Use of the Ramberg−Bäcklund Rearrangement for the Synthesis of Medium and Large Heterocyclic Alkenes: Stereoselective Olefin Formation

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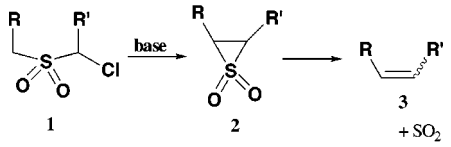
The number of biologically active natural products that have been isolated and characterized and which also contain medium- or large-ring heterocycles has increased dramatically over the past decade.[1] Consequently, there is an urgent need for the development of procedures for heterocyclic ring formation that are generally applicable, high-yielding, and done under mild conditions. Recently, our group required such a method for introducing a double bond stereoselectively into the 11-membered ring of manzamine C.[2] One method which proved to be viable was the Ramberg−Bäcklund rearrangement.[3] Previous work[4] in the formation of medium- and large-ring systems using the Ramberg−Bäcklund rearrangement did not extend to the formation of the types of ring systems encountered in many of these natural products, especially the manzamines. Since several of our synthetic projects are targeted toward the manzamines and related alkaloids, it was felt that the utility of this approach should be investigated for its efficiency in the construction of medium and large azacycles.

The Ramberg−Bäcklund rearrangement involves conversion of an α-chlorosulfone, of type **1**, to an olefin under basic conditions through the formation of episulfone **2** and then extrusion of SO_2 (Scheme 1).[3,5] The advantages of this reaction include its general applicability to most substrates, requiring only that the molecule contain the structural elements of a sulfonyl group, an α-halogen, and at least one α′-hydrogen atom.[6] As well, the reaction conditions are quite mild, requiring dilute base and moderate temperatures (ca. RT to 100 °C).[7]

Scheme 1



This reaction has been used in both acyclic and cyclic systems, although, generally, it has been used in the formation of strained rings or systems in which the olefin can only be of the *cis* geometry.[5b,6,7b] Since the double bond in the product cleanly and unequivocally supplants the sulfonyl group in the starting material and there is no further reaction of the olefin once it is formed under the Ramberg−Bäcklund conditions, these reactions tend to be very clean with few side reactions occurring.[5a,6,8] The literature indicates that predominantly the *cis*-olefin is formed in acyclic systems[5,6,7] when the reaction is carried out with bases such as NaOH, KOH, or PhLi. It should be noted, however, that when a strong, hindered base, such as potassium *tert*-butoxide (KOtBu), is used in either protic or aprotic solvents, there is a profound change in the stereochemistry to yield predominantly the *trans*-alkene.[6] It was felt that perhaps these trends might extend to the large flexible systems which we wished to build.

To investigate the applicability of this route, a series of azacycles (**4**−**10**) of varying sizes (Scheme 2), ranging from 6 to 12 carbons, were synthesized from their corresponding amino-alcohols and lactones following routine functional group manipulations.[9] The sulfides **4**−**10** were oxidized to the chlorosulfones by standard procedures,[10] and each chlorosulfone was then treated with KOtBu and aqueous KOH to generate alkenes **11**−**17**. Additionally, sulfides **4**−**10** were oxidized to the corresponding sulfones and then treated with alumina-supported KOH and dibromodifluoromethane according to the procedure developed by Chan.[11] The results from these reactions are presented in Table 1.[12]

The most striking result from Table 1 is that when the Ramberg−Bäcklund reaction is done with KOtBu, the *trans*-olefin is produced with high stereoselectivity for ring sizes 9−13 (olefins **13**−**17**). Not unexpectedly, only the *cis*-olefin was formed for seven- and eight-membered rings, regardless of the conditions used. Unfortunately,

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(1) (a) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201. (b) Satake, M.; Fukui, M.; Legrand, A.; Cruchet, P.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 1197. (c) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565. (d) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855.

(2) Beck, E. J. Ph.D. Dissertation, Universtiy of New Brunswick, Fredericton, NB, 2000.

(3) Ramberg, L.; Bäcklund, B. *Ark. Kemi. Mineral. Geol.* **1940**, *13A*, No. 27; *Chem. Abstr.* **1940**, *34*, 4725.

(4) (a) Gassman, P. G.; Mlinaric-Majerski, K. *J. Org. Chem.* **1986**, *51*, 2397. (b) Alverez, E.; Diaz, M. T.; Hanxing, L.; Martin, J. D. *J. Am. Chem. Soc.* **1995**, *117*, 1437. (c) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.

(5) (a) Paquette, L. A. *Org. React.* **1977**, *25*, 1. (b) Paquette, L. A. *Acc. Chem. Res.* **1968**, *1*, 209.

(6) Neureiter, N. P. *J. Am. Chem. Soc.* **1966**, *88*, 558.

(7) (a) Paquette, L. A.; Wittenbrook, L. S. *J. Am. Chem. Soc.* **1968**, *90*, 6783. (b) Clough, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 13, pp 861−886.

(8) Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1991**, 217.

(9) See the Experimental Section for details on a representative procedure for the synthesis of these cyclic sulfides.

(10) Gassman, P. G.; Bosner, S. M.; Mlinaric-Majerski, K. *J. Am. Chem. Soc.* **1989**, *111*, 2652.

(11) Chan, T.; Fong, S.; Li, Y.; Man, T.; Poon, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1771.

(12) The stereochemistries for alkenes **11**, **12**, **13**, and **15** were determined by removing the amine protecting group and comparing their spectra with known compounds: **11**: Grob, C. A.; Kunz, W.; Marbet, P. R. *Tetrahedron Lett.* **1975**, 2613. **12**: Wilson, S. R. W.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 287. **13**: Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 300. **15**: Torisawa, Y.; Hasimoto, A.; Nakagawa, M.; Seki, H.; Hara, R.; Hino, T. *Tetrahedron* **1991**, *47*, 8067. For the remaining azacycles a decoupling experiment was performed, and the *J* values were measured for the vinyl protons. Since it is known that the *J* value for t*rans*-olefins is approximately 12−18 Hz while for *cis*-olefins it is approximately 7−11 Hz, the major olefin isomer could be determined and its ratio correlated with GC analysis. This analysis was confirmed by independent synthesis of the *cis*-alkenes (**14**, **16**, **17**) following the procedure described by Hino for compound **15**.

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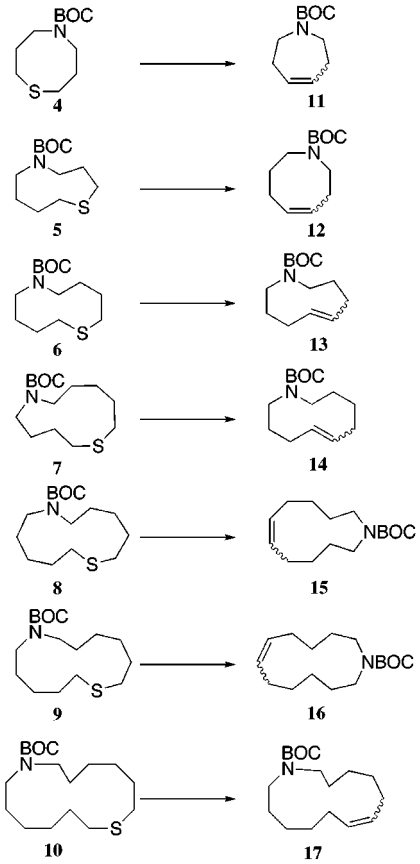
Scheme 2

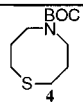
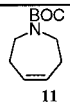
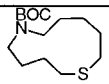
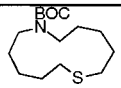
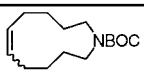
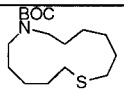
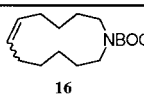
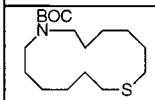
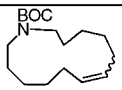


the yields for the formation of the smaller ring sizes (**11**, **12**) were consistently lower than those for the larger rings. Although the reasons for this are not immediately obvious, it may be due to severe transannular interactions encountered within the smaller rings when trying to adopt the required conformation for episulfone formation, thus facilitating other side reactions.

The larger ring sizes showed a marked decrease in the stereoselectivity of the olefin formation when the base was changed to aqueous potassium hydroxide. Rather than getting exclusively one isomer, the *trans:cis* mixture was approximately 60:40 for the 11- and 12-membered rings (**15**, **16**, respectively) and slightly less (44:56) for the 13-membered ring **17**. In addition, the yields were also significantly decreased when compared to the KOtBu values. It is apparent that these cyclic systems do not mimic similar acyclic systems found in the literature since the *cis*-olefin predominates in most cases.[5−8]

Unfortunately, there were problems in forming the α-chlorosulfones for the 10- and 11-membered ring sulfides (**6**, **7**).[13] This problem was also observed for the 7- and 13-membered alkenes (rings **11** and **17**), although not to the same extent. Attempts to perform the chlorination under a variety of conditions, including stirring at RT, or 0 °C, or using SO_2Cl_2,[14] did not lead to any significant improvements. Although the structure of the major product from these oxidation reactions was not rigorously proven, it appeared from the ^{1}H NMR data that an eliminated product, possibly **18** and **19**, was being

Table 1. *Trans:Cis* Ratio Obtained in the Ramberg−Bäcklund Rearrangement with a Variety of Bases. Ratios Were Determined by GC Analysis. See Experimental for Details.

Sulfide	Olefin	Base	Trans:cis	Yield (%)
 **4**	 **11**	KOtBu	cis	66
		Aq. KOH	cis	43
		Anh. KOH	cis	63
 **5**	 **12**	KOtBu	cis	41
		Aq. KOH	cis	33
		Anh. KOH	cis	33
 **6**	 **13**	KOtBu	94:6	100
		Anh. KOH	65:35	59
 **7**	 **14**	KOtBu	95:5	54
		Anh. KOH	60:40	67
 **8**	 **15**	KOtBu	98:2	97
		Aq. KOH	61:39	57
		Anh. KOH	73:27	68
 **9**	 **16**	KOtBu	99:1	76
		Aq. KOH	62:38	70
		Anh. KOH	85:15	62
 **10**	 **17**	KOtBu	94:6	93
		Aq. KOH	44:56	79
		Anh. KOH	61:39	53

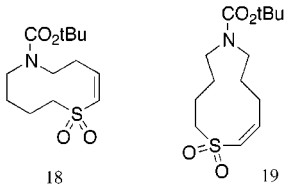


Figure 1. Elimination products obtained in chlorosulfone formation leading to alkenes **13** and **14**.

formed (Figure 1). Some characteristic resonances that were supportive of this conjecture are δ 6.46 (dd, 1H), 6.31 (dt, 1H), 4.19 (bs 2H), 3.47 (bq, 2H), and 3.29 (abq, 2H) for **18**, and δ 6.88 (dt, 1H), 6.25 (d, 1H), 3.21 (t, 4H), 3.07 (t, 2H), and 2.36 (bt, 2H) for **19**. This difficulty in forming the chlorosulfide has been noted previously.[15] To circumvent this problem, attempts were made to directly α-chlorinate the sulfone. They included anion formation with LHMDS or LDA followed by quenching with NCS[16] or hexachloroethane[17] and stirring the sulfone with KOtBu and CBr_2F_2 at temperatures ranging from −20 °C − 0 °C. Unfortunately, none of these procedures gave

(13) The yield for chlorosulfone formation for these two ring systems was always 15−25% overall.

(14) Truce, W. E.; Birum, G. H.; McBee, E. T. *J. Am. Chem. Soc.* **1952**, *74*, 3594.

(15) Dilworth, B. M.; McKervey, M. A. *Tetrahedron* **1986**, *42*, 3731.

(16) a) Rigby, J. H.; Warshakoon, N. C. *J. Org. Chem.* **1996**, *61*, 7644. (b) Rigby, J. H.; Warshakoon, N. C. *J. Am. Chem. Soc.* **1999**, *121*, 8237.

(17) Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682.

better results. Since the yield for chlorosulfone formation was low for the 9- and 10-membered rings (**13** and **14**, respectively) and since the other aqueous KOH reactions showed no stereoselectivity, no attempt was made to form the 9- and 10-membered rings with aqueous KOH.

The Chan modification of the Ramberg−Bäcklund rearrangement proved successful for synthesizing all ring sizes; however, it was not very useful in terms of stereoselectivity for larger rings. Table 1 shows that there is a wide range of *trans*/*cis* ratios for the various ring sizes with none being stereoselective except for the seven- and eight-membered rings (**11**, **12**).

On the basis of literature data for acyclic systems, it had been anticipated that the *cis*-olefins would be formed in excess when aqueous KOH was used.[6] In addition, although the *trans*-olefin was known to predominate when using KOtBu, our results showed a greater stereoselectivity than expected. If it is assumed that the mechanism put forth by Paquette and Wittenbrook[7a] is applicable to both acyclic and cyclic systems, then their arguments do not explain the anomalous *trans*-selectivity that the larger cyclic systems seem to exhibit. Clearly this means that there are other interactions inherent in these rings that must be considered. A possible explanation is that significant transannular interactions are encountered when the α-chlorosulfones try and adopt the proper conformation to allow for formation of the *cis*-episulfone. If these transannular interactions become large enough relative to the other steric factors in forming the *cis*-episulfone, then an increase in the activation barrier for its formation must occur. Similar transannular interactions may be argued for the *trans*-episulfone formation; however, to account for the preponderance of *trans*-alkene, these interactions must be much less pronounced. If this analysis is correct, then we would expect the ratio of *cis*- to *trans*-product to erode under all conditions, and in fact, this is what we see.

An alternative possibility is that since all of the substrates in our study contain a sp^2-hybridized nitrogen atom, that this might affect the stereochemical outcome. To investigate this, thiacyclodecane[18] was subjected to the same rearrangement conditions as used for sulfide **7**. After appropriate workup and purification, GC analysis indicated that, within experimental error, identical *cis*:*trans* ratios were obtained.[19] These results prove that the sp^2-hybridized nitrogen atom plays little or no role in influencing the stereochemical outcome of the reaction.

An alternative explanation of the higher than expected levels of *trans*-alkene is to postulate that the reaction is "somewhat" thermodynamically controlled. This would mean that the episulfone intermediate would have to be long-lived enough to allow for equilibration to occur, or at least compete, before extrusion of SO_2. By default this would also mean that the *trans*-alkene is more stable than the *cis*-alkene. Although this is the rationale used by Paquette to explain the stereoselectivity of the KOtBu reactions, he also notes that this is not likely the case for the hydroxide-initiated reactions. Molecular mechanics calculations using the AMBER94 program appear to support this. Accounting for the Boltzman distribution of the lowest energy conformers[20] (those within 3 kcal of the minimum) for the 9-, 10-, and 11-membered *cis*- and *trans*-episulfones, intermediates for the formation of alkenes **10**, **11**, and **12** indicated that the *cis*-isomer should predominate for the nine-membered case (68:32 *cis*:*trans*) and that the *trans*-isomer should predominate for the other two (5:95 and 4:94 *cis*:*trans*, respectively). It should be noted, however, that these calculations were done at 25 °C and may not be as meaningful at 100 °C. Although we cannot rule out the equilibration pathway for the hydroxide-mediated reactions in our study, we do not believe that this is occurring.

If indeed it is the transannular interactions which are affecting the *cis*/*trans* ratios, then as the ring size increases, a change in the ratios might be expected, since these interactions would presumably become less dominating. It is interesting to note that the results for the azacycles show that as the ring size gets larger, the stereoselectivity seems to drop slightly (compare the formation of **15** and **16** relative to **17**). Whether this drop in stereoselectivity is real or not would have to be determined by synthesizing several larger rings to see if the same trend appears.

In conclusion, the use of KOtBu in the Ramberg−Bäcklund rearrangement has been shown to be useful in introducing double bonds stereoselectively into azamacrocyclic systems. The use of this protocol for the synthesis of alkaloid natural products is currently under investigation.

Experimental Section

All reactions were carried out in a flame-dried or oven-dried (140 °C) glassware under an argon atmosphere. Temperatures indicated refer to external bath temperatures, and all reactions were stirred magnetically. Air-sensitive reagents were transferred through rubber septa via syringes. The phrase "removed under reduced pressure" refers to removal of solvent with a Büchi rotary-evaporator using a water aspirator and a bath temperature of 30 °C. All commercial reagents were purchased from Aldrich Chemicals and were used without further purification. Aluminum oxide was purchased from Aldrich Chemicals and had a surface area ≥ 60 m^2/g. Tetrahydrofuran was dried over Na/benzophenone and was transferred via syringe. Extraction solvents were purchased in bulk and distilled prior to use. Column chromatography was performed on Merck silica gel (230−400 mesh) following the procedure of Still.[21] Reagent grade solvents were used without further purification for chromatographic separations.

General Procedures for the Synthesis of Alkenes 11−17 from Sulfides 4−10. Method A. To a solution of sulfide (1 equiv) in carbon tetrachloride was added *N*-chlorosuccinimide (1 equiv). The reaction was refluxed for 3 h, cooled to 0 °C, and filtered, and the solvent was evaporated. After dissolving the residue in dichloromethane and cooling to 0 °C, *m*-chloroperbenzoic acid (2.6 equiv) was added, and the reaction was stirred for 18 h at room temperature. The reaction mixture was then cooled to 0 °C and filtered. The filtrate was washed with 1% NaOH (×2) and brine, dried over K_2CO_3, and filtered and the solvent removed in vacuo. Purification by silica gel flash chromatography (2:1 hexanes:ethyl acetate) furnished the chlorosulfone.

A 1.0 M solution of potassium *tert*-butoxide in THF (4 equiv) was added dropwise to a solution of chlorosulfone in DMSO at room temperature. The reaction was stirred for 10 min and then diluted with ether and poured into water. The layers were separated, and the aqueous phase was extracted with ether (×3). The combined organic phases were then washed with water (×2) and brine, dried over $MgSO_4$, and filtered, and the solvent was

(18) Singh, A.; Mehrotra, A.; Regen, S. L. *Synth. Commun.* **1981**, *11*, 409.

(19) GC analysis on the cyclodecene produced from these reactions indicated a 36:64 *cis:trans* ratio when using the anhydrous KOH method, and a 11:89 *cis:trans* ratio when using KOtBu.

(20) Computations were done with a *N*-formyl group instead of a *tert*-butoxycarbony to simplify the calcuations.

(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

removed in vacuo. Purification by silica gel flash chromatography (10:1 hexanes:ethyl acetate) furnished the olefins.

Method B. Chlorosulfone was formed as in method A above.

A solution of chlorosulfone in 2 M aqueous potassium hydroxide was refluxed for 1 to 3 h and then cooled to room temperature. The reaction mixture was extracted with diethyl ether (×3). The combined organic layers were washed with water and then brine, dried over $MgSO_4$, and filtered, and the solvent was evaporated in vacuo. Purification by silica gel flash chromatography (10:1 hexanes:ethyl acetate) furnished the olefins.

Method C. *m*-Chloroperbenzoic acid (2.6 equiv) was added to a solution of sulfide in dichloromethane at 0 °C. After stirring for 1 h at room temperature, the solution was again cooled to 0 °C and filtered. The filtrate was washed with 1% NaOH (×2) and then brine, dried over $MgSO_4$, and filtered and the solvent evaporated to furnish the sulfone as a white solid. No further purification was necessary.

A mixture of sulfone and potassium hydroxide supported on alumina (1 g of KOH−alumina per 0.1 mmol of sulfone) in *tert*-butyl alcohol was heated to 60−80 °C. To the vigorously stirring mixture was added excess dibromodifluoromethane through a pipet. After stirring the mixture for 1 h at 60−80 °C, the reaction was cooled and filtered through Celite, rinsing with dichloromethane. The solvent was evaporated, and the residue was taken up in dichloromethane. The solution was washed with water and brine, dried over $MgSO_4$, and filtered and the solvent removed in vacuo. Purification by silica gel flash chromatography (10:1 hexanes:ethyl acetate) furnished the olefins.

Characterization Data. (*Z*)-2,3,6,7-Tetrahydroazepine-1-carboxylic Acid *tert*-Butyl Ester, 11. Alkene **11** was prepared via methods A and B from the corresponding chlorosulfone in 66% and 43% yields, respectively, and via method C from the corresponding sulfone in 64% yield, as a clear colorless oil. An isothermal GC program (110 °C) was used to elute the single isomer (retention time 37.5−37.7 min). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 1.48 (s, 9 H), 2.30 (m, 4 H), 3.46 (m, 4 H), 5.74 (t, J = 2.7 Hz, 2 H). ^{13}C NMR (DMSO-d_6, 400 MHz, 90 °C): δ 28.6, 29.6, 46.5, 78.8, 129.6, 154.7. IR (NaCl cells), cm^{-1} (intensity): 2910 (m), 1665 (s). HRMS (EI): $[C_{11}H_{19}NO_2]_{calcd}$ = 197.14167; $[m^+/z - C_4H_9O]_{calcd}$ = 124.0763; $[m^+/z - C_4H_9O]_{found}$ = 124.07603.

(*Z*)-3,4,7,8-Tetrahydro-2*H*-azocine-1-carboxylic Acid *tert*-Buty Ester, 12. Alkene **12** was prepared via method A and B in 41% and 32% yields, respectively. It was also prepared via method C in 33% yield. In each case a clear colorless oil was obtained. The following GC program was used to elute the single isomer: 110 °C for 45 min, followed by an increase of 1 °C/min up to 150 °C (retention time 51.9−52.2 min). ^{1}H NMR (DMSO-d_6, 400 MHz, 90 °C): δ 1.43 (s, 9 H), 1.70 (m, 2 H), 2.01 (m, 2 H), 2.17 (m, 2 H), 3.16 (m, 2 H), 3.27 (m, 2 H), 5.70 (m, 2 H). ^{13}C NMR ($CDCl_3$, 400 MHz, 25 °C): δ 23.3, 23.5, 26.5, 27.0, 27.3, 27.8, 28.5, 46.8, 47.3, 49.1, 50.0, 79.0, 79.7, 128.7, 129.3, 130.7, 131.3, 155.1, 155.8. N.B.: The ^{13}C NMR spectrum of alkene **12** showed two peaks for most carbons due to the possible rotamers for this molecule. Upon heating, the peaks became very broad and in some cases disappeared into the baseline. Therefore, the spectrum obtained in $CDCl_3$ at room temperature has been reported and appears to be doubled. IR (NaCl cells), cm^{-1} (intensity): 2920 (m), 1670 (s). HRMS (EI): $[C_{12}H_{21}NO_2]_{calcd}$ = 211.15733; $[m^+/z - C_4H_9O]_{calcd}$ = 138.09196; $[m^+/z - C_4H_9O]_{found}$ = 138.09214.

2,3,4,7,8,9-Hexahydroazonine-1-carboxylic Acid *tert*-Butyl Ester, 13 (mixture of *E* and *Z*). Alkene **13** was prepared via method A in 100% yield and by method C in 59% yield as a clear colorless oil. The following GC program was used to separate the isomers: 110 °C for 45 min, followed by an increase of 1 °C per minute up to 150 °C (retention times: cis 67.6−67.7 min, *trans* 72.1−72.5 min). *cis*-olefin ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C): δ 1.37 (s, 9 H), 1.60 (m, 4 H), 2.14 (m, 4 H), 3.07 (m, 4 H), 5.48 (m, 2H). *trans*-olefin ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 1.45 and 1.55 (two singlets due to the carbamate rotamers, both singlets together integrate for 9 H), 1.72−1.93 (m, 4 H), 2.17 (m, 4 H), 3.09−3.20 (m, 4 H), 5.54 (t-like, J = 5.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 400 MHz, 25 °C): δ 22.7, 22.8, 25.6, 26.7, 28.6, 29.1, 29.8, 29.9, 30.0, 51.8, 52.2, 52.4, 78.3, 78.4, 129.7, 129.9, 130.9, 131.4, 155.5, 155.6. N.B.: The ^{13}C NMR spectrum of alkene **13** is quite complex due to the presence of both cis and trans isomers in this sample. In addition, this spectrum shows two peaks for most carbons due to the possible rotamers for this molecule. Upon heating, the peaks became very broad and in some cases disappeared into the baseline. Therefore, the spectrum obtained in $CDCl_3$ at room temperature has been reported and appears to be doubled. IR (NaCl cells), cm^{-1} (intensity): 2920 (m), 2860 (w), 1665 (s). HRMS (EI): $[C_{13}H_{23}NO_2]_{calcd}$ = 225.17299; $[m^+/z - C_4H_9O]_{calcd}$ = 152.10762; $[m^+/z - C_4H_9O]_{found}$ = 152.10759.

3,4,5,8,9,10-Hexahydro-2*H*-azecine-1-carboxylic Acid *tert*-Butyl Ester, 14 (mixture of *E* and *Z*). Alkene **14** was prepared by methods A and C in 54% and 67% yields, respectively, as a clear colorless oil. The isomer ratio was determined by GC using the following isothermal program: 130 °C for 45 min followed by an increase of 1 °C/min up to 175 °C (retention times: *cis* 56.2−58.0 min, *trans* 60.4−61.7 min). The NMR spectra for this compound was very complicated so assignments for each isomer were determined by 2D-COSY and HMQC spectra. ^{1}H NMR (DMSO-d_6, 400 MHz, 90 °C) *cis*-olefin: δ 1.42 (s, 9H), 1.55 (m, 2 H), 1.56 (m, 2H), 1.61 (m, 2 H), 1.80 (m, 2 H), 2.07 (m, 4 H), 2.17 (m, 2 H), 3.01 (m, 2 H), 3.23 (m, 2 H), 5.34 (m, 1 H), 5.43 (m, 1H). *trans*-isomer: 1.38 (m, 2H), 1.40 (s, 9H), 1.61 (m, 2 H), 1.67 (m, 2 H), 1.70 (m, 2 H), 2.01 (q like, J = 6.1 Hz, 2 H), 2.07 (m, 2 H), 2.98 (m, 2 H), 3.07 (m, 2 H), 5.48 (m, 4 H). ^{13}C NMR (DMSO-d_6, 400 MHz, 90 °C) *cis*-olefin: δ 22.2, 23.3, 24.4, 25.7, 25.8, 27.8, 44.8, 48.9, 77.9, 129.1, 129.5, 155.4. *trans*-olefin: δ 26.8, 27.8, 29.2, 30.0, 32.6, 32.8, 52.5, 52.5, 77.5, 129.3, 132.0, 155.4. IR (NaCl cells), cm^{-1} (intensity): 2910 (m), 2850 (w), 1660 (s). HRMS (EI): $[C_{14}H_{25}NO_2]_{calcd}$ = 239.18865; $[m^+/z - C_4H_9O]_{calcd}$ = 166.12328; $[m^+/z - C_4H_9O]_{found}$ = 166.12328.

Azacycloundec-6-ene-1-carboxylic Acid *tert*-Butyl Ester, 15. Alkene **15** was prepared by methods A, B, and C in 97%, 57%, and 68% yields, respectively, as a clear colorless oil in all cases. The following GC program was used to separate the isomers: 130 °C for 45 min, followed by an increase of 1 °C/min up to 175 °C (retention times: cis 82.0−82.1 min, *trans* 86.0−86.1 min). ^{1}H NMR (DMSO-d_6, 400 MHz, 90 °C): *cis*-olefin: δ 1.41 (s, 9H), 1.46 (m, 4H), 1.52 (m, 4H), 2.17 (m, 4H), 3.27 (t, J = 5.7 Hz, 4H), 5.37 (t, J = 5.9 Hz, 2H). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): *trans*-olefin: δ 1.32 (m, 4H), 1.42 (s, 9H), 1.50 (m, 4H), 2.15 (m, 4H), 3.15 (m, 2H), 3.25 (m, 2H), 5.44 (t-like, J = 4.3 Hz, 2H). ^{13}C NMR (DMSO-d_6, 400 MHz, 90 °C): *cis*-olefin: δ 24.4, 26.0, 26.1, 28.6, 48.9, 78.6, 130.7, 155.4. *trans*-olefin: δ 23.6, 25.7, 28.6, 33.8, 44.3, 78.4, 131.0, 154.7. IR (NaCl cells), cm^{-1} (intensity): 2955 (s), 1665 (s). HRMS (EI): $[C_{15}H_{27}NO_2]_{calcd}$ = 253.20431; $[m^+/z - C_4H_9O]_{calcd}$ = 180.13894; $[m^+/z - C_4H_9O]_{found}$ = 180.13891.

Azacyclododec-6-ene-1-carboxylic Acid *tert*-Butyl Ester, 16. Alkene **16** was prepared by methods A, B, and C in 76%, 70%, and 62% yields, respectively, as clear colorless oils in all cases. The following GC program was used to separate the isomers: 130 °C for 45 min, followed by an increase of 1 °C up to 175 °C (retention times: *cis* 95.1−95.4 min, *trans* 96.7−96.9 min). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C): *cis*-olefin: δ 1.34−1.58 (m, 10H), 1.38 (s, 9H), 2.09 (m, 4H), 3.04 (br, 2H), 3.25 (t, J = 6.5 Hz, 2H), 5.32 (m, 2H). *trans*-olefin: δ 1.34−1.64 (m, 10H), 1.38 (s, 9H), 2.09 (m, 4H), 3.04 (br, 2H), 3.13 (t, J = 6.5 Hz, 2H), 5.38 (m, 2H). ^{13}C NMR (DMSO-d_6, 400 MHz, 90 °C): *cis*-olefin: δ 23.8, 24.6, 25.3, 25.4, 26.1, 26.5, 27.1, 28.6, 44.9, 47.3, 78.6, 130.6, 131.0, 155.6. t*rans*-olefin: δ 24.3, 24.9, 25.7, 26.0, 28.6, 31.5, 31.7, 46.7, 47.0, 78.5, 130.5, 132.8, 155.6. IR (NaCl cells), cm^{-1} (intensity): 2950 (m), 2890 (m), 1675 (s). HRMS (EI): $[C_{16}H_{29}NO_2]_{calcd}$ = 267.21997; $[m^+/z - C_4H_9O]_{calcd}$ = 194.1546; $[m^+/z - C_4H_9O]_{found}$ = 194.15442.

Azacyclotridec-7-ene-1-carboxylic Acid *tert*-Butyl Ester, 17. Alkene **17** was prepared via methods A, B, and C in 93%, 79%, and 53% yields, respectively, as a clear colorless oil in all cases. The following GC program was uses to separate the isomers: 130 °C for 45 min, followed by an increase of 1 °C/min up to 175 °C (retention times: *cis* 105.8−105.9 min, *trans* 107.6−108.2 min). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C): *cis*-olefin: δ 1.25−1.49 (m, 12H), 1.36 (s, 9H), 2.04 (m, 4H), 3.13 (t, J = 6.3 Hz, 4H), 5.22 (t, J = 4.6 Hz, 2H). *trans*-olefin: δ 1.33−1.46 (m, 8H), 1.40 (s, 9H), 1.52 (m, 4H), 2.05 (m, 4H), 3.14 (t, J = 6.5 Hz, 4H), 5.35 (m, 2H). ^{13}C NMR (DMSO-d_6, 400 MHz, 90 °C): *cis*-olefin: δ 25.0, 25.2, 27.9, 28.6, 29.1, 49.9, 78.4, 131.0, 155.7.

trans-olefin: δ 25.4, 26.9, 28.6, 29.3, 31.8, 49.4, 78.5, 131.5, 155.7. IR (NaCl cells), cm^{-1} (intensity): 2920 (m), 2850 (w), 1660 (s). HRMS (EI): $[C_{17}H_{31}NO_2]_{calcd} = 281.23563$; $[m^+/z - C_4H_9O]_{calcd} = 208.17026$; $[m^+/z - C_4H_9O]_{found} = 208.17077$.

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Supporting Information Available: A detailed procedure for the synthesis of sulfide **8**, and ^1H and ^{13}C NMR and MS data for sulfides **4**−**10** and the chlorosulfones. In addition, copies of ^1H and ^{13}C NMR spectra for compounds **11**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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