*Tetrahedron* Vol. 49, No. 36, pp. 7931-7942, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00


# A Novel One-Flask Cyclopentannulation Involving a Dilithiomethane Equivalent as a β-Connector of Two Enones. A Highly Efficient Total Synthesis of (±)-Hirsutene†

**Theodore Cohen,* Kevin McNamara,[1] and Michael A. Kuzemko[2]**

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

**Keith Ramig,*,[3] John J. Landi, Jr., and Yong Dong**

Synthesis Development Department, Hoffmann-La Roche, Inc., 340 Kingsland St., Nutley, NJ 07110

(*Received in USA* 30 *March* 1993; *accepted* 6 *May* 1993)

***Abstract***: Five- and six-membered rings can be constructed in one flask from two different enones and tris(phenylthio)methyllithium. The latter behaves as a dilithiomethane equivalent when its central carbon atom adds in conjugate fashion to one enone, becomes nucleophilic again when one of its phenylthio groups is exchanged for lithium in the presence of *sec*-butyllithium, and then undergoes conjugate addition to a second enone to provide a dienolate dianion. The latter can be oxidized to a 1,4-diketone incorporating a cyclopentane ring or induced to undergo an aldol reaction to produce a six-membered ring. In some of the cases, an interesting stereochemical equilibration occurs during the oxidation leading to one of two possible diastereomers and the overall process results in a highly efficient, stereospecific synthesis of (±)-hirsutene **13**.

We report here a new one-pot procedure for constructing five- and six-membered rings by the conjugate addition of a dilithiomethane synthon to two different enones followed by either the oxidative connection of the α-positions of the two resulting enolates or an intramolecular aldol reaction. The oxidative method is illustrated by a highly efficient synthesis of the triquinane (±)-hirsutene **13**.[4,5]

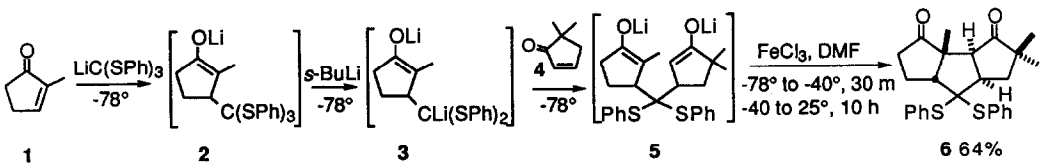
## RESULTS AND DISCUSSION

*Synthesis of (±)-Hirsutene*

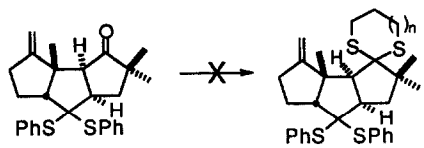
Scheme **1** shows a one pot, completely stereoselective synthesis of the linear triquinane **6** using the oxidative procedure. Previous reports from this laboratory[6] have demonstrated that enolate-carbanions of the type **3** can be generated by the conjugate addition of tris(phenylthio)methyllithium to an enone[7] followed by S–Li exchange promoted by *sec*-butyllithium. The lithiothioacetal portion of such species behaves as a nucleophile at -78 °C and as an electrophilic carbenoid[6b] at slightly higher temperatures. We now reveal that **3** is capable of efficient conjugate addition to the cyclopentenone **4**, prepared by a high-yielding modification of the method of Agosta and Smith[8] (see Experimental); oxidation of the resulting dienolate **5** with two equivalents of ferric chloride[9] in N,N-dimethylformamide (DMF), resulted in a 64% yield of the diketotriquinane **6**. Cupric chloride

†Dedicated to Professor Sir Derek Barton on the occasion of his 75th birthday.

has also been used for intramolecular dienolate couplings[10,11] but in the present case it provided inferior yields.The single diastereomer of the triquinane isolated was the desired cis,anti,cis isomer **6** as indicated by the subsequent conversion to hirsutene. The stereochemistry of **5** is addressed below.

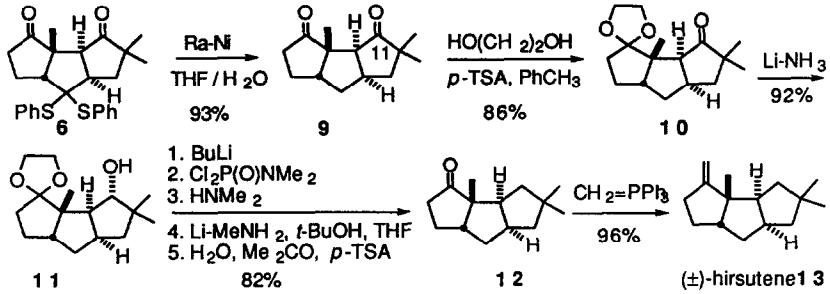



**Scheme 1**

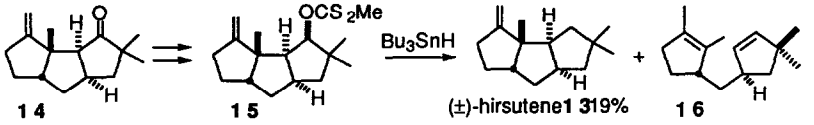



Plans for a very direct route to hirsutene by manipulation of the carbonyl groups of **6** followed by desulfurization of **8** (n = 0 or 1) were thwarted by the inability to perform thioacetal formation on **7**. Molecular models indicated that the carbonyl group of **7** is extremely crowded and that an earlier desulfurization would be required in order to alleviate such crowding. Although attempts to desulfurize **7** by a variety of methods failed, desulfurization of dione **6** with Raney nickel (Ra-Ni) in THF / water[12] delivered the dione **9** in good yield (Scheme 2). Mehta, et al.[4b] have converted dione **9** to (±)-hirsutene **13** in an overall yield of 13%. This low yield was due mainly to the difficulty of deoxygenating the highly hindered carbon-11. The main problem appears to be the fragmentation to an allyl radical and production of **16** upon Barton reduction[13] of **15** which was derived from the Wittig olefination product **14** of **9**. We were unable to deoxygenate **14** by means of the Wolf-Kishner procedure[14] or to convert **14** to a tosylhydrazone[15] for conversion[16] to the deoxygenated material.

The successful conclusion of our synthesis involved protection of the less hindered carbonyl group of **9** and treatment of the monoketone **10** with lithium in ammonia, a reducing agent that we surmised would have minimum steric requirements. The resulting alcohol **11**[17] was subjected to Ireland's method for hindered alcohol deoxygenation,[18] followed by hydrolysis of the resulting crude ketal to provide the ketone **12** in 82% overall yield. Conversion of ketone **12** to (±)-hirsutene **13**, identical in all respects to an authentic sample,[19] proceeded in 96% yield by methylenation of the carbonyl group using Fitjer's procedure[20] which requires that the Wittig reagent be prepared by deprotonation using potassium *t*-butoxide.




**Scheme 2**

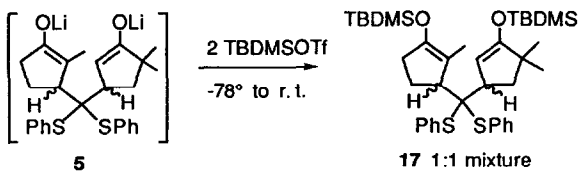



Latter part of Mehta's hirsutene synthesis.

This synthesis of (±)-hirsutene, in which the triquinane nucleus is stereoselectively assembled in one flask from readily available materials, appears to be the most efficient ever reported. It proceeds from tris(phenylthio)methane and enones **1** and **4** through only five isolated intermediates in 37% overall yield.[21]

*Origin of the Stereoselectivity*

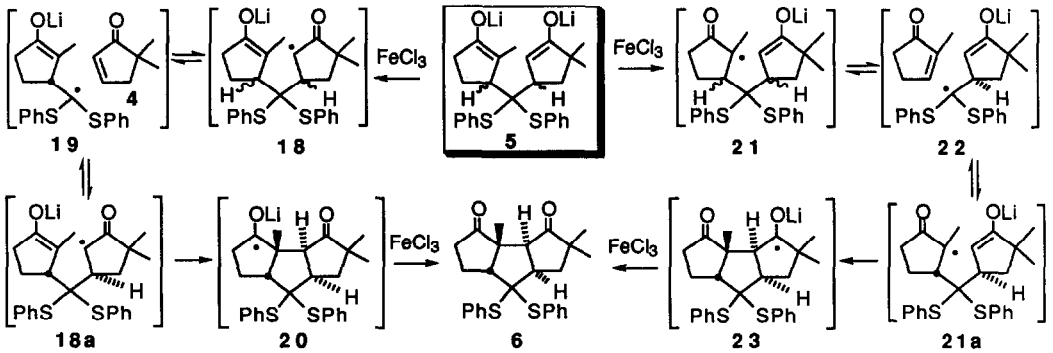
In the preliminary communication,[5] it was suggested that it was unlikely that the reaction of **3** and **4** would be completely stereoselective, yielding a single diastereomer of bis(enolate) **5** and that the production of a single diastereomer of **6** most likely involves stereochemical equilibration during the oxidation. However, we were not able to provide definitive evidence for the stereochemical state of **5** since quenching of the reaction after the formation of **5** but before oxidation led to an intractable mixture. We now demonstrate that the production of **5** is indeed not stereoselective. When bis(enolate) **5**, formed in the usual manner, is treated in situ with two equivalents of *t*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) at -78 °C to 25 °C (eq 1), the generated bis(enol silane) **17** is completely stereorandom, as judged by $^1$H NMR. Two doublets at 4.26 and 4.15 ppm (J = 1.1 Hz and 1.4 Hz, respectively), assigned to the vinyl proton of each diastereomer, integrate to a 1:1 ratio.




(1)

In view of the 64% yield of oxidation product **6**, the fact that the conjugate addition producing bis(enolate) **5** is stereorandom means that isomerization is probably occurring during the oxidative coupling step which produces dione **6**. A reasonable mechanism for this oxidative coupling and the attendant stereochemical equilibration is shown in Scheme 3. One-electron oxidation produces radical enolate **18** and / or its isomer **21**.

It is suggested that these are in equilibrium with their fragmentation products **19** and **22** and it is this equilibrium that allows stereochemical inversion. Ring closure occurs by attack of the radical upon the enolate; enolate anions are known to be subject to radical attack in this manner.[22] It appears likey that those diastereomers (**18a** and / or **21a**) of **18** and **21** which would lead to **6** rather than to the more congested cis,syn,cis isomer would close faster than the other diastereomers. Attempts were made to trap the supposed enolate-radical **19** or **22** with methyl vinyl ketone added during the oxidative coupling, but the results were inconclusive.



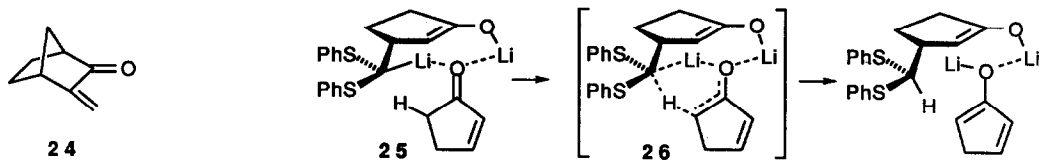

**Scheme 3**

*Generalization of the Reaction*

Extensive attempts to generalize the type of novel [2+1+2] coupling depicted in Scheme 1 yielded the startlingly discouraging finding that the procedure is successful only for enone **4**! To our dismay, treatment of enolate-carbenoid **3**, and related enolate carbenoids prepared from 2-cyclopentenone and 2-cyclohexenone, with enolizable enones resulted in isolation of no addition products. In every case where the second enone contained a proton $\alpha'$ to the carbonyl group, protonated enolate carbenoids were the products isolated. The only other enone besides **4** that gave any success in conjugate addition of **3** was another non-enolizable ketone, 3-methylene-2-norbornanone **24**, and then in only 32% yield. Attempts at forming various types of cuprates of the enolate-carbenoids were fruitless; carbenoid decomposition products[6] were isolated in these cases.

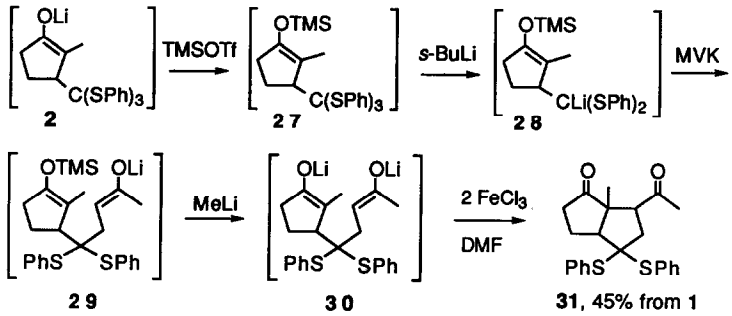
That lithiothioacetals such as **3** failed to add to enolizable enones was curious since closely related sulfur-stabilized anions, including lithiated bis(phenylthio)methane, had been found previously to add to enones uneventfully.[23] Thus, it appeared that the enolate function may play a key role in causing preferential deprotonation of the enones. It was speculated that the facilitation of proton removal from the enones may occur through a large ring transition state containing a trans alkene linkage (e.g. **26**), in which the enolate function plays a critical role in the recognition of the enone and its activation toward deprotonation (Scheme 4). This idea is somewhat reminiscent of that proposed for the addition of sulfoxide stabilized allyllithiums to enones.[24] In this scheme, the presence of the enolate group in an enolate-carbenoid causes formation of an aggregate, e.g. **25**, in which the enone is suitably positioned for proton removal. Use of hexamethylphosphoramide to break up the proposed aggregate was tried, but enolization was still the outcome. It was clear at this point that the effect of the enolate group would have to be neutralized, perhaps by temporary formation of an enol silane after the initial conjugate addition of tris(phenylthio)methyllithium to an enone. If the enol silane could survive the

intermediate reaction conditions, it was thought that the enolate group could be unmasked after the second conjugate addition, prior to the oxidative coupling step.



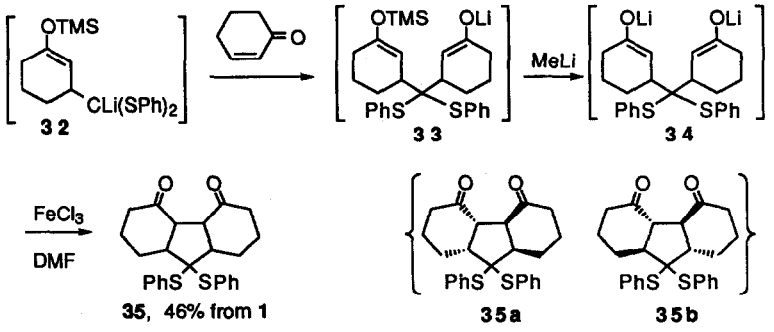

**Scheme 4**

The conjugate adduct **2** of tris(phenylthio)methyllithium and enone **1** (see Scheme 1) was silylated with trimethylsilyl trifluoromethanesulfonate (TMSOTf), providing enol silane **27** (Scheme 5). Sulfur-lithium exchange occured uneventfully, yielding enol silane-carbenoid **28**. To our gratification, treatment with methyl vinyl ketone (MVK) gave a new compound (determined by thin layer chromatography), presumably enol silane-enolate **29**. This is in contrast to the reaction of enolate carbenoid **3** with MVK, which gives no addition product. Removal of the trimethylsilyl group with methyllithium[25,26] furnished bis-enolate **30**, which was oxidatively coupled as usual to afford dione **31** obtained as a 1:1 mixture of two diastereomers in 45% overall yield. The $^{13}C$ NMR spectrum of dione **31** shows four peaks from 207-222 ppm, assignable to the four carbonyl carbon atoms of the two isomers. The $^{1}H$ NMR spectrum confirms this structure by showing four three-proton singlets at 0.90, 1.66, 2.26, and 2.30 ppm, assignable to the methyl groups of the isomers.




**Scheme 5**

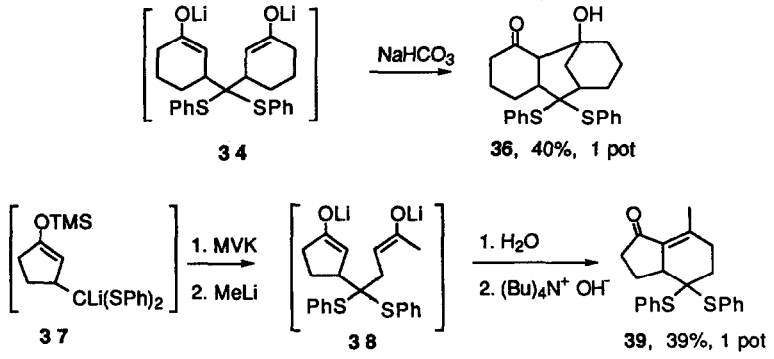
Another example of tricycle formation starts with enol silane-carbenoid **32**, which was prepared in the usual manner (see Schemes 1 and 5) using 2-cyclohexenone in place of enone **1** (Scheme 6). Treatment with another equivalent of 2-cyclohexenone yielded enol silane-enolate **33**. Deprotection of the latter with methyllithium and oxidative coupling of the resulting bis-enolate **34** provided dione **35** as a single isomer in 46% yield. The stereochemistry of this diastereomer cannot be unequivocally assigned based on the available spectroscopic data. The highly symmetrical nature of the molecule is suggested by appearance of only ten peaks[27] in its $^{13}C$ NMR spectrum. The fact that only one carbonyl carbon atom resonance (211.1 ppm) and four aromatic carbon atom resonances (137 to 128 ppm) were seen further limits the number of possibilities to two, diones **35a** and **35b**.




**Scheme 6**

*Use of the Bis-Enolates in Aldol Reactions*

To further demonstrate the utility of the new conjugate addition method developed here, two bis-enolates produced by this method were subjected to intramolecular aldol reactions (Scheme 7). Bis-enolates **34** (see Scheme 6) underwent a facile aldol reaction upon treatment of the crude reaction mixture with sodium bicarbonate, delivering ketoalcohol **36** as a mixture of inseparable diastereomers in 40% overall yield. Enol silane-carbenoid **37**, produced from 2-cyclopentenone by the usual method, was treated with MVK and then methyllithium to afford bis-enolates **38**. Quenching with water and then additon of tetrabutylammonium hydroxide furnished enone **39** in 39% overall yield.




**Scheme 7**

The phenyl thioketal functionality of all of the products derived from these conjugate additions is particularly useful for further elaboration. In addition to its capability of being reduced to a methylene group as in the hirsutene synthesis, it is a masked carbonyl group,[28] and, after protection of the carbonyl group, it can be reductively lithiated to a versatile sulfur-stabilized organolithium.[29]

## EXPERIMENTAL

All reactions were carried out in flame- or oven-dried glassware under an atmosphere of prepurified argon or nitrogen. All solvents were dried by using standard procedures and distilled. Ferric chloride was dried by treatment with thionyl chloride at reflux.[11a] A dry ice / 2-propanol slush bath was used to obtain a temperature of -78 °C, dry ice / 1-hexanol was used for -45 °C, and an ice bath was used to obtain 0 °C. Infrared spectra were recorded using an IBM IR/32 FTIR spectrometer. NMR spectra were recorded either on a Bruker WH-300 or a Bruker AF-300 spectrometer. Chemical shift data are reported in units of δ (ppm) relative to tetramethylsilane used as an internal standard. $^1$H NMR data are reported as follows: chemical shift; multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet); coupling constant; integration. High resolution mass spectra were recorded on a CH-5 double focussing Varian Mat mass spectrometer or on a VG 70-G mass spectrometer. The $R_f$ values reported are from thin layer chromatograms developed on glass supported 250 μ silica gel GF plates (Analtech). TLC plates were visualized using 7% phosphomolybdic acid in ethanol, 5% *p*-anisaldehyde in ethanol, or with UV light. Flash chromatography[30] was performed using 40 - 60 μm silica gel 60 (E. Merck). Radial chromatography was performed using a Harrison Research model 7924T chromatotron.

***5,5-Dimethyl-2-cyclopenten-1-one (4).***[8] 2,2-Dimethyl-4-pentenoic acid[31] (11 g, 86 mmol) was placed into 50 ml of dry $CH_2Cl_2$ at 0 °C under argon. Oxalyl chloride (7.53 ml, 86 mmol) was added slowly via syringe and the solution allowed to stir for 4 h at 0 °C. The solution was then cannulated slowly into a well-stirred slurry of $AlCl_3$ (11.5 g, 86 mmol) in 60 ml of $CH_2Cl_2$ at 0 °C. The resulting reddish-black mixture was allowed to come to room temperaturee over the course of 12 h and was quenched in 100 ml of ice water. The organic layer was drained and discarded, and the aqueous layer was extracted with ether (2 x 100 ml), with the ether layer being then discarded as well. The aqueous phase was acidified with conc'd HCl until pH = 1, and then extracted with ether (3 x 100 ml). The combined ether layer was washed with $NaHCO_3$ and then dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting black oil was distilled under water aspirator pressure to yield 6.5 g (60%) of product.

***7,7-bis(Phenylthio)-2,10,10-trimethyl-cis,anti,cis-tricyclo[6.3.0.0$^{2,6}$]undecan-3,11-dione (6).*** *n*-BuLi (22.7 mL, 1.60 *M* in hexane, 36.3 mmol) was added to a solution of tris(phenylthio)methane (12.4 g, 36.3 mmol) in 250 mL of THF at -78 °C under argon. After 0.5 h, 2-methyl-2-cyclopenten-1-one **4** (3.50 g, 36.3 mmol) was added dropwise and the solution was stirred for 1 h. *s*-BuLi (27.9 mL, 1.30 *M* in cyclohexane, 36.3 mmol) was added and the solution was stirred for 2 h. 5,5-Dimethyl-2-cyclopenten-1-one (4.00 g, 36.3 mmol) was added and the solution was stirred for 0.5 h. $FeCl_3$ (11.8 g, 72.6 mmol) in 60 mL of DMF was then cannulated as quickly as possible into the reaction mixture, yielding a purple, opaque mixture. The reaction mixture was warmed to -40 °C for 0.5 h before being warmed to ambient temperature overnight. The mixture was poured into 250 mL of 5% HCl and extracted with ether (3 X 250 mL). The combined layer was washed with 5% HCl (2 x 20 mL) and then with brine (2 x 20 mL) and then dried ($MgSO_4$). Removal of the ether layer under reduced pressure gave a crude oil which was purified by flash chromatography (20% EtOAc / hexane) to yield 10.1 g (64%) of a white solid: mp = 183.4 - 184.5 °C; $R_f$ in 5% EtOAc / benzene = 0.33; IR ($CH_2Cl_2$) 1740 cm$^{-1}$; $^1$H NMR ($C_6D_6$) δ 0.54 (s, 3H), 0.85 (s, 3H), 0.97 (s, 3H), 1.00 - 1.40 (m, 2H), 1.69 - 1.74 (m, 2H), 1.89 - 2.02 (m, 1H), 2.18 - 2.32 (m, 1H), 2.75 (ddd, J = 10.15, 10.15, 7.40 Hz, 1H), 2.92 (t, J = 8.95 Hz, 1H), 3.48 (d, J = 7.40 Hz, 1H), 6.85 - 7.85 (m, 10H); $^{13}$C NMR ($CDCl_3$) 17.7, 21.6, 23.0, 24.5, 35.2, 41.0, 48.2, 49.7, 54.5, 59.6, 61.1, 75.5, 128.9, 129.0, 129.6, 129.9, 130.2, 130.8, 133.4, 136.1, 137.1, 137.8, 219.0, 220.4; exact mass calcd for $C_{20}H_{23}O_2S$ (M - SPh) 327.1419, found 327.1419.

***2,10,10-Trimethyl-cis,anti,cis-tricyclo[6.3.0.0$^{2,6}$]undecan-3,11-dione (9).*** To 40.0 g of a suspension of W-2 Raney nickel in water was added 4.00 g (9.16 mmol) of **6** dissolved in 25.0 mL of THF. The resulting suspension was stirred for 4 h and then filtered through 10.0 g of celite followed by mixing with

500 mL of ether. The filtrate was concentrated under reduced pressure to yield a colorless oil. After purification by flash chromatography (10% EtOAc / hexane), 1.89 g (93.3%) of a white solid was isolated: mp = 67.1 - 68.0 °C; lit mp = 64 - 65°C.[4b] $R_f$ in 10 % EtOAc / hexane = 0.25; IR ($CH_2Cl_2$) 2949, 2935, 1730, 1455, 1149 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.02 (s, 6H), 1.03 (s, 3H), 1.35 - 1.51 (m, 2H), 1.80 (dt, J = 12.4, 5.2 Hz, 2H), 1.90 - 1.98 (m, 1H), 1.98 - 2.11 (m, 1H), 2.12 - 2.33 (m, 1H), 2.41 - 2.48 (m, 2H), 2.77 (m, 1H), 2.95 (t, J = 8.65 Hz, 1H); exact mass calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1464. The $^1H$ NMR spectrum is very similar to that reported.[4b]

***3,3-(Ethylenedioxy)-2,10,10-trimethyl-cis,anti,cis-tricyclo[6.3.0.0$^{2,6}$]undecan-11-one (10).*** To a 25.0 mL flask equipped with a reflux condenser and a Dean Stark trap was added 1.00 g (4.54 mmol) of **9** and a catalytic amount of *p*-toluenesulfonic acid in 12.0 mL of benzene. The solution was heated at reflux until all water was azeotropically removed. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure to yield the crude product as a colorless oil. Flash chromatography (10% EtOAc / hexane) yielded 1.03 g (85.8%) of pure product: $R_f$ in 20% EtOAc / hexanes = 0.23; IR (neat) 2958, 2904, 2896, 2887, 2869, 1737, 1731, 1462 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.86 (s, 3H), 0.88 (s, 3H), 0.91 (s, 3H), 1.21 - 1.30 (m, 1H), 1.31 - 1.39 (m, 1H), 1.56 - 1.67 (m, 2H), 1.61 - 1.82 (m, 4H), 2.13 - 2.22 (m, 1H), 2.69 - 2.81 (m, 1H), 2.86 (d, J = 8.01 Hz, 1H), 3.72 - 3.96 (m, 4H); exact mass calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1725.

***3,3-(Ethylenedioxy)-2,10,10-trimethyl-11-hydroxy-cis,anti,cis-tricyclo[6.3.0.0$^{2,6}$]undecane (11).*** To a flask at -78 °C containing 12.0 mL of ammonia, freshly distilled from sodium, was added 32.6 mg (4.72 mmol) of lithium wire. After 1 h, 250 mg (0.953 mmol) of **10**, dissolved in 0.5 mL of tetrahydrofuran, was added via syringe. The reaction mixture was stirred for an additional 0.5 h before 1 mL of saturated ammonium chloride was added. The ammonia was allowed to evaporate followed by extraction of the residue with ether (3 x 50 mL) and brine (2 x 50). The combined etheral layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product as an oil. Purification by flash chromatography (20% EtOAc / hexane) yielded 230 mg (91.5%) of pure product: $R_f$ in 20% EtOAc / hexane = 0.25; IR (neat) 3484, 2938, 1458, 1183, 1144, 1059 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.87 (s, 3H), 0.96 (s, 3H), 1.01 (s, 3H), 1.20 - 1.37 (m, 2H), 1.59 - 2.03 (m, 7H), 2.16 - 2.30 (m, 1H), 2.27 - 2.34 (t, J = 9.15 Hz, 1H), 2.53 - 2.60 (m, 1H), 3.51 (d, J = 9.15 Hz, 1H), 3.79 - 3.91 (m, 4H); $^{13}C$ NMR ($CDCl_3$) 16.2, 20.2, 25.9, 27.0, 34.3, 39.1, 39.2, 45.3, 45.6, 51.9, 54.8, 56.3, 64.8, 64.9, 80.4, 120.8; exact mass calcd for $C_{16}H_{26}O_3$ 266.1910, found 266. 1910.

***2,10,10-Trimethyltricyclo[6.3.0.0$^{2,3}$]-undecan-3-one (12).*** To a flask containing 143 mg (0.545 mmol) of alcohol **11** in 6.00 mL of 1,2-dimethoxyethane and 2.0 mL of N,N,N',N'-tetramethylethylenediamine at ambient temperature was added 0.42 mL of *n*-BuLi (1.08 mmol, 2.50 M in hexanes). After the solution had been stirred for 10 min., 0.320 mL (2.72 mmol) of N,N-dimethylphosphoramidic dichloride was added. After 30 min, the reaction mixture was cooled to 0 °C and 10.0 mL of anhydrous dimethylamine was distilled into the reaction flask. The resulting mixture was stirred at 0 °C for 4 h, and then 50.0 mL of water was added. After extraction with ether (5 x 50 mL) the combined organic layer was dried ($MgSO_4$). The organic layer was concentrated under reduced pressure to yield the crude phosphorodiamidate which was then used without further purification. The phosphorodiamidate was dissolved in THF (6 mL) and added to 30.0 mL of freshly distilled methylamine (distilled from lithium wire), 1.00 mL (10.8 mmol) of *t*-butyl alcohol, and 42.1 mg (6.05 mmol) of lithium wire. The reaction immediately turned dark blue. The blue reaction mixture was maintained at reflux (dry ice condenser) for 3 h, and then slowly quenched with solid ammonium chloride. The reaction mixture was allowed to warm to room temperature. After methylamine completely evaporated, 10.0 mL of acetone and 1.0 mL of water along with a catalytic amount of *p*-toluenesulfonic acid was added. The reaction mixture was heated at reflux for 6 h, after which the reaction mixture was cooled and extracted with 20.0 mL of brine and ether (3 X 50 mL). The combined ether

layer was dried ($MgSO_4$), and concentrated under reduced pressure to yield the crude product as an oil: HPLC (10% EtOAc / hexane) yielded 91.4 mg (82.1%) of pure product: $R_f$ in 10 % EtOAc / hexane = 0.32; IR (neat) 2936, 2866, 1738, 1458, 1408, 1028 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.88 (s, 3 H), 0.92 (s, 3 H), 0.98 (d, J = 3.47 Hz, 1 H), 1.02 (s, 3 H), 1.18 (t, J = 5.13 Hz, 1 H), 1.32 - 1.45 (m, 2 H), 1.53 - 1.74 (m, 3 H), 1.91 - 2.04 (m, 1 H), 2.19 - 2.42 (m, 3 H), 2.43 - 2.56 (m, 1 H), 2.73 - 2.82 (dd, J = 19.3, 8.8 Hz, 1 H); $^{13}C$ NMR (ppm, $CDCl_3$) 17.3, 22.4, 26.6, 29.3, 34.2, 37.6, 41.1, 41.9, 43.3, 46.7, 48.9, 59.4, 224.8; exact mass calcd for $C_{14}H_{22}O$ 206.1671, found 206.1671. The $^{13}C$ NMR spectrum is virtually identical to that reported by Little.[32]

***(±)-Hirsutene (13).*** To a 10.0 mL flask equipped with a reflux condenser was added 5.00 mL of toluene, 100 mg (0.284 mmol) methyltriphenylphosphonium bromide, 31.3 mg (0.284 mmol) of potassium *t*-butoxide, and 50.1 mg (0.244 mmol) of ketone **12**. The resulting yellow suspension was heated to reflux for 20 min before being cooled and concentrated under reduced pressure to yield the crude product. Purification by HPLC (hexanes) yielded 47.7 mg (96.3%) of pure product: $R_f$ in hexanes = 0.75; IR (neat) 2941, 2865, 1647, 1363, 875 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.92 (s, 3H), 0.95 (s, 3H), 1.05 (s, 3H), 1.11 - 1.20 (t, J = 3.12 Hz, 2H), 1.40 - 1.50 (m 4H), 1.55 - 1.75 (m, 2H), 2.14 - 2.17 (m, 1H), 2.43 - 2.50 (m, 2H), 2.50 - 2.63 (m, 2H), 4.78 - 4.82 (d, J = 12.72 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) 23.3, 26.9, 27.3, 29.8, 31.0, 38.7, 41.0, 41.9, 44.3, 49.1, 50.0, 53.5, 56.0, 103.6, 162.9; exact mass calcd for $C_{15}H_{24}$ 204.1877, found 204.1877.

***Conjugate Addition of Enolate-Carbanion 3 to 3-Methylene-2-norbornanone 24.*** *n*-BuLi (9.1 mL, 1.0 M, 10 mmol) was added to a solution of tris(phenylthio)methane (3.4 g, 10 mmol) in 70 mL of THF at -78 °C under argon. After 0.5 hr., 2-methyl-2-cyclopentenone (0.98 mL, 10 mmol) was added and the solution was stirred for 1 hr. *sec*-BuLi (10.5 mL, 0.95 M, 10 mmol) was added slowly and the resulting orange solution was stirred for 2 hr. 3-Methylene-2-norbornanone (**24**, 1.23 g, 10.1 mmol) was then added and the solution was stirred for 0.5 hr. The reaction was quenched with 200 mL of MeOH and the aqueous layer was extracted with ether (3 x 100 mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Chromatography (50% EtOAc / Hexane, $R_f$ = 0.5) yielded the conjugate adduct as a solid white compound (1.43 g, 31.7%): m.p. = 185-189 °C; IR (nujol) 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.85 (d, 3H, J = 7.32), 1.0-1.18 (m, 1H), 1.25-1.4 (m, 2H), 1.48-1.62 (m, 2H), 1.65-1.75 (m, 2H), 1.83-2.0 (m, 2H), 2.26-2.38 (m, 3H), 2.45 (m, 1H), 2.72-2.8 (m, 2H), 3.09-3.25 (m, 2H), 7.7.29-7.8 (m, 10H); $^{13}C$ ($CDCl_3$) 221.2, 220.5, 136.5-128.0 (aromatic), 71.8, 58.7, 51.0, 50.3, 43.8, 41.5, 40.9, 36.4, 32.2, 26.3, 24.7, 23.8, 13.1; exact mass (M–PhS) calcd for $C_{21}H_{25}O_2S$ 341.1573; found 341.1573. Anal. calcd for $C_{27}H_{30}O_2S_2$: C, 71.97; H, 6.71; S, 14.23. Found: C, 71.87; H, 6.65; S, 14.23.

***Disilylation of Dienolate 5.*** A solution of bis(enolate) **5**, using 2.00 mmol **1** as starting material, was generated as in the preparation of dione **6** (vide supra). *t*-Butyldimethylsilyl trifluoromethanesulfonate (0.965 mL, 4.20 mmol) was added dropwise at -78 °C. After 10 min, the mixture was warmed and maintained at room temperature for 17 h. The mixture was poured into a swirled mixture of 100 mL of 10% $NH_4Cl$ / 50 mL of ether, followed by immediate agitation. The organic phase was drawn off, and the aqueous phase was extracted with 50 mL ether. The combined ether layer was washed with 50 mL water and dried ($MgSO_4$). The solvent was removed under reduced pressure affording 1.46 g of crude **17** as a viscous orange-brown oil. $^1H$ NMR analysis at this point showed two one-proton doublets at 4.26 and 4.15 ppm (J = 1.1 Hz and 1.4 Hz, respectively). The crude product was purified by radial chromatography (1% ethyl acetate / hexanes, $R_f$ = 0.23) to give 1.35 g (20%) of **17**. $^1H$ NMR ($CDCl_3$) δ 0.0-0.2 (m, 24H), 0.89-1.0 (overlapping singlets, 12H), 1.29 (s, 18H), 1.62 (s, 3H), 1.82 (s, 3H), 1.9-2.2 (m, 4H), 2.51-2.59 (m, 4H), 3.05-3.4 (m, 4H), 4.15 (d, 1H, J = 1.4 Hz), 4.26 (d, 1H, J = 1.1 Hz), 7.23-7.7 (m, 20H); $^{13}C$ NMR ($CDCl_3$) 137.5, 137.0, 136.9, 136.8, 133.9, 133.7, 133.5, 133.2, 128-129 (overlapping aromatics); exact mass calcd for $C_{31}H_{53}O_2SSi_2$ (M - SPh) 545.9897, found 545.9897. Anal. calcd for $C_{37}H_{58}O_2S_2Si_2$ : C, 67.82; H, 8.92; S, 9.79. Found: C, 67.90; H, 8.90; S, 9.71.

***4-Bis(phenylthio)-2-(1-oxoethyl)-1-methylbicyclo[3.3.0]oct-8-one (31).*** BuLi (1.29 mL, 1.5 *M* in hexane, 2 mmol) was added to a solution of tris(phenylthio)methane (681 mg, 2.00 mmol) in 20 mL THF at -78 °C. After 0.5 hr, 2-methyl-2-cyclopentenone (0.190 mL, 2.00 mmol) was added dropwise and the solution was stirred for 1 hr. Trimethylsilyl triflouromethanesulfonate (0.405 mL, 1.05 eq) was added and the solution was warmed to 0 °C for 20 min. The solution was cooled to -78 °C and the dropwise addition (over 10 min.) of *s*-BuLi (1.80 mL, 1.10 *M* in cyclohexane, 2.00 mmol) gave a clear, orange color. The solution was allowed to stir for 2.5 hr, at which time methyl vinyl ketone (0.166 mL, 2.00 mmol) was added and the resulting clear, pale yellow solution was stirred for 45 min. MeLi (1.69 mL, 1.10 eq) was slowly added to the solution, which was then warmed and maintained at room temperature for 10 hr. The mixture was brought to -78 °C and $FeCl_3$ (648 mg, 2.00 eq) in 7 mL of DMF was cannulated into the reaction mixture, giving a characteristic, purple, opaque solution. The reaction was placed into a -40 °C bath for 0.5 hr and then allowed to warm to room temperature for 10 hr, at which time the reaction was quenched by pouring into 5% HCl. The layers were separated and the aqueous phase was extracted with ether (3 x 100 mL). The combined organic layers were consecutively washed with 5% HCl, water, and brine and dried over $MgSO_4$. Solvent removal under reduced pressure afforded a yellow oil. Chromatography (15% ethyl acetate / hexanes, Rf = 0.27) gave the product as a light colored oil (325 mg, 44.5%). IR (neat) 3050, 1751, 1379, 1209 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.66 (s, 3H), 1.84-2.01 (m, 8H), 2.26 (s, 3H), 2.30 (s, 3H), 2.45 (m, 2H), 2.69 (m, 4H), 3.36 (m, 2H), 7.3-7.7 (m, 20H); $^{13}C$ NMR ($CDCl_3$) 221.7, 220.2, 208.3, 207.9, 137.4, 135.5, 135.1, 133.1, 131.9, 129.9, 128.9, 128.8, 128.7, 128.5, 72.7, 65.7, 60.9, 60.3, 59.6, 59.2, 57.1, 53.1, 41.1, 38.1, 36.4, 32.7, 31.4, 26.9, 24.5, 15.2; exact mass calcd for $C_{17}H_{19}O_2S$ (M - SPh) 287.4151, found 287.4151. Anal. calcd for $C_{23}H_{24}O_2S_2$ : C, 69.65; H, 6.10; S, 16.17. Found: C, 69.79; H, 6.13; S, 16.07.

***8-Bis(phenylthio)tricyclo[7.4.0.0$^{2,7}$]tridecan-3,13-dione (35).*** BuLi (1.42 mL, 1.40 *M* in hexane, 2.00 mmol) was added dropwise to a stirred solution of tris(phenylthio)methane (681 mg, 2.00 mmol) in 20 mL of THF at -78 °C under argon. After 0.5 hr, 2-cyclohexen-1-one (0.192 mL, 2.00 mmol) was added and the solution was stirred for 1 hr. Trimethylsilyl triflouromethanesulfonate (0.405 mL, 1.05 eq) was added and the solution warmed to 0 °C for 20 min. The solution was brought back to -78 °C and dropwise addition (over 15 min.) of *s*-BuLi (1.80 mL, 1.10 *M* in cyclohexane, 2.00 mmol) gave a clear, orange color. After the solution had stirred for 2.5 hr, 2-cyclohexen-1-one (0.192 mL, 2.00 mmol) was added and stirring was continued for 30 min. MeLi (1.69 mL, 1.1 eq) was added and the solution was warmed and maintained at room temperature for 2 hr. It was cooled to -78 °C and $FeCl_3$ (648 mg, 2.00 eq) in 7 mL of DMF was cannulated into the reaction mixture. The reaction was placed into a -40 °C bath (dry ice / hexanol) for 0.5 hr and then allowed to warm to room temperature for 10 hr, at which time the reaction was quenched by pouring into 5% HCl. The layers were separated, and the aqueous phase extracted with ether (3 x 100 mL). The combined organic layers were consecutively washed with 5% HCl, water, and brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded a reddish oil. Chromatography (15% ethyl acetate / hexanes) afforded the fairly pure title compound (392 mg, 46%). Further chromatography (10% ethyl acetate/hexanes) afforded a solid, mp = 133-135 °C. $^1H$ NMR ($CDCl_3$) δ 1.26 -1.32 (m, 2H), 1.60 - 1.72 (m, 2H), 1.78 - 1.93 (m, 4H), 2.25 (ddd, J = 16.83, 9.95, 6.88 Hz, 2H), 2.38 (ddd, J = 16.83, 6.36, 3.47, 2H), 2.87 - 2.96 (m, 2H), 3.32 (dd, J = 15.18, 6.21 Hz, 2H), 7.30 - 7.72 (m, 10H); $^{13}C$ ($CDCl_3$) 211.1, 136.5, 131.5, 129.3, 128.8, 50.9, 50.6, 38.0, 24.3, 21.9; exact mass calcd for $C_{25}H_{27}O_2S_2$ (M + H) 422.1453, found 423.1443. Anal. calcd for $C_{25}H_{26}O_2S_2$: C,71.05; H, 6.20; S, 15.18. Found: C, 70.94; H, 6.26; S, 14.89.

***Aldol 36 from Dienolate 34.*** A solution of bis(enolate) **34**, generated as in the preparation of dione **35**, was quenched with 35 mL sat'd aqueous $NaHCO_3$ solution at room temperature. Extraction with ethyl acetate (3 X 20 mL), drying ($Na_2SO_4$), and removal of the solvent under reduced pressure gave crude product, which was purified by radial chromatography (5-20% EtOAc / hexanes). Isolated was 340 mg (40%) of product as a white solid, mp = 46-50 °C. IR (KBr) 3447, 1696, 1685, 749, 691 $cm^{-1}$. DEPT NMR

experiments indicate that there are 12 tertiary aliphatic CH bonds and 4 carbon atoms bearing two PhS- groups each. The latter also is indicated by the four $^{13}C$ peaks between 69.6 and 75.8 ppm (see below). These facts indicate that **36** is a mixture of all four possible stereoisomers. The same conclusion can be drawn from the 46 non-aromatic carbon resonances, a number that lies between 39 and 52 required, respectively, for 3 and 4 isomers. The deficit in $^{13}C$ peaks is very probably due to coincidences. $^1H$ NMR ($CDCl_3$) δ 1.06 - 2.88 (m, 17.06H), 3.06 (d, J = 14.6 Hz, 0.19H), 3.20 (d, J = 8.87 Hz, 0.28H), 3.88 (br s, 0.19H), 4.54 (br s, 0.28H), 7.13 - 7.72 (m, 10H); $^{13}C$ NMR ($CDCl_3$) 216.0, 213.5, 211.0, 137.2, 137.0, 136.8, 136.4, 135.6, 135.4, 134.2, 133.9, 133.0, 132.6, 131.6, 131.1, 129.8, 129.7, 129.5, 129.1, 129.0, 128.8, 128.7, 127.6, 127.4, 127.3, 127.2, 75.8, 74.4, 70.7, 69.6, 60.9, 56.3, 49.6, 47.2, 44.8, 44.6, 44.1, 42.1, 41.7, 41.4, 41.1, 40.7, 40.1, 40.0, 39.3, 38.5, 38.4, 37.8, 37.1, 35.9, 35.3, 35.1, 33.9, 30.5, 30.4, 29.3, 28.2, 28.0, 27.8, 27.6, 27.4, 27.1, 25.1, 24.6, 24.4, 22.4, 22.2, 21.4, 21.2, 20.7, 20.4, 19.8; exact mass calcd for $C_{25}H_{28}NaO_2S_2$ (M + Na)[33] 447.1429, found 447.1427.

***6-Bis(phenylthio)-7-methylbicyclo[4.3.0]-2-oxo-1-nonene (39).*** A solution of enol silane-carbenoid **37**, generated in the usual manner (see preparation of dione **31**) from 6.00 mmol each of tris(phenylthio)methane and 2-cyclopentenone, was treated with MVK (0.50 mL, 26 mmol) for 0.5 hr. MeLi (6.0 mL, 1.1 eq) was then slowly added to the solution, which was allowed to warm to room temperature for 1 hr. 10 mL of wet ether was added and the reaction volume was reduced on the rotary evaporator. Ether (12 mL) and THF (12 mL) were added and 40 drops of tetrabutylammonium hydroxide (40 wt. % solution in water) was added to the stirred solution at room temperature. The mixture was then heated at reflux for 5 hr, cooled and poured into 100 mL of 5% HCl. The organic layer was separated and the aqueous layer extracted with ether (3 x 100 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting reddish oil was purified by chromatography (20% ethyl acetate / hexanes) to yield the title compound as an oil (890 mg, 39%, $R_f = 0.18$). IR (neat) 1709, 1639 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.61-1.79 (m, 2H), 1.81-1.86 (m, 2H), 1.95-2.1(m, 2H), 2.13 (s, 3H), 2.33-2.51 (m, 2H), 3.0 (br s, 1H), 7.3-7.9 (m, 10H); $^{13}C$ NMR 206.3, 147.6, 137.8, 136.9, 129.9, 129.5, 129.3, 128.9, 64.7, 48.1, 38.7, 33.2, 32.9, 22.8, 18.7; exact mass calcd for $C_{16}H_{17}O_2S$ (M - SPh) 273.1981, found 273.1983.

**ACKNOWLEDGMENTS.** We thank the National Science Foundation for financial support of the work at Pittsburgh and Professors Tadhg Begley (Cornell University) and Peter Wipf (University of Pittsburgh) for helpful suggestions. We also thank the Hoffmann-LaRoche Physical Chemistry Department for recording the spectra of **35** and **36**.

## REFERENCES AND NOTES

1. Current address: Dupont-Merck Pharmaceutical Co, P.O. Box 80353 18, Wilmington, DE 19880-0353.
2. Current address: Hoffmann-La Roche Inc., 340 Kingsland St., Nutley, NJ 07110.
3. Current address: Anaquest Inc., 100 Mountain Ave., Murray Hill, NJ 07974.
4. Leading references to previous syntheses of hirsutene: (a) Plamondon, L.; Wuest, J. *J. Org. Chem.* **1991**, *56*, 2066-72. (b) Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443-52. For triquinanes in general, see: Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Berlin, Heidelberg, Germany, 1987; p 184. See also: Curran, D. P. *Advances in Free Radical Chemistry*; JAI Press: Greenwich, 1990; Vol. 1, p 121-57.
5. Preliminary communication: Ramig, K.; Kuzemko, M. A.; McNamara, K.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 1968-69.
6. (a) Cohen, T.; Yu, L. -C. *J. Org. Chem.* **1985**, *50*, 3266-69. (b) Ramig, K.; Bhupathy, M.; Cohen, T. *J. Am. Chem. Soc.* **1988**, *110*, 2678-80. Ramig, K.; Bhupathy, M.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 4404-12.

7. Smith, R. A. J.; Lal, A. R. *Aust. J. Chem.* **1979**, *32*, 353-60. Cohen, T.; Nolan, S. M. *Tetrahedron Lett.* **1978**, 3533-36. Manas, A. R.-B.; Smith, R. A. J. *J. Chem. Soc., Chem. Commun.* **1975**, 216-17.
8. Agosta, W. C.; Smith, A. B. III *J. Am. Chem. Soc.* **1971**, *93*, 5513-20.
9. Poupart, M.-A.; Lassalle, G.; Paquette, L. A. *Org. Synth.* **1990**, *69*, 173-79.
10. Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487-98. Paquette, L. A.; Snow, R. A.; Muthard, J. L.; Cynkowski, T. *J. Am. Chem. Soc.* **1978**, *100*, 1600-02. Kobayashi, Y.; Tagushi, T.; Morikawa, T. *Tetrahedron Lett.* **1978**, 3555-56.
11. Intermolecular oxidative coupling of enolates: a) Frazier, R. H.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408-11. b) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 2549-55. Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1988**, *110*, 5209-11. Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969-72. Belletire, J. L.; Spletzer, E. G. *Synth. Commun.* **1987**, *17*, 1701-07.
12. Mitchell, R. H.; Lai, Y.-H. *Tetrahedron Lett.* **1980**, *21*, 2637-38.
13. Barton, D. H. R.; McCrombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574-85.
14. Minlon, H. *J. Am. Chem. Soc.* **1949**, *71*, 3301-03.
15. Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923-26.
16. Iida, T.; Tamura, T.; Matsumoto, T. *Synthesis* **1984**, 957-59.
17. The configuration of the alcohol is assumed to be the thermodynamically stable one due to the method of production.
18. Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001-13. Ireland, R. E.; Dawson, M. I.; Welch, S. C.; Hagenbach, A.; Border, J.; Trus, B. *J. Am. Chem. Soc.* **1973**, *95*, 7829-41.
19. We thank Professor Dennis Curran for kindly providing the sample of authentic (±)-hirsutene.
20. Fitjer, L.; Quabeck, U. *Synth. Comm.* **1985**, *15*, 855-64.
21. The yield from commercially available materials is 18%. This includes the preparation of **4**.
22. Russell, G. A. *Adv. Phys. Org. Chem.* **1987**, *23*, 271-322. (b) Russell, G. A.; Khanna, R. K. *J. Am. Chem. Soc.* **1985**, *107*, 1450-52.
23. Cohen, T.; Abraham, W. D.; Myers, M. *J. Am. Chem. Soc.* **1987**, *109*, 7923-24. Cohen, T.; Myers, M. *J. Org. Chem.* **1988**, *53*, 457-460. Myers, M. R.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 1290-95.
24. Binns, M. R.; Chai, O. L.; Haynes, R. K.; Katsifis, A. A.; Shober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1569-72.
25. House, H. O. *Modern Synthetic Reactions* (2nd ed.); W. A. Benjamin, Inc.: Menlo Park, CA, 1972; p 568.
26. When the methyllithium treatment was omitted, no intramolecular coupling product was observed.
27. The resonance assignable to the quaternary carbon atom of the tricyclic ring system was not evident. It is possible that this peak overlapped with the $CDCl_3$ solvent peaks; quaternary carbon atoms of this type are known to resonate near these frequencies (see Experimental).
28. Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357-402.
29. Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152-161. Cherkauskas, J. P.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 6-8.
30. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-25.
31. Creger, P. L. *J. Am. Chem. Soc.* **1967**, *89*, 2500-01.
32. Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744-49. See also: Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1049-50.
33. Sodium chloride was added to the sample to enhance the spectrum; hence M + Na was observed.