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Reactivity and Rearrangements of Dialkyl- and Diarylvinylsulfonium Salts with Indole-2- and Pyrrole-2-carboxaldehydes

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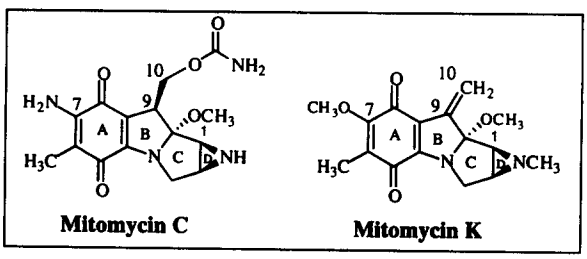
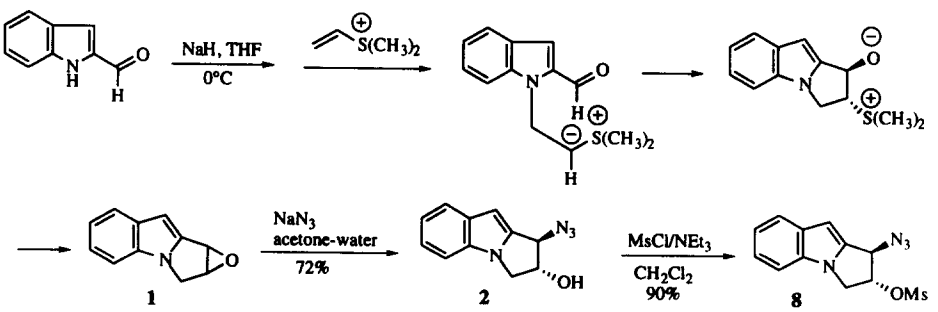
Abstract: Various dialkyl- and diarylvinylsulfonium salts react with indole-2-carboxaldehydes in the presence of sodium hydride and sodium azide to form tricyclic azido alcohols analogous to **2**. With pyrrole-2-carboxaldehyde, [2,3] sigmatropic and other rearrangements occur except in the case of diphenylvinylsulfonium trifluoromethanesulfonate where the annulation reaction does take place to give a low yield of **29**.

Keywords: sulfonium salts; rearrangements; bicyclic heterocyclic compounds; natural products.

Our interest in developing an efficient synthesis of the tetracyclic ring system of the antitumor antibiotic, mitomycin C, led to the discovery that reaction of dimethylvinylsulfonium iodide with the sodium salt of indole-2-carboxaldehyde gave the formation of the tetracyclic oxirane **1**, which upon treatment with sodium azide forms the azido alcohol **2** in a 72% yield (Scheme 1).[1] This reaction allows for the formation of the C ring of the mitomycin skeleton and the introduction of the precursor groups to the aziridine ring. This annulation was a key step in our total synthesis of mitomycin K.[2] The formation of a minor sideproduct **3** was observed which, if moisture was not rigorously excluded, could become a major product in this reaction (Scheme 2).



Scheme 1



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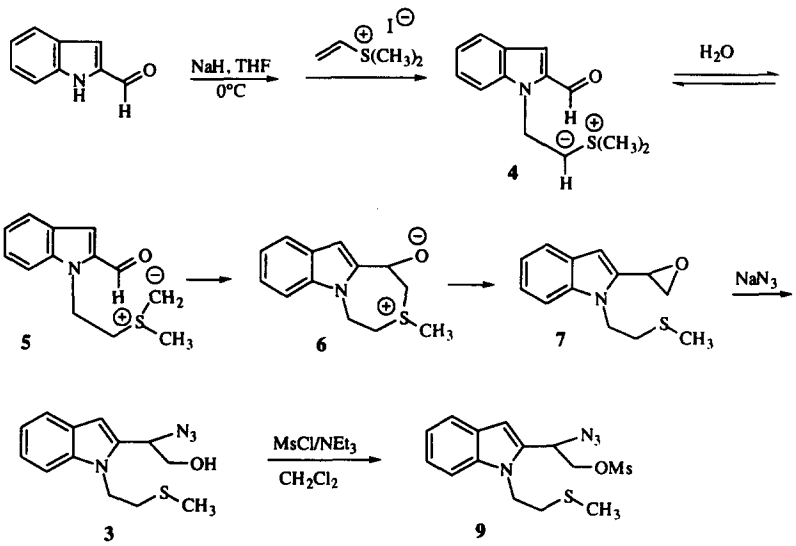
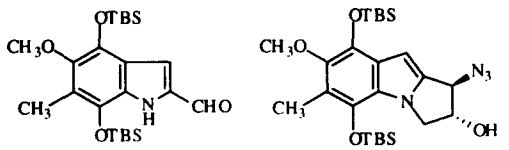
The formation of **3** can be rationalized by protonation of the sulfur ylide **4**, followed by deprotonation of one of the readily accessible methyl hydrogens to give the ylide **5**, which then reacts at the carbonyl center to give the seven-membered ring intermediate **6**. The methyl sulfide is then displaced by the alkoxide to give the oxirane **7**, which upon addition of sodium azide, opens up to the azido alcohol **3**. The mixture of **2** and **3** is treated with methanesulfonyl chloride and triethylamine to form the corresponding mesylates, **8** and **9**, which are then separated by flash chromatography.

Scheme 2

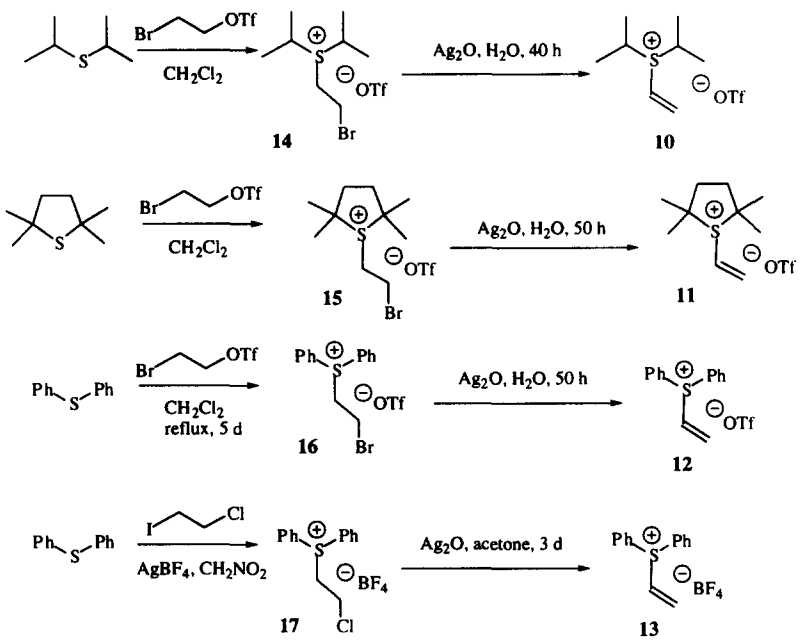


In an effort to suppress this formation of an alternative sulfur ylide, diisopropylvinylsulfonium trifluoromethanesulfonate **10**, 2,3,4,5-tetrahydro-2,2,5,5-tetramethylvinylthiophenium trifluoromethanesulfonate **11**, diphenylvinylsulfonium trifluoromethanesulfonate **12**, and diphenylvinylsulfonium tetrafluoroborate **13** were synthesized. Vinylsulfonium salts **10**, **11**, and **12** were prepared by reaction of diisopropyl sulfide, 2,2,5,5-tetramethyltetrahydrothiophene,[3] or diphenylsulfide with 2-bromoethyl trifluoromethanesulfonate[4] to form **14**, **15**, or **16** respectively (Scheme 3). Elimination of HBr was achieved with silver (I) oxide to give the corresponding vinylsulfonium salts.[5] These reagents underwent the annulation reaction with indole-2-carboxaldehyde in the presence of sodium hydride and sodium azide in THF to form the azido alcohol **2**. The yields are given in Table I. Compound **13** was prepared by reacting diphenylsulfide with 1-chloro-2-iodoethane and silver tetrafluoroborate to give the 2-chloroethylsulfonium salt **17**.[6] Crude **17** was treated with silver (I) oxide to effect the elimination of HCl to form **13** as an extremely hydroscopic solid in a 62% yield. This vinylsulfonium salt was not very soluble in THF at 0°C and did not give a detectable yield of **2** when used in the annulation reaction with indole-2-carboxaldehyde. Reaction with the substituted indole-2-carboxaldehyde **18** gave a 30% yield of the corresponding azido alcohol **19** (Table I).[7]



18 19

Scheme 3



Of the vinylsulfonium salts tested, **10** works best in the cyclization reaction with indole-2-carboxaldehydes. Vinylsulfonium salt **10** will initially form ylide **20** after attack of a nucleophile at the β carbon of the vinyl group. Equilibrium with ylide **21** is possible through protonation and deprotonation processes (Scheme 4). Apparently the sterically hindered **21** undergoes addition to the aldehydic group much less readily than ylide **5**, thus decreasing the formation of sideproducts from these undesired intermediates. For this reason **10** has become our achiral vinylsulfonium salt of choice in the annulation reaction with indole-2-carboxaldehyde.

Scheme 4

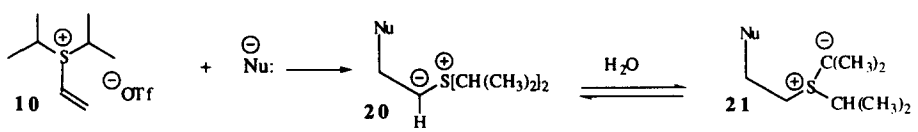
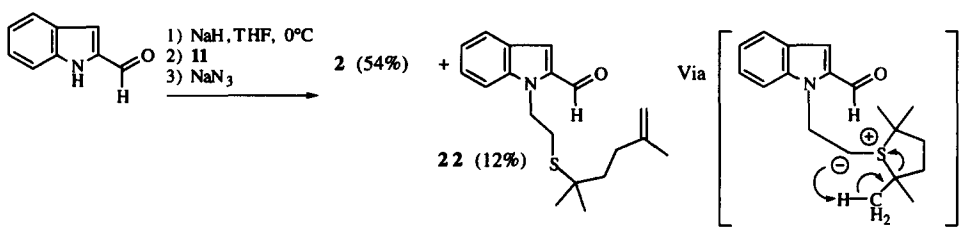


Table I. Yields of the azido alcohols **2** and **19** from **10-13**.

Substrate	Sulfonium Salt	Product	Yield (%)
indole-2-carboxaldehyde	**10**	**2**	72
indole-2-carboxaldehyde	**11**	**2**	54
indole-2-carboxaldehyde	**12**	**2**	62
18	**10**	**19**	72[8]
18	**12**	**19**	39
18	**13**	**19**	30

Vinylsulfonium salts **11-13** have no α hydrogens and therefore no other ylide is possible. When this annulation is carried out with **11** a 12% yield of **22** is obtained in addition to the 54% yield of **2**. Sulfide **22** apparently forms as the result of a [2,3] sigmatropic rearrangement (Scheme 5). The yield of **2** is 62% when **12** is used as the vinylsulfonium reagent.

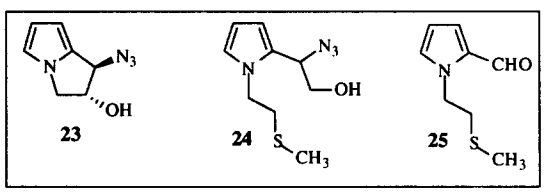
Scheme 5



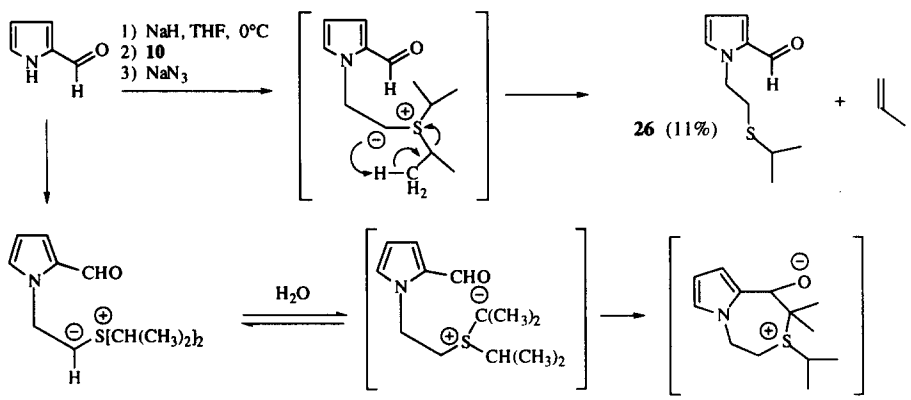
Pyrrole-2-carboxaldehyde was reacted with dimethylvinylsulfonium iodide and the vinylsulfonium salts **10-12** in the presence of sodium hydride in an effort to form the bicyclic azido alcohol **23**. The reaction with dimethylvinylsulfonium iodide resulted in several products by tlc. No formation of **23** was detected and low yields of **24** and **25** were isolated.[9] Compound **24** presumably forms by a mechanism analogous to that for **3** (Scheme 2), while **25** must be formed by conjugate additon of the pyrrole anion to the vinylsulfonium salt, protonation, and then demethylation. It seemed logical to try the annulation reaction with **10-12** in an attempt to suppress the rearrangement illustrated in Scheme 2. When the annulation was attempted with **10**, the rearrangement products **26** and **27** were isolated in 11 and 18% yields, respectively (Scheme 6). Sulfide **26** appears to be the result of a [2,3] sigmatropic rearrangement, while **27** is formed by a mechanism similar to that for **3** and **24**. Use of **11** as the vinylsulfonium salt reagent results in an 84% yield of the [2,3] sigmatropic

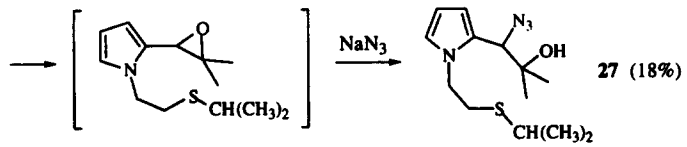
rearrangement product **28** (Scheme 7). The advantage of **12** as the vinylsulfonium salt reagent is that neither a [2,3] sigmatropic rearrangement nor the formation of an alternative ylide (no α hydrogens) is possible. In this case, a 20% yield of **29** was isolated. Although not the desired product, it does show that when other rearrangements are not possible, the annulation with pyrrole-2-carboxaldehyde takes place as was observed for indole-2-carboxaldehyde. The formation of an intermediate oxirane **30** (analogous to **1**) may be inferred (Scheme 8). Oxirane **30** may be a more strained intermediate than **1**, which could account for the rearrangements observed in the pyrrole system compared to the indole. Annelated aziridines **31** are known to be extremely prone to ring-opening in the presence of nucleophiles.[10] The site of nucleophilic attack is C-1. Compound **30** which has the oxirane ring adjacent to the aromatic pyrrole ring, may undergo a similar initial bond breaking (or partial bond breaking) at C-1, followed by nucleophilic attack at this site.

In conclusion, the formation of a by-product **3** in the annulation of indole-2-carboxaldehyde with dimethylvinylsulfonium iodide (Scheme 2) led to the synthesis of several vinylsulfonium salts with either less accessible α hydrogens or no α hydrogens. The diisopropylvinylsulfonium salt **10** gave the optimum yield in this annulation. With pyrrole-2-carboxaldehyde, both the side reaction described in Scheme 2 and an unexpected [2,3] sigmatropic rearrangement were observed with **10**. The [2,3] sigmatropic rearrangement product **28** was the only product observed with **11**. A bicyclic product **29** was obtained with **12**, a vinylsulfonium salt with no α hydrogens and incapable of undergoing a [2,3] sigmatropic rearrangement.

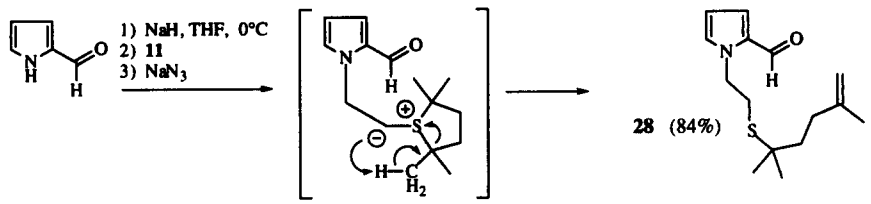


Scheme 6

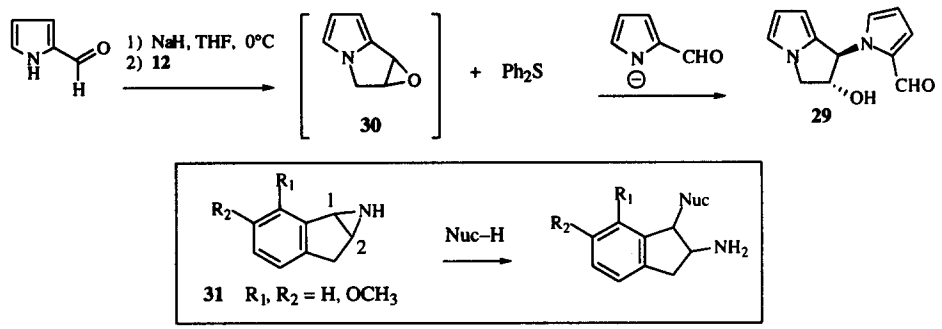




Scheme 7



Scheme 8



Experimental

Nuclear magnetic resonance (NMR) spectra were acquired using a Varian-Gemini 200 MHz or a Varian Unity 400 MHz spectrometer. Melting points were determined on a Thomas Hoover melting point apparatus. NMR chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS) or relative to internal $CHCl_3$. Infrared spectra were recorded by using a Genesis Series FT-IR instrument. Elemental analyses were obtained from Quantitative Technologies, Inc. (Whitehouse, NJ). Mass spectra were obtained either from University of California, Riverside Mass Spectrometry Facility or Rutgers University, Food Science Mass Spectrometry Facility. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Tetrahydrofuran (THF) and dichloromethane were distilled from calcium hydride under a nitrogen atmosphere. Chromatographic purification was performed with EM Science 230-400 mesh silica gel. Reactions and chromatography fractions were monitored and analyzed by thin layer chromatography (TLC) using EM Science 250-μm 60 F_{254} silica plates. EtOAc = ethyl acetate, PE = petroleum ether, 30-60°C.

2-Bromoethyl trifluoromethanesulfonate:[4] A total of 0.85 mL (10.5 mmol) anhydrous pyridine and 10 mL dry dichloromethane were added to a 50-mL, 3-necked round-bottomed flask under a nitrogen atmosphere. The reaction flask was then cooled to about -20 °C with a dry ice/ethylene glycol bath. A total of

1.7 mL (10 mmol) trifluoromethanesulfonic anhydride was added, whereupon a white precipitate formed immediately. A total of 0.71 mL (10 mmol) of 2-bromoethanol was added after 5 min. The white precipitate disappeared and then after a few minutes a new white precipitate formed. The reaction mixture was stirred for 10 min during which time it gradually warmed to room temperature. The reaction mixture was then filtered and the residue was washed by 2 x 5 mL 1:1 dichloromethane/petroleum ether. The filtrate was then run through a 4 cm silica plug with 200 mL of 1:1 dichloromethane/petroleum ether solution. The solvent was removed *in vacuo* to give 2.2 g (8.7 mmol) of 2-bromoethyl trifluoromethanesulfonate as a colorless oil (87%).

^{1}H NMR ($CDCl_3$): δ 3.61 (t, J = 6.4 Hz, 2H), 4.75 (t, J = 6.4 Hz, 2H).

Formation of **2** with various vinylsulfonium salts:

With **10**: To a 50 mL, 3-necked round-bottomed flask under a N_2 atmosphere, 145 mg (1 mmol) 2-indolecarboxaldehyde was added and dissolved in 5 mL dry THF. The reaction vessel was then cooled to -5°C with an ice-salt bath and 60 mg NaH (60% in mineral oil, 1.5mmol) was added quickly. After 10 min a clear yellow solution was obtained and then 440 mg (1.5 mmol) **10** dissolved in 10 mL dry THF was added to the reaction mixture via syringe. After 4 h the starting material had disappeared by tlc and 400 mg sodium azide was dissolved in 5 mL deionized water and added to the reaction mixture. After 20 min the solvent was removed under reduced pressure and the residue was extracted with dichloromethane twice. The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Column chromatography with 3:1 PE:EtOAc yielded 154 mg (72%) of **2**. ^{1}H NMR ($CDCl_3$): δ 2.42 (br s, 1H), 3.88 (dd, 1H, *J* = 2.9, 11), 4.31 (dd, 1H, *J* = 5.5, 11), 4.60-4.75 (m, 1H), 4.75-4.80 (m, 1H), 6.52 (s, 1H), 7.00-7.30 (m, 3H), 7.63 (d, 1H, J = 7.7). ^{13}C NMR ($CDCl_3$): δ 50.4, 64.7, 80.1, 96.7, 109.8, 120.0, 121.6, 122.3, 132.0, 133.0, 137.0. IR (NaCl): 3414, 3054, 2950, 2886, 2099, 1463, 1310, 1222, 1084 cm^{-1}. HRMS, (*m/z* M^+, $C_{11}H_{10}N_4O$); calcd. 214.0854, obsd. 214.0855.

With **11**: The vinylsulfonium salt **11** was freshly made and dried over P_2O_5 for 3 h under vacuum. A total of 80 mg (0.55 mmol) 2-indolecarboxaldehyde was added to a dry 50 mL 3-neck round-bottomed flask under a nitrogen atmosphere, dissolved in 5 mL dry THF, and cooled down to -8°C with an ice-salt bath. A total of 27 mg NaH (60% in mineral oil, 0.67mmol) was added to the reaction vessel in one portion After 10 min a clear yellow-brown solution was obtained and 200 mg of **11** (0.62 mmol) was added in one portion. The solution turned into a dark yellow color in one h. The reaction was monitored by tlc and after a further h, 400 mg NaN_3 (6 mmol) was dissolved in 5 mL deionized water and added to the reaction mixture. After 30 min the solvent was removed under reduced pressure and the residue was extracted with dichloromethane twice. The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Column chromatography with dichloromethane yielded 63 mg (54%) of **2** and 18 mg of **22** as a yellow oil (12%). **22**: ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 6H), 1.6-1.75 (m, 2H), 1.72 (s, 3H), 2.05-2,15 (m, 2H), 2.86 (t, *J* = 7.8 Hz, 2H), 4.6-4.75 (m, 4H), 7.15-7.25 (m, 2H), 7.28 (s, 1H), 7.4-7.45 (m, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 9.88 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.2, 28.6, 29.4, 33.4, 41.0, 45.8, 46.5, 110.1, 111.1, 118.7, 121.6, 123.9, 126.9, 127.5, 135.6, 140.7, 146.4, 182.9. IR (KBr): 2962, 2926, 1671 cm^{-1}. HRMS, *m/z* (M^+, $C_{19}H_{25}NOS$)

Calcd. 315.1657, obsd. 315.1649. Anal. Calcd. for $C_{19}H_{25}NOS$: C, 72.33; H, 7.99; N, 4.44; found: C, 72.28; H, 8.21; N, 4.24.

With **12**: To a dry 50-mL, 3-necked round-bottomed flask under a nitrogen atmosphere, 83mg (0.58 mmol) of indole-2-carboxaldehyde was added. It was dissolved in 10 mL dry THF and the reaction flask was cooled with an ice-salt bath to 0°C, then 32 mg (8 mmol) NaH (60% in mineral oil) was added in one portion. Hydrogen evolution took place for about 10 min, then 250 mg (0.69 mmol) of **12** was dissolved in 10 mL dry THF and added via cannula. The solution turned a yellow-brown color immediately. The reaction was monitored by tlc; after 45 min no indole-2-carboxaldehyde was left. The reaction was allowed to proceed for another 1 h and then 200 mg NaN_3 dissolved in 10 mL deionized water was poured into the reaction mixture. It was stirred vigorously for 1 h, then the reaction mixture was concentrated under reduced pressure and extracted with CH_2Cl_2 twice. The organic layers were combined and dried over anhydrous Na_2SO_4. After a vacum filtration, the filtrate was concentrated and then column chromatography with 3:1 PE/EtOAc gave 77 mg of **2** (62%).

2-(1-Azido-2-methylsulfonyloxy)ethyl-1-(2-methylthio)ethylindole (**9**): In a 100-mL round bottom flask, a total of 1.9 g (13 mmol) of indole-2-carboxaldehyde and 780 mg (26 mmol) of NaH (80% dispersion in mineral oil) was stirred in 150 mL of dry THF under nitrogen at 0°C. A total of 3.39 g (17.7 mmol) of dimethylvinylsulfornium iodide was added after 20 min, then the reaction mixture was stirred for 5 h. A total of 3.38 g of NaN_3 (50 mmol) in 20 mL of 1:1 acetone:water was added to the reaction mixture, then the reaction mixture was stirred at rt for about 6 h. The mixture was evaporated under reduced pressure, then extracted with dichloromethane three times. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product was used without further purification. It was dissolved in 10 mL of dry dichloromethane at 0°C. A total of 0.5 mL of triethylamine was added, followed by 500 mL of methanesulfonyl chloride. The reaction mixture was stirred at 0°C for 30 min. and then 10 mL of dichloromethane and 10 mL of water were added. The phases were separated, and the organic layer was washed with saturated $NaHCO_3$ (2 x 10 mL), water (1 x 10 mL). Then the organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (2:1 PE:EtOAc), giving two products: **8**[1] and the side product **9** whose characterization is as follows: ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H), 2.88 (t, J = 8 Hz, 2 H), 3.10 (s, 3H), 4.40 (t, J = 8 Hz, 2H), 4.59-4.63 (m, 2H), 5.10 (dd, J = 5.4, 7.2 Hz, 1H), 6.60 (s, 1H), 7.10-7.38 (m, 3H), 7.62 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 16.5, 34.2, 38.5, 44.2, 56.6, 69.3, 102.5, 110.0, 121.1, 122.0, 123.6, 127.7, 132.1, 137.3. IR (NaCl): 2917, 2103, 1350, 1172 cm^{-1}. MS (EI): *m/z* 354 (M^+), 312 ($M^+ - N_3$). Anal. Calcd. for $C_{14}H_{18}N_4S_2O_3$: C, 47.45; H, 5.08; N, 15.82. Found: C, 47.00; H, 5.08; N, 15.54.

Diisopropylvinylsulfonium trifluoromethanesulfonate (10):

Procedure A: A total of 1.46 g **14** (3.9 mmol) was dissolved in 10 mL deionized water in a 50 mL round-bottomed flask, and 928 mg Ag_2O (4.0 mmol) was added. The reaction mixture was stirred vigorously at room temperature for 40 h. The reaction mixture was filtered and washed with acetone. The water/acetone mixture was removed under reduced pressure and then dried overnight with P_2O_5 under vacuum to give 875 mg of a colorless oil (75%). ^{1}H NMR ($CDCl_3$): δ 1.54 (d, J = 6.7 Hz, 6H), 1.58 (d, J = 6.7 Hz, 6H), 4.17 (h, J = 6.7 Hz, 2H), 6.46 (d, J = 16.4 Hz, 1H), 6.64 (d, J = 8.9 Hz, 1H), 7.01 (dd, J = 8.9, 16.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ

17.6, 18.6, 45.7, 117.3, 141.8. IR (neat): 3052, 2983, 1464, 1397, 1261, 1225, 1155, 1032, 642 cm^{-1}. MS (FAB): *m/z* 145 (M^+). Anal. Calcd. for $C_9H_{17}F_3O_3S_2$: C, 36.72; H, 5.82; found: C, 36.14; H, 5.48.

Procedure B: To a flame-dried flask purged with nitrogen, add 2-bromoethyldiisopropylsulfonium trifluoromethanesulfonate (2.09 g, 6.09 mmol, 1.0 eq.) and 15 mL acetone. To this mixture, add activated 4Å molecular sieves (3.05 g) followed by Ag_2O (706 mg, 3.04 mmol, 0.50 eq.). Shield the reaction mixture from light with aluminum foil and stir in a dark hood for three days. Filter the olive green mixture was through a pad of Celite® and rinse the pad with acetone (25 mL). Remove the acetone *in vacuo* to obtain 1.66 g of an amber oil (93%). This material was sufficiently pure for subsequent use.

2,3,4,5-Tetrahydro-2,2,5,5-tetramethyl-1-vinylthiophenium trifluoromethanesulfonate (11): A total of 540 mg **15** (1.3 mmol) was dissolved in 10 mL deionized water in a 25 mL round-bottomed flask, and 460 mg Ag_2O (2.0 mmol) was added. The reaction mixture was stirred vigorously at room temperature for 50 h. The reaction mixture was filtered and washed with three 5-mL portions of dichloromethane. The filtrate was concentrated and the phases were separated. The aqueous layer was washed with ether and then lyophilized. A total of 400 mg (1.2 mmol) of a white crystalline solid was obtained (92%). Mp decomposed 111-112°C. ^1H NMR ($CDCl_3$): δ 1.67 (s, 6H), 1.78 (s, 6H), 2.2-2.4 (m, 2H), 2.55-2.75 (m, 2H), 6.47 (dd, J = 1.0, 16.2 Hz, 1H), 6.67 (dd, *J* = 1.0, 8.9 Hz, 1H), 7.16 (dd, *J* = 8.9, 16.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.6, 29.5, 43.1, 73.5, 119.1, 142.6. IR ($CHCl_3$): 3067, 2955, 1465, 1447, 1254, 1165, 1148, 1027 cm^{-1}. MS (FAB): *m/z* 171 (M^+). HRMS, (*m/z* $M^+ - 1$, $C_{10}H_{18}S^+$); Calcd. 170.1129, obsd. 170.1129.

Diphenylvinylsulfonium trifluoromethanesulfonate (12): To a dry 50-mL round-bottomed flask, 2.65 g (6.0 mmol) of **16** was added and dissolved in 5 mL THF and 5 mL deionized water, then 1.6 g Ag_2O (6.4 mmol) was added in one portion and stirred vigorously under a nitrogen atmosphere. After 10 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and the solution was eluted through a 1cm silica gel plug with 150 mL CH_2Cl_2. A total of 1.49 g of a colorless oil was obtained (69%). This material was used without further purification in the annulation reactions with indole-2- and pyrrole-2-carboxaldehyde. ^1H NMR ($CDCl_3$): δ 6.46 (dd, *J* = 1.4, 10.6 Hz, 1H), 6.70 (dd, *J* = 1.4, 6.0 Hz, 1H); 7.54 (dd, *J* = 6.0, 10.6 Hz, 1H); 7.65-7.75 (m, 6H); 7.8-7.85 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 123.4, 125.0, 130.6, 131.7, 134.8, 137.9. IR ($CHCl_3$): 3057, 2917, 1447, 1158, 1030 cm^{-1}. HRMS, (*m/z* M^+, $C_{14}H_{13}S^+$); Calcd. 213.0738, obsd. 213.0738.

Diphenylvinylsulfonium tetrafluoroborate (13): To a flame dried flask purged with nitrogen, a total of 628 mg (1.87 mmol, 1.0 eq.) of **17** was added, followed by the addition of 5 mL of acetone and 935 mg of 4Å molecular sieves. A total of 216 mg (0.93 mmol, 0.50 eq.) of silver (I) oxide was added and the reaction mixture was stirred under nitrogen at room temperature. After three days the once black reaction mixture had turned green. The solids were filtered through Celite® and washed with acetone (25 mL). After removing the solvent *in vacuo*, 545 mg of an off-white semisolid was isolated which was triturated with 30 mL of 10% acetone/ether at room temperature to -20°C under a nitrogen atmosphere. A total of 350 mg of an *extremely hydroscopic* off-white powder was isolated (62%). This material was handled in a glove bag under nitrogen and was used without further purification in the annulation reaction with **18** to form **19**. ^1H NMR ($CDCl_3$): δ 6.49,

(dd, J = 2.4, 16 Hz, 1 H), 6.66 (dd, J = 2.4, 8.8 Hz, 1 H), 7.28, (dd, J = 8.8, 16 Hz, 1 H), 7.75-7.61, (m, 6H), 7.85-7.79, (m, 4H). ^{13}C NMR ($CDCl_3$): δ 122.4, 125.0, 130.2, 131.4, 134.4, 138.3. IR (neat): 3636, 3560, 3105, 3067, 1580, 1572, 1474, 1444, 1390, 1277, 1057, 753, 685, 632 cm^{-1}. HRMS, (*m/z* M^+, $C_{14}H_{13}S^+$); Calcd. 213.0738, obsd. 213.0736.

2-Bromoethyldiisopropylsulfonium trifluoromethanesulfonate (14):

Procedure A: A total of 2.03 g (7.9 mmol) $TfOCH_2CH_2Br$ and 10 mL of dry dichloromethane were added to a 25 mL round-bottomed flask. Subsequently 944 mg (8.0 mmol) diisopropyl sulfide was added in one portion. The reaction mixture was stirred vigorously at room temperature for 72 h, during which the colorless solution became more and more sticky and turned a yellow-brown color. The solvent was removed *in vacuo*. The residue is washed by adding petroluem ether three times and then carefully removing the petroleum ether with a pipet. After removing the remaining solvent under reduced pressure, 2.94 g of a colorless oil was obtained (92%). ^{1}H NMR ($CDCl_3$): δ 1.63 (d, J = 6.8 Hz, 6H), δ 1.66 (d, J = 6.8 Hz, 6H), 3.79 (t, J = 6.1 Hz, 2H).), 4.00 (t, J = 6.1 Hz, 2H), 4.06 (h, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 18.8, 19.6, 27.1, 39.4, 46.0. IR (neat): 3566, 3509, 2986, 2942, 1464, 1398, 1384, 1278, 1152, 1033, 636 cm^{-1}. MS (FAB): *m/z* 225 (M^+), 227 (M^+ + 2), 183 (M^+ – CH_2=$CHCH_3$), 185 (M^+ + 2 – CH_2=$CHCH_3$), 145 (M^+ – HBr). Anal. Calcd. for $C_9H_{18}BrF_3O_3S_2$: C, 28.81; H, 4.83; found: C, 28.47; H, 4.89.

Procedure B: To a flame-dried flask purged with nitrogen, dissolve 2-bromoethyl trifluoromethanesulfonate (6.90 g, 26.8 mmol, 1.0 eq.) in 26 mL dry dichloromethane. Add diisopropylsulfide (3.90 mL, 26.8 mmol, 1.0 eq.) and cover the reaction flask with aluminum foil. Stir in a dark hood for seven days. Concentrate the reaction mixture *in vacuo*, pour into a separatory funnel containing 15 mL H_2O and 15 mL Et_2O and extract. Separate layers and back extract the aqueous layer with EtOAc (4 x 15 mL). Combine EtOAc layers and dry over Na_2SO_4. Filter and concentrate *in vacuo* to give 7.23 g of an amber oil (85%).

2-Bromoethyl-2,3,4,5-tetrahydro-2,2,5,5-tetramethylthiophenium trifluoromethanesulfonate (15): A total of 350 mg (2.4 mmol) 2,3,4,5-tetrahydro-2,2,5,5-tetramethylthiophene and 5 mL of dry dichloromethane were added to a 25-mL, round-bottomed flask under a nitrogen atmosphere. Subsequently 590 mg (2.3 mmol) $TfOCH_2CH_2Br$ was added in one portion and the reaction mixture was stirred vigorously at room temperature for 60 h, during which the solution became purple. The solvent was removed *in vacuo*. A purple solid was obtained which was washed with three 5 mL aliquots of petroleum ether to give 545 mg (1.4 mmol, 58%) of white solid. Mp decomposed 105°C. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 6H), 1,84 (s, 6H), 2.2-2.55 (m, 4H), 3.87 (t, J = 5.6 Hz, 2H), 4.06 (t, J = 5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 25.9, 26.9, 29.9, 39.5, 43.2, 72.6. IR ($CHCl_3$): 2953, 1461, 1263, 1150, 1031 cm^{-1}. MS (FAB): *m/z* 251 (M^+), 253 (M^+ + 2), 171 (M^+ – HBr). Anal. Calcd. for $C_{11}H_{20}BrF_3O_3S_2$: C, 32.92; H, 5,03; found: C, 32.72; H, 4.75.

2-Bromoethyldiphenylsulfonium trifluoromethanesulfonate (16): To a dry 50-mL round-bottomed flask, 2.0 g (7.8 mmol) of 2-bromoethyl trifluoromethanesulfonate and 1.45 g (7.8mmol) of diphenylsulfide were added and dissolved in 10 mL dry CH_2Cl_2. The reaction mixture was refluxed for 5 d under a nitrogen atmosphere. During the process, the colorless, transparent solution turned into a light black clear solution. The reaction mixture was concentrated *in vacuo* to a few mL, then 10 mL of anhydrous ether was

added and the heterogenous mixture was stirred vigorously to precipitate out the product. After vacum filtration and washing with a small amount of ether, 2.83 g of an off-white solid was obtained (82%). This material was used in the next reaction without further purification. Mp 86.5-88.0°C. ^{1}H NMR ($CDCl_3$): δ 3.72 (t, J = 5.8 Hz, 2H), 4.94 (t, J = 5.8 Hz, 2H), 7.7-7.8 (m, 6H); 8.1-8.15 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 24.0, 48.6, 122.7, 131.1, 132.0, 135.4. IR ($CHCl_3$): 3065, 2984, 2963, 1447, 1148, 1030 cm^{-1}. MS (EI): *m/z* 293 (M^+), 295 ($M^+ + 2$), 186 ($M^+ - CH_2CH_2Br$).

2-Chloroethyldiphenylsulfonium tetrafluoroborate (17): To an oven dried flask purged with nitrogen and equipped with a thermocouple and covered with aluminum foil to protect it from light, 1-chloro-2-iodoethane (5.33 g, 28.0 mmol, 1.05 eq.) was weighed out in the dark. Nitromethane (10mL) and diphenylsulfide (4.44 mL, 26.7 mmol, 1.0 eq) were added via syringe. A total of 5.45 g (28.0 mmol, 1.05 eq.) of silver (I) tetrafluoroborate was then added in one portion (immediately the reaction temperature rose to 40°C). After 20 h, the lime green reaction mixture was filtered through a pad of Florsil® and the pad was rinsed with ca. 25 mL of dichloromethane. After concentrating *in vacuo*, the filtration was repeated in order to remove additional solids not removed previously. After concentrating again, the brown residue was treated with 30 mL ether and shaken vigorously — a solid separated. A stir bar was added and this mixture was stirred for ca. 10 min. The ether was then decanted off and this procedure was repeated 3 times. The resulting solid was filtered off and washed with 2 x 25 mL ether. A total of 9.36 g was isolated as a slightly hydroscopic taupe solid in a quantitative yield. This crude material was used directly in the next step to form **13**. ^{1}H NMR ($CDCl_3$): δ 3.42, (t, J = 6.6 Hz, 2H), 4.70, (t, J = 6.6 Hz, 2H), 7.65-7.8, (m, 6H), 8.0-8.05, (m, 4H). ^{13}C NMR ($CDCl_3$): δ 48.3, 122.8, 130.9, 131.8, 135.1. IR (neat): 3443, 3093, 3024, 1474, 1446, 1182, 1047, 764, 748, 688 cm^{-1}.

Formation of **19** from **12**: To a flame-dried flask purged with nitrogen, **18** (31 mg, 0.069 mmol, 1.0 eq.), was dissolved in 1.0 mL dry THF and cooled to 0°C. A total of 3.6 mg of NaH (0.089 mmol, 1.3 eq.) was then added in one portion, yielding an amber solution. After 15 min, this anion was cooled to -40°C and a solution of **12** (32 mg, 0.089 mmol) in 0.50 mL dry THF was added dropwise. The resulting amber solution was allowed slowly warm to 10°C overnight. After 12 h, LiN_3 (17 mg, 0.034 mmol, 5.0 eq.) in 0.50 mL DMF was added. After stirring at ambient temperature for 12 h, the mixture was partitioned between ether (10 mL) and water (3 mL). The ether layer was separated and washed with brine (1 x 3 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purfication by preparative TLC (80:17:3 hexanes/CH_2Cl_2/EtOAc, 2 elutions) gave 14 mg (39%) of a yellow glass. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.16 (s, 6H), 0.17 (s, 6H), 1.02 (s, 9H), 1.05 (s, 9H), 2.19 (s, 3H), 3.68 (s, 3H), 4.17 (dd, J = 2.0, 11.6 Hz, 1H), 4.46 (dd, J = 4.8, 11.6 Hz, 1H), 4.65-4.70 (br m, 1H), 4.72 (d, J = 3.0 Hz, 1H), 6.50 (s, 1H). ^{13}C NMR ($CDCl_3$): δ -4.4, -3.1, 11.0, 18.6, 26.0, 53.1, 60.0, 64.0, 80.3, 95.8, 117.1, 125.2, 126.0, 133.6, 135.7, 136.2, 142.7. IR: 2099 (N_3), 3439 (broad, OH) cm^{-1}. Anal. Calcd. for $C_{25}H_{42}N_4O_4Si_2$: C, 57.88; H, 8.16. Found: C, 58.14; H, 7.99.

Formation of **19** from **13**: To a flame-dried flask purged with nitrogen, 165 mg (0.37 mmol, 1.0 eq.) of **18**[8] was dissolved in 2.5 mL dry THF and the reaction flask was cooled to 0°C. A total of 18.3 mg of NaH (0.46 mmol, 1.25 eq.) was then added in one portion resulting in an amber solution. After 15 min, this anion was

transferred via cannula to a mixture of **13** (132 mg, 0.44 mmol) in 2.5 mL dry THF at 0°C, followed by rinsing the cannula with another 1.5 mL of THF. The resulting dark brown solution was allowed to warm to room temperature overnight. After 15 h, 202 mg of sodium azide (3.12 mmol, 8.5 eq) in 3 mL of 1:1 acetone/water was added. After stirring at ambient temperature for 24 h, the mixture was concentrated under reduced pressure and purfied by prep tlc (65% dichloromethane/hexanes) to give 56 mg of **19** as an amber oil (30%).

1-(2-Isopropylthioethyl)pyrrole-2-carboxaldehyde (26) and **2-(1-Azido-2-hydroxy-2-methylpropyl)-1-(2-isopropylthioethyl)pyrrole-2-carboxaldehyde (27)**: A total of 190 mg (2 mmol) pyrrole-2-carboxaldehyde was added to a 50 mL, 3-necked round-bottomed flask under a N_2 atmosphere and dissolved in 5 mL dry THF. The reaction vessel was then cooled down to -5°C with an ice-salt bath and 100 mg NaH (60% in mineral oil, 2.5 mmol) was added. After 10 min a clear colorless solution was obtained (after H_2 evolution) and 550 mg (2.55 mmol) **10** was dissolved in 5 mL dry THF and added to the reaction flask via syringe. After a further 160 min (the reaction was monitored by tlc), 400 mg NaN_3 (6 mmol) was dissolved in 5 mL deionized water and added to the reaction mixture. The reaction mixture was stirred at room temperature overnight and then most of the THF was removed under reduced pressurse. Water was added and the aqueous layer was extracted with dichloromethane twice. The dichloromethane layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Column chromatograpy with 1:3 EtOAc:PE gave the rearrangement products **26** (43 mg, colorless oil) and **27** (102 mg, pale yellow oil) with yields of 11% and 18% respectively.[11] **26**: ^{1}H NMR ($CDCl_3$): δ 1.24 (d, J = 6.7 Hz, 6H), 2.81 (h, J = 6.7 Hz, 1H), 2.89 (t, J = 7.1 Hz, 2H), 4.47 (t, J = 7.1 Hz, 2H), 6.24 (dd, J = 2.5, 4.0 Hz, 1H), 6.95-7.05 (m, 2H), 9.54 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.9, 31.9, 35.5, 50.2, 110.1, 125.7, 132.5, 179.8. IR (KBr): 2958, 1726, 1664 cm^{-1}. MS (EI): *m/z* 197 (M^+), 168 ($M^+ - CHO$), 154 ($M^+ - C_3H_7$). Anal. Calcd. for $C_{10}H_{15}NOS$: C, 60.87; H, 7.67; N, 7.10; found: C, 61.17; H, 7.40; N, 6.58. **27**: ^{1}H NMR ($CDCl_3$): δ 1.25-1.3 (m, 12H), 1.88 (broad s, 1H), 2.84 (m, 1H), 2.85 (t, J = 7.4 Hz, 2H), 4.0-4.25 (m, 2H), 4.46 (s, 1H), 6.15-6.2 (m, 1H), 6.31 (dd, J = 1.7, 3.7 Hz, 1H), 6.73 (dd, J = 1.7, 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 23.4, 23.5, 26.4, 31.9, 35.4, 47.5, 66.3, 73.,8, 108.0, 109.6, 122.2, 126.1. IR (KBr): 3476, 2970, 2104 cm^{-1}. MS (CI): *m/z* 283 ($M^+ + 1$), 240 ($M^+ - N_2$). Anal. Calcd. for $C_{13}H_{22}N_4OS$: C, 55.29; H, 7.85; N, 19.84; found: C, 54.90; H, 7.62; N, 19.27.

1-(4,4,7-Trimethyl-3-thio-7-octenyl) pyrrole-2-carboxaldehyde (28): A total of 20 mg (0.21 mmol) pyrrole-2-carboxaldehyde was added to a 25-mL, 3-necked round-bottomed flask under a N_2 atmosphere and dissolved in 5 mL dry THF. The reaction vessel was then cooled down to -20°C with an ethylene glycol-dry ice bath and 11 mg NaH (60% in mineral oil, 0.28 mmol) was added. After 10 min a clear colorless solution was obtained (after H_2 evolution) and 82 mg (0.26 mmol) **11** was added to the reaction vessel. The reaction mixture was stirred at room temperature for 4 h and then 165 mg (2.5 mmol) sodium azide dissolved in 5 mL of deionized water were added. After 1 h most of the THF was removed under reduced pressure and the concentrated solution was extracted with dichloromethane three times. The dichloromethane layer was dried over anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure. Column chromatography with 1:4 EtOAc:PE gave 48 mg of **28** (84%). ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 6H), 1.55-1.65 (m. 2H), 1.71 (s, 3H), 2.0-2.15 (m, 2H), 2.85 (t, J = 7.0 Hz, 2H), 4.42 (t, J = 7.0 Hz, 2H), 4.65-4.7 (m, 2H), 6.21 (dd, J =

2.5, 4.0 Hz, 1H), 6.9-7.0 (m, 2H), 9.52 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.3, 29.2, 29.5, 33.4, 40.9, 46.4, 50.2, 110.0, 110.1, 125.7, 131.5, 132.6, 146.4, 179.7. IR (neat): 2957, 2928, 1728, 1463, 1274, 1124 cm^{-1}. MS (EI): *m/z* 265 (M^+), 196 ($M^+ - CH_2CH_2(C{=}CH_2)CH_3$). Anal. Calcd. for $C_{15}H_{23}NOS$: C, 67.88; H, 8.73; N, 5.28; found: C, 68.37; H, 8.90; N, 4.94.

1-(2-Formylpyrrolyl)-2,3-dihydro-2-hydroxy-1*H*-pyrrolizine (29): To a dry 50-mL round-bottomed flask under a nitrogen atmosphere, 76 mg (0.80 mmol) pyrrole-2-carboxaldehyde was added and dissolved in 10 mL dry THF. The reaction flask was cooled with an ice-salt bath to 0°C, then 38 mg (0.95mmol) NaH (60% in mineral oil) was added in one portion. A total of 300 mg (0.82 mmol) **12** was dissolved in 10 mL dry THF and added via cannula dropwise over 1 h. The solution turned pale yellow gradually. After 5 h, 280 mg NaN_3 was dissolved in 10 mL deionized water and poured into the reaction mixture, which was stirred at room temperature overnight. The reaction mixture was then evaporateded under reduced pressure and extracted with CH_2Cl_2 twice, the CH_2Cl_2 layers were combined and dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. After flash chromatography (5:3 hexanes:EtOAc), 12 mg of pyrrole-2-carboxaldehyde were recovered and 35 mg (20%) of **29** as a yellow oil were obtained. ^{1}H NMR ($CDCl_3$): δ 2.83 (s, 1H), 3.84 (dd, *J* = 7.0, 10.8 Hz, 1H), 4.30 (dd, *J* = 6.8, 10.8 Hz, 1H), 5.1-5.2 (m, 1H), 6.05-6.1 (m, 1H), 6.22 (dd, *J* = 2.7, 4.0 Hz, 1H), 6.27 (d, *J* = 5.9 Hz, 1H), 6.33 (t, *J* = 3 Hz, 1H), 6.55-6.6 (m, 1H), 6.77 (dd, *J* = 1.2, 2.7 Hz, 1H), 7.08 (dd, *J* = 1.7, 4.0 Hz, 1H), 9.56 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 50.3, 58.2, 75.6, 104.1, 110.1, 112.7, 113.0, 116.0, 126.6, 130.8, 132.7, 181.1. IR (NaCl): 3412, 2922, 1641 cm^{-1}. MS (CI): *m/z* 217 ($M^+ + 1$), 196 ($M^+ - H_2O$), 122 ($M^+ - C_5H_4NO$). HRMS, (*m/z* $M^+ - H_2O$, $C_{12}H_{10}N_2O$): Calcd. 198.0793, obsd. 198.0799.

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9. **24**: ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H), 2.83 (t, J = 7 Hz, 2H), 3.9-4.0 (m, 2H), 4.14 (t, J = 7 Hz, 2H), 4.56 (t, J = 5.6 Hz, 1H), 6.15-6.25 (m, 2H), 6.79 (dd, J = 1,8, 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 16.3, 36.0,

47.3, 59.2, 64.6, 108.6, 108.8, 123.5, 126.2. MS (EI): *m/z* 226 (M^+), 184 ($M^+ - N_3$). **25**: ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H), 2.84 (t, J = 6.8 Hz, 2H), 4.48 (t, J = 6.8 Hz, 2H), 6.2 (m, 1H), 6.9-7.05 (m, 2H), 9.52 (s, 1H). MS (EI): *m/z* 169 (M^+), 122 ($M^+ - SCH_3$), 108 ($M^+ - CH_2SCH_3$), 94 ($M^+ - CH_2CH_2SCH_3$). Anal. Calcd.. for $C_8H_{11}NOS$: C, 56.75; H, 6.55; N, 8.27; found: C, 56.78; H, 6.51; N, 8.07.

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11. Flushing the column with 5:95 methanol:dichloromethane produced what appeared to be the impure conjugate addition adduct shown below. This seemed to account for most of the rest of the mass balance.