

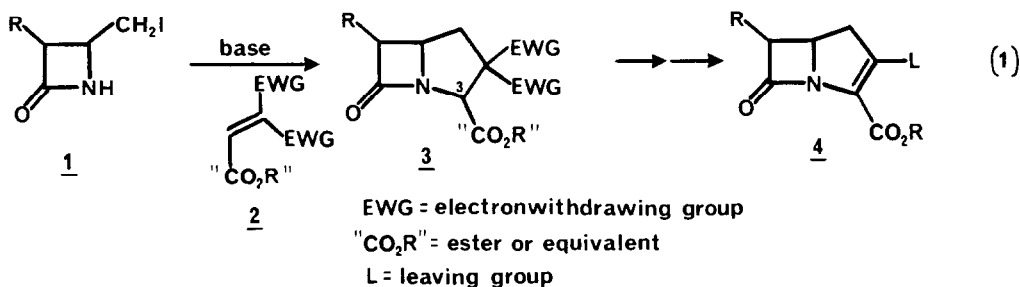
AN ALTERNATIVE APPROACH TO THE SYNTHESIS OF THE CARBAPENAM RING SYSTEM.  
 ALLENES AS ACCEPTOR-DONOR REAGENTS IN 3 + 2 ANNELATIONS

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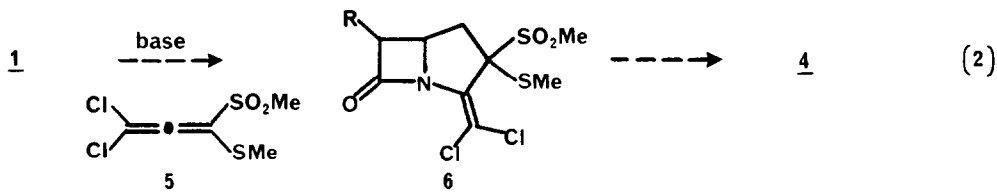
**Abstract:** 1,1-Dichloro-3-methylsulfonyl-3-methylthio-1,2-propadiene, generated *in situ* under basic conditions, reacted with a 4-iodomethylazetidione to give a carbapenam. Subsequent efforts to convert this material to a  $\Delta$ -2-carbapenam by rearrangement of an allylic sulfoxide led instead to the formation of a novel  $\Delta$ -1-carbapenam.

Recently several groups <sup>1,2</sup> have described syntheses of the carbapenam ring system via the base-promoted reaction of 4-iodomethylazetidiones 1 with Michael acceptors 2 (equation 1). Although appealingly simple, this approach has not yet evolved into a general carbapenam synthesis. A major problem lies in the choice of functional groups to be included in the Michael acceptor. These must impart the necessary reactivity to the double bond without making it prone to side reactions such as polymerization, provide the required regiochemical control in the addition-cyclization step, and then be open to any manipulations that may be required to transform the cyclized adduct 3 to the carbapenam 4<sup>3</sup>. With acceptors already containing an ester function (which becomes the C-3 carboxyl group in 3) it has been found<sup>1</sup> that the cyclization proceeds in low yield. When this ester group is replaced by an ester equivalent<sup>2</sup> which can later be oxidatively unmasked, the cyclization proceeds in high yield but the subsequent transformation of 3 to 4 proves to be unusually troublesome.



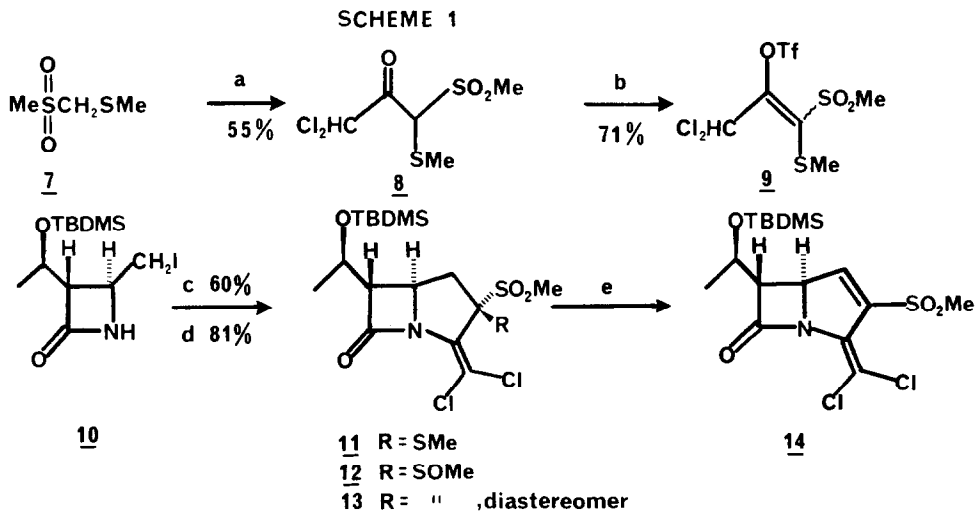
We would like to report the results of work undertaken to see if an allene such as 5 could be employed as an acceptor-donor reagent to prepare the carbapenam 6 (equation 2). It

was thought that 6 could be transformed to the carbapenem 4 in a two step sequence involving oxidation to give a sulfoxide which might subsequently be induced to undergo a 'self-immolative' [2,3] sigmatropic arrangement<sup>4</sup> in the presence of an alcohol and an acid scavenger.



To prepare the allene 5, we examined the following route<sup>5</sup> (Scheme 1). The anion of the Ogura-Tsuchihashi reagent<sup>6</sup> 7 was allowed to react with ethyl 2,2-dichloroacetate to give the ketone 8. Treatment of 8 with triflic anhydride followed by base afforded the enol triflate<sup>7</sup> 9 as a single isomer. It was anticipated that treatment of 9 with an additional equivalent of base would effect the elimination of triflic acid to give 5. Although this did lead to a new compound (single isomer) whose elemental analysis and <sup>1</sup>H n.m.r. spectrum [(acetone *d*<sub>6</sub>) δ 2.60 (s) and 3.33 (s), integrating 1:1] were consistent with the structure 5 this material did not exhibit the characteristic allene absorption in its i.r. spectrum. Evidently we had obtained a dimer<sup>8</sup> of 5 but it was not possible to assign a structure on the basis of our spectral data.

Unable to obtain the free allene, we investigated the possibility of generating it directly in the presence of the azetidinone<sup>9</sup> 10 to see if it could be trapped in the desired manner before undergoing dimerization. This led to the observation that addition of powdered

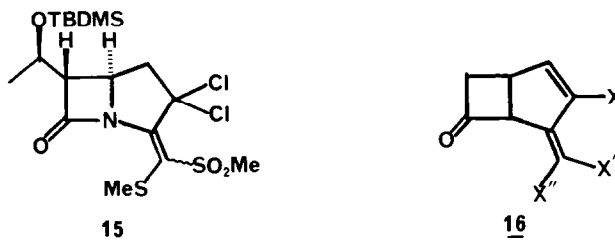


a) THF, *n*-BuLi (1.0 equiv.), -78° then ethyl 2,2-dichloroacetate (1.0 equiv), -78° + 0°. b) CH<sub>2</sub>Cl<sub>2</sub>, -20°, Tf<sub>2</sub>O (1.1 equiv.), then EtN(*i*-Pr)<sub>2</sub> (1.1 equiv.), -20° + R.T. c) DME, 9 (1.1 equiv.), (*n*-Bu)<sub>4</sub>NBr (0.1 equiv.), powdered KOH (3.0 equiv.), 1.5 h, 0°, d) CH<sub>2</sub>Cl<sub>2</sub>, *m*-chloro-perbenzoic acid<sup>4</sup> (1.0 equiv.), -20° + R.T. e) CCl<sub>4</sub> reflux; 12 with cyclohexene (1.0 equiv), 1.5 h, 60 + 70% yield; 12 with trimethylphosphite (1.0 equiv.), 1.5 h, 63% yield; 13 with cyclohexene (1.0 equiv.), 1.5 h, 50% yield.

potassium hydroxide to a stirred, ice-cooled solution of 10, the enol triflate 9, and a phase transfer catalyst<sup>10</sup>, gave the carbapenam<sup>7</sup> 11 as a single diastereomer in a 60% yield<sup>11</sup>. The assignment of the configuration at C-2 remains tentative but it seems reasonable that cyclization to give a product with the bulky sulfone group in an *exo* orientation would be energetically more favorable. The alternative structure 15 can be excluded from consideration in view of the subsequent chemistry.

We proceeded to examine the proposed transformation (6 + 4) with 11. Peracid oxidation of 11 gave a 5:1 mixture of sulfoxide diastereomers<sup>7</sup> 12 and 13 which could be separated by chromatography. However, upon being heated in carbon tetrachloride, it was found that both sulfoxides under went a facile elimination<sup>12</sup> of methanesulfenic acid to give the diene<sup>7</sup> 14 rather than products resulting from a [2,3] sigmatropic rearrangement. It is difficult to account for this result in view of the diverse array of substituents attached to the allylic system; molecular models do not reveal any unusual features which might prevent either sulfoxide diastereomer from adopting a conformation suitable for rearrangement. Possibly, delocalization of the lone pair of electrons on the nitrogen atom into the allylic system raises the energy required for rearrangement and thereby allows the competing elimination reaction to predominate.

The diene 14 is similar to intermediates<sup>13</sup>, (i.e., 16) which were converted to cyclobutane analogs of carbapenems by hydrolysis of the heteroatom-substituted exocyclic double bond. Similar efforts with 14 or 11 are being examined<sup>14</sup>.



**Acknowledgement.** We would like to thank Professor T. Durst for providing us with the results of his work prior to their disclosure<sup>2</sup> and also we would like to thank him, Professor B. Belleau, Dr. A. Martel, Dr. E. Ruediger and Dr. J. Philips for helpful discussions.

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2. T. Durst, 'Bicyclic  $\beta$ -Lactams via Michael Addition-Cyclization Sequences' paper presented at 67th Annual CIC Conference, Montreal, Canada, June 3, 1984.
3. Intermediate 4 is useful for the synthesis of thienamycin analogs. For examples where the leaving group is a sulfinyl or a sulfonyl group see respectively: K. Yamamoto, T. Yoshioka, Y. Kato, K. Isshiki, M. Nishino, F. Nakamura, Y. Shimauchi, T. Ishidura, *Tetrahedron Lett.* 1982, 897 and Jap. Patent 58/157788, 9 Sept. 1983 (*Chem. Abstr.* 1984, 100, 120773j).
4. P.T. Lansbury, R.W. Britt, *J. Amer. Chem. Soc.*, 1976, 98, 4577.
5. In preliminary work, we developed this procedure to prepare the allene i [i.r. (neat) 1950  $\text{cm}^{-1}$ ] from ethyl acetate. For a related synthesis of allenes involving the elimination of triflic acid from enol triflates, see: T.W. Doyle, J.L. Douglas, B. Belleau, T.T. Conway, C.F. Ferrari, D.E. Horning, G. Lim, B. Luh, A. Martel, M. Menard, L.R. Morris, M. Misiak, *Can. J. Chem.*, 1980, 58, 2508.



6. K. Ogura, M. Suzuki, G. Tsuchihashi, *Bull. Chem. Soc.* 1980, **53**, 1414. For recent work describing the condensation of reagents of this type with esters, see: K. Ogura, N. Yahata, K. Takahashi and H. Iida, *Tetrahedron Lett.* 1983, 5761.
7. Satisfactory elemental analyses (where possible) and spectral data were obtained for all new compounds. Selected physical and spectral data follow. **9**: m.p. 132-133°C; u.v. (EtOH) 216 ( $\epsilon$ 7900), 316 ( $\epsilon$ 1400) nm; i.r. (CHCl<sub>3</sub>) 1340, 1140 cm<sup>-1</sup>; <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>)  $\delta$  2.65 (s, 3H), 3.24 (s, 3H), 7.29 (s, 1H). **11**: m.p. 145-146°C;  $[\alpha]_D^{23}$ -30.5° (CH<sub>2</sub>Cl<sub>2</sub>, c 1.0); u.v. (EtOH)  $\lambda_{\max}$  256 ( $\epsilon$ 9400) nm; i.r. (KBr) 1790, 1300, 1135 cm<sup>-1</sup>; <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>)  $\delta$  0.08 (s, 6H), 0.91 (s, 9H), 1.18 (d, 3H, J=7.7 Hz), 3.01 (dq, 2H,  $\delta_A$ =3.20,  $\delta_B$ =2.81, J<sub>AX</sub>=3.3 Hz, J<sub>BX</sub>=10.4 Hz, J<sub>AB</sub>=15.7 Hz), 3.26 (s, 3H), 3.48 t, 1H, J=3.6 Hz), 4.25 (m, 2H, w/2=12 Hz). **14**: m.p. 166-167°C;  $[\alpha]_D^{23}$  + 5.7 (CH<sub>2</sub>Cl<sub>2</sub>, c 0.5); u.v. (EtOH)  $\lambda_{\max}$  296 ( $\epsilon$ 6500) cm<sup>-1</sup>; i.r. (film) 1785, 1320 cm<sup>-1</sup>; <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>)  $\delta$  0.09 (s, 6H), 0.90 (s, 9H), 1.24 (d, 3H, J=6.2 Hz), 3.25 (s, 3H), 3.34 (t, 1H, J=3.6 Hz), 4.35 (dq, 1H, J=6.2, 3.6 Hz), 4.73 (dd, 1H, 3.6, 2.0 Hz), 7.54 (d, 1H, J=2.0 Hz). The sulfoxides **12** and **13** were unstable oils and were characterized as follows: **12**: Rf 0.37 (silica gel; EtOAc: hexane, 1:1); i.r. (KBr) 1790, 1320, 1140, 1075 cm<sup>-1</sup>; <sup>1</sup>Hnmr (CDCl<sub>3</sub>)  $\delta$  0.07 (s, 6H), 0.88, (s, 9H), 1.22 (d, 3H, J=6.3 Hz), 2.88 (s, 3H), 3.1 (m, 3H) 3.13 (s,3H), 4.2 (m, 2H), **13**: Rf 0.18 (silica gel; EtOAc: hexane, 1:1); i.r. (KBr), 1795, 1320, 1140, 1075 cm<sup>-1</sup>; <sup>1</sup>Hnmr (CDCl<sub>3</sub>) 0.09 (s, 6H), 0.89 (s, 9H), 1.23 (d, 3H, J=6.2 Hz), 2.67 (s, 3H), 2.71 (dd, 1H, J=16.4, 6.0 Hz), 3.18 (s, 3H), 3.37 (dd, 1H, J=16.4, 8.3 Hz), 3.42 (dd, 1H, J=4.3, 2.6 Hz), 4.14 (ddd, 1H, J=2.6, 8.3, 6.0 Hz), 4.27 (dq, 1H, J=6.2, 4.3 Hz).
8. For observations regarding the rates of dimerization of a variety of 1,1-dichloro-3,3-disubstituted allenes, see: A. Roedig, W. Ritschel, *Chem. Ber.* 1982, **115**, 3324.
9. K. Hirai, Y. Iwano, K. Fujimoto, *Tetrahedron Lett.*, 1982, 4025.
10. For the N-alkylation of azetidiones using phase transfer conditions, see: D. Reuschling, H. Pietsch, A. Linkies, *Tetrahedron Lett.*, 1978, 615; P.G. Mattingly, M.J. Miller, *J. Org. Chem.*, 1981, **46**, 1557.
11. The yield of **11** was found to be quite solvent dependent. The choice of DME as solvent was the result of a quick HPLC study (yield of **11** with solvents examined: DME >CH<sub>3</sub>CN >THF >> DMF). The only other product that we could isolate from the reaction mixture was a trace amount of the allene dimer.
12. The ease with which this elimination occurred is surprising. For instance,  $\alpha$ -methylsulfinyl esters require prolonged heating at higher temperatures (ca. 110°C) to be converted to  $\alpha,\beta$ -unsaturated esters: B.M. Trost, T.N. Saltzman, K. Hiro, *J. Amer. Chem. Soc.*, 1976 **98**, 4887.
13. E.M. Gordon, J. Pluscec, M.A. Ondetti, *Tetrahedron Lett.*, 1981, 1871; T. Cocuzza, 'Cyclobutanone Analogs of  $\beta$ -Lactam Antibiotics' paper presented at the Spring Synthesis Symposium of the Ottawa-Carlton Institute for Research and Graduate Studies in Chemistry, Ottawa, Canada, May 23, 1984.
14. Due to the instability of **14** (significant decomposition at -20° after several days), we have concentrated our efforts on converting the dichlorovinyl group in **11** to a carboxyl function. Existing procedures for this type of transformation involve harsh conditions (strong acid hydrolysis; C.A. Buehler, D.E. Pearson, 'Survey of Organic Synthesis' vol.1, Wiley-Interscience, New York, 1970, p. 755) which the  $\beta$ -lactam ring would not be expected to survive. Attempts to find some milder alternative have been unsuccessful to date. Under the following conditions only unreacted **11** was recovered: treatment with PdCl<sub>2</sub> catalytic) and NaOAc (excess) in CH<sub>3</sub>CN at 60° for 24 h (cf. M. Julia, C. Blasioli, *Bull. Soc. Chim. Fr.*, 1976, 1941); photolysis with  $\phi S_2$  in benzene; treatment with Hg(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub> in CH<sub>3</sub>CN. Peracid oxidation (MCPBA, 3 equiv., in CH<sub>2</sub>Cl<sub>2</sub> at R.T. for 16 h) gave the bi-sulfone analog of **11**.

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