Sulfur-Mediated Ring Expansions in Total Synthesis

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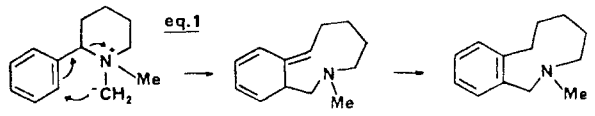
About 10 years ago, we began a study of sulfur-mediated 2,3-sigmatropic ring expansions and their use in complex synthesis. No rearrangements of this type had been observed with cyclic sulfides, but the analogous acyclic process was well known and there was a precedent in the Sommelet–Hauser ring expansion of nitrogen ylides (eq 1).[1] Soon we were able to show that α-alkenylthiacycloalkanes ring expand efficiently and provide rapid access to medium and large ring sulfides (eq 2).[2]



Our first intentions were goal oriented, and for good reason. None of the macrolide antibiotics had yet been synthesized; macrocyclizations were limited to a few special cases; and syringe pumps were an oddity.

The timing could not have been better. Within a few months, methynolide was synthesized by Masamune et al. and the first papers on the Corey macrolactonization method appeared. By 1976, the first few examples were published of the many challenging macrocycles to be reproduced synthetically,[3] and it was time to reevaluate our project to define what might be learned that had implications beyond any specific sequence or target molecule. We decided to view strategy as a tool, not as a goal or a science, and to concentrate on issues that had emerged from our early experiments. There would be an important element of complex synthesis for the unequaled stimulation and variety of experience that it provides, but strong goal orientation would be reserved for those structures that we might need to answer specific questions.

We became especially intrigued by an inherent feature of the ring-expansion approach to complex synthesis. In those examples where this technique is directed at natural products or their subunits, intermediates of unusual ring size and functionality are encountered at an early stage and thereafter. The inevitable "conventional steps" are performed on highly unconventional ring systems about which much remains to be learned regarding conformation, stereochemistry, and reactivity.

From the preparative point of view, it was clear from the start that no likely target structure would contain sulfur. It would be necessary to develop general methods for sulfur removal in a complex environment and to use these for the transition from a cyclic sulfide to a lactone, carbocycle, etc. We did not anticipate that our work would also require an intensive reexamination of sulfur alkylation methodology and thioaldehyde chemistry.

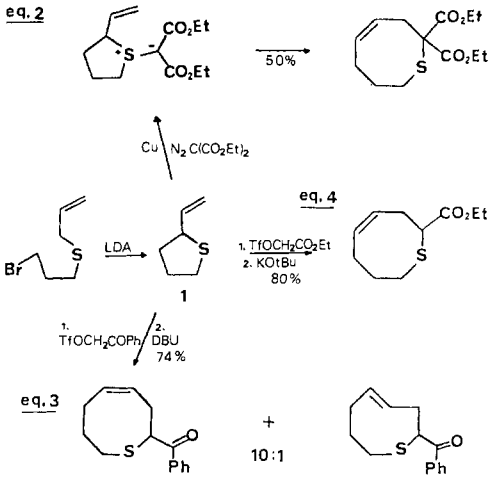
Edwin Vedejs was born in Riga, Latvia, on January 31, 1941. His family emigrated to Germany (1944) and then to the U.S. in 1950. Professor Vedejs received his B.S. from the University of Michigan and his Ph.D. from Wisconsin with H. Muxfeldt. After a postdoctoral year with E. J. Corey, he returned to Wisconsin (1967). His other research interests include ylides of S, N, and P, unusual rings and functional groups, and stereochemistry.

Table I
$CF_3SO_3CH(R)X$

entry	1	2	3	4
triflate subst	R = H, X = CO_2Et	R = H, X = CN	R = CH_3, X = CO_2Et	R = CH_3, X = COC_2H_5

Simple Systems: Basic Principles

The first ring expansion (eq 2) on a sulfur substrate was performed by using the carbenoid route to sulfur ylides from copper-catalyzed diazomalonate decomposition.[2] This was not entirely by choice. Our plans had focused on stabilized sulfur ylides in order to avoid strongly basic conditions, but we found that standard α-halo esters or ketones were useless for alkylation of α-alkenylthiacycloalkanes such as 1 due to nucleophilic dealkylation of the sulfonium salt by halide ion. Although the diazo decomposition route now appears quite promising from the recent work by Doyle et al. using rhodium catalysts,[4] our efforts to optimize the copper-catalyzed reaction were not successful. The diazo esters worked to some extent, but diazoketones did not.



A general and completely reliable route to stabilized ylides was essential for basic studies and perhaps also for complex applications. We soon found that triflate alkylating agents solved the problem. None of those listed in Table I had been made before, but all are easily prepared from the corresponding alcohols by the standard triflic anhydride method.[5] The important

(1) Lednicer, D.; Hauser, C. R. *J. Am. Chem. Soc.* **1957**, *79*, 4449.
(2) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878.
(3) Reviews: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem.* **1977**, *89*, 602. Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683.
(4) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917.
(5) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

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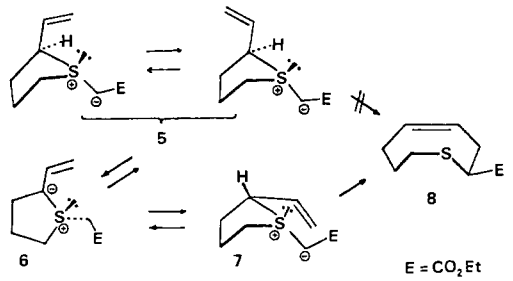
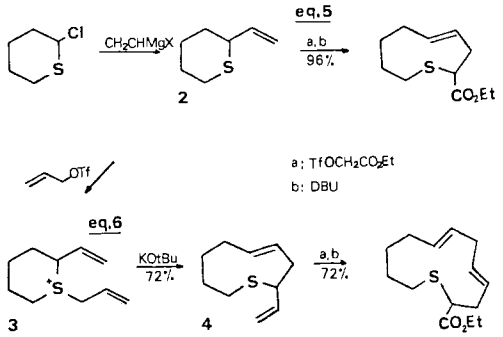


Figure 1.

entry 1 is more easily available from triflic acid and ethyl diazoacetate. The triflates are reasonably stable, far more reactive than the corresponding bromides, and far less lachrymatory. Most important, the derived sulfonium salts are not dealkylated by the nonnucleophilic triflate ion.

As shown in eq 3–6, the triflate-alkylation method followed by deprotonation with the amidine base DBU allows efficient ring expansion in virtually any ring size.[6,7] In the special case of eq 6, allyl triflate is used to initiate a sequence of ring expansions.[7] Here, the initial product **4** has the same α-vinyl functionality as the starting material **2**, and the 2,3-shift can be easily repeated as often as desired. Similar experiments by Schmid and Schmid have made available cyclic sulfides of up to 17 members.[8] The deprotonation step from **3** is best performed with a bulky base to ensure exocyclic ylide formation.



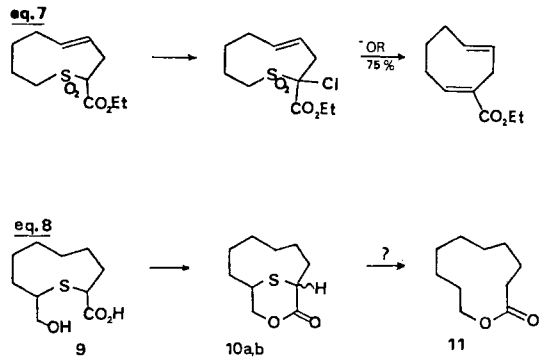
The stereochemical consequences of typical ring expansions feature the same strong preference for (*E*)-alkene formation as seen in acyclic analogues, provided that the starting sulfide is a reasonably flexible ring of at least six members. The underlying principles are not so simple as may be appreciated by considering the five-membered ring system where sulfur stereochemistry cannot be ignored.

As shown in eq 2–4 the product eight-membered rings prefer the (*Z*)-olefin geometry, but *E* isomers can also be formed, especially in the nonstabilized ylide systems studied by Fava et al.[9,10] This is a problem because the starting sulfonium salts, and therefore, also the ylide **5**, have trans vinyl and alkyl groups due to kinetically controlled alkylation at sulfur and cannot possibly rearrange to (*Z*)-olefins by a concerted process. The necessary orbital interactions are not geometrically feasible.

Rearrangement to the (*Z*)-olefin **8** requires the cis disubstituted ylide **7** (Figure 1). It has been shown that conversion of **5** to the cis isomer **7** involves equilibration via the less stable endocyclic ylide **6**.[6a,10] Diastereomer interconversion by pyramidal inversion at sulfur is also possible in principle but is not fast enough to compete at 20 °C or below where these reactions are usually performed. The exact origin of (*E*)-olefin side-products has not been determined in all cases, but both ylide diastereomers could adopt the necessary transoid conformation.

In summary, the familiar generalization that 2,3-shifts prefer (*E*)-olefin products can be applied to ring expansions unless the starting sulfide is a five-membered ring or has a strong conformational bias. In these special cases, one must consider the stereochemistry carefully. Rearrangement may be slow relative to diastereomer equilibration.

The time had come to consider how cyclic sulfides might be converted into other interesting ring systems. For relatively simple carbocycles, the familiar Ramberg–Backlund sulfur extrusion method proved quite convenient, especially in the case of the strained cis,-trans 1,4-cyclooctadienoate ester (eq 7).[11] The same technique has been used by Fava et al. to prepare unusual molecules of the "betweenanene" family where an *E* double bond in an eight-membered ring is also part of a second bridging ring.[12]



Most of our initial plans were based on the hope that other conventional reactions might be used to connect the α,α'-positions by a chain of atoms to make a bicyclic sulfide as in eq 8. After desulfurization, an interesting product **11** would result with net ring expansion. Hindsight based on unsatisfactory experience reveals possible difficulties in this plan.

Whether or not such bridging reactions will succeed depends on ring conformation and the relative stereochemistry of the α,α'-substituents as well as on the feasibility of the bicyclic structures **10a,b**. One of these diastereomers must be an "inside–outside" bicyclic molecule and its stability will depend on ring size. In any event, the apparently trivial lactonization of **9** to **10** failed under standard acyl activation conditions. Of many methods examined, only the Corey–Mukaiyama activation method worked, and even this required syringe pump-controlled high dilution![13]

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

(7) Vedejs, E.; Mullins, M. J.; Renga, J. M.; Singer, S. P. *Tetrahedron Lett.* **1978**, 519.

(8) Schmid, R.; Schmid, H. *Helv. Chim. Acta* **1977**, *60*, 1361.

(9) Cerè, V.; Pollicino, S.; Sandri, E.; Fava, A. *J. Am. Chem. Soc.* **1978**, *100*, 1516.

(10) Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1979**, *44*, 4128; **1981**, *46*, 3315.

(11) Vedejs, E.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4884.

(12) Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1981**, *46*, 486.

(13) Vedejs, E.; Gapinski, D. M.; Hagen, J. P. *J. Org. Chem.* **1981**, *46*, 5451.

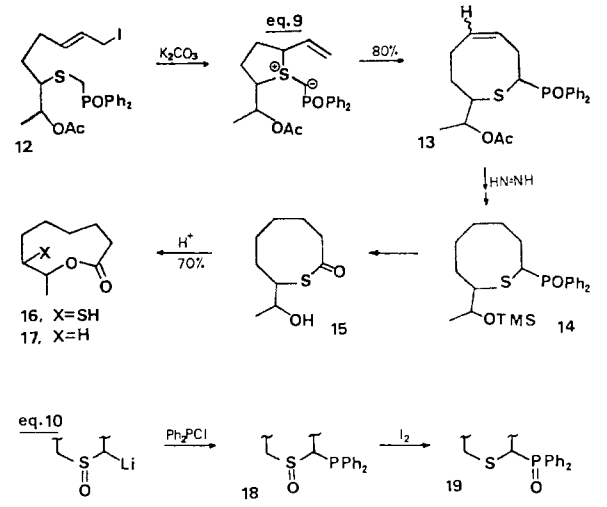


Figure 2.

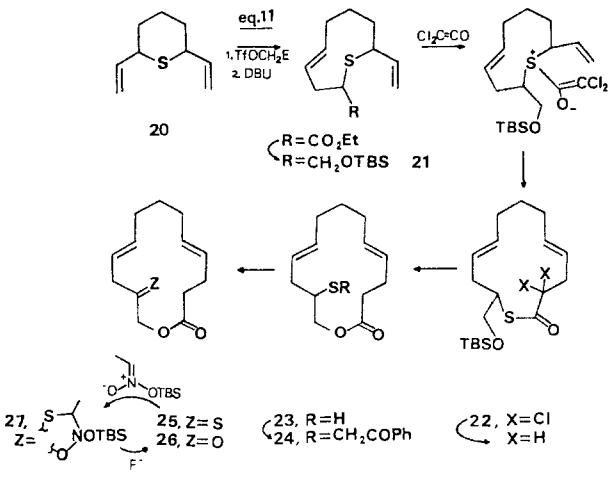


Figure 3.

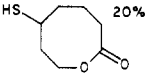
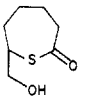
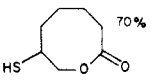
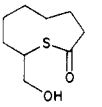
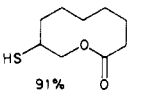
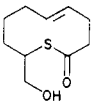
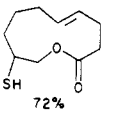
After this experience we decided to restrict our examination of α,α'-bridging methods to systems where the transition state for bond formation depends on the stereochemistry and conformation of only one substituent. This is not asking too much of a medium-sized ring.

The most extensive effort to date has been made in the area of macrolide synthesis. The strategy proceeds from a cyclic sulfide to a thiolactone and from there to lactone by *S*- to *O*-acyl transfer. The concept is illustrated in Figures 2 and 3 with relatively simple 10- and 14-membered lactones as target structures.

The first approach (eq 9) also illustrates an important variant of the ylide ring expansion. Instead of reacting a cyclic α-vinyl sulfide with an esoteric alkylating agent (in this case, the unstable $TfOCH_2POPh_2$), the reaction closes the five-membered ring by intramolecular S-alkylation. Formation of predominantly the (*Z*)-alkene **13** from trans allylic halide **12** rules out an internal enolate alkylation and requires the usual ylide rearrangement mechanism. The intramolecular S-alkylation is convenient because the intermediate sulfonium salt need not be isolated. This can be an important advantage with complex substrates. Also, the technique is more versatile with respect to convergent synthesis as will be shown later.

After diimide reduction and protection steps, the α-phosphinyl sulfide **14** can now be converted into

Table II

entry	starting thiolactone	method[c]	product lactone	K_{eq}
1		B	 20%	*a*, *b*
2		B	 70%	3:1
3	**15**	A	**16**, 70%	>15:1
4		A	 91%	>15:1
5		C	 72%	>10:1
6	**22** (TBS = X = H)	C	**23**, 96%	>15:1

[a] Dimeric material also formed. [b] Approximately 1:1 but not a true equilibrium due to decomposition. [c] Method A, phosphinyl-mediated ring expansion; method B, sulfoxide anion phosphenylation, oxidation; method C, dichloroketene ring expansion.

thiolactone **15** by a variant of Horner–Bestmann oxygenation (73%). Upon treatment with camphorsulfonic acid, **15** rearranges smoothly to mercapto lactone **16** (70%) and desulfurization with 2.1 equiv of Bu_3SnH affords the nine-membered lactone **17**.[14]

Several other α-hydroxyalkyl thiolactones have been made by a variety of methods based on ring expansion. As shown in Table II, acyl transfer to form mercapto lactones is essentially complete in all cases except those leading to an eight-membered ring.[14,15] The thermodynamic advantage of *O*-acyl relative to *S*-acyl is comparable to the strain in the eight-membered ring relative to a six- or seven-membered ring. Starting materials for entries 3 and 4 in Table I are derived from the phosphinyl-mediated ring expansion (method A) described in Figure 2. Method B refers to a more general variation (eq 10) where a sulfoxide anion is treated with $ClPPh_2$ and the resulting sulfoxide phosphine **18** is converted into a sulfide phosphine oxide **19** by redox manipulations. The best way to achieve this result in medium rings is by the iodine-catalyzed intramolecular migration of oxygen from sulfoxide sulfur to phosphorus.[16] This internal redox process also works well in smaller rings, but it occurs via a four-center mechanism and requires that the sulfoxide oxygen is cis with respect to the phosphorus substituent. The usual anion oxygenation can then be used to prepare the thiolactone.

Method C, Table II (dichloroketene ring expansion), will be described in goal-oriented context because it is the most convenient route to thiolactones for those cases where a substantial increase in ring size is desired. The key reaction was initially discovered by Belluš and Malherbe and was used for the ring expansion of an α-vinyltetrahydropyran and for related acyclic rearrangements of allylic ethers and sulfides.[17] We have

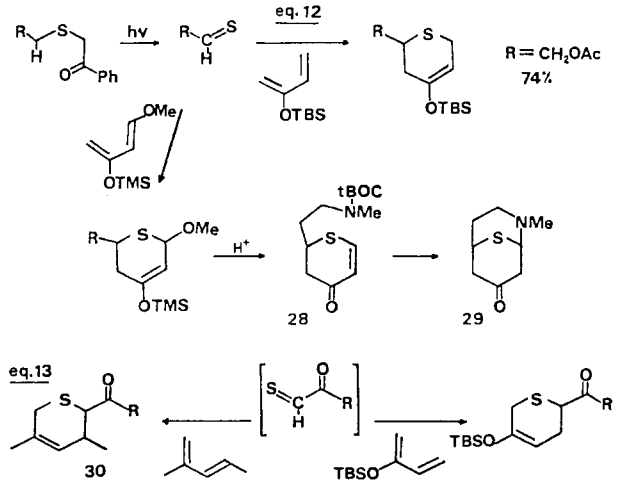
(14) Vedejs, E.; Powell, D. *J. Am. Chem. Soc.* **1982**, *104*, 2046.
(15) Vedejs, E.; Buchanan, R. A. *J. Org. Chem.* **1984**, *49*, 1840.
(16) Vedejs, E.; Meier, G. P.; Powell, D. W.; Mastalerz, H. *J. Org. Chem.* **1981**, *46*, 5253.

found that a similar procedure gives excellent results (Figure 3) when applied to α-alkenyl sulfide rings.[15]

The example of Figure 3 describes synthesis of a 14-membered macrolide and begins with a typical 2,3-sigmatropic ring expansion of α,α'-divinyltetrahydrothiopyran (**20**; eq 11, 85%). The derived nine-membered ring **21** then reacts with dichloroketene to give **22** (74%) by the 3,3-sigmatropic ring expansion. After dechlorination (Zn, HOAc) and deprotection steps, acid-induced acyl transfer affords the 14-membered mercapto lactone **23** (96%). This substance has been converted into the keto lactone **26** by a new photochemical oxidation method which we have developed for use in highly functionalized molecules.[18] The reaction is simple to perform, although the details are not so simple. A phenacyl sulfide **24** is made from the mercaptan by alkylation with phenacyl bromide. Photofragmentation using an ordinary sunlamp generates a thioketone **25**, which is trapped in situ by a stable nitronate ester. The resulting 2 + 3 cycloadduct **27** need not be isolated and can be cleaved under nearly neutral conditions with $Et_3NH^+F^-$ to give the ketone. Aldehydes can be made in the same way.

A variant of the phenacyl sulfide photofragmentation is most useful for the synthesis of six-membered starting materials for ring expansion. Photochemically generated thioaldehydes are trapped efficiently by dienes to give Diels–Alder adducts (eq 12).[19,20] With simple alkanethials, the trapping agent must be an electron-rich diene. Best results are obtained with the Danishefsky diene which affords dihydrothiopyrone **28** after acid treatment. The specific example illustrates a variation of the α,α'-bridging process. Thus, **28** is deprotected and the resulting amine undergoes internal Michael addition to give **29**.

If the thioaldehyde XCH=S contains a strong acceptor group X = acyl, ester, nitrile, etc., then the regiochemistry of the Diels–Alder addition is inverted (eq 13),[19] in accord with frontier MO expectations.[20] This group of thioaldehydes is easy to trap with relatively simple dienes and has proved to be especially useful in highly substituted systems.



(17) Malherbe, R.; Belluš, D. *Helv. Chim. Acta* **1978**, *61*, 3096. Malherbe, R.; Rist, G.; Belluš, D. *J. Org. Chem.* **1983**, *48*, 860.
(18) Vedejs, E.; Perry, D. *J. Org. Chem.* **1984**, *49*, 573.
(19) Vedejs, E.; Eberlein, T.; Varie, D. *J. Am. Chem. Soc.* **1982**, *104*, 1445.
(20) Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1983**, *105*, 6999.

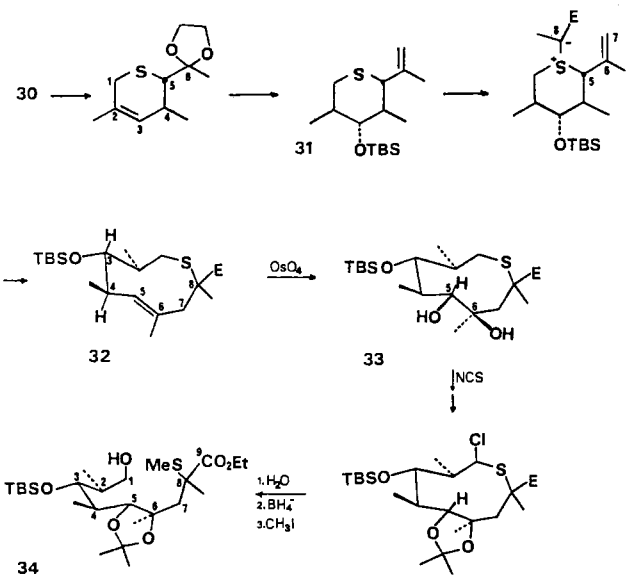


Figure 4.

Complex Applications: Stereocontrol

Two applications will now be described where the primary goal is to control stereochemistry in medium-sized rings. The first example (Figure 4) involves preparation of the C_1–C_9 segment of macrolides in the erythromycin family. The route begins with Diels–Alder addition of transient thiopyruvaldehyde, already mentioned in eq 13. A highly selective hydroboration on the ketal of adduct **30** introduces two asymmetric centers by least hindered approach, and standard methods lead to the starting material for ring expansion (**31**). Typical triflate S-alkylation followed by ylide generation with DBU affords the nine-membered *E* trisubstituted alkene **32** (86% isolated).

Stereocontrolled introduction of the C_5C_6 hydroxyls must now be performed. We expected the natural stereochemistry from X-ray evidence that shows numerous medium-ring (*E*)-alkenes exist in a conformation where the olefin plane is approximately perpendicular to the "plane" of the nearby ring carbons to minimize transannular interactions. In molecules similar to **32**, having an allylic alkyl group, the preferred local conformation is crownlike and the alkyl substituent is pseudoequatorial.[22] We have found that a similar local conformation can be used to approximate the transition-state geometry for medium-ring olefin epoxidations and, in a restricted sense, for osmylations (most reliable for trisubstituted olefins). In the more complex system **32** → **33**, osmylation occurs from the predicted olefin face in a 24:1 ratio of desired **33** to the other diastereomer (not shown).

Such high selectivity for cis-addition reactions is not unusual in medium-ring alkenes having an allylic alkyl substituent. By comparison, the far more familiar reactions of cyclohexenes are at the borderline of synthetic utility. Still et al. have shown that even more remote substituents can be quite effective in controlling the stereochemistry of medium-ring alkylations.[23] In their approach, MM2 computation is used to identify

(21) Vedejs, E.; Dolphin, J. M.; Mastalerz, H. *J. Am. Chem. Soc.* **1983**, *105*, 127.
(22) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058 and references therein.
(23) Still, W. C. Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

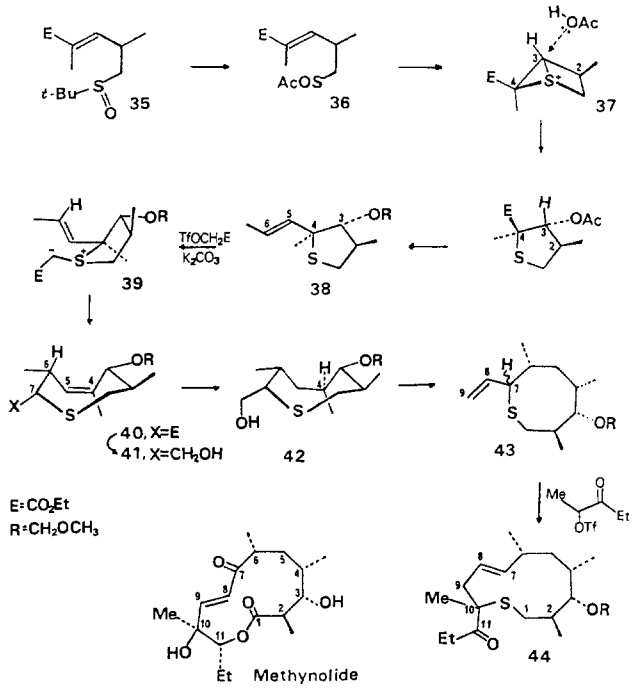


Figure 5.

the preferred transition states.

To complete the C_1–C_9 segment of erythronolide, it is now necessary to activate sulfur for removal. This is easily done by α-chlorination with *N*-chlorosuccinimide because only one side of the sulfur atom has α-CH bonds. For good results, it is important to have an electron-withdrawing substituent at the α'-position (CO_2Et in this case) to inhibit carbonium ion ring cleavage by heterolysis of the S–$C_{\alpha'}$ bond. After solvolysis, borohydride reduction, and S-methylation, the erythronolide C_1–C_9 segment **34** is then obtained, 70% overall.[21] If desired, desulfurization of the remaining C–S bond is easily achieved with Raney Ni.

In terms of strategy, the above sequence follows a pattern that is useful for complex molecules. In the first stage, a small cyclic sulfide is functionalized by conventional means. Ring expansion comes next, followed by stereocontrolled functionalization of the resulting double bond. Depending on the application, the ring expansion and alkene addition steps can be repeated if necessary. After sulfur has served its role, an activation step is performed to allow C–S cleavage. The strategy works best if the starting sulfur ring corresponds to the most complex part of the target structure. However, the most important consideration is to match the location of C–S bonds with product functionality and sulfur removal methodology.

These points are encountered again in the second complex example (Figure 5). This sequence is designed to study stereocontrol in the methynolide family of 12-membered lactones. The starting sulfur ring corresponds to the complex C_1–C_6 subunit and is made by a highly selective cyclization. Heating sulfoxide **35** with acetic anhydride generates the sulfenyl acetate **36**, which cyclizes exclusively via the less hindered transition state **37** (exo C_2 methyl).[24]

After conversion to the alkenyl sulfide **38**, the first ring expansion must be performed. Only one transition-state geometry (**39**) is capable of rearrangement to a (*Z*)-thiacyclooctene **40**, and the product must have the desired C_6 stereochemistry due to the familiar consequences of a 2,3-sigmatropic rearrangement. However, only one of the two possible sulfur diastereomers is able to rearrange because stereochemical equilibration by the usual proton-transfer process is prevented by the C_4-methyl group. This specific system does not tolerate higher temperatures where sulfur pyramidal inversion might occur. Thus, ring expansion to **40** occurs in an unusually low yield of 40%.

Realization of one of the main goals was now at hand. Local conformer effects were predicted to favor a geometry with pseudoequatorial allylic methyl as shown for **40**. The same geometry appears to hold for simple cyclic (*Z*)-olefins and especially for the transition states of medium-ring cis additions which occur from the more exposed olefin face.[22] In the case of epoxidation, osmylation, or hydroboration of representative examples, this generalization is even more reliable than in the analogous reactions of (*E*)-alkene isomers. Thus, hydrogenation of **41** from the less hindered direction should complete the stereochemistry of the C_1–C_6 segment.

A lengthy search failed to unearth a hydrogenation catalyst that would reduce the hindered alkene in the presence of sulfur. However, diimide, which is unique among hydrogen donors in its greater reactivity toward cyclooctene relative to more typical substrates such as cyclohexene, did reduce **41** to the desired **42** as the sole product. In fact, diimide was the first reducing agent that we tried. Unfortunately, we did not select the critical temperature window of 120–160 °C which is essential for this specific reduction until much later. Slow addition of (*p*-tolylsulfonyl)hydrazine to preheated **41** is the preferred technique. As mentioned before (Figure 2), diimide reduces disubstituted (*Z*)-thiacyclooctenes quite easily. Disubstituted (*E*)-thiacyclononenes are especially reactive and reduce rapidly at room temperature.

The methynolide series has been taken through another ring-expansion stage by the usual S-alkylation–deprotonation method (**43** to **44**). The yield is 80–85% and the product is formed as one predominant diastereomer with exclusive (*E*)-olefin geometry even though the starting α-vinylthiacyclooctane **43** is a mixture of vinyl diastereomers. All of the ring carbons of the 12-membered macrolides are now incorporated into the molecule, and the synthesis has reached the stage where sulfur must be activated for removal. Solutions to this problem are not yet optimized.[25]

Goal-Oriented Applications

We will now turn to a complex application in medium-ring carbocycle synthesis. This (final) example deals with the cytochalasin–zygosporin family (Figure 6) and uses sulfur to mediate the construction of the unusual 11-membered carbocycle.

The stereochemically most congested part of the molecule is made by the highly optimized *N*-benzoylpyrrolinone Diels–Alder reaction **45** to **46** (Figure 6). The details of this process are described elsewhere,[26] but the yield of the desired isomer is >90%. The

(24) Vedejs, E.; Mullins, M. J. *J. Org. Chem.* **1979**, *44*, 2947.

(25) Vedejs, E.; Buchanan, R.; Conrad, P.; Meier, G. P.; Watanabe, Y., unpublished results.

(26) Vedejs, E.; Campbell, J.; Gadwood, R. G.; Spear, K. L.; Rodgers, J.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534. Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4617.

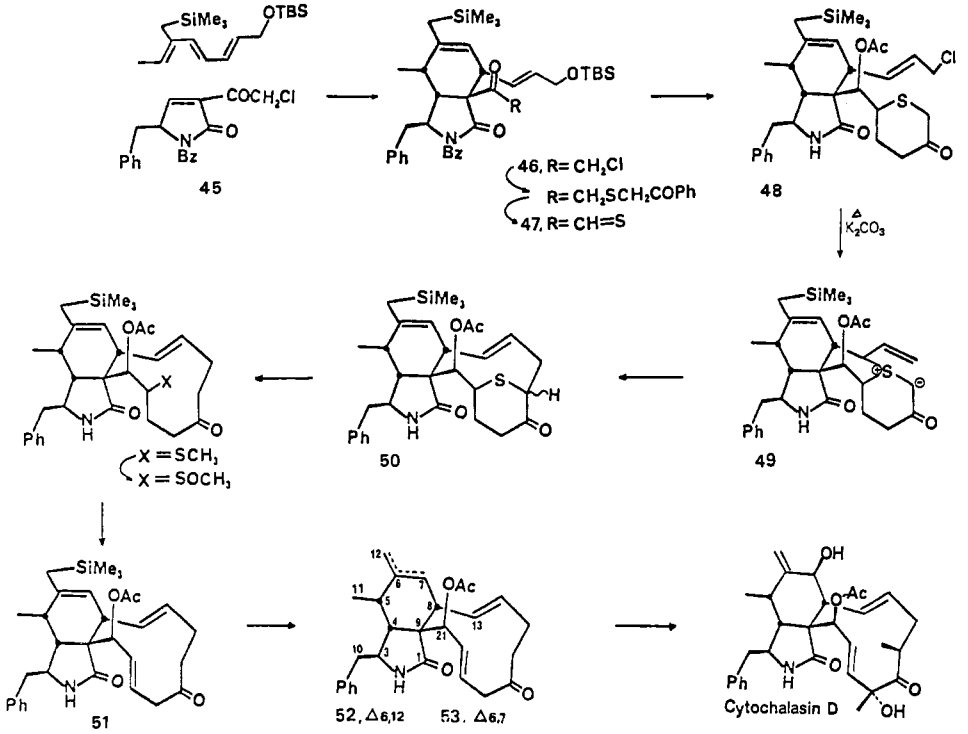


Figure 6.

reactants have followed the endo transition state (cyclic π-system dominant), least hindered approach to dienophile, correct head to tail regiochemistry, and reaction at the most substituted diene subunit. The allylic silane serves as a latent allylic alcohol for cytochalasin synthesis (allylic inversion) or as a "latent proton" for zygosporin synthesis (allylic retention). Interestingly, the analogous triene without silicon reacts more slowly in the Diels–Alder step and gives approximately a 1:1 mixture of diastereomers!

Thioaldehyde methodology can now be used to connect the remaining medium-ring carbons and to incorporate the functionality needed for ring expansion. In fact, it was this specific problem that stimulated our study of the potential of thioaldehydes for hetero-Diels–Alder reactions. Our first model experiments used a relatively inefficient nucleophilic displacement method to generate S=CHCN, which did react with dienes but in less than 20% yield.[27] We were encouraged to try the photochemical method by the timely news that photogenerated thioaldehydes can be intercepted by diazo compounds in certain cases.[28] In our case, the transient thioaldehyde **47** is trapped in 75–85% yield, depending on the diene, to give adduct **48**.

Essentially identical results are obtained with simple thioaldehydes containing acceptor substituents. If anything, **47** is better behaved, probably because its polymerization is sterically inhibited to a greater extent than is the 4 + 2 cycloaddition. The thioaldehyde method can be an ideal way to form C–C bonds in a demanding environment.

After minor peripheral modifications, the allylic chloride **48** can be obtained and is ready for the ring-expansion stage. In an earlier example (eq 9), a relatively simple allylic halide was used to initiate a ring expansion by internal sulfur alkylation. In the present case, the sulfur is incorporated into an additional ring that becomes part of an 11-membered carbocyclic periphery during the sequence **48** to ylide **49** to bicyclic sulfide **50**. The overall result is that the α,α'-positions of the starting six-membered sulfide **48** are bridged by a six-carbon chain to give **50** (60%). So far, we have used this new α,α'-bridging method with only one other combination of starting ring size and bridging chain length (eq 9).

The product **50** is a mixture of diastereomers at the newly formed C–C bond. As discussed in connection with eq 8, one of these products must be an "inside–outside" bicyclic structure. Apparently, the question of bridgehead stereochemistry by itself is not crucial in these ring expansions. Neither diastereomer of **50** is unusually sensitive.

In the next stage of our cytochalasin synthesis, the sulfur must be activated for removal. This is relatively simple in molecules having carbonyl adjacent to sulfur, but direct reduction of the sulfide is not effective when both the sulfur and ketone are incorporated into a six-membered ring. Much better results are obtained by first alkylating the sulfur with $(CH_3)_3O^+BF_4^-$. Zinc reduction then works smoothly, and sulfur oxidation followed by sulfoxide pyrolysis affords the cytochalasin ring system **51** in excellent yield. Exclusive formation of the (*E*)-alkene in the thermal elimination step is noteworthy since analogous acyclic five-center eliminations are not nearly as selective. This welcome result is probably due to conformational preferences in the medium-sized ring, a topic that deserves further study.

The methods by which **51** has been converted to cytochalasin D and zygosporin G analogues **52** and **53** are described elsewhere.[26] We shall also postpone a discussion of plans for dealing with the medium-ring substitution pattern and stereochemistry although we can say that these will revolve around the conforma-

(27) Vedejs, E.; Arnost, M. J.; Dolphin, J. M.; Eustache, J. *J. Org. Chem.* **1980**, *45*, 2601.

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tional properties of the unusual 11-membered carbocycles.

Concluding Remarks

Where might this chemistry lead? Certainly, several of the problems that were encountered are now solved sufficiently for general applications. Methods for generation of sulfonium salts, ylides, and simple cyclic sulfides of virtually any desired size are optimized and well understood. On the other hand, there are many opportunities for further study in related areas.

Stereocontrol in medium and large rings is one possibility. So far, excellent selectivity has been observed in alkene epoxidations, osmylations, and reductions in our laboratory. Except for the enolate alkylations and enone 1,4-additions explored by Still et al., there have been no extensive studies on other reaction types.

In the thioaldehyde area there are also many options. We have just begun to appreciate the potential of this simple and highly reactive functional group for selective bond formation in complex surroundings. Virtually any thioaldehyde is easily generated, including some whose oxygen counterparts remain unknown.

Projects that include some element of total synthesis also encounter other, relatively mundane problems. We have learned to respect one of these well beyond initial expectations: there is still no reliable way to achieve the $CH_2SR \rightarrow COR^1$ transformation at any carbon oxidation state. Of course there are many "paper solutions" that work in simple systems, but the extrapolation from di-*n*-butyl sulfide to some of our macrolide precursors has proved to be long indeed. In such situations, the scientific value of total synthesis is clear, regardless of the target. Nothing else provides the motivation to compare old and new methodology in a realistic setting.

I express my appreciation to the many co-workes who have contributed their ideas, enthusiasm, and hard work to the projects described here. Thanks are also due to the National Institutes of Health and to the National Science Foundation for funding and to the University of Wisconsin for maintaining an atmosphere where research is enjoyable.

Structural Studies on Some Antibiotics of the Vancomycin Group, and on the Antibiotic-Receptor Complexes, by ^{1}H NMR

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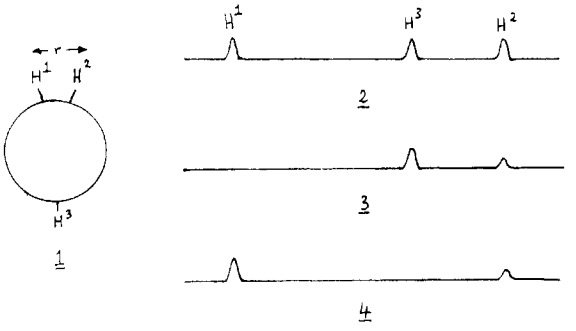
This Account is concerned with the story of the first structure elucidations of antibiotics of the vancomycin group (of vancomycin itself and of ristocetin) and with the discovery of the molecular basis of action of these drugs by binding to cell-wall analogues termining in -D-Ala-D-Ala. The work has been particularly rewarding, since in parallel with an increase in our understanding of the molecular basis of the drug action over the last decade, vancomycin itself has enjoyed a great increase in importance as a result of the occurrence of pathogenic strains of Gram-positive bacteria that are resistant to penicillin and cephalosporin therapy.

The success of the work is in large measure due to the use of the negative nuclear Overhauser effect (NOE), a phenomenon observed in nuclear magnetic resonance spectra. When nuclei which behave like bar magnets are placed in a magnetic field, they can occupy a high- and a low-energy state. A nuclear magnetic resonance absorption signal is obtained from such nuclei when, upon supplying electromagnetic radiation of a suitable frequency, ν, there is a net passage of nuclei from the low- to the high-energy state. Nuclei may pass back from the high- to the low-energy state by a process known as relaxation. Proton nuclei are normally relaxed by a mechanism which involves neighboring protons. The effectiveness of such neighboring protons in bringing about relaxation depends upon r^{-6}, where r is the internuclear distance between the proton being relaxed and the proton effecting the relaxation.

If the intensity of the resonance of one proton (H^1) is normally I, then if $r_{1,2}$ (the internuclear distance between protons H^1 and H^2) is relatively small (as a useful guide for our present purposes say, <0.3 nm), the effect of irradiating a second proton (H^2) before recording the intensity of the resonance of H^1 is to change its intensity to I'; i.e., $I \neq I'$. This change in intensity is called NOE. The effect is indicated schematically in 1–4. Three hydrogen nuclei in a molecule are indicated



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