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Organolithium-Mediated Conversion of β-Alkoxy Aziridines into Allylic Sulfonamides: Effect of the *N*-Sulfonyl Group and a Formal Synthesis of (±)-Perhydrohistrionicotoxin†

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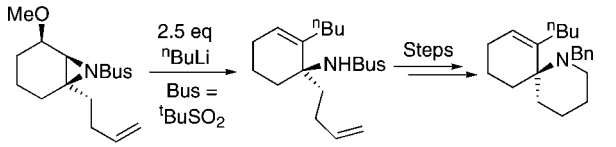
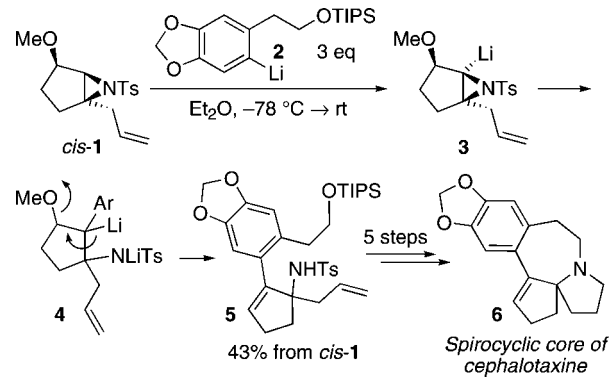


In 18 out of 20 examples of the organolithium-mediated conversion of β-alkoxy aziridines into substituted allylic sulfonamides, use of a Bus (Bus = *t*-$BuSO_2$) substituent on the nitrogen gave higher yields compared to the analogous *N*-Ts compounds. The success with the *N*-Bus aziridines facilitated the development of a new route to the spirocyclic core of the histrionicotoxins and completion of a formal synthesis of (±)-perhydrohistrionicotoxin.

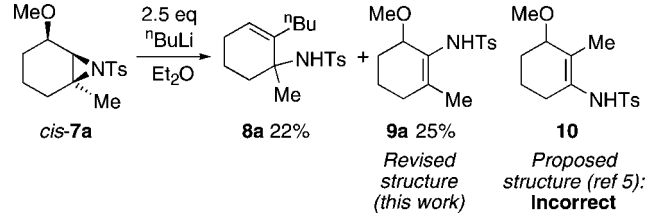
As part of our ongoing studies into the synthetic opportunities offered by lithiated aziridine intermediates,[1,2] we recently reported a new route to azaspirocycles such as the core of cephalotaxine (Scheme 1).[3] Thus, treatment of β-methoxy aziridine *cis*-**1** with 3 equiv of functionalized aryllithium **2** (prepared by bromine−lithium exchange) gave, after aqueous workup, allylic sulfonamide **5** in 43% yield. It is likely that this transformation proceeds via lithiated aziridine **3** from which carbenoid insertion into the aryllithium **2** to give **4** is followed by elimination of lithium methoxide. A five-step sequence was then used to convert **5** into the azaspirocycle **6**.

Since there are a number of biologically interesting azaspirocycles equipped with an azaspiro[5.5]undecane motif such as

SCHEME 1. Lithiated Aziridines in Action: Synthesis of the Spirocyclic Core of Cephalotaxine



SCHEME 2. Low-Yielding Reaction of a Cyclohexene-Derived β-Methoxy Aziridine with *n*-BuLi



members of the histrionicotoxin family,[4] we were especially keen to extend our methodology to reactions of 3-substituted cyclohexene-derived β-methoxy aziridines. Unfortunately, in our earlier work[5] we had found that reactions of such aziridines with organolithium reagents gave low yields of cyclohexenyl sulfonamides due, in part, to the competing formation of an enesulfonamide. An example is shown in Scheme 2. Reaction of aziridine *cis*-**7a** with 2.5 equiv of *n*-BuLi gave allylic sulfonamide **8a** in 22% yield and enesulfonamide **9a** in 25% yield. Note that we had originally proposed[5] the regioisomeric structure **10** (in which a 1,2-alkyl shift had occurred) as the enesulfonamide generated from this process. However, in light of the results presented in this paper (vide infra), we are confident that enesulfonamide **9a** is the correct structure, and we now wish to correct our previous erroneous report.

Our planned synthetic efforts toward the histrionicotoxins required the preparation of azaspiro[5.5]undecanes, and this necessitated higher yielding transformation of β-methoxy aziridines such as *cis*-**7a** into substituted allylic sulfonamides such as **8a**. We elected to evaluate the use of *N*-Bus-substituted aziridines (Bus = *t*-$BuSO_2$) in place of the *N*-Ts aziridines used in our previous studies[2,3,5] for two reasons: (i) we were concerned that *ortho*-lithiation[6] of the *N*-Ts group might be a deleterious competing process and (ii) we wondered whether the different electronic properties of the *N*-sulfonyl substituent might affect the efficiency of the carbenoid insertion into the organolithium reagent. With this in mind, we directly compared

† This paper is dedicated to the memory of Professor C. Mioskowski for his numerous pioneering contributions to organic chemistry and lithiated epoxide methodology in particular.

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(3) Moore, S. P.; Coote, S. C.; O'Brien, P.; Gilday, J. *Org. Lett.* **2006**, *8*, 5145.

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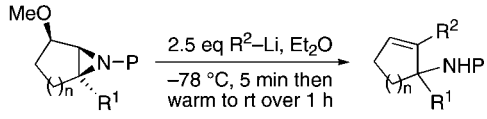
TABLE 1. Comparison of *N*-Bus and *N*-Ts for the Organolithium-Mediated Reactions of *β*-Methoxy Aziridines



cis-**11**, n = 1, R^1 = H
cis-**12**, n= 1, R^1 = Me
cis-**13**, n = 1, R^1 = $(CH_2)_2CH{=}CH_2$
cis-**14**, n = 2, R^1 = H

a: P = Ts
b: P = Bus

15-28

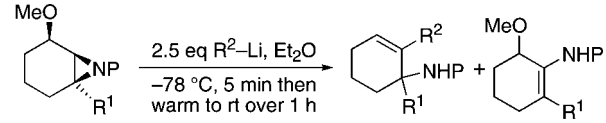
entry	SM	*n*	R^1	R^2	prod	**a**: P = Ts yield (%)	**b**: P = Bus yield (%)
1	**11**	1	H	*n*-Bu	**15**	53	67
2	**11**	1	H	Me_3SiCH_2	**16**	67	71
3	**11**	1	H	Ph	**17**	58	75
4	**12**	1	Me	*n*-Bu	**18**	76	87
5	**12**	1	Me	Me_3SiCH_2	**19**	67	75
6	**12**	1	Me	Ph	**20**	66	76
7	**13**	1	homoallyl	*n*-Bu	**21**	80	82
8	**13**	1	homoallyl	*s*-Bu	**22**	84	84
9	**13**	1	homoallyl	*t*-Bu	**23**	76	80
10	**13**	1	homoallyl	Me_3SiCH_2	**24**	82	84
11	**13**	1	homoallyl	Ph	**25**	63	75
12	**14**	2	H	*n*-Bu	**26**	34	81
13	**14**	2	H	Me_3SiCH_2	**27**	67	76
14	**14**	2	H	Ph	**28**	47	81

20 examples of organolithium-mediated reactions of *N*-Bus and *N*-Ts cyclopentene- and cyclohexene-derived *β*-methoxy aziridines. As part of this study, two X-ray structures of enesulfonamides like **9a** were obtained, establishing the structures of the enesulfonamide byproduct. Ultimately, the results enabled us to carry out a formal synthesis of (±)-perhydrohistrionicotoxin.

Twelve different *β*-methoxy aziridines (*cis*-**7a/b**,**11**−**14a/b**, and **29a/b**, Tables 1 and 2) were prepared by standard methylation (KHMDS, THF, MeI or Ag_2O, MeCN, MeI; see Supporting Information) of the corresponding hydroxy aziridines. The hydroxy aziridines were in turn prepared by *cis*-stereoselective Sharpless aziridination of the allylic alcohols using Chloramine-T (TsNClNa)[7] or BusNClNa,[8] the details of which are described elsewhere.[9] The following standard procedure was adopted for the *β*-methoxy aziridine → allylic sulfonamide reactions: 2.5 equiv of the organolithium reagent was reacted with the aziridine in Et_2O at −78 °C for 5 min, and then the reaction was allowed to warm to room temperature over 1 h before quenching. The reactions of *β*-methoxy aziridines *cis*-**11**−**14a/b** yielded allylic sulfonamides (**15a/b**−**28a/b**) as the only isolable products after chromatography; the results are shown in Table 1.

In all but one (entry 8) of the examples in Table 1, the *N*-Bus-substituted aziridines gave higher yields of the allylic sulfonamides than the corresponding *N*-Ts aziridine. In one case, the yield improvement was dramatic: *N*-Bus **26b** was formed in 81% yield, whereas *N*-Ts **26a** was obtained in only 34% yield (entry 12). Thus, there is a significant improvement on using the *N*-Bus aziridines in these reactions. Hodgson and co-workers have noted a similar positive effect in a number of reactions of aziridines.[10]

TABLE 2. Comparison of *N*-Bus and *N*-Ts for the Organolithium-Mediated Reactions of 3-Substituted Cyclohexene-Derived *β*-Methoxy Aziridines



cis-**7**, R^1 = Me
cis-**29**, R^1 = $(CH_2)_2CH{=}CH_2$

a: P = Ts
b: P = Bus

8, 30-34 **9, 35**

entry	SM	R^1	R^2	**a**: P = Ts prod, yield (%)		**b**: P = Bus prod, yield (%)	
1	**7**	Me	*n*-Bu	**8a**, 22	**9a**, 25	**8b**, 69	**9b**, 19
2	**7**	Me	*s*-Bu	**30a**, 32	**9a**, 27	**30b**, 86	**9b**, 0
3	**7**	Me	*t*-Bu	**31a**, 72	**9a**, 0	**31b**, 65	**9b**, 0
4	**7**	Me	Me_3SiCH_2	**32a**, 47	**9a**, 19	**32b**, 53	**9b**, 30
5	**7**	Me	Ph	**33a**, 12	**9a**, 34	**33b**, 23	**9b**, 49
6	**29**	homoallyl	*n*-Bu	**34a**, 18	**35a**, 42	**34b**, 44	**35b**, 35
7[a]	**29**	homoallyl	*n*-Bu	-	-	**34b**, 73	**35b**, 24

[a] Reaction carried out in THF on 3.0 mmol scale.

Next, we determined whether a similar yield improvement would be found with the more troublesome 3-substituted aziridines *cis*-**7a/b** and *cis*-**29a/b** (Table 2). Pleasingly, use of the *N*-Bus-substituted aziridines led to significant increases in the yields of the allylic sulfonamides **8b** and **30**−**34b**. These are the highest yields we have ever obtained for the organolithium-mediated transformations of 3-substituted cyclohexene-derived aziridines. The reaction of *N*-Bus homoallyl-substituted aziridine *cis*-**29b** (entries 6 and 7) required some further optimization, and it was found that the best reproducible yield (73%, entry 7) could be obtained using THF as the solvent.

In addition, we have now unequivocally established the structure of the enesulfonamide byproduct from these reactions as **9a/b** and **35a/b** with X-ray crystal structures of enesulfonamides **9b** and **35a** (see Supporting Information). It is likely that the enesulfonamides form from a lithiated aziridine (analogous to **3**, Scheme 1) and subsequent elimination in which the ring-CH_2 and the 3-substituent (R^1) can stabilize a developing positive charge as the C−N bond breaks. Such a mechanistic pathway occurs for 3-substituted cyclohexene-derived aziridines such as *cis*-**7a/b** and **29a/b** (as well as for structurally related acyclic analogues[2]) but not for the corresponding 3-substituted cyclopentene aziridines *cis*-**12a/b** and **13a/b** and cyclohexene aziridines *cis*-**14a/b**, which lack a 3-substituent.

Finally, having established that the use of *N*-Bus-substituted aziridines enabled high yields of allylic sulfonamides to be obtained from 3-substituted cyclohexene-derived *β*-methoxy aziridines, we then applied our methodology to the synthesis of the azaspiro[5.5]undecane motif of the histrionicotoxins (Scheme 3).[4] *N*-Bus aziridine *cis*-**29b** was reacted with excess *n*-BuLi to give allylic sulfonamide **34b** in 73% yield. Then,

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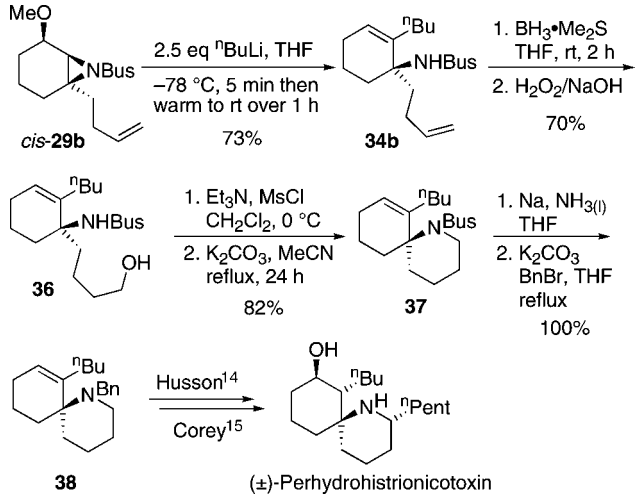
SCHEME 3. Formal Synthesis of (±)-Perhydrohistrionicotoxin



hydroboration of the least sterically hindered alkene in **34b** was accomplished using $BH_3 \cdot Me_2S$ and oxidative workup; alcohol **36** was generated in 70% yield. In our previously reported azaspirocycle syntheses,[3] Mitsunobu conditions (DEAD or DIAD, PPh_3) were used to form the piperidine ring. However, in model studies, we found that the *N*-Bus sulfonamides gave ≤52% yield for cyclization using Mitsunobu conditions. Hence, mesylation of the hydroxyl group and base-mediated cyclization (in refluxing MeCN) were utilized for the conversion of **36** into azaspirocycle **37** (82% yield).

To demonstrate the synthetic usefulness of the *N*-Bus aziridine methodology and to complete a formal synthesis of (±)-perhydrohistrionicotoxin, it was crucial to show that the *N*-Bus group could be deprotected. Disappointingly, use of TFA or TfOH (in the presence of anisole), conditions reported by Weinreb,[11] led only to decomposition of spirocycle **37**. Attempted deprotection of the *N*-Bus group in **37** using Red-Al in refluxing toluene (or xylenes)[12] or lithium naphthalenide[13] each returned recovered starting material. Finally, it was found that *N*-Bus deprotection could be effected by treating **37** with excess sodium in liquid ammonia and THF at −40 °C. The free amine was generated in quantitative yield and subsequent *N*-benzylation using benzyl bromide also proceeded quantitatively to give *N*-Bn azaspirocycle **38**. A combination of Husson's[14] and Corey's[15] syntheses can then be used to convert **38** into (±)-perhydrohistrionicotoxin. We also briefly explored intercepting Corey's route to (±)-perhydrohistrionicotoxin more directly by hydroboration of the alkene in **37** using $BH_3 \cdot Me_2S$ in refluxing THF. However, as expected, hydroboration occurred opposite to the sterically bulky *N*-Bus group to give a 50% yield of a diastereomer of the compound required for perhydrohistrionicotoxin (incorrect relative stereochemistry between the OH, *n*-Bu, and *N*-Bus groups).

In summary, with 18 examples, we have demonstrated that *N*-Bus-substituted β-methoxy aziridines give higher yields than their *N*-Ts analogues in their organolithium-mediated conversion into allylic sulfonamides. In particular, reaction of *n*-BuLi with *N*-Bus cyclohexene-derived aziridine *cis*-**29b** generated **34b** in 73% yield, which enabled a formal synthesis of (±)-perhydrohistrionicotoxin to be completed. As part of this study, a useful method for *N*-Bus deprotection (sodium in liquid ammonia) has been identified.

Experimental Section

General Procedure for the Organolithium-Mediated Reactions of β-Methoxy Aziridines. Organolithium reagent (2.5 equiv) was added dropwise to a stirred solution of methoxy aziridine (0.5 mmol) in Et_2O (5 mL) at −78 °C under argon. After stirring at −78 °C for 5 min, the resulting solution was allowed to warm to room temperature over 1 h. Then saturated $NH_4Cl_{(aq)}$ (10 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

***N*-(2-Butyl-1-methyl-2-cyclopenten-1-yl)-2-methyl-2-propanesulfonamide 18b.** Using the general procedure, *n*-butyllithium (0.8 mL of a 1.20 M solution in hexanes, 1.0 mmol) and methoxy aziridine *cis*-**12b** (99 mg, 0.4 mmol) in Et_2O (5 mL) gave the crude product. Purification by flash column chromatography on silica with petrol−Et_2O (7:3) as eluent gave allylic sulfonamide **18b** (95 mg, 87%) as a white solid, mp 52−55 °C (petrol−Et_2O); R_f (7:3 petrol−Et_2O) 0.2; IR (Nujol mull) 3269 (NH), 1305 (SO_2), 1128 (SO_2); ^{1}H NMR (400 MHz, C_6D_6) δ 5.22 (app. quintet, J = 2.0, 1H, =CH), 3.70 (s, 1H, NH), 2.63−2.55 (m, 1H, CH), 2.29−2.19 (m, 1H, CH), 2.05−1.80 (m, 4H, 4 × CH), 1.43−1.33 (m, 2H, 2 × CH), 1.38 (s, 3H, Me), 1.27 (app. sextet, J = 7.5, 2H, CH_2Me), 1.23 (s, 9H, CMe_3), 0.89 (t, J = 7.5, 3H, Me); ^{13}C NMR (100.6 MHz, C_6D_6) δ 148.5 (=C), 125.5 (=CH), 70.6 (CN), 59.0 (SO_2C), 40.1 (CH_2), 30.3 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 24.7 (CH_2), 24.4 (CMe_3), 23.0 (CH_2), 14.3 (Me); MS (CI, NH_3) *m*/*z* 291 [(M + NH_4)$^+$, 5], 155 (45), 137 (100); HRMS (CI, NH_3) *m*/*z*: [M + NH_4]$^+$ calcd for $C_{14}H_{27}NO_2S$, 291.2106; found, 291.2104.

***N*-(2-Butyl-1-methyl-2-cyclohexen-1-yl)-2-methyl-2-propanesulfonamide 8b and *N*-(6-Methoxy-2-methyl-1-cyclohexen-1-yl)-2-methyl-2-propanesulfonamide 9b.** Using the general procedure, *n*-butyllithium (0.8 mL of a 1.15 M solution in hexanes, 1.0 mmol) and methoxy aziridine *cis*-**7b** (100 mg, 0.4 mmol) in Et_2O (4 mL) gave the crude product. Purification by flash column chromatography on silica with petrol−Et_2O (7:3) as eluent gave allylic sulfonamide **8b** (75 mg, 69%) as a colorless oil, R_f (7:3 petrol−Et_2O) 0.3; IR (film) 3282 (NH), 2955, 2932, 2871, 1456, 1305 (SO_2), 1129 (SO_2), 1106, 951; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53−5.51 (m, 1H, =CH), 3.62 (s, 1H, NH), 2.46−2.40 (m, 1H, CH), 2.15−1.93 (m, 4H, 4 × CH), 1.81−1.63 (m, 3H, 3 × CH), 1.49 (s, 3H, Me), 1.45−1.31 (m, 4H, 4 × CH), 1.41 (s, 9H, CMe_3), 0.93 (t, J = 7.5, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.1 (=C), 125.0 (=CH), 59.9 and 59.8 (SO_2C and CN), 37.9 (CH_2), 31.1 (CH_2), 30.4 (CH_2), 25.4 (CH_2), 24.6 (Me), 24.4 (CMe_3), 22.8 (CH_2), 18.6 (CH_2), 14.1 (Me); MS (CI, NH_3) *m*/*z* 288 [(M + H)$^+$, 40], 272 (20), 168 (55), 151 (100); HRMS (CI, NH_3) *m*/*z*: [M + H]$^+$ calcd for $C_{15}H_{29}NO_2S$, 288.1997; found, 288.1997 and enesulfonamide **9b** (19 mg, 19%) as a white solid, mp 94−95 °C (petrol−Et_2O); R_f (8:2 petrol−Et_2O) 0.1; IR (Nujol mull) 3213 (NH), 1297 (SO_2), 1125 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (s, 1H, NH), 3.97−3.95 (m, 1H, CHO), 3.39 (s, 3H, OMe), 2.15−2.02 (m, 2H, 2 × CH), 1.81 (s, 3H, Me), 1.81−1.63 (m, 3H, 3 × CH), 1.58−1.49 (m, 1H, CH), 1.49 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.7 (=C), 126.5 (=C), 76.1 (CHO), 59.9 (SO_2C), 56.4 (OMe), 31.6 (CH_2), 26.6 (CH_2), 24.3 (CMe_3), 19.2 (Me), 17.6 (CH_2); MS (CI, NH_3) *m*/*z* 279 [(M + NH_4)$^+$, 10], 262 (20), 261 (30), 247 (25), 230 (100), 141 (30), 110 (35); HRMS (CI, NH_3) *m*/*z*: [M + NH_4]$^+$ calcd for $C_{12}H_{23}NO_3S$, 279.1742; found, 279.1748.

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***N*-[1-(3-Butenyl)-2-butyl-2-cyclohexen-1-yl]-2-methyl-2-propanesulfonamide 34b and *N*-[2-(3-butenyl)-6-methoxy-1-cyclohexen-1-yl]-2-methyl-2-propanesulfonamide 35b.** *n*-Butyllithium (5.2 mL of a 1.40 M solution in hexanes, 7.3 mmol) was added dropwise to a stirred solution of methoxy aziridine *cis*-**29b** (880 mg, 2.9 mmol) in THF (40 mL) at −78 °C under argon (reaction carried out in 500 mL flask). After stirring at −78 °C for 5 min, the resulting solution was allowed to warm to room temperature over 1 h. Then saturated $NH_4Cl_{(aq)}$ (10 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol−Et_2O (7:3) as eluent gave allylic sulfonamide **34b** (699 mg, 73%) as a colorless oil, R_F (7:3 petrol−Et_2O) 0.3; IR (Nujol mull) 3288 (NH), 2956, 2931, 2872, 1454, 1309 (SO_2), 1127 (SO_2), 973, 907; ^{1}H NMR (400 MHz, C_6D_6) δ 5.80 (ddt, J = 17.0, 10.0, 6.5, 1H, C*H* = CH_2), 5.66−5.63 (m, 1H,=CH), 5.01 (app. dq, J = 17.0, 1.5, 1H, CH=CH_ACH_B), 4.95 (app. dq, J = 10.0, 1.5, 1H, CH=CH_ACH_B), 3.69 (s, 1H, NH), 2.44−2.38 (m, 1H, CH), 2.32−2.24 (m, 1H, CH), 2.16−1.91 (m, 5H, 5 × CH), 1.88−1.67 (m, 5H, 5 × CH), 1.51−1.37 (m, 2H, 2 × CH), 1.41 (s, 9H, CMe_3), 1.35 (app. sextet, J = 7.5, 2H, CH_2Me), 0.93 (t, J = 7.5, 3H, Me); ^{13}C NMR (100.6 MHz, C_6D_6) δ 139.5 (=C), 138.3 (=C*H*CH_2), 126.9 (=CH), 114.6 (=CH_2), 63.2 (CN), 60.0 (SO_2C), 35.3 (CH_2), 32.7 (CH_2), 30.8 (CH_2), 30.1 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 24.4 (C*Me*$_3$), 22.8 (CH_2), 18.4 (CH_2), 14.1 (Me); MS (CI, NH_3) *m*/*z* 328 [(M + H)$^+$, 5], 272 (20), 191 (100); HRMS (CI, NH_3) *m*/*z*: [M + H]$^+$ calcd for $C_{18}H_{33}NO_2S$, 328.2310; found, 328.2320 and enesulfonamide **35b** (216 mg, 24%) as a white solid, mp 111−113 °C (petrol−Et_2O); R_f (7:3 petrol−Et_2O) 0.1; IR (Nujol mull) 3226 (NH), 1298 (SO_2), 1124 (SO_2), 1079, 911, 890; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, J = 17.0, 10.0, 6.5, 1H, =CH), 5.36 (s, 1H, NH), 5.03 (dq, J = 17.0, 1.5, 1H, CH=CH_AH$_B$), 4.95 (ddt, J = 10.0, 2.0, 1.0, 1H, CH=C$H_A$$H_B$), 3.94 (t, J = 4.0, 1H, CHO), 3.37 (s, 3H, OMe), 2.36 (ddd, J = 13.0, 9.0, 7.5, 1H, CH), 2.29−2.07 (m, 5H, 5 × CH), 1.85−1.78 (m, 1H, CH), 1.76−1.50 (m, 3H, 3 × CH), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.1 (=C), 138.0 (=CH), 126.7 (=C), 115.0 (=CH_2), 76.2 (CHO), 59.9 (SO_2C), 56.4 (CN), 31.8 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 26.5 (CH_2), 24.2 (C*Me*$_3$), 17.6 (CH_2); MS (CI, NH_3) *m*/*z* 302 [(M + H)$^+$, 25], 287 (20), 270 (100), 150 (20), 140 (20); HRMS (CI, NH_3) *m*/*z*: [M + H]$^+$ calcd for $C_{15}H_{27}NO_3S$, 302.1790; found, 302.1788.

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Supporting Information Available: Full experimental procedures, characterization data and copies of ^{1}H/^{13}C NMR spectra of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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