4e-Si, 117582-01-1; **5t**, 117676-80-9; **5e**, 117581-81-4; [2*S*-(1*R*,2*S*)]-**6t**, 117676-81-0; [2*R*-(1*R*,2*S*)]-**6t**, 117581-82-5; **6e**, 117676-76-3; **7et**, 117676-79-6; **7ee**, 117676-78-5; **7te**, 117581-83-6; **7tt**, 117676-77-4; **7tt** (THP ether), 117582-08-8; **8et**, 117582-02-2; **8et** (1,3-diol), 117676-87-6; **8ee**, 117581-85-8; **8ee** (1,3-diol), 117676-85-4; **8te**, 117582-03-3; **8te** (1,3-diol), 117676-86-5; **8tt**, 117581-84-7; **8tt** (1,3-diol), 117582-11-3; **9et**, 117581-87-0; **9ee**, 117582-04-4; **9te**, 117581-86-9; **9te** (THP ether), 117582-12-4; **9te** (1,3-diol; 3-THP ether), 117582-13-5; **9te** (1,3-diol; 1-tosylate, 3-THP ether), 117582-14-6; **9tt**, 117582-05-5; **10t**, 117581-88-1; **10e**, 117581-89-2; (*R*)-**11**, 117581-76-7; **12et**, 117581-92-7; **12ee**, 117581-91-6; **12tt**, 117581-90-5; **12tt** (diol), 117582-10-2; **13et**, 117676-84-3; **13ee**, 117676-82-1; **13te**, 117676-83-2; **13tt**, 117581-93-8; **14te**, 117581-94-9; (*S*)-$BnOCH_2CF(CH_3)COOEt$, 117581-95-0; (*S*)-$HOCH_2CF(CH_3)COOEt$, 105314-05-4; BnBr, 100-39-0; (*R*)-$BnOCH_2CF(CH_3)CH_2OH$, 117581-96-1; (*S*)-$BnOCH_2CF(CH_3)CH_2OSiMe_2Bu$-*t*, 117581-97-2; (*S*)-$HOCH_2CF(CH_3)CH_2OSiMe_2Bu$-*t*, 117581-98-3; (4*R*,5*S*,6*S*)-$BnOCH_2CF(CH_3)CH(OTHP)CH(CH_3)CEt_2OH$, 117582-09-9; $CH_2=C(OLi)Bu$-*i*, 76638-96-5; $CH_2=C(OMgBr)Bu$-*i*, 117582-15-7; $CH_2=C(OZnCl)Bu$-*i*, 117582-16-8; $CH_2=C(OAlEt_2)Bu$-*i*, 117582-17-9; $CH_2=C(OTMS)Bu$-*i*, 59417-87-7; $CH_2=C(OTMS)Bu$-*t*, 17510-46-2; $CH_2=C(OTMS)OEt$, 42201-84-3; (*E*)-$CH_3CH=C(OTMS)Et$, 51425-53-7; (*Z*)-$CH_3CH=C(OTMS)Et$, 51425-54-8; $CH_3CH=C(OLi)OEt$, 81355-01-3; (*E*)-$CH_3CH=C(OTMS)SBu$-*t*, 76943-95-8; (*Z*)-$CH_3CH=C(OTMS)SBu$-*t*, 76943-94-7; TiCl4, 7550-45-0; $EtAlCl_2$, 563-43-9; BF_3·OEt, 109-63-7; cyclohexanone trimethylsilyl enol ether, 6651-36-1.

Synthesis of the Furanoheliangolide Ring Skeleton

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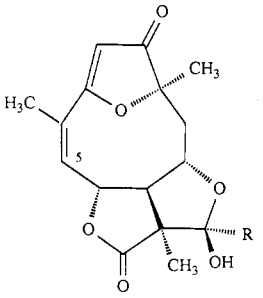
Received June 29, 1988

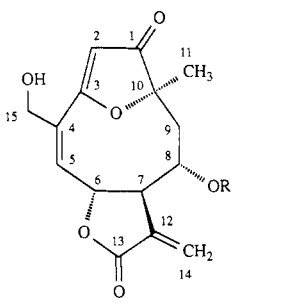
A synthesis of the 11-oxabicyclo[6.2.1]undecane ring system found in the furanoheliangolide and abestinane classes of natural products is described. The key reaction involves the ozonolysis of an oxa-bridged Δ^9-octalin (**28**) to yield an oxa-bridged 1,6-cyclodecanedione (**29**). Selective reduction of the dione with sodium borohydride yielded a hemiketal **30**, whose structure was determined by an X-ray analysis. Attempts to synthesize the above ring system via a palladium(II)-catalyzed Cope rearrangement of a 2,3-divinyl-7-oxanorborane (**19**) failed and instead produced cyclopentenes **21a** and **21b** via a palladium-catalyzed cyclization.

Germacranes are a ubiquitious class of sesquiterpenoid natural products that possess a variety of biological activities, including cytotoxic activity.[1] Over 30 germacranolides have demonstrated either in vitro or in vivo antineoplastic activity. Many of the active compounds belong to a subgroup of the germacranes sometimes referred to as the furanoheliangolides. These compounds have an oxygen atom bridging C-3 and C-10. The resulting tetrahydrofuran ring is usually further oxidized and is often found as a 3(2*H*)-furanone as in the eremantholides (**1**) and lynchnophorolides (**2**). Several representative examples of this compound class are listed below.[2,3] All these particular substances have demonstrated cytotoxic behavior.

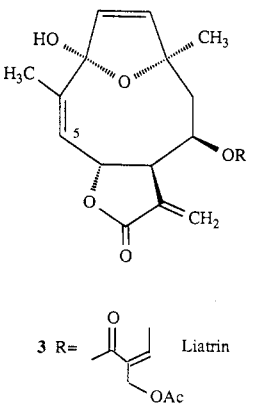
Unfortunately all the active germacranolides, except for the eremantholides **1**, contain an α-methylene lactone. This structural unit, while consistently identified with cytotoxic activity, has proven to be too toxic for clinical use.[4] That the eremantholides maintain cytotoxic activity despite the absence of an α-methylene lactone may therefore be significant. In analogy with the work of Smith and co-workers on vinyl-3(2*H*)-furanones[5] it would seem



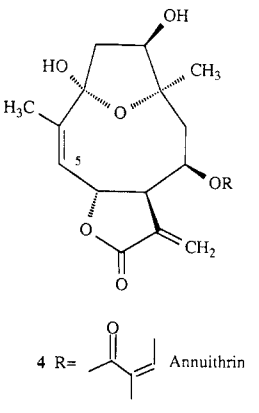
1a R=i-Pr Eremantholide A
1b R=s-Bu Eremantholide B
1c R= Eremantholide C



2a R= Lychnophorolide A
2b R= Lychnophorolide B



3 R= Liatrin



4 R= Annuithrin

plausible that C-5 is the electrophilic center responsible for the activity of the eremantholides. Further support for this contention was garnered by LeQuesne who found that eremantholide A (**1a**) undergoes clean thiol addition at C-5.[2a] Interestingly all the cytotoxic furanoheliangolides

(1) (a) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47. (b) Rodriquez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573.

(2) (a) Eremantholides: Le Quesne, P. W.; Levery, S. B.; Menachery, M. D.; Brennan, T. F.; Raffauf, R. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1952. (b) Lychnophorolides: Le Quesne, P. W.; Menachery, M. D.; Pastore, M. P.; Kelley, C. J.; Brennan, T. F.; Onan, K. D.; Raffauf, R. F.; Weeks, C. M. *J. Org. Chem.* **1982**, *47*, 1519. (c) Liatrin: Kupchan, S. M.; Davies, V. H.; Fujita, T.; Cox, M. R.; Restivo, R. J.; Bryan, R. F. *J. Org. Chem.* **1973**, *38*, 1853. (d) Annuithrin: Spring, O.; Albert, K.; Waltraud, G. *Phytochemistry* **1981**, *20*, 1883.

(3) A number of structural misassignments have persisted in this class of compounds. For correct structures, see: Herz, W.; Goeden, V. L. *J. Org. Chem.* **1982**, *47*, 2798.

(4) (a) Powell, R. G.; Smith, C. R., Jr. *Recent Advances in Phytochemistry*; Swain, T., Kleiman, R., Eds.; Plenum: New York, 1980; Vol. 14, Chapter 3.

(5) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.

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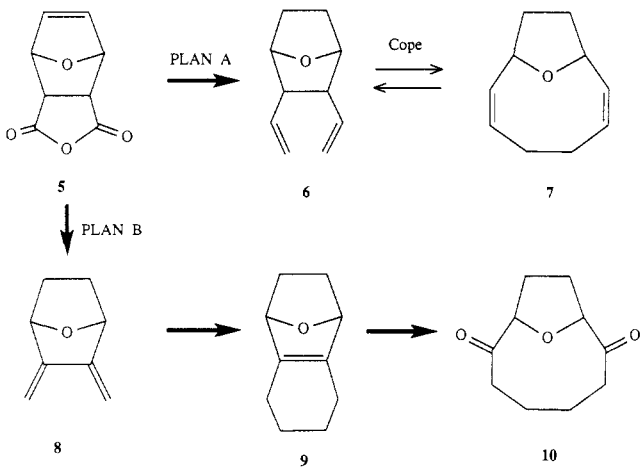
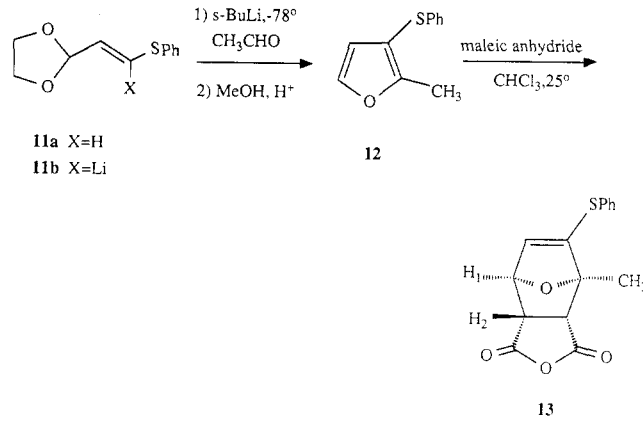
Scheme I



Scheme II



are primed, usually but not always via the auspices of a vinylfuranone, for electrophilic attack at C-5. To test whether C-5 activation is sufficient for the elicitation of antineoplastic activity we initiated a synthesis of the furanoheliangolide ring skeleton. It is our activity in this area that is the subject of this paper.

Results and Discussion

Synthetic Strategy. The underlying framework of the furanoheliangolides is the 11-oxabicyclo[6.2.1]undecane ring system (see structures **7** and **10**, Scheme I). Despite the fact that this ring system is also found in the abestinane class of marine diterpenes,[6] no reports on a general preparation of this ring system have yet appeared in the literature.[7] Analysis of the parent ring system reveals it to be a simple bridged tetrahydrofuran. Smaller bridged furans, specifically two-carbon bridged furans, are known to be available via the Diels–Alder reaction of furan.[8] Therefore, if a method could be found that would expand the bridging system by four carbons, a facile route to the furanoheliangolide skeleton would be in hand.

As depicted in Scheme I, we had two plans for the expansion of the bridging system. The first, plan A, involved the Cope rearrangement of a *cis*-2,3-divinyloxanorbornane (**6** → **7**). While one must be concerned with where the equilibrium lay in this reversible rearrangement, it was surmised that relief of ring strain in the starting [2.2.1] system might serve to drive the reaction toward the ring-expanded product **7**. In addition one might benefit from the technology developed by Overman wherein palladium(II) salts are used to catalyze the rearrangement.[9] The alternative plan, plan B, was equally direct. In this case simple oxidative cleavage of the oxa-bridged Δ^9-octalin **9** would produce the furanoheliangolide skeleton **10**. While the parent 1,6-cyclodecanedione has been prepared via ozonolysis of Δ^9-octalin,[10] to our knowledge there are no examples in which such a clevage has been used to prepare substituted 1,6-cyclodecanediones for use in natural product synthesis. The necessary octalin should in turn be available from the Diels–Alder reaction of the 2,3-bis(methylidene) derivative **8**, a reaction well studied by Vogel and co-workers.[11]

The starting material for both of these approaches was envisioned to be the Diels–Alder adduct between maleic anhydride and a suitable furan. While the parent adduct **5** is commercially available, our desire to ultimately target the naturally occurring furanoheliangiolides forced us to consider alternative Diels–Alder adducts. We settled on the Diels–Alder product **13** resulting from the cycloaddition of the thio-substituted furan **12** (see Scheme II).[12] This material was chosen as it placed a methyl group at the bridgehead position and incorporated functionality into the furan ring for future elaboration into a 3(2*H*)-furanone, both important considerations for the synthesis of the naturally occurring furanoheliangolides. An additional advantage afforded by the choice of furan **12** was its expected reactivity in the Diels–Alder reaction. In analogy with 3-alkoxyfurans,[13] the 3-(phenylthio)furans should show enhanced reactivity relative to furan. As will be seen, path B has yielded the desired ring skeleton. Our discussion, however, will begin with the less successful path A as an interesting palladium-catalyzed cyclization was observed in the course of this work.

Path A: Attempted Cope Rearrangement. The requisite furan **12** was easily available via our previously described methodology for the synthesis of 3-(phenylthio)furans.[12] The key step in this sequence is the site-selective α-lithiation of vinyl sulfide **11a** (see Scheme II). The resulting organolithium **11b** is quenched with acetaldehyde, and the crude adduct is subsequently cyclized in acidic methanol to produce the desired furan in a 54% distilled yield. The starting sulfide **11a** (*E*/*Z*, 95/5) is readily prepared from the conjugate addition product of thiophenol and acrolein[14] (see the Experimental Section for details) so that furan **12** could be prepared in large quantities. As expected the electron-rich furan **12** underwent clean cycloaddition with maleic anhydride to yield the exo product **13**. Lack of any observable coupling be-

(6) For a list of representative structures, see: Krebs, H. Chr. *Fortschr. Chem. Org. Naturst.* **1986**, *47*, 151.

(7) (a) Mihailovic, M. L.; Andrevic, V.; Jakovljevic, M.; Jeremic, D.; Stoziljkovic, A.; Partch, R. E. *Chem. Commun.* **1970**, 854. (b) Ronald, R. C.; Lillie, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 5709. (c) An approach to the bottom half of the eremantholides has been published, see: Boeckman, R. K., Jr.; Heckendorn, D. K.; Chinn, R. L. *Tetrahedron Lett.* **1987**, *28*, 3551.

(8) Sargent, M. V.; Dean, F. M. In *Comprehensive Heterocyclic Chemistry*; Katritsky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 619.

(9) (a) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865. (b) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225. (c) For a review, see: Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

(10) House, H. O.; Lee, J. H. C.; VanDerveer, D.; Wissinger, J. E. *J. Org. Chem.* **1983**, *48*, 5285 and references therein.

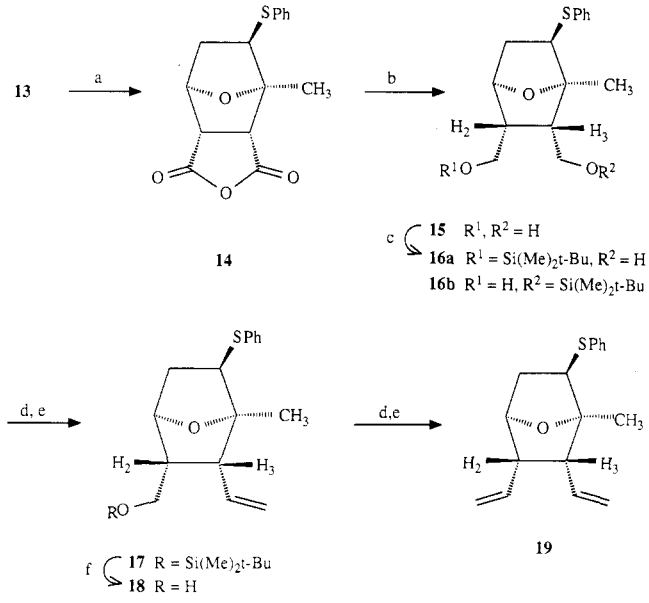
(11) (a) Tornare, J.-M.; Vogel, P. *Helv. Chim. Acta* **1985**, *68*, 2195. (b) Métral, J.-L.; Vogel, P. *Tetrahedron Lett.* **1984**, *25*, 5387. (c) Hahaim, C.; Vogel, P. *Tetrahedron Lett.* **1982**, *23*, 866.

(12) McDougal, P. G.; Oh, Y.-I. *Tetrahedron Lett.* **1986**, *27*, 139 and references therein.

(13) (a) Murai, A.; Takahashi, K.; Taketsura, H.; Masamune, T. *Chem. Commun.* **1981**, 221. (b) Iten, P. X.; Hofmann, A. A.; Eugster, C. H. *Helv. Chim. Acta* **1979**, *62*, 2202.

(14) Inomata, K.; Sumita, M.; Kotake, H. *Chem. Lett.* **1979**, 709.

Scheme III[a]

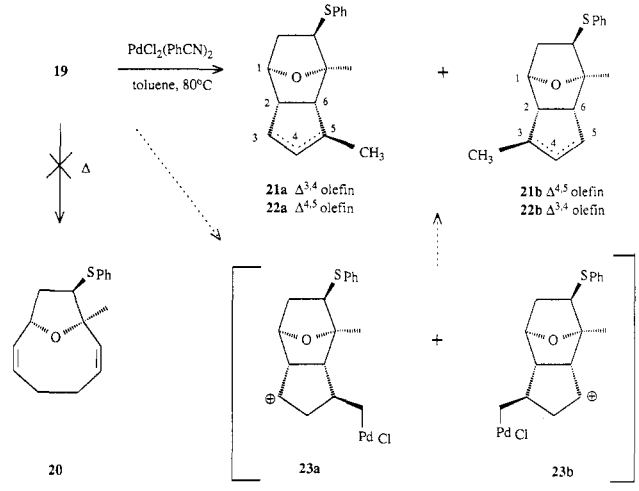


[a] Reagents: (a) Pd/C, H_2, EtOAc; (b) $LiAlH_4$, THF, 75% from **12**; (c) *tert*-butyldimethylsilyl chloride, NaH, THF, 96%; (d) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2; (e) $(Ph)_3PCH_3Br$, s-BuLi, THF, 81% from **16a**, 43% from **18**; (f) $(n\text{-}Bu)_4NF$, THF, 98%.

tween the endo proton H_2 and the bridgehead proton H_1 (see **13**, Scheme II) indicated the exo product had been formed.[15] The remainder of the synthesis is illustrated in Scheme III. Without purification the crude Diels–Alder adduct **13** was subjected to catalytic hydrogenation on a Parr apparatus. Due to the presence of sulfur it was found that the Pd/C catalyst was deactivated during the course of this reaction, so that it was necessary to replace the catalyst several times in order to complete the reduction of the olefin. The resulting anhydride was then immediately reduced with lithium aluminum hydride to give the crystalline diol **15** in a 75% yield from starting furan **12**. As expected hydrogenation had occurred on the exo face to produce the endo sulfide **15**.

Sequential introduction of the vinyl groups necessitated the monoprotection of diol **15**. In this instance we were not concerned with selecting one alcohol over the other as ultimately both were to be converted to the same terminal vinyl moiety. Rather we wished to maximize the yield of monoprotected product relative to diprotected and unprotected material. This was accomplished by quenching the monosodium salt of diol **15** with 1 equiv of *tert*-butyldimethylsilyl chloride.[16] This procedure yielded the two monoprotected diols **16a** (58%) and **16b** (38%) in good yield. The major isomer **16a** was then carried on to the divinyl target **19** without event. Swern oxidation[17] of alcohol **16a** followed by the methylene Wittig reaction gave olefin **18** in an 81% yield. Following deprotection, another round of oxidation and olefination produced the desired diene **19** in a 43% yield. In transforming **16a** to **19** care was taken to monitor the stereochemistry at C-2 and C-3 in order to assure that no epimerization had occurred during the formation and/or reaction of the intermediate aldehydes. In all instances a 9.0-Hz coupling constant was

Scheme IV



observed between H_2 and H_3 consistent with their endo,endo relationship.[15]

While it would seem logical that diol **15** would undergo preferential silylation at the alcohol moiety removed from the bridgehead methyl group, the assignment of structure **16a** to the major silylated isomer is also supported by ^1H NMR spectroscopy. Close inspection of the chemical shifts for compounds **14**–**19**, reveals that the endo proton that resides directly across from the endo phenylthio substituent, that is at C-2, is deshielded by approximately 0.6 ppm relative to a similiarly situated proton at C-3 (see the Experimental Section for exact chemical shifts). This allows the structure of the olefinic alcohol **18** to be assigned by relating the chemical shift of H_2 to that of H_2 in diol **15** (2.28 versus 2.38 ppm) and that of H_3 to that of H_3 in diene **19** (3.29 versus 3.41 ppm).[18] Since **18** was prepared from **16a** the structure of isomers **16a** and **16b** can be assigned. As will be seen the chemical shift difference between endo protons at C-2 and C-3 proved useful in some other structural assignments.

With diene **19** in hand the key Cope rearrangement was attempted as depicted in Scheme IV. Thermolysis of the diene in hydrocarbon solvent lead to either recovered starting material (dodecane, 200 °C, 8 h) or slow decomposition (dodecane, 220 °C, 20 h). In retrospect, even in the event of a successful Cope rearrangement, the resulting bridged allylic ether **20** was probably susceptible to solvolytic decomposition. In an attempt to lower the temperature needed to effect rearrangement, we carried out the reaction in the presence of $PdCl_2(PhCN)_2$.[9] Exposure of diene **19** to this Pd^{2+} salt in toluene at 80 °C lead to clean formation of a new material. Inspection of the ^1H NMR spectrum (300 MHz) revealed that a 3:5:1 mixture of two products had been formed and could be assigned structures **21a** (major product) and **21b** (minor product). The presence of a new set of methyl doublets indicated that the desired Cope reaction had not taken place. The similiarity of both the chemical shifts and coupling patterns in the two inseparable products indicated that their structures were similar (see the Experimental Section for a detailed assignment). The assigned structures are entirely consistent with the ^1H NMR data. In particular the rather small vinylic coupling constant (5.6 Hz) is perfect for a cyclopentene ring attached to a bicyclo[2.2.1]heptane ring.[19] The rather small coupling between H_5 and H_6 (3.5

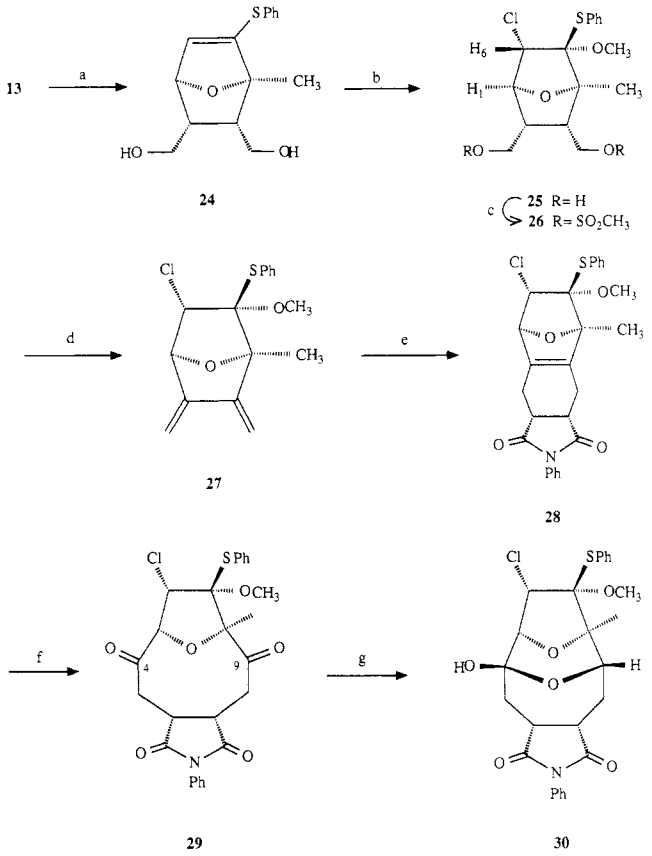
(15) (a) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance in Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1969; p 289. (b) Marchand, A. P.; *Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems*; Verlag Chemie International: Deerfield Beach, 1982.

(16) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *57*, 3388.

(17) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(18) If the vinyl and hydroxymethyl groups of **18** were transposed one would have expected H_2 to have a chemical shift of ~2.74 ppm and H_3 to have a chemical shift of ~2.90 ppm.

Scheme V[a]



[a] Reagents: (a) $LiAlH_4$, THF, 0 °C, 68% from **12**; (b) NCS, CH_3OH, 25 °C, 80%; (c) CH_3SO_2Cl, Et_3N, THF, 0 °C; (d) KOt-Bu, HMPA–DMF, 0 °C, 58% from **25**; (e) *N*-phenylmaleimide, toluene, 90 °C, 53%; (f) O_3, EtOAc, −78 °C, $(CH_3)_2S$ workup, 92%; (g) $NaBH_4$, EtOAc

Hz) in **21a** signalled that these protons were trans and hence established the stereochemistry of the newly formed methyl group.[19] Finally, as discussed above, the deshielding of the endo protons residing at C-6 relative to similiarly situated protons at C-2 allowed structure **21a** to be assigned to the major product. It should also be mentioned that the 300-MHz ^1H NMR spectrum revealed small amounts (<10%) of two other products tentatively assigned as **22a** and **22b**. These two products seemed to have an intact oxanorbornane skeleton (i.e. H_1 was present) along with an allylic methyl group (δ 1.70 and 1.75, br s) and a single vinyl proton (δ 5.35 and 5.42, br s) consistent with a trisubstituted olefin.

While there is certainly precedent for the palladium-catalyzed cyclization of 1,5-hexadienes,[9c,20] the cyclization reported here is somewhat unusual in that both olefins are monosubstituted. In all of the previously reported cyclizations and rearrangements one of the olefins was substituted, most notably with oxygen,[20b] so as to stabilize the developing carbocation center in the putative intermediates **23a** and **23b**.[9c] It is tempting to speculate that the relative proximity of the two olefins in diene **19** is responsible for the success of the observed cyclization.

Path B: Olefinic Cleavage. Concurrent with the approach discussed above we attempted to prepare the desired oxabicyclo[6.2.1]undecane skeleton via path B as

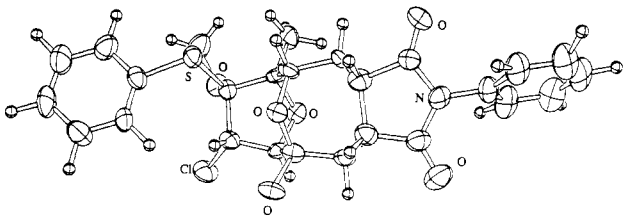


Figure 1. ORTEP picture of hemiketal **30**.

outlined in Scheme I. The initial stage of this route called for the conversion of a furan Diels–Alder adduct into a 2,3-bis(methylidene) derivative (see Scheme 1; **5** → **8**). Again we chose to begin our synthesis with the readily available Diels–Alder product **13**. However in this instance we chose not to reduce the vinyl sulfide, but rather explored the oxidation of this moiety with an eye toward the preparation of the 3(2*H*)-furanone ring found in the naturally occurring furanoheliangolides.

As delineated in Scheme V the sequence began with a lithium aluminum hydride reduction of anhydride **13**. This reaction proceeds smoothly as long as the reaction temperature is kept at 0 °C. Higher temperatures lead to addition of hydride to the vinyl sulfide with concomitant opening of the oxygen bridge. Following a basic workup the highly sensitive diol **24** is immediately oxidized with *N*-chlorosuccinimide (NCS) in methanol.[21] It is important that the NCS be added as soon as the diol is dissolved in methanol as the diol itself decomposes slowly in methanol. Despite the sensitivity of diol **24**, this sequence yielded the stable chloride **25** in 80% based on furan **12**. The exo orientation of the chlorine was supported by the absence of coupling between H_1 and H_6, while the endo phenylthio group was identified by the 0.6 ppm downfield shift of H_3 versus H_2 (vide supra). Conversion of diol **25** to diene **27** followed the methodology reported by Vogel for related bicyclic systems.[11b] Mesylation and subsequent elimination produced the crystalline diene **27** in 58% yield.

As expected the diene was a respectable participant in the Diels–Alder reaction and upon thermolysis (toluene, 90 °C) with *N*-phenylmaleimide produced the adduct **28** as a single stereoisomer in a 54% yield. In analogy with Vogel's work it was assumed that the maleimide had added to the exo face of the diene. Attempts to increase the yield via Lewis acid catalysis have failed due to the acid lability of the cycloadduct **28**. Tetracycle **28** was subjected to ozonolysis at −78 °C, and following a mild reductive workup the crystalline dione **29** was obtained in a 92% yield. While all the spectroscopic data were consistent with the expected product, absolute confirmation of the structure was difficult due to the absence of related molecules in the literature. Nonetheless, we explored the chemistry of dione **29** in an effort to convert it to a vinyl-3(2*H*)-furanone derivative.

It was obvious that at some point in this transformation it would be necessary to distinguish between the ketones at C-4 and C-9. Since we assumed that the C-4 ketone would be more sterically accessible, we attempted to selectively add a one carbon nucleophile to C-4. These attempts included reaction with methyllithium, methylmagnesium bromide, and the methylene Wittig reagent. In all cases a complex mixture of products resulted. Switching to hydride-type nucleophiles such as K-Selectride (Aldrich), $NaBH_4$ (in ethanol), or Dibal H did nothing

(19) Ramey, K. C.; Lini, D. C. *J. Magn. Reson.* **1970**, *3*, 94.
(20) (a) Overman, L. E.; Renaldo, A. F. *Tetrahedron Lett.* **1983**, *24*, 2235. (b) Kende, A. S.; Wustrow, D. J. *Tetrahedron Lett.* **1985**, *26*, 5411 and references therein.

(21) This oxidation is similar to the lead tetraacetate oxidation of certain vinyl sulfides in which two acetate groups are added across the double bond, see: Trost, B. M.; Tanigawa, Y. *J. Am. Chem. Soc.* **1979**, *101*, 4413.

to improve the situation.[22] Finally a $NaBH_4$ reduction was mistakenly performed in ethyl acetate, and one clean product was obtained in a 77% yield. X-ray analysis of this new high melting compound (mp 239–240 °C) revealed it to be the cyclic hemiketal **30** (see Figure 1 for an ORTEP picture).[25] Happily this structure confirmed that we had synthesized the furanoheliangolide skeleton. In addition it indicated that it was the C-9 ketone that had undergone selective reduction. Presumably conformational preferences in the [6.2.1] bicycle render the C-9 ketone more reactive. The stereochemistry of hydride addition allows the resulting keto alcohol to exist as a stable hemiketal thereby protecting the C-4 ketone from reduction.[23] The success of the sodium borohydride reduction may depend on the generation of an acetoxyborohydride formed in situ from the reaction of sodium borohydride with adventious acetic acid in the ethyl acetate. Sodium triacetoxyborohydride has exhibited selectivity in the reduction of diones.[24]

Having developed an efficient six-step synthesis of the desired ring system from the Diels–Alder adduct **13**, our initial attempts to convert either the dione **29** or the ketal **30** into a vinylfuranone derivative have been unsuccessful. In general elimination of the elements of HCl from either dione **29** or hemiacetal **30** have produced unstable products.[26] These results seem to indicate that unprotected oxygen functionality at C-9 in the form of a ketone or a hydroxy group render the bicyclic furanone susceptible to ring opening reactions. At present we are exploring the range of dienophiles that can be reacted with diene **27** in an effort to expand the range of chemistry that can subsequently be used to elaborate the 4,9-dione gotten from the key ozonolysis reaction.[22]

In summary a short, efficient preparation of the underlying 11-oxabicyclo[6.2.1]undecane ring system found in the furanoheliangolide and abestinane classes of natural products has been developed. The route described should be amenable to numerous modifications and as such should represent a general approach to the this important ring system. Besides targeting the naturally occurring heliangolides, we are presently attempting to prepare simplified model compounds containing the vinyl furanone moiety in order to evaluate the hypothesis (vide supra) that C-5 activation is sufficient for the elicitation of cytotoxic activity.

Experimental Section

General Methods. All reactions were run under a positive pressure of dry nitrogen. Reactions requiring anhydrous conditions were performed in flame-dried glassware, which was cooled under dry nitrogen. Solvents were distilled before use as follows: hexamethylphosphoramide (HMPA), dimethylformamide (DMF), methylene chloride, pyridine, hexane, pentane, benzene, and toluene from calcium hydride; tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and diethyl ether from sodium benzophenone ketyl; methanol from magnesium. Thin-layer chromatography (TLC) was performed on plastic plates coated with 254-nm fluorescent indicator, layer thickness of 250 μM. Flash chromatography was performed with use of silica gel from E. Merck Reagents (Kieselgel 60, 230–400 mesh). Proton nuclear magnetic resonance (^1H NMR) spectra were determined on a Varian Model T-60A NMR spectrometer (60 MHz) or with a Bruker Model WM-300 NMR spectrometer (300 MHz).

(*E*)-2-[2-(Phenylthio)ethenyl]-1,3-dioxolane (11a). To a solution of 2-[2-(phenylthio)ethyl]-1,3-dioxolane[14] (11.0 g, 52.4 mmol) in CCl_4 (90 mL) at 25 °C was added *N*-chlorosuccinimide (8.4 g, 62.8 mmol) in three portions. After stirring at 25 °C for 3 h the mixture was diluted with hexane (50 mL) and filtered through Celite. The precipitate was further extracted with fresh hexane (25 mL). The combined organics were concentrated to yield a slightly yellow oil. The crude α-chloro sulfide dissolved in THF (10 mL) was added to a solution of potassium *tert*-butoxide (7.6 g, 68.1 mmol) in THF (90 mL) at 0 °C. After addition, the mixture was stirred for 4.5 h at 25 °C, diluted with hexane (150 mL), washed with 10% aqueous potassium carbonate (2 × 50 mL), dried ($MgSO_4$), and concentrated. The resulting oil was purified by bulb-to-bulb distillation to yield **11a** (7.7 g, 71%) as a colorless oil: bp 140 °C (0.5 mm); ^1H NMR (300 MHz, $CDCl_3$) δ 3.98–3.86 (4 H, m), 5.31 (1 H, d, J = 5.9 Hz), 5.62 (1 H, dd, J = 15.2, 5.9 Hz), 6.66 (1 H, d, J = 15.2 Hz), 7.43–7.25 (5 H, m); the *Z* isomer had a proton at δ 6.57 (J = 9.4 Hz); IR (CCl_4) 3080, 1620, 1150, 942 cm^{-1}; MS (*m/e*, percent) 208 (38), 136 (68), 135 (95), 99 (100); exact mass calcd for $C_{11}H_{12}O_2S$ 208.0555, found 208.0554.

2-Methyl-3-(phenylthio)furan (12). To the vinyl sulfide **11a** (20.9 g, 0.1 mol) in DME (200 mL) at −78 °C was added *sec*-butyllithium (109 mL of a 1.4 M solution in cyclohexane, 0.15 mol). After being warmed to −40 °C for 15 min, the reaction mixture was recooled to −78 °C, and acetaldehyde (6.61 g, 0.15 mol) was added neat. Upon being warmed to 0 °C, the reaction mixture was diluted with hexane–ether (9:1, 600 mL), washed with aqueous potassium carbonate (2 × 250 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting yellow oil was dissolved in methanol (450 mL) and stirred in the presence of *d*-camphorsulfonic acid (1.0 g) for 2 h at 25 °C. Dilution with hexane (600 mL) followed by washing with 10% aqueous potassium carbonate (2 × 200 mL), drying ($MgSO_4$), and concentrating gave a yellow oil. The resulting oil was purified by bulb-to-bulb distillation to yield **12** (10.3 g, 54%) as a colorless oil: bp 100–110 °C (0.9 mm); ^1H NMR (60 MHz, CCl_4) δ 2.3 (3 H, s), 6.3 (1 H, d, J = 2 Hz), 7.0 (5 H, m), 7.2 (1 H, d, J = 2 Hz); IR (CCl_4) 3080, 3075, 2970, 2930, 1480, 1440, 1225, 1130, 1090 cm^{-1}; MS (*m/e*, percent) 190 (100.0), 161 (37.4), 147 (40.0), 77 (12.1), 51 (26.9), 43 (27.9). Anal. Calcd for $C_{11}H_{10}OS$: C, 69.46; H, 5.30; S, 16.8; MW 190.0453. Found: C, 69.57; H, 5.34; S, 16.79; MW 190.0437.

4-Methyl-5-*endo*-(phenylthio)-7-oxabicyclo[2.2.1]heptane-2-*exo*,3-*exo*-dimethanol (15). To 2-methyl-3-(phenylthio)furan (**12**) (1.00 g, 5.26 mmol) in chloroform (2.6 mL) was added maleic anhydride (1.03 g, 10.5 mmol). The reaction was stirred at 25 °C for 12 h and then concentrated under reduced pressure to afford crude **13** as a solid. This solid (1.53 g, 5.26 mmol) dissolved in ethyl acetate (80 mL) was shaken on a Parr apparatus with 5% Pd/C (300 mg) at a hydrogen pressure of 55 psi. After 2.5 h the mixture was filtered through a plug of Celite and concentrated under reduced pressure. As the hydrogenation proceeded only to partial completion, this procedure was repeated three times to yield **14** as a solid residue (1.53 g). To a suspension of $LiAlH_4$ (1.01 g, 26.7 mmol) in THF (13 mL) was added a solution of the reduced Diels–Alder adduct **14** (1.53 g, 5.26 mmol) in THF (13 mL) at 0 °C. Following the addition, the reaction was warmed to 40 °C and stirred for 20 h at 40 °C. The reaction was then carefully quenched at 0 °C with 10% aqueous sulfuric acid (40 mL) and extracted twice with ethyl acetate (2 × 60 mL). The combined organic extracts were washed with 10% aqueous sodium hydrogen carbonate (1 × 40 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford **15** (1.10 g, 75%) as a solid. The solid was washed with CCl_4 to remove colored impurities and yield a white solid. An analytical sample was prepared by recrystallization from ethyl acetate–ether (1:5): mp 98–100 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (3 H, s), 1.53 (1 H, dd, J = 12.5, 5.2 Hz), 2.38 (1 H, td, J = 8.8, 4.5 Hz), 2.5 (1 H, ddd, J = 12.5, 11.2, 5.6 Hz), 2.90 (1 H, td, J = 8.7, 4.8 Hz), 3.24 (1 H, dd, J = 11.2, 5.2 Hz), 3.5 (2 H, br s), 3.7–3.9 (4 H, m), 4.20

(22) A complicating factor in the reaction of dione **29** with organometallic reagents is the presence of the fairly reactive imide carbonyls.

(23) The parent 6-hydroxycyclodecanone exists as a mixture of the opened ketone and the bicyclic hemiketal, see: Mijs, W. J.; De Vries, K. S.; Westra, J. G.; Angad Gaur, H. A.; Smidt, J.; Vriend, J. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 580.

(24) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449.

(25) Details concerning the solving of the crystal structure for hemiketal **30** can be found in the supplementary material.

(26) Dione **29** undergoes facile elimination of HCl upon treatment with DBU at 0 °C. Unfortunately the resulting vinylfuran is unstable toward purification and/or further manipulation.

(1 H, d, J = 5.6 Hz), 7.2–7.4 (5 H, m); IR ($CHCl_3$) 3300–3400 (br), 2930, 1700, 1685, 1450, 1385, 1100 cm^{-1}; MS (m/e, percent) 280 (1), 262 (34), 113 (44), 109 (39), 96 (43), 83 (45), 43 (100). Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.20; S, 11.4; MW 280.1134. Found: C, 64.15; H, 7.18; S, 11.49; MW 280.1129.

2-*exo*-[(*tert*-Butyldimethylsiloxy)methyl]-3-*exo*-ethenyl-4-methyl-5-*endo*-(phenylthio)-7-oxabicyclo[2.2.1]-heptane (17). To oxalyl chloride (0.21 mL, 2.39 mmol) in CH_2Cl_2 (2 mL) was added dimethyl sulfoxide (0.30 mL, 4.21 mmol) in CH_2Cl_2 (1 mL) at −60 °C. After the mixture was stirred for 15 min at −60 °C, the alcohol (554 mg, 1.40 mmol) **16a**[16] in CH_2Cl_2 (2 mL) was added and stirred for 15 min. Finally triethylamine (1.47 mL, 10.56 mmol) was added, and the reaction mixture was stirred for 5 min at −60 °C and then warmed to 25 °C. At 25 °C, water (5 mL) was added and stirred for 10 min. The reaction mixture was diluted with 80% ether–hexane (1 × 50 mL), washed with 10% aqueous sodium hydrogen sulfate (1 × 50 mL) and 10% aqueous potassium carbonate (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford crude aldehyde (553 mg) as a yellow oil. To a suspension of methyltriphenylphosphonium bromide (753 mg, 2.11 mmol) in THF (7 mL) was added s-BuLi (1.5 mL of a 1.4 M solution in cyclohexane, 2.11 mmol) at −78 °C, and the mixture was allowed to warm to 25 °C. To the resulting ylid was added the above aldehyde (553 mg, 1.40 mmol) in THF (7 mL), and the reaction mixture was stirred for 1.5 h at 25 °C. The mixture was diluted with ether, washed with 10% aqueous potassium carbonate (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the vinyl compound **17** as a yellow oil. This oil was purified by flash chromatography (3 × 20 cm, 1:10 ethyl acetate–hexane) to yield purified **17** (443 mg, 80.9%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6 H, s), 0.88 (9 H, s), 1.14 (3 H, s), 1.53 (1 H, dd, J = 12.4, 4.8 Hz), 2.20 (1 H, td, J = 9.0, 6.6 Hz), 2.53 (1 H, td, J = 12.4, 5.6 Hz), 3.20 (1 H, t, J = 9.0 Hz), 3.32 (1 H, dd, J = 11.2, 4.8 Hz), 3.40 (1 H, d, J = 9.0 Hz), 3.41 (1 H, d, J = 6.6 Hz), 4.42 (1 H, d, J = 9.0 Hz), 5.05 (1 H, dd, J = 10.0, 2.1 Hz), 5.12 (1 H, dd, J = 16.7, 2.1 Hz), 5.55 (1 H, dt, J = 17.0, 10.2 Hz), 7.19–7.39 (5 H, m); IR (CCl_4) 3080, 2920–2980 (br), 2860, 1480, 1470, 1460, 1440, 1385, 1060–1130 (br) cm^{-1}; MS (m/e, percent) 390 (9.2), 333 (18.9), 258 (20.2), 245 (50.2), 135 (100.0), 75 (38.5), 73 (36.5), 43 (17.1). Anal. Calcd for $C_{22}H_{34}O_2SSi$: C, 67.66; H, 8.78. Found: C, 68.18; H, 8.60.

3-*exo*-Ethenyl-4-methyl-5-*endo*-(phenylthio)-7-oxabicyclo[2.2.1]heptane-2-*exo*-methanol (18). To the olefin **17** (120 mg, 0.308 mmol) in THF (1.5 mL) was added tetrabutylammonium fluoride (104 mg, 0.4 mmol). The reaction was stirred at 25 °C for 1 h, diluted with ether (1 × 50 mL), washed with 10% aqueous potassium carbonate (2 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford **18** as a yellow oil. This oil was purified by flash chromatography (2.5 × 14 cm, 1:2 ethyl acetate–hexane) to yield the alcohol **18** (83.2 mg, 98%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (3 H, s), 1.55 (1 H, dd, J = 12.5, 4.9 Hz), 1.64 (1 H, s), 2.28 (1 H, td, J = 8.4, 6.3 Hz), 2.55 (1 H, ddd, J = 12.5, 11.2, 5.5 Hz), 3.29 (1 H, dd, J = 10.6, 8.3 Hz), 3.33 (1 H, dd, J = 11.3, 4.9 Hz), 3.50 (1 H, dd, J = 10.6, 8.2 Hz), 3.61 (1 H, dd, J = 10.7, 6.2 Hz), 4.38 (1 H, d, J = 4.4 Hz), 5.14 (1 H, dd, J = 9.9, 2.1 Hz), 5.18 (1 H, dd, J = 16.5, 1.7 Hz), 5.71 (1 H, td, J = 17.0, 10.5 Hz), 7.19–7.40 (5 H, m); IR (CCl_4) 3650, 3080, 2985, 2940, 2890, 1540, 1480, 1390, 1200–1250 (br), 1110, 1000 cm^{-1}; MS (m/e, percent) 276 (9.4), 258 (12.2), 245 (14.1), 149 (12.0), 136 (13.3), 135 (100.0), 123 (13.9), 122 (16.0), 109 (11.4), 43 (13.3); exact mass calcd for $C_{16}H_{20}O_2S$ 276.1184, found 276.1164.

2-*exo*,3-*exo*-Diethenyl-4-methyl-5-(phenylthio)-7-oxabicyclo[2.2.1]heptane (19). To oxalyl chloride (0.057 mL, 0.654 mmol) in CH_2Cl_2 (1 mL) was added dimethyl sulfoxide (0.082 mL, 1.15 mmol) in CH_2Cl_2 (0.5 mL) at −60 °C. After 15 min at −60 °C, the alcohol **18** (106 mg, 0.385 mmol) in CH_2Cl_2 (1 mL) was added and stirred for 15 min. Finally triethylamine (0.403 mL, 2.89 mmol) was added, and the reaction mixture was stirred for 5 min at −60 °C and then warmed to 25 °C. At 25 °C water (1 mL) was added, and the mixture was stirred for 10 min. The reaction mixture was diluted with 80% ether–hexane (1 × 50 mL), washed with 10% aqueous sodium hydrogen sulfate (1 × 50 mL) and 10% aqueous potassium carbonate (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford an aldehyde as a yellow oil (99 mg, 0.36 mmol). To a suspension of methyltriphenylphosphonium bromide (194 mg, 0.54 mmol) in THF (1 mL) was added s-BuLi (0.39 mL of a 1.4 M solution in cyclohexane, 0.54 mmol) at −78 °C. The mixture was allowed to warm to 25 °C. To the resulting ylid was added the above aldehyde (99 mg, 0.36 mmol) in THF (1 mL), and the reaction mixture was stirred for 1.5 h at 25 °C. The mixture was diluted with anhydrous ether, washed with 10% aqueous potassium carbonate (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the diene **19** as a yellow oil. This oil was purified by flash chromatography (2.5 × 16 cm, 1:40 ethyl acetate–hexane) to yield the purified diene **19** (45 mg, 43%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3 H, s), 1.57 (1 H, dd, J = 12.5, 5.0 Hz), 2.53 (1 H, ddd, J = 12.5, 11.2, 5.6 Hz), 2.74 (1 H, t, J = 9.0 Hz), 3.41 (1 H, dd, J = 10.2, 9.0 Hz), 4.24 (1 H, d, J = 5.3 Hz), 5.00–5.07 (4 H, m), 5.54–5.78 (2 H, m), 7.20–7.40 (5 H, m); IR (CCl_4) 3080, 2990, 2940, 1640, 1485, 1445, 1385, 1060, 990 cm^{-1}; MS (m/e, percent) 272 (12.6), 149 (100.0), 136 (31.0), 91 (20.8), 79 (22.6), 43 (34.9). Anal. Calcd for $C_{17}H_{20}OS$: C, 74.97; H, 7.41. Found: C, 74.67; H, 7.30.

Pd^{2+} Cyclization of Diene 19 to 21a and 21b. To diene **19** (30.0 mg, 0.110 mmol) in toluene (1 mL) was added dichlorobis(benzonitrile) palladium(II) (31.3 mg, 0.110 mmol). The reaction was stirred at 80 °C for 26 h. Dilution with ether (30 mL), followed by washing with water (1 × 30 mL), drying ($MgSO_4$), and concentrating yielded a yellow oil. This oil was passed through a plug of silica gel to give a mixture of **21a** and **21b** (3:5:1) (22 mg, 73%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) **21a** δ 0.99 (d, J = 7.1 Hz, CH_3 group), 1.28 (s, CH_3 group), 1.54 (dd, J = 12.3, 4.5 Hz, H_{9endo}), 2.46 (ddd, J = 12.6, 11.1, 5.5 Hz, H_{9exo}), 2.52 (dd, J = 7.7, 3.5 Hz, H_6), 2.73 (1 H, br m, H_5), 3.05 (1 H, dq, J = 7.5, 2.0 Hz, H_2), 3.32 (1 H, dd, J = 11.1, 4.5 Hz, H_8), 4.17 (1 H, d, J = 5.3 Hz, H_1), 5.48 (1 H, dt, J = 5.6, 2.0 Hz, H_3), 5.68 (1 H, dt, J = 5.6, 2.0 Hz, H_4) 7.2–7.4 (m); **21b** δ 0.98 (d, J = 7.1 Hz, CH_3 group), 1.24 (s, CH_3 group), 1.52 (dd, J = 12.4, 4.4 Hz, H_{9endo}), 2.05 (dd, J = 7.4, 3.2 Hz, H_2), 2.46 (ddd, J = 12.6, 11.1, 5.5 Hz, H_{9exo}), 2.58 (1 H, br m, H_3), 3.54 (1 H, dq, J = 7.5, 2.0 Hz, H_6), 4.25 (1 H, d, J = 5.6 Hz, H_1), 5.47 (1 H, dt, J = 5.6, 2.0 Hz, H_5), 5.73 (dt, J = 5.6, 2.0 Hz, H_4), 7.2–7.4 (m); IR (CCl_4) 3060, 2960, 2880, 1480, 1385, 1115 cm^{-1}; MS (m/e, percent) 272 (56.0), 163 (49), 149 (69), 136 (29), 119 (31); exact mass calcd for $C_{17}H_{20}OS$ 272.1235, found 272.1238.

4-Methyl-5-(phenylthio)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-*exo*-dimethanol (24). To 2-methyl-3-(phenylthio)furan (**12**) (4.97 g, 26.2 mmol) in chloroform (13 mL) was added maleic anhydride. The reaction was stirred at 25 °C for 19 h and then concentrated under reduced pressure to afford **13** as a solid. To a suspension of $LiAlH_4$ (4.97 g, 131 mmol) in THF (70 mL) was added a solution of crude Diels–Alder adduct **13** (7.54 g, 26.2 mmol) in THF (61 mL) at 0 °C. Following the addition, the reaction was stirred at 0 °C for 4 h and then carefully quenched at 0 °C by successive dropwise addition of 5 mL of water, 5 mL of 15% sodium hydroxide solution, and 15 mL of water. The resulting white precipitate was slurried with ethyl acetate (50 mL) and filtered through Celite. The precipitate was further washed and filtered with fresh ethyl acetate (2 × 25 mL). The combined organics were concentrated to yield a slightly yellow oil. The oil was purified by flash chromatography (4.5 × 9 cm, ethyl acetate) to yield the purified diol **24** (4.91 g, 68%) as a colorless oil: ^1H NMR (60 MHz, CCl_4) δ 1.45 (3 H, s), 2.05 (1 H, m), 2.18 (1 H, m), 3.40 (2 H, m), 3.76 (2 H, m), 3.84 (2 H, br s), 4.50 (1 H, d, J = 1.5 Hz), 5.69 (1 H, d, J = 1.5 Hz), 7.28 (5 H, m); IR ($CHCl_3$) 3450, 2930, 1765, 1603, 1584, 1425, 1380, 1115, 1062 cm^{-1}; MS (m/e percent) 278 (1.4), 218 (3), 190 (7), 158 (4.9), 109 (18), 43 (100), 41 (19).

1-Methyl-5-*exo*-methoxy-5-*endo*-(phenylthio)-6-*exo*-chloro-7-oxabicyclo[2.2.1]heptane-2-*exo*,3-*exo*-dimethanol (25). To the diol **24** (4.91 g, 17.7 mmol) in methanol (88.3 mL) was added *N*-chlorosuccinimide (2.83 g, 21.2 mmol). The reaction was stirred at 25 °C for 15 min, diluted with 50% ethyl acetate–ether (1 × 200 mL), washed with 10% aqueous sodium thiosulfate (1 × 200 mL) and 10% aqueous potassium carbonate (1 × 200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude chloride **25** (4.81 g) as a yellow oil. This oil was purified by flash chromatography (4.5 × 16 cm, 1:1 ethyl acetate–hexane) to yield the purified chloride **25** (4.81 g,

80%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (3 H, s), 2.50 (1 H, td, J = 8.6, 4.8 Hz), 3.14 (1 H, dt, J = 8.6, 4.2 Hz), 3.55 (1 H, dd, J = 11.2, 4.2 Hz), 3.63 (1 H, dd, J = 11.2, 8.7 Hz), 3.73 (1 H, dd, J = 11.2, 4.8 Hz), 3.78 (3 H, s), 3.84 (1 H, dd, J = 11.2, 9.2 Hz), 3.70–3.90 (2 H, br s), 3.99 (1 H, s), 4.18 (1 H, s), 7.24–7.36 (3 H, m), 7.45–7.48 (2 H, m); IR ($CHCl_3$) 3430, 2930, 2400, 1790, 1605, 1430, 1380, 1180, 1120, 1085 cm^{-1}; MS (m/e, percent) 291 (11.7), 259 (18.4), 235 (36.4), 181 (42.0), 139 (47.4), 121 (23.4), 109 (37.3), 95.1 (22.3), 65 (20.3), 43 (100.0); MSCI (m/e, percent) 313 (100), 315 (38). Anal. Calcd for $C_{16}H_{21}O_4SCl\cdot H_2O$: C, 53.02; H, 6.40. Found: C, 53.04; H, 6.26.

1-Methyl-2,3-bis(methylene)-5-*exo*-methoxy-5-*endo*-(phenylthio)-6-*exo*-chloro-7-oxabicyclo[2.2.1]heptane (27). To the diol **25** (4.81 g, 14.1 mmol) in THF (71 mL) was added methanesulfonyl chloride (3.83 mL, 49.5 mmol) and triethylamine (6.9 mL, 49.5 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h, diluted with 25% ethyl acetate–ether (1 × 200 mL), washed with 10% aqueous sodium hydrogen sulfate (1 × 200 mL) and 10% aqueous potassium carbonate (1 × 200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford **26** as a solid. To a solution of the crude mesylate **26** (7.02 g, 14.1 mmol) in 10% HMPA–DMF (70 mL) was added potassium *tert*-butoxide (5.56 g, 49.5 mmol) at 0 °C. The reaction was stirred at 0 °C for 13 h, diluted with 50% anhydrous ether–hexane (1 × 200 mL), washed with water (1 × 200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the diene **27** as a solid. This diene was purified by flash chromatography (4.5 × 10 cm, 1:20 ethyl acetate–hexane) to yield the purified diene **27** as a crystalline compound (2.54 g, 58%): mp 85–86 °C (crystallized upon standing, not recrystallized); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.30 (3 H, s), 3.73 (3 H, s), 4.10 (1 H, s), 4.59 (1 H, s), 4.73 (1 H, s), 5.13 (1 H, s), 5.33 (1 H, s), 5.43 (1 H, s), 7.30 (5 H, s); IR (CCl_4) 3070, 2960, 2945, 2840, 1795, 1476, 1440, 1383, 1185, 1115, 1090, 950, 894 cm^{-1}; MS (m/e, percent) 308 (4.3), 273 (33.4), 199 (53.9), 121 (83.9), 110 (34.2), 77 (38.5), 43 (100.0); exact mass calcd for $C_{16}H_{17}O_2SCl$ 308.0638, found 308.0617.

(1*S,4*R**,5*S**,8*R**,9*S**,10*S**)-*N*-Phenyl-8-methyl-9-methoxy-9-(phenylthio)-10-chloro-11-oxatricyclo[6.2.1.0^{2,7}]undec-2(7)-ene-4,5-dicarboximide (28).** To the crystalline diene **27** (0.60 g, 1.97 mmol) in toluene was added 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (0.069 g, 0.20 mmol) and *N*-phenylmaleimide (0.855 g, 4.93 mmol). The reaction was stirred at 90 °C for 4 h and then concentrated under reduced pressure to afford the Diels–Alder adduct **28** as a solid. The solid was purified by flash chromatography (4.5 × 10 cm, 1:5 ethyl acetate–hexane) to yield the purified imide **28** as a crystalline solid (0.509 g, 53.6%): mp 170–171 °C (not recrystallized); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (3 H, s), 2.40 (1 H, br d, J = 17 Hz), 2.60 (2 H, m), 2.88 (1 H, d, J = 17.1 Hz), 3.33 (2 H, m), 3.78 (3 H, s), 3.90 (1 H, s), 4.63 (1 H, s), 7.28–7.48 (10 H, m); IR (CCl_4) 3690, 2940, 2840, 1790, 1715, 1600, 1585, 1380, 1310, 1115, 1090, 1000 cm^{-1}; MS (m/e, percent) 282 (20.0), 281 (100.0), 202 (9.96), 200 (21.9), 165 (39.2), 133 (92.1), 79 (15.0), 77 (28.2). Anal. Calcd for $C_{26}H_{24}O_4ClNS$: C, 64.85; H, 5.03; MW 481.1116. Found: C, 64.80; H, 5.02.

(1*R,4*S**,5*R**,8*S**,9*R**,10*R**)-*N*-Phenyl-2,7-dioxo-8-methyl-9-methoxy-9-(phenylthio)-10-chloro-11-oxabicyclo-[6.2.1]undecane-4,5-dicarboximide (29).** Ozone was passed through a solution of the olefin **28** (0.100 g, 0.208 mmol) in ethyl acetate (20 mL) at −78 °C for 10 min wherein a blue color persisted. Methyl sulfide (0.5 mL) was then added at −78 °C, and the reaction mixture was warmed to 25 °C and stirred for 5 h. The reaction mixture was then diluted with anhydrous ether (1 × 50 mL), washed with 10% aqueous sodium thiosulfate (1 × 50 mL) and 10% aqueous potassium carbonate (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford **29** as a solid. This solid was purified by flash chromatography (2 × 14 cm, 1:3 ethyl acetate–hexane) to yield the purified crystalline dione **29** (0.098 g, 91.9%). An analytical sample of the compound was prepared by recrystallization from $CHCl_3$–acetone (5:1): mp 177–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$, resolution poor perhaps due to slow intraconversion of conformers on NMR time scale) δ 1.66 (3 H, s), 2.84–3.05 (2 H, br m), 3.50–3.65 (3 H, br m), 3.84 (3 H, s), 3.95 (1 H, br m), 4.69 (1 H, s), 4.89 (1 H, s), 7.22–7.58 (10 H, br m); IR ($CHCl_3$) 3680, 3550, 2980, 2390, 2280, 1785, 1715, 1595, 1370, 1100 cm^{-1}; MS (m/e, percent) 477 (35.6), 220 (29.5) 217 (24.5), 81 (16.4), 77 (13.7), 53 (13.3), 43 (100.0). Anal. Calcd for $C_{26}H_{24}O_6ClSN$: C, 60.81; H, 4.71. Found: C, 60.69; H, 4.75.

(1*R,2*S**,4*S**,5*R**,7*R**,8*S**,9*R**,10*R**)-*N*-Phenyl-2-hydroxy-8-methyl-9-methoxy-9-(phenylthio)-10-chloro-11,12-dioxatricyclo[6.2.1.1^{2,7}]dodecane-4,5-dicarboximide (30).** To the dione **29** (0.010 g, 0.019 mmol) in ethyl acetate (0.2 mL) was added sodium borohydride (1.5 mg, 0.04 mmol) at 0 °C. The reaction was stirred at 0 °C for 0.5 h, diluted with 1:6 ethyl acetate–ether, washed with 10% aqueous potassium hydrogen sulfate (1 × 50 mL) and 10% aqueous potassium carbonate (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the hemiketal **30** as a solid. This solid compound was purified by flash chromatography (1.5 × 10 cm, 1:3 ethyl acetate–hexane) to yield the purified ketal **30** (7.7 mg, 77%) as a crystalline solid. The purified compound was recrystallized from acetone–water (4:1) to yield **30** as fine needles: mp 239–240 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3 H, s), 2.17–2.26 (2 H, m), 2.35 (1 H, dd, J = 14.0, 3.5 Hz), 2.71 (1 H, t, J = 14.5 Hz), 3.22–3.45 (2 H, m), 3.46 (1 H, s), 3.93 (3 H, s), 4.09 (1 H, s), 4.32 (1 H, t, J = 9.0 Hz), 4.77 (1 H, s), 7.25–7.58 (10 H, m); IR ($CHCl_3$) 3360, 2930, 1780, 1705, 1600, 1376, 1050 cm^{-1}; MS (m/e, percent) 406 (22), 370 (31), 258 (74), 237 (33), 159 (48), 125 (52), 109 (100), 93 (52), 91 (67), 83 (72), 77 (84), 65 (47), 42 (45). Anal. Calcd for $C_{26}H_{26}O_6ClSN$: C, 60.57; H, 5.09; MW 515.1171. Found: C, 60.55; H, 5.11. An ORTEP picture of **30** can be found in Figure 1.[25]

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Registry No. **11a**, 105621-12-3; **12**, 105621-16-7; (±)-**13**, 117707-07-0; (±)-**14**, 117626-57-0; (±)-**15**, 117707-08-1; (±)-**16a**, 117707-09-2; (±)-**16a** (aldehyde), 117626-73-0; (±)-**16b**, 117707-10-5; (±)-**17**, 117626-58-1; (±)-**18**, 117626-59-2; (±)-**18** (aldehyde), 117626-74-1; (±)-**19**, 117626-60-5; (±)-**20**, 117626-61-6; (±)-**21a**, 117626-62-7; (±)-**21b**, 117626-63-8; (±)-**24**, 117626-64-9; (±)-**25**, 117626-65-0; (±)-**26**, 117626-66-1; (±)-**27**, 117626-67-2; (±)-**28**, 117626-68-3; (±)-**29**, 117626-69-4; (±)-**30**, 117626-70-7; $Ph_3P^+CH_3Br^-$, 1779-49-3; 2-[2-(phenylthio)ethyl]-1,3-dioxolane, 56161-48-9; (±)-2-[2-chloro-2-(phenylthio)ethyl]-1,3-dioxolane, 117626-71-8; (±)-(*E*)-4-(1,3-dioxolan-2-yl)-3-(phenylthio)-3-buten-2-ol, 117626-72-9; maleic anhydride, 108-31-6; *N*-phenylmaleimide, 941-69-5.

Supplementary Material Available: Details for the determination of the crystal structure, ORTEP diagram, fractional coordinates, anisotropic thermal parameters, selected interatomic distances, and selected interatomic angles for **30** (7 pages). Ordering information is given on any current masthead page.