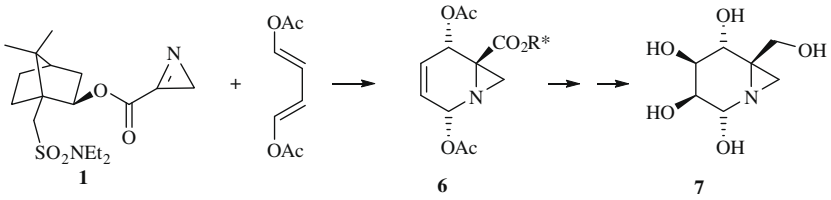
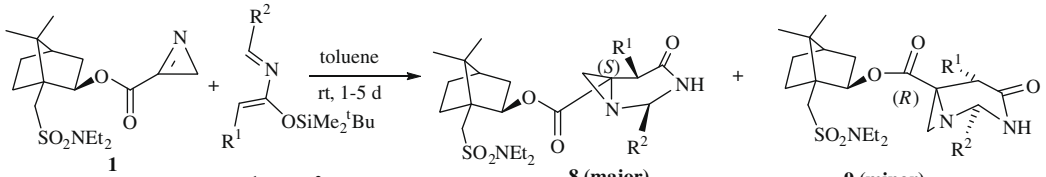


Scheme 1. Cycloadditions of 2*H*-azirine ester **3** to 2-aza-butadienes.[8,9]



Scheme 2. Cycloadditions of 2*H*-azirine ester **1** to *E,E*-1,4-diacetoxy-1,3-butadiene.



2a, R^1=Ph, R^2=Ph
2b, R^1=Ph, R^2=4-MeOC_6H_4
2c, R^1=Ph, R^2=furyl
2d, R^1=4-MeOC_6H_4, R^2=Ph
2e, R^1=4-FC_6H_5, R^2=Ph
2f, R^1=Me, R^2=Ph
2g, R^1=H, R^2=Ph

8 yield %,[a]	**8:9** *d.r.*[b]
55	**8a:9a**, 6:1
36	**8b:9b**, 5.5:1
45	**8c:9c**, 8:1
16	**8d:9d**, 9:1
33	**8e:9e**, 5.6:1
18	**8f:9f**, 2.1:1
65	**8g:9g**, 2.6:1

a) isolated yield, after chromatography
b) in crude reaction mixtures

Scheme 3. Cycloaddition of 2*H*-azirine **1** to 1,4-disubstituted-2-aza-1,3-dienes **2a**–**g**.

The structure of the major isomer obtained in the reaction with **2a** was established by means of X-ray crystal structure analysis and assigned as **8** (**8a**). When R^1 is a methyl group, the two isomers are in closer proportion, the major isomer being shown to be structure **8** (**8f**) by X-ray crystallography (Figs. 1 and 2). Both isomers **8** and **9** would form by the *endo* approach of reagents according to a general

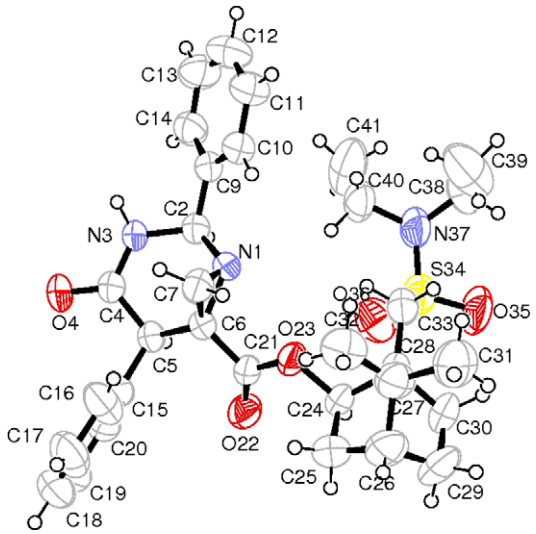


Figure 1. ORTEP view of the molecular structure of the cycloadduct **8a**.

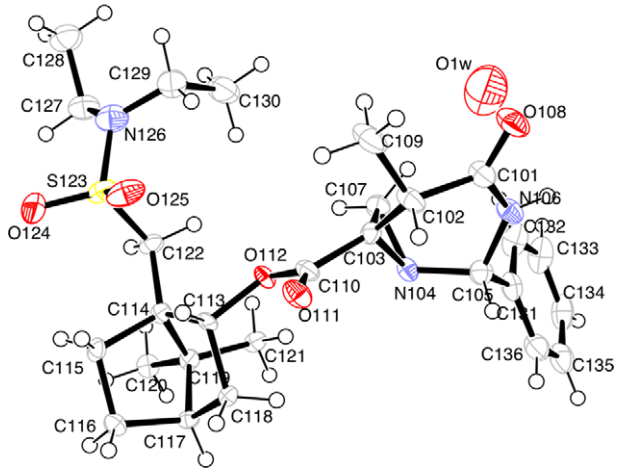


Figure 2. ORTEP view of the molecular structure of the cycloadduct **8f**.

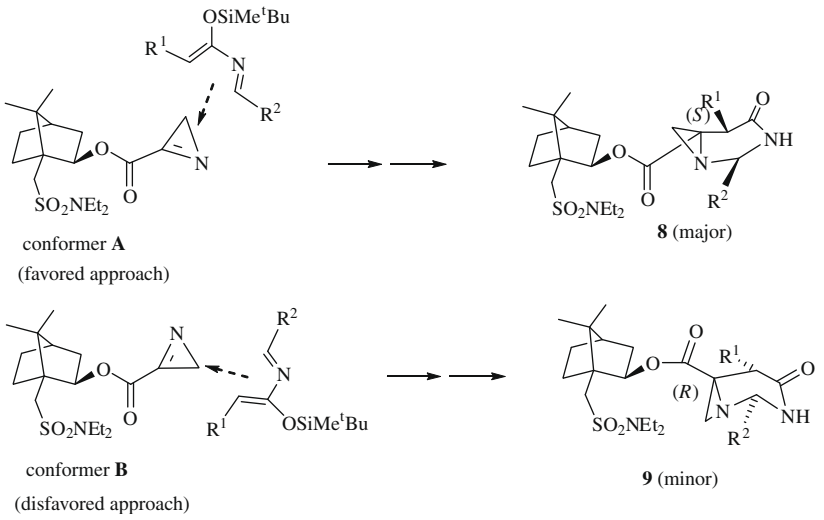


Figure 3. Approach of 2-aza-1,3-butadienes **2** to the less hindered face of conformers **A** and **B** of 2*H*-azirine **1**.

feature of Diels–Alder cycloaddition involving 2*H*-azirines, with the exception of furan and derivatives that form *exo* products.[11]

In an attempt to further improve the selectivity, a parallel experiment using Somfaís Lewis acid conditions was attempted.[1,2] The reaction of azirine **1** and diene **2a** in the presence of 2 equiv of $MgBr_2{\cdot}EtO_2$, resulted in a complex mixture of products with no cycloadduct formed.

It has been claimed that 2*H*-azirine-3-carboxylic esters occur in the two minimum energy conformers *s-cis* and *s-trans*.[3] The *s-cis* form is represented as conformer **A** and the *s-trans* form as conformer **B** (Fig. 3). There is one likely approach of the diene **2** to each conformer of the 2*H*-azirine **1**, that is shown in Figure 3.

In the upper approach, the diene attacks the rear face of conformer A (*si* face). This arrangement will give the major isomer, with an (*S*)-configuration at C-6. In the lower approach, the diene attacks the rear face of conformer **B** (*re* face). The interference of the methylene unit at the isobornyl group (α to the ester function) with the R^1 group attached to the diene was predicted. This will become a more difficult approach when R^1 are bulky groups.

Table 1
$[\alpha]_D^{20}$ Values of enriched/pure samples of compounds **8**, taken in CH_2Cl_2

8:**9**	Diastereomeric ratio **8**:**9**	*c* (g/100 mL)	$[\alpha]_D^{20}$ (cm^2 g^{-1})
a	**8a** (pure)	5.71	+0.1
b	3.2: 1	0.60	−30.0
c	**8c** (pure)	4.00	−4.7
d	11.0: 1	0.33	−19.8
e	5.7: 1	0.40	−45.0
f	1.5: 1	0.13	−51.7
g	3.0: 1	0.09	−59.6

In Table 1 the $[\alpha]_D^{20}$ values of pure **8a**,**c** and of enriched **8b**,**d**,**e**,**f**,**g** samples are shown.

Commercially available 1,4-diacetoxy-1,3-butadiene was combined with freshly made azirine **1** in toluene and stirred for 5 days at room temperature. (Scheme 4) The crude product was analysed by ^{1}H NMR spectroscopy, which showed a single diastereomer **11a** isolated in 54% yield after chromatography.

An X-ray structure of the product showed it to be structure **11a**, (Fig. 4) with the configuration on the stereocentres corresponding to the L-nojirimycin derivative precursor, instead of the D-isomer precursor expected **7**. The reason for such a turnover in the approach of reagents in the Diels–Alder cycloaddition is possibly

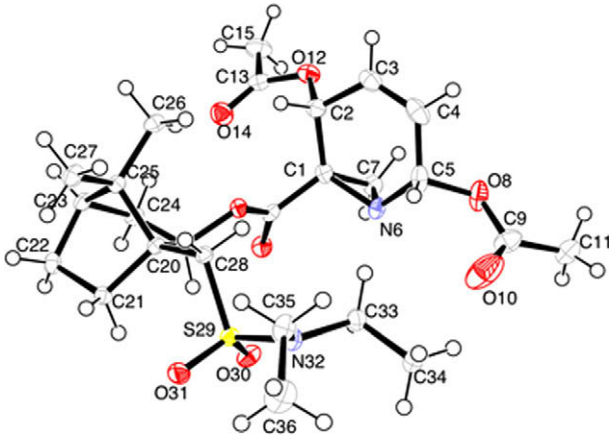
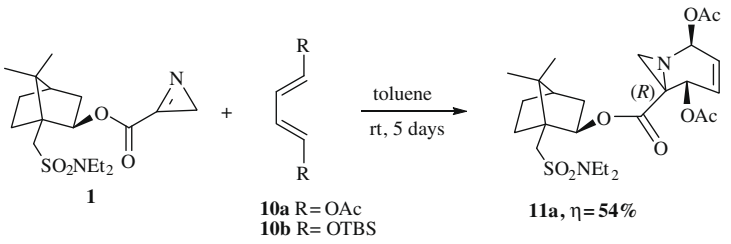


Figure 4. ORTEP view of the molecular structure of the cycloadduct **11a**.



Scheme 4. Cycloaddition of 2*H*-azirine **1** to 1,4-disubstituted 1,3-butadienes **10a**,**b**.

due to the electronic repulsion between ester groups, in both the azirine and the diene that would be higher in the *si* face of conformer **A** than in the *re* face of conformer **B**.

The reaction of the azirine **1** with 1,4-*tert*-butyldimethylsiloxy-1,3-butadiene proved to be too slow at rt. A ^{1}H NMR spectrum of the reaction mixture showed that after 15 days at rt, large quantities of reagents were still present together with a mixture of products. After the addition of a new portion of the azirine (0.7 equiv) and another 5 days run, the ^{1}H NMR spectrum of an aliquot showed that a complex mixture of products formed. The large bulk of the siloxy groups may explain the difficulty of this cycloaddition.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), doublets of doublets (dd), doublets of doublets of doublets (ddd), doublets of triplets (dt), triplets (t), quartets (q) and multiplets (m). *J* values are in Hertz and d in parts per million. Infrared spectra were recorded on a Bomem MB 104 or on a Perkin–Elmer spectrophotometer. Samples were run as Nujol mulls and oils as thin films. MS spectra were recorded on a VG Autospec M. spectrometer. Microanalyses were performed in a LECO-CHNS-932 analyser. Melting points (mps) were determined on a Gallenkamp block and are uncorrected. Dry column flash chromatography was carried out using Kieselgel 60 and water pump vacuum. Toluene was dried over sodium followed by distillation. Dichloromethane (DCM) was dried over CaH_2. Acetonitrile (ACN) used was not dried. Petroleum ether 40–60 °C was distilled before use.

3.2. Cycloadditions of [(*R*)-10-(*N*,*N*-diethylsulfamoyl)-isobornyl] 2*H*-azirine 1 to 1,4-disubstituted 2-aza-1,3-dienes 2a–g

3.2.1. General methodology

A solution of [(*R*)-10-(*N*,*N*-diethylsulfamoyl)-isobornyl] 2-azidoacrylate[1,2] (ca. 0.05 M; 15–25 mL) in toluene was refluxed for 1.5 h under nitrogen. After cooling down the solution to rt, dienes **2a**–**g**[8] dissolved in toluene (0.5–0.75 M; 5–8 mL) were added. Reaction mixtures were stirred under nitrogen for n days at rt and evaporated. Crude products were subjected to flash chromatography (silica, pet. ether: ether, crescent polarity) giving cycloadducts **8a**–**g**.

3.2.1.1. Synthesis of 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylate 8a. Freshly made 2*H*-azirine **1**[3,4] (500 mg; 1.23 mmol) in toluene (25 mL) was combined with freshly made diene **2a**.[8] The reaction mixture was stirred under nitrogen for 2.5 days. After solvent removal, the crude showed a reasonably clean mixture of diastereomers **8a**/**9a** in a 6:1 ratio by ^{1}H NMR analysis. The crude was subjected to dry flash chromatography giving pure **8a** in 55% yield, as a white solid, mp 214.6–216.4 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H = 0.80–0.90 (m, 12H, 4 × Me), 1.02–1.20 (m, 3H), 1.40–1.60 (m, 1H), 1.61–1.80 (m, 2H), 1.85–2.00 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 1H, H-7), 2.56 (d, *J* = 13.5 Hz, 1H, CH*H*SO_2), 2.73 (s, 1H, H-7), 2.92–3.20 (m, 5H), 4.52 (s, 1H, H-5), 4.93 (dd, *J* = 3.3, 7.8 Hz, 1H, H-1′), 5.80 (s, 1H, H-2), 5.84 (s, 1H, NH), 7.20–7.54 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C = 14.2 (Me), 19.9 (Me), 20.3 (Me), 26.2 (C-7), 26.8 (CH_2), 29.4 (CH_2), 39.0 (CH_2), 41.1 (CH_2), 43.0 (C), 44.2 (CH), 46.4 (C-5), 48.8, 49.0, 49.1 (CH_2, 2C), 69.7 (C-2), 78.9 (C-1′), 126.5 (CH, Ar), 128.4 (CH, Ar), 129.1 (CH, Ar), 129.4 (CH, Ar), 129.5 (CH, Ar), 135.2 (C), 137.8 (C), 167.5 (CO), 169.7 (CO). Anal. Calcd for $C_{32}H_{41}N_3O_5S$: C, 66.28; H, 7.14; N, 7.25; S, 5.53. Found: C, 66.36; H, 6.76; N, 7.06; S, 5.10. IR (neat) ν_{max} (cm^{-1}) 3198, 1729, 1683, 1644.

3.2.1.2. Synthesis of 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylate 8b. [(*R*)-10-(*N*,*N*-Diethylsulfamoyl)-isobornyl] 2-azidoacrylate (0.43 g; 1.20 mmol) in toluene (25 mL). Diene **2b**[8] (1.25 equiv; 1.50 mmol; 0.55 g) in toluene (2 mL). Reaction time: 2.5 days. Cycloadduct **8b** as a white solid, slightly contaminated with its diastereomer **9b** (0.26 g; 0.43 mmol; 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H = 0.86 (s, 3H, Me), 0.87 (s, 3H, Me), 0.94 (t, 6H, *J* = 7.2 Hz, 2 × Me), 1.10–1.80 (m, 3H), 1.40–1.55 (m, 1H), 1.61–1.80 (m, 2H), 1.85–1.90 (m, 1H), 2.51 (d, *J* = 1.5 Hz, 1H, H-7), 2.59 (d, *J* = 13.5 Hz, 1H, CH*H*SO_2), 2.73 (s, 1H, H-7), 2.95–3.20 (m, 5H), 3.83 (s, 3H, OMe), 4.53 (d, *J* = 1.8 Hz, 1H, H-5), 4.93 (dd, *J* = 3.3, 8.1 Hz, 1H, H-1′), 5.73 (s, 1H, H-2), 5.88 (br s, 1H, NH), 6. 92 (d, *J* = 8.7, 2H, Ar), 7.32–7.40 (m, 7H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C = 14.2 (Me), 19.8 (Me), 20.3 (Me), 26.0 (C-7), 26.8 (CH_2), 29.4 (CH_2), 38.9 (CH_2), 41.1 (CH_2), 42.9 (C), 44.1 (CH), 46.4 (C-5), 48.8 (CH_2), 48.9 (C), 49.1 (C), 55.3 (OMe), 69.2 (C-2), 78.8 (C-1′), 114.3 (C), 127.7 (CH, Ar), 128.3 (CH, Ar), 129.3 (CH, Ar), 130.0 (C), 135.3(C), 160.3 (C), 167.5 (CO), 169.7 (CO). HRMS *m/z* 610.2931 (MH^+ [$C_{33}H_{44}N_3O_6S$ = 610.2931]). IR (neat) ν_{max} (cm^{-1}) 3230, 3089, 1731, 1884, 1659, 1614.

3.2.1.3. Synthesis of 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylate 8c. [(*R*)-10-(*N*,*N*-Diethylsulfamoyl)-isobornyl] 2-azidoacrylate (0.38 g; 1.07 mmol) in toluene (20 mL). Diene **2c**[8] (1 equiv; 1.07 mmol; 0.35 g) in toluene (2 mL). The reaction time: 2.5 days. Cycloadduct **8c** as a white solid (0.29 g; 0.48 mmol; 45%), mp 159.6–160.4 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H = 0.83 (s, 6H, 2 × Me), 1.03 (t, 6H, *J* = 7.2 Hz, 2 × Me), 1.10–1.30 (m, 3H), 1.40 –1.60 (m, 1H), 1.60–1.80 (m, 2H), 1.85–2.00 (m, 1H), 2.42 (d, *J* = 1.8 Hz, 1H, H-7), 2.59 (d, *J* = 13.5 Hz, 1H, CH*H*SO_2), 2.59 (s, 1H, H-7), 3.02–3.30 (m, 5H), 4.56 (d, *J* = 1.2 Hz, 1H, H-5), 4.93 (dd, *J* = 3.3, 7.8 Hz, 1H, H-1′), 5.80 (s, 1H, H-2), 6.19 (br s, 1H, NH), 6.46 (t, *J* = 0.9 Hz, 1H, Furyl), 7.22–7.28 (m, 5H), 7.44 (s, 1H, Furyl), 7.55 (s, 1H, Furyl). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C = 14.3 (Me), 19.8 (Me), 20.3 (Me), 25.9 (CH_2), 26.8 (CH_2), 29.4 (CH_2), 38.9 (CH_2), 41.1 (CH_2), 43.3 (C), 44.1 (CH), 46.1 (C-5), 48.8 (CH_2), 49.0 (C), 49.1 (C), 63.3 (C-2), 78.8 (C-1′), 108.0 (CH, Furyl), 127.7 (CH), 128.3 (CH), 129.4 (CH), 135.2 (C), 140.2 (CH, Furyl), 143.9 (CH, Furyl), 167.4 (CO), 169.6 (CO). HRMS *m/z* 592.2443 (MH^+ [$C_{30}H_{39}N_3NaO_6S$ = 592.2452]). IR (neat) ν_{max} (cm^{-1}) 3197, 3106, 1729, 1683. $[\alpha]_D^{20} = -4.7$ (*c*, 4.0 g/100 mL, DCM).

Some distinct peaks of compound **9c** were registered from an enriched sample obtained by chromatography: ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H = 2.25 (s, 1H, H-7), 2.45 (s, 1H, H-7), 4.41 (d, *J* = 1.2 Hz, 1H, H-5), 4.85 (dd, *J* = 3.3, 7.8 Hz, 1H, H-1′), 5.78 (s, 1H, H-2), 6.20 (br s, 1H, NH), 6.43 (t, *J* = 0.9 Hz, 1H, Furyl).

3.2.1.4. Synthesis of 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylate 8d. [(*R*)-10-(*N*,*N*-Diethylsulfamoyl)-isobornyl] 2-azidoacrylate (0.43 g; 1.20 mmol) in toluene (25 mL). Diene **2d**[8] (0.8 eq.; 0.96 mmol; 0.35 g) in toluene (2 mL). The reaction time: 3 days. Cycloadduct **8d** as a white solid (0.27 g; 0.44 mmol; 46%), slightly contaminated with its diastereomer **9d**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H = 0.82–0.92 (m, 12H, 4 × Me), 1.10–1.30 (m, 4H), 1.60–1.88 (m, 2H), 1.89 –2.04 (m, 1H), 2.50 (d, *J* = 1.8 Hz, 1H, H-7), 2.56 (d, *J* = 13.5 Hz, 1H, CH*H*SO_2), 2.71 (s, 1H, H-7), 2.94–3.20 (m, 5H), 3.81 (s, 3H, OMe), 4.84 (d, *J* = 1.5 Hz, 1H, H-5), 4.93 (dd, *J* = 3.0, 7.8 Hz, 1H, H-1′), 5.75 (s, 1H, NH), 5.79 (br s, 1H, H-2), 6.90 (d, *J* = 8.7 Hz, 2H, Ar), 7.26 (d, *J* = 8.7 Hz, 2H, Ar), 7.45 (s, 5H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C = 14.2 (Me), 19.9 (Me), 20.3 (Me), 26.1(CH_2), 26.9 (CH_2), 30.3 (CH_2), 39.1 (CH_2), 41.1 (CH_2), 43.0 (C), 44.2 (CH), 45.6 (C-5), 48.8, 49.0, 49.1 (CH_2 + 2C), 55.2 (OMe), 69.6 (C-2), 78.9 (C-1′), 114.0 (CH), 125.5(CH), 126.4 (CH), 129.1 (CH),

129.5 (C), 130.4 (CH), 137.8 (C), 159.0 (C), 167.45(CO), 170.0 (CO). HRMS *m/z* 632.2765 (MH^+ [$C_{33}H_{43}N_3NaO_6S$ = 632.2765]). IR (neat) ν_{max} (cm^{-1}) 3214, 1731, 1681, 1612.

3.2.1.5. Synthesis of 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylate 8e. [(*R*)-10-(*N*,*N*-Diethylsulfamoyl)-isobornyl] 2-azidoacrylate (0.38 g; 1.06 mmol) in toluene (20 mL). Diene **2e**[8] (0.4 equiv; 0.42 mmol; 0.25 g) in toluene (1.0 mL). The reaction time: 5 days. Cycloadduct **8e** as a white solid (83.7 mg; 0.14 mmol; 33%), slightly contaminated with its diastereomer **9e**. ^1H NMR ($CDCl_3$, 300 MHz) δ_H = 0.81–0.90 (m, 12H, 4 × Me), 1.10–1.30 (m, 5H), 1.60–2.00 (m, 2H), 2.51 (d, *J* = 1.8 Hz, 1H, H-7), 2.56 (d, *J* = 13.5 Hz, 1H, CH*H*SO_2), 2.71 (s, 1H, H-7), 2.90–3.30 (m, 5H), 4.53 (d, *J* = 1.2 Hz, 1H, H-5), 4.94 (dd, *J* = 2.7, 8.1 Hz, 1H, H-1′), 5.75 (s, 1H), 5.80 (br s, 1H), 7.00–7.15 (m, 4H), 7.30–7.38 (m, 2H), 7.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C = 14.2 (Me), 19.9 (Me), 20.3 (Me), 26.1 (CH_2), 26.8 (CH_2), 30.3 (CH_2), 39.1 (CH_2), 41.1 (CH_2), 42.9 (C), 44.1 (CH), 45.7 (C-5), 48.8, 49.0, 49.1 (CH_2 + 2C), 69.6 (C-2), 79.0 (C-1′), 115.4 (d, $J_{F,3\sim}$ = 21.5 Hz, CH), 125.5 (CH), 126.4 (CH), 129.1 (CH), 131.0 (d, $J_{F,2\sim}$ = 7.8 Hz, CH), 132.4 (C), 137.7 (C), 159.9 (d, $J_{F,4\sim}$ = 244.0 Hz, C), 167.4(CO), 169.6 (CO). HRMS *m/z* 620.2572 (MH^+ [$C_{32}H_{40}FN_3NaO_5S$ = 620.2565]). IR (neat) ν_{max} (cm^{-1}) 3206, 3093, 1731, 1681.

3.2.1.6. Synthesis of 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylate 8f. [(*R*)-10-(*N*,*N*-Diethylsulfamoyl)-isobornyl] 2-azidoacrylate (0.25 g; 0.65 mmol) in toluene (15 mL). Diene **2f**[8] (1 eq.; 0.65 mmol; 0.18 g) in toluene (1.5 mL). The reaction time: 1 day. Cycloadduct **8f** as a white solid (60 mg; 0.12 mmol; 18%), contaminated with its diastereomer **9f**.

Compound **8f** ^1H NMR ($CDCl_3$, 300 MHz) δ_H = 0.88 (s, 3H, Me), 0.96 (s, 3H, Me), 1.16 (t, *J* = 7.2 Hz, 6H, 2 x Me), 1.41 (d, *J* = 6.6 Hz, 3H, Me), 1.58 (d, *J* = 0.6, 6.6 Hz, H-5), 1.62–1.82 (m, 4H), 1.83–2.10 (m, 3H), 2.22 (s, 1H, H-7), 2.31 (d, *J* = 1.8 Hz, 1H, H-7), 2.70 (d, *J* = 13.2 Hz, 1H, CH*H*SO_2), 3.15–3.35 (m, 5H), 4.53 (d, *J* = 1.2 Hz, 1H, H-5), 4.94 (dd, *J* = 3.0, 8.4 Hz, 1H, H-1′), 5.64 (br s, 1H), 5.90 (br s, 1H), 7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C = 12.9 (Me), 14.5 (Me), 19.8 (Me), 20.3 (Me), 24.9 (CH_2), 26.9 (CH_2), 30.0 (CH_2), 34.1 (C-5), 34.2 (CH), 38.9 (CH_2), 41.5 (CH_2), 43.2 (C), 44.4 (CH), 49.1, 49.0, 49.6 (CH_2 + 2C), 69.2 (C-2), 79.1 (C-1′), 126.3 (CH), 129.0 (CH), 137.8 (C), 168.4 (CO), 171.4 (CO). HRMS *m/z* 518.2686 (MH^+ [$C_{27}H_{40}N_3O_5S$ = 518.2688]). IR (neat) ν_{max} (cm^{-1}) 3325, 3214, 1729, 1679.

3.2.1.7. Synthesis of 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylate 8g. [(*R*)-10-(*N*,*N*-Diethylsulfamoyl)-isobornyl] 2-azidoacrylate (0.36 g; 1.02 mmol) in toluene (20 mL). Diene **2g**[8] (0.4 equiv; 0.41 mmol; 107 mg) in toluene (1 mL). The reaction time: 5 days. Cycloadduct **8g** as a white solid (126 mg; 0.25 mmol; 65%), contaminated with its diastereomer **9g**. ^1H NMR ($CDCl_3$, 300 MHz) δ_H = 0.89 (s, 3H, Me), 0.90 (s, 3H, Me), 1.19 (t, *J* = 7.2 Hz, 6H, 2 × Me), 1.60–2.10 (m, 7H), 2.28 (d, *J* = 0.9 Hz, 1H, H-7), 2.34 (s, 1H, H-7), 2.73 (d, *J* = 13.8 Hz, 1H, CH*H*SO_2), 3.05–3.34 (m, 7H), 4.95–5.01 (m, 1H, H-1′), 5.62 (br s, 1H, H-2), 5.77 (br s, 1H, NH), 7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C = 14.5 (Me), 19.9 (Me), 20.3 (Me), 26.9 (CH_2), 27.2 (CH_2), 30.3 (CH_2), 30.8 (C-5), 38.1 (CH_2), 39.3 (CH_2), 41.4 (C), 44.4 (CH), 49.3, 49.4, 50.1 (CH_2 + 2C), 69.7 (C-2), 79.5 (C-1′), 126.1 (CH), 129.1 (CH), 129.3 (CH), 137.6 (C), 168.6 (CO), 168.7 (CO). HRMS *m/z* 504.2513 (MH^+ [$C_{26}H_{38}N_3O_5S$ = 504.2527]). IR (neat) ν_{max} (cm^{-1}) 3200, 3085, 1733, 1677.

4. Cycloaddition of [(*R*)-10-(*N*,*N*-diethylsulfamoyl)-isobornyl] 2*H*-azirine 1 to 1,4-diacetoxy-1,3-butadiene 10

[(*R*)-10-(*N*,*N*-Diethylsulfamoyl)-isobornyl] 2-azidoacrylate[1,2] (0.24 g; 0.68 mmol) in toluene (15 mL) was refluxed for 1.5 h under nitrogen. The reaction mixture was concentrated in the rotary evaporator until 1/3 of the initial volume and diene **10** (0.12 g; 0.68 mmol) was added. The mixture was stirred under nitrogen for 5 days at rt. The solvent was removed and the crude subjected to dry flash chromatography (pet. ether/ether, crescent polarity) to give a white solid (184 mg; 0.35 mmol; 51%), mp 166.7–167.4 °C, that proved to be the cycloadduct **11a**. ^1H NMR ($CDCl_3$, 300 MHz) δ_H = 0.87 (s, 3H, Me), 0.85 (s, 3H, Me), 1.20 (t, *J* = 6.6 Hz, 6H, 2 × Me), 1.50–2.05 (m, 7H), 2.06 (s, 3H, Me), 2.11 (s, 3H, Me), 2.27 (s, 1H, H-7), 2.38 (s, 1H, H-7), 2.68 (d, *J* = 13.5 Hz, 1H, CH*H*SO_2), 3.20–3.32 (m, 5H), 4.97 (dd, *J* = 2.1, 7.2 Hz, 1H, H-1′), 5.49 (br d, *J* = 10.5 Hz, 1H, H-3 or H-4), 5.77 (dt, *J* = 0.9, 10.5 Hz, H-4 or H-3), 6.10 (s, 1H, H-5), 6.20 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C = 14.6 (Me), 19.8 (Me), 20.2 (Me), 21.0 (Me), 21.1 (Me), 26.9 (CH_2), 29.7 (CH_2), 30.4 (CH_2), 39.2 (CH_2), 39.3 (C), 41.5 (CH_2), 44.4 (CH), 49.3 (C), 49.4 (C), 49.6 (CH_2), 64.3 (CH), 78.4 (CH), 80.2 (CH), 123.9 (CH), 126.0 (CH), 168.0 (CO), 169.2 (CO), 170.4 (CO). IR (neat) ν_{max} (cm^{-1}) 1747. Elem. Anal. Calcd for $C_{25}H_{38}N_2O_8S$: C, 57.01; H, 7.29; N, 5.32. Found: C, 57.18; H, 7.26; N, 5.64. $[\alpha]_D^{20} = -77.5$ (*c* 2 g/100 mL, DCM).

CCDC 723973–723975 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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