Metal-Catalyzed Stereospecific Michael Reaction Equivalent

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The addition of nucleophiles to vinyl sulfide–allylic acetates mediated by (π-allyl)palladium intermediates has been shown to occur exclusively on the allyl terminus remote from sulfur, thereby effecting the equivalent to a Michael reaction. Due to the intervention of the palladium intermediate the process is completely stereospecific as contrasted to the Michael reaction itself where control of stereochemistry is often not readily exercised. A Diels–Alder–palladium–Michael equivalent provided definition of stereochemistry complementary to that obtainable in the native Michael reaction.

Introduction

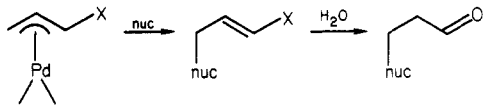
The control of stereochemistry in Michael reactions remains a vexing problem in organic chemistry.[1] The source of the difficulty often resides in the inability to situate oneself experimentally in a position of complete kinetic or thermodynamic control. The former is particularly troublesome because of the ready reversibility often exhibited in these reactions. Furthermore, even if one is safely ensconsed in the kinetic regime, the definition of the preferred mode of addition in reactions involving cyclohexenone derivatives has been alternatively claimed as proceeding by axial[2] and equatorial[3] attack. The stereochemical result of a Michael reaction also appears to be inordinately sensitive to reaction conditions.[1,3]

The limited control that can be exercised in this process can be briefly summarized to include the following cases: (1) single isomers are often obtained in the addition of nucleophiles to α-substituted α,β-unsaturated carbonyls, although the control evidenced here is clearly in the subsequent enolate protonation step;[4] (2) γ-substituents will usually efficiently direct addition to the less hindered side of the olefin;[5] (3) control by more remote substituents is not well-precedented except in the presence of a rigid polycyclic system;[6] (4) chiral acyclic Michael acceptors and nucleophiles that typically impose rigidity by counterion chelation have been found to provide good to excellent asymmetric induction.[7] Despite these examples, the prediction of the stereochemical outcome of Michael additions often remains quite difficult.

We have designed and developed an equivalent to the Michael reaction employing (π-allyl)palladium chemistry in the key nucleophilic addition. The intervention of this metal intermediate allows the potential for complete stereochemical control in this process. A previous report by Negishi[8] on the Pd-catalyzed allylation of potassium enoxyborates has appeared in which 1,3-dichloro-2-butene was employed as an electrophile, thereby effecting (after hydrolysis) an equivalent to the Michael process, but none of the stereochemical aspects of this reaction were investigated. Additional reports of transition-metal catalysis of Michael reactions have appeared,[9] although none deals with the stereochemistry of this reaction.

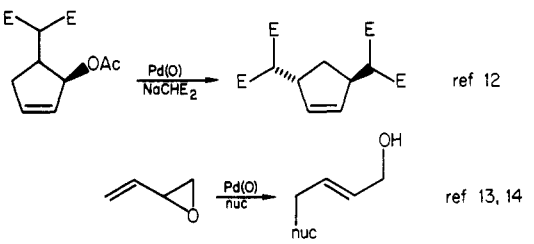
Results and Discussion

The application of (π-allyl)palladium chemistry to the construction of an equivalent to the Michael reaction requires the regiospecific attack of a nucleophile on a heteroatom-substituted allyl moiety[10] on the terminus remote from the substituent. Regiochemical directing effects in



X = SR, NR_2, OR, Cl

unsymmetrically substituted allylpalladium complexes have been studied.[11] The results of these investigations show that the less substituted allyl terminus is preferentially attacked by a nucleophile. Modest selectivity is effected by alkyl groups based presumably on steric grounds[11] and substantial regioselectivity is exerted by substituents capable of σ-electron withdrawal.[8,12-17] Examples of the latter are listed below.



Thus, the obtention of the required regioselectivity for a Michael equivalent was well-precedented. Any further mechanistic rationalization of the basis of this electronic effect with respect to, e.g., a possible induced asymmetric disposition of the metal in these complexes suffers from a significant lack of structural data on the presumed in-

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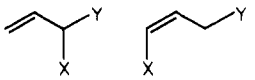
termediate π-allyl complexes.

In principle, two general precursors could be employed to obtain the required heteroatom-substituted π-allyl complex, namely, 1 or 2, where Y serves as the designated

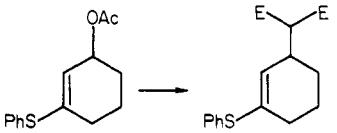


1 2

leaving group subject to displacement by the nucleophilic Pd(0) complex. As the goal to our work was to establish a stereospecific Michael equivalent, π-allyl precursor 2 appeared more desirable as specific control of C–Y stereochemistry as well as definition of leaving groups C–Y > C–X in the enone acetal or ketal 1 appeared to be nontrivial problems.

Complete retention of configuration in the Pd-catalyzed allylic alkylation of "soft" carbon nucleophiles has been demonstrated[18] and as a result any stereochemistry defined with respect to the C–Y bond in 2 will be completely maintained in the addition of the nucleophile.

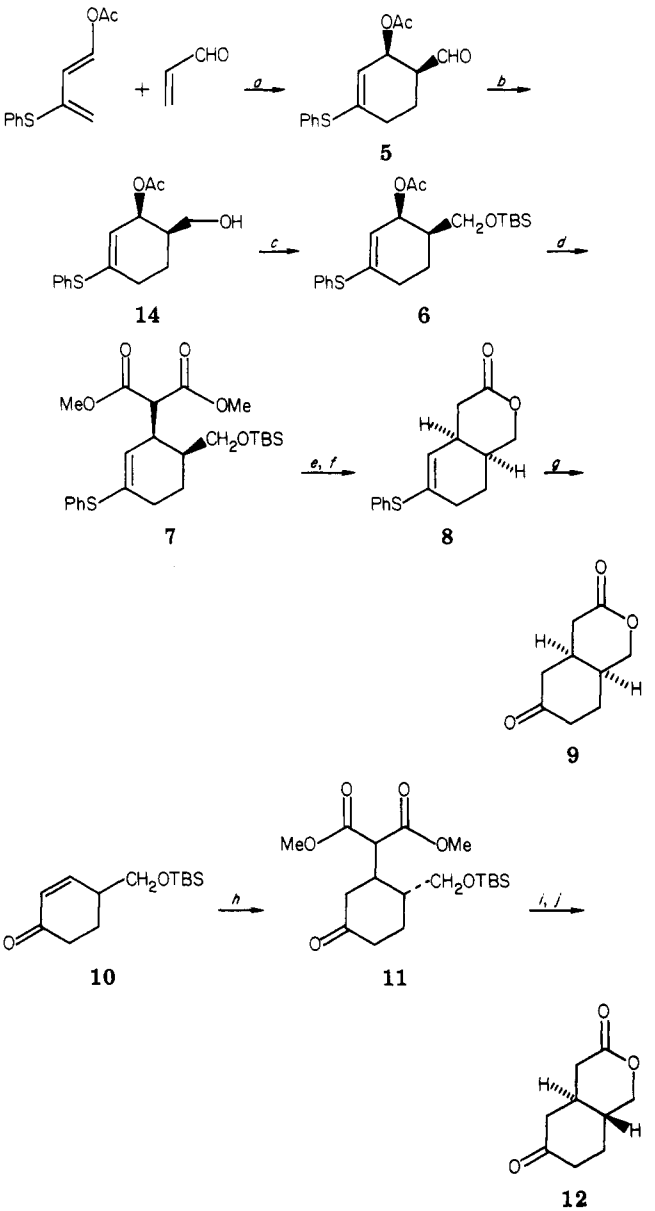
In order to verify our predictions regarding regiochemical control as exerted by the heteroatom, the simple (phenylthio)cyclohexenyl allylic acetate 3 (X = SPh, Y = OAc) was prepared and subjected to treatment by sodium dimethylmalonate and 10% Pd(diphos)$_2$ in DME (80 °C, 10 min). The desired regioisomer product 4 was obtained exclusively in an isolated yield of 78%.[19]



3 4

The preparation of a stereochemically defined precursor was accomplished by the use of a Diels–Alder reaction. The required diene was assembled by the following reaction sequence: thiophenol was conjugatively added to crotonaldehyde, the resulting product was chlorinated with NCS and then treated with NEt_3 to provide 3-(phenylthio)but-2-enal. Ketal exchange with isopropenyl acetate yielded 1-acetoxy-3-(phenylthio)-1,3-butadiene (5:1 ratio *E,E*:*E,Z*). Reaction of the *E,E* diene with acrolein provided *cis*-3-acetoxy-4-formyl-1-(phenylthio)cyclohexene (5) (Scheme I) (63%). The aldehyde 5 was selectively reduced with $NaBH_4$ (–23 °C, MeOH–toluene, 1 h, 78.4%) and the resulting alcohol protected as its dimethyl-*tert*-butylsilyl ether (TBSCl), DMF, (imidazole, 0 °C, 0.5 h, 92%) to provide the π-allyl precursor 6. This type of precursor affords a particularly stringent challenge for the predicted dominance of the electronic directing effect of SPh vs. the steric directing of CH_2OTBS as the entering nucleophile is required to add cis at the position adjacent to the silyl ether. Reaction of the allylic acetate 6 with Pd(diphos)$_2$ (4.0 mol %) and sodium dimethylmalonate (85 °C, 45 min, DME) yielded a single product 7 in 78% yield. In order to verify the stereochemical integrity of this process as well as demonstrate the potential synthetic applicability of this methodology, 7 was lactonized ($Et_3NH^+F^-$, CH_3CN, 50 °C, 36 h, 88%) and decarboxylated (LiCl, Me_2SO, H_2O, 66%) to give the bicyclic system 8. Mercury-catalyzed hydrolysis ($HgCl_2$, CH_3CN–H_2O, 76 °C, 24 h, 74%) provided the cis bicyclic keto lactone 9 as a single product. Treatment of the cyclohexenone 10 (Scheme I) with sodium diethylmalonate gave essentially exclusively the trans Michael product 11, which on decarboxylation and lactonization gave the trans keto lactone 12. The preparation of 12 allowed for a spectral comparison with the cis product 9 and verified the stereochemical assignment.[20] In addition, the preparation of 12 points out the stereochemical complementarity of the "native" Michael reaction and the tandem Diels–Alder–palladium equivalent to the Michael

Scheme I



[a] $PhCH_3$ (room temperature, 27 h, 63%). [b] $PhCH_3$, MeOH, $NaBH_4$, –23 °C, 1 h, 78%. [c] DMF, TBSCl, imidazole, 0 °C, 0.5 h, 92%. [d] DME, Pd(diphos)$_2$, $NaCH(CO_2Me)_2$, 85 °C, 40 min, 78%. [e] CH_3CN, Et_3NHF, 50 °C, 36 h, 88%. [f] Me_2SO–H_2O, LiCl, 100 °C, 4.5 h, 66%. [g] CH_3CN–H_2O, $HgCl_2$, 78 °C, 40 h, 74%. [h] THF, $NaCH(CO_2Me)_2$, room temperature, 2 h, 82%. [i] CH_3CN, NEt_3HF, room temperature, 15 h, 43%. [j] Me_2SO–H_2O, LiCl, 100 °C, 19 h, 30%.

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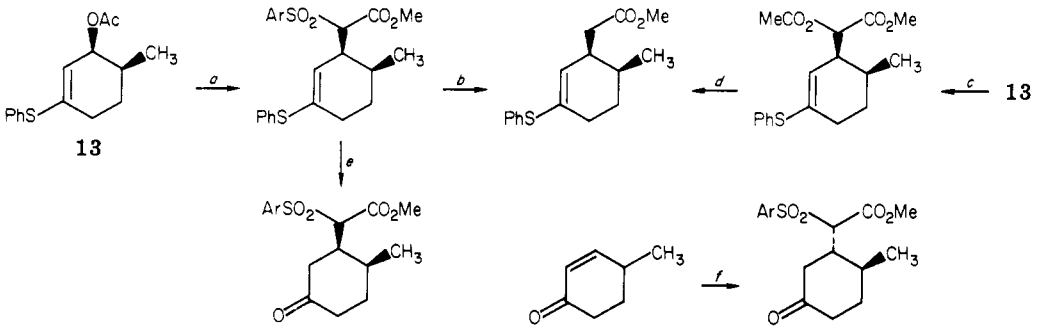
(19) Appropriate control reactions were run under identical conditions except no catalyst was included. These showed no nucleophilic addition.

(20) The coupling constants of the allylic CHOAc in the π-allyl precursors 6, 13, 15 were uniformly ≤5 Hz, indicating a cis disposition in these compounds; likewise the products derived from these materials, namely, 8, the malonate and sulfone products of 13, and 16, clearly show the allylic methine which in each case possesses no large (>5 Hz) coupling constants to the adjacent ring position, demonstrating the cis stereochemistry in each case. Preparation of the corresponding trans products verifies these assignments.

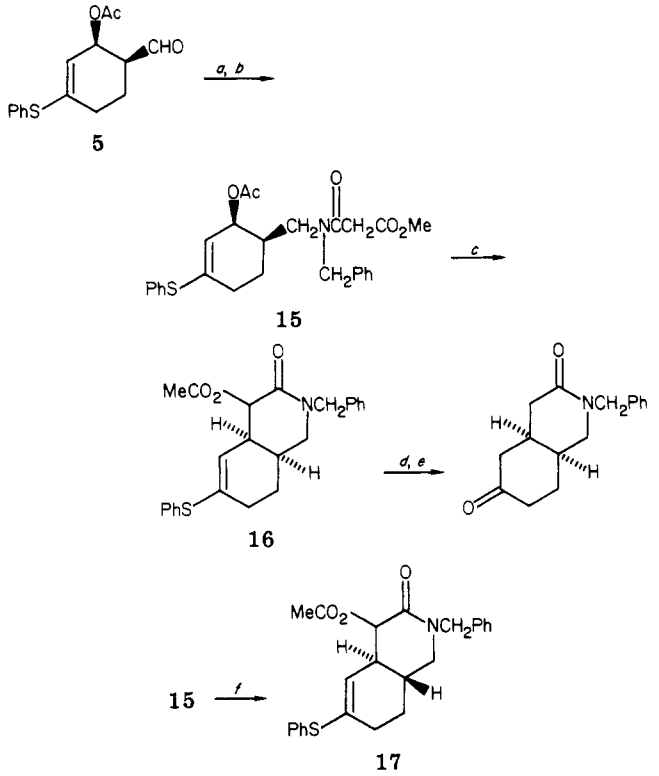
Scheme II



Ar = *p*-tolyl

[a] DME, $NaCH(SO_2Ar)CO_2Me$, $Pd(diphos)_2$, 85 °C, 20 min, 89%. [b] MeOH, Na_2HPO_4, 6% Na-Hg, room temperature, 2 h, 51%. [c] DME, $NaCH(CO_2Me)_2$, $Pd(diphos)_2$, 80 °C, 0.5 h, 72%. [d] Me_2SO-H_2O, LiCl, 100 °C, 12 h, 78%. [e] CH_3CN-H_2O, $HgCl_2$, 76 °C, 24 h, 66%. [f] DME, $NaCH(SO_2Ar)CO_2Me$, room temperature, 28 h, 30%.

Scheme III



[a] CH_2Cl_2, benzylamine, $MgSO_4$, −23 °C, 6 h, then MeOH, $NaBH_4$, −23 °C, 0.75 h, 86%. [b] CH_2Cl_2, $ClCOCH_2CO_2Me$, $CaCO_3$, −23 °C, 1.25 h, 78%. [c] DME, NaH, $Pd(diphos)_2$, 45 °C, 10 min, 81%. [d] Me_2SO-H_2O, LiCl, 100 °C, 9.25 h, 92%. [e] CH_3CN-H_2O, $HgCl_2$, reflux, 20 h, 65%. [f] THF, NaH, 0.5 h, 45 °C, 60%.

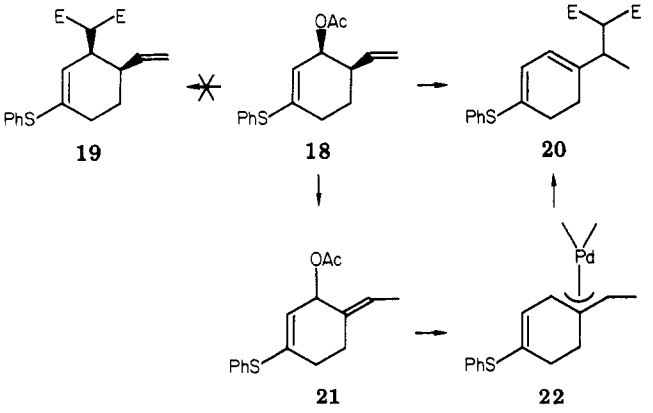
reaction which clearly enhances the synthetic potential of the latter.

As a further demonstration of this methodology, *cis*-3-acetoxy-4-methyl-1-(phenylthio)cyclohexene (**13**) was prepared by mesylation, LAH reduction, and reacetylation of the previously prepared alcohol (**14**). Treatment of **13** with $Pd(diphos)_2$ (10 mol %) and either sodium dimethylmalonate (DME, 80 °C, 0.5 h, 72%) or methyl sodio[(4-methylphenyl)sulfonyl]acetate (DME, 85 °C, 20 min, 89%)[19] followed by hydrolysis yielded the corresponding cis products (Scheme II). Reaction of 4-methyl-cyclohex-2-enone with the same nucleophiles was shown to again provide the corresponding trans products.[20]

An additional synthetic strategy was demonstrted by the elaboration of the aldehyde **5** to the π-allyl precursor **15** (Scheme III) which can effect an intramolecular version of the palladium reaction. The precursor was assembled by reductive amination (benzylamine, CH_2Cl_2, $MgSO_4$, 6 h followed by MeOH, $NaBH_4$, 0.75 h, all at −23 °C) of **5** (86%) followed by acylation of the amine ($ClCCH_2CO_2Me$, CH_2Cl_2, $CaCO_3$, −23 °C, 1.25 h, 78%). Reaction of **15** with NaH and $Pd(diphos)_2$ (10 mol %) (DME, 45 °C, 10 min) gave the cis bicyclic lactam **16** in 81% yield.[19] Interestingly, reaction of **15** in the absence of catalyst (NaH, DME, 45 °C, 0.5 h) gave exclusively the trans product **17**, again demonstrating the complementarity of the Pd-based methodology (now to the S_N2 reaction) and simplifying the spectral stereochemical characterization.[20]

Both the lactone and lactam cases amply demonstrate not only the novel stereospecific nature of this reaction but also elucidate the rich menu of functional groups available for further elaboration.

A curious result was obtained on attempted reaction of the vinyl substituted analogue of **18** (prepared by Wittig methylenation of **5**) under the standard Pd reaction conditions. Rather than simple malonate addition to provide **19**, the malonate addition product **20** was isolated.

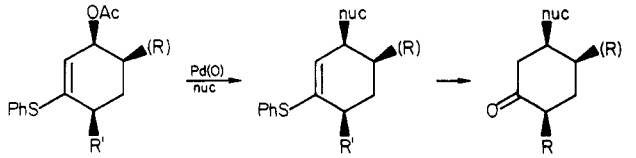


This product is assumed to result from Pd-mediated isomerization of the terminal olefin to give **21**, which can then form the pentadienylpalladium complex **22**. Interestingly, the addition of the nucleophile to **22** proceeds exclusively on the terminus most remote from SPh, again demonstrating the powerful directing effect of this group.

Conclusions

The viability of a palladium-mediated stereospecific equivalent to the Michael reaction has been demonstrated. The Diels–Alder–(π-allyl)palladium tandem of reactions allows the obtention of stereochemistry opposite to that typically available in the Michael reaction. Furthermore,

additional stereodefinitions by the Diels–Alder reaction at positions more remote to the site of nucleophilic addition will permit the realization of complete stereocontrol where effectively none could be anticipated in the "native" Michael process.[21] We are currently actively exploring



this extension as well as the employment of heteroatom nucleophiles in the Pd reaction.

Experimental Section

General Data. Proton nuclear magnetic resonance spectra (NMR) were recorded on a Varian Model EM-390 (90 MHz) or a Bruker WH-400 (400 MHz) spectrometer. Chemical shifts were expressed in δ units (ppm) with tetramethylsilane as an internal standard unless otherwise stated. Coupling constants (J) are reported in hertz; splitting patterns are designated as follows: s, singlet; d, doublet, t, triplet; q, quartet; b, broad.

Low-resolution mass spectra were recorded on a DuPont 21-490B spectrometer at an ionizing voltage of 70 eV. Precise masses were obtained on a VG 7035 instrument.

Infrared spectra (IR) were recorded on a Perkin-Elmer PE 467 spectrophotometer and are calibrated with the 1601-cm^{-1} peak of polystyrene. All absorption frequencies are reported in reciprocal centimeters.

Medium-pressure liquid chromatography (MPLC) and flash chromatography were run by using Woelm silica gel (32–63 μm) in the indicated solvent. Preparative TLC plates were supplied by Analtech.

Chemical analyses were performed by Galbraith Laboratories, Inc. in Knoxville, TN.

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl immediately before use. Pyridine, hexanes, methylene chloride (CH_2Cl_2), and triethylamine were distilled from calcium hydride.

All palladium catalysts were handled in an inert atmosphere of nitrogen. All reactions were run under a positive pressure of nitrogen.

3-Acetoxy-1-(phenylthio)cyclohexene (3). 3-(Phenylthio)cyclohex-2-enone[22] (0.397 g, 1.95 mmol) was dissolved in 4 mL of THF and cooled to −78 °C under N_2. Dibal-H (1.92 mL of 2 M solution in THF) was added and the reaction stirred at −78 °C for 1 h. Standard aqueous workup provided the allylic alcohol as a light yellow oil (84%), which was immediately carried into the next reaction. The crude alcohol (0.327 g, 1.59 mmol) was dissolved in 1.5 mL of CH_2Cl_2 and cooled to 0 °C. 4-(Dimethylamino)pyridine (0.19 g, 1.61 mmol) was then added followed by acetic anhydride (0.152 mL, 1.61 mmol). The reaction was stirred at 0 °C for 10 min and then quenched with 5 mL of saturated aqueous NH_4Cl. CH_2Cl_2 (20 mL) was added and the organic phase was separated, washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated to yield **3** as a light yellow oil (0.36 g, 91%): ^1H NMR ($CDCl_3$) δ 7.4 (d, J = 5 Hz, 2 H), 7.3 (m, 3 H), 5.6 (d, J = 4 Hz, 1 H), 5.26 (d, d, J = 5 Hz, 4 Hz, 1 H), 2.15 (m, 2 H), 2.02 (s, 3 H), 1.75 (m, 4 H); IR (CCl_4) 2930, 1735, 1370, 1230, 1000, 905 cm^{-1}; MS, m/e 248 (M^+), 205, 187, 173, 155, 110, 109, 97, 91, 77, 60, 43, exact mass calcd for $C_{14}H_{16}O_2S$ 248.0870, found 248.0861.

3-[Bis(methoxycarbonyl)methyl]-1-(phenylthio)cyclohexene (4). 3-Acetoxy-1-(phenylthio)cyclohexene (**3**) (0.20 g, 0.81 mmol) was dissolved in 1.6 mL of DME and added to a solution containing $Pd(diphos)_2$ (0.073 g, 0.0081 mmol) and sodium dimethylmalonate (0.81 mL of 1 M DME solution) under N_2. The reaction mixture was heated at 80 °C for 1 h and then cooled to room temperature; the solvent was then removed under reduced pressure. Flash chromatography (hexene:ether, 15:1) on silica gel yielded 0.20 g of **4** (78%): ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.75 (d, J = 2 Hz, 1 H), 3.72 (s, 3 H), 3.70 (s, 3 H), 3.3 (d, J = 9 Hz, 1 H), 3.03 (m, 1 H), 2.1 (m, 2 H), 1.8 (m, 2 H), 1.6 (m, 2 H); IR ($CDCl_3$) 2920, 1730, 1430, 1250, 1135 cm^{-1}; MS, m/e 320 (M^+), 260, 189, 111, 110, 109, 91, 79, 77, 43; exact mass calcd for $C_{17}H_{20}O_4S$ 320.1081, found 320.1093.

1-Acetoxy-3-(phenylthio)-1,3-butadiene. Crotonaldehyde (47.1 mL, 0.49 mol) was dissolved in 100 mL of $CHCl_3$ and the solution cooled to 0 °C under N_2. Thiophenol (47.9 mL, 0.47 mol) was then added followed by 0.1 mL of NEt_3. The reaction mixture was allowed to warm to room temperature and was stirred for 24 h. The solution was then concentrated at aspirator pressure and the resulting oil distilled (0.1 mm, 97–103 °C) to provide the Michael adduct (75.3 g) in 90% yield as a colorless oil. This compound was immediately carried on to the next reaction.

3-(Phenylthio)butanal (37.5 g, 0.21 mol) was dissolved in 420 mL of CCl_4 and the solution cooled to 0 °C. *N*-Chlorosuccinimide (33.4 g, 0.25 mol) was then added and the reaction was stirred at 0 °C for 13 h. The solution was then filtered and the filtrate was treated with NEt_3 (34.9 mL, 0.25 mol) at 0 °C. The reaction mixture was then filtered and the filtrate concentrated to 100 mL on a rotary evaporator with minimum heating. Toluene (300 mL) was added and the solution was again filtered and concentrated to 50 mL and chromatographed on silica gel. Hexane was used as eluant until all the toluene was off the column, and then hexane:ether (6:1) was employed, yielding 3-(phenylthio)but-2-enal (21.3 g, 57%) as an orange oil. The product consisted of a 7:1 mixture of the *E*:*Z* isomers as determined by ^1H NMR, which was contaminated with a small amount of starting material. This compound was immediately carried on to the next reaction.

3-(Phenylthio)but-2-enal (19.2 g, 0.108 mol), isopropenyl acetate (178 mL, 1.6 mol), *p*-toluenesulfonic acid (catalytic amount), and hydroquinone (catalytic amount) were dissolved in toluene (216 mL) in a 1-L flask equipped with a short-path distillation head. The reaction mixture was heated to 80 °C and acetone was slowly removed from the mixture via distillation over 48 h. The solution was then cooled to room temperature and concentrated on a rotary evaporator with minimum heating. The resulting oil was chromatographed on silica gel with use of 15:1 hexane:ether as eluant, yielding 12.5 g (53%) of the diene as a 5:1 *E,E*:*E,Z* mixture: (*E*) ^1H NMR ($CDCl_3$) δ 7.7 (d, J = 12 Hz, 1 H), 7.25 (m, 5 H), 6.1 (d, J = 12 Hz, 1 H), 5.45 (s, 1 H), 5.15 (s, 1 H), 2.10 (s, 3 H); (mixture) IR (CCl_4) 3030, 1735, 1340, 1200, 1170 cm^{-1}; MS, m/e 220 (M^+), 178, 110, 109, 87, 69, 43; exact mass calcd for $C_{12}H_{12}O_2S$ 220.0557, found 220.0552.

***cis*-3-Acetoxy-4-formyl-1-(phenylthio)cyclohexene (5).** 1-Acetoxy-3-(phenylthio)-1,3-butadiene (11.3 g, 0.05 mol), acrolein (17.1 mL, 0.256 mol), and a catalytic amount of hydroquinone were dissolved in 102 mL of toluene under N_2. The mixture was stirred at room temperature for 27 h and then the solvent was removed under reduced pressure. Crystallization of the resulting oil was effected in pentane–ether at −78 °C, yielding 8.9 g (63%) of **5** as a light yellow powder: mp 58–59 °C; ^1H NMR ($CDCl_3$) δ 9.7 (s, 1 H), 7.4 (m, 2 H), 7.3 (m, 3 H), 5.7 (bs, 2 H), 2.6 (bd, J = 10 Hz, 1 H), 2.3 (d, t, J = 12.3 Hz, 1 H), 2.2 (m, 1 H), 2.1–1.8 (m, 2 H), 1.98 (s, 3 H); IR ($CDCl_3$) 2920, 1730, 1535, 1445, 1375, 1235, 1110, 880 cm^{-1}; MS, m/e 276 (M^+), 233, 218, 217, 216, 205, 189, 188, 187, 178, 177, 152, 147, 125, 111, 110, 109, 107, 79, 77, 60, 57, 43; exact mass calcd for $C_{15}H_{16}O_3S$ 276.0819, found 276.0782.

3-Acetoxy-4-(hydroxymethyl)-1-(phenylthio)cyclohexene. The aldehyde **5** (1.0 g, 3.62 mmol) was dissolved in 7.2 mL of toluene and cooled to −23 °C under N_2. Methanol (3.6 mL) was then added, followed by $NaBH_4$ (0.14 g, 3.8 mmol) in small portions. The solution was stirred at −23 °C for 1 h and then partitioned between 50 mL of ice-cold aqueous NH_4Cl and 50 mL of CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with two 50-mL portions of CH_2Cl_2. The CH_2Cl_2 solutions were combined, washed with 100 mL of H_2O and 100 mL of brine, dried over anhydrous Na_2SO_4, and concentrated to yield a yellow oil. Flash chromatography (ether:hexane, 1:1) provided 0.789 g of alcohol (78%): ^1H NMR ($CDCl_3$) δ 7.41 (m, 2 H), 7.35 (m, 3 H), 5.61 (d, J = 5.4 Hz, 1 H), 5.38 (d,

(21) Eventual vinyl sulfide hydrolysis must then proceed without epimerization in order to maintain the stereospecificity. We have already obtained preliminary evidence to show that this can be accomplished.
(22) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235.

d, J = 5.4, 4.9 Hz, 1 H), 3.4 (m, 2 H), 2.45 (m, 1 H), 2.25 (m, 2 H), 2.05 (s, 3 H), 1.95 (m, 1 H), 1.55 (m, 2 H); IR ($CDCl_3$) 3620, 3520, 2930, 1720, 1440, 1370, 1250, 1025 cm^{-1}; MS, m/e 278 (M^+), 235, 219, 218, 187, 110, 109, 91, 81, 79, 43; exact mass calcd for $C_{15}H_{18}O_3S$ 278.0976, found 278.0989.

***cis*-3-Acetoxy-4-[(dimethyl-*tert*-butylsiloxy)methyl]-1-(phenylthio)cyclohexene (6).** *cis*-3-Acetoxy-4-(hydroxymethyl)-1-(phenylthio)cyclohexene (1.13 g, 4.06 mmol) was dissolved in 20.3 mL of DME and the solution cooled to 0 °C under N_2. Imidazole (0.279 g, 4.1 mmol) and dimethyl-*tert*-butylsilyl chloride (1.23 g, 8.13 mol) were added, and the reaction was stirred at 0 °C for 0.5 h. The solution was then partitioned between 100 mL of ether and 100 mL of aqueous NH_4Cl cooled to 0 °C. The organic phase was separated and the aqueous phase was washed twice with 50 mL of ether. The combined ether solutions were washed twice with 100 mL of H_2O and 100 mL brine, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure to yield a yellow oil. Flash chromatography on silica gel (hexane:ether, 2:1) gave 1.47 g of **6** (92.4%): ^1H NMR ($CDCl_3$) δ 7.4 (d, J = 6 Hz, 2 H), 7.3 (m, 3 H), 5.8 (d, J = 4.9 Hz, 1 H), 5.27 (d, d, J = 4.4, 4.4 Hz, 1 H), 3.6 (d, d, J = 9.8 Hz, 1 H), 3.45 (d, d, J = 9.8 Hz, 1 H), 2.2 (m, 2 H), 2.0 (s, 3 H), 1.9 (m, 1 H), 1.6 (m, 2 H), 0.85 (s, 9 H), 0.0 (s, 6 H); IR ($CDCl_3$) 2930, 2860, 1725, 1250, 840 cm^{-1}; MS, m/e 332, 223, 202, 201, 200, 186, 117, 109, 91, 89, 75, 73, 43. Anal. Calcd for $C_{21}H_{32}O_3SiS$: C, 64.25; H, 8.22; Si, 7.13; S, 8.15. Found: C, 64.30; H, 8.26; Si, 6.94; S, 7.95.

***cis*-3-[Bis(methoxycarbonyl)methyl]-4-[(dimethyl-*tert*-butylsiloxy)methyl]-1-(phenylthio)cyclohexene (7).** Sodium dimethylmalonate (12.2 mL of a 1 M DME solution) was added to a flask and the solvent was removed by evaporation. Pd(diphos)$_2$ (0.0369 g, 0.041 mmol) was then added followed by 4 mL of DME and the reaction was heated to 85 °C under an N_2 atmosphere. The allylic acetate **6** (0.40 g, 1.00 mmol) was dissolved in ~2 mL of DME and the solution added to the reaction mixture. The solution is maintained at 85 °C for 40 min and then cooled to room temperature and partitioned between 100 mL of EtOAc and 100 mL of H_2O. The organic phase was separated and the aqueous phase was extracted twice with 50 mL of EtOAc. The EtOAc solutions were combined, washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting oil was flash chromatographed on silica gel (hexane:ether, 20:1) to yield **7** (0.371 g, 78.4%) as a clear yellow oil: ^1H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 5.71 (bs, 1 H), 3.75–3.40 (m, 3 H), 3.71 (s, 3 H), 3.65 (s, 3 H), 3.25 (m, 1 H), 2.1 (m, 2 H), 1.8–1.4 (m, 3 H), 0.85 (s, 9 H), 0.0 (s, 6 H); IR ($CDCl_3$) 2930, 2860, 1738, 1460, 1440, 1250, 1200, 1150, 1080, 910, 890, 750 cm^{-1}; MS, m/e 464 (M^+), 433, 407, 332, 304, 201, 189, 163, 91, 89, 73, 59, 57, 55, 43, 41; exact mass calcd for $C_{24}H_{36}O_5SiS$ 464.2051, found 464.2055.

5-(Methoxycarbonyl)-4-oxo-8-(phenylthio)-*cis*-3-oxabicyclo[4.4.0]dec-7-ene. The silyl ether **7** (0.316 g, 0.681 mmol) was dissolved in 2.7 mL of CH_3CN under an N_2 atmosphere. Triethylammonium hydrogen fluoride (0.715 mL, 2 M solution in CH_3CN) was then added and the mixture was heated at 50 °C for 36 h. The reaction mixture was then cooled to room temperature and partitioned between saturated aqueous $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL). The phases were separated, and the aqueous phase was extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed twice with 100 mL of H_2O and 100 mL of brine, dried over $MgSO_4$, and concentrated at reduced pressure. Flash chromatography on silica gel (hexane:ether, 2:1) provided 0.190 g (87.7%) of product as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.6 (d, J = 3.9 Hz, 1 H), 4.4 (d, d, J = 11.2, 4.9 Hz, 1 H), 4.1 (d, d, J = 11.2, 4.9 Hz, 1 H), 3.8 (s, 3 H), 3.32 (d, J = 8.8 Hz, 1 H), 3.18 (m, 1 H), 2.35 (m, 1 H), 2.15 (m, 2 H), 1.81 (m, 1 H), 1.6 (m, 1 H); IR ($CDCl_3$) 2920, 1730, 1260, 1210, 1080 cm^{-1}; MS, m/e 318 (M^+), 260, 259, 246, 201, 109, 97, 91, 83, 79, 77, 71, 69, 65, 57, 55, 43, 41; exact mass calcd for $C_{17}H_{18}O_4S$ 318.0925, found 318.0917.

4-Oxo-8-(phenylthio)-*cis*-3-oxabicyclo[4.4.0]dec-7-ene (8). The ester lactone (0.182 g, 0.572 mmol) and LiCl (0.121 g, 2.86 mmol) were dissolved in Me_2SO (2.27 mL) and H_2O (0.2 mL), the solution was and heated in a 120 °C oil bath for 4.5 h. The reaction was then cooled and partitioned between 100 mL of CH_2Cl_2 and 100 mL of H_2O. The phases were separated and the aqueous phase was extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The resulting yellow oil was flash chromatographed on silica gel (hexane:ether, 2:1) to give 0.099 g (66.4%) of **8** as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.7 (d, J = 3.4 Hz, 1 H), 4.35 (d, d, J = 11.7, 5.4 Hz, 1 H), 4.1 (d, d, J = 11.7, 7.3 Hz, 1 H), 2.8 (m, 1 H), 2.7 (d, d, J = 16.6, 7.3 Hz, 1 H), 2.35 (d, d, J = 16.6, 8.8 Hz, 1 H), 2.25 (m, 1 H), 2.15 (m, 2 H), 1.75 (m, 1 H), 1.6 (m, 1 H); IR ($CDCl_3$) 2940, 1740, 1455, 1390, 1250, 1100, 860, 800, 680, 640 cm^{-1}; MS, m/e 260 (M^+), 201, 151, 110, 109, 107, 105, 91, 79, 77, 65, 51, 41; exact mass calcd for $C_{15}H_{16}O_2S$ 260.0870, found 260.0874.

4-Oxo-*cis*-3-oxabicyclo[4.4.0]decan-8-one (9). $HgCl_2$ (0.084 g, 0.31 mmol) dissolved in 1.23 mL of CH_3CN:H_2O (3:1) was added to the vinyl sulfide **8** (0.08 g, 0.31 mol) dissolved in an equal volume of CH_3CN:H_2O (3:1). The reaction mixture was heated at reflux for 24 h, then cooled, and filtered through Celite. The filtrate was concentrated and then taken up in CH_2Cl_2 and refiltered through Celite and glass wool. The filtrate was then concentrated and purified by flash chromatography on silica gel (hexane:ether, 2:1), providing 0.038 g of **9** (73.8%): ^1H NMR ($CDCl_3$) δ 4.40 (d, d, J = 11.3, 3.9 Hz, 1 H), 4.25 (d, d, J = 11.3, 5.9 Hz, 1 H), 2.7 (m, 2 H), 2.5–2.2 (m, 6 H), 1.95 (m, 2 H); IR (CCl_4) 2920, 1740, 1255, 1230 cm^{-1}; MS, m/e 168, 127, 96, 86, 84, 81, 68, 67, 57, 55, 54, 53, 47, 41; exact mass calcd for $C_9H_{12}O_3$ 168.0786, found 168.0785. *trans*-**12**: exact mass calcd for $C_9H_{12}O_3$ 168.0786, found 168.0790; ^1H NMR ($CDCl_3$) δ 4.46 (d, d, J = 15.0, 3.9 Hz, 1 H), 3.95 (d, d, J = 15, 12 Hz, 1 H), 2.75 (d, d, J = 16, 4 Hz, 1 H), 2.5 (m, 3 H), 2.3 (d, d, J = 16, 10 Hz, 1 H), 2.1 (m, 4 H), 1.5 (m, 1 H).

***cis*-3-Acetoxy-4-methyl-1-(phenylthio)cyclohexene (13).** The allylic acetate-alcohol **14** (0.707 g, 2.54 mmol) was dissolved in CH_2Cl_2 (12.7 mL) and cooled to −10 °C under an N_2 atmosphere. Triethylamine (0.53 mL, 3.81 mmol) and methanesulfonyl chloride (0.216 mL, 2.79 mmol) were then added, and the reaction mixture was stirred at −10 °C for 15 min. The solution was then partitioned between 100 mL of CH_2Cl_2 and 100 mL of ice-cold H_2O. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined CH_2Cl_2 solutions were washed with 100 mL of ice-cold 1.0 N HCl, 100 mL of ice-cold H_2O, and 100 mL of 0 °C aqueous $NaHCO_3$, 8 × 100 mL of ice-cold H_2O, 100 mL of 0 °C brine, dried over anydrous Na_2SO_4, concentrated, and quickly taken on to the next reaction.

The mesylate (0.906 g, 2.54 mmol) was dissolved in 2 mL of THF and added to a 0 °C slurry of LAH (0.289 g, 7.62 mmol) in 5 mL of THF. The mixture was allowed to warm to room temperature, stirred for 0.5 h, and then subjected to a standard H_2O–aqueous NaOH workup. Flash chromatography of the resulting *cis*-3-hydroxy-4-methyl-1-(phenylthio)cyclohexene on silica gel (hexane:ether, 10:1) provided 0.31 g (55.3%), which was immediately carried on to the next reaction.

cis-3-Hydroxy-4-methyl-1-(phenylthio)cyclohexene (0.367 g, 1.67 mmol) was dissolved in CH_2Cl_2 (1.67 mL) and cooled to 0 °C under N_2. 4-(Dimethylamino)pyridine (0.206 g, 1.68 mmol) and acetic anhydride (0.16 mL, 1.68 mmol) were then added. The reaction was complete in 5 min and was quenched with ice-cold saturated aqueous NH_4Cl (20 mL), and the aqueous phase was extracted three times with 30 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed twice with 50 mL of H_2O and 50 mL of brine, dried over Na_2SO_4, and concentrated at reduced pressure. The resulting oil was flash chromatographed on silica gel (hexane:ether, 4:1), yielding 0.419 g (96%) of **13**: ^1H NMR ($CDCl_3$) δ 7.4 (d, J = 5 Hz, 2 H), 7.3 (m, 3 H), 5.65 (d, J = 4.9 Hz, 1 H), 5.2 (d, d, J = 4.9, 4.4 Hz, 1 H), 2.15 (m, 2 H), 2.05 (s, 3 H), 1.85 (m, 1 H), 1.6 (m, 2 H), 0.9 (d, J = 9 Hz, 3 H); IR (CCl_4) 2920, 1730, 1365, 1230, 1000, 690 cm^{-1}; MS, m/e 262 (M^+), 202, 110, 109, 95, 93, 91, 77, 43; exact mass calcd for $C_{15}H_{18}O_2S$ 262.1026, found 262.1016.

***cis*-3-[Bis(methoxycarbonyl)methyl]-4-methyl-1-(phenylthio)cyclohexene.** The allylic acetate **13** (0.3 g, 1.14 mmol) was dissolved in 2.8 mL of DME under an N_2 atmosphere. Pd(diphos)$_2$ (0.10 g, 0.114 mmol) and sodium dimethylmalonate (1.14 mL of 1 M solution in DME) were added, and the solution was heated at 80 °C for 0.5 h. The solution was cooled to room temperature and flash chromatographed on silica gel (hexane:ether, 15:1) to yield a colorless oil (0.273 g, 72%): ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.6 (bs, 1 H), 3.75 (s, 3 H), 3.65 (s, 3 H),

3.35 (d, J = 9 Hz, 1 H), 3.2 (m, 1 H), 2.1 (m, 3 H), 1.7 (m, 1 H), 1.6 (m, 1 H), 0.85 (d, J = 7 Hz, 3 H); IR ($CDCl_3$) 2920, 1740, 1435, 1260, 1200, 1020 cm^{-1}; MS, m/e 334 (M^+), 274, 204, 203, 133, 93, 91, 77; exact mass calcd for $C_{18}H_{22}O_4S$ 334.1237, found 334.1232.

***cis*-4-Methyl-3-[[[(*p*-tolylsulfonyl)methoxy]carbonyl]-methyl]-1-(phenylthio)cyclohexene.** The allylic acetate **13** (0.078 g, 0.298 mmol) was dissolved in 1.49 mL of DME under N_2. $Pd(diphos)_2$ (0.027 g, 0.03 mmol) and 0.31 mL of a 1 M solution of methyl sodio[*p*-tolylsulfonyl)acetate in DME were added, and the solution was heated at 85 °C for 20 min. The reaction mixture was cooled to room temperature and concentrated at reduced pressure to yield a yellow-brown precipitate. The crude product was subjected to flash chromatography on silica gel (hexane:ether, 5:1), yielding 0.113 g (88.6%) of product was a 1.5:1 mixture of cis diastereomers: ^1H NMR ($CDCl_3$) δ 7.75 (d, J = 8 Hz, 0.6 H), 7.65 (d, J = 8 Hz, 0.4 H), 7.3 (m, 8 H), 6.35 (bs, 0.4 H), 5.3 (bs, 0.6 H), 4.01 (d, J = 8.3 Hz, 0.6 H), 3.96 (d, J = 11.7 Hz, 0.4 H), 3.55 (s, 1.2 H), 3.45 (s, 1.8 H), 3.2 (m, 0.6 H), 3.0 (m, 0.4 H), 2.45 (s, 3 H), 2.2–2.0 (m, 2 H), 1.8 (m, 0.6 H), 1.7–1.5 (m, 2.4 H), 0.95 (d, J = 6.9 Hz, 1.8 H), 0.81 (d, J = 6.8 Hz, 1.2 H); IR (CCl_4) 2920, 1745, 1330, 1200, 1140, 1080, 905 cm^{-1}; MS, m/e 430 (M^+), 275, 274, 243, 242, 203, 165, 105; exact mass calcd for $C_{23}H_{26}O_4S_2$ 430.1271, found 430.1238.

***cis*-3-[(Methoxycarbonyl)methyl]-4-methyl-1-(phenylthio)cyclohexene. 1. Decarboxylation of *cis*-3-[Bis(methoxycarbonyl)methyl]-4-methyl-1-(phenylthio)cyclohexene.** The malonate addition product (0.17 g, 0.52 mmol), LiCl (0.11 g, 2.6 mmol), and H_2O (0.25 mL) were added to Me_2SO (1.0 mL) and heated in a 120 °C oil bath for 12 h. The reaction mixture was then cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The aqueous phase was separated and extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with 100 mL of brine, dried over Na_2SO_4, and concentrated at reduced pressure. The resulting oil was flash chromatographed on silica gel (hexane:ether, 10:1), yielding 0.11 g of product (78%).

2. Na/Hg Reduction of *cis*-4-Methyl-3-[(*p*-tolylsulfonyl)(methoxycarbonyl)methyl]-1-(phenylthio)cyclohexene. The vinyl sulfide (0.013 g, 0.031 mmol), Na_2HPO_4 (0.017 g, 0.12 mmol), and 6% sodium amalgam (0.046 g, 0.23 mmol) were added to MeOH (0.6 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was then partitioned between 50 mL of H_2O and 50 mL of ether. The aqueous phase was separated and further extracted with 2 × 50 mL of ether. The combined ether solutions were washed with 50 mL of brine, dried over Na_2SO_4, and concentrated. The resulting oil was chromatographed on a preparative-layer silica gel plate (hexane:ether, 2:1), yielding 0.0043 g (51%) of the vinyl sulfide–methyl ester: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.84 (d, J = 1.9 Hz, 1 H), 3.65 (s, 3 H), 2.81 (m, 1 H), 2.39 (d, d, J = 15.1, 6.8 Hz, 1 H), 2.2 (d, d, J = 15.1, 8.8 Hz, 1 H), 2.1 (m, 2 H), 1.95 (m, 1 H), 1.7–1.5 (m, 2 H), 0.9 (d, J = 7 Hz, 3 H); IR (CCl_4) 2920, 1740, 1435, 1260, 1150, 685 cm^{-1}; MS, m/e 276 (M^+), 204, 203, 167, 161, 160, 125, 110, 109, 107, 94, 93, 91, 79, 77, 75, 65, 43, 41; exact mass calcd for $C_{16}H_{20}O_2S$ 276.1183, found 276.1173.

***cis*-3-[(Methoxycarbonyl)(*p*-tolylsulfonyl)methyl]-4-methylcyclohexanone.** *cis*-3-[(Methoxycarbonyl)(*p*-tolylsulfonyl)methyl]-4-methyl-1-(phenylthio)cyclohexene (0.033 g, 0.076 mmol) and $HgCl_2$ (0.21 g, 0.076 mmol) were dissolved in 0.3 mL of CH_3CN:H_2O (3:1) and heated at 76 °C for 24 h. The solution was then cooled to room temperature, diluted with CH_2Cl_2, and filtered through Celite, and the filtrate was concentrated at reduced pressure. The resulting oil was redissolved in 1 mL of CH_2Cl_2, cooled to −78 °C, filtered through glass wool, and concentrated. Chromatography on a silica gel preparative plate (ether:hexane, 2:1) gave 0.017 g (65.8%) of the product as a 1.5:1 mixture of *cis* diastereomers: ^1H NMR ($CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 4.0 (d, J = 9.8 Hz, 0.6 H), 3.9 (d, J = 11.2 Hz, 0.4 H), 3.55 (s, 1.2 H), 3.45 (s, 1.8 H), 3.05 (d, d, J = 15, 3.5 Hz, 0.4 H), 2.85–2.6 (m, 1 H), 2.45 (s, 3 H), 2.4–2.2 (m, 4 H), 2.03 (d, d, J = 14.9, 3.9 Hz, 0.6 H), 1.85 (m, 2 H), 1.15 (d, J = 7 Hz, 1.8 H), 1.05 (d, J = 7 Hz, 1.2 Hz); IR (CCl_4) 2930, 1740, 1720, 1435, 1335, 1140, 905 cm^{-1}; MS, m/e 281, 249, 228, 183, 182, 151, 150, 139, 123, 95, 91. Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.33; H, 6.56; S, 9.46, Found: C, 60.36; H, 6.75; S, 9.20. *trans*-3-[(Methoxycarbonyl)(*p*-tolylsulfonyl)methyl]-4-methylcyclohexanone: ^1H NMR ($CDCl_3$) single diasteromer δ 7.75 (d, J = 8.3 Hz, 2 H), 7.34 (d, J 8.3 Hz, 2 H), 4.15 (d, J = 3.4 Hz, 1 H), 3.65 (s, 3 H), 2.9 (d, d, J = 14.3 Hz, 1 H), 2.6–2.2 (m, 5 H), 2.45 (s, 3 H), 2.0 (m, 1 H), 1.85 (m, 1 H), 1.0 (d, J = 7 Hz, 3 H).

***cis*-3-Acetoxy-4-[(*N*-benzylamino)methyl]-1-(phenylthio)cyclohexene.** The aldehyde **5** (1.0 g, 3.62 mmol) was dissolved in 7.2 mL of CH_2Cl_2 and cooled to −23 °C under N_2. Anhydrous $MgSO_4$ (0.87 g, 7.24 mmol) was then added, followed by benzylamine (0.40 mL, 3.66 mmol). The solution was stirred at −23 °C for 6 h, and then 3.6 mL of MeOH and $NaBH_4$ (0.15 g, 3.98 mmol) were added. The reaction mixture was stirred at −23 °C an additional 0.75 h and then partitioned between 100 mL of EtOAc and 100 mL of ice-cold H_2O. The aqueous phase was separated and extracted twice with 50 mL of EtOAc. The combined EtOAc phases were washed with 100 mL of H_2O and 100 mL of brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the resulting oil (hexane:ether, 2:1) yielded 1.14 g (86%) of the amine: ^1H NMR ($CDCl_3$) δ 7.3 (m, 10 H), 5.7 (d, J = 5.4 Hz, 1 H), 5.3 (pseudo t, J = 5.4, 1 H), 3.75 (AB quartet, J = 12 Hz, 2 H), 2.6 (d, d, J = 12.8 Hz, 1 H), 2.5 (d, d, J = 12.8 Hz, 1 H), 2.2 (bs, 2 H), 1.95 (s, 3 H), 1.9 (m, 1 H), 1.7–1.5 (m, 3 H); IR ($CDCl_3$) 2920, 2830, 1725, 1460, 1370, 1250, 1010, 900, 680 cm^{-1}; MS, m/e 367 (M^+), 188, 121, 120, 119; exact mass calcd for $C_{22}H_{25}O_2NS$ 367.1604, found 367.1617.

***cis*-3-Acetoxy-4-[[*N*-benzyl-*N*-[(methoxycarbonyl)-acetyl]amino]methyl]-1-(phenylthio)cyclohexene (15).** *cis*-3-Acetoxy-4-[(*N*-benzylamino)methyl]-1-(phenylthio)cyclohexene (1.11 g, 3.01 mmol) was dissolved in 6.0 mL of CH_2Cl_2 and the solution cooled to −23 °C under N_2. $CaCO_3$ (0.331 g, 3.31 mmol) and $ClCOCH_2CO_2Me$ (0.31 mL, 3.01 mmol) were then added, and the mixture was stirred at −23 °C for 75 min. The solution was then partitioned between 100 mL of CH_2Cl_2 and 100 mL of H_2O. The aqueous phase was separated and extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The residual oil was flash chromatographed on silica gel (hexane:ether, 1:1), yielding 1.09 g (78%) of **15**. ^1H NMR($CDCl_3$) shows two diastereomers due to amide resonance (ratio 2:1). Amide resonances were demonstrated by observing coalescence of NMR signals at 60 °C. Major isomer: ^1H NMR δ 7.4–7.1 (m, 10 H), 5.7 (d, J = 4.9 Hz, 1 H), 5.13 (pseudo t, J = 4.8 Hz, 1 H), 4.55, 4.45 (AB quartet, J = 15 Hz, 2 H), 3.7 (s, 3 H), 3.5 (m, 4 H), 2.2 (m, 2 H), 2.00 (s, 3 H), 1.6 (m, 3 H). Minor isomer: ^1H NMR δ 7.4–7.1 (m, 10 H), 5.66 (d, J = 5.1 Hz, 1 H), 5.05 (pseudo t, J = 4.8 Hz, 1 H), 4.8, 4.6 (AB quartet, J = 15 Hz, 2 H), 3.75 (s, 3 H), 3.3 (m, 4 H), 2.2 (m, 2 H), 2.00 (s, 3 H), 1.6 (m, 3 H); IR (CCl_4) 2930, 1735, 1660, 1430, 1230, 900 cm^{-1}; MS, m/e 407, 316, 222, 221, 220, 208, 201, 200, 199, 186, 130, 121, 120, 109, 106, 93, 92, 91, 60, 56, 55, 45, 43. Anal. Calcd for $C_{26}H_{29}O_5NS$: C, 66.78; H, 6.26. Found: C, 66.57; H, 6.36.

***N*-Benzyl-4-oxo-5-(methoxycarbonyl)-8-(phenylthio)-*cis*-3-azabicyclo[4.4.0]dec-7-ene (16).** The allylic acetate **15** (0.131 g, 0.28 mmol) was dissolved in 0.5 mL of DME under N_2 and cooled to 0 °C. NaH (0.009 g, 0.393 mmol) was then added, followed immediately by $Pd(diphos)_2$ (0.025 g, 0.0281 mmol). The solution was then heated at 45 °C for 10 min, then cooled to room temperature, and subjected to preparative TLC on silica gel (ether:hexane, 5:1), yielding **16** (0.093 g, 81%): ^1H NMR ($CDCl_3$) single diastereomer at C-5 δ 7.3 (m, 10 H), 5.74 (d, J = 2 Hz, 1 H), 4.65, 4.55 (AB quartet, J = 15 Hz, 2 H), 3.75 (s, 3 H), 3.35 (d, J = 7 Hz, 2 H), 3.05 (m, 2 H), 2.2 (m, 1 H), 2.1 (m, 2 H), 1.6 (m, 2 H); IR ($CDCl_3$) 2920, 2875, 1740, 1650, 1440, 1160, 865 cm^{-1}; MS, m/e 407 (M^+), 348, 187, 120, 109, 106, 97, 91, 79, 77, 65; exact mass calcd for $C_{24}H_{25}O_3NS$ 407.1554, found 407.1589 Trans isomer **17** formed by treatment of **15** with 1.4 equiv of NaH in DME at 45 °C for 0.5 h. *trans*-**17**: ^1H NMR ($CDCl_3$), one diastereomer at C-5, δ 7.4–7.1 (m, 10 H), 5.89 (d, J = 5.1 Hz, 1 H), 4.65, 4.40 (AB quartet, J = 16 Hz, 2 H), 4.3 (d, J = 4 Hz, 1 H), 4.1 (pseudo t, J = 10 Hz, 1 H), 4.0 (bs, 1 H), 3.7 (s, 3 H), 2.7 (d, J = 12 Hz, 1 H), 2.2 (m, 3 H), 1.7 (m, 2 H).

***N*-Benzyl-4-oxo-8-(phenylthio)-*cis*-3-azabicyclo[4.4.0]-dec-7-ene.** The lactam **16** (0.056 g, 0.14 mmol) and LiCl (0.058 g, 1.38 mmol) were dissolved in Me_2SO (0.55 mL) and ~0.1 mL of H_2O. The mixture was heated in a 110 °C oil bath for 9 h, then cooled to room temperature, and partitioned between 100 mL of CH_2Cl_2 and 100 mL of H_2O. The aqueous phase was separated

and washed with 100 mL of brine, dried over $MgSO_4$, and concentrated. The resulting oil was flash chromatographed (ether:hexane, 2:1), yielding the product as a yellow oil (0.04 g, 92%). ^1H NMR ($CDCl_3$) δ 7.3 (m, 10 H), 5.86 (pseudo t, J = 2 Hz, 1 H), 4.63, 4.50 (AB quartet, J = 14.7 Hz, 2 H), 3.3 (d, d, J = 12.7, 5.9 Hz, 1 H), 3.05 (d, d, J = 12.7, 6.4 Hz, 1 H), 2.7 (m, 2 H), 2.35 (m, 1 H), 2.1 (m, 2 H), 1.6 (m, 3 H); IR (CCl_4) 2900, 1650, 1440, 690 cm^{-1}; MS, m/e 349 (M^+), 91, 72; exact mass calcd for $C_{22}H_{23}ONS$ 349.1499, found 349.1468.

***N*-Benzyl-4-oxo-*cis*-3-azabicyclo[4.4.0]decan-8-one.** The vinyl sulfide (0.06 g, 0.17 mmol) and $HgCl_2$ (0.049 g, 0.18 mmol) were dissolved in CH_3CN:H_2O (3:1), 0.69 mL) under N_2. The mixture was heated at reflux for 20 h, then cooled to room temperature, diluted with 2 mL of CH_2Cl_2, and filtered through Celite. The solution was concentrated and the resulting oil was taken up in CH_2Cl_2 (5 mL) and filtered through glass wool and Celite. The filtrate was concentrated and purified by flash chromatography (ethyl acetate:hexane, 3:1) on silica gel, yielding 0.029 g (65%) of the ketone: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 4.75, 4.45 (AB quartet, J = 14 Hz, 2 H), 3.4 (d, d, J = 12.7, 5.4 Hz, 1 H), 3.2 (d, d, J = 12.7, 5.9 Hz, 1 H), 2.65–2.4 (m, 3 H), 2.25 (m, 5 H), 1.9 (m, 1 H), 1.8 (m, 1 H); IR (CCl_4) 2920, 1720, 1645, 900 cm^{-1}; MS, m/e 257 (M^+), 106, 92, 91, 88, 86, 84, 65, 49, 47, 43, 41; exact mass calcd for $C_{16}H_{19}O_2N$ 257.1415, found 257.1449.

***cis*-3-Acetoxy-4-vinyl-1-(phenylthio)cyclohexene (18).** The aldehyde **5** (0.1 g, 0.36 mmol) was treated with $CH_2{=}PPh_3$ (0.36 mL of 1 M solution in ether) at room temperature for 15 min and then subjected to a standard aqueous workup. The desired product was obtained by preparative plate chromatography in silica gel (hexane:ether, 2:1), 0.024 g (25%), and immediately carried on to the next reaction: ^1H NMR ($CDCl_3$) δ 7.4 (d, J = 6 Hz, 2 H), 7.3 (m, 3 H), 5.8 (d, d, d, J = 15.8, 6 Hz, 1 H), 5.65 (d, J = 5 Hz, 1 H), 5.25 (pseudo t, J = 5 Hz, 1 H), 5.05 (d, J = 15 Hz, 1 H), 5.04 (d, J = 8 Hz, 1 H), 2.45 (m, 1 H), 2.2 (m, 2 H), 2.0 (5.3 H), 1.75 (m, 2 H); MS, m/e 274 (M^+), 220, 215, 214, 178, 165, 123, 110, 105.

4-[1-[Bis(methoxycarbonyl)methyl]ethyl]-1-(phenylthio)-1,4-cyclohexadiene (20). The allylic acetate **18** (0.03 g, 0.11 mmol), Pd(diphos)$_2$ (0.0098 g, 0.011 mmol), and 0.65 mL of a 1 M DME solution of sodium dimethylmalonate were added to 0.4 mL of DME under N_2. The solution was then heated at 80 °C for 15 min, whereupon it was cooled to room temperature and subjected to preparative plate chromatography on silica gel (hexane:ether, 2:1), yielding 0.045 g of **20** (82%): ^1H NMR ($CDCl_3$) δ 7.4 (d, J = 6 Hz, 2 H), 7.3 (m, 3 H), 5.9 (d, J = 6 Hz, 1 H), 5.7 (d, J = 6 Hz, 1 H), 3.7 (s, 3 H), 3.65 (s, 3 H), 3.45 (d, J = 10 Hz, 1 H), 3.0 (d, t, J = 10, 7 Hz, 1 H), 2.2 (m, 4 H), 1.1 (d, J = 7 Hz, 3 H); *MS*, m/e 346 (M^+), 215, 214, 213, 184, 149, 109, 108, 105, 91, 79, 77, 71, 69, 65, 57, 55, 51, 43.

Registry No. **3**, 90083-78-6; **3** (alcohol), 90083-79-7; **4**, 90083-80-0; **5**, 90083-86-6; **6**, 90083-88-8; **7**, 90083-89-9; **8**, 90084-07-4; **8** (ester lactone), 90083-90-2; **9**, 90083-91-3; **10**, 90084-09-6; **11**, 90084-10-9; **12**, 90083-92-4; **13**, 90083-93-5; **13** (alcohol), 90083-95-7; **14**, 90083-87-7; **14** (mesylate), 90083-94-6; **15**, 90084-02-9; *trans*-**15**, 90084-03-0; **15** (amine), 90084-01-8; **16**, 90084-11-0; **18**, 90084-06-3; **20**, 90084-08-5; Pd(DIPHOS)$_2$, 31277-98-2; TBSCl, 18162-48-6; $NaCH(CO_2Me)_2$, 18424-76-5; (*E*)-$CH_2{=}C(SPh)CH{=}CHOAc$, 90083-81-1; (*Z*)-$CH_2{=}C(SPh)$-$CH{=}CHOAc$, 90083-85-5; $CH_3CH{=}CHCHO$, 4170-30-3; PhSH, 108-98-5; $CH_3CH(SPh)CH_2CHO$, 38160-59-7; $CH_3CH(SPh)$-$CHClCHO$, 90083-82-2; (*E*)-$CH_3C(SPh){=}CHCHO$, 90083-84-4; (*Z*)-$CH_3C(SPh){=}CHCHO$, 90083-83-3; $CH_2{=}CHCHO$, 107-02-8; Et_3NHF, 29585-72-6; LiCl, 7447-41-8; $HgCl_2$, 7487-94-7; $NaCH$-$(SO_2Ar)CO_2Me$, 90083-98-0; $CH_2{=}PPh_3$, 3487-44-3; 3-(phenylthio)cyclohex-2-enone, 75717-39-4; isopropenyl acetate, 108-22-5; *cis*-3-[bis(methoxycarbonyl)methyl]-4-methyl-1-(phenylthio)-cyclohexene, 90083-96-8; 4-methyl-3-[(*p*-tolylsulfonyl)(methoxycarbonyl)methyl]-1-(phenylthio)cyclohexene (isomer 1), 90083-97-9; 4-methyl-3-[(*p*-tolylsulfonyl)(methoxycarbonyl)methyl]-1-(phenylthio)cyclohexene (isomer 2), 90130-47-5; *cis*-3-[(methoxycarbonyl)methyl]-4-methyl-1-(phenylthio)cyclohexene, 90083-99-1; 3-[(methoxycarbonyl)(*p*-tolylsulfonyl)methyl]-4-methylcyclohexanone (isomer 1), 90084-00-7; 3-[(methoxycarbonyl)(*p*-tolylsulfonyl)methyl]-4-methylcyclohexanone (isomer 2), 90130-48-6; *N*-benzyl-4-oxo-8-(phenylthio)-*cis*-3-azabicyclo-[4.4.0]dec-7-ene, 90084-04-1; *N*-benzyl-4-oxo-*cis*-3-azabicyclo-[4.4.0]decan-8-one, 90084-05-2.

Synthesis of Protected 4-Desmethoxy-8-nordaunomycinone

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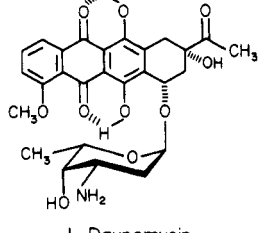
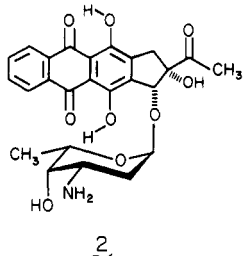
The synthesis of 4-desmethoxy-8-nordaunomycinone in protected form is described. Two separate routes were investigated which share a common strategy for the construction of this new five-membered anthracycline ring system.

The clinical utility of anthracycline antibiotics[1] such as daunomycin **1** has prompted varied approaches to their synthesis[2] and derivatization. The major thrust in analogue development has been to diminish the cumulative cardiotoxic liability of these antitumor agents.[3] Deletion of the 4-methoxyl group in daunomycin has resulted in increased potency.[4] With these thoughts in mind, the desmethoxy-8-nor analogue **2** was chosen as a desirable target whose degradation after glycolysis might be facilitated by the vicinal diol portion of the aglycone.



1 Daunomycin



2

Utilizing existing methodology for the incorporation of the naphthoquinone portion of anthracycline aglycones,[5]

(1) For recent reviews see: Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley Interscience: Somerset, NJ, 1979, Vol. 1, Chapter 2; "Anthracyclines: Current Status and New Developments"; Crooke, S. T., Reich, S. D., Eds.; Academic Press: New York, 1980.

(2) For a recent elegant synthesis of (±)-daunomycinone see: Kelly, T. Ross; Vaya, J.; Ananthasubramanian, L. *J. Am. Chem. Soc.* **1980**, *102*, 5983–5984 and references sited therein.

(3) Israel, M.; Potti, G. *J. Med. Chem.* **1982**, *25*, 187–191.

(4) Arcamone, F. "Doxorubicin-Anticancer Antibiotics"; Academic Press: NY, 1981; Vol. 17; *Cancer. Treat. Rep.* **1976**, *60*, 829.

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