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Consecutive reactions with sulfoximines: a direct access to 2-sulfonimidoylylidene tetrahydrofurans and 6-sulfonimidoylmethyl-3,4-dihydro-*2H*-pyrans

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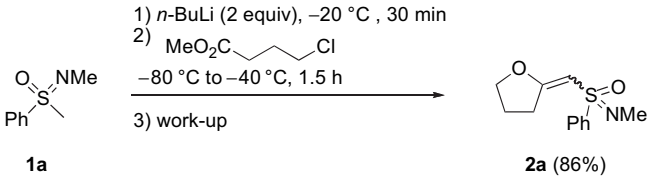
ABSTRACT

2-Sulfonimidoylylidene tetrahydrofurans and 2-sulfonimidoylylidene-5-vinyl tetrahydrofurans were readily synthesized via a consecutive acylation/SN2 sequence with total regio- and chemoselectivity from Johnson's sulfoximine derivatives. The same consecutive reaction could also be applied to the expeditious synthesis of 6-sulfonimidoylmethyl-3,4-dihydro-*2H*-pyrans.

1. Introduction

Nature has produced a diverse array of molecules with widespread biological activity. To obtain the large quantities of these substances necessary for biological evaluation and drug development, the pharmaceutical industry relies upon organic synthesis.[1] Indeed organic synthesis can often compete with nature in supplying these molecules. However as the molecular complexity of the natural products increases, the length of syntheses also increases, which often translates into poor overall efficiency, prohibitive cost, and the production of a considerable amount of waste. In the current 'economy' context[2,3] associated with environmental considerations[4] in the science of organic synthesis, the research for new methodologies that allows for rapid and controlled synthetic access to these target molecules is crucial. Consecutive and domino processes have emerged as powerful tools for the efficient and ecocompatible[5] creation of molecular complexity and chemical diversity from simple substrates in a single operation.[6]

In our laboratory there is an ongoing interest in multiple bond-forming transformations.[7] In the course of our research program on the reactions of *bis*-nucleophiles with *bis*-electrophiles, we have recently reported[8] preliminary results for the chemo- and regioselective synthesis of 2-sulfonimidoylylidene tetrahydrofurans by a consecutive reaction of sulfoximines with α,ω-haloesters. The dianion generated from Johnson's sulfoximine[9] (**1a**) and two equivalents of *n*-butyllithium at −20 °C reacts with readily available α,ω-haloesters via an acylation/heterocyclization consecutive reaction to efficiently provide the functionalized 2-sulfonimidoylylidene tetrahydrofuran **2a** (Scheme 1).



1a **2a** (86%)

Scheme 1.

Functionalized tetrahydrofurans are structural motifs in a number of highly interesting natural products (for example, nactin derivatives, tetronasin, tetronomycin,[10] terpenes,[11] medium size lactones,[12] charlic, and charolic acids, terrestric acids,[13] chalcogran,[14] and acetogenins[15]) and are of pharmacological relevance.[16] Several methods[17] have been developed for the construction of these useful building blocks[18] but there is still an interest in the development of an efficient, convenient and stereoselective approach. The regio- and diastereoselective synthesis of 2-ylidene tetrahydrofurans via anionic domino or consecutive reactions has been developed in the past few years independently in our group[8,19] and the groups of Zhao,[20] Hagiwara[21] and Langer.[17c]

In this context, chiral sulfoximines particularly turned our attention due to the presence of a modulable stereogenic sulfur atom and their use in asymmetric synthesis is well-established.[9,22] In fact both the steric and electronic demand can be easily modified by changing the nature of the substituent group on the nitrogen atom.

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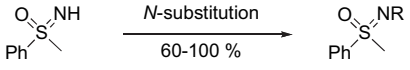
In addition this chiral auxiliary can be removed, recycled or even exploited for further coupling.[23]

Herein we wish to report in full details our original methodology for the synthesis of valuable 2-sulfonimidoylylidene tetrahydrofurans, and its significant extension to the hydropyran series.

2. Results and discussion

The requisite *N*-protected sulfoximines **1** were prepared. Known compounds were obtained according to reported literature procedures in similar yields,[24] and three previously unknown analogues (**1h**, **1k**, and **1m**) were also prepared. A range of *N*-substituted sulfoximines bearing various electron-donating, electron-withdrawing, and sterically hindered groups was obtained (**1a**–**m**, Scheme 2).



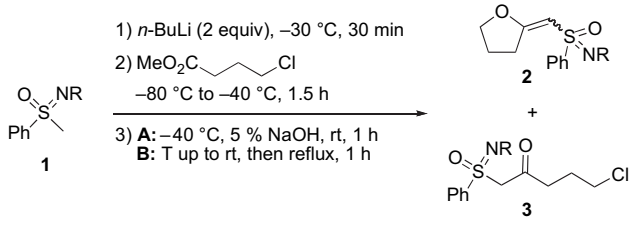
1a-m

1a: R = Me (84%)[24a]
1b: R = Ts (92%)[24b]
1c: R = Allyl (77%)[24c]
1d: R = TMS (quant.)[24d]
1e: R = TBS (87%)[24e]
1f: R = Boc (84%)[24f]
1g: R = Bz (72%)[24g]
1h: R = Alloc; $ClCO_2$allyl, Py, THF, 0 °C (85%)
1i: R = Piv (97%)[24h]
1j: R = neopentyl (60%)[24h]
1k: R = Cbz; CbzCl, Py, THF, 0 °C (78%)
1l: R = Eoc (64%)[24i]
1m: R = Mes; MesBr, *t*BuOK, $Pd_2(dba)_3$ (2 mol%), IPr·HCl (2 mol%), dioxane, 80 °C (96%)[24j]

Abbreviations used:
Ts = *p*-toluenesulfonyl, TBS = *tert*-butyldimethylsilyl,
Alloc = allyloxycarbonyl, Boc = *tert*-butyloxycarbonyl,
Bz = benzoyl, Piv = pivaloyl, Cbz = benzyloxycarbonyl,
Eoc = ethoxycarbonyl, Mes = mesityl = 2,4,6-trimethylphenyl,
IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Scheme 2.

Due to the acidic character of the α-protons in sulfoximines, deprotonation can be easily achieved by strong bases to yield the corresponding α-metallated intermediates.[25] Indeed, treatment of *N*-substituted sulfoximines **1** with two equivalents of *n*-butyllithium at −30 °C in THF generated the corresponding dianion (vide infra). Subsequent addition of commercially available methyl 4-chlorobutyrate at −80 °C followed by low temperature hydrolysis with 5% aqueous sodium hydroxide solution (conditions A) allowed the formation of 2-sulfonimidoylylidene tetrahydrofurans (**2**), in moderate to good yields, as an easily separable mixture of *E* and *Z* isomers[26] (Scheme 3 and Table 1). Although compounds with Ts, TBS, and Bz (entries 3, 6, 7, and 10) on the nitrogen atom gave modest yields, all other substituents gave synthetically valuable yields. Attempts to directly cyclize the lithiated intermediate by simply increasing the reaction temperature to reflux (conditions B) failed to improve either the yields or the selectivities (entries 2, 4, 9, and 11).



Scheme 3.

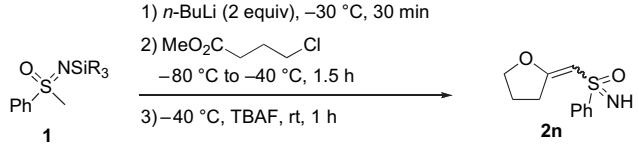
It is interesting to note that under conditions A (5% NaOH hydrolysis) the *N*-pivaloyl group allowed the best selectivity in the series (entry 13), but in this case the cyclization step is not efficient as evidenced by the isolation of 21% of acyl product **3**.

Table 1
Consecutive reaction of sulfoximines **1** with methyl 4-chlorobutyrate

Entry	Product	R	Condition	Yield (%)	*E*/*Z* ratio
1	**2a**	Me	A	86	52:48
2	**2a**	Me	B	55	86:14
3	**2b**	Ts	A	23	61:39
4	**2b**	Ts	B	17	70:30
5	**2c**	Allyl	A	58	41:59
6	**2e**	TBS	A	31[b]	—
7	**2e**	TBS	A[a]	35[b]	—
8	**2f**	Boc	A	67	37:63
9	**2f**	Boc	B	53	57:43
10	**2g**	Bz	A	19	53:47
11	**2g**	Bz	B	17	53:47
12	**2h**	Alloc	A	64	37:63
13	**2i**	Piv	A	64[c]	21:79
14	**2j**	Neopentyl	A	70	35:65
15	**2k**	Cbz	A	48	36:64
16	**2l**	Eoc	A	49	37:63

[a] NaOH was added at rt.
[b] The *E* isomer probably decomposed during silica gel flash chromatography.
[c] 21% of acyl product **3** was isolated.

When the *N*-silylated sulfoximine **2e** (Table 1, entries 6 and 7) was submitted to the consecutive acylation/SN2 reaction, the sole isomer isolated was the *Z* one. Indeed, the *E* isomer appeared to be unstable and decomposed during the flash chromatography on silica gel, presumably after cleavage of the *N*–Si bond. In order to validate this hypothesis we thought it could be relevant to study the deprotection of the silyl group in the same pot. The deprotection successfully occurred in presence of TBAF under the same experimental conditions but again with poor yields. However both *Z* and *E* isomers of **2n** were isolated in moderate yields with, as expected,[22b,27,28] an increased selectivity for the TBS substituent compared to TMS (Scheme 4).

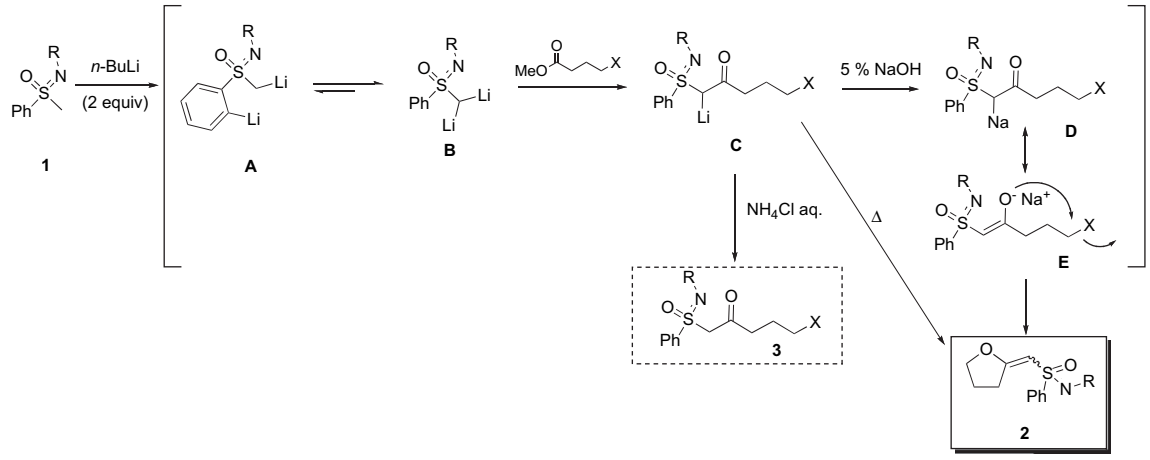


from **1d** (SiR_3 = TMS): 37 %, *E*/*Z* = 43:57
from **1e** (SiR_3 = TBS): 22 %, *E*/*Z* = 86:12

Scheme 4.

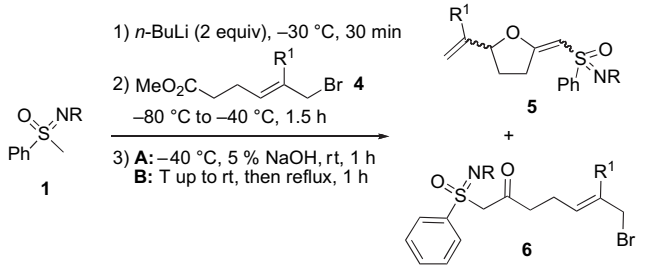
A mechanism to account for the observed formation of 2-sulfonimidoylidene tetrahydrofurans **2** is proposed in Scheme 5. The α,*ortho*-dilithiosulfoximine **A** undergoes a rearrangement to the α,α-dilithiosulfoximine **B**, which then reacts chemoselectively with the α,ω-halogenoester to give the α-sulfonimidoylcarbanion **C**. The assumption of a dianion species is based on work reported by Gais and Müller on the α,*ortho* to α,α-transmetallation of dilithiated alkylphenylsulfones[29] and dilithiosulfoximines, respectively.[30]

Depending on the work-up, different products would then be produced. Addition of a 5% aqueous solution of sodium hydroxide (conditions A) could lead after transmetallation, to the corresponding α-Na-sulfoximine **D**. The latter would then undergo a rapid *O*-cyclization providing the observed sulfonimidoylylidene tetrahydrofurans **2**. Upon treatment with a saturated aqueous solution of ammonium chloride the lithiated species **C** is simply hydrolyzed to the corresponding acyl adduct **3**. In this case, no product arising from the heterocyclization was detected thus confirming that the acylation precedes the *O*-cyclization. Finally heating the reaction mixture to reflux for an hour (conditions B) produced the same heterocycle **2** but in moderate to low yields. The overall transformation consisted therefore in an acylation/SN2 cascade reaction.



Scheme 5.

This consecutive one-pot acylation/SN2 reaction involved the formation of two chemical bonds in the same operation (a C–O bond and a C–C bond), thus providing a practical, chemo- and regioselective access to versatile building blocks of type **2**. In order to generalize this multiple bond-forming transformation, we next examined the reaction of the sulfoximine dianion with methyl esters bearing an allylic bromide as the second electrophilic position, namely methyl 6-bromo-hex-4-eneoate (**4a**, R^1=H) and methyl 5-methyl-6-bromo-hex-4-eneoate (**4b**, R^1=Me). Both would allow for the synthesis of the corresponding 2-sulfonimidoylylidene-5-vinyl tetrahydrofurans via an intramolecular SN2′ displacement. As anticipated the reaction proceeded well under the previously optimized reaction conditions (conditions A) and afforded the expected compounds **5** in fair to good yields (Scheme 6 and Table 2). Conditions B were proved less efficient (entries 2, 4, 6, and 8) and in two cases, afforded predominately the corresponding acyl derivatives **6** (entries 4 and 6). Finally, increasing the steric demand on the nitrogen of the sulfoximine (entries 3, 9, and 10) led to an increased diastereoselectivity in favor of the *Z* isomer.



Scheme 6.

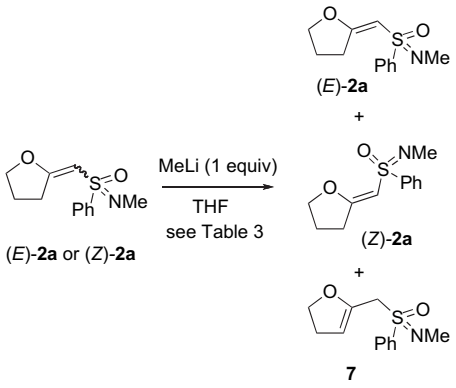
Table 2
Consecutive reactions of sulfoximines **1** with **4**

Entry	**5**	R	R^1	Cond	Yield of **5** (%)	Yield of **6** (%)	*E*/*Z* ratio[a]
1	**5a**	Me	H	A	40	—	58:42
2	**5a**	Me	H	B	9	—	55:45
3	**5b**	Boc	H	A	79	—	28:72
4	**5b**	Boc	H	B	6	54	100:0
5	**5c**	Boc	Me	A	81	—	47:53
6	**5c**	Boc	Me	B	12	65	100:00
7	**5d**	Me	Me	A	56	—	47:53
8	**5d**	Me	Me	B	41	—	63:37[b]
9	**5e**	Piv	H	A	60[c]	—	Trace:100
10	**5f**	Neopentyl	H	A	78	—	24:76

[a] Both *E* and *Z* isomers were obtained as a 1:1 mixture of diastereomers.
[b] The diastereoselectivity of this previously reported reaction proved to be non-reproducible.[8]
[c] Yield based on recovered starting material (30% of starting material was recovered).

Such consecutive acylation/SN2′ transformations allow for the installation of an extra vinyl group in a chemoselective and regioselective manner. This C-5 vinyl group should prove useful in the context of natural products total synthesis.

Subsequently we extended our investigation to study the equilibrium between *E* and *Z* isomers of **2a** in the presence of a base, to try to understand the reactivity of these stereoisomers but mainly to find conditions leading to one major diastereomer. Treatment of **2a** (*E* or *Z*) with one equivalent of methyllithium in dry THF under different conditions followed by quenching with water gave a mixture of *E* and *Z* isomers along with dihydrofuran derivative **7** (Scheme 7 and Table 3).

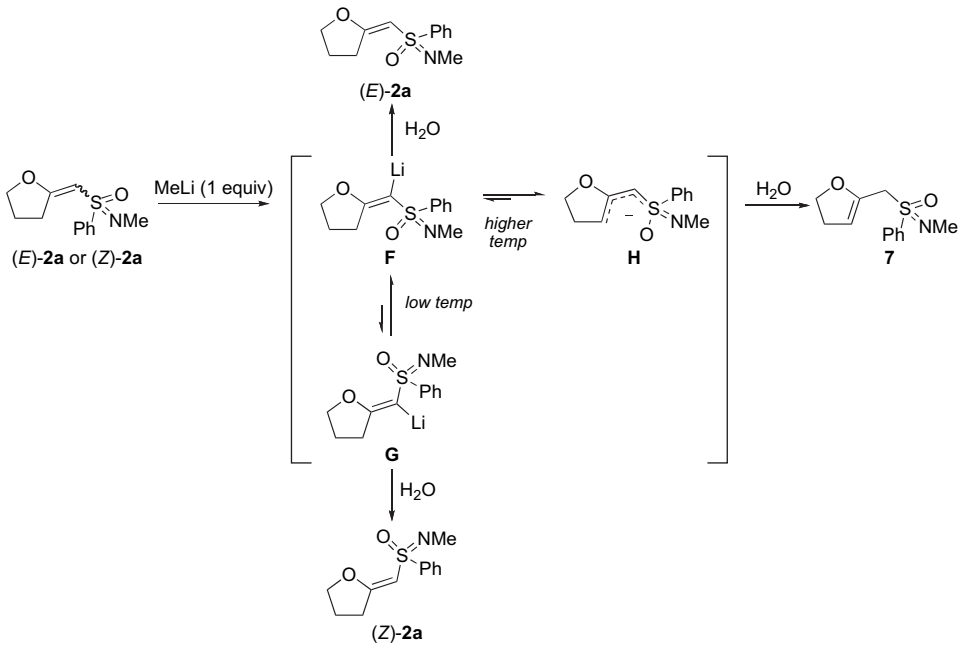


Scheme 7.

Table 3
Equilibrium studies of (*E*)-**2a** and (*Z*)-**2a**

Entry	**2a**	Conditions	(*E*)-**2a** (%)	(*Z*)-**2a** (%)	**7** (%)
1	(*E*)-	−70 °C, 2 h; then H_2O	59	11	30
2	(*Z*)-	−70 °C, 2 h; then H_2O	63	19	18
3	(*E*)-	−70 °C, 2 h, then −30 °C, 2 h; then H_2O	18	3	79
4	(*E*)-	−70 °C, 2 h, then rt, 2 h; then H_2O	18	5	77
5	(*Z*)-	−70 °C, 2 h, then −30 °C, 2 h; then H_2O	20	3	77
6	(*Z*)-	−70 °C, 2 h, then rt, 2 h; then H_2O	11	3	86

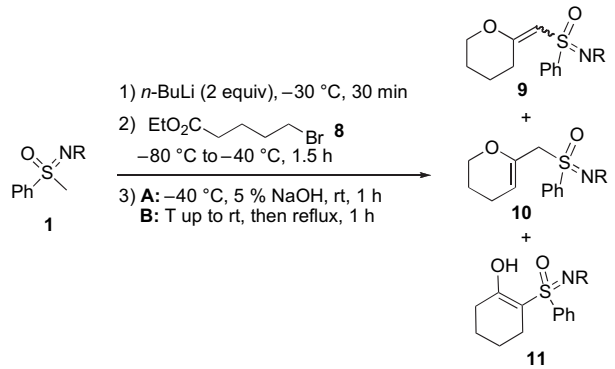
First it should be noted that very comparable product distributions were obtained under similar conditions starting either with (*E*)-**2a** or (*Z*)-**2a**, indicating that in each case the equilibrium is reached. Upon treatment with MeLi at low temperature (−70 °C) for 2 h, the *E* isomer was the major product (ca. 60%) and the remaining 40% was a mixture of *Z* isomer and **7** (entries 1 and 2) irrespective of the configuration of the starting double bond. Increasing the temperature of the reaction mixture to −30 °C or to room temperature (entries 3–6) allowed the formation of



Scheme 8.

compound **7** (in 77–86% yield). Based on these results we came to the conclusion that the anionic species **F**, **G** and **H** are in equilibrium in the presence of methyllithium in THF (Scheme 8). Species **F** and **G** are the direct lithiation products of *E* and *Z* isomers, respectively.[31] At −70 °C, **F** and **G** are in equilibrium and **F** predominates over **G**. These results are supported by Gais et al. observations. Indeed, they reported that treatment of (*Z*)-alkenyl sulfoximines with MeLi at −78 °C gave the (Z)-configured α-lithioalkenyl sulfoximines, which upon warming of the reaction mixture to −30 °C underwent a complete isomerization to the more stable (*E*)-isomers.[25b,32] However in our case the isomerization was not complete and any attempt to improve this ratio in favor of the *E* isomer led to the formation of more of the *endo* olefin **7**. The formation of the latter could be rationalized by the generation of a novel ambident carbanion **H**, which can be regarded as a γ-lithiated α,β-unsaturated sulfoximine. This hypothesis is based on Bellur and Langer's observations, who first revealed the formation of this ambident carbanion in their studies about the lithiation and alkylation of 2-alkylidene tetrahydrofuran in the ester series.[17e]

With in hands a straightforward synthetic access to hydrofuran derivatives exhibiting a chiral sulfur atom, we logically explored the possibilities to extend the reaction to the hydropyran series. Thus, the dianions obtained from the sulfoximines **1** were treated with ethyl 5-bromovalerate (**8**) according to our optimized protocols. The results are summarized on Scheme 9 and in Table 4.



Scheme 9.

Table 4
Consecutive reactions of sulfoximine **1** with **8**

Entry	Sulfoximine	Cond.	Yield of **9** (%)	Yield of **10** (%)	Yield of **11** (%)
1	**1a** (R=Me)	A	—	**10a**:35	**11a**:36
2	**1a** (R=Me)	B	—	**10a**:58	**11a**:42
3	**1m** (R=Mes)	A	(*E*)-**9m**:31 (*Z*)-**9m**: 53	—	**11m**:14
4	**1f** (R=Boc)	A	(*E*)-**9f**: 7	**10f**:72	—
5	**1l** (R=Piv)	A	(*E*)-**9l**:29[a,b] (*Z*)-**9l**: 10[a,b]	**10l**:32[a]	—

[a] Yield based on recovered starting material (23% of starting material was recovered).
[b] The two diastereomers could not be separated by flash chromatography on silica gel.

With in mind the pioneering results of Umani-Ronchi and coworkers in the sulfonyl series, the reactions were expected to yield mixtures of *C*- and *O*-cyclization products.[33] Very interestingly, we showed that the regioselectivity of the reaction was in part controlled by the electronic properties of the substituent at the nitrogen atom: indeed electron-rich substituent yielded a mixture of *C*- and *O*-cyclization products (entries 1–3), while electron-withdrawing substituent afforded only the *O*-cyclization product (entries 4 and 5) in good overall yields in every cases. By contrast to the sulfonyl series,[33] reaction with sulfoximine **1a** (entries 1 and 2), gave only the *endo* isomer **10a**, while sulfoximine **1m** (entry 3) gave only the *exo* isomers **9m**. Sulfoximines **1f** and **1l** (entries 4 and 5, respectively) proved unselective however. The ratio of the two *O*-cyclization regioisomers appears to be highly dependent on the substituent at the nitrogen atom. In this series, the best selectivity (*C*- vs *O*-cyclization, and *exo* vs *endo* product) was obtained with the sulfoximine **1f** exhibiting a *tert*-butyloxycarbonyl (Boc) substituent at the nitrogen atom allowing the preparation of **10f** in 72% yield (entry 4).

3. Conclusion

In conclusion, we have developed an efficient, chemo- and regioselective method for the synthesis of functionalized 2-sulfonimidoylylidene tetrahydrofurans, 2-sulfonimidoylylidene-5-vinyl

tetrahydrofurans and 6-sulfonimidoylmethyl-3,4-dihydro-*2H*-pyrans featuring a consecutive reaction of the chiral dilithiocarbanion of *S*-methyl-*S*-phenyl-sulfoximines with α,ω-halogenoesters. This study demonstrates that subtle variations of the substituent at the nitrogen atom of the sulfonimidoyl group can have a profound impact on both the reactivity and the selectivity in these reactions. The balance between the steric and electronic properties observed with the *N*-pivaloyl sulfoximine **1i** appears the most promising for further development in the hydrofuran series, while the *N*-*tert*-butyloxycarbonyl sulfoximine **1f** appears the most suitable in the hydropyran series.

These five- and six-membered ring heterocycles are synthetically important building blocks and should be amenable for further transformations. For example Michael addition, cross coupling reaction,[23] cycloaddition transformations or subsequent multicomponent/domino processes could be envisioned.[9b–c,22b] Studies directed at the synthesis of naturally occurring products using this methodology are under investigation in our laboratory and will be reported in due course.

4. Experimental

4.1. General

Anhydrous dichloromethane and tetrahydrofuran were obtained from a Solvent Purification System. Anhydrous 1,4-dioxane was obtained by distillation over Na/benzophenone. All experiments were performed under anhydrous conditions and an inert atmosphere of argon and, using oven-dried glassware and employing standard techniques for handling air-sensitive materials. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F254 plates. Visualization of chromatograms was accomplished using ultraviolet light (254 nm) and/or heating the plate after staining with either a solution of potassium permanganate w/v in H_2O, anisaldehyde w/v in EtOH or phosphomolybdic acid w/v in EtOH. Flash column chromatography was carried out on Merck Kieselgel 40–63 μm silica gel under a positive pressure generated by regulated compressed air. NMR data were recorded at 300 MHz in $CDCl_3$ using as internal standards the residual $CHCl_3$ signal for ^1H NMR (δ=7.26) and at 75 MHz using the deuterated solvent signal for ^{13}C NMR (δ=77.0). Chemical shift (δ) are given in ppm and the usual abbreviations are used to describe the signal multiplicity. Low resolution mass spectra (MS) were obtained with an ion trap (ESI source), and high resolution mass spectrometry (HRMS) were recorded at the Spectropole (http://www.spectropole.u-3mrs.fr/).

4.2. Synthesis of sulfoximines 1

*4.2.1. General procedure for **1h** and **1k**.* To a solution of *S*-methyl-*S*-phenylsulfoximine (1 equiv) and pyridine (1.5 equiv) in dry THF (0.5 M) at 0 °C was slowly added the corresponding chloroformate (1.5 equiv). A light pink suspension appeared. The temperature was allowed to rise to room temperature and the solution was then stirred for 15 h. A small portion of chloroformate (0.5 equiv) was added and the mixture stirred for 5 h. The reaction mixture was quenched by addition of water and the product was extracted three times with diethyl ether. The joined ether extracts were washed with HCl 1 N and saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to give the crude product, which was used without further purification.

*4.2.1.1. **1h**.* 6.58 g (85%), white solid. Mp 91–92 °C. IR (neat) ν_{max} 2995, 2903, 1656, 1218, 1118 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.30 (s, 3H), 4.53 (d, *J*=5.7 Hz, 2H), 5.16 (dd, *J*=10.4, 1.5 Hz, 1H), 5.26 (dd, *J*=17.2, 1.6 Hz, 1H), 5.88 (ddd, *J*=17.2, 10.4, 5.7 Hz, 1H), 7.45–7.81 (m, 3H), 7.99 (d, *J*=7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.8, 67.0, 118.2, 127.7, 130.0, 132.7, 134.3, 138.6, 158.8. HRMS (ESI): *m*/*z* calcd for $C_{11}H_{13}NO_3S$ $[M+Na]^+$ 262.0508, found 262.0509.

*4.2.1.2. **1k**.* 23.21 g (78%), white solid. Mp 84–86 °C. IR (neat) ν_{max} 1659, 1245, 1080 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H), 5.01 (d, *J*=12.3 Hz, 1H), 5.01 (d, *J*=12.3 Hz, 1H), 5.08 (d, *J*=12.3 Hz, 1H), 7.15–7.39 (m, 5H), 7.49–7.68 (m, 3H), 7.94 (d, *J*=7.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.7, 67.9, 127.5, 128.1, 128.3, 128.5, 129.8, 134.1, 136.4, 138.4, 158.7. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}NO_3S$ $[M+H]^+$ 290.0845, found 290.0844.

*4.2.1.3. **1m**.* In a round bottom flask equipped with a condenser, a solution of *S*-methyl-*S*-phenylsulfoximine (1.15 g, 7.37 mmol) and bromomesitylene (1.03 mL, 1.34 mmol) in 1,4-dioxane (67 mL) was prepared at room temperature. To this solution was added $Pd_2(dba)_3$ (307 mg, 0.33 mmol), IPr·HCl (145 mg, 0.34 mmol), and *t*BuOK (1.13 g, 10.1 mmol). The resulting dark brown solution was heated at 80 °C for 24 h and concentrated to afford the crude product, which was directly purified by flash chromatography eluted with ethyl acetate/petrol ether to afford 1.76 g of **1m** (96%) as a brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.35 (s, 6H), 3.04 (s, 3H), 6.86 (s, 2H), 7.58 (d, *J*=7.6 Hz, 2H), 7.61 (m, 1H), 8.16 (dd, *J*=7.6, 1.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 20.6, 43.2, 127.9, 129.0, 129.1, 132.3, 132.9, 133.7, 137.9, 141.3. MS (ESI+) *m*/*z* $[M+Na]^+$ 296.

4.3. Synthesis of 2-sulfonimidoylylidene tetrahydrofurans (2) and the endocyclic compound 7

To a stirred cold solution of **1** (10 mmol) in THF (50 mL) at −30 °C was added *n*-BuLi (20 mmol, 2 equiv) and stirring was continued for 30 min. The solution was cooled to −80 °C and methyl 4-chlorobutyrate (20 mmol, 2 equiv) was added. The reaction mixture was warmed to −40 °C during 1.5 h and 5% NaOH solution (25 mL) was added and stirred for 1 h at room temperature, extracted with ether, dried ($MgSO_4$) and concentrated. Pure products of *E* and *Z* isomers were separated by silica column with a gradient of ethyl acetate in petroleum ether. In every case, the *E* isomer was eluted faster than the *Z* isomer.

*4.3.1. (Z)-**2b**.* Solid. Mp 98–99 °C. IR (neat) ν_{max} 3041, 2939, 1610, 1436, 1304, 1143, 1082 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.83–2.20 (m, 2H), 2.32 (s, 3H), 2.60–2.70 (m, 2H), 4.09–4.22 (m, 1H), 4.23–4.39 (m, 1H), 5.73 (s, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.39–7.70 (m, 3H), 7.79 (d, *J*=8.1 Hz, 2H), 7.92 (d, *J*=7.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 23.1, 32.5, 75.9, 96.2, 126.8, 127.6, 128.9, 129.2, 133.2, 141.2, 141.5, 142.4, 172.0. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}NO_4S_2$ $[M+H]^+$ 378.0828, found 378.0825.[34]

*4.3.2. (E)-**2c**.* Viscous liquid. IR (neat) ν_{max} 2875, 2801, 1615, 1435, 1211, 1113 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.90–2.14 (m, 2H), 2.71–2.86 (m, 1H), 3.10–3.25 (m, 1H), 3.51 (ddd, *J*=15.3, 5.5, 1.1 Hz, 1H), 3.64 (2ddd, *J*=15.3, 5.4, 1.3 Hz, 2H), 4.08–4.24 (m, 2H), 5.02 (ddd, *J*=10.2, 1.9, 1.5 Hz, 1H), 5.24 (ddd, *J*=17.0, 3.8, 3.0, 1.9 Hz, 1H), 5.24 (dddd, *J*=17.0, 3.8, 3.0, 1.9 Hz, 1H), 5.80 (d, *J*=1.1 Hz, 1H), 5.95 (dddd, *J*=17.0, 10.2, 5.5, 1.1 Hz, 1H), 7.39–7.65 (m, 3H), 7.89 (d, *J*=8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 29.0, 46.3, 72.2, 99.8, 114.4, 128.1, 129.1, 132.0, 138.5, 142.7, 173.6. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}NO_2S$ $[M+H]^+$ 264.1053, found 264.1057.

*4.3.3. (Z)-**2c**.* Viscous liquid. IR (neat) ν_{max} 3004, 1618, 1435, 1209, 1133, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.86–2.06 (m, 2H), 2.65 (dd, *J*=8.0, 7.3 Hz, 2H), 3.48 (dddd, *J*=15.1, 5.6, 4.1, 1.5 Hz, 1H), 3.64 (dddd, *J*=15.3, 5.3, 1.7, 1.5 Hz, 1H), 4.16–4.26 (m, 1H), 4.30–4.40 (m, 1H), 5.00 (dd, *J*=10.2, 1.3 Hz, 1H), 5.23 (dd, *J*=17.0, 1.9 Hz, 1H),

5.48 (s, 1H), 5.94 (ddd, J=17.0, 10.2, 5.7 Hz, 1H), 7.35–7.55 (m, 3H), 7.96 (d, J=8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 31.6, 45.8, 74.5, 97.3, 113.8, 128.1, 128.3, 131.6, 138.3, 141.8, 168.2. HRMS (ESI): m/z calcd for $C_{14}H_{17}NO_2S$ $[M+H]^+$ 264.1053, found 264.1054.

*4.3.4. (Z)-**2e**.* tlsb .00102Liquid. IR (neat) ν_{max} 3446, 2954, 2927, 2854, 1635, 1295, 1270, 1032, 830, 689 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.93 (s, 9H), 1.91–2.04 (m, 2H), 2.54–2.63 (m, 2H), 4.20–4.38 (m, 2H), 5.46 (dd, J=1.3, 1.3 Hz, 1H), 7.36–7.55 (m, 3H), 7.99 (dd, J=7.8, 1.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.3, −2.2, 18.4, 23.5, 26.4, 31.8, 74.3, 104.7, 127.2, 128.4, 131.3, 147.9, 165.6. HRMS (ESI): m/z calcd for $C_{17}H_{27}NO_2SiS$ $[M+H]^+$ 338.1605, found 338.1600.[34]

*4.3.5. (E)-**2f**.* Solid. Mp 113–114 °C. IR (neat) ν_{max} 3051, 2955, 1659, 1264, 1145 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.88–2.14 (m, 2H), 2.59–2.75 (m, 1H), 3.10–3.25 (m, 1H), 4.05–4.27 (m, 2H), 5.81 (s, 1H), 7.37–7.60 (m, 3H), 7.87 (d, J=7.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 28.2, 29.4, 72.9, 80.0, 98.3, 127.1, 129.2, 132.7, 142.3, 157.8, 175.3. HRMS (ESI): m/z calcd for $C_{16}H_{21}NO_4S$ $[M+H]^+$ 324.1264, found 324.1270.

*4.3.6. (Z)-**2f**.* Solid. Mp 150–151 °C. IR (neat) ν_{max} 3108, 3008, 1651, 1437, 1259, 1147 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.88–2.11 (m, 2H), 2.61–2.76 (m, 2H), 4.14–4.24 (m, 1H), 4.34–4.43 (m, 1H), 5.68 (s, 1H), 7.40–7.57 (m, 3H), 7.99 (d, J=7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 28.0, 32.1, 75.3, 79.5, 96.2, 127.4, 128.6, 132.3, 141.3, 157.9, 170.9. HRMS (ESI): m/z calcd for $C_{16}H_{21}NO_4S$ $[M+H]^+$ 324.1264, found 324.1270.

*4.3.7. (Z)-**2g**.* Viscous liquid. IR (neat) ν_{max} 3041, 2901, 1596, 1438, 1263, 1121 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92–2.11 (m, 2H), 2.65–2.85 (m, 2H), 4.15–4.25 (m, 1H), 4.32–4.44 (m, 1H), 5.85 (s, 1H), 7.30–7.64 (m, 6H), 8.06–8.12 (m, 2H), 8.13–8.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 32.5, 75.6, 96.2, 127.7, 128.2, 129.1, 129.6, 132.0, 132.8, 136.7, 141.6, 171.1, 174.3. HRMS (ESI): m/z calcd for $C_{18}H_{17}NO_3S$ $[M+H]^+$ 328.1002, found 328.0999.[34]

*4.3.8. (Z)-**2h**.* Solid. Mp 97–99 °C. IR (neat) ν_{max} 3070, 2914, 1661, 1614, 1239 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90–2.15 (m, 2H), 2.64–2.81 (m, 2H), 4.18–4.28 (m, 1H), 4.35–4.45 (m, 1H), 4.48–4.55 (m, 2H), 5.13 (ddd, J=10.6, 2.9, 1.4 Hz, 1H), 5.25 (ddd, J=17.3, 3.1, 1.5 Hz, 1H), 5.71 (s, 1H), 5.88 (ddd, J=17.3, 10.6, 5.6 Hz, 1H), 7.45–7.62 (m, 3H), 8.20 (d, J=8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 32.4, 66.4, 75.6, 95.9, 117.5, 127.6, 128.9, 132.8, 133.0, 140.9, 158.9, 171.6. HRMS (ESI): m/z calcd for $C_{15}H_{17}NO_4S$ $[M+H]^+$ 308.0951, found 308.0951.[34]

*4.3.9. (Z)-**2i**.* Solid. Mp. 113–114 °C. IR (neat) ν_{max} 2928.1, 2846.7, 1615.4, 1283.3, 1163.6 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 9H), 1.99–2.06 (m, 2H), 2.71–2.76 (m, 2H), 4.15–4.24 (m, 1H), 4.34–4.41 (m, 1H), 5.70 (s, 1H), 7.47–7.54 (m, 3H), 8.01–8.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 28.2, 32.4, 41.7, 75.5, 96.6, 127.7, 129.0, 132.7, 141.9. HRMS (ESI): m/z calcd for $C_{16}H_{21}NO_3S$ $[M+H]^+$ 308.1315, found: 308.1312.[34]

*4.3.10. (E)-**2j**.* Solid. Mp. 76–77 °C. IR (neat) ν_{max} 2928.4, 1617.5, 1232.9, 1115.5 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.96–2.11 (m, 2H), 2.59 (d, J=12.0 Hz, 1H), 2.74 (d, J=12.0 Hz, 1H), 2.82–2.96 (m, 1H), 3.14–3.26 (m, 1H), 4.11–4.23 (m, 2H), 5.74 (s, 1H), 7.47–7.60 (m, 3H), 7.88–7.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 28.1, 29.2, 32.7, 55.8, 72.2, 100.4, 128.3, 129.1, 131.9, 143.5, 173.2. HRMS (ESI): m/z calcd for $C_{16}H_{23}NO_2S$ $[M+H]^+$ 294.1522, found: 294.1521.

*4.3.11. (Z)-**2j**.* Solid. Mp. 59–60 °C. IR (neat) ν_{max} 2928.1, 1620.2, 1230.4, 1118.9 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.91–2.03 (m, 2H), 2.55–2.74 (m, 4H), 4.10–4.23 (m, 1H), 4.30–4.41 (m, 1H), 5.46 (s, 1H), 7.44–7.46 (m, 3H), 7.94–7.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 28.0, 31.9, 32.6, 55.5, 74.7, 98.3, 128.7, 131.8, 143.0, 168.1. HRMS (ESI): m/z calcd for $C_{16}H_{23}NO_2S$ $[M+H]^+$ 294.1522, found: 294.1524.

*4.3.12. (Z)-**2k**.* Solid. Mp 52–53 °C. IR (neat) ν_{max} 3055, 2987, 1673, 1628, 1265, 739, 705 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90–2.10 (m, 2H), 2.65–2.75 (m, 2H), 4.14–4.21 (m, 1H), 4.32–4.41 (m, 1H), 5.02 (d, J=12.4 Hz, 1H), 5.09 (d, J=12.4 Hz, 1H), 5.69 (s, 1H), 7.18–7.35 (m, 5H), 7.43–7.60 (m, 3H), 8.01 (d, J=8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 31.6, 66.5, 75.1, 94.7, 126.8, 127.2, 127.4, 127.7, 128.3, 132.2, 136.2, 140.4, 158.2, 171.6. HRMS (ESI): m/z calcd for $C_{19}H_{19}NO_4S$ $[M+H]^+$ 358.1108, found 358.1104.[34]

*4.3.13. (Z)-**2l**.* Solid. Mp 92–93 °C. IR (neat) ν_{max} 3060, 2983, 2907, 1669, 1627, 1249, 1019, 875, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J=7.2 Hz, 3H), 1.86–2.09 (m, 2H), 2.57–2.80 (m, 2H), 3.91–4.06 (m, 2H), 4.12–4.21 (m, 1H), 4.30–4.40 (m, 1H), 5.65 (s, 1H), 7.40–7.56 (m, 3H), 7.96 (dd, J=8.2, 1.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 23.2, 32.4, 61.7, 75.6, 96.2, 127.7, 128.9, 132.8, 141.1, 159.3, 171.4. HRMS (ESI): m/z calcd for $C_{14}H_{17}NO_4S$ $[M+H]^+$ 296.0951, found 296.0950.[34]

*4.3.14. (E)-**2n**.* Solid. Mp. 96–97 °C. IR (neat) ν_{max} 3224, 3043, 2883, 1622, 1435, 1212, 1156 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90–2.15 (m, 2H), 2.77–2.94 (m, 1H), 3.11–3.26 (m, 1H), 4.06–4.26 (m, 2H), 5.82 (s, 1H), 7.35–7.60 (m, 3H), 7.93 (dd, J=8.4–1.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 29.1, 72.3, 101.9, 127.2, 129.2, 132.2, 146.2, 173.4. HRMS (ESI): m/z calcd for $C_{11}H_{13}NO_2S$ $[M+H]^+$ 224.0740, found 224.0744.

*4.3.15. (Z)-**2n**.* Solid. Mp. 100–102 °C. IR (neat) ν_{max} 3043, 2913, 1660, 1604, 1240, 1079 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93–2.05 (m, 2H), 2.56–2.75 (m, 2H), 4.22–4.42 (m, 2H), 5.50 (s, 1H), 7.37–7.58 (m, 3H), 8.03 (dd, J=7.9–1.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 32.2, 75.1, 100.2, 127.9, 128.8, 132.3, 145.7, 168.4. HRMS (ESI): m/z calcd for $C_{11}H_{13}NO_2S$ $[M+H]^+$ 224.0740, found 224.0742.

4.3.16. 7. Viscous liquid. IR (neat) ν_{max} 2882.5, 1618.5, 1230.3, 1136.6 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55–2.61 (m, 2H), 2.76 (s, 3H), 3.99 (s, 2H), 4.13–4.25 (m, 2H), 4.87 (t, J=3.0 Hz, 1H), 7.52–7.61 (m, 3H), 7.87–7.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 30.6, 56.2, 70.7, 103.6, 129.3, 130.0, 133.3, 137.7, 147.4. HRMS Calcd for $C_{12}H_{15}NO_2S$: 238.0896, found: 238.0894.

4.4. Synthesis of 5-vinyl-sulfonimidoylylidene tetrahydrofurans (5)

To a stirred cold solution of **1** (10 mmol) in THF (50 mL) at −30 °C was added *n*-BuLi (20 mmol, 2 equiv) and stirring was continued for 30 min. The solution was cooled to −80 °C and methyl 6-bromo-hex-4-enoate (**4a**) or methyl 5-methyl-6-bromo-hex-4-enoate (**4b**) (12–15 mmol) was added. The reaction mixture was warmed to −40 °C during 1.5 h and 5% NaOH solution (25 mL) was added and stirred for 1 h at room temperature, extracted with ether, dried ($MgSO_4$) and concentrated. Products **5** were separated by silica column with a gradient of ethyl acetate in petroleum ether. In every case, the *E* isomer was eluted faster than the *Z* isomer.

*4.4.1. (E)-**5a**.* First eluted diastereomer, viscous liquid. IR (neat) ν_{max} 2894.7, 1618.9, 1230.1, 1138.8 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79–1.92 (m, 1H), 2.13–2.24 (m, 1H), 2.69 (s, 3H), 2.71–2.77 (m, 1H), 3.31–3.41 (m, 1H), 4.70–4.81 (m, 1H), 5.22–5.34 (m, 2H), 5.76–5.88 (m, 2H), 7.50–7.54 (m, 3H), 7.86–7.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 29.8, 30.1, 84.6, 100.0, 118.3, 128.3, 129.4,

132.2, 135.8, 142.2, 173.1. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}NO_2S$ $[M+H]^+$ 264.1053, found: 264.1052.

*4.4.2. (E)-**5a**.* Second eluted diastereomer, viscous liquid. IR (neat) ν_{max} 2890.2, 2852.1, 1620.2, 1225.0, 1140.6 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.69–1.81 (m, 1H), 2.20–2.30 (m, 1H), 2.52–2.62 (m, 1H), 2.69 (s, 3H), 3.00–3.08 (m, 1H), 4.74–4.83 (m, 1H), 5.19–5.32 (m, 2H), 5.73–5.83 (m, 2H), 7.50–7.54 (m, 3H), 7.87–7.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3, 29.7, 30.1, 84.8, 99.8, 118.5, 128.2, 129.4, 132.2, 135.7, 142.2, 173.1. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}NO_2S$ $[M+H]^+$ 264.1053, found: 264.1052.

*4.4.3. (Z)-**5a**.* Mixture of two diastereomers, viscous liquid. IR (neat) ν_{max} 2895.2, 2852.4, 1621.5, 1228.1, 1138.8 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.61–1.80 (m, 1H), 2.08–2.20 (m, 1H), 2.63–2.69 (m, 2H), 2.66 (s, 1.5H), 2.71 (s, 1.5H), 4.73–5.00 (m, 2H), 5.15–5.27 (m, 1H), 5.40–5.56 (m, 1.5H), 5.70–5.88 (m, 0.5H), 7.44–5.51 (m, 3H), 7.93–7.99 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3, 29.4, 29.6, 29.7, 31.4, 31.6, 86.6, 86.8, 97.9, 98.7, 116.8, 117.6, 128.8, 128.9, 129.0, 129.2, 132.1, 135.3, 135.5, 141.4, 141.8, 167.7. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}NO_2S$ $[M+H]^+$ 264.1053, found: 264.1053.

*4.4.4. (E)-**5b**.* Mixture of two diastereomers, viscous liquid. IR (neat) ν_{max} 2906.6, 1655.7, 1436.9, 1266.2, 1146.7 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.74–1.96 (m, 1H), 2.18–2.36 (m, 1.5H), 2.60–2.71 (m, 0.5H), 2.92–3.02 (m, 0.5H), 3.12–3.26 (m, 0.5H), 3.36–3.47 (m, 0.5H), 3.60–3.67 (m, 0.5H), 4.78–4.87 (m, 0.5H), 5.22–5.35 (m, 1.5H), 5.72–5.91 (m, 2H), 7.53–7.59 (m, 3H), 7.94–7.97 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 29.5, 29.9, 80.3, 85.4, 98.5, 98.8, 118.7, 118.8, 127.3, 129.5, 132.9, 135.4, 142.5, 158.0, 174.8. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{23}NO_4S$ $[M+H]^+$ 350.1421, found: 350.1423.

*4.4.5. (Z)-**5b**.* Mixture of two diastereomers, solid. Mp. 74–75 °C. IR (neat) ν_{max} 2957.0, 1655.2, 1437.0, 1264.3, 1150.9 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.63–1.85 (m, 1H), 2.10–2.25 (m, 1H), 2.68–2.75 (m, 2H), 4.65–5.03 (m, 2H), 5.19–5.50 (m, 1.5H), 5.68–5.85 (m, 1.5H), 7.46–7.58 (m, 3H), 8.01–8.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 29.3, 31.9, 80.0, 80.1, 87.5, 97.2, 97.6, 117.1, 117.9, 128.1, 128.3, 128.9, 132.7, 135.0, 141.6, 141.7, 158.4, 170.0, 170.5. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{23}NO_4S$ $[M+H]^+$ 350.1421, found: 350.1420.

*4.4.6. (E)-**5c**.* Mixture of two diastereomers, viscous liquid. IR (neat) ν_{max} 2957, 2906, 1656, 1437, 1267, 1147 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14–1.41 (m, 9H), 1.46–1.75 (m, 3H), 2.01–2.50 (m, 0.5H), 2.52–2.80 (m, 1H), 2.84–3.01 (m, 0.5H), 3.05–3.20 (m, 0.5H), 3.25–3.47 (m, 0.5H), 3.51–3.71 (m, 1H), 4.34–4.44 (m, 0.5H), 4.54–4.66 (m, 0.5H), 4.70–4.85 (m, 0.5H), 4.81–4.97 (m, 1H), 5.05–5.15 (m, 0.5H), 5.43 (bs, 0.5H), 5.83–5.88 (m, 0.5H), 7.39–7.73 (m, 3H), 7.80–8.01 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 17.9, 27.9, 28.0, 28.1, 28.2, 29.4, 29.7, 80.1, 80.9, 87.2, 87.3, 98.1, 98.3, 112.9, 113.2, 127.1, 128.2, 129.3, 129.7, 132.7, 141.9, 142.2, 157.8, 174.8. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{25}NO_4S$ $[M+H]^+$ 364.1577, found 364.1577.

*4.4.7. (Z)-**5c**.* Mixture of two diastereomers, viscous liquid. IR (neat) ν_{max} 3044, 2956, 1656, 1616, 1437, 1267, 1148 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 4.5H), 1.36 (s, 4.5H), 1.61 (s, 1.5H), 1.66 (s, 1.5H), 2.05–2.21 (m, 2H), 2.65–2.79 (m, 2H), 4.39 (d, *J*=1.0 Hz, 0.5H), 4.65 (s, 0.5H), 4.76 (dd, *J*=7.2, 7.1 Hz, 0.5H), 4.89 (d, *J*=1.0 Hz, 0.5H), 4.93 (dd, *J*=7.2, 7.1 Hz, 0.5H), 4.98 (d, *J*=1.0 Hz, 0.5H), 5.68 (s, 0.5H), 5.79 (s, 0.5H), 7.40–7.69 (m, 3H), 8.01 (d, *J*=7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 18.0, 27.7, 27.8, 28.1, 28.2, 32.0, 79.9, 80.0, 89.5, 90.0, 96.9, 97.2, 112.6, 112.7, 127.9, 128.2, 128.7, 128.8, 132.5, 141.3, 141.4, 141.6, 158.1, 158.2, 169.8, 170.4. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{25}NO_4S$ $[M+H]^+$ 364.1577, found 364.1571.

*4.4.8. (E)-**5d**.* Mixture of two diastereomers, viscous liquid. IR (neat) ν_{max} 3394, 3062, 2916, 2801, 629, 1445, 1244, 832, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.35–1.43 (m, 0.5H), 1.66 (s, 1.5H), 1.70 (s, 1.5H), 1.72–1.94 (m, 1H), 2.08–2.28 (m, 1H), 2.68 (s, 1.5H), 2.69 (s, 1.5H), 2.98–3.13 (m, 1H), 3.37 (dddd, *J*=17.9, 8.9, 4.7, 1.3 Hz, 0.5H), 4.65–4.78 (m, 1H), 4.86 (s, 0.5H), 4.90 (s, 0.5H), 4.93 (s, 0.5H), 4.97 (s, 0.5H), 5.80 (d, *J*=1.6 Hz, 0.5H), 5.83 (d, *J*=1.6 Hz, 0.5H), 7.41–7.60 (m, 3H), 7.79–7.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 17.9, 28.3, 28.4, 28.8, 29.1, 29.5, 86.4, 86.5, 99.3, 99.5, 112.6, 113.8, 128.0, 128.1, 129.1, 129.2, 132.0, 142.0, 141.9, 142.1, 142.2, 173.1. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{19}NO_2S$ $[M+H]^+$ 278.1209, found 278.1203.

*4.4.9. (Z)-**5d**.* Mixture of two diastereomers, viscous liquid. IR (neat) ν_{max} 3388, 3064, 2917, 1633, 1239, 1147, 862, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 1.5H), 1.35 (s, 1.5H), 1.63–1.84 (m, 2H), 2.02–2.15 (m, 2H), 2.64 (s, 1.5H), 2.71 (s, 1.5H), 4.46 (s, 0.5H), 4.65 (s, 0.5H), 4.76–4.94 (m, 2H), 5.41 (s, 0.5H), 5.53 (s, 0.5H), 7.38–7.63 (m, 3H), 7.85–8.04 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 17.7, 27.5, 27.6, 29.1, 29.3, 31.4, 88.7, 88.9, 97.3, 98.1, 112.0, 112.2, 128.4, 128.5, 128.6, 128.9, 131.7, 132.9, 141.0, 141.4, 141.6, 141.7, 167.4, 167.5. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{19}NO_2S$ $[M+H]^+$ 278.1209, found 278.1206.

*4.4.10. (E)-**5e**.* Mixture of two diastereomers, viscous liquid. IR (neat) ν_{max} 2930.0, 1618.4, 1233.4, 1115.1 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.73–1.91 (m, 1H), 2.18–2.28 (m, 1H), 2.56–2.80 (m, 3H), 3.06–3.13 (m, 0.5H), 3.32–3.45 (m, 0.5H), 3.59–3.69 (m, 0.5H), 4.10–4.20 (m, 0.5H), 4.71–4.81 (m, 0.5H), 5.19–5.34 (m, 2H), 5.74–5.89 (m, 1.5H), 7.50–7.62 (m, 3H), 7.86–7.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5, 30.5, 30.8, 31.6, 34.2, 57.2, 85.8, 85.9, 101.9, 102.1, 119.6, 119.7, 129.6, 129.7, 130.6, 133.4, 137.3, 137.4, 144.9, 173.9. HRMS Calcd for $C_{18}H_{25}NO_2S$: 334.1471, found: 334.1473.

*4.4.11. (Z)-**5e**.* Mixture of two diastereomers, solid. Mp. 72–73 °C. IR (neat) ν_{max} 2943.4, 1618.1, 1277.5, 1175.5 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 9H), 1.68–1.79 (m, 1H), 2.12–2.21 (m, 1H), 2.69–2.74 (m, 2H), 4.09–4.16 (m, 0.5H), 4.75–5.02 (m, 1.5H), 5.15–5.22 (m, 1H), 5.45–5.56 (m, 0.5H), 5.66–5.77 (m, 1.5H), 7.49–7.61 (m, 3H), 8.00–8.06 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 28.2, 29.3, 31.8, 41.7, 87.3, 96.8, 97.2, 117.3, 117.8, 127.8, 128.9, 132.8, 135.0, 135.2, 141.6, 141.8, 169.2, 170.1, 188.2. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{23}NO_3S$ $[M+H]^+$ 334.1471, found: 334.1468.

*4.4.12. (E)-**5f**.* Mixture of two diastereomers, viscous liquid. IR (neat) ν_{max} 2930.0, 1618.4, 1233.4, 1115.1 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.73–1.91 (m, 1H), 2.18–2.28 (m, 1H), 2.56–2.80 (m, 3H), 3.06–3.13 (m, 0.5H), 3.32–3.45 (m, 0.5H), 3.59–3.69 (m, 0.5H), 4.10–4.20 (m, 0.5H), 4.71–4.81 (m, 0.5H), 5.19–5.34 (m, 2H), 5.74–5.89 (m, 1.5H), 7.50–7.62 (m, 3H), 7.86–7.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5, 30.5, 30.8, 31.6, 34.2, 57.2, 85.8, 85.9, 101.9, 102.1, 119.6, 119.7, 129.6, 129.7, 130.6, 133.4, 137.3, 137.4, 144.9, 173.9. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{25}NO_2S$ $[M+H]^+$ 320.1679, found: 320.1678.

*4.4.13. (Z)-**5f**.* First eluted diastereomer, viscous liquid. IR (neat) ν_{max} 2929.2, 1622.4, 1231.9, 1122.0 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.69–1.84 (m, 1H), 2.05–2.18 (m, 1H), 2.64–2.77 (m, 4H), 4.81–4.87 (m, 1H), 5.15–5.28 (m, 2H), 5.45 (s, 1H), 5.71–5.82 (m, 1H), 7.43–7.50 (m, 3H), 8.00–8.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 29.4, 31.4, 32.7, 55.8, 86.4, 98.6, 117.4, 128.7, 129.1, 131.9, 135.6, 143.1, 167.0. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{25}NO_2S$ $[M+H]^+$ 319.1606, found: 319.1673.

*4.4.14. (Z)-**5f**.* Second eluted diastereomer, Mp. 90–91 °C. IR (neat) ν_{max} 2929.5, 1626.0, 1231.6, 1120.7 cm^{-1}. ^1H NMR (300 MHz,

$CDCl_3$) δ 0.92 (s, 9H), 1.63–1.74 (m, 1H), 2.10–2.21 (m, 1H), 2.51–2.76 (m, 4H), 4.75–4.99 (m, 3H), 5.48–5.59 (m, 2H), 7.43–7.50 (m, 3H), 7.95–7.99 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 29.3, 31.4, 32.7, 55.5, 86.4, 99.7, 116.8, 128.7, 129.4, 131.8, 135.5, 142.8, 167.0. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{25}NO_2S$ $[M+H]^+$ 319.1606, found: 319.1671.

4.5. Synthesis of 9–11

The protocol for the preparation of compounds **9**–**11** is identical to the protocol for the preparation of **5** except that ethyl 5-bromovalerate (**8**) was used instead of **4a**,**b**.

*4.5.1. (E)-**9m**.* Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.86 (m, 4H), 2.22 (s, 3H), 2.32 (s, 6H), 2.39–2.57 (m, 1H), 2.71–2.84 (m, 1H), 3.88–4.17 (m, 2H), 5.74 (s, 1H), 6.81 (s, 2H), 7.44–7.59 (m, 3H), 8.06 (dd, *J*=8.1, 1.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 19.9, 20.6, 23.0, 24.0, 68.1, 106.6, 127.3, 128.7, 128.8, 131.8, 131.9, 133.9, 138.5, 143.9, 169.7. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{26}NO_2S$ $[M+H]^+$ 356.1684, found: 356.1678.

*4.5.2. (Z)-**9m**.* Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.71 (m, 4H), 2.12–2.28 (m, 2H), 2.22 (s, 3H), 2.33 (s, 6H), 3.55–3.73 (m, 2H), 5.56 (s, 1H), 6.81 (s, 2H), 7.39–7.58 (m, 3H), 8.13 (dd, *J*=8.4, 1.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.1, 20.6, 22.8, 28.1, 68.1, 105.3, 128.0, 128.3, 128.7, 131.6, 131.7, 134.0, 139.0, 143.7, 164.6. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{26}NO_2S$ $[M+H]^+$ 356.1684, found: 356.1676.

*4.5.3. (E)-**9f**.* Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.49–1.88 (m, 4H), 2.17–2.36 (m, 2H), 3.49–3.60 (m, 1H), 3.92–4.03 (m, 1H), 5.81 (s, 1H), 7.43–7.58 (m, 3H), 7.98 (d, *J*=6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 22.6, 27.9, 28.0, 68.5, 79.7, 105.1, 127.8, 128.4, 132.2, 141.4, 158.0, 167.9. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{24}NO_4S$ $[M+H]^+$ 338.1426, found: 338.1431.

*4.5.4. (E)-**9l**.* Viscous oil. Isolated as the major component of a mixture with (***Z***)-**9l** after flash chromatography on silica gel. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.51–1.79 (m, 4H), 2.24–2.32 (m, 2H), 3.52–3.62 (m, 1H), 3.83–3.92 (m, 1H), 5.78 (s, 1H), 7.41–7.58 (m, 3H), 7.97 (d, *J*=7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 22.6, 27.7, 27.9, 41.1, 68.3, 104.9, 127.5, 128.3, 132.1, 141.5, 167.2, 188.0. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{24}NO_3S$ $[M+H]^+$ 322.1477, found: 322.1471.

*4.5.5. (Z)-**9l**.* Viscous oil. Isolated as the minor component of a mixture with (***E***)-**9l** after flash chromatography on silica gel. Selected data: ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 24.4, 28.1, 30.1, 41.7, 68.6, 105.2, 127.2, 129.4, 132.8, 142.6, 172.5, 188.2. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{24}NO_3S$ $[M+H]^+$ 322.1477, found: 322.1471.

*4.5.6. **10a**.* Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47–1.69 (m, 2H), 1.75–1.99 (m, 2H), 2.64 (s, 3H), 3.54–3.72 (m, 2H), 3.71 (d, *J*=14.3 Hz, 1H), 3.79 (d, *J*=14.3 Hz, 1H), 4.56–4.62 (m, 1H), 7.39–7.59 (m, 3H), 7.77 (d, *J*=7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 21.3, 29.6, 61.9, 66.0, 104.8, 128.6, 129.5, 132.5, 137.1, 143.6. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}NO_2S$ $[M+H]^+$ 252.1058, found: 252.1067.

*4.5.7. **10f**.* Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.44–1.57 (m, 2H), 1.73–87 (m, 2H), 3.41–3.59 (m, 2H), 3.95 (d, *J*=13.8 Hz, 1H), 4.15 (d, *J*=13.8 Hz, 1H), 4.55–66 (m, 1H), 7.37–7.58 (m, 3H), 7.82 (d, *J*=8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 20.9, 27.6, 60.9, 65.8, 79.8, 105.8, 128.2, 128.4, 133.2, 136.2, 142.3, 157.5. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{24}NO_4S$ $[M+H]^+$ 338.1426, found: 338.1433.

*4.5.8. **10l**.* Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.54–1.68 (m, 2H), 1.87–1.98 (m, 2H), 3.56–3.65 (m, 2H), 4.05 (d, *J*=13.8 Hz, 1H), 4.47 (d, *J*=13.8 Hz, 1H), 4.70 (dd, *J*=3.9, 3.6 Hz, 1H), 7.48–7.65 (m, 3H), 7.92 (d, *J*=7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 21.3, 27.7, 41.5, 60.4, 66.1, 105.7, 128.4, 128.6, 133.4, 137.1, 143.1, 188.5. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{24}NO_3S$ $[M+H]^+$ 322.1477, found: 322.1470.

*4.5.9. **11a** (known compound[35]).* Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42–1.92 (m, 5H), 2.15–2.51 (m, 3H), 2.61 (s, 3H), 7.42–7.64 (m, 3H), 7.79 (d, *J*=6.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 21.9, 22.6, 27.9, 30.3, 97.3, 128.7, 129.1, 132.5, 138.0, 166.2. MS (ESI+): *m*/*z* 274 $[M+Na]^+$.

*4.5.10. **11m**.* Viscous oil. Isolated as a mixture with (***E***)-**9m** after flash chromatography on silica gel. Selected data: ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.6, 22.0, 22.0, 22.7, 30.3, 97.1, 126.8, 128.8, 128.8, 132.0, 133.4, 135.0, 135.3, 141.2, 167.4. MS (ESI+): *m*/*z* 378 $[M+Na]^+$.

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