THE JOURNAL OF Organic Chemistry

VOLUME 53, NUMBER 16

© Copyright 1988
by the American Chemical Society

AUGUST 5, 1988

# Seven-Ring Annulation: A Linch-Pin Approach to a Tetracyclic Precursor of the Lathrane Diterpenes[1]

T. F. Braish, J. C. Saddler, and P. L. Fuchs*

*Department of Chemistry, Purdue University, West Lafayette, Indiana 47907*

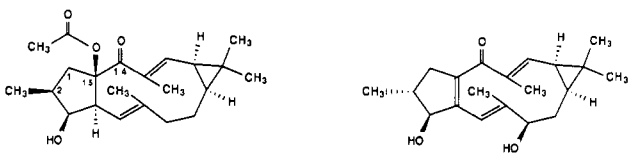
*Received September 10, 1987*

The synthesis of a chiral tetracyclic intermediate (**5b**) as a precursor of the lathrane diterpenes is described. The key step is the addition of chiral thioacetal **47** to a chiral vinyl sulfone **40** in the absence of HMPA. Further elaboration of the resulting intermediate **59** provided enol ether **67**, which was cyclized with dimethyl(methylthio)sulfonium tetrafluoroborate to give the tetracyclic intermediate **5b**.

Jolkinol D (**1**)[2] is a prototypical member of the lathrane diterpenes, which is a group of about a dozen members that have been isolated from the plant families Euphorbiacae and Thymelaeaceae.[3] These compounds all contain a central 11-membered ring that is fused on either side by a cyclopentyl ring and a *gem*-dimethylcyclopropane moiety. Synthetic activity in this area has been sparse,[4-6] with the most notable accomplishment being the total synthesis of bertyadionol (**2**) by the Smith group.[6]

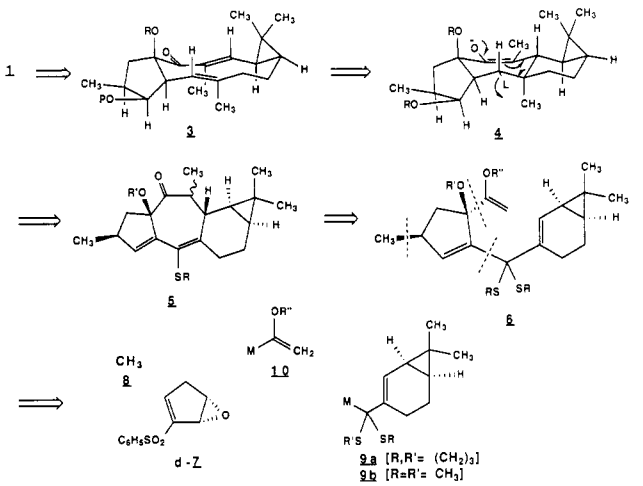
Our interest in this area was stimulated by the prospect of construction of the central cycloundecenone ring by an intraannular enolate-promoted fragmentation (**4** to **3**), a reaction we had earlier developed in a different context.[7]

**Scheme I**



**1** Jolkinol D **2** Bertyadionol

**Scheme II**



Synthesis of the precursor ketone for enolate **4** was envisaged to arise in several steps from dienyl sulfide **5**, which was to be prepared from cyclization of bisallyl thioacetal **6**.[8] The preparation of **6** required new methodology involving chiral substrate **7** as the focal point for a sequence

(1) Syntheses via Vinyl Sulfones. 28. For a review, see: Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903.

(2) Uemura, D.; Nobuhara, K.; Nakayama, Y.; Shizuri, Y.; Hirata, Y. *Tetrahedron Lett.* **1976**, 4593.

(3) (a) Ghisalberti, E. L.; Jeffries, P. R.; Payne, T. J.; Worth, G. K. *Tetrahedron Lett.* **1970**, 4599. (b) Adolf, W.; Hecker, E. *Tetrahedron Lett.* **1970**, 2241. (c) Zechmeister, K.; Röhrl, M.; Brandl, R.; Hechtfischer, S.; Hoppe, W.; Hecker, E.; Adolf, W.; Kubinyi, H. *Tetrahedron Lett.* **1970**, 3071. (d) Adolf, W.; Hecker, E. *Experientia* **1971**, *27*, 1393. (e) Narayanan, P.; Röhrl, M.; Zechmeister, K.; Engel, D. W.; Hoppe, W.; Hecker, E.; Adolf, W. *Tetrahedron Lett.* **1971**, 1325. (f) Ghisalberti, E. L.; Jeffries, P. R.; Payne, T. J.; Worth, G. K. *Tetrahedron* **1973**, *29*, 403. (g) Ghisalberti, E. L.; Jeffries, P. R.; Toia, R. F.; Worth, G. K. *Tetrahedron* **1974**, *30*, 3269. (h) White, A. H.; Maslen, E. N.; Toia, R. F.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 1684. (i) Adolf, W.; Hecker, E. *Isr. J. Chem.* **1977**, *16*, 75. (j) Ghisalberti, E. L.; Jefferies, P. R.; Toia, R. F. *Tetrahedron* **1978**, *34*, 233. (k) Lotter, H.; Opkerkuch, H. J.; Hecker, E. *Tetrahedron Lett.* **1979**, 77. (l) Seip, E. H.; Hecker, E. *Phytochemistry* **1983**, *22*, 1791. (m) Shizuri, Y.; Ohtsuka, J.; Kosemura, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 5547. (n) Naengchomnong, W.; Thebtaranonth, Y.; Wiriyachitra, P.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1986**, *27*, 5675.

(4) Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2112.

(5) (a) Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B., III. *J. Org. Chem.* **1982**, *47*, 3960. (b) Maas, D. D.; Blagg, M.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 853. (c) Satoh, T.; Okuda, T.; Kaneo, Y.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 1401. (d) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525.

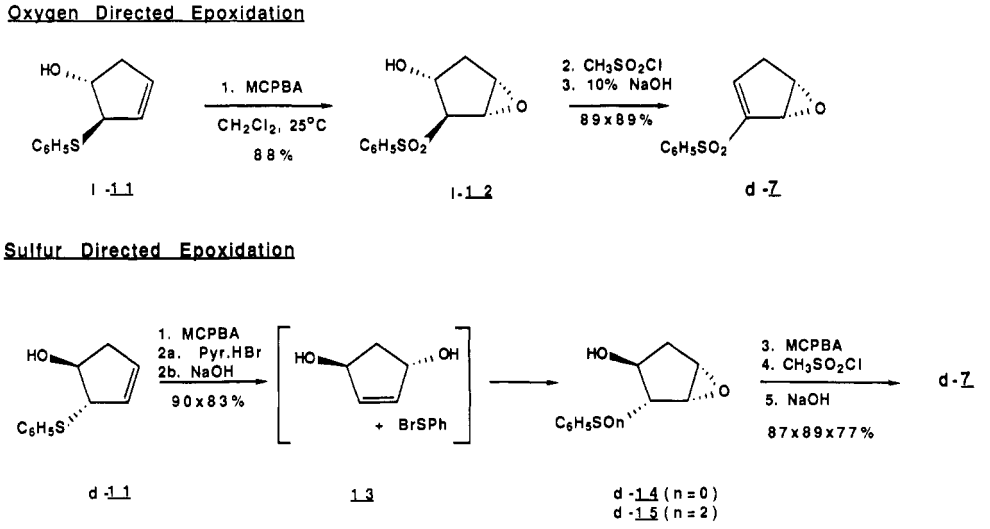
(6) Smith, A. B., III; Dorsey, B. D.; Visnick, M.; Maeda, T.; Malamas, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 3110.

(7) Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3567.

(8) The difficulty of establishing a 5/7/6 ring system by construction of the central seven-membered ring has recently been pointed out by Paquette: Belmont, D. T.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 4102.

0022-3263/88/1953-3647$01.50/0 © 1988 American Chemical Society

**Scheme III**




of three nucleophilic additions with reagents **8**, **9**, and **10**.

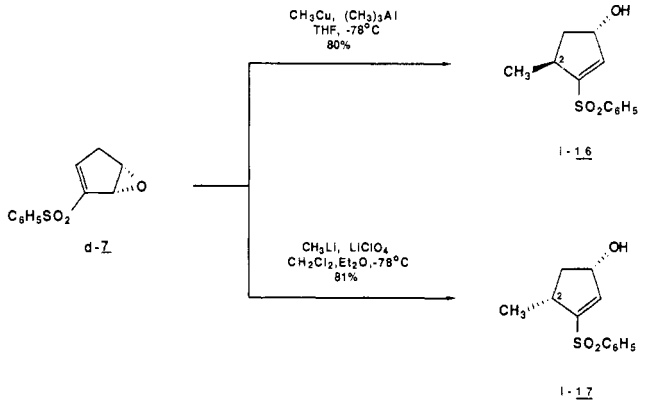
## Results and Discussion

Synthesis of the chiral epoxy vinyl sulfone *d*-**7** was accomplished in an enantioconvergent manner.[9a] Resolution of 5 mol of sulfide alcohol **11**[9c] was carried out with the Donaldson modification[9b] of Evans' $\alpha$-phenethyl isocyanate procedure[9d] to provide 1.65 mol of each of the two enantiomers. Treatment of *l*-**11** with 3 equiv of MCPBA affords *l*-**12** in 88% yield.[9c] Conversion of this material to *d*-**7** in 80% overall yield was smoothly accomplished by mesylation/elimination.

The enantiomeric sulfide alcohol *d*-**11** can also be utilized for the production of *d*-**7**. Oxidation of *d*-**11** to the corresponding sulfoxide followed by electrophilic cleavage of the sulfenate with pyridine hydrobromide produces chiral diol **13**, which undergoes in situ bromosulfenylation by the phenylsulfenyl bromide coproduct to afford an unstable bromohydrin, which is transformed to epoxide *d*-**14** by addition of sodium hydroxide during workup of the reaction.[9a] Oxidation of **14** with MCPBA gives sulfone *d*-**15**,[9a] which smoothly affords epoxy vinyl sulfone *d*-**7** in 68% yield. These two reaction sequences correspond to an oxygen-directed epoxidation and (formally) a sulfur-directed epoxidation. As can readily be seen from Scheme III, *l*-**7** is equally accessible from *either* of the enantiomeric sulfide alcohols **11**.

Establishment of the C-2 $\beta$-methyl stereochemistry (Lathrane numbering) required either a method for trans addition to *d*-**7** or cis addition to *l*-**7**. Both of these reactions can be realized in the laboratory.[4] Thus, treatment of *d*-**7** with catalytic methylcopper and trimethylaluminum in THF at −78 °C provides *trans*-$\gamma$-hydroxy vinyl sulfone *l*-**16** with better than 98% stereoselectivity. Alternatively, cis addition can be achieved by reaction of *d*-**7** with methyllithium in methylene chloride/ether under conditions that promote epoxide-directed $S_N2'$ reaction and produces *l*-**17** and *l*-**16** as a 95:5 mixture.[4,10] Thus for pragmatic purposes, we have elected to utilize *l*-**16** as the sole substrate for further elaboration in this study.

**Scheme IV**




Synthesis of the chiral "eastern zone" organometallic reagent **9** was easily accomplished.[4] Treatment of (*S*)-(−)-perrilaldehyde (**18**) with dry HCl in liquid sulfur dioxide affords a quantitative crude yield of the tertiary chloride **19a**. Addition of HCl to aldehyde **18** failed to occur in numerous other solvents. Tertiary halide **19a** was not further purified but dissolved in THF and added to a suspension of potassium *tert*-butoxide at 0 °C to provide a 94% yield of cyclopropyl aldehyde *d*-**20**. Aldehyde *d*-**20** had previously been prepared by Buchi in 41% yield by *tert*-butoxide cyclization of the very labile tertiary bromide **19b**.[11] Reaction of *d*-**20** with 1,3-propanedithiol in the presence of boron trifluoride etherate provided allyldithiane **21** in 68% yield after purification. Metalation of **21** by treatment with *n*-butyllithium in THF at −78 °C smoothly afforded 2-lithiodithiane **9a** as assayed by low-temperature quenching with $CH_3OD$ to return monodeuterio derivative **22** in 90% yield.

Sequential treatment of *l*-**16** in THF at −78 °C with 0.95 equiv of methyllithium (to effect deprotonation of the alcohol moiety) followed by addition of 1.2 equiv of **9a** and quenching with ammonium chloride at −78 °C provides alcohol **23** as a single diastereomer in 63% yield.[12,13]

(9) (a) Saddler, J. C.; Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2110. (b) Donaldson, R. E.; Saddler, J. C.; McKenzie, A. T.; Byrn, S.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2167. (c) Evans, D. A.; Crawford, T. C.; Fujimoto, T. T.; Thomas, R. C. *J. Org. Chem.* **1974**, *39*, 3176. (d) Thomas, R. C. Ph.D. Thesis, University of California, Los Angeles, 1976.

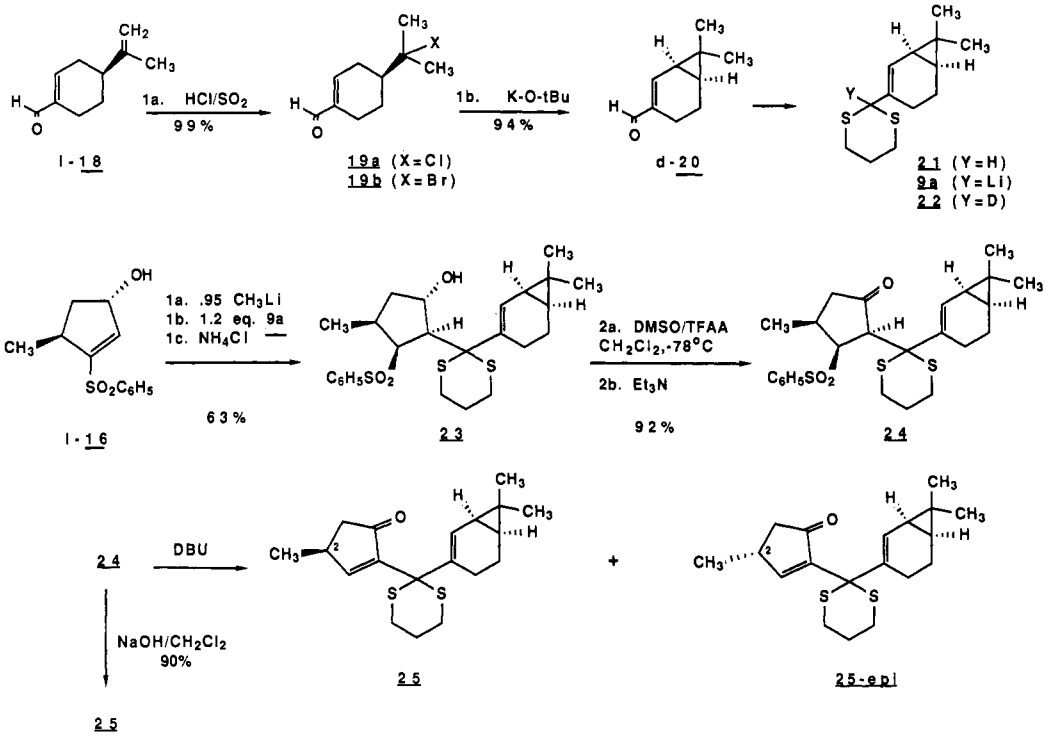
(10) While this sequence is capable of affording either enantiomer of **16** or **17**, it is *not general* for the stereospecific introduction of other R groups onto the cyclopentyl sulfone. For an alternative strategy that is completely general, see: Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137.

(11) Büchi, G.; Hofheinz, W.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1969**, *91*, 6473.

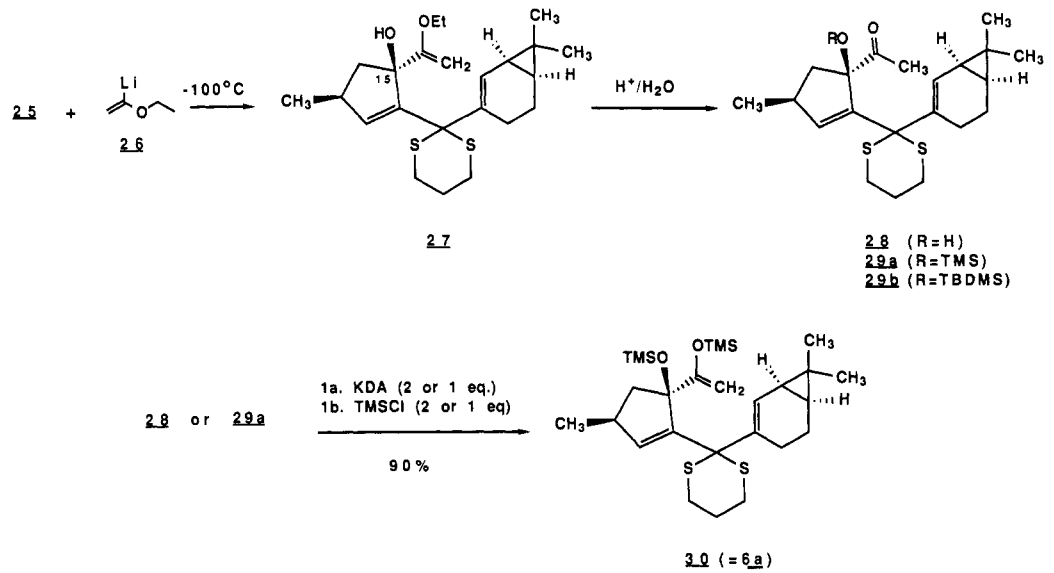
(12) Reaction of **9a** with the lithium alkoxide of *l*-**17** gives a 1:2 mixture of alcohols that results from[13] reaction of the allyl dithiane in *both* the $\alpha$ and $\gamma$ (major) position.

(13) Saddler, J. C. Ph. D. Thesis, Purdue University, 1982.

**Scheme V**




**Scheme VI**

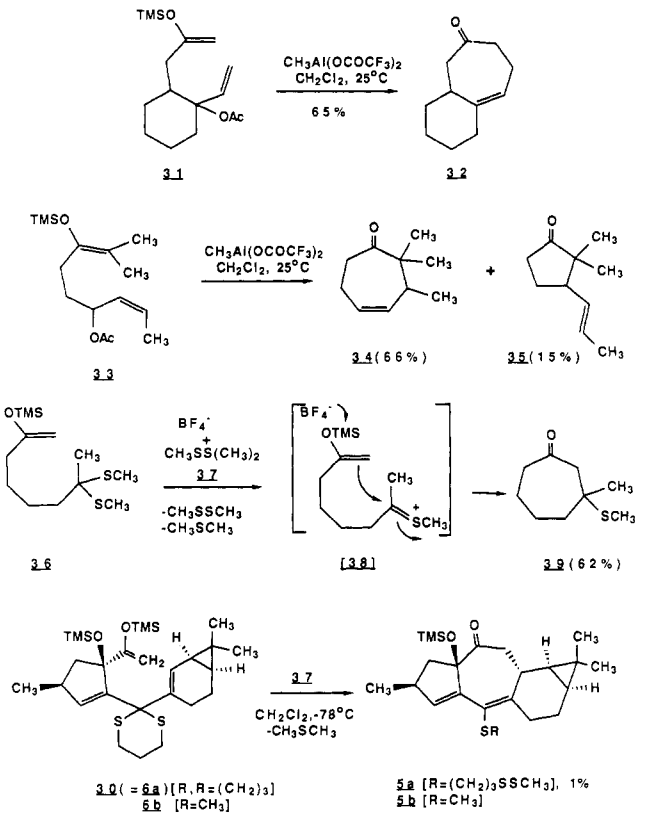



Oxidation of **23** with chromium reagents or DMSO/oxaloyl chloride[14] results in overoxidation, producing keto dithiane monosulfoxides in addition to the desired ketone **24**. However, use of the DMSO/TFAA variant[15] of the Swern oxidation produced ketone **24** in 92% yield. Elimination of the sulfinic acid with DBU was accompanied by unwanted epimerization of the C-2 methyl group, affording a 1:1 mixture of **25** and *epi*-**25**. Fortunately, this potentially disastrous epimerization reaction was completely avoided by employing aqueous sodium hydroxide in the elimination reaction, thereby producing **25** to the complete exclusion of *epi*-**25**. The overall yield for the conversion of **23** to **25** was 83%.

Attention was next turned to introduction of the two-carbon acyl anion moiety required for construction of cyclization progenitor **6**. On the basis of Baldwin's approach vector considerations,[16] it was anticipated that the γ-methyl group would serve as a control element to establish the C-15 alcohol group. Reaction of enone **25** with excess 1-lithio-1-ethoxyethylene (**26**)[17] in THF at −100 °C gives the acid-labile enol ether **27**, which could not be isolated without partial hydrolysis to ketone **28**. In practice, enone **25** was added to excess **26** at −100 °C, warmed to −78 °C, quenched with saturated ammonium chloride, and washed

(14) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(15) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.
(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.
(17) (a) Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7126. (b) Schöllkopf, U.; Hänssle, P. *Liebigs Ann. Chem.* **1972**, *763*, 208. (c) Brimacombe, J. S.; Mather, A. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 269.

**Scheme VII**




with 5% HCl in the workup to directly afford a 70% yield of α-hydroxy ketone **28** as a single diastereomer.[18] The C-15 stereochemistry was not directly verified at this stage.

In anticipation of the seven-ring cyclization (**6** → **5**), a number of derivatives of hydroxy ketone **28** were prepared. The tertiary alcohol was silylated with both the trimethylsilyl (LDA/TMSCl) and the *tert*-butyldimethylsilyl (pyridine/TBDMSTf[19a]) groups to afford **29a** (77%) and **29b** (39%). Synthesis of bissilyl derivative **30** could be efficiently achieved either by direct treatment of α-hydroxy ketone **28** with 2 equiv of potassium diisopropylamide[19b] at −78 °C followed by oxygen silylation with TMSCl or by monosilylation at the potassium enolate of **29a**, also prepared by KDA; the yield for both of these reactions was routinely 90%. A number of alternative methods for activation of the methyl ketone moiety for cyclization of the central seven-membered ring of **5** were investigated,[20] but all of those proved vastly inferior to silyl enol ether **30**.

Precedent for "7-enol endo"[8,21] cyclizations was relatively sparse. At the initiation of this work the only relevant examples were found in the work of Yamamoto,[22] who reported the solvolytic, Lewis acid catalyzed cyclizations of silyl enol ethers **31** and **33**. The key to effecting the target cyclization was revealed in the work of Trost,[23a] who found that thiosulfonium salt **37**[23] effected chemospecific sulfenylation of the methyl sulfide moiety of thioacetal **36** to produce a thionium ion intermediate [**38**], which suffered fluoroborate-promoted cyclization to cycloheptanone **39**.

The cyclization required in our application was essentially a composite of the Yamamoto/Trost types; accordingly, treatment of bisallyldithiane **30** with the thiosulfonium salt reagent **37** in methylene chloride at −78 °C afforded the desired cycloheptanone **5a** as the only nonpolar product produced in the reaction. While the yield was a minuscule 1%, we had established that the reaction was mechanistically viable.[24] Further confidence in the cyclization was provided by the observation that when the reaction was run to only 5–10% completion, the yield was 70% based upon recovered starting material. While this experimental mode was clearly impractical with respect to the needs of the total synthesis, it did establish that the low yield in the stoichiometric reaction was a consequence of incompatibility of the disulfide moiety of product **5a** with reagent **37**. As can be seen in the Trost example, sulfenylation[25] of the dimethyl disulfide coproduct by the thiosulfonium salt reagent **37** is a degenerate process, which only serves to regenerate the sulfenylating reagent, while in the cyclization of **6a**, sulfenylation of the disulfide moiety of **5a** initiates product destruction. Avoidance of this problem would seemingly simply require synthesis of acyclic *dimethyl* thioacetal **6b**, which should cyclize to the vinyl sulfide **5b**, a product devoid of the labile disulfide moiety.

Nevertheless, implementation of such a strategy was far from simple. Initial efforts to prepare a dimethyl thioacetal from **20** were severely hampered by the proclivity of this substrate to undergo 1,4-addition of methyl mercaptan under a wide variety of conditions.[26] Therefore, we embarked upon a course of action that involved the study of addition of alternative acyl anion synthons to vinyl sulfone *l*-**16**. Metalation of cyanohydrin acetal **41** followed by addition to *l*-**16** or its TBDMS ether **40** only affords bond formation in the γ position.[26] Reasoning that a "smaller" nucleophile was required to effect coupling of the heteroallyl anion in the α position, we next investigated the addition of the anion of nitrile **43** since simple α-nitrile anions are known to smoothly undergo conjugate addition to vinyl sulfones.[27] While it was impossible to synthesize nitrile **43** by cyanide displacement of the activated allylic alcohol derived from *d*-**20** because of solvolytic scission of the *gem*-dimethylcyclopropane moiety, this substrate could be very efficiently prepared by reductive cyclization of **42**.[28]

Treatment of nitrile **43** in THF at −78 °C with either LDA or KDA affords α-nitrile anions **44**-Li and **44**-K, respectively. While the lithium derivative would not undergo addition to **40**, **44**-K added within several minutes at low temperature; this result is in accord with a general counterion effect previously observed with vinyl sulfone additions.[27] The reaction provided three products; the desired α addition predominated, giving a pair of adducts **45A**/**45B** in 64% isolated yield along with 9% of **46**, a rearranged adduct resulting from addition at the γ carbon

(18) Attempts at direct introduction of the requisite three-carbon fragment employing the same chemistry using 1-lithio-1-methoxypropene (Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077) resulted only in enolization of **25** in the α position.[13]

(19) (a) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455. (b) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1978**, *43*, 3794.

(20) These included synthesis of a dimethylhydrazone derivative of **28**, as well as unsuccessful attempts at synthesis of "softer" carboxylated or sulfonylated derivatives of **29**.[13]

(21) For a discussion of the (enol endo) extension of Baldwin's rules for ring closure, see: Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939.

(22) Hashimoto, S.; Itah, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192.

(23) (a) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (b) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719.

(24) A vast number of the other sulfur-activation strategies failed to effect cyclization of **30**.[13]

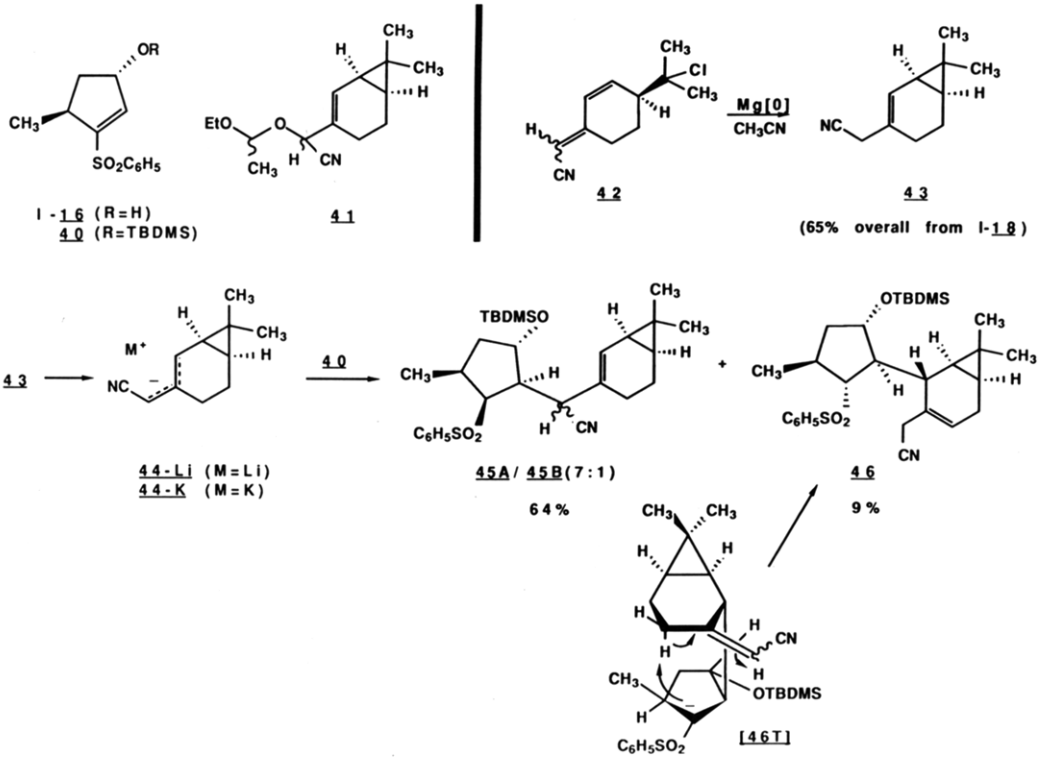
(25) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826.

(26) Braish, T. F. Ph.D. Thesis, Purdue University, 1986.

(27) Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 914.

(28) Braish, T. F.; Fuchs, P. L. *Synth. Commun.* **1985**, *15*, 549.

**Scheme VIII**




of the allyl nitrile anion. The chemistry of **45A/45B** was extensively investigated, but did not ultimately lead to a method of effecting seven-membered ring formation.[26]

Nevertheless, adduct **46** provided some mechanistic information that proved of considerable value later in the synthesis. This material was obtained as a single isomer, whose stereochemistry has been verified by X-ray analysis.[29] Two major features are apparent simply by examining the structure of **46**: The exocyclic vinyl nitrile that was initially produced in this reaction has undergone regiospecific isomerization to the endocyclic positions, and quenching of the $\alpha$-sulfonyl anion has occurred from the more hindered face of the substrate, in direct contrast to results that have routinely been obtained with well over 50 other cases[30] (cf. **45A/45B**). These facts strongly implicate intramolecular proton transfer from intermediate [**46T**] as being responsible for the generation of **46**.

In addition to this chemical information, compound **46** exhibits a fascinating physical property. Since **46** was a minor product that was not required for further elaboration, the chromatography fractions containing **46** were concentrated, transferred to a vial, and left to slowly evaporate. Over the course of 2 weeks' time it was found that the solvent had evaporated and **46** had crystallized in a unique and unprecedented helical manner (Figure 1). This phenomenon was repeated two additional times in vials of different sizes with production of helices of the same directionality. It is important to note that this result appears to be a colligative property of the *group of crystals* of **46** and is not associated with the known property of propagation of a helical fault in a single crystal.[32] Compound **46** belongs to point group $P2_12_12_1$, which is common to many chiral organic molecules (X-ray structural information on compound **46** can be found in the Supplementary Material). Although synthesis of the enantiomer of **46** was deemed to involve an unacceptable effort, we wished to further probe the crystallization process. Accordingly, the sample of **46** was sent to the Southern

**Figure 1.** Helical array of compound **46**.

(29) See Supplementary Material for the X-ray parameters of **46**.
(30) Reference 1 and unpublished results, P. L. Fuchs' laboratories.
(31) Supplementary material available for the X-ray data.
(32) Elwell, D.; Scheel, H. J. *Crystal Growth from High-Temperature Solutions*; Academic: London, 1975; pp 158–166, 176–183. Bunn, C. W. *Chemical Crystallography*; Oxford University Press: Oxford, 1961; p 58.

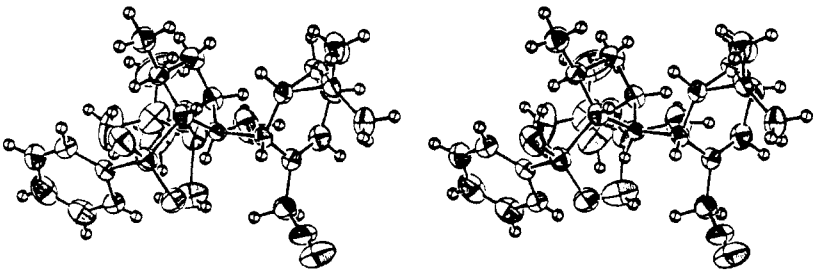
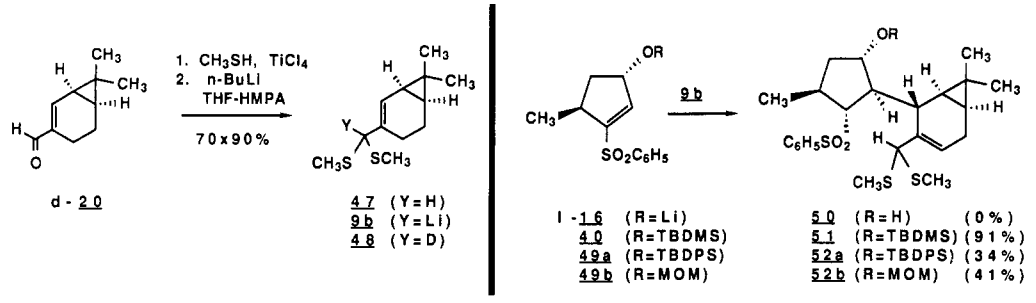
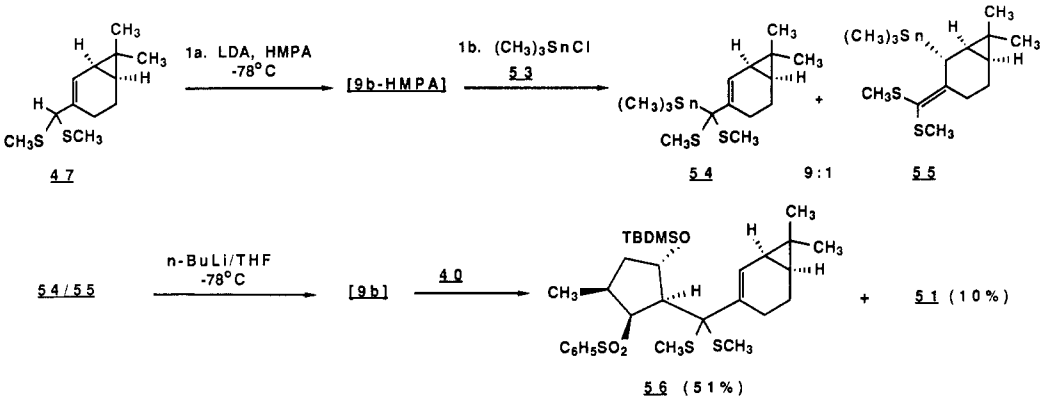


**Figure 2.** Stereoscopic drawing of compound **46**.

**Scheme IX**




**Scheme X**




Hemisphere, where it crystallizes in the *opposite helical sense*![33,34]

At this point we returned to the problem of thioacetylation of *d*-**20** with methyl mercaptan. Examination of an extensive survey of Lewis acids revealed that titanium tetrachloride[35] in the presence of a variety of amines produced the desired thioacetal **47** in yields of 10–30%.[26] Further experimentation revealed that catalytic titanium tetrachloride in neat methyl mercaptan at −78 °C afforded a 70% yield of the desired thioacetal **47**. In contrast to the cyclic thioacetal **21**, metalation of **47** was not a facile process. Treatment of **47** with *n*-butyllithium for extended periods of time at −78 °C routinely only revealed 50–60% metalation; attempted use of such mixtures demonstrated the presence of a substantial quantity of unreacted *n*-butyllithium to be present in solution. Use of higher temperatures or *tert*-butyllithium resulted in poor recovery. The optimum conditions for metalation involved treatment of **47** with *n*-butyllithium in THF *containing 5 equiv of HMPA* for 5 min at −78 °C, which afforded α-thioacetal anion **9b** in high yield; quenching of this solution with $D_2O$ provided a 90% yield of **48** that was 95% deuteriated.

Reaction of *l*-**16** (as its monoalkoxide) with **9b** failed to occur even at 0 °C. Monoprotected vinyl sulfones **40**, **49a**, and **49b** reacted with α-thioacetal anion **9b** to afford adducts **51**, **52a**, and **52b**, respectively. These were the undesired γ adducts that had undergone the same intramolecular proton transfer that had been observed in the formation of **46**. All attempts to alter the mode of addition by use of different solvents (ether, DME, benzene) or different counterions (Na, K, Mg, $Cu^I$, $Cu^{II}$, Zn, Al) were to no avail.

Although HMPA is beneficial at fostering α-alkylation reactions in the conjugate addition reactions with enones,[37] it was suspected that HMPA was responsible for the re-

(33) The Southern Hemisphere recrystallizations were conducted at the Australian National University by Mr. Bruce Twitchin. We wish to thank Professor Lew Mander for his assistance in this regard. In the first three trials **46** formed the opposite helix to that which was observed in the Northern Hemisphere; a fourth trial produced the "Northern helix".

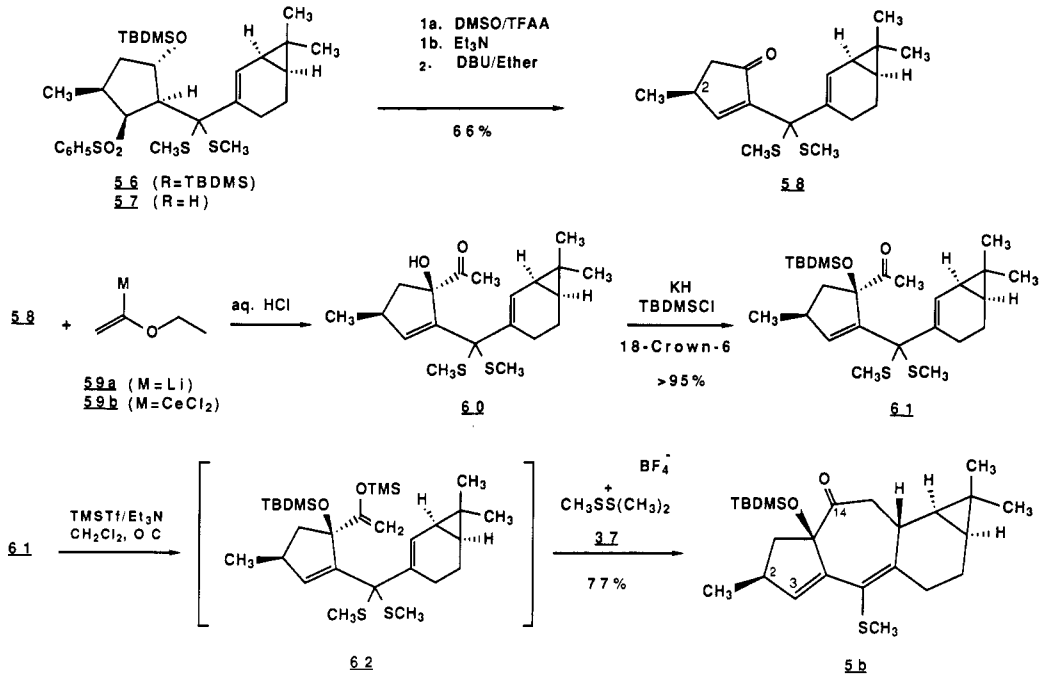
(34) Our best hypothesis for this unusual effect simply involves the Coriolis force operating on a bubble of air which becomes trapped under the lattice of crystals of **46**; slow evaporation of the solvent through the crystal roof propagates the helix. Nevertheless, if this were the only factor involved, it is clear that this effect would have been previously observed.

(35) (a) Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, *24*, 1289. (b) Bulman-Page, P. C.; Roberts, R. A.; Paquette, L. A. *Tetrahedron Lett.* **1983**, *24*, 3555.

(36) **52b-d** show no tendency toward helical crystallization.

(37) (a) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2678. (b) Ziegler, F. E.; Fang, J.-M.; Tam, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 7174. (c) Ziegler, F. E.; Chakraborty, U. R.; Wester, R. T. *Tetrahedron Lett.* **1982**, *23*, 3237. (d) Fang, J.-M.; Liao, L.-F.; Hong, B.-C. *J. Org. Chem.* **1986**, *51*, 2828. (e) Bo, L.; Fallis, A. G. *Tetrahedron Lett.* **1986**, *27*, 5193. (f) Fang, J.-M.; Hong, B.-C.; Liao, L.-F. *J. Org. Chem.* **1987**, *52*, 855. (g) Wilson, S. R.; Misra, R. N.; Georgiadis, G. M. *J. Org. Chem.* **1980**, *45*, 2460.

Scheme XI




giochemical difference obtained with the two thioacetals **9a** and **9b**.[38] In order to cleanly generate **9b** in the absence of both HMPA and excess *n*-butyllithium, an indirect method was adopted. Metalation of **47** in the presence of HMPA was conducted in the standard fashion; to the resulting **9b**-HMPA solution was added a slight excess of trimethylchlorostannane (**53**) at −78 °C to afford a 92% yield of allylstannanes **54** and **55**. Both allylstannanes are quite labile toward chromatography on silica gel and were therefore used without purification in a subsequent reaction with *n*-butyllithium in THF at −78 °C. To this *HMPA-free* solution of **9b** was added chiral vinyl sulfone **40** to afford a 51% yield of the long-sought $\alpha$ adduct **56** in addition to a 10% yield of the $\gamma$ adduct **51**.

Desilylation of **56** was smoothly effected with tetra-*n*-butylammonium fluoride, which provides alcohol **57** in 86% yield. Swern oxidation[14,15] of alcohol **57** gave a $\beta$-sulfonyl ketone which was not further purified but eliminated with DBU to provide enone **58** in 65% overall yield. It is critical to conduct the DBU reaction in ether where the DBU and the product DBU–$HSO_2Ph$ are very insoluble; use of other solvents leads to epimerization at C-2 as well as production of a vast array of undesirable coproducts. Addition of $\alpha$-alkoxyvinyl anions to **58** was more problematical than the corresponding reaction with dithiane **27**; while the lithium reagent **59a** afforded only traces of adduct **60**, addition of the less basic[39] organocerium reagent **59b** followed by an aqueous HCl workup afforded 71% yield of $\alpha$-hydroxy ketone **60**. Protection of alcohol **60** using the KDA/TMSCl conditions that afforded **29a,b** was unsuccessful but was smoothly accomplished using KH/18-crown-6,[40] providing **61** in >95% yield. Conversion of **61** to silyl enol ether **62** was easily effected with trimethylsilyl triflate and triethylamine in methylene chloride.[41] This enol ether was highly labile with respect to hydrolysis and was not purified but rather directly treated with reagent **37** at −78 °C to provide the tetracyclic cycloheptanone **5b** in 77% overall yield from **61**.

Considerable effort was expended at conversion of **5b** (and the corresponding C-14 $\beta$-alcohol derived therefrom) to fragmentation substrate **4**. These attempts were marred by the extreme lability exhibited by all tetracyclic substrates prepared. These materials had to be stored as a frozen benzene matrix at −78 °C for prolonged storage. Oxidation of the C-5 vinyl sulfide to either the sulfoxide or sulfone moiety could be accomplished, but all attempts at activation of the C-3 olefin by oxidation were unrewarding.[42] In spite of the hard-won success in achieving a reasonable synthesis of chiral tetracyclic ketone **5b**, the difficulties inherent in continuing to elaborate fragile intermediates have forced a reluctant termination of this approach to the lathrane diterpenes.

## Experimental Section

**General Procedures.** All melting and boiling points are uncorrected. Infrared spectra were recorded neat (NaCl) or in solution) ($CHCl_3$) and the data are reported in microns. $^1H$ and $^{13}C$ NMR spectra were determined in chloroform-*d* solution unless otherwise stated. $^1H$ NMR spectra were recorded at 60 or 470 MHz. $^{13}C$ NMR spectra were recorded at 50 MHz as either a full proton-decoupled/single-frequency off-resonance decoupled pair of spectra, a single full proton-decoupled spectrum, or a single APT[43] spectrum. Off-resonance splitting patterns are designated as for $^1H$ NMR splitting patterns. APT spectra are reported with carbons having one or three attached hydrogens, assigned as o (odd), and carbons with zero or two attached hydrogens, assigned as e (even).

All experiments were carried out under a positive pressure of nitrogen in a dry flask equipped with a rubber septum for introduction of reagents via syringe. All solvents used for workup or recrystallization were distilled. Reactions were monitored by TLC on precoated thin-layer Sil G-25 $UV_{254}$ plates. The plates were visualized by immersing in a *p*-anisaldehyde solution (1350 mL of EtOH, 50 mL of concentrated $H_2SO_4$, 15 mL of HOAc, 37

(38) In the presence of HMPA **9a** gives a 1:1 mixture of $\alpha$ and $\delta$ adducts.[26]

(39) Organocerium reagents are far less basic than the corresponding lithium reagents and provide enhanced addition/enolization ratios for acidic carbonyl substrates. For leading references and an example of a vinyl cerium reagent, see: (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873. (b) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31. (c) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

(40) Braish, T. F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 111.

(41) Simchen, G.; Kober, W. *Synthesis* **1976**, 259.

(42) Braish, T. F., unpublished results.

(43) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.

mL of *p*-anisaldehyde). Flash chromatography was carried out as described by Still, using silica gel 60 (230–400 mesh). All other chromatography was run on open columns of silica gel (60–200 mesh).

Reaction solvents were purified as follows: THF and $Et_2O$ were distilled from sodium/benzophenone; benzene, toluene, methylene chloride, DMSO, HMPA, and DMF were distilled from $CaH_2$ and stored over 4A molecular sieves. Stock solutions of organolithium reagents were titrated in benzene at 25 °C with menthol, using 2,2′-dipryridyl as the indicator.

Many of the compounds in this study were quite labile as well as being oils; combustion analysis of these materials was not satisfactory. These materials were >95% pure by TLC and NMR criteria at the time of the recording of their spectra.

**(5*S*,7*R*,10*R*,11*S*,13*S*)-2-(1,5,6-Trithia-1-heptyl)-5,12,12-trimethyl-8-oxo-7-(trimethylsiloxy)tetracyclo-[8.5.0.0$^{3,7}$.0$^{11,13}$]pentadeca-1,3-diene (5a).** To a solution of 138 mg (0.84 mmol) of dimethyl(methylthio)sulfonium tetrafluoroborate (**37**) in 10 mL of $CH_2Cl_2$ at −78 °C was added silyl enol ether **30** (200 mg, 0.38 mmol) in 5 mL of $CH_2Cl_2$. After 1.5 h at −78 °C, the solution was quenched with water, diluted with 50 mL of $CH_2Cl_2$, washed with cold dilute sodium bicarbonate, dried ($K_2CO_3$), and purified by flash chromatography (10% ether/hexane) to give 2 mg (1% yield) of **5a**: $^1$H NMR ($CDCl_3$) 6.02 (d, $J$ = 1, 1 H, vinyl H), 2.78 (dd, 1 H, C6 syn-H), 1.45 (dd, 1 H, C6 anti-H), 2.75 (m, 1 H, C5H), 2.6 (m, 1 H, C10H), 1.13 (d, $J$ = 6.8, 3 H, C5 methyl), 1.02 (s, 3 H, C12 syn-methyl), 1.05 (s, 3 H, C12 anti-methyl), 2.4 (s, 3 H, *S*-methyl), 0.85 (m, C11H), 1.0–3.0 (m, 11 H, aliphatics); IR ($CHCl_3$) 3.4 (CH), 5.85 (C=O).

**(5*S*,7*R*,10*R*,11*S*,13*S*)-2-(Methylthio)-5,12,12-trimethyl-8-oxo-7-((*tert*-butyldimethylsilyl)oxy)tetracyclo-[8.5.0$^{3,7}$.0$^{11,13}$]pentadeca-1,3-diene (5b).** To α-hydroxy ketone **60** (50 mg) in 3 mL of THF were added excess TBDMSCl, 18-crown-6, and KH in oil.[40] The reaction was judged to be complete in 10 min (TLC: $R_f$ 0.33, 5% ethyl acetate in hexane), and it was carefully quenched with water. The product was extracted with 10 mL of $CH_2Cl_2$, and the organic layer was dried. Evaporation of the solvent followed by chromatography (4% ethyl acetate–96% hexane) provided product **61** quantitatively. Ketone **61** was dissolved in 2 mL of $CH_2Cl_2$ and was cooled to 0 °C before triethylamine (3 equiv) and TBDMSO–Tf (2 equiv) were added. TLC analysis ($R_f$ 0.66, 5% ethyl acetate in hexane) showed a major product (**62**) forming, and that product was unstable to TLC. The reaction mixture was diluted with 10 mL of $CH_2Cl_2$) washed with 5% HCl solution and 5 mL of water, dried, and evaporated. The instability of the resulting enol ether to storage demanded it be used instantly; hence, the crude product was dissolved in 2 mL of $CH_2Cl_2$ and cooled to −78 °C. To that solution dimethyl(methylthio)sulfonium tetrafluoroborate (**37**) was added dropwise as a solution in $CH_2Cl_2$. A yellow color instantly formed and persisted with further addition of the reagent. TLC analysis ($R_f$ 0.25) showed the formation of a more polar product. Purification of the product via chromatography with 20% $CH_2Cl_2$–80% hexane provided tetracyclic product **56** in 65% yield: $^1$H NMR ($CDCl_3$) 5-ring 5.62 (d, 1 H, $J$ = 2.8 Hz, vinyl), 2.63 (m, 1 H, C5H), 2.98 (m, 1 H, C6H syn-OSi), 1.93 (m, 1 H, C6H anti-OSi), 1.14 (d, 3 H, $J$ = 6.8 Hz, $CH_3$); TBDMS 0.87 (s, 9 H, *tert*-butyl), 0.10 (s, 3 H, $CH_3$), 0.08 (s, 3 H, $CH_3$); 6-ring 1.20 (m, 1 H, C11H 3-ring), 2–1.5 (m, complex, ring Hs), 0.78 (m, 1 H, C13H 3-ring), 1.1 (s, 3 H, $CH_3$ 3-ring), 1.01 (s, 3 H, $CH_3$ 3-ring); 1.41 (m, 1 H, C10H), 2.83 and 2.76 (m, 2 H, α-ketone), 2.18 (s, 3 H, $SCH_3$); IR 3.36, 3.39, 3.51, 5.87 (m, carbonyl), 6.87, 8.0, 8.80, 12.0.

**(1*R*,4*R*)-*trans*-4-Methyl-3-(phenylsulfonyl)-2-cyclopenten-1-ol (*l*-16).** To a solution of methylcopper [made by addition of 1.88 mL (2.2 mmol) of methyllithium to 440 mg (2.3 mmol) of cuprous iodide in 6 mL of tetrahydrofuran at −78 °C] and 0.9 mL (2.2 mmol) of trimethylaluminum in 6 mL of THF at −78 °C was added 320 mg (1.44 mmol) of vinyl sulfone *d*-**7**, and the mixture was allowed to warm to room temperature over ca. 30 min. The solution was diluted with 50 mL of ether, carefully quenched with water, washed twice with 15% ammonia in saturated ammonium chloride, twice with 5% hydrochloric acid, and brine, dried, evaporated, and purified by preparative thin-layer chromatography to give 276 mg of an oil *l*-**16** (81%): $[\alpha]^{25}_D$ −88° (*c* 2.76, $CHCl_3$); $^1$H NMR ($CDCl_3$) 7.95 (m, 2 H, aryl *o*), 7.6 (m, 3 H, aryl *m* and *p*), 6.62 (dd, $J$ = 1.9, 1.0, 1 H, vinyl H), 4.99 (ddd, $J$ = 7.3, 4.0, 1.9, 1 H, CHOH), 3.04 (m, $J$ = 8.0, 6.9, 2.4, 1.0, 1 H, C4H), 2.4 (bs, 1 H, OH), 2.04 (t, $J$ = 8, 2 H, methylene), 1.11 (d, $J$ = 6.9, 3 H, $CH_3$); $^{13}$C NMR ($CDCl_3$) 139.3 (s, *i*), 133.8 (d, *p*), 129.3 (d, *o*), 128.0 (d, *m*), 150.7 (s, C3), 143.5 (d, C2), 74.4 (d, C1), 43.9 (t, C4), 20.0 (q, $CH_3$); IR ($CHCl_3$) 2.9, 9.2 (OH), 3.5 (CH), 6.8, 6.9, 14.5 (aryl), 7.7, 8.7, ($SO_2$); exact mass calcd for $C_{12}H_{14}SO_3$ 238.066, found 238.067.

**(1*R*,4*S*)-*cis*-4-Methyl-3-(phenylsulfonyl)-2-cyclopenten-1-ol (*l*-17).** To a solution of 300 mg (1.35 mmol) of vinyl sulfone *d*-**7** and 200 mg (1.9 mmol) of anhydrous lithium perchlorate[44] in 6 mL of ether and 6 mL of $CH_2Cl_2$ at −78 °C was added slowly 1.3 mL (1.48 mmol) of methyllithium in ether. The mixture was warmed to 0 °C and stirred ca. 20 min before being quenched with saturated ammonium chloride. The mixture was diluted with 40 mL of ether, washed with saturated ammonium chloride and brine, dried, and evaporated in vacuo to give 260 mg as an oil (81%) (95% cis/5% trans): $[\alpha]^{25}_D$ −48° (*c* 2.25, $CHCl_3$); $^1$H NMR ($CDCl_3$) 7.9 (m, 2 H, aryl *o*), 7.6 (m, 3 H, aryl *m* and *p*), 6.65 (dd, $J$ = 1.9, 1.7, 1 H, vinyl H), 4.82 (m, $J$ = 7.9, 6.0, 1.9, 1.1, 1 H, CHOH), 2.85 (m, $J$ = 7.9, 7.0, 6.0, 1.7, 1.1, 1 H, C4H), 2.63 (dt, $J$ = 13.5, 7.9, 1 H, methylene syn-OH), 2.5 (bs, 1 H, OH), 1.49 (dt, $J$ = 13.5, 6.0, 1 H, methylene anti-OH), 1.18 (d, $J$ = 7.0, 3 H, methyl); $^{13}$C NMR ($CDCl_3$) 139.8 (s, *i*), 133.7 (d, *p*), 129.3 (d, *o*), 127.9 (d, *m*), 150.5 (s, C3), 143.9 (d, C2), 74.0 (d, C1), 43.2 (t, C5), 38.1 (d, C4), 20.5 (q, methyl); IR ($CDCl_3$) 3.0, 9.5 (OH), 3.5 (CH), 6.8, 7.0, 14.5 (aryl), 7.7, 8.7 ($SO_2$); exact mass calcd for $C_{12}H_{14}SO_3$ 238.066, found 238.072.

**(4*S*)-4-(1-Chloro-1-methylethyl)-1-cyclohexenecarboxaldehyde (19a).** Into a solution of 22.5 g (150 mmol) of *l*-perillaldehyde in 500 mL of liquid sulfur dioxide at −45 °C hydrogen chloride was bubbled for ca. 40 min until complete disappearance of the starting material by NMR. The sulfur dioxide was distilled out and replaced with 20 mL of ether, and the solution was rotary evaporated to give **19a** as a brown liquid: $^1$H NMR ($CDCl_3$) 9.45 (s, 1 H, aldehyde), 6.85 (m, 1 H, vinyl H), 1.8–2.7 (m, 5 H, C3H, C6H, and C4H), 1.6 (bs, 6 H, both $CH_3$), 1.0–1.4 (m, 2 H, C5H).

**(1*R*,6*S*)-7,7-Dimethylbicyclo[4.1.0]hept-2-ene-3-carboxaldehyde (*d*-20).** Crude chloride **19a** was dissolved in 150 mL of THF and added to a solution of 17.6 g (158 mmol) of potassium *tert*-butoxide in 350 mL of THF at 0 °C over ca. 10 min. The mixture was immediately quenched with 100 mL of saturated ammonium chloride solution and extracted twice with 450 mL of ether. The organic phases were combined and washed once with saturated ammonium chloride and twice with water, dried ($Na_2SO_4$), and evaporated in vacuo to give 22.6 g (quantitative) of *d*-**20** as a light orange liquid that could be used directly or distilled at reduced pressure to give 14.8 g (66%) of pure *d*-**20**: bp 50–54 °C (0.025 mmHg); $[\alpha]^{25}_D$ +120° (*c* 1.50, $CHCl_3$); $^1$H NMR ($CDCl_3$) 9.4 (s, 1 H, aldehyde), 7.05 (d, $J$ = 4, 1 H, vinyl H), 2.3 (m, 1 H, C4H), 1.8 (m, 2 H, C4H and C5H), 1.2–1.4 (m, 2 H, C1H and C5H), 1.2 (s, 3 H, $CH_3$), 0.9 (s, 4 H, $CH_3$ and C6H); $^{13}$C NMR ($CDCl_3$) 193.7 (d, C=O), 152.0 (d, C2), 138.2 (s, C3), 28.4 (d, C1), 25.1 (d, C6), 18.8 (t, C4), 16.3 (t, C5), 31.3 (s, C7), 29.5 (q, $CH_3$), 16.0 (q, $CH_3$); IR ($CHCl_3$) 3.4 (CH), 3.8, 5.95 (CHO), 6.2 (olefin); exact mass calcd for $C_{10}H_{14}O$ 150.104, found 150.100.

**(1*R*,6*S*)-7,7-Dimethyl-3-(1,3-dithia-2-cyclohexyl)bicyclo-[4.1.0]hept-2-ene (21).** To a solution of 40.9 (273 mmol) of aldehyde *d*-**20** and 30.1 mL (300 mmol) of propanedithiol in 550 mL of $CH_2Cl_2$ at 0 °C was added 1.85 mL (15 mmol) of boron trifluoride etherate. The mixture was stirred ca. 2.5 h and then quenched with cold dilute sodium bicarbonate. The layers were separated and the aqueous phase was extracted twice with 300 mL of $CH_2Cl_2$. The organic phases were washed with water, dried ($Na_2SO_4$), and rotary evaporated to give the crude thioacetal. Purification by either distillation at reduced pressure (35–45% yield) or flash chromatography (20% $CH_2Cl_2$/hexane; 46% yield) gave pure **21**: bp 140 °C (0.01 mmHg); $[\alpha]^{25}_D$ +19° (*c* 2.66, $CHCl_3$); $^1$H NMR ($CDCl_3$) 6.07 (d, $J$ = 4.4, 1 H, vinyl H), 4.56 (s, 1 H, $CHS_2$), 2.9 (m, 4 H, CHS), 2.1 (m, 2 H, C5′H and C4H), 1.85 (m, 4 H, C5′H, C4H, and C5 methylene), 1.08 (s, 3 H, $CH_3$), 1.06 (dd, $J$ = 4.4, 8.7, 1 H, C1H), 0.93 (m, $J$ = 8.7, 1 H, C6H), 0.90 (s, 3 H, $CH_3$); $^{13}$C NMR ($CDCl_3$) 135 (s, C3), 125 (d, C2), 24.9 (t, C4),

(44) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371.

25.2 (s, C7), 22.8 (d, C1), 22.5 (d, C6), 54 (d, C2′), 31.4 (t, C4′), 25.5 (t, C5′), 28.6 (q, $CH_3$), 15.4 (q, $CH_3$); IR ($CHCl_3$) 3.5 (CH), 6.0 (S–C–S); exact mass calcd for $C_{13}H_{20}S_2$ 240.101, found 240.104.

**2-[(1*S*,2*R*,3*S*,4*S*)-1-Hydroxy-4-methyl-3-(phenylsulfonyl)-2-cyclopentyl]-2-[(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]hept-2-en-3-yl]-1,3-dithiacyclohexane (23).** To a solution of 20.0 g (83.3 mmol) of thioacetal **21** in 200 mL of THF at −78 °C was added in ca. 10 min 56 mL (80.0 mmol) of butyllithium, and the solution was maintained at −78 °C for 1 h. In a separate flask 30 mL (60.5 mmol) of methyllithium was added dropwise over ca. 40 min to a solution of 15.2 g (63.7 mmol) of vinyl sulfone *l*-**16** in 200 mL of THF at −78 °C. The solution of α-sulfonyl anion (flask 2) was added to flask 1 via cannula, and flask 2 was rinsed twice with 20 mL of THF, which was also added via cannula to flask 1. The mixture was stirred for 10 min at −78 °C, warmed to 0 °C, and stirred 20 min at 0 °C before quenching with saturated ammonium chloride. The mixture was diluted with 400 mL of ether and washed with saturated ammonium chloride. The aqueous layer was extracted with 400 mL of ether, and the organic phases were combined, washed with 5% hydrochloric acid and water, dried, and rotary evaporated to give as a yellow foam 34.4 g of crude adduct. Rough chromatography (1 kg of $SiO_2$; 6 L of 1:1 hexane/chloroform and then 7 L of 5% ether in chloroform) gave 7.6 g of recovered thioacetal **21** and 19.2 g (63%) of pure adduct **23** as a foam: mp 86–89 °C; $[\alpha]^{25}_D$ +43° (*c* 1.46, $CHCl_3$); $^1H$ NMR ($CDCl_3$) 8.0 (d, *J* = 7.5, 2 H, aryl *o*), 7.7 (t, *J* = 7.5, 1 H, aryl *p*), 7.6 (t, *J* = 7.5, 2 H, aryl *m*), 6.41 (d, *J* = 3.9, 1 H, vinyl H), 4.12 [d, *J* = 4.4 (C5′ anti-H), 1 H, CHOH], 3.92 [dd, *J* = 6.1 (C4′H)], 2.9 [(C2′H), 1 H, $CHSO_2$], 2.85 [d, *J* = 2.9 (C3′H), 1 H, 5-ring C2′H], 2.87 (m, 1 H, 5-ring C4′H), 2.6, 2.4 (m, 4 H, $CH_2S$), 2.15 (m, 1 H, bicyclic ring C4″ anti-H), 2.07 (m, 1 H, bicyclic ring C4″ syn-H), 2.0 (m, 1 H, C5″ anti-H), 2.0 (m, 1 H, C5′ syn-H), 1.8 (m, 1 H, C5′ anti-H), 1.95, 1.7 (m, 2 H, 6-ring C5H), 1.62 (m, 1 H, C5″ syn-H), 1.14 (buried, 1 H, C1″H), 1.00 (m, 1 H, C6″H), 1.14 (s, 3 H, C7″ anti-methyl), 1.00 (s, 3 H, C7″ syn-methyl), 0.91 [d, *J* = 6.8 (C4′H), 3 H, 5-ring methyl]; $^{13}C$ NMR ($CDCl_3$) 138.0 (s, *i*), 133.9, 129.2 (d, aryl), 5-ring 75.5 (d, C1′), 72.5 (d, C3′), 57.6 (d, C2′), 44.7 (t, C5′), 35.2 (d, C4′), 19.0 (q, 6-ring methyl), 63.0 (s, C2), 27.8 (t, C4 and C6), 24.6 (t, bicyclic ring, C5), 135.7 (s, C3″), 129.4 (d, C2″), 24.4 (d, C1″), 27.4 (t, C4″), 20.0 (t, C5″), 22.5 (d, C6″), 24.5 (s, C7″), 28.7 (q, anti-methyl), 16.3 (q, syn-methyl); IR ($CHCl_3$) 2.9, 9.2 (OH), 3.4 (CH), 6.3, 6.9, 14.5 (aryl), 7.8, 8.7 ($SO_2$).

**2-[(2*R*,3*S*,4*S*)-4-Methyl-1-oxo-3-(phenylsulfonyl)-2-cyclopentyl]-2-[(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]hept-2-en-3-yl]-1,3-dithiacyclohexane (24).** To a solution of 0.33 mL (4.6 mmol) of dimethyl sulfoxide in 10 mL of $CH_2Cl_2$ at −78 °C was added 0.24 mL (3.1 mmol) of trifluoroacetic anhydride, and the mixture was stirred for 10 min. To this was added 370 mg (0.77 mmol) of alcohol **23** in 5 mL of $CH_2Cl_2$, and the solution stirred for 30 min at −78 °C. Triethylamine was added (1.7 mL (12.3 mmol)), and the mixture was warmed to room temperature over ca. 1 h. The solution was diluted with 50 mL of $CH_Cl_2$, washed twice with 5% hydrochloric acid and water, dried, and evaporated in vacuo to give as a white solid 341 mg (92%) of **24**: mp 171–174 °C; $[\alpha]^{25}_D$ +41° (*c* 3.19, $CHCl_3$); $^1H$ NMR ($CDCl_3$) 8.0 (m, 2 H, aryl *o*), 7.65 (m, 3 H, aryl *m* and *p*), 6.3 [d, *J* = 4 (C1″H), 1 H, vinyl H], 4.05 [dd, *J* = 5 (C2′H), *J* = 6 (C4′H), 1 H, $CHSO_2$], 3.0 [d, *J* = 5 (C3′H), 1 H, C2′H], 1.5–2.9 (m, 13 H, ring Hs), 1.2 (m, 1 H, C1″H), 1.0 (m, 1 H, C6″H), 1.1 (d, *J* = 7, 3 H, 5-ring methyl), 1.1 (s, 3 H, C7″ anti-methyl), 0.97 (s, 3 H, C7″ syn-methyl); $^{13}C$ NMR $CDCl_3$) 137.8 (s, *i*), 134.0, 129.2 (d, aryl), 5-ring 207.8 (s, C1′), 55.2 (d, C2′), 69.3 (d, C3′), 28.4 (d, C4′), 47.2 (t, C5′), 20.5 (q, C4′ methyl), 6-ring 62.3 (s, C2), 26.9, 23.8 (t, C4 and C6), 24.6 (t, C5), bicyclic ring 133.0 (s, C3″), 129.4 (d, C2″), 24.4 (d, C1″), 27.8 (t, C4″), 19.7 (t, C5″), 22.5 (d, C6″), 24.5 (s, C7″), 28.7 (q, anti-methyl), 16.2 (q, syn-methyl); IR ($CHCl_3$) 3.4, 3.5 (cH), 5.85 (C=O), 6.3, 6.9, 7.0, 14.5 (aryl), 7.7, 8.7 ($SO_2$).

**2-[(4*S*)-4-Methyl-1-oxo-2-cyclopenten-2-yl]-2-[(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]hept-2-en-3-yl]-1,3-dithiacyclohexane (25).** A solution of ketone **24** (40.2 mmol) in 300 mL of $CH_2Cl_2$ at room temperature was stirred over 15 g (375 mmol) of powdered sodium hydroxide until the elimination was complete by TLC, ca. 2 h. The mixture was filtered, diluted with 300 mL of $CH_2Cl_2$, washed with 5% hydrochloric acid solution and three times with water, and dried. Evaporation of the solvent followed by flash chromatography (30% ether, 70% hexane) afforded 11.1 g of enone **25** (83% yield from alcohol **23**). **25**: mp 80–82 °C; $[\alpha]^{25}_D$ −48° (*c* 1.69, $CHCl_3$); $^1H$ NMR ($CDCl_3$) 7.66 [d, *J* = 2.5 (C4′H), 1 H, 5-ring vinyl H], 6.25 [d, *J* = 4.5 (C1″H), 1 H, bicyclic ring vinyl H], 2.94 (m, 1 H, C4′H), 2.77 (m, 4 H, C4H and C6H), 2.71 [dd, *J* = 18.8 (geminal)], 6.4 [(C4′H), 1 H, C5′H anti-Me], 2.11 (m, 1 H, C4″ syn-H), 2.06 [dd, *J* = 18.8 (geminal)], 2.3 [(C4′H), 1 H, C5′H syn-Me], 1.96 (m, 2 H, C5H), 1.83 (m, 2 H, C4″ anti-H and C5″ anti-H), 1.65 [m, *J* = 2 (C6″H), 1 H, C5″ syn-H], 1.24 [d, *J* = 7.2 (C4′H), 3 H, 5-ring methyl], 1.12 [dd, *J* = 8.5 (C6″H)], 4.5 [(C2″H), 1 H, C1″H], 1.08 (s, 3 H, C7″ anti-methyl), 0.93 (s, 3 H, C7″ syn-methyl), 0.91 (m, 1 H, C6″H); $^{13}C$ NMR ($CDCl_3$) 5-ring 204.3 (s, C1′), 144.2 (s, C2′), 167.0 (d, C3′), 32.3 (d, C4′), 44.9 (t, C5′), 20.7 (q, C4′ methyl), 6-ring 56.4 (s, C2), 28.0 (t, C4 and C6), 24.0 (t, C5), bicyclic ring 23.8 (d, C1″), 126.4 (d, C2″), 134.7 (s, C3″), 24.8 (t, C4″), 19.4 (t, C5″), 22.6 (d, C6″), 25.3 (s, C7″), 28.7 (q, anti-methyl), 15.7 (q, syn-methyl); IR ($CHCl_3$) 3.4 (CH), 5.9 (C=O), 6.2 (olefin); exact mass calcd for $C_{19}H_{26}OS_2$ 334.143, found 334.145. Anal. Calcd for $C_{19}H_{26}OS_2$: C, 68.22; H, 7.83; S, 19.17. Found: C, 67.99; H, 7.88; S, 19.37.

**2-[(1*R*,4*S*)-1-Acetyl-1-hydroxy-4-methyl-2-cyclopenten-2-yl]-2-[(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]hept-2-en-3-yl]-1,3-dithiacyclohexane (28).** To a solution of 1-lithio-1-ethoxyethene (**26**) [prepared by the dropwise addition of 140 mL (168 mmol) of *tert*-butyllithium over ca. 15 min to 32 mL (335 mmol) of ethyl vinyl ether in 75 mL of THF at −78 °C, warming on an ice bath until the yellow color is discharged, and immediate recooling to −78 °C] was added 5.60 g (16.8 mmol) of enone **25** in 50 mL of THF slowly to maintain the temperature at ca. −60 °C (liquid $N_2$ was simultaneously added to the cooling bath). The mixture was warmed to 0 °C over 30 min, quenched with 5% hydrochloric acid, diluted with 600 mL of ether, and washed with 5% hydrochloric acid. The layers were separated, the aqueous phase was extracted twice with 300 mL of ether, and the organic layers were combined and washed with 5% hydrochloric acid and water, dried, rotary evaporated, and chromatographed on Florisil (5% ethyl acetate/hexane) to give as an oil 4.43 g (70%) of **28**: $[\alpha]^{25}_D$ −101° (*c* 6.48, $CHCl_3$); $^1H$ NMR ($CDCl_3$) 6.41 [d, *J* = 4.8 (C1″H), 1 H, 6-ring vinyl H], 6.12 [d, *J* = 1.9 (C4′H), 1 H, 5-ring vinyl H], 2.74 [m, *J* = 7.4 both C5′H)], 6.7 (5-ring methyl), 1.9 [(5-ring vinyl), 1 H, C4′H], 2.74 (m, 2 H, C4 and C6 equatorial Hs), 2.70 (m, 1 H, C4 axial H), 2.61 (m, 1 H, C6 axial H), 2.41 [dd, *J* = 13.4 (geminal)], 7.4 (C4′H), C5′H syn-OH), 2.31 (s, 3 H, acetal methyl), 2.07 [dt, *J* = 16.4 (geminal)], 6.8 [(C5″ Hs), 1 H, C4″ syn-H], 1.94 [dt, *J* = 16.7 (geminal), *J* = 7 (C5″ Hs), 1 H, C4″ anti-H], 1.89 (m, 2 H, C5 Hs), 1.82 (m, 1 H, C5″ anti-H), 1.68 (m, 1 H, C5″ syn-H), 1.58 [dd, *J* = 13.4 (geminal)], 7.4 [(C4′H), 1 H, C5′H anti-OH], 1.56 (s, 1 H, OH), 1.15 [dd, *J* = 8.3 (C6″H)], 4.8 [(C2″H), 1 H, C1″H], 1.12 [d, *J* = 6.7 (C4′H), 3 H, 5-ring methyl], 1.12 (s, 3 H, C7″ anti-methyl), 0.97 (s, 3 H, C7″ syn-methyl), 0.96 (m, 1 H, C6″H); $^{13}C$ NMR ($CDCl_3$) 5-ring 91.7 (s, C1′), 143.0 (s, C2′), 144.1 (d, C3′), 36.2 (d, C4′), 47.9 (t, C5′), 20.9 (q, C4′ methyl), 25.1 (q, acetyl methyl), 210.6 (C=O), 6-ring 59.3 ( s, C2), 28.5 (t, C4), 24.6 (t, C5), 28.1 (t, C6), bicyclic ring 23.8 (d, C1″), 126.7 (d, C2″), 136.1 (s, C3″), 24.5 (t, C4″), 19.3 (t, C5″), 22.7 (d, C6″), 25.2 (s, C7″), 28.8 (q, anti-methyl), 16.1 (q, syn-methyl); IR ($CHCl_3$) 3.0, 8.2 (OH), 3.5 (CH), 5.9 (C=O), 6.2 (olefin).

**2-[(1*R*,4*S*)-1-Acetyl-4-methyl-1-(trimethylsiloxy)-2-cyclopenten-2-yl]-2-[(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]-hept-2-en-3-yl]-1,3-dithiacyclohexane (29a).** To a solution of potassium diisopropylamide [prepared by the addition of 0.27 mL (0.25 mmol) of stock lithium diisopropylamide solution to 30 mg (0.26 mmol) of potassium *tert*-butoxide in 2 mL of THF at −78 °C] was added 42 mg (0.11 mmol) of alcohol **28** in 3 mL of THF, and the solution was stirred at −78 °C for 5 min. To this was added 71 μL (0.5 mmol) of chlorotrimethylsilane, and the mixture was warmed to 0 °C and stirred for 1 h. The solution was diluted with 50 mL of hexane, washed twice with cold dilute sodium bicarbonate, dried ($K_2CO_3$), and evaporated in vacuo to give 38 mg of an oil **29a** (77% yield); $^1H$ NMR ($CDCl_3$) 6.35 [d, *J* = 5 (C1″H), 1 H, 6-ring vinyl H], 6.05 [d, *J* = 2 (C4′H), 1 H, 5-ring vinyl H], 2.3–2.8 (m, 5 H), 2.2 (s, 3 H, acetyl methyl), 1.4–2.0 (m, 8 H), 1.1 (m, 1 H, C1″H), 1.0 (s, 3 H, C7″ anti-methyl), 0.95 [d, *J* = 7 (C4′H), 3 H, 5-ring methyl], 0.85 (s, 3 H, C7″ syn-methyl), 0.85 (m, 1 H, C6″H); IR ($CHCl_3$) 3.4 (CH), 5.9 (C=O), 6.1 (olefin).

**2-[(1*R*,4*S*)-1-Acetyl-4-methyl-1-((*tert*-butyldimethylsilyl)oxy)-2-cyclopenten-2-yl]-2-[(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]hept-2-en-3-yl]-1,3-dithiacyclohexane (29b).** To a solution of 38 mg (0.1 mmol) of alcohol **28** and 40 mg (0.15 mmol) of *tert*-butyldimethylsilyl triflate in 2 mL of $CH_2Cl_2$ at room temperature was added 20 μL (0.25 mmol) of pyridine. After 12 h, the mixture was diluted with 25 mL of $CH_2Cl_2$, washed twice with 5% hydrochloric acid and water, dried, rotary evaporated, and purified by preparative thin-layer chromatography (10% ether/hexane) to give 19 mg of an oil **29b** (39% yield): $[\alpha]^{25}_D$ −10° (*c* 0.19, $CHCl_3$); $^1H$ NMR ($CDCl_3$) 6.42 [d, *J* = 5 (C1″H), 1 H, bicyclic vinyl H], 6.1 [d, *J* = 2 (C4′H), 1 H, 5-ring vinyl H], 2.85 (m, 1 H, C4′H), 2.8 (m, 1 H, C4H), 2.58 (m, 2 H, C4H and C6H), 2.48 (m, 1 H, C6H), 2.45 [dd, *J* = 13.8 (geminal), *J* = 6 (C4″H), 1 H, C5′H syn-OR], 2.3 (s, 3 H, acetyl methyl), 2.03 [t, *J* = 6 (C4 and C6 Hs), 2 H, C5 Hs], 1.85 (m, 2 H, C4″ syn-H and C5″ anti-H), 1.75 (m, 1 H, C4″ anti-H), 1.7 (m, 1 H, C5″ syn-H), 1.6 [dd, *J* = 13.8 (geminal), *J* = 6 (C4′H), 1 H, C5′H anti-OR], 1.15 (s, 3 H, C7″ anti-methyl), 1.15 (m, 1 H, C1″H), 1.10 [d, *J* = 7 (C4′H), 3 H, 5-ring methyl], 0.95 (s, 3 H, C7″ syn-methyl), 0.9 (s, 9 H, *tert*-butyl), 0.9 (m, 1 H, C6″H), 0.3, 0.1 (2 s, 6 H, Si methyls); IR ($CHCl_3$) 3.4, 3.5 (CH), 5.85 (C=O), 6.1 (olefin).

**2-[(1*R*,4*S*)-4-Methyl-1-(trimethylsiloxy)-1-(1-(trimethylsiloxy)vinyl)-2-cyclopenten-2-yl]-2-[(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]hept-2-yl]-1,3-dithiacyclohexane (30).** To a solution of 142 mg (1.27 mmol) of potassium *tert*-butoxide and 0.18 mL (1.27 mmol) of diisopropylamine in 7 mL of THF at −78 °C was added 0.86 mL (1.22 mmol) of butyllithium. To this solution was added 200 mg (0.53 mmol) of hydroxy ketone **28** in 3 mL of THF, and the mixture was warmed to 0 °C for ca. 15 min. The mixture was recooled to −78 °C, 0.4 mL (3.0 mmol) of chlorotrimethylsilane was added, and the resultant mixture was warmed to 0 °C for 1 h. Dilution with 50 mL of hexane, washing twice with cold dilute sodium bicarbonate, drying ($K_2CO_3$), and rotary evaporation gave as an oil 240 mg (87% yield) of **30**: $[\alpha]^{25}_D$ −40° (*c* 0.22, $CHCl_3$); $^1H$ NMR ($CHCl_3$) 6.52 [d, *J* = 4.6 (C1″H), 1 H, C2″H], 6.10 [d, *J* = 1.4, (C4′H), 1 H, C3′H], 4.50 (s, 1 H, *Z*-enol H), 4.02 (s, 1 H, *E*-enol H), 2.62 (m, 1 H, C4′H), 2.38 [dd, *J* = 11 (geminal), *J* = 8 (C4′H), 1 H, C5′ syn-H], 1.6 (m, 2 H, C5′ anti-H), 1.98 (m, 1 H, C4″ syn-H), 1.94 (m, 1 H, C4″ anti-H), 1.92 (m, 1 H, C5″ anti-H), 1.6 (m, 1 H, C5″ syn-H), 1.17 (m, 1 H, C1″H), 0.94 (m, 1 H, C6″H), 2.88, 2.69 (m, 2 H, C4 and C6 axial Hs), 2.54 (m, 2 H, C4 and C6 equatorial Hs), 1.85 (m, 2 H, C5 Hs), 1.19 (s, 3 H, C7″ anti-methyl), 1.10 [(d, *J* = 7.1), 3 H, 5-ring methyl)], 1.05 (s, 3 H, C7″ syn-methyl), 0.2 (2 s, 18 H, TMS); IR ($CHCl_3$) 3.5 (CH), 6.2 (enol ether).

**1-[(1′*S*,2′*R*,3′*S*,4′*S*)-1′-((*tert*-Butyldimethylsilyl)oxy)-3′-(phenylsulfonyl)-4′-methylcyclopent-2′-yl]-1-[(1″*R*,6″*S*)-7″,7″-dimethylbicyclo[4.1.0]hept-2″-en-3″-yl]-acetonitrile (45A,B) and (1*R*,6*S*)-2-[(1′*S*,2′*R*,3′*R*,4′*S*)-1′-((*tert*-Butyldimethylsilyl)oxy)-3′-(phenylsulfonyl)-4′-methylcyclopent-2′-yl]-3-(cyanoethyl)-7,7-dimethylbicyclo-[4.1.0]hept-3-ene (46).** To a solution of diisopropylamine (5.4 mL, 38.4 mmol) in 150 mL of THF at −78 °C *n*-BuLi (23.2 mL, 35.5 mmol) was added. The mixture was stirred for 10 min, potassium *tert*-butoxide (22.2 mL, 35.5 mmol) was added, and the mixture was allowed to stir for 15 additional min. Allyl nitrile **43** (5.26 g, 32.7 mmol) in 50 mL of THF was then added slowly (10 min), and the color turned reddish-yellow instantly. The reaction was stirred at −78 °C for 1 h to ensure complete metalation of the allyl nitrile before vinyl sulfone **40** (10 g, 28.4 mmol) in 50 mL of THF was added. The mixture was allowed to stir for 10 min and then quenched by pouring it in 200 mL of water. The aqueous layer was extracted with two 300-mL portions of $CH_2Cl_2$. The combined organic layers were washed successively with two 150-mL portions of 5% HCl solution, 80 mL of saturated $NaHCO_3$ solution, and 80 mL of saturated NaCl solution and dried. Evaporation of the solvent followed by chromatography (20% $CH_2Cl_2$–5% ether–75% hexane) afforded 7.1 g of a major adduct (oil) **45A**, 2.2 g of a minor adduct **45B** (solid) (64% combined yield), and 0.45 g of the crystalline γ-adduct **46** (TLC: $R_f$ 0.4, 0.33, 0.29, respectively, in 40% $CH_2Cl_2$–5% ether–55% hexane).

**45A**: $^1H$ NMR ($CDCl_3$) 8–7.5 (5 H, sulfone pattern), 5-ring 4.03 (m, 1 H, CHOSi), 2.62 (m, 1 H, C2′H), 2.95 (dd, 1 H, *J* = 8.7 Hz, α-sulfone), 2.40 (m, 1 H, C4′), 1.72 (m, 1 H, C5′ syn to OSi), 1.63 (m, 1 H, anti to OSi), 1.07 (d, 3 H, *J* = 6.6 Hz, $CH_3$), 6-ring 6.10 (m, 1 H, vinyl), 2.11 (m, 1 H, C4H), 1.70 (m, 1 H, C4H), 1.95 (m, 1 H, C5H), 1.63 (m, 1 H, C5H), 1.04 (m, 1 H, C1 3-ring), 0.92 (m, 1 H, C6 3-ring), 1.1 (s, 3 H, $CH_3$ 3-ring), 0.9 (s, 3 H, $CH_3$ 3-ring), 3.68 (m, 1 H, α-CN), 0.69 (s, 9 H, *tert*-butyl Si), −0.08 (s, 3 H, $CH_3Si$), −0.09 (s, 3 H, $CH_3Si$); $^{13}C$ NMR ($CDCl_3$) phenyl sulfone 130.7 (e, ipso), 129.2 (o, ortho), 129.1 (o, meta), 125 (o, para), 5-ring 73.7 (o, C1′ α-OSi), 50.9 (o, C2′), 72.7 (o, α-sulfone), 34.5 (o, C4′), 44.1 (e, C5′), 18.5 (o, $CH_3$), 6-ring 22.9 (o, C1 3-ring), 134 (o, C2 vinyl), 136.9 (e, C3 vinyl), 25.0 (e, C4), 18.3 (e, C5), 21.04 (o, C6), 24.9 (e, C7 quaternary 3-ring), 28.2 (o, $CH_3$), 15.43 (o, $CH_3$), 43.0 (o, α-CN), 118.6 (e, CN); exact mass calcd ($M^+$ + 1, self-protonating), 514.273, found 514.279.

**45B**: NMR ($CDCl_3$) 8–7.5 (5 H, sulfone pattern), 5-ring 4.1 (m, 1 H, CHOSi), 2.7 (m, 1 H, C2′H), 2.96 (dd, 1 H, *J* = 6.7 Hz, α-sulfone), 2.60 (m, 1 H, C4′), 1.75 (m, 1 H, C5′H syn to OSi), 1.4 (m, 1 H, C5′H trans to OSi), 0.9 (d, 3 H, *J* = 6.1 Hz, $CH_3$), 6-ring 1.1 (m, 1 H, C1H 3-ring), 5.9 (d, 1 H, *J* = 5.9 Hz, C2H vinyl), 1.96–1.75 (m, 4 H, C4 and C5 Hs), 0.95 (m, 1 H, C6 3-ring), 1.08 (s, 3 H, $CH_3$ 3-ring), 0.91 (s, 3 H, $CH_3$ 3-ring), 4.04 (s, 1 H, α-CN), 0.81 (s, 9 H, *tert*-butyl Si), 0.24 (s, 3 H, $CH_3$), −0.22 (s, 3 H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) phenyl sulfone 129.6 (e, ipso), 129.2 (o, ortho), 129.2 (o, meta), 128.9 (o, para), 5-ring 74.6 (o, C1′ α-OSi), 51.0 (o, C2′), 71.9 (o, C3′ α-sulfone), 34.1 (o, C4′), 42.5 (e, C5′), 19.8 (o, $CH_3$), 6-ring 25.6 (o, C1 3-ring), 133.8 (o, C2 vinyl), 138 (e, C3 vinyl), 25.7 (e, C4), 18.2 (e, C5), 23.0 (o, C6 3-ring), 24.5 (e, C7 quaternary 3-ring), 28.43 (o, $CH_3$ 3-ring), 15.6 (o, $CH_3$ 3-ring), −4.5 (o, $SiCH_3$), −4.49 (o, $SiCH_3$), 42.2 (o, α-CN), 119 (e, CN); exact mass ($M^+$ + 1, self-protonating) calcd 514.273, found 514.279; mp 105–107 °C.

**46**: NMR ($CDCl_3$) 8–7.5 (5 H, sulfone pattern), 5-ring 3.92 (m, 1 H, *J* = 3 Hz, CHOSi), 2.5 (m, 1 H, C2′), 2.99 (dd, 1 H, *J* = 3, 8.2 Hz, α-sulfone), 2.5 (m, 1 H, C4′), 1.67 (m, 1 H, *J* = 5.7, 3.2, 3.8 Hz, C5′ syn to OSi), 1.42 (m, 1 H, *J* = 5.4, 4.1, 3.7 Hz, C5′ anti to OSi), 1.1 (d, 3 H, *J* = 6.7 Hz, $CH_3$), 6-ring 0.71 (m, 1 H, C1 3-ring), 2.38 (m, 1 H, C2), 5.77 (m, 1 H, C4 vinyl), 2–2.2 (m, 2 H, C5 Hs), 0.24 (d, 1 H, *J* = 9 Hz, C6 3-ring), 0.99 (s, 3 H, $CH_3$ 3-ring), 0.70 (s, 3 H, $CH_3$ 3-ring), 2.8 (d, 1 H, *J* = 18.6 Hz, α-CN), 3.2 (d, 1 H, *J* = 18.8 Hz, α-CN), 0.671 (s, 9 H, Si *tert*-butyl), −0.143 (s, 3 H, $SiCH_3$), −0.170 (s, 3 H, $SiCH_3$); $^{13}C$ NMR ($CDCl_3$ phenyl sulfone 127.3 (e, ipso), 129.2 (o, ortho), 128.9 (o, meta), 126.5 (o, para), 5-ring 74.4 (o, CHOSi), 53.6 (o, C2′), 72.8 (o, α-sulfone), 34.1 (o, C4′), 44.8 (e, C5′), 19.5 (o, $CH_3$ 5-ring), 6-ring 20.8 (o, C1 3-ring), 35.2 (o, C2), 137.6 (e, C3 vinyl), 133.9 (o, C4 vinyl), 21.6 (e, C5), 17.8 (o, C6 3-ring), 23.6 (e, quaternary 3-ring), 13.3 (o, $CH_3$ 3-ring), 28.7 (o, $CH_3$ 3-ring), 25.5 (o, *tert*-butyl Si), −5.2 (o, $SiCH_3$), −4.5 (o, $SiCH_3$), 17.5 (e, α-CN), 117.4 (e, CN); exact mass calcd ($M^+$) 513.273, found 513.273; mp 137–139 °C.

**(1*R*,6*S*)-7,7-Dimethyl-3-(bis(methylthio)methyl)bicyclo-[4.1.0]hept-2-ene (47).** Methyl mercaptan was condensed in a 500-mL round-bottom flask at −78 °C (approximately 100 mL, 1.5 mol), and to that aldehyde *d*-**20** (29 g, 133 mmol) was added. While the mixture stirred at −78 °C, $TiCl_4$ (0.2 mL, 1.8 mmol) was added. The color of the reaction turned brown and then yellow, indicating the consumption of the $TiCl_4$ (7–10 min). TLC analysis of the reaction ($R_f$ 0.25, 0.5% ether in hexane) indicated the presence of some unreacted starting material, and sufficient $TiCl_4$ (0.2 mL) was added to complete the reaction. Removal of excess methyl mercaptan was effected by removing the dry ice bath and allowing the methyl mercaptan to evaporate into three $KMnO_4$ traps (5–8 h). The remaining oil was diluted with 300 mL of ether, washed 3 times with water, and dried. Evaporation of the solvent followed by preparative HPLC (0.2% $CH_2Cl_2$ in hexane) provided 21.2 g of pure thioacetal **47** as a colorless oil, which represents a 70% yield. $^1H$ NMR ($CDCl_3$) 5.87 (d, 1 H, *J* = 4.1 Hz, vinyl H), 3.61 (s, 1 H, $CHS_2$), 2.09 (s, 3 H, $SCH_3$), 2.07 (s, 3 H, $SCH_3$), 2.15 (m, 2 H, C4H and C5H, s), 1.75 (m, 1 H, C5H), 1.08 (m, 1 H, C1H), 0.95 (m, 1 H, C6H), 1.1 (s, 3 H, $CH_3$ 3-ring), 0.92 (s, 3 H, $CH_3$ 3-ring); $^{13}C$ NMR ($CDCl_3$) 23.07 (d, C1), 123.98 (d, C2), 133.96 (s, C3), 23.6 (t, C4), 18.23 (t, C5), 22.5 (d, C6), 22.5 (d, C6), 25.18 (s, C7), 28.65 (q, C8), 15.7 (q, C9), 60.14 (d, C10), 14.55 (q, $SCH_3$), 14.9 (q, $SCH_3$); *m/e* 181 ($M^+$ − $SCH_3$, 100), 133 (26), 105 (15.1), 91 (26.5), 66 (14.3).

**2-[(1′*S*,2′*R*,3′*R*,4′*S*)-1′-((*tert*-Butyldimethylsilyl)oxy)-4′-methyl-3′-(phenylsulfonyl)cyclopent-2′-yl]-3-(bis(methylthio)methyl)-(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]hept-3-ene**

(51). LDA was generated as follows: to 2.8 mL of THF, diisopropylamine (104 μL, 0.74 mmol) was added, and the flask was cooled to −78 °C; to that *n*-BuLi (0.48 mL, 1.54 M) was added, and the mixture was allowed to stir for 10 min; HMPA (0.75 mL, 0.85 mmol) in 1 mL of THF was then added. After an additional 5 min thioacetal **47** (254 mg, 1.11 mmol) in 2 mL of THF was also added, and the resulting purple solution was allowed to stir for 30 min. Vinyl sulfone **40** (200 mg, 0.57 mmol) in 2 mL of THF was added, and the reaction was quenched with saturated $NH_4Cl$ solution after 15 min. The product was then diluted with 40 mL of $CH_2Cl_2$, washed with 10 mL of 5% HCl solution and with 4 × 10 mL fractions of water, and then dried. Plug filtration with 8% ethyl acetate–92% hexane ($R_f$ 0.27) to remove excess thioacetal provided 299 mg of crystalline solid **51**, which represents a 91% yield based on the vinyl sulfone.

$^1H$ NMR ($CDCl_3$) 5.84 (d, 1 H, $J$ = 3 Hz, vinyl H), 3.94 (s, 1 H, $CHS_2$), 4.07 (m, 1 H, CHOSi), 2.78 (m, 1 H, C2′), 2.71 (m, 1 H, C4′), 2.50 (m, 1 H, C5), 2.23 (m, 1 H, C5), 2.49 (m, 1 H, C2), 3.15 (m, 1 H, α-sulfone), 1.96 (m, 1 H, C5′), 1.55 (m, 1 H, C5′), 2.19 (s, 3 H, $SCH_3$), 2.02 (s, 3 H, $SCH_3$), 1.09 (d, 3 H, $J$ = 6.9 Hz, $CH_3$ 5-ring), 1.05 (s, 3 H, $CH_3$ 3-ring), 0.84 (s, 3 H, $CH_3$ 3-ring), 0.88 (s, 9 H, *tert*-butyl Si), 0.21 (s, 3 H, $CH_3$ Si), 0.10 (s, 3 H, $CH_3$ Si), sulfone protons 7.99 (d), 7.71 (m), 7.62 (m); $^{13}C$ NMR ($CDCl_3$) phenyl sulfone 137.5 (e, ipso), 129.5 (o, ortho), 129.1 (o, meta), 123.9 (o, para), 136.0 (e, C3), 133.7 (e, C4), 75.0 (o, C1′), 73.0 (o, C3′), 56.1 (o, C2), 56.0 (o, CS2), 45.9 (e, C5′), 36.2 (o, C2′), 35.0 (o, C4′), 29.8 (o, $CH_3$), 22.2 (o, quaternary 3-ring), 21.9 (o, C1), 18.9 (o, 5-ring $CH_3$), 18.7 (o, C6), 15.4 (o, $CH_3$ 3-ring), 13.6 (o, $SCH_3$), 11.8 (o, $SCH_3$), 1.1 (o, $CH_3Si$), 2.4 (o, $CH_3Si$); mp 140–142 °C.

**3-((Trimethylstannyl)bis(methylthio)methyl)-(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]hept-2-ene (54).** In 30 mL of THF LDA was generated at −78 °C by the addition of *n*-BuLi (1.97 mL, 2.4 mmol, 1.35 M), to diisopropylamine (0.35 mL, 2.52 mmol). The mixture was allowed to stir for 10 min after which HMPA (1.9 mL, 11 mmol) was added in 3 mL of THF. To the mixture thioacetal **47** (500 mg, 2.19 mmol) in 5 mL of THF was added dropwise, and the mixture turned purple instantly. Removal of the dry ice bath and further stirring for an additional 15 min ensures complete metalation of the thioacetal. The reaction was then recooled to −78 °C, and trimethyltin chloride **53** (0.48 g, 2.41 mmol) in 5 mL of THF was added. TLC analysis of the mixture showed the presence of two new compounds ($R_f$ 0.27 and 0.24 in 100% hexane). The reaction was then quenched with 30 mL of water and was extracted with 140 mL of ether. The organic layer was washed successively with 300 mL of 5% HCl solution, 4 × 30 mL of water, and 40 mL of saturated NaCl solution and dried. Evaporation of the solvent provided the crude products (95% yield), which were very labile to silica gel. Plug filtration of only 50 mg of the crude product with 100% hexane provided 10 mg of the pure α-stannyl thioacetal **54** in 11% yield: $^1H$ NMR ($CDCl_3$) 5.94 (d, 1 H, vinyl), 1.92 (s, 6 H, $SCH_3$), 2.2–1.5 (m, 5 H, ring protons), 1.05 (s, 3 H, 3-ring $CH_3$), 1.06 (buried, 1 H, C1, H), 0.83 (buried, 1 H, C6, H), 0.82 (s, 3 H, $CH_3$), 0.17 (s, 9 H, $Sn(CH_3)_3$).

**[(1′*S*,2′*R*,3′*S*,4′*S*)-1′-Hydroxy-3′-(phenylsulfonyl)-4′-methylcyclopent-2′-yl][(1″*R*,6″*S*)-7″,7″-dimethylbicyclo-[4.1.0]hept-2″-en-3″-yl]bis(methylthio)methane (57).** To a solution of stannanes **54** and **55** (3.0 g, 7.94 mmol) in 50 mL of THF at −78 °C was added *n*-BuLi (6.94 mL, 9.4 mmol). The color changed instantly to purple, indicating the formation of thioacetal anion **9b**. After 20 min of stirring at −78 °C, vinyl sulfone **40** (1.4 g, 3.97 mmol) was added in 20 mL of THF. The color of the reaction slowly turned yellow, and after 45 min the reaction was allowed to warm to 0 °C over a period of 30 min (TLC, $R_f$ 0.32, 10% ethyl acetate–90% hexane). The reaction was then quenched with water (60 mL) and extracted with 150 mL of $CH_2Cl_2$. The organic layer was washed with 3 × 50 mL of water and dried. Evaporation of the solvent afforded 2.25 g of a 5:1 mixture of **56** and **51** (61% total yield). The crude mixture was dissolved in 40 mL of THF, and $(n\text{-}Bu)_4NF$ (8 mL, 8 mmol, 1 M solution) was added. The mixture was allowed to stir for 48 h at room temperature, diluted with 120 mL of $CH_2Cl_2$, washed with 40 mL of 5% HCl solution, 30 mL of saturated $NaHCO_3$, solution, and 30 mL of saturated NaCl solution, and dried. The solvent was removed under reduced pressure, and the residual oil was chromatographed with 20% ethyl acetate–80% hexane ($R_f$ 0.18) to afford 875 mg of an oil (**57**), which represents a 47% yield based on vinyl sulfone **40**: NMR ($CDCl_3$) 5-ring 4.4 (m, 1 H, α-OH), 3.15 (m, 1 H, C2′H), 3.65 (m, 1 H, α-sulfone, 2.75 (m, 1 H, C4′H), 3.42 (m, 1 H, C5′H syn-OH), 2.0 (m, 1 H, C5′H anti-OH), 0.68 (d, 3 H, $J$ = 6.8 Hz, $CH_3$), 6-ring 1.11 (m, 1 H, C1″H 3-ring), 6.29 (d, 1 H, $J$ = 4.3 Hz, vinyl), 2.2–1.8 (m, 4 H, ring Hs), 0.96 (m, 1 H, C6″H 3-ring), 1.09 (s, 3 H, $CH_3$), 0.91 (s, 3 H, $CH_3$), 1.99 (s, 3 H, $SCH_3$), 1.97 (s, 3 H, $SCH_3$); exact mass calcd ($M^+ - SCH_3$) 418.164, found 418.165.

**[(4′*S*)-1′-Oxo-4′-methylcyclopent-2′-en-2′-yl][(1″*R*,6″*S*)-7″,7″-dimethylbicyclo[4.1.0]hept-2″-en-3″-yl]bis(methylthio)methane (58).** To DMSO (1.9 mL, 26.6 mmol) in 150 mL of $CH_2Cl_2$ at −78 °C was added TFAA (2.5 mL, 17.7 mmol). A white precipitate formed instantly, and it was allowed to stir for 15 min. Alcohol **57** (1 g, 2.22 mmol) dissolved in 50 mL of $CH_2Cl_2$ was then added, and the mixture was stirred vigorously for 4 h. To that triethylamine (5 mL, 35.5 mmol) was then added, and stirring was continued for 0.5 h at −78 °C and 0.5 h at 0 °C. The reaction became clear at this stage and was diluted with 50 mL of $CH_2Cl_2$. The organic layer was washed with 3 × 30 mL of 5% HCl solution and 40 mL of saturated $NaHCO_3$ solution and dried. The solvent was evaporated, and the remaining oil was dissolved in 100 mL of ether. The mixture was cooled to 0 °C, DBU (1.7 mL, 11.1 mmol) was added, and stirring was resumed for 3 h. At this stage the reaction was judged complete by TLC analysis ($R_f$ 0.43, 20% ethyl acetate–80% hexane). The reaction was diluted with 50 mL of ether, washed with 3 × 40 mL of 5% HCl solution and 30 mL of saturated $NaHCO_3$ solution, and dried (403 mg, 66% overall from **57**): NMR ($CDCl_3$) 5-ring 7.43 (m, 1 H, enone H), 2.92 (m, 1 H, C4′H), 2.6 (m, 1 H, C5′H), 2.02 (m, 1 H, C5′H), 1.1 (d, 3 H, $J$ = 4.4 Hz, $CH_3$), 6 ring: 1.11 (m, 1 H, C1″H 3-ring), 6.05 (d, 1 H, $J$ = 3.6 Hz, vinyl), 2–1.5 (m, 4 H, ring Hs), 0.90 (m, 1 H, C6″H 3-ring), 1.07 (s, 3 H, $CH_3$), 0.99 (s, 3 H, $CH_3$), 1.81 (s, 6 H, $2SCH_3$); *m/e* 275 ($M^+ + 1 - SCH_3$, 100), 228 (1.05), 227 (9.4), 185 (5.5), 157 (3.1).

**[(1′*R*,4′*S*)-1′-Acetyl-1′-hydroxy-4′-methylcyclopent-2′-en-2′-yl][(1″*R*,6″*S*)-7″,7″-dimethylbicyclo[4.1.0]hept-2″-en-3″-yl]bis(methylthio)methane (60).** Anhydrous $CeCl_3$[39c] (0.6 g, 2.4 mmol) was stirred in 16 mL of THF for 14 h. In a separate flask, *t*-BuLi (1.6 mL, 2.4 mmol) was added to a solution of ethyl vinyl ether (0.48 mL, 5 mmol) in 12 mL of THF at −78 °C. The yellow mixture was allowed to warm to 0 °C until the yellow color was discharged, and the reaction was quickly cooled back to −78 °C. The anion generated was transferred via cannula to the $CeCl_3$ suspension (cooled to −78 °C before the addition), and the resulting canary yellow mixture was allowed to stir for 5 min before enone **58** (80 mg, 0.24 mmol) was added in 4 mL of THF. TLC analysis ($R_f$ 0.62, 20% ethyl acetate–80% hexane) showed a new product had formed, and the reaction was quenched with 10 mL of water after 30 min. The aqueous layer was extracted with 50 mL of $CH_2Cl_2$. The organic layer was washed once with 10 mL of 5% HCl solution and 10 mL of water and was dried. Evaporation of the solvent provided 57 mg of an oil (**60**), which represents a 71% yield: NMR ($CDCl_3$) 5-ring 5.96 (d, 1 H, $J$ = 1.53 Hz, vinyl), 2.79 (m, 1 H, C4′H), 2.38 (m, 1 H, C5′H syn-OH), 1.52 (m, 1 H, C5′H anti-OH), 1.13 (d, 3 H, $J$ = 6.9 Hz, $CH_3$), 2.22 (s, 3 H, $CH_3$ ketone), 6 ring 1.07 (m, 1 H, C1″ 3-ring), 6.1 (d, 1 H, $J$ = 4.3 Hz, vinyl), 2–1.5 (m, 4 H, ring Hs), 0.90 (m, 1 H, C6″ 3-ring), 1.09 (s, 3 H, $CH_3$), 0.95 (s, 3 H, $CH_3$), 1.86 (s, 3 H, $SCH_3$), 1.80 (s, 3 H, $SCH_3$); IR 2.91 (br, OH), 3.38, 3.42, 3.48, 5.87 (vs. carbonyl), 7.42, 8.85; *m/e* 319 ($M^+ - SCH_3$, 16.5), 229 (12.6), 211 (6.92), 185 (10.0), 167 (2.2), 157 (3.9), 143 (5.8), 141 (4.5), 91 (11.8), 69 (13.5).

**Acknowledgment.** We thank the NIH for generous support of this research (Grant GM 32693). $^{13}C$ NMR spectra reported in this study were obtained on a Varian XL-200 spectrometer (NSF Grant 7841) and were provided by Drs. Mike Nantz and John Toth. We also thank the Purdue University Biological Magnetic Laboratory (NIH Grant RR 01077) for access to the 470-MHz NMR spectrometer. Valuable discussions with Professor Dale Boger are gratefully acknowledged.

**Registry No.** 1, 62820-14-8; 2, 30272-36-7; **5a**, 115047-36-4; **5b**, 115047-40-0; **6a**, 115047-35-3; *d*-**7**, 77520-15-1; **9a**, 78012-42-7; **9b**, 115047-56-8; *l*-**16**, 78087-19-1; *l*-**17**, 115115-24-7; *l*-**18**, 18031-

40-8; **19a**, 78012-40-5; *d*-**20**, 14917-83-0; **21**, 78012-41-6; **23**, 115115-25-8; 2-*epi*-**23**, 115115-28-1; **24**, 115047-41-1; **25**, 78012-44-9; *epi*-**25**, 115047-42-2; **26**, 40207-59-8; **27**, 115047-44-4; **28**, 115047-43-3; **28** (dimethylhydrazone), 115047-58-0; **29a**, 115047-45-5; **29b**, 115047-46-6; **37**, 5799-67-7; **40**, 115047-47-7; **43**, 101245-15-2; **45** (isomer 1), 115115-26-9; **45** (isomer 2), 115115-27-0; **46**, 115047-48-8; **47**, 115047-49-9; **49a**, 115115-29-2; **49b**, 115047-60-4; **51**, 115047-50-2; **52a**, 115047-61-5; **52b**, 115047-62-6; **53**, 1066-45-1; **54**, 115047-51-3; **55**, 115047-52-4; **56**, 115047-53-5; **57**, 115047-54-6; **57** (ketone), 115047-57-9; **58**, 115047-55-7; **59b**, 94616-76-9; **60**, 115047-37-5; **61**, 115047-38-6; **62**, 115047-39-7; $CH_2$=CHOEt, 109-92-2; 2-[(1′*S*,2′*R*,3′*S*,4′*R*)-1′-hydroxy-4′-methyl-3′-(phenylsulfonyl)cyclopent-2′-yl]-3-(1,3-dithian-2-ylidene)-(1*R*,6*S*)-7,7-dimethylbicyclo[4.1.0]heptane, 115047-59-1.

**Supplementary Material Available:** Crystal data and data collection parameters, positional parameters and their estimated standard deviations, general temperature factors, bond distances, and bond angles for compound **46** (12 pages). Ordering information is given on any current masthead page.

# Octahydroquinoline Synthesis via Immonium Ion Based Diels–Alder Chemistry: Synthesis of (-)-8a-Epipumiliotoxin C

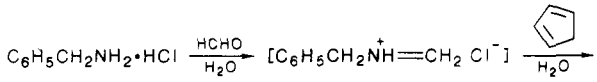
Paul A. Grieco* and David T. Parker[1]

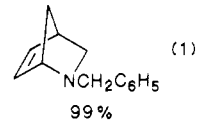
*Department of Chemistry, Indiana University, Bloomington, Indiana 47405*

*Received January 13, 1988*

A total synthesis of (-)-8a-epipumiliotoxin C has been developed which features an intramolecular immonium ion based Diels–Alder reaction. Cyclocondensation of the immonium ion **8** derived from optically pure aldehyde **2** and ammonium chloride provided two octahydroquinolines **9** and **10**, in a ratio of 2.2:1. The formation of **9** and **10** is rationalized on the basis of the chair-like conformations **16** and **17** respectively. Reduction of the double bond in **9** afforded (-)-8a-epipumiliotoxin C.

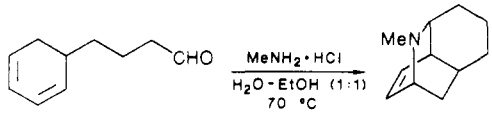
The ability of immonium ions to function as heterodienophiles in Diels–Alder reactons carried out under Mannich-like conditions holds considerable promise for the construction of nitrogen-containing ring systems. During our preliminary study, efforts were focused on probing the potential of utilizing immonium ions in simple intermolecular[2] (cf. eq 1) and intramolecular[3] (cf. eq 2) Diels–Alder cycloaddition reactions.




(1)

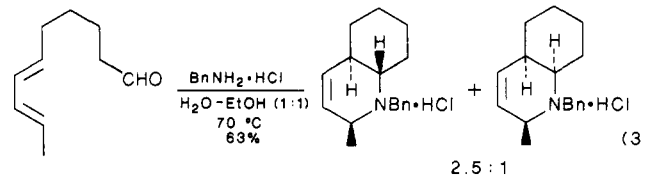
99%




(2)

66%

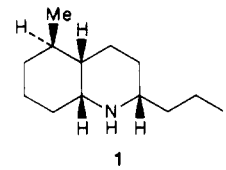
As an extension of our earlier work, we set out to investigate whether the intramolecular immonium ion based Diels–Alder reaction could be employed in the construction of substituted octahydroquinoline systems and, more importantly, to explore the stereochemical outcome of such processes wherein a substituent is located on the tether between diene and heterodienophile. Previous work during the early stages of our investigation had also established the feasibility of constructing octahydroquinoline ring systems[2] (cf. eq 3). Accordingly, we set out to explore the



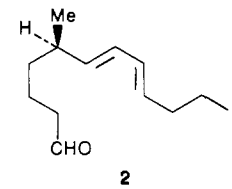

(3)

2.5 : 1

possibility of elaborating octahydroquinolines which could serve as precursors to decahydroquinolines related to pumiliotoxin C (**1**),[4] a toxin isolated from the skin of Central American poison arrow frogs.

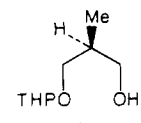



**1**

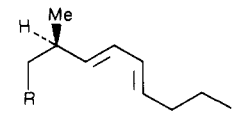



**2**

Our strategy for elaborating octahydroquinoline systems centered around intramolecular cyclocondensation of the immonium ion derived from aldehyde **2** and ammonium chloride. The known chiral alcohol **3**[5] conveniently served as a starting point for the preparation of **2**. Oxidation




**3**




**4**, R = OH
**5**, R = I
**6**, R = $CH_2COOMe$
**7**, R = $CH_2CH_2CN$

(1) Procter and Gamble Predoctoral Fellow, 1987–1988.
(2) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.
(3) Larsen, S. D.; Grieco, P. A. *J. Org. Chem.* **1986**, *51*, 3553.
(4) Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Justus Liebigs Ann. Chem.* **1969**, *729*, 198.
(5) Mori, K. *Tetrahedron* **1983**, *39*, 3107.

0022-3263/88/1953-3658$01.50/0 © 1988 American Chemical Society