Total Synthesis of *d,l*-Methynolide. Medium-Ring Sulfides by Ylide Ring Expansion

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Abstract: The sulfur-based ring expansion methodology required for the total synthesis of the title compound is described in detail. The successful route employs the ring expansion of sulfonium ylide **10** to an eight-membered sulfide **11**, followed by conversion to alcohol **40** and reduction of the double bond to form the saturated analogue **53**. Two routes to the precursors of **10** were developed. The first depends on a stereoselective sulfenic acetate cyclization from **3** to **5**. An alternative sequence involves an internal sulfide alkylation from **30** to generate the same ylide **10** and the eventual ring expansion product **11**. A second sigmatropic rearrangement from the eight-membered ylides **57** or **58** affords the 11-membered sulfide **60** with four of the six asymmetric centers of methynolide.

Some time ago, an effort was initiated in our laboratory to develop a synthetic approach to methynolide, the aglycon of the macrolide antibiotic methymycin, based on sulfur-mediated ring expansion technology.[1] Two related retrosynthetic analyses (routes A and B) were considered as shown in Scheme I. Both approaches rely upon sequential 2,3-sigmatropic rearrangements of stabilized sulfonium ylides[3] to build a series of cyclic sulfides containing five-, eight- (**B-4**), and 11-membered (**B-3** or **A-4**) rings. After oxidative activation α to sulfur, hydroxyalkyl thiolactones **A-3** or **B-2** would be converted into the corresponding lactone mercaptans **A-2** or **B-1** by intramolecular acyl transfer, thereby avoiding the problem of macrolactonization. Our investigations of both approaches up to the stage of 11-membered cyclic sulfides are described below. Final steps leading to methynolide according to the route A strategy are considered in the following paper.

There are several unusual features in the sulfur-mediated synthetic plan. First, and most important, this is an approach that depends upon *relative* stereocontrol. Each of the stereocenters from C_3 to C_{11} (methynolide numbering) is defined by taking advantage of the predictable consequences of 2,3-sigmatropic shift[4] or of conformational properties inherent in the medium-ring intermediates.[5] Sulfur plays an important role in the process by providing a relay point for conveying stereochemical information. In contrast to most approaches to methynolide or other complex macrocycles,[6,7] stereocontrol does not depend on the coupling of optically pure subunits. To emphasize this point, the selected target is the hitherto unknown *d,l*-methynolide.

After sulfur has served its role in defining ring size and stereochemistry, it must be removed without disturbing adjacent asymmetric centers. The crucial step in this process, the acyl transfer from **A-3** to **A-2** or from **B-2** to **B-1**, produces a sulfhydryl group that must be transformed into oxygen functionality. We were unable to reach this stage according to the route B strategy, but the alternative approach of route A was eventually successful.

I. Synthesis of Thiacyclooctenes

Our first objectives were to demonstrate repeatable sulfur ylide ring expansions, to establish the geometric preferences of the sigmatropic rearrangements, and to develop viable routes to cyclic sulfonium ylides. These topics have been described in depth.[1-3] On the basis of the model studies, the prediction was made that a cyclic sulfonium ylide **10** derived from the cyclic sulfide **6** (Scheme II) would rearrange to a (*Z*)-thiacyclooctene **11**. A preliminary account of this work described stereocontrolled access to the necessary five-membered sulfide starting material **6** via sulfenyl acetate cyclization.[10]

The key precursor sulfoxide **3** was prepared by a conventional route starting from the 1,4-adduct of methacrolein and *tert*-butylmercaptan via the enal **1** and the Horner–Emmons product **2**. Highly stereoselective cyclization to a single thiolane ester **5a** was observed when the sulfoxide **3** was treated with acetic anhydride under the conditions of sulfenyl acetate generation.[8,9] Although we have no independent proof for the assigned stereochemistry of **5a**, a comparison of the two possible episulfonium intermediates **4** and **4'** (corresponding to internal electrophilic attack at either olefin face) reveals that the latter is destabilized by a severe 1,3-dimethyl interaction. Assuming net trans addition and kinetic control, **5** is the expected product. The assigned C_2–C_3 stereochemistry was eventually confirmed by X-ray structure determination of an advanced intermediate.

After adjusting the hydroxyl-protecting group, **5a** was converted into **6a** by the Et_3BHLi reduction of the corresponding allylic mesylate. This proved to be a challenging transformation due to the solvolytic sensitivity of the mesylate, but good yields could be obtained consistently. On the other hand, the critical ring expansion from **6a** to **11a** worked poorly under conditions that had been optimized for simple analogues.[1-3] Alkylation of **6a** with the triflate derived from ethyl glycolate gave the salt **7a**, but treatment with K_2CO_3 in acetonitrile afforded only 36% of an eight-membered ring expansion product. Structure **11a** was supported by the NMR data, and the presence of a $\dot{Z}$ double bond was clear from NOE experiments. Since the stereochemistry of **6a** was defined by the method of synthesis, ylide rearrangement to a (*Z*)-alkene requires a tub-like transition state resembling the cisoid propenyl rotamer **10a**. This results in the correct C_6 stereochemistry as illustrated in the eight-membered sulfide **11a**.

(1) (a) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358. (b) For the preliminary account of the methynolide synthesis, see: Vedejs, E.; Buchanan, R. A.; Conrad, P. C.; Meier, G. P.; Mullins, M. J.; Watanabe, Y. *J. Am. Chem. Soc.* **1987**, *109*, 5878.

(2) (a) Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046. (b) Vedejs, E.; Buchanan, R. A. *J. Org. Chem.* **1984**, *49*, 1840.

(3) (a) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878. (b) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *J. Org. Chem.* **1978**, *43*, 1185.

(4) (a) Baldwin, J. E.; Hackler, R. E.; Kelly, D. P. *J. Chem. Soc., Chem. Commun.* **1972**, *1311*. (b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. (c) Grieco, P. A.; Finkelhor, R. S. *J. Org. Chem.* **1973**, *38*, 2245. Grieco, P. A.; Boxler, D.; Hiroi, K. *J. Org. Chem.* **1973**, *38*, 2572.

(5) (a) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058. (b) Vedejs, E.; Dophin, J. M.; Gapinski, D. M.; Mastalerz, H. *Current Trends in Organic Synthesis*; Pergamon Press: New York, NY, 1983; p 221. (c) Vedejs, E.; Dent, W. H. III; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437.

(6) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(7) (a) Masamune, S.; Kim, C. V.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) Inanaga, J.; Katsuki, T.; Takimoto, S.; Ouchida, S.; Inoue, K.; Nakano, A.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1021. (c) Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647.

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(9) Chauvette, R. R.; Pennington, P. A.; Ryan, C. W.; Cooper, R. D. G.; Jose, F. L.; Wright, I. G.; Van Heyningen, E. M.; Huffman, G. W. *J. Org. Chem.* **1971**, *36*, 1259.

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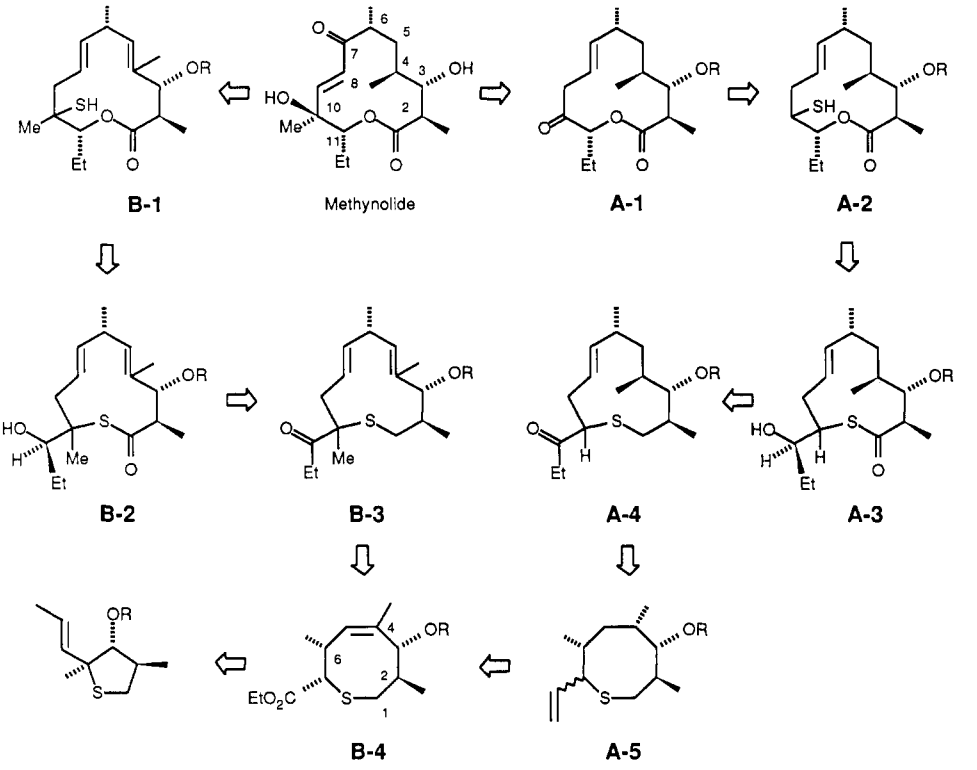
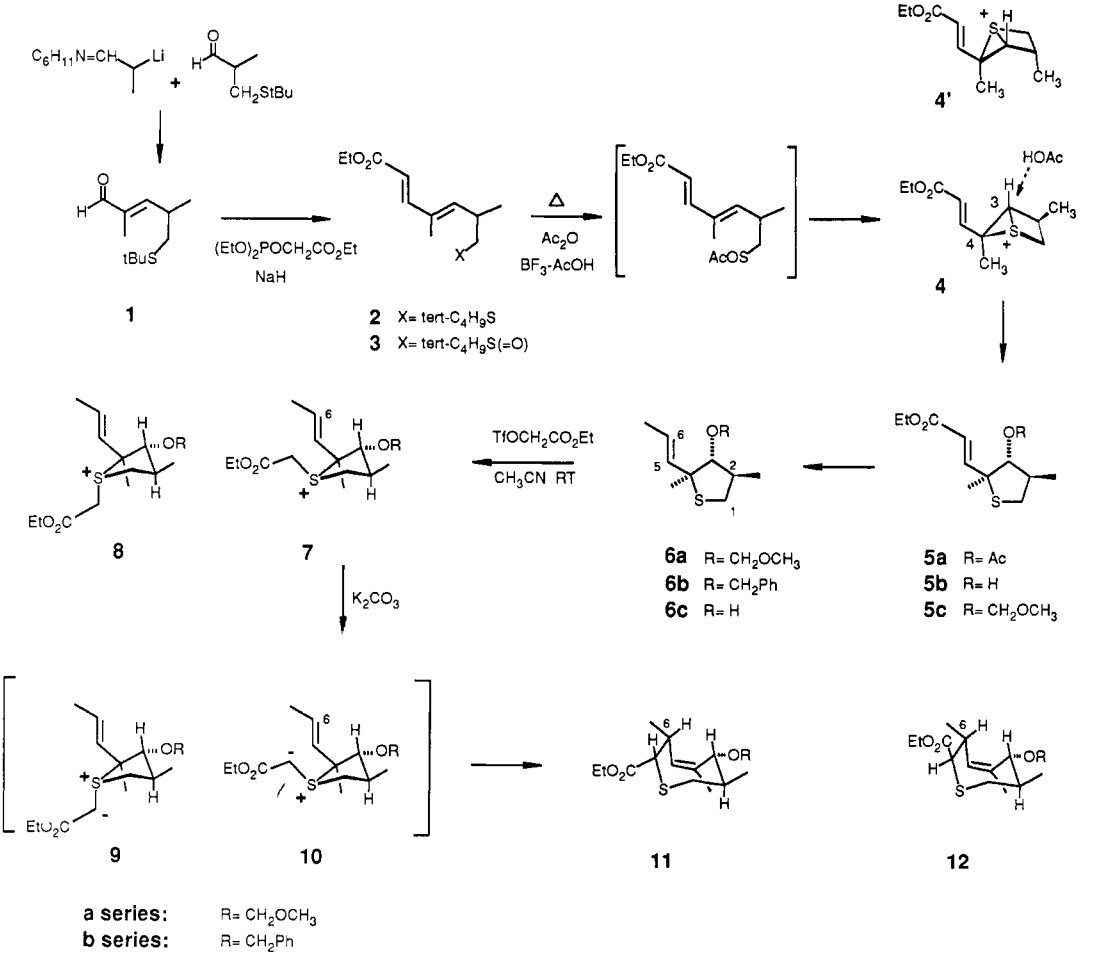
Scheme I



Scheme II

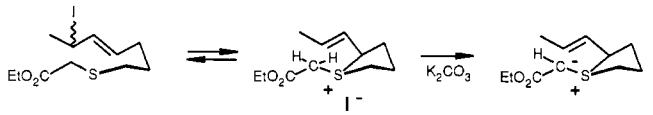


The choice of **11** over the C_7 epimer **12** is less important, but the assignment is secure since **10** should be the less hindered ylide rotamer.

Our initial study of the S-alkylation was based on the assumption that **6** would be sensitive to dealkylation by nucleophiles and that alkylation agents having a non-nucleophilic counterion

such as triflate would be essential. However, observations made in connection with an alternative route to **6** (next section) caused us to re-examine the alkylation step. After extensive optimization of conditions, it was found that heating **6** with ethyl bromoacetate/NaI in trifluoroethanol/2,6-lutidine is a superior technique for ring expansion and improves the yield of **11** to 59%. The reasons for this result are not fully understood, but ylide stereochemistry is clearly important. Alkylation of sulfide **6** is expected to afford diastereomeric sulfonium salts **7** and **8**, and deprotonation would produce ylide diastereomers **9** and **10**. As mentioned above, **10** can easily adopt the geometry needed for rearrangement to **11**, but this is not possible for **9** due to the distance between propenyl and ylide groups. The bromoacetate/trifluoroethanol conditions must allow improved access to **10**, either by increasing the ratio of **7** to **8** in the alkylation step or by facilitating interconversion of sulfonium salt (**7** and **8**) or ylide (**9** and **10**) diastereomers. Pyramidal inversion at sulfur is one conceivable pathway for diastereomer interconversion, but this pathway is unlikely according to our model experiments or to the more extensive studies of Fava et al.[11,3] The transition state for pyramidal inversion is destabilized by the five-membered ring, and other equilibration pathways are usually faster.[11] Sulfonium salt diastereomer interconversion via heterolysis of the ring C–S bond is one reasonable option that might allow conversion of **8** to **7** under the trifluoroethanol conditions. Evidence for some contribution from this mechanism has been obtained in an investigation of alternative routes to **7** as described in the next section.

Alternative Synthesis of 7 and 11. Early difficulties with the ring expansion of **6** prompted an investigation of routes that avoid the troublesome intermolecular S-alkylation step. The alternative plan generates the cyclic sulfonium salts by *intramolecular* sulfide alkylation by using a tethered allylic halide as the alkylation agent[12] (eq 1). This approach avoids the need to isolate cyclic sulfide or sulfonium intermediates, but it sacrifices predictable control over thiolane stereochemistry at the tertiary carbon. We had initially assumed that this stereocenter would be critical to ylide ring expansion with the correct C_6 stereochemistry, but our concern proved to be unfounded.

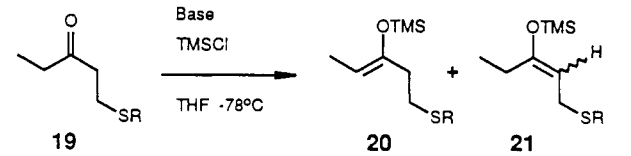


(1)

A synthesis of a suitable acyclic sulfide corresponding to methynolide C_1–C_7 is described in Scheme III. The sequence begins with the condensation of 3-pentanone, formaldehyde, and benzyl mercaptan by the method of Dronov et al.[13] to produce the ketone **13**. Enolization of **13** with lithium hexamethyldisilazide at −78 °C, followed by condensation with 2-((*tert*-butyldiphenylsilyl)oxy)propionaldehyde[14] gave a mixture of diastereomeric aldol adducts **14**. Mesylation of **14** (MsCl, Et_3N, Et_2O, −20 °C) followed by treatment of the crude mesylates with DBU in acetonitrile gave enone **15** (as a mixture of two inseparable diastereometers) in a combined overall yield of 60% based on ketone **13**. No effort was made to evaluate or control remote stereochemistry at this stage because the complication is removed by subsequent transformations.

Numerous other conditions were explored for the aldol condensation of ketone **13**. Surprisingly, the use of stronger bases in place of lithium hexamethyldisilazide for enolate generation gave substantial amounts of the undesired, more highly substituted enolate. This result was established by enolate trapping with Me_3SiCl in situ at −78 °C. Thus, reaction of **13** with LDA produced an ca. 65:35 mixture in favor of the less substituted enolate, but mesityllithium[15] in pentane–THF favored the most substituted enolate. Similar results were obtained with a related, sterically unbiased ketone **19** where reliable product analysis was possible by NMR spectroscopy (Table I). Deprotonation of **19** using LDA in the presence of Me_3SiCl gave a mixture of enol ethers **21** (major; *E,Z* mixture) and **20** (minor; >95% *Z* isomer[16]), while mesityllithium gave >95% **21**. The reasons for this selectivity are not clear, but a similar β-heteroatom effect on kinetic enolate generation is reported for the corresponding β-*tert*-butyldimethylsiloxy ketone.[17,18]

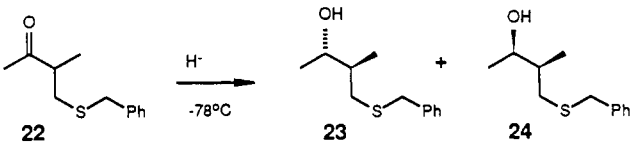
Table I



19 20 21

	R	base	20:21	(*Z*)-**21**:(*E*)-**21**
1	CH_2Ph	LDA	15:85	1:1
2	CH_2Ph	LiHMDS	<9:91	1.2:1
3	CH_2Ph	MesLi	<5:95	2:1
4	CH_2Ph	MesLi −110 to −78 °C	<5:95	3.6:1
5	Ph	MesLi	<5:95	2.7:1
6	$CH_2CH_2SCH_3$	MesLi	<5:95	2.3:1

Table II



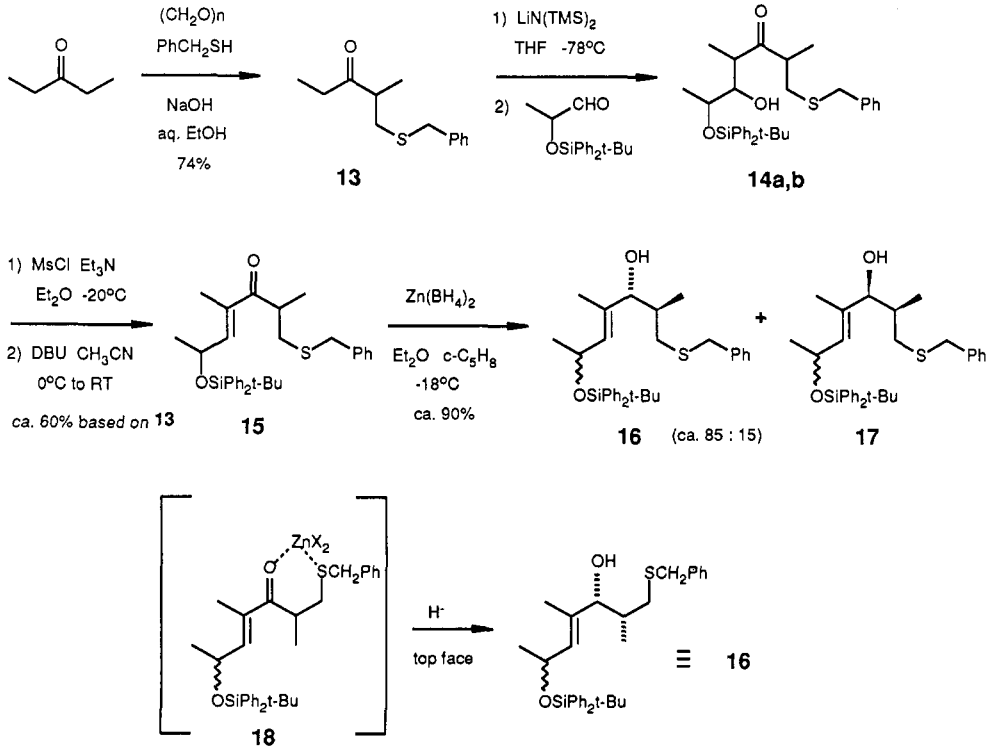
22 23 24

	hydride	solvent	**23**:**24**
1	DIBAL	Et_2O	1:2
2	$Zn(BH_4)_2$	Et_2O	2:1
3	$LiBH_4$	Et_2O	1:1
4	$SnCl_4$–$LiBH_4$	Et_2O	2:1
5	$SnCl_4$–$Zn(BH_4)_2$	Et_2O	5.5:1
6	$SnCl_4$–$Zn(BH_4)_2$	Et_2O–$PhCH_3$	6.3:1

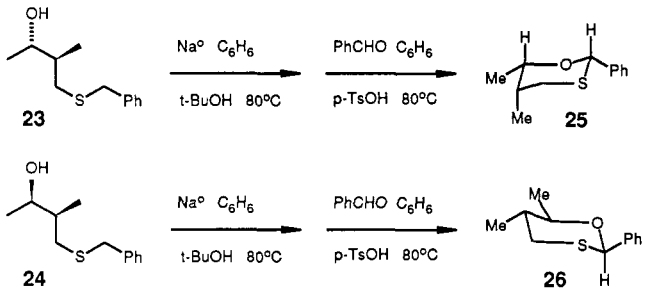
In the next stage of synthesis, methynolide C_2, C_3 stereochemistry was introduced by the reduction of enone **15** with zinc borohydride[19,20] (Et_2O, −18 °C). The reaction produced the alcohols **16** and **17** in a ratio of 85:15 (90%). For best results, cyclopentene was added to the reaction mixture to trap borane byproducts, and this procedure was employed routinely for preperative scale experiments (45% **16** overall from **13**). The stereochemical result was eventually proved by X-ray analysis, but indirect evidence from a model study was also obtained (Table II). Reduction of the model ketone **22** gave the sulfide alcohols **23** and **24**, and stereochemistry was established by NMR coupling constant analysis of the derived cycylic benzylidine derivatives **25** and **26** (Scheme IV). The zinc borohydride experiment gave **23** as the major product, although selectivity was not as high as

(10) Vedejs, E.; Mullins, M. J. *J. Org. Chem.* **1979**, *44*, 2947.
(11) (a) Fava, A.; Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E. *J. Org. Chem.* **1979**, *44*, 4128. (b) Fava, A.; Paolucci, C.; Pollicino, S.; Sandri, E. *Ibid.* **1978**, *43*, 4826. (c) Fava, A.; Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E. *Ibid.* **1981**, *46*, 3315.
(12) For previous examples of the acyclic route to cyclic ylides, see ref 2a.
(13) Dronov, V. I.; Nigmatullina, R. F.; Krivonogov, V. P.; Spirikhin, L. V.; Nikitin, Yu., E. *Zh. Org. Khim.* **1976**, *12*, 1672.
(14) Baker, D. C.; Hawkins, L. D.; Massad, S. K. *J. Org. Chem.* **1983**, *48*, 5180.
(15) Seebach, D.; Beck, A. K.; Hoeckstra, M. S. *Tetrahedron Lett.* **1977**, 1187.
(16) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
(17) Martin, V. A.; Albizati, K. F. *J. Org. Chem.* **1988**, *53*, 5986.
(18) Reversible elimination–readdition of the β-sulfide substituent was not detected when enolization was performed in the presence of PhSLi.
(19) Gensler, W. J.; Johnson, F.; Sloan, A. B. D. *J. Am. Chem. Soc.* **1960**, *82*, 6074.
(20) For evidence of chelation by α-sulfur, see: (a) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, J.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775. (b) Shimagaki, M.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Ibid.* **1984**, *25*, 4779.

Scheme III



Scheme IV



in the analogous reduction of **15**. Better selectivity for **23** was obtained in the presence of added Lewis acids, but this was not necessary in the more complex substrate **15**. The major product **16** corresponds to least hindered reduction of an internally chelated substrate geometry such as **18**.

With the C_2, C_3 stereochemistry of methynolide established in the synthetic intermediates, it was now necessary to introduce the substituents required for sulfur ylide generation. After protection of hydroxyl as the benzyl ether **27**, conversion of the sulfide directly into the related α-alkylthioacetate **28** was achieved simply by heating **27** with ethyl bromoacetate to partial conversion (74% isolated **28**). The initially formed sulfonium ion was debenzylated by attack of nucleophilic bromide ion, and undesired S-alkylation of the product **28** was easily avoided because sulfur is inductively deactivated by the ester group. Finally, removal of the silyl ether ($Bu_4N^+F^-$) gave the allylic alcohol **29**, and treatment with Bu_3P/CCl_4[21] afforded allylic chloride **30**, the key precursor for generation of cyclic sulfonium salts (63% overall from **16**).

Conversion of the chloride **30** into **7b** via intramolecular S-alkylation required activation by NaI. When the experiment was performed in acetonitrile containing 2,6-lutidine, conversion occurred at room temperature to give a mixture of products consisting of **11b** (47%), a diastereomer tentatively assigned the structure **12b** (trace), and the dienes **32** (30%) and **33** (9%). Diene formation could be suppressed by performing the reaction in trifluoroethanol. This variation gave much faster conversion, presumably due to solvent assistance in the ionization of an intermediate allylic iodide **31**. However, **11b** was obtained in only 25% yield, and a new major product **34** (59%) was formed by solvent capture of allylic cation intermediates. The best compromise in conditions proved to be the combination of 6:1 CH_3CN/CF_3CH_2OH and NaI/2,6-lutidine at room temperature, resulting in conversion of **30** into **11b** (66%), diene **33** (ca. 8–10%), and traces of the other products.

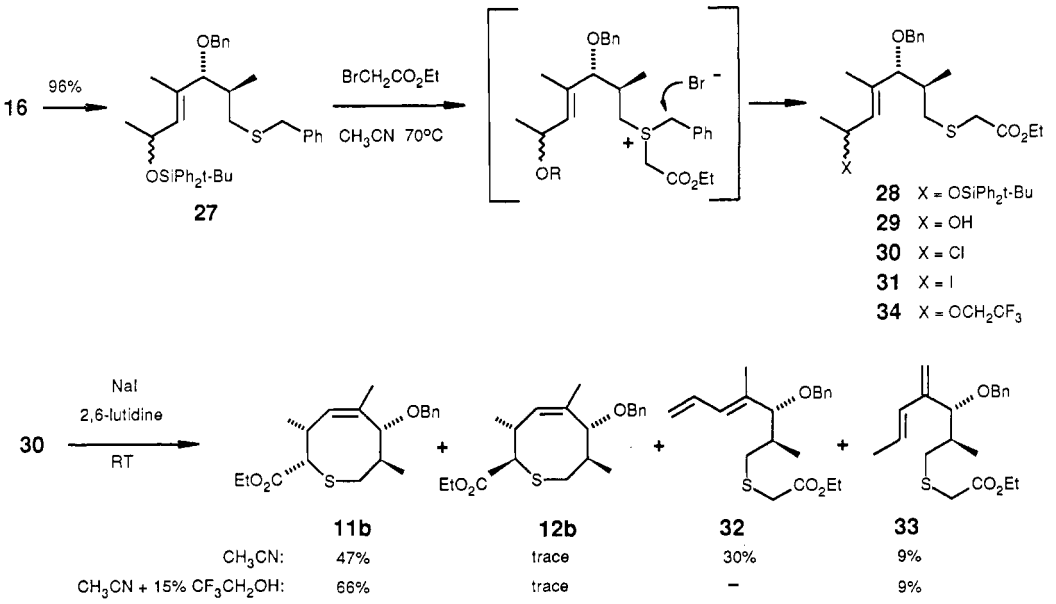
The 66% yield of **11b** in the above experiment indicates efficient access to the ylide diastereomer **10b** and, therefore, to the precursor sulfonium salt diastereomer **7b**. However, selective cyclization of the allylic iodide **31** or the allylic cation **35** to **7b** seems unlikely since three other sulfonium salt diastereomers **8b**, **36b**, and **37b** are possible (Scheme VI). If all four salts are formed nonselectively, then at least partial diastereomer interconversion is necessary for efficient ring expansion. Interconversion could occur via reversible formation of the allylic cation **35**, and some evidence for this pathway has been obtained. The key experiment has already been mentioned briefly in connection with Scheme II. Thus, reaction of **6b** with ethyl bromoacetate/NaI in trifluoroethanol + 2,6-lutidine at 80 °C gave the usual ring expansion product **11b** (59%) and some of the epimeric **12b** (8%). In addition, this experiment afforded **34** (7%), the product expected from ionization to the allylic cation **35** followed by solvent capture.

Assuming that **6b** is alkylated nonselectively, both **7b** and **8b** would be formed in the initial step. Since no ring expansion products (strained (*E*)-thiacyclooctenes) derived from **8b** via the ylide **9b** have been detected, **8b** probably undergoes C–S heterolysis in the ionizing solvent trifluoroethanol to give the cation **35**. Solvent capture of the cation to form **34** occurs in competition with internal S-alkylation, and some fraction of **35** will reclose to generate all of the possible sulfonium diastereomers. This process provides a pathway for the partial conversion of **8b** into **7b** and, ultimately, into the ring expansion product **11b**.

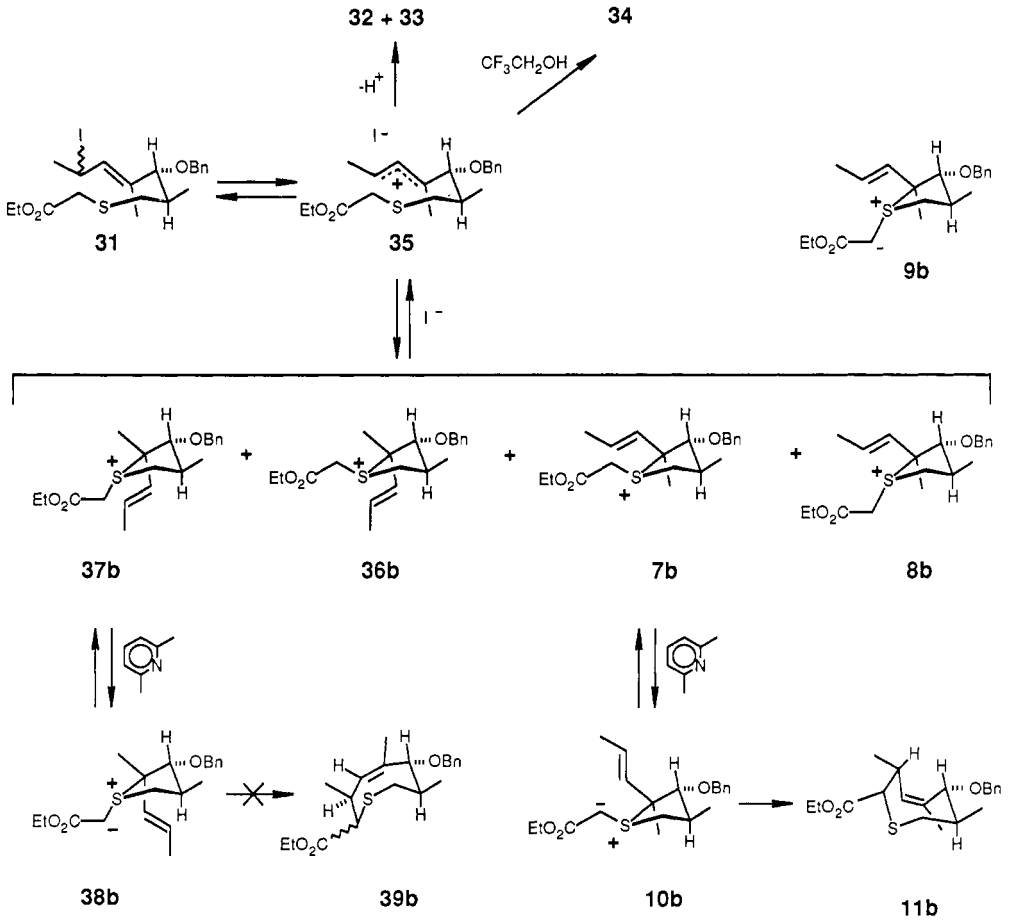
In principle, the trifluoroethanol conditions allow the reversible generation of four sulfonium salt or ylide diastereomers. It is therefore surprising that only one product (**11b**) of ylide rearrangement or decomposition is produced in substantial amounts. For example, a diastereomeric (*Z*)-thiacyclooctene **39b** could have been formed via the sulfonium salt **37b** and the corresponding ylide **38b**. Apparantly, the 2,3-sigmatropic shift of ylide **38b** is retarded by the gauche interaction between the propenyl group and the

(21) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

Scheme V



Scheme VI

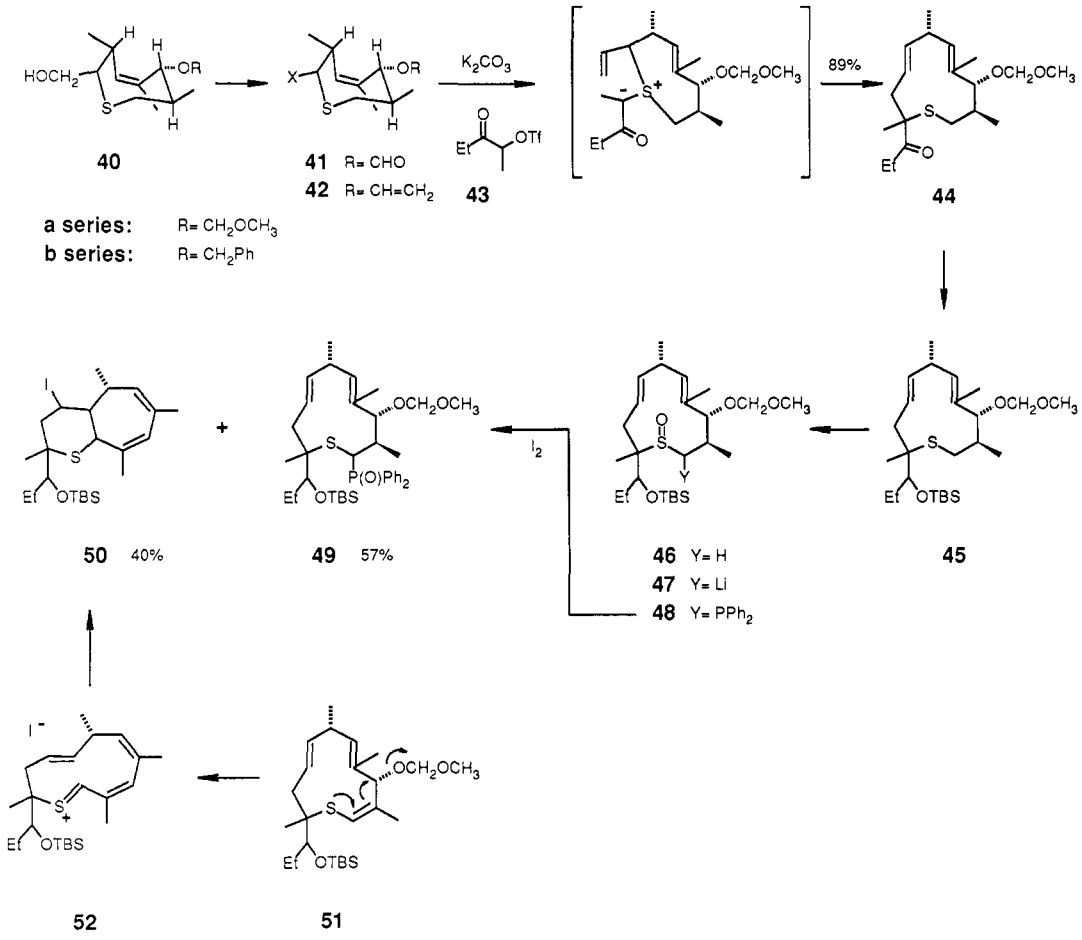


five-membered ring C–H bond. There must be a significant kinetic advantage for the ring expansion from **7b** to **11b**, and this feature is ultimately responsible for the yield improvement under equilibrating conditions in the presence of trifluoroethanol.

II. Conversion of Thiacyclooctenes to 11-Membered Sulfides

In the next stage of synthesis, a choice had to be made between the two strategies considered in Scheme I. Ideally, the trisubstituted *Z* double bond would be reduced at the eight-membered ring stage (**11**) because there are no other double bonds present to raise selectivity issues. On the other hand, the presence of sulfur in **11** severely restricts the choice of catalytic hydrogenation conditions. After numerous unsuccessful attempts to hydrogenate the alkene ester **11a** or the corresponding alkene alcohol **40a**, we decided to evaluate route B (Scheme VII). There are potential disadvantages in this approach, including the need for solvolytic sulfur replacement by oxygen and the need to discriminate between two double bonds in the hydrogenation step. However, the attractive feature of route B is that this sequence postpones the olefin hydrogenation step until sulfur has been removed from the molecule, after the sequence of ylide ring expansions and acyl transfer.

Scheme VII



1. Evaluation of the Route B Strategy. Conversion of **11a** to the necessary ring expansion substrate **42a** required reduction of **11a** to **40a** (DIBAL) and oxidation to **41a** under the Swern conditions,[23] followed by Wittig olefination. This sequence worked well, but the vinyl derivative **42a** was obtained as a mixture of diastereomers. Ring expansion to the 11-membered ring stage was achieved in excellent yield by treatment of the sulfide **42a** with keto triflate **43**. Alkylation occurred smoothly at room temperature, and the sensitive sulfonium salt intermediate was deprotonated in situ with potassium carbonate to give **44** as a mixture of diastereomers. Diastereomer formation at this stage was of some concern, but no attempt was made to optimize the product ratio pending a demonstration of subsequent steps in the synthesis.

The critical sulfur activation sequence for conversion to a thiolactone was the primary concern since this transformation is essential for the acyl transfer strategy.[8] The major ring expansion isomer was oxidized with MCPBA to the sulfoxide **46** without difficulty, but subsequent steps encountered unexpected complications. Thus, reaction of **46** with *n*-butyllithium followed by chlorodiphenylphosphine afforded the unstable phosphine sulfoxide **48**. By analogy to the model studies,[8] treatment of the phosphine sulfoxide with iodine induced the internal migration of oxygen from sulfur to phosphorus, resulting in the thermodynamically more stable sulfide phosphine oxide **49** (57%). However, a second product was also formed (40%) in the phosphenylation experiment.[22b] This substance had lost the C_3 oxygen substituent, and the UV chromophore at 270 nm (ϵ = 3200) indicated a conjugated diene. Disappearance of the disubstituted olefin protons in the NMR spectrum, a molecular ion containing iodine in the mass spectrum, and the presence of characteristic NMR signals served to define **50** as a likely structure for the undesired product. Further exposure of **49** to the reaction conditions did not induce the conversion to **50**. However, decomposition of the phosphenylation mixture containing **48** in the absence of the usual iodine catalyst afforded a new product, the vinyl sulfide **51**. Treatment of **51** with aqueous acid resulted in efficient conversion into **50**. This reaction probably involves the sulfur-assisted elimination of the doubly allylic oxygen substituent at C_3 to give the cation **52**, followed by transannular cyclization to **50**. However, the origins of vinyl sulfide **51** remain obscure.

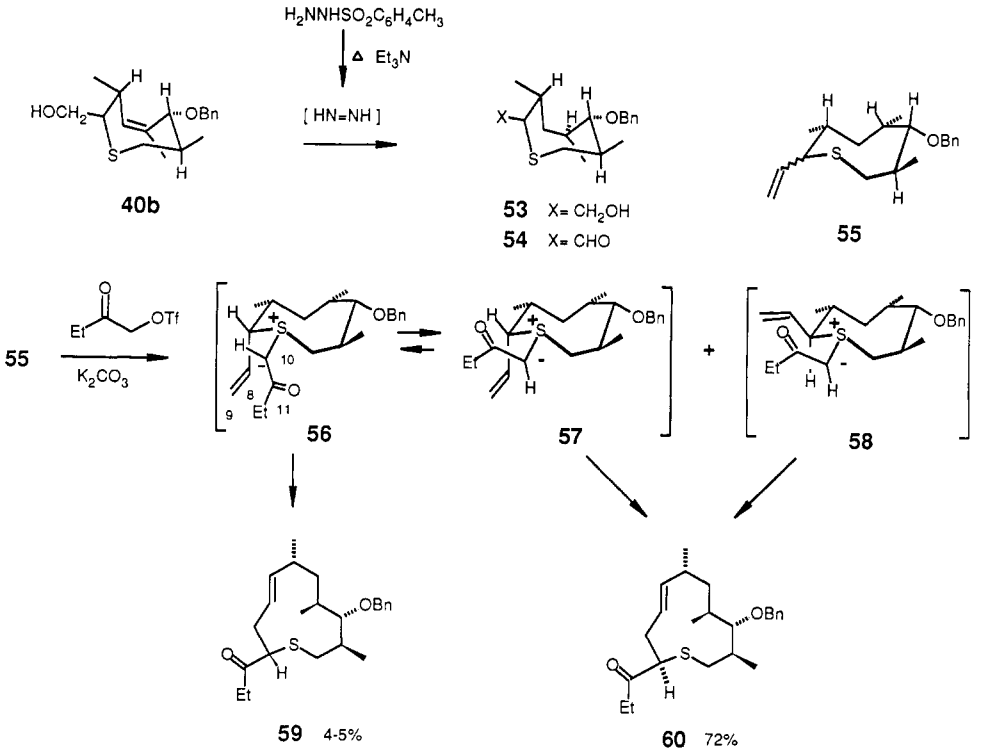
The final blow to the strategy of route B came when all attempts to deprotonate the phosphine oxide **49** as required for Horner–Bestmann oxygenation[8] to the thiolactone failed. According to the principles that govern medium-ring conformational preferences,[5] the bulky diphenylphosphinyl group undoubtedly prefers a pseudoequatorial location. The far less demanding α-proton at C_1 is therefore placed in the hindered interior of the medium-sized ring where base cannot easily find it. In view of these complications, work on route B was discontinued.

2. Demonstration of the Route A Strategy. To make route A viable, conditions had to be developed that would reduce the hindered trisubstituted double bond in **40**. It was finally found that **40** could be hydrogenated by treatment with diimide at temperatures above 120 °C.[24] For best results, a solution of **40**

(22) (a) For details of structure proof and procedures, see: Meier, G. P. Ph.D. Dissertation, University of Wisconsin, 1981. (b) **50**: 270 MHz NMR ($CDCl_3$) δ 5.78 (1 H, d, J = 8.8 Hz), 5.62 (1 H, br s), 4.35 (1 H, ddd, J = 11.4, 11.4, 4.8 Hz), 3.39 (1 H, dd, J = 7.0, 3.3 Hz), 3.36 (1 H, d, J = 11 Hz), 3.02 (1 H, dq, J = 8.8 Hz), 2.73 (1 H, dd, J = 12.9, 4.8 Hz), 2.65 (1 H, dd, J = 12.9, 11.4 Hz), 2.30 (1 H, dd, J = 11, 11 Hz), 1.88 (3 H, s); 1.78 (1 H, m), 1.73 (3 H, s), 1.43 (1 H, m), 1.38 (3 H, s), 0.94 (3 H, t, J = 7.7 Hz), 0.90 (9 H, s), 0.86 (3 H, d, J = 7.7 Hz), 0.12 (3 H, s), 0.04 (3 H, s). **51**: 270 MHz NMR ($CDCl_3$) δ 5.82 (1 H, s), 5.22 (1 H, m), 5.16 (1 H, ddd, J = 15.4, 9.6, 5.5 Hz), 4.92 (1 H, dd, J = 15.4, 8.9 Hz), 4.8 (1 H, s), 4.58 (1 H, d, J = 6.3 Hz), 4.55 (1 H, d, J = 6.3 Hz), 3.63 (1 H, dd, J = 7.0, 3.3 Hz), 3.4 (3 H, s), 2.77 (1 H, m), 2.53 (1 H, dd, J = 13.2, 5.5 Hz), 2.03 (1 H, dd, J = 13.2, 9.6 Hz), 1.80 (1 H, m), 1.73 (6 H, br s), 1.51 (1 H, m), 1.26 (3 H, s), 1.02 (3 H, d, J = 6.6), 0.98 (3 H, t, $J \approx$ 7.4 Hz), 0.89 (9 H, s), 0.07 (3 H, s), 0.06 (3 H, s).

(23) Swern, D.; Marcuso, A. J. *Synthesis* **1981**, 165, and references therein.

Scheme VIII



was refluxed in ethylene glycol–diglyme/Et_3N, while toluenesulfonylhydrazide was slowly added with a syringe pump. The high dilution technique probably minimizes bimolecular pathways for diimide self-destruction and allows reduction of the stubborn alkene. Only one isomer could be detected from this experiment, and the stereochemistry as shown in **53** is proved by eventual conversion to methynolide. The correct result was anticipated from the preferred bonding of diimide to the back side of the double bond (peripheral attack) in a transition state similar to the geometry suggested for **40**. This conformation, and the corresponding partially rehybridized bicyclic transition state for diimide reduction, avoids serious transannular as well as 1,3-eclipsing interactions and features the pseudoequatorial local conformation for allylic substituents that has been demonstrated in other cis addition reactions involving medium-sized rings.[5] Complete conversion of the alkene was difficult, but a practical result was achieved by performing the reduction to 50–60% conversion. Recycling unreacted **40** eventually gave >80% isolated yields of **53**, and as high as 84% product recovery was possible depending on the protecting group used at secondary hydroxyl and on the number of recycle operations. Comparable results were obtained in either series (**40a** or **40b**), but the benzyl ethers (series b) proved more suitable for later steps and were used in subsequent transformations.

To set the stage for the last 2,3-sigmatropic ring expansion, **53** was converted into the sensitive aldehyde **54** with use of the Swern conditions.[23] Conventional Wittig olefination then gave the vinyl derivative **55** in 86% overall yield. However, it proved impossible to avoid epimerization of **54** through this sequence, and the derived **55** was obtained as an ca. 1:1 mixture of α and β isomers. This fact was of great initial concern because the next stage of synthesis involves a 2,3-sigmatropic ring expansion to **59** or **60** with critical consequences for remote stereocontrol. The same situation had been encountered in route B, and the presence of diastereomers in the starting materials had resulted in a diastereomer mixture in the products **44**. Such a result would have complicated plans for using stereochemistry α to sulfur (C_{10}) to control the eventual stereocenter at C_{11}. However, the reaction of either diastereomer of **55** with the ketotriflate reagent[25] (Scheme VIII) in the presence of potassium carbonate gave the same major product **60**: A kinetic selectivity of ca. 15:1 in favor of **60** over **59** was achieved from the 1:1 mixture of **55**.[26] One of the separated isomers reacted with exceptional selectivity (>40:1 **60**:**59**), but separation of **55** was not necessary for a practical result and was not usually done. Special care was required in the purification of **60** due to facile equilibration, but ratios in excess of 10:1 **60**:**59** were routinely obtained after product isolation (76% efficiency based on ca. 10% recovered **55**).

The most plausible explanation for the above stereochemical result is that sulfur alkylation of either diastereomer of **55** occurs from the "peripheral" direction in the conformation shown, regardless of vinyl stereochemistry. Either ylide diastereomer **56**,**57** (both ylide α-carbon rotamers illustrated) or **58** (favored rotamer illustrated) can then adopt the necessary transoid vinyl geometry for rearrangement to an (*E*)-alkene. In the case of rotamer **57**, formation of the major product **60** requires an exceptional "pseudoaxial" COC_2H_5 substituent with respect to the five-center transition state for 2,3-shift. However, the conformational preferences of the eight-membered ring are more important, and rearrangement via rotamer **57** is favored over the competing pathway via rotamer **56**. The likely reason is that rotamer **56** encounters increased interactions between the COC_2H_5 substituent and the adjacent ring CH_2 group. The diastereomeric ylide **58** can undergo ring expansion to **60** with the preferred pseudoequatorial COC_2H_5 orientation with respect to the five-center transition state and with the same favored eight-membered ring environment suggested for **57**. Due to the combination of favorable conformational factors, it is likely that ylide **58** is the diastereomer that undergoes ring expansion with the high >40:1 preference for **60** over **59**.

The above results settled the choice of strategies in favor of route A. Access to an 11-membered cyclic sulfide containing four of the six asymmetric centers of methynolide had been achieved by using sulfur ylide ring expansion technology. A solution to the remaining stereochemical problems, the removal of sulfur from the molecule, and final adjustment of functionality are described in the following paper.

(24) Büchi, G.; Wüest, H. *J. Org. Chem.* **1979**, *44*, 546.

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III. Experimental Section

3-(*tert*-Butylthio)-2-methylpropanal. A mixture of 2-methyl-2-propanethiol (45.0 g, 0.50 mol, Aldrich, 90% purity) and 2-methylpropenal (35 g, 0.50 mol) was refluxed with Et_3N (5.0 mL) as catalyst overnight. A distilling apparatus was substituted for the reflux condenser, and pure product (73.1 g, 0.46 mol, 92%) was distilled: bp 80–85 °C at 14 mm: MS, exact mass = 160.09226; calcd for $C_8H_{16}OS$, 160.09218, error = 0.5 ppm; IR (CCl_4, cm^{-1}) CHO 2801 (m), 1727 (s); 100 MHz NMR (CCl_4) δ 9.61 (1 H, s), 2.8 (1 H, m), 2.95–2.70 (2 H, m), 1.33 (9 H, s), 1.17 (3 H, d, J = 7 Hz).

(*E*)-5-(*tert*-Butylthio)-2,4-dimethyl-2-pentenal (1). A solution of the cyclohexylimine of propionaldehyde[27] (4.58 g, 33.0 mmol) in THF (25 mL) at 0 °C was treated with LDA (33 mmol, 1.4 M in THF–hexane). After 10 min, the green-yellow solution was cooled to −78 °C, and 3-(*tert*-butylthio)-2-methylpropanal from above (4.51 g, 28.2 mmol) was added dropwise. After 2 h the solution was allowed to warm, and the solvent was evaporated. Oxalic acid (13 g), 40 mL of water, and 10 mL of THF were then added, and the mixture was refluxed for 1 h; 40 mL of Et_2O and 40 mL of water were then added. The upper layer was washed with saturated NaCl (1 × 40 mL), saturated $NaHCO_3$ (1 × 40 mL), and saturated NaCl (1 × 40 mL), dried with $MgSO_4$, and evaporated (aspirator). Distillation (97–100 °C at 0.55 mm) afforded 3.48 g (61%) of enal sufficiently pure for the next step. IR (CCl_4, cm^{-1}) 2820, 2708, 1691; 100 MHz NMR (CCl_4) δ 9.33 (1 H, s), 6.17 (1 H, dq, J = 1.8, 10 Hz), 3.0–2.65 (1 H, m), 2.55–2.40 (2 H, m), 1.73 (3 H, s), 1.29 (9 H, s), 1.15 (3 H, d, J = 6 Hz).

Ethyl 7-(*tert*-Butylthio)-4,6-dimethyl-2,4-heptadienoate (2). Neat $(EtO)_2P(O)CH_2CO_2Et$ (Aldrich, 5.95 mL, 30.0 mmol) was dropped into a suspension of NaH (Ventron, 724 mg, 30.0 mmol) in THF (50 mL) under slight N_2 pressure. After an additional hour of stirring at ambient temperature, unsaturated aldehyde **1** (5.0 g, 25 mmol) was slowly added. A gummy precipitate formed during this addition and made even mechanical stirring difficult. After 1 day, the yellow supernatant was decanted, and the solid was washed with 50 mL of Et_2O. The solvent was evaporated, and the product was distilled (5.14 g, 76%, bp 130 °C at 0.18 mm). **2**: MS, exact mass = 270.16678; calcd for $C_{15}H_{26}O_2S$, 270.16536; error = 5.3 ppm; IR (CCl_4, cm^{-1}) C=O, 1694; 100 MHz NMR (CCl_4) δ 7.20 (1 H, d, J = 16 Hz), 5.74 (1 H, d, J = 16 Hz), 5.68 (1 H, d, J = 7 Hz), 4.12 (2 H, q, J = 6 Hz), 2.9–2.3 (3 H, m), 1.81 (3 H, s), 1.28 (9 H, s), 1.26 (3 H, t, J = 6 Hz), 1.09 (3 H, d, J = 6 Hz).

Ethyl 3-(3-Acetoxy-2,4-dimethylthiolan-2-yl)propenoate (5a). A solution of the diene sulfide **2** (45.5 g, 169 mmol) in CH_3CO_2H (200 mL) was treated with 30% H_2O_2 (Fischer, 19.3 g, 170 mmol) over a 20-min period. The rate of addition was adjusted to maintain a reaction temperature of about 45 °C. Following overnight stirring, the solvent was partially distilled (aspirator), leaving 110 mL of a solution of the sulfoxide **3**. The above solution (10.0 mL, 15.3 mmol sulfoxide) was injected with a syringe pump (0.15 mL/min) into refluxing 1:1 $(CH_3CO)_2O$/CH_3CO_2H (50 mL) containing $BF_3{\cdot}Et_2O$ (0.10 mL) as catalyst. The nearly black reaction was refluxed for an additional 15 min whereupon 0.25 g of $NaO_2CCH_3{\cdot}H_2O$ was added, and the solvents were removed by distillation (aspirator). The dark residue was dissolved in 20 mL of Et_2O and stirred with 20 mL of saturated $NaHCO_3$ for 30 min. The Et_2O solution was washed with water (1 × 20 mL), dried (Na_2SO_4), evaporated, and distilled (bp 133 °C at 0.09 mm) to yield a viscous yellow oil **5a** (3.36 g, 81%). An analytical sample was obtained by preparative GLPC (5 ft × 1/4 in. 8% SE-30/Chromosorb W). MS, exact mass = 272.10899; calcd for $C_{13}H_{20}O_4S$, 272.10824, error = 2.8 ppm; IR (CCl_4, cm^{-1}) C=O, 1720; 100 MHz NMR (CCl_4) δ 6.84 (1 H, d, J = 16 Hz), 5.68 (1 H, d, J = 16 Hz), 4.88 (1 H, d, J = 10 Hz), 4.11 (2 H, q, J = 5 Hz), 2.89 (1 H, dd, J = 10, 8 Hz), 2.59 (1 H, dd, J = 10 Hz, 10 Hz), 2.6–2.4 (1 H, m), 2.04 (3 H, s), 1.46 (3 H, s), 1.27 (3 H, t, J = 5 Hz), 1.07 (3 H, d, J = 6 Hz).

Ethyl-3-(3-(Methoxymethoxy)-2,4-dimethylthiolan-2-yl)propenoate (5c). A solution of the acetate **5a** (29.8 g, 0.109 mol) in CH_3OH (110 mL) was stirred for 45 min with K_2CO_3 (4.0 g). The base was then neutralized with aqueous HCl (4.8 mL of a 6 M solution), and the solvent was evaporated. The yellow oil was then dissolved in 50% Et_2O/hexane (200 mL) and washed with 3 × 200 mL water. After drying ($MgSO_4$) and evaporation, the alcohol **5b** was sufficiently pure for the next step. The methoxy methyl ether **5c** was prepared according to the procedure of Fujita et al.[28] A solution of the hydroxythiolane **5b** (85.6 g, 0.396 mol) in 100 mL of dry $CHCl_3$ and 500 mL of dry dimethoxymethane was rapidly stirred (magnetic stir bar) and P_2O_5 (79.0 g) was added in 5 portions over 1 h, during which a gummy precipitate formed. After stirring for an additional 3 h no alcohol was detected by TLC. The solution was decanted into 200 mL of saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3 × 100 mL), dried ($MgSO_4$), and filtered, and solvent was removed (aspirator). The resulting yellow oil was distilled (bp 105–115 °C at 0.05 mmHg) to give a light yellow oil (87.6 g, 85%). An analytical sample of **5c** was obtained by preparative TLC (50% ether/hexane, R = 0.47); MS, exact mass 260.1083; calcd for $C_{12}H_{20}O_4S$, 260.1084, 0.4 ppm error). IR (neat, cm^{-1}) C=O, 1710 (s); 270 MHz NMR ($CDCl_3$) δ 7.10 (1 H, d, J = 15.8 Hz), 5.86 (1 H, d, J = 15.8 Hz), 4.62 (1 H, d, J = 6.8 Hz), 4.56 (1 H, d, J = 6.8 Hz), 3.74 (3 H, s), 3.61 (1 H, d, J = 9.6 Hz), 3.34 (3 H, s), 2.87 (1 H, dd, J = 10.2, 6.8 Hz), 2.7–2.3 (2 H, m), 1.52 (3 H, s), 1.16 (3 H, d, J = 6.3 Hz).

2,4-Dimethyl-3-(methoxymethoxy)-2-(1-propenyl)thiolane (6a). To a solution of the thiolane enoate **5c** (35.4 g, 0.136 mol) in 200 mL of dry CH_2Cl_2 at −78 °C under N_2 was added DIBAL (1.0 M in THF, 300 mL, 0.300 mol) via cannula. After the solution had been stirred for 20 min at −78 °C and then had been brought to 24 °C, it was added slowly to 100 mL of 10% HCl via cannula. The organic phase was separated, and the aqueous phase was extracted with 100 mL of CH_2Cl_2 (3 × 100 mL). The combined organics were washed with 10% HCl (3 × 100 mL) followed by brine (2 × 100 mL), dried (K_2CO_3), and filtered, and solvent was removed (aspirator) to give a yellow oil (30.0 g) which was used in the subsequent step without further purification. The resulting allylic alcohol (30.00 g, 0.129 mmol) was dissolved in 300 mL of dry THF under N_2 and was cooled to −78 °C. A solution of *n*-butyllithium (95 mL, 0.162 mol) in hexane was added over 0.5 h. The solution was stirred for 15 min at −78 °C, and then methanesulfonyl chloride (12.5 mL, 0.162 mol) was rapidly added. The solution was stirred at −78 °C for 0.75 h, and lithium triethylborohydride (1 M in THF, 194 mL, 0.194 mol) was then added over 0.75 h. The solution was stirred at −78 °C for 0.5 h and warmed to 24 °C. After cannula transfer into 500 mL of 10% HOAc, the mixture was extracted with ether (4 × 50 mL). The combined organics were washed (4 × 50 mL of 10% aqueous NaOH, 3 × 50 mL of H_2O, and 2 × 50 mL of brine), dried (K_2CO_3), and filtered, and solvent was removed (aspirator) to give a yellow oil. The yellow oil was eluted through 0.45 Kg of Al_2O_3 (Fisher) with 2 L of 10% ether/hexane, the solvent was evaporated, and the residual oil was distilled to give the title compound (bp 62–65 °C at 0.5 mmHg, 22.54 g, 80%). **6a**: MS, exact mass 216.11840; calcd for $C_{11}H_{20}O_2S$, 216.11839, 0.0 ppm error; IR (neat, cm^{-1}) C–O, 1050, 1030; 100 MHz NMR (CCl_4) δ 5.7–5.3 (2 H, m), 4.6 (1 H, d, J = 7 Hz), 4.32 (1 H, d, J = 7 Hz), 3.36 (1 H, d, J = 4 Hz), 3.22 (3 H, s), 2.9–2.0 (3 H, m), 1.60 (3 H, d, J = 5 Hz), 1.32 (3 H, s), 1.05 (3 H, d, J = 7 Hz).

2,4-Dimethyl-3-(benzyloxy)-2-(1-propenyl)thiolane (6b). The methoxymethoxy ether **6a** was heated at 65 °C in methanol (5 mL) containing 2 drops concentrated HCl for 1.5 h. After cooling, the mixture was diluted with ether (15 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), and evaporated (aspirator) to give the deprotected secondary alcohol **6c** as an oil. Preparation of the benzyl ether **6b** was performed by adding the alcohol **6c** (115 mg, 0.668 mmol) in THF (5 mL) to a stirred suspension of NaH (20 mg, 0.834 mmol) in 0.5 mL of THF. After 1 h, benzyl bromide (0.24 mL, 2.02 mmol) and tetra-*n*-butylammonium iodide (5 mg) were added, and the reaction was stirred 18 h at room temperature. After dilution with ether (15 mL), the mixture was washed with saturated aqueous NH_4Cl, water, and brine (7 mL each), dried ($MgSO_4$), and concentrated (aspirator). Purification by flash chromatography[29] (2% ethyl acetate/hexane) gave 131 mg (74%) of **6b**: oil, analytical TLC (silica gel F254, 10% ethyl acetate/hexane, R_f = 0.51); MS, exact mass 262.1397; calcd for $C_{16}H_{22}OS$, 262.1392; error = 2.1 ppm; 200 MHz NMR ($CDCl_3$) δ 7.36–7.22 (5 H, m), 5.79–5.50 (2 H, m), 4.68 (1 H, d, J = 11.4 Hz), 4.45 (1 H, d, J = 11.4 Hz), 3.35 (1 H, d, 9.9 Hz), 2.85–2.74 (1 H, m), 2.53–2.28 (2 H, m), 1.69 (3 H, d, J = 4.8 Hz), 1.53 (3 H, br s), 1.08 (3 H, d, J = 6.2 Hz).

2-Carbethoxy-6-(methoxymethoxy)-3,5,7-trimethylthiacyclooct-4-ene (11a) from 6a via Triflate Alkylation and Ring Expansion. The thiolane **6a** (0.4115 g, 1.90 mmol) was dissolved in 5 mL of dry CH_3CN at 24 °C, and K_2CO_3 (freshly roasted, 0.276 g, 2.0 mmol) was added. Carbethoxymethyl trifluoromethylsulfonate[25] was added, and the slurry was stirred 7.5 h. The reaction was quenched with 2 mL of 25% Me_2NH in H_2O and extracted three times with 10-mL portions of 20% ether/hexane, and the organic phase was washed twice with 10 mL of H_2O and twice with 10 mL of brine. The organic phase was dried ($MgSO_4$), filtered, and evaporated to give a yellow oil (0.6997 g). Preparative TLC (SiO_2/15% ether/hexane) gave **11a** as a colorless oil (R_f 0.28, 0.2050 g, 36%, bp 90–110 °C at 0.05 mmHg). MS, exact mass 302.1551; calcd for $C_{15}H_{26}O_4S$, 302.1545, 0.3 ppm error; IR (neat, cm^{-1}) CO_2Et, 1710; 270 MHz NMR ($CDCl_3$) δ 5.46 (1 H, d, J = 8.5 Hz), 4.70 (1 H, d, J = 10.3 Hz), 4.54 (2 H, s), 4.19 (1 H, dq, J = 11.0, 7.0 Hz), 4.14 (1 H,

(26) Kinetic selectivity was determined by NMR methods on the crude product obtained from rapid workup at 0 °C.

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dq, J = 11.0, 7.0 Hz), 3.42 (3 H, s), 3.40–3.30 (1 H, m), 3.22 (1 H, d, J = 2.6 Hz), 3.15–2.90 (1 H, m), 2.30 (1 H, dd, J = 15.1, 2.2 Hz), 2.18 (1 H, m), 1.67 (3 H, br s), 1.28 (3 H, t, 7.0 Hz), 1.18 (3 H, d, J = 6.3 Hz), 1.10 (3 H, d, J = 7.0 Hz).

Ring Expansion of Thiolane 6b (CF_3CH_2OH Conditions). A solution of sulfide **6b** (47.4 mg, 0.181 mmol), ethyl bromoacetate (61 μL, 0.613 mmol), 2,6-lutidine (32 μL, 0.275 mmol), and sodium iodide (86.0 mg, 0.574 mmol) in 3 mL of 2,2,2-trifluoroethanol was heated at 80 °C for 23 h. The reaction was cooled, diluted with ca. 15 mL of ether, washed with saturated aqueous NH_4Cl, water, and brine (7 mL each), and the organics were dried. After filtration and solvent removal the residue was eluted down a short silica gel plug (10% ethyl acetate/hexane) to remove polar impurities. Solvent evaporation followed by chromatography (HPLC, 4% ethyl acetate/hexane, 5 mL/min) yielded 2.7 mg (4%) of the starting sulfide **8**, 42.6 mg (67%) of **11b** and **12b** (7:1), and 5.7 mg (7%) of the trifluoroethyl ethers **34**.

6-(Benzyloxy)-2-(hydroxymethyl)-3,5,7-trimethylthiacyclooct-4-ene (40b). To a stirred, 0 °C solution of the esters **11b** containing residual **33** (10.0 mg, 28.7 μmol; 3.5:1 ratio, respectively) in 2 mL of ether was added lithium aluminum hydride (1.6 mg, 42.1 μmol). The reaction was stirred for 10 min at 0 °C followed by warming to room temperature. After 34 min the reaction was quenched with 3 drops of water, diluted with ca. 10 mL of ether, and washed with water and brine (5 mL each), and the organics were dried ($MgSO_4$). After filtration and solvent removal the residue was eluted down a short silica gel plug (20% ethyl acetate/hexane) to remove polar impurities. Solvent removal and chromatography (HPLC, 20% ethyl acetate/hexane, 5 mL/min) gave 6.6 mg of alcohol **40b**, 97% based on **11b**. **40b**: oil, analytical TLC (silica gel F254), 20% ethyl acetate/hexane, R_f = 0.29; MS, exact mass calcd for $C_8H_{26}O_2S$ = 306.1653; found = 306.1648, error = 1.8 ppm; IR (neat, cm^{-1}) O–H, 3450; C–O, 1050, 200 MHz NMR ($CDCl_3$) δ 7.38–7.26 (5 H, m), 5.22 (1 H, br d, J = 9.0 Hz), 4.48 (1 H, d, J = 11.4 Hz), 4.32 (1 H, d, J = 10.0 Hz), 4.23 (1 H, d, J = 11.4 Hz), 3.78 (1 H, ddd, J = 11.0, 11.0, 4.4 Hz), 3.47 (1 H, dd, J = 11.0, 11.0 Hz), 3.14–2.98 (1 H, m), 2.84 (1 H, dd, J = 14.5, 3.5 Hz), 2.72 (1 H, br d, J = 11.0 Hz), 2.42 (1 H, br d, J = 11.0 Hz), 2.23–2.09 (1 H, m), 2.10 (1 H, dd, J = 14.5, 2.4 Hz), 1.66 (3 H, br s), 1.16 (3 H, d, J = 6.4 Hz), 1.11 (3 H, d, J = 7.0 Hz).

Diimide Reduction of 40b. Preparation of 6-(Benzyloxy)-2-(hydroxymethyl)-3,5,7-trimethylthiocane (53b). To a stirred solution of olefin **40b** (340.8 mg, 1.113 mmol) and Et_3N (3.30 mL, 23.6 mmol) in 5 mL of ethylene glycol in a 190 °C silicone oil bath was added dropwise via cannula a solution of *p*-toluenesulfonylhydrazide (4.14 g, 22.4 mmol; Aldrich) in 16 mL of diglyme. After addition was complete (4 h) the reaction was heated an additional 30 min and cooled. The mixture was diluted with ca. 30 mL of ether, washed with 5% aqueous NaOH (2 × 15 mL), water (2 × 15 mL), and brine (15 mL). The combined aqueous washes were extracted with 10 mL of ether, and the combined organics were dried ($MgSO_4$). After filtration, ether evaporation, and Kugelrohr distillation (ca. 120 °C at 0.5 mmHg) to remove diglyme, the residue was eluted down a short silica gel plug (20% ethyl acetate/hexane). Solvent evaporation and chromatography (HPLC, 16% ethyl acetate/hexane, 5 mL/min) afforded 146 mg of starting olefin **40b** and 172 mg of sulfide **53b**. The recovered olefin (146 mg, 0.478 mmol) was resubmitted to the reaction conditions with use of Et_3N (1.40 mL, 10.0 mmol), ethylene glycol (2 mL), and *p*-toluenesulfonylhydrazide (1.80 g, 9.66 mmol) in 7 mL of diglyme. Identical workup of the reaction and chromatography as above gave 63.3 mg of recovered olefin **40b** (18% based on starting **40b**) and 53.7 mg of **53b**, for a combined yield of 225.7 mg (66% based on **40b**) of **53b**: oil, analytical TLC (silica gel F254), 20% ethyl acetate/hexane, R_f = 0.28; MS, exact mass calcd for $C_8H_{28}O_2S$ = 308.181; found = 308.1805, error = 1.6 ppm; IR (neat, cm^{-1}) O–H, 3450, C–O, 1075; 200 MHz NMR ($CDCl_3$) δ 7.36–7.27 (5 H, m), 4.63 (1 H, d, J = 11.2 Hz), 4.51 (1 H, d, J = 11.2 Hz), 3.62 (1 H, ddd, J = 11.0, 11.0, 4.6 Hz), 3.41 (1 H, dd, J = 11.0, 11.0 Hz), 3.22 (1 H, dd, J = 8.1, 2.4 Hz), 3.11 (1 H, ddd, J = 10.3, 3.9, 3.7 Hz), 2.67 (1 H, d, J = 14.1 Hz), 2.39–2.14 (3 H, m), 2.07–1.84 (3 H, m), 1.10 (1 H, dd, J = 13.9, 7.1 Hz), 1.09 (3 H, d, J = 6.4 Hz), 1.06 (3 H, d, J = 6.2 Hz), 0.78 (3 H, d, J = 6.4 Hz).

Diimide Reduction of 40a. 2-(Hydroxymethylene)-6-(methoxymethoxy)-3,5,7-trimethylthiocane (53a). *p*-Toluenesulfonhydrazide (52 g, 20 equiv) in diglyme (170 mL) was added dropwise over 10.5 h via a pressure equalizing funnel to olefin **40a** (3.63 g, 14.0 mmol) in ethylene glycol (180 mL, distilled from sodium hydroxide) and triethylamine (41 mL, 21 equiv) which had been preheated to 180 °C. The yellow mixture was heated at this temperature another 0.5 h. After cooling to room temperature the solvents were removed at reduced pressure (5 mmHg, 71 °C). The residue was dissolved in ether (200 mL) and was washed with 10% NaOH (3 × 30 mL), water (2 × 20 mL), and brine (1 × 20 mL). The combined aqueous layers were extracted with ether (2 × 100 mL), and the above wash procedure was repeated. The organic layers were combined, and the resulting yellow oil was passed through a silica gel plug (60–200 mesh, 50 g), eluting with chloroform to remove tosylhydrazide byproducts. Elution with 50% ethyl acetate gave a yellow viscous oil (3.58 g), from which starting material 570 mg) was obtained by recrystallization from 5% ethyl acetate. Preparative HPLC of the mother liquor (27% ethyl acetate, 13% methylene chloride, 60% hexane) separated the reduction product **53a**, a clear oil (retention time 19.4 min), from the starting material **40a** (retention time 15.1 min). After solvent removal the ratio of reduction product **53a** (2.35 g, 64%) to olefin **40a** (0.85 g, 23%) was found to be 2.8:1. **53a**: oil; silica gel, 1:4 ether/hexane, R_f = 0.11; *m/e*: exact mass calcd for $C_{13}H_{26}O_3S_1$ = 262.1596; found = 262.1599, error = 1.2 ppm; IR (neat, cm^{-1}) OH, 3450; 270 MHz NMR ($CDCl_3$) ppm 4.66 (1 H, d, J = 6.8 Hz), 4.63 (1 H, d, J = 6.8 Hz), 3.61 (1 H, ddd, J = 11.3, 10.9, 4.3 Hz), 3.41 (1 H, dd, J = 10.9, 10.7 Hz), 3.37 (3 H, s), 3.30 (1 H, dd, J = 8.0, 1.8 Hz), 3.09 (1 H, ddd, J = 10.7, 4.3, 4.3 Hz), 2.89 (1 H, dd, J = 15.4, 1.3 Hz), 2.39 (1 H, d, J = 11.3 Hz), 2.33 (1 H, dd, J = 15.4, 7.7 Hz), 2.18–1.98 (1 H, m), 2.14 (1 H, dddq, 8.0, 7.7, 1.3, 6.9), 1.97–1.83 (2 H, m), 1.18–1.08 (1 H, m); 1.06 (3 H, d, J = 6.9 Hz), 0.97 (3 H, d, J = 6.9 Hz), 0.78 (3 H, d, J = 6.6 Hz).

Preparation of 6-(Benzyloxy)-3,5,7-trimethyl-2-vinylthiocanes (55). To a stirred, −78 °C solution of oxalyl chloride (10 μL, 0.114 mmol) in 2 mL of CH_2Cl_2 was added DMSO (17 μL, 0.239 mmol).[23] After ca. 2 min the alcohol **53** (32.0 mg, 0.104 mmol) in 2 mL of CH_2Cl_2 was added dropwise via cannula, and the mixture was stirred for 20 min. Triethylamine (58 μL, 0.416 mmol) was added, and the reaction was stirred at −78 °C for 20 min. The ice bath was removed, and the reaction mixture was stirred an additional 7 min. It was then diluted with ca. 10 mL of ether and washed with saturated aqueous NH_4Cl, water, and brine (5 mL each), and the organics were dried ($MgSO_4$). Filtration and solvent removal afforded 30.7 mg of an oil which was carried on without further purification due to the sensitivity of the aldehyde **54**.

To a stirred suspension of methyltriphenylphosphonium bromide (52.9 mg, 0.148 mmol; Aldrich) in 2 mL of toluene was added potassium *tert*-butoxide (0.36 mL, 0.40 M in THF). After 1 h the bright yellow ylide solution was cooled to −78 °C, and the aldehyde **54** in 2 mL of toluene was added dropwise via cannula. The reaction was stirred for 1 h at −78 °C followed by removal of the ice bath and stirring an additional 30 min. The mixture was applied directly to a short silica gel plug and eluted with 5% ethyl acetate/hexane to afford 27.1 mg (86%) of the vinyl epimers **55** (α:β = 1.3:1 by NMR integration). These were separated by HPLC (2% ethyl acetate/hexane, 5 mL/min) to give 13.4 mg of α-vinyl **55** and 11.0 mg of β-vinyl **55** (stereochemical assignments are tentative).

α-55. Oil, analytical TLC (silica gel F254), 20% ethyl acetate/hexane, R_f = 0.54; MS, exact mass calcd for $C_9H_{28}OS$ = 304.1861; found = 304.1877, error = 5.2 ppm; IR (neat, cm^{-1}) C=C, 1640, C–O, 1050; 270 MHz NMR ($CDCl_3$) δ 7.36–7.25 (5 H, m), 5.90 (1 H, ddd, J = 16.8, 10.1, 7.4 Hz), 5.22 (1 H, ddd, J = 16.8, 1.4, 1.4 Hz), 5.13 (1 H, ddd, J = 10.1, 1.2, 1.2 Hz), 4.60 (1 H, d, J = 11.2 Hz), 4.49 (1 H, d, J = 11.2 Hz), 3.49 (1 H, dd, J = 8.8, 3.2 Hz), 3.33 (1 H, dd, J = 7.6, 3.8 Hz), 2.91 (1 H, dd, J = 15.5, 2.9 Hz), 2.41 (1 H, dd, J = 15.5, 5.3 Hz), 2.22–2.05 (3 H, m), 1.82 (1 H, ddd, J = 15.2, 8.8, 8.6 Hz), 1.19 (1 H, ddd, J = 15.2, 6.5, 2.6 Hz), 1.07 (3 H, d, J = 6.8 Hz), 1.02 (3 H, d, J = 7.1 Hz), 0.89 (3 H, d, J = 6.8 Hz).

β-55. Oil, analytical TLC (silica gel F254), 20% ethyl acetate/hexane, R_f = 0.54; MS, exact mass calcd for $C_9H_{28}OS$ = 304.1861; found = 304.186, error = 0.4 ppm; IR (neat, cm^{-1}) C=C, 1640, C–O, 1050; 270 MHz NMR ($CDCl_3$) δ 7.36–7.22 (5 H, m), 5.62 (1 H, ddd, J = 16.8, 10.1, 9.2 Hz), 5.14 (1 H, ddd, J = 16.8, 0.9, 0.9 Hz), 5.06 (1 H, dd, J = 10.1, 1.4 Hz), 4.52 (2 H, s), 3.48 (1 H, dd, J = 6.9, 2.2 Hz), 3.15 (1 H, dd, J = 15.5, 2.6 Hz), 3.06 (1 H, dd, J = 9.3, 9.3 Hz), 2.71 (1 H, dd, J = 15.5, 3.8 Hz), 2.49–2.39 (1 H, m), 2.20–2.08 (1 H, m), 1.88–1.70 (2 H, m), 1.32 (1 H, dd, J = 13.9, 6.2 Hz), 1.06 (3 H, d, J = 6.8 Hz), 0.98 (3 H, d, J = 6.8 Hz), 0.91 (3 H, d, J = 6.5 Hz).

Ring Expansion of 55. Thiacycloundecenes 59 and 60. To a mixture of sulfides **55**, R = benzyl (987 mg, 3.246 mmol), in dry CH_3CN (11 mL) at 0 °C was added the triflate from 1-hydroxy-2-butanone[25] (890 mg, 1.24 equiv). 2,6-Lutidine (0.5 mL, 1.3 equiv) was added 0.5 h later, and the temperature was maintained between 0 °C and 5 °C for 6 h. K_2CO_3 (550 mg, 1.2 equiv) was added, and the reaction mixture turned yellow over the next 0.5 h. After warming to room temperature for 3 h, the mixture was extracted with hexane (4 × 50 mL). The hexane soluble material was washed with 10% H_2SO_4 (1 × 10 mL) and saturated $NaHCO_3$ (1 × 10 mL). After drying and solvent removal, the resulting yellow oil was passed through a silica gel plug (60–200 mesh, 10 g, 20% ether) and purified further by HPLC (Waters Prep-500) using as eluant a mixture of 7% ether, 3% CH_2Cl_2, and 90% hexane, flow rate = 6.0 mL/min, to obtain **60** (6.8 min, 782 mg, 64%), **59** (8.3 min, 50 mg, 4%),

and starting material (4.7 min, 93 mg, 9.4%) as clear oils. The combined yield of **60** and **59** (15.7:1) based upon recovered starting material was 76%. **60**: oil; silica gel, 1:4 ether/hexane, R_f = 0.39; MS, exact mass calcd for $C_{23}H_{34}O_2S_1$ = 374.2271; found 374.2281, error = 2.6 ppm; IR (neat, cm^{-1}) C=O, 1719; 200 MHz NMR ($CDCl_3$) δ 7.38-7.20 (5 H, m), 5.79 (1 H, ddd, J = 15.4, 8.7, 5.3 Hz), 5.36 (1 H, dd, J = 15.4, 9.4 Hz), 4.52 (1 H, d, J = 11.7 Hz), 4.49 (1 H, d, J = 11.7 Hz), 3.31 (1 H, dd, J = 6.4, 3.9 Hz), 3.20 (1 H, dd, J = 8.0, 2.1 Hz), 2.85 (1 H, dq, J = 17.5, 7.3 Hz), 2.65-2.55 (1 H, m), 2.63 (1 H, dd, J = 13.2, 4.9 Hz), 2.50 (1 H, dq, J = 17.5, 7.3 Hz), 2.26 (1 H, ddd, J = 13.3, 8.7, 3.9 Hz), 2.12 (1 H, dd, J = 13.2, 4.2 Hz), 2.05-1.75 (3 H, m), 1.55 (1 H, ddd, J = 15.2, 8.0, 4.5 Hz), 1.20-0.95 (1 H, m), 1.08 (3 H, t, J = 7.3 Hz), 1.02 (3 H, d, J = 7.1 Hz), 1.00 (3 H, d, J = 6.2 Hz), 0.98 (3 H, d, J = 6.7 Hz). **59**: oil; silica gel, 1:4 ether/hexane, R_f = 0.28; MS, exact mass calcd for $C_{23}H_{34}O_2S_1$ = 374.2271; found 374.228, error = 2.4 ppm; IR (neat, cm^{-1}): C=O, 1716; 200 MHz NMR (C_6D_6) δ 7.39-7.21 (5 H, m), 5.21 (1 H, ddd, J = 15.0, 9.0, 0.9 Hz), 4.91 (1 H, ddd, J = 15.0, 10.1, 4.9 Hz), 4.46 (1 H, d, J = 11.5 Hz), 4.32 (1 H, d, J = 11.5 Hz), 2.97 (1 H, dd, J = 10.9, 2.3 Hz), 2.84-1.85 (7 H, m), 1.90-1.10 (2 H, m), 1.06 (3 H, d, J = 6.6 Hz), 1.05 (3 H, t, J = 7.3 Hz), 1.04 (3 H, d, J = 7.1 Hz), 1.03 (3 H, d, J = 7.3 Hz), 0.92 (3 H, d, J = 6.4 Hz).

Supplementary Material Available: Experimental details for the acyclic route to **11b**, dienes **32** and **33**, and ether **34** and spectral data (R_f, IR, MS, and ^{1}H NMR) for **13**, **15**, **16**, **27**, **28**, **30**, **11b**, **32**, **33**, and **34** (6 pages). Ordering information is given on any current masthead page.

Total Synthesis of *d,l*-Methynolide. Sulfur Removal and Remote Stereocontrol

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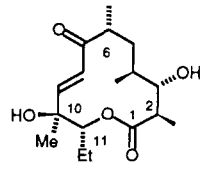
Abstract: The details for the conversion of **1** into *d,l*-methynolide are described. Key steps include the highly selective reduction to alcohol **3**, the oxidation α to sulfide sulfur from **3** to thiolactone **13**, and the acyl transfer from **14** to the lactone **16**. Photochemical oxidation converts phenacyl sulfide **17** into the ketone **21** via an intermediate thione and the derived 2 + 3 adduct **20**. Finally, selective Grignard addition to enone alcohol **24** introduces the last asymmetric center. Redox adjustments and deprotection completes the total synthesis. A similar route to C_{10}-*epi*-methynolide **37** is also reported. The synthetic sequence depends on relative stereocontrol. This is achieved by using the predictable conformational properties of medium-sized ring intermediates and by taking advantage of the stereoelectronic effect of sulfur α to ketone carbonyl.

We now describe the final stages in the sulfur-mediated total synthesis of *d,l*-methynolide. Two potential precursors of methynolide, the thiacycloundecenes **1** and **2** (Scheme I), are available by a sequence of sulfur ylide ring expansions.[1] Selectivity as high as 40:1 for the isomer-assigned structure **1** can be achieved by starting with purified precursors, but substantial amounts of **2** can also be obtained by base-induced equilibration or by performing the isolation procedure without suitable precautions. In principle, either **1** or **2** can be reduced to give the correct C_{11} hydroxyl stereochemistry of methynolide, depending on whether the reducing agent is chosen to maximize Felkin-Nguyen (Anh) or chelation control.[2-4] This key feature of the sulfur-based strategy for remote stereocontrol requires only that one of the two isomers can be obtained with high selectivity, as demonstrated in the preceding paper.



METHYNOLIDE

Initially, the stereochemical assignment at C_{10} (α to sulfur) was not known with certainty because neither ketone was crystalline. Accordingly, both **1** and **2** were treated with $LiEt_3BH$ to promote Felkin-Nguyen selectivity, and each gave a unique preponderant alcohol. The major byproduct in each case (ca. 5%) proved to be the alcohol derived from reduction of the epimerized starting material, suggesting that minor interconversion of the ketones **1** and **2** by enolization was competitive with reduction. In any event, the alcohol obtained from the minor ring expansion ketone **2** could be crystallized, and the structure **3*** was established by X-ray crystallography. This evidence proved that previous stereochemical assignments had been made correctly and that Felkin-Nguyen facial selectivity had in fact been followed in the reduction of **2**. Assuming that **1** likewise had been reduced under Felkin-Nguyen control by $LiEt_3BH$, the (noncrystalline) alcohol product must be **3** (94% yield). If so, then this isomer has the methynolide stereochemistry at all five relevant asymmetric centers. Alcohol **3** is of course also the most accessible isomer since it corresponds to the kinetic product (**1**) from ring expansion.

To confirm the above assignment of stereochemistry, both **3** and **3*** were carried through several of the subsequent steps, up to the point of final sulfur removal. We will use the asterisk (*) designation to identify the unnatural stereochemistry at C_{11} in a series of intermediates derived from **2** (these isomers also differ at C_{10} compared to precursors of methynolide). Thus, **3** was protected as the silyl ether **4** (99%) and oxidized with MCPBA to give sulfoxide **5** (99%), and **3*** was similarly taken on to **5***. Earlier model studies had established a technique for conversion of sulfoxides into the thiolactones required for acyl transfer,[5] and the sequence of sulfoxide anion phosphenylation to **7** followed by

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