5-aminovaleric acid, 660-88-8; allylamine, 107-11-9; isobutylamine, 78-81-9; diethylamine, 109-89-7; benzylamine, 100-46-9; piperidine, 110-89-4; *N*-allylcyclohexanecarboxamide, 70659-83-5; *N*-isobutylcyclohexanecarboxamide, 70659-84-6; *N,N*-diethylcyclohexanecarboxamide, 5461-52-9; *N*-benzylcyclohexanecarboxamide, 35665-26-0; *N*-allyloctanamide, 70659-85-7; *N*-isobutyloctanamide, 70659-86-8; *N,N*-diethyloctanamide, 996-97-4; *N*-benzyloctanamide, 70659-87-9; 1-octanoylpiperidine, 20299-83-6; *N*-allylbenzamide, 10283-95-1; *N*-isobutylbenzamide, 5705-57-7; *N,N*-diethylbenzamide, 1696-17-9; *N*-benzylbenzamide, 1485-70-7; *N*-allyl-*p*-chlorobenzamide, 5866-99-9; *N*-isobutyl-*p*-chlorobenzamide, 7461-33-8; *N,N*-diethyl-*p*-chlorobenzamide, 7461-38-3; *N*-benzyl-*p*-chlorobenzamide, 7461-34-9; *N*-benzyl-*p*-methoxybenzamide, 7465-87-4; 2-pyrrolidinone, 616-45-5; hexahydro-2*H*-azepin-2-one, 105-60-2; 2-piperidinone, 675-20-7.

Communications

Studies in Macrolide Synthesis: Control of Remote Stereochemistry by Sulfenic Acid Cyclization and 2,3-Sigmatropic Ring Expansion

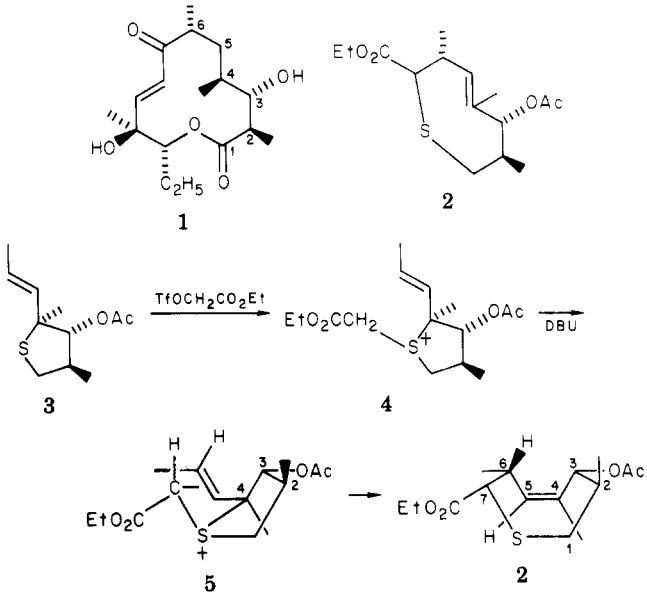
Summary: Three asymmetric centers are generated stereospecifically by cyclization of a γ,δ-unsaturated sulfenic acid derivative, **7**, to give an α-alkenyl tetrahydrothiophene, **9a**, the starting material for stereospecific synthesis of a 4-thiacyclooctene, **2**.

Sir: Synthetic approaches to macrolide antibiotics must solve the difficult problem of stereochemical control at remote asymmetric centers. In this communication we outline the construction of a sulfur heterocycle **2** which incorporates the C_1–C_7 segment of methynolide **1** with the natural stereochemistry at C_2, C_3, and C_6. Our main purpose is to describe a synthesis of the tetrahydrothiophene **3** by a remarkably stereospecific sulfenic acid cyclization and to show that the C_4 stereochemistry of **3** can be transformed into the C_6 stereochemistry of **2** (Scheme I). The latter process is achieved by taking advantage of the predictable geometry of 2,3-sigmatropic ring expansion reactions.[1] A description of strategy for conversion of **2** into methynolide precursors will be deferred to subsequent publications.

Ylides derived from α-alkenyl tetrahydrothiophenes rearrange to 4-thiacyclooctenes.[1a] The major product from stabilized ylides is invariably the cis double bond isomer of an eight-membered ring, so the transition state geometry for ylide ring expansion can be drawn as the tub conformation **5**. The required cisoid propenyl rotamer is then constrained to rearrange to **2** with predictable stereochemistry at C_6 as shown. It is the relative stereochemistry of C_4 with respect to C_3 and C_2 which ultimately controls C_6; if C_4 were inverted, it would be necessary to use an analogue of **5** having a *cis*-propenyl group to afford the same stereoisomer **2**. Inspection of **5** suggests that C_7 geometry can also be predicted since the ester will undoubtedly prefer an exo orientation with respect to the bicyclo[3.3.0]octane-type transition state.

The synthesis of **3** is outlined in Scheme II. A sulfenic acid precursor **6** is available by a simple, precedented sequence which controls the geometry of the trisubstituted double bond.[2] Slow addition of **6** to refluxing 1:1 acetic acid–acetic anhydride (boron trifluoride etherate catalyst) gives a single volatile product **9a** (81%) isolated by simple distillation. As shown by Morin and co-workers, thermolysis of *tert*-alkyl sulfoxides in acetic anhydride generates sulfenic acetates via initial fragmentation to the sulfenic acid.[3] Electrophilic addition of the sulfenic acetate **7** to the internal double bond is responsible for the formation of **9a**.

Scheme I



To convert acrylate derivative **9a** into the desired α-propenyl tetrahydrothiophene structure, a two-stage operation was performed. First, methanolysis of the acetate (K_2CO_3) and alcohol protection (dihydropyran, TsOH) gave **9b**. Without isolation of intermediates, **9b** was reduced (DIBAL) to an allylic alcohol and mesylated (BuLi; MsCl), and the sensitive allylic mesylate was converted into a propenyl derivative **9c** by $Li^+Et_3{}^-BH$[4] (35% overall from **9a**).

The crucial cyclization of sulfenic acetate **7** was expected to give **9a** according to the following argument. Morin cyclizations are believed to involve episulfonium ion intermediates,[3] and two such species, **8A** and **8B**, are possible depending on which face of the double bond is attacked by electrophilic sulfur. The undesired intermediate **8B** is strongly destabilized relative to **8A** by a severe *endo*-methyl–*endo*-methyl interaction, and also suffers from steric congestion along the path for S_N2 attack by acetate

(1) (a) E. Vedejs, J. P. Hagen, B. L. Roach, and K. L. Spear, *J. Org. Chem.*, **43**, 1185 (1978); (b) E. Vedejs, M. J. Arco, D. W. Powell, J. M. Renga, and S. P. Singer, *ibid.*, **43**, 4831 (1978).

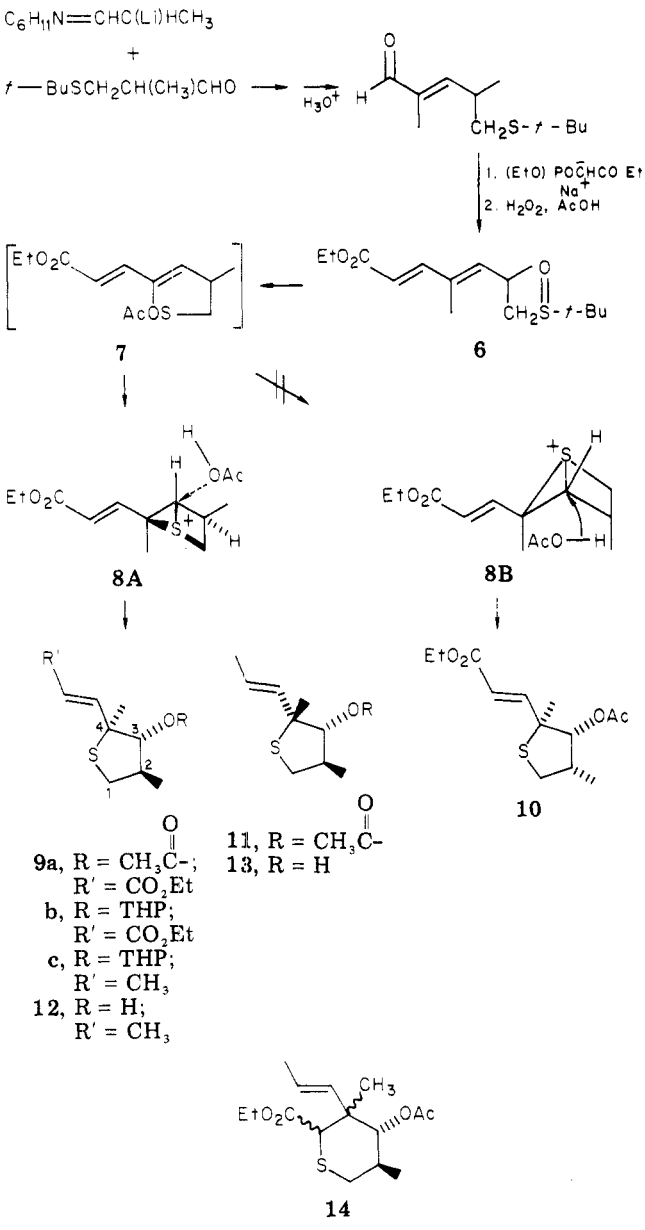
(2) G. Wittig, *Top. Curr. Chem.*, **67**, 1 (1976); G. Wittig and H. Reiff, *Angew. Chem., Int. Ed. Engl.*, **7**, 7 (1968).

(3) R. B. Morin, B. G. Jackson, R. A. Muller, E. R. Lavagino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969); see also D. O. Spry, *ibid.*, **92**, 5006, 5010 (1970); R. R. Chanvette, P A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heymingen, and G. W. Juffman, *J. Org. Chem.*, **36**, 1259 (1971).

(4) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **41**, 3064 (1976).

0022-3263/79/1944-2947$01.00/0

Scheme II

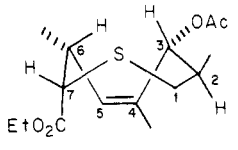


at C_3. No sign of the corresponding isomeric cyclization product **10** has been detected, nor can we find elimination products which might reflect involvement of carbonium ions.

The acrylate **9a** is reasonably stable to the conditions of cyclization and shows no tendency for stereochemical change. However, derivatives having the propenyl side chain are much more susceptible to acid-induced equilibration.[5] Thus, α-propenyltetrahydrothiophene **3** (available from **9c** by protecting group manipulation) interconverts with an isomer when exposed to the conditions of sulfenic acetate cyclization. The new isomer is assigned structure **11** because its HC_2–C_3H J value of 10.5 Hz is identical with the analogous coupling constants for tetrahydrothiophenes **9a–c**, **3**, and **12**. In all of these structures, the conformation which minimizes eclipsing interactions of ring substituents results in an HC_2–C_3H dihedral angle close to 180°. The corresponding angle for **10** is ca. 30°, and a much smaller J value would be expected.

A europium-induced shift comparison between the isomeric alcohols **12** (desired) and **13** confirms all of the stereochemical assignments. Thus, both ring methyls of **13** are shifted to a smaller extent ($\Delta\delta$ for C_4–CH_3 = 2.73 ppm; $\Delta\delta$ for C_2–CH_3 = 3.77 ppm), consistent with both methyls trans to OH. In the correct stereoisomer **12**, the europium effect on the methyl group cis to OH is considerably larger ($\Delta\delta$ for C_4–CH_3 = 4.45 ppm; $\Delta\delta$ for C_2–CH_3 = 2.51 ppm) as expected.

Ring expansion of **3** by successive S-alkylation ($CF_3SO_3CH_2CO_2C_2H_5$)[6] and ylide generation (DBU) affords **2** as the major product (ca. 40% over two steps). No isomeric thiacyclooctenes can be detected among the products. However, an inseparable mixture of at least two isomers which retain an unrearranged propenyl group is also isolated (10–15% each). Tentatively, these substances are presumed to be diastereomeric Stevens rearrangement products **14**.[7] Assignment of stereochemistry to **2** is based on the transition state argument mentioned earlier, and is supported by available NMR evidence. A conformation which minimizes transannular interaction of substituents nicely accounts for the observed vicinal coupling constants.



$J_{2,3}$ = 10.5 Hz
$J_{5,6}$ = 8.1 Hz
$J_{6,7}$ = 3.0 Hz

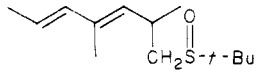
2

The stereochemical control which has been achieved is presumed to result from conformational preferences in the formation of strained bicyclic episulfonium intermediates. We suggest that similar steric interactions will control stereochemistry in any cyclization process which forms a five-membered ring by net trans addition to an endocyclic double bond. Interesting examples of relevant stereospecific cyclization to form five-membered iodo ethers or iodo lactones have been reported recently.[8,9]

Acknowledgments. This work was supported by grant GD 43891X from the National Science Foundation.

Registry No. **2**, 70775-45-0; **3**, 70775-46-1; **6**, 70775-47-2; **7**, 70775-48-3; **9a**, 70775-49-4; **9b**, 70775-50-7; **9c**, 70775-51-8; **10**, 70775-52-9; **11**, 70775-53-0; **12**, 70775-54-1; **13**, 70775-55-2; **14**, 70775-56-3; $CF_3SO_3CH_2CO_2C_2H_5$, 61836-02-0.

(5) Equilibration probably occurs by way of acid-catalyzed regeneration of episulfonium salt **8A** and reversible S–C_4 cleavage to give a tertiary allylic carbonium ion. In **9a**, the inductive effect of the carboethoxy group inhibits carbonium ion formation and equilibration does not take place.



i

The equilibration process is also observed when dienyl sulfoxide i is subjected to conditions of sulfenic acid generation. Inevitably, mixtures of **3** and **11** are formed from i.

(6) E. Vedejs, D. A. Engler, and M. J. Mullins, *J. Org. Chem.*, **42**, 3109 (1977).

(7) For a review of Stevens rearrangement, see B. M. Trost and L. S. Melvin, Jr., "Sulfur Ylides; Emerging Synthetic Intermediates", Academic Press, New York, 1975, Chapter 7.

(8) P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978); E. J. Corey and T. Hase, *Tetrahedron Lett.*, 335 (1979).

(9) Related examples of stereospecific cyclization to form five-membered bromosulfides have also been reported, although the mechanistic details may be somewhat different: P. N. Confalone, G. Pizzolato, E. G. Baggiolini, D. Lollar, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **99**, 7020 (1977).

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Received May 8, 1979