Total Synthesis of (−)-Silphiperfol-6-ene and (−)-Methyl Cantabradienate

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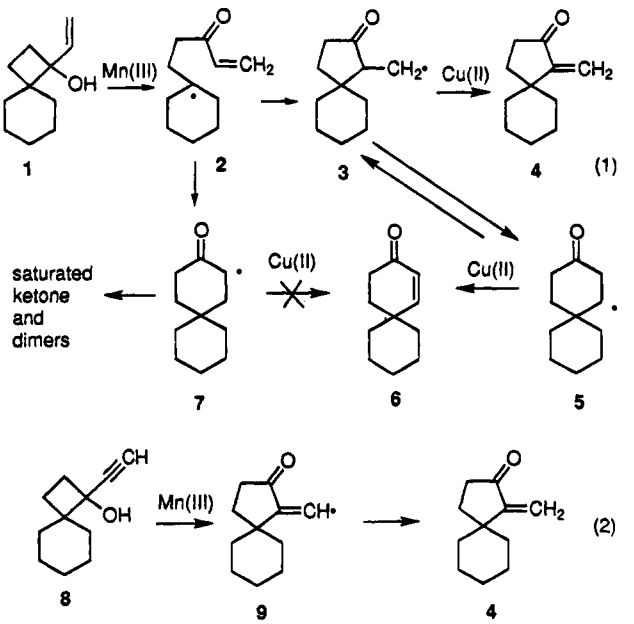
Received May 20, 1994[⊗]

(−)-Silphiperfol-6-ene (**10**) and (−)-methyl cantabradienate (**11**) have been prepared in seven steps from (*R*)-3-methyl-1-cyclopentenecarboxaldehyde in 13 and 9% overall yield, respectively. Addition of isopentenylmagnesium bromide to imine **22** afforded 65% of aldehyde **14**. Oxidation provided acid **15**, which was converted to ketene **20**, which underwent an intramolecular [2 + 2] cycloaddition to afford cyclobutanone **13**. Mn(III)-based oxidative fragmentation–cyclization of ethynyl cyclobutanol **25** provided an efficient route to the key methylenecyclopentanone **12**. Addition of methyllithium and Birch reduction completed the synthesis of (−)-silphiperfol-6-ene **10**. Formation of dienyl triflate **29** and palladium-catalyzed carbonylation concluded the first synthesis of (−)-methyl cantabradienate (**11**).

Introduction

We recently reported a Mn(III)-based oxidative fragmentation–cyclization sequence that converts vinyl and ethynyl cyclobutanols to 2-methylenecyclopentanones and 2-cyclohexenones as shown in eqs 1 and 2.[1] Oxidation of a vinyl cyclobutanol such as **1** with Mn(III) gave tertiary radical **2** that underwent 5-*exo* cyclization to yield **3**, which was oxidized by Cu(II) to give 2-methylenecyclopentanone **4**. Rearrangement of β-keto radical **3** afforded β-keto radical **5**, which was oxidized by Cu(II) to give cyclohexenone **6**. 6-*endo*-Cyclization of **2** provided α-keto radical **7**, which was not oxidized, and instead dimerized and abstracted a hydrogen atom to give the saturated ketone. 2-Methylenecyclopentanones were produced selectively from some vinyl cyclobutanols. Other cyclobutanols, including **1**, gave complex mixtures of products as shown in eq 1. We therefore developed an alternate route to 2-methylenecyclopentanones from ethynyl cyclobutanols. Oxidative fragmentation and cyclization of **8** with Mn(III) afforded β-keto vinyl radical **9**, which abstracted a hydrogen to give 45% of **4**.



The ring expansion of cyclobutanones to form 2-methylenecyclopentanones should be generally useful for the synthesis of triquinane sesquiterpenes since the requisite cyclobutanones are readily available by intramolecular ketene [2 + 2] cycloadditions.[2,3] We report here the use of this strategy for short and efficient syntheses of two members of the silphiperfolane family, (−)-silphiperfol-6-ene (**10**), and (−)-methyl cantabradienate (**11**). (−)-Silphiperfol-6-ene (**10**) was isolated from the roots of *Silphium perfoliatum* by Bohlmann in 1980[4] and has been synthesized several times in racemic[5] and optically pure form.[6] (−)-Methyl cantabradienate (**11**) was isolated by San Feliciano from *Artemisia cantabrica* in 1986[7] and has not been synthesized.[8]

Both **10** and **11** should be available from methylenecyclopentanone **12** in only two steps. Addition of methyllithium to **12** and reduction should yield silphiperfol-6-ene (**10**). Formation of the dienyl triflate and palladium-catalyzed carbonylation should provide methyl cantabradienate (**11**). Methylenecyclopentanone **12** will be prepared from cyclobutanone **13** by Mn(III) oxidation of the vinyl or ethynyl cyclobutanol as discussed above (see eq 1 and 2).[1] Cyclobutanone **13** should be readily available by intramolecular [2 + 2] cycloaddition of the ketene generated by base treatment of acid chloride **16**. Conjugate addition of the isopentenyl anion to 3-methyl-1-cyclopentenecarboxaldehyde (**17**) will provide a simple route to **16**.

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1994.

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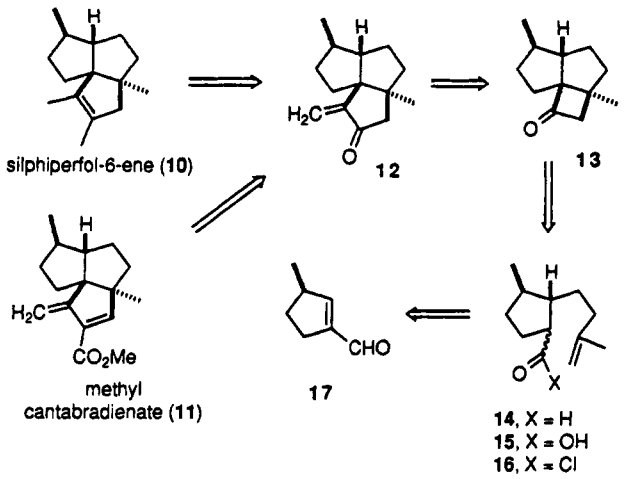
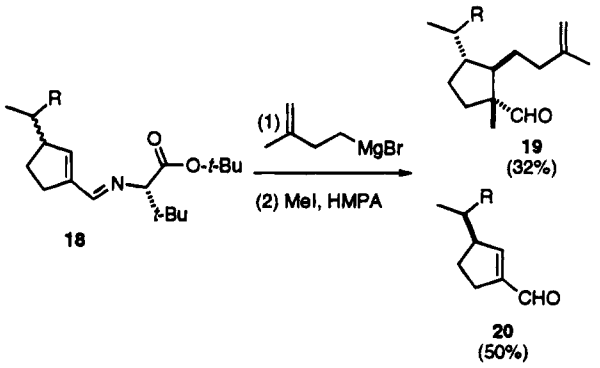
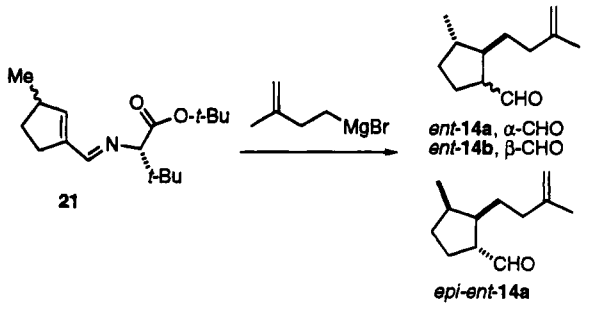


Results and Discussion

Tomioka and Koga developed a very efficient approach for the formation of optically pure 2-vinyl- and 2-arylcyclopentanecarboxaldehydes by addition of Grignard reagents to the imine prepared from 1-cyclopentenecarboxaldehyde and *tert*-leucine *tert*-butyl ester.[9] In our synthesis of (−)-reiswigin A we found that this reaction occurred with a high degree of kinetic resolution.[10,11] Addition of isopentenylmagnesium bromide to **18** (1:1 diastereomeric mixture) followed by methylation and hydrolysis of the imine afforded 32% (64% based on the proper diastereomer) of **19** and 50% of unreacted enal, which was highly enriched in the unreactive enantiomer **20**. The *tert*-butyl group on the imine directed addition to the top face. Addition occurred readily if the cyclopentane substituent was on the bottom face. Grignard addition was very slow if there was a bulky substituent on the top face of the cyclopentane so that unreacted resolved enal **20** was recovered.



We initially investigated the preparation of *ent*-**14** from the imine **21**, which was prepared in quantitative yield from racemic 3-methyl-1-cyclopentenecarboxaldehyde[12] and the less expensive *L*-*tert*-leucine *tert*-butyl ester. Addition of isopentenylmagnesium bromide to imine **21** at −35 °C provided an inseparable 12:1:1 mixture of *ent*-**14a**, *ent*-**14b**, and *epi*-*ent*-**14a** in 33% yield. The stereochemistry was assigned based on the chemical shifts of the methyl doublet at δ 1.03, 1.01 and 0.86, respectively.[13] The methyl was shifted upfield in the isomer with the methyl group cis to the isopentenyl side chain. This mixture was carried through to (+)-silphiperfol-6-ene as described below for the (−)-isomer. A 13:1 mixture of diastereomers at the methyl bearing carbon was obtained. At no point in the sequence could the diastereomers be separated.



These results indicate the limits of kinetic resolution using the Koga procedure. The large substituent on the cyclopentene in **18** effectively blocked addition from that face. The smaller methyl group of **21** hindered but did not completely prevent addition from that face so that kinetic resolution was less effective and a 13:1 mixture of *ent*-**14** and *epi*-*ent*-**14** was obtained.

We therefore prepared imine **22** as a single stereoisomer with the proper absolute stereochemistry in quantitative yield from (*R*)-3-methyl-1-cyclopentenecarboxaldehyde[14] and *D*-*tert*-leucine *tert*-butyl ester. Since both the methyl and *tert*-butyl groups direct addition to the bottom face, addition of isopentenylmagnesium bromide to imine **22** provided 65% of a 20:1 mixture of aldehydes **14a** and **14b**. Oxidation of this mixture with PDC in DMF[15] afforded 84% of a 20:1 mixture of acids **15a** and **15b**. Acid chlorides **16a** and **16b** prepared from the mixture of acids with oxalyl chloride were added to DMAP and Et(*i*-Pr)$_2$N in toluene at reflux[2,3,16] to generate ketene **23**, which underwent intramolecular cyclization to give 79% of the required cyclobutanone **13**.

We initially examined procedures for the conversion of vinyl cyclobutanol **24** to methylenecyclopentanone **12**. Addition of **13** to vinyllithium at −78 °C yielded 92% of **24** as a 2:1 epimeric mixture. Unfortunately, oxidation of **24** with 2 equiv Mn(OAc)$_3$ and 1 equiv of Cu(OAc)$_2$ in EtOH[1] provided a low yield of a 1:1 mixture of **12** and the cyclohexenone analogous to **6**.

Clark reported the palladium-catalyzed oxidative rearrangement of vinyl cyclobutanols to give 2-methyl-2-cyclopentenones that proceeded through 2-methylenecyclopentanones.[17] This reaction has been used several times for the preparation of 2-methylenecyclopentanones in systems in which isomerization of the double bond into the ring was blocked by disubstitution.[18] Reaction of **24** with 1 equiv of PdCl$_2$(C$_6$H$_5$CN)$_2$ as previously described[17]

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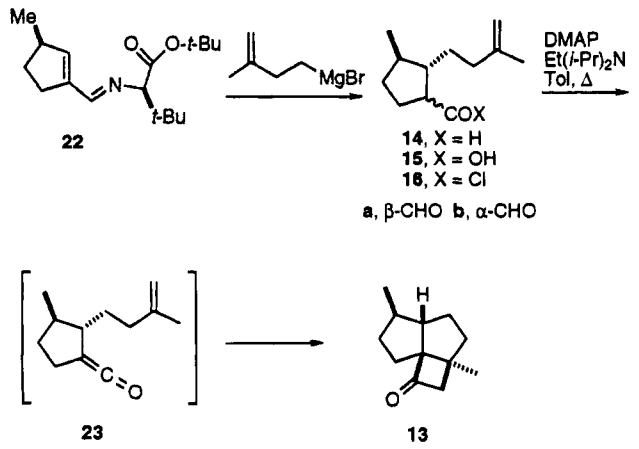
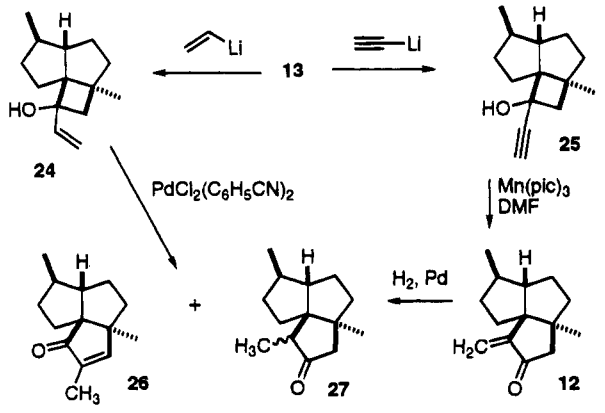


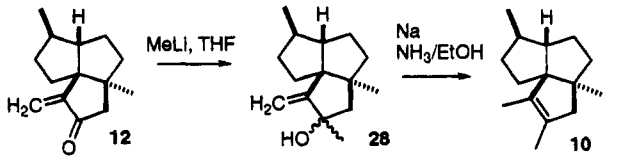
gave an 8:2:10:1 mixture of **12**, **26**, and a mixture of the two stereoisomers of **27**, respectively. The formation of **26** indicates that, contrary to previous reports,[17,18] the more substituted carbon does not migrate regiospecifically. The structure of **27** was confirmed by hydrogenation of **12** over Pd/C which gave 99% of **27** in the same isomeric ratio. Presumably **12** is hydrogenated during the reaction by $HPdXL_2$, as has been observed previously in a single example.[17]

Pd can be used in catalytic amounts if benzoquinone is used to oxidize $HPdXL_2$ to PdX_2L_2.[17] Hydrogenation should be less of a problem under these conditions. Oxidative rearrangement of **24** with 5 mol % of $PdCl_2(C_6H_5CN)_2$ and 2 equiv of benzoquinone in THF at reflux for 2 d gave 64% of a 30:5:10:1 mixture of **12**, **26**, and a mixture of the two stereoisomers of **27**, respectively. This procedure produced less **27** but was still not attractive so we turned our attention to the rearrangement of ethynyl alcohol **25**.

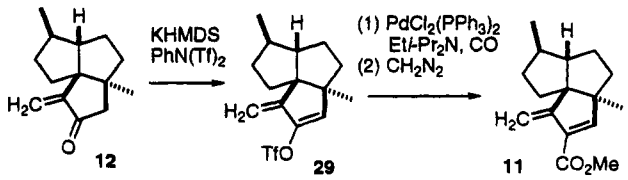


Addition of cyclobutanone **13** to lithium acetylide ethylenediamine complex provided a 1:1 mixture of unreacted **13** and **25** which was resubjected to the reaction conditions to afford 79% (83% based on recovered **13**) of **25** as a 2:1 mixture of epimers. Treatment of **25** with $Mn(OAc)_3$ in ethanol at reflux as previously described[1] provided **12** in 46% yield. Use of $Mn(pic)_3$ in DMF[19] at 100 °C provided 58% of **12**.

(−)-Silphiperfol-6-ene (**10**) was prepared from **12** in two steps. Addition of **12** to excess methyllithium provided 47% (93% based on recovered **12**) of allylic alcohol **28** as a mixture of diastereomers. Reduction with excess Na in NH_3/EtOH[20] gave 69% of **10** as a volatile colorless oil with spectral data identical to that previously described and comparable optical rotation.[4-6]



The first synthesis of (−)-methyl cantabradienate (**11**) was also completed in two steps from **12**. Enolization of **12** with KHMDS at −78 °C followed by quenching with *N*-phenyltrifluoromethanesulfonimide[21] provided 85% of **29**. $PdCl_2(PPh_3)_2$ catalyzed carbonylation[22] of **29** in THF/MeOH furnished a mixture of **11** and the carboxylic acid that was treated with diazomethane to provide 53% of **11**. The spectral data of **11** were identical to those of the natural product.[7,23] The optical rotation, $[\alpha]^{23}_D$ = −56.7°, was identical in sign, but much larger than that reported for the natural product, $[\alpha]^{24}_D$ = −22.3°.



In conclusion, (−)-silphiperfol-6-ene and (−)-methyl cantabradienate have been prepared in only seven steps from (*R*)-3-methyl-1-cyclopentenecarboxaldehyde in 13 and 9% overall yield, respectively. The use of an intramolecular [2 + 2] ketene cycloaddition followed by Mn(III)-based oxidative rearrangement of an ethynyl cyclobutanol provided a very efficient route to the key methylenecyclopentanone **12**.

Experimental Section

General. NMR spectra were taken in $CDCl_3$. Chemical shifts are reported in δ and coupling constants are reported in hertz.

Preparation of Imine 22. A slurry of *D-tert*-leucine *tert*-butyl ester (487 mg, 2.55 mmol), (*R*)-3-methyl-1-cyclopentenecarboxaldehyde[14] (284 mg, 2.58 mmol), and 4 Å molecular sieves in hexane (13 mL) was stirred for 15 h at rt. The reaction mixture was filtered through a thin layer of Celite and concentrated under reduced pressure providing 707 mg (100%) of imine **22**: ^{1}H NMR 7.98 (s, 1), 6.07 (d, 1, J = 1.7), 3.37 (s, 1), 2.96−2.82 (m, 1), 2.80−2.68 (m, 1), 2.58−2.45 (m, 1), 2.16 (dddd, 1, J = 4.4, 8.7, 8.7, 12.8), 1.20−1.05 (m, 1), 1.46 (s, 9), 1.07 (d, 3, J = 7.0), 0.97 (s, 9); ^{13}C NMR 170.9, 159.7, 145.9, 143.6, 83.1, 80.8, 40.6, 35.0, 31.9, 30.3, 28.2, 26.8, 20.4; IR (neat) 2956, 2868, 1740, 1639, 1610, 1478, 1456, 1392, 1367, 1282, 1255, 1214, 1142, 1081, 847; $[\alpha]^{23}_D$ = +175.7° (*c* 1.0, $CHCl_3$).

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(23) We thank Professor San Feliciano for copies of the ^{1}H NMR and ^{13}C NMR spectral data. The peak reported in ref 7 at δ 107.02 in the ^{13}C NMR is a typographical error. The actual absorption is δ 157.02.

Imine 21 was prepared analogously as a 1:1 mixture from (±)-3-methyl-1-cyclopentenecarboxaldehyde[13] with *L-tert*-leucine *tert*-butyl ester. The data for the epimer of the enantiomer of **22** were determined from the mixture: ^{1}H NMR 7.98 (s, 1), 6.07 (d, 1, J = 2), 3.37 (s, 1), 2.96–2.82 (m, 1), 2.80–2.44 (m, 2), 2.24–2.10 (m, 1), 1.20–1.05 (m, 1), 1.45 (s, 9), 1.09 (d, 3, J = 7.0), 0.98 (s, 9); ^{13}C NMR 170.9, 159.6, 145.9, 143.7, 83.0, 80.6, 40.5, 35.0, 31.9, 30.3, 28.1, 26.8, 20.3.

Preparation of 14a and 14b. Isopentenylmagnesium bromide (16.9 mL of 0.5 M in ether, 8.44 mmol) was added to a solution of **22** (590 mg, 2.11 mmol) in THF (30.0 mL) at −78 °C. The reaction mixture was stirred at −35 °C for 24 h and then acidified with ice-cold 10% citric acid solution. The resulting solution was stirred at rt for 30 min and extracted with ether (2 × 30 mL). The combined ether layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (98:2 hexane/EtOAc) provided 249 mg (65%) of a 20:1 mixture of **14a** and **14b**: ^{1}H NMR (**14a**) 9.58 (d, 1, J = 3.3), 4.71 (br s, 1), 4.66 (br s, 1), 2.51–2.42 (m, 1), 2.10–1.97 (m, 2), 1.95–1.59 (m, 6), 1.71 (br s, 3), 1.51–1.36 (m, 1), 1.32–1.18 (m, 1), 1.03 (d, 3, J = 6.2); (**14b**) ^{1}H NMR 9.76 (d, 1, J = 3.9), 1.01 (d, 3, J = 6); ^{13}C NMR 203.9, 145.5, 110.0, 58.2, 47.6, 41.2, 36.0, 34.3, 32.0, 25.4, 22.4, 19.0; IR (neat) 3074, 2953, 2869, 2707, 1723, 1649, 1451, 1376, 886; $[\alpha]^{23}_D$ = −28.3° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.58; H, 11.51.

An identical reaction carried out on **21** afforded a 12:1:1 mixture of *ent*-**14a**, *ent*-**14b** ,and *epi-ent*-**14a**, respectively, in 33% yield: ^{1}H NMR (*epi-ent*-**14a**) 9.56 (d, 1, J = 3.4), 0.86 (d, 3, J = 7.0).

Preparation of 15. PDC (1.02 g, 2.66 mmol) was added to a solution of **14a** and **14b** (239 mg, 1.33 mmol) in DMF (6 mL). The reaction mixture was stirred at rt under nitrogen for 1 d, diluted with H_2O (30 mL), and extracted with ether (2 × 30 mL). The combined ether layers were washed with brine (3 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (8:2 hexane/EtOAc) provided 218 mg (84%) of an approximately 20:1 mixture of **15a** and **15b**: ^{1}H NMR (**15a**) 4.69 (br s, 1), 4.67 (br s, 1), 2.54–2.44 (m, 1), 2.04 (apparent br dd, 2, J = 7, 7), 1.94–1.56 (m, 6), 1.72 (br s, 3), 1.50–1.31 (m, 2), 1.03 (d, 3, J = 6.3); (**15b**) 0.95 (d, 3, J = 6.4); ^{13}C NMR 183.6, 145.9, 109.7, 50.9, 50.1, 40.8, 35.6, 34.3, 32.2, 29.2, 22.5, 19.2; IR (neat) 3075, 2953, 2870, 1702, 1650, 1449, 1423, 1376, 1291, 1224, 945, 886; $[\alpha]^{23}_D$ = +8.3° (*c* 0.80, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.77; H, 10.56.

Preparation of Cyclobutanone 13. Oxalyl chloride (0.51 mL, 5.79 mmol) was added to a solution of the mixture of **15a** and **15b** (190 mg, 0.97 mmol) in ether (2 mL) at 0 °C. The mixture was stirred at rt for 30 min and then at reflux for an additional 30 min. Solvent and excess oxalyl chloride were removed under reduced pressure. The resulting crude acid chloride in 10 mL of dry toluene was added to a refluxing solution of DMAP (24 mg, 0.19 mmol) and Et*i*-Pr$_2$N (756, 5.79 mmol) in toluene (20 mL). The reaction was heated at reflux for 36 h, cooled to rt, diluted with ether (20 mL), washed with H_2O (3 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (49:1 hexane/EtOAc) provided 136 mg (79%) of pure **13**: ^{1}H NMR 2.83 (d, 1, J = 17.8), 2.53 (d, 1, J = 17.8), 2.04 (br dd, 1, J = 6.7, 10.1), 1.94 (ddd, 1, J = 2.2, 8.7, 14.0), 1.92–1.64 (m, 5), 1.58–1.38 (m, 2), 1.35–1.24 (m, 1), 1.21 (s, 3), 0.97 (d, 3, J = 6.3); ^{13}C NMR 214.8, 82.0, 59.7, 54.0, 41.1, 40.0, 38.2, 35.9, 26.8, 25.8, 21.3, 18.0; IR (neat) 2948, 2867, 1768, 1456, 1393, 1376, 1245, 1105, 1040; $[\alpha]^{23}_D$ = +78.9° (*c* 1.0, $CHCl_3$).

Preparation of Vinyl Cyclobutanol 24. A solution of cyclobutanone **13** (30 mg, 0.17 mmol) in THF (2 mL) was added dropwise to a solution of vinyllithium (0.56 mL of 1.5 M in THF, 0.84 mmol) at −78 °C over 30 min. The reaction was quenched by addition of a saturated NH_4Cl solution. The resulting mixture was diluted with ether (20 mL), washed with H_2O (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (49:1 hexane/EtOAc) provided 32 mg (92%) of **13** as a 2:1 mixture of epimers: ^{1}H NMR (major) 6.05 (dd, 1, J = 10.7, 17.2), 5.22 (dd, 1, J = 1.4, 17.2), 5.05 (dd, 1, J = 1.4, 10.7), 2.11 (dd, 1, J = 8, 8), 1.98–1.80 (m, 1), 1.93 (d, 1, J = 12.7), 1.83 (d, 1, J = 12.7), 1.74–1.32 (m, 7), 1.16–1.02 (m, 1), 1.07 (s, 3), 0.98 (d, 3, J = 6.5); (minor) 5.88 (dd, 1, J = 10.7, 17.2), 5.13 (dd, 1, J = 1.4, 17.2), 5.06 (dd, 1, J = 1.4, 10.7), 2.09 (d, 1, J = 12.7), 1.88 (d, 1, J = 12.7), 1.22 (s, 3), 0.93 (d, 3, J = 6.5); ^{13}C NMR (major) 144.2, 109.9, 73.0, 65.4, 54.6, 43.6, 41.0, 39.9, 39.2, 35.3, 28.2, 28.1, 22.2, 19.5; (minor) 140.9, 112.2, 75.9, 65.6, 56.0, 44.4, 41.3, 40.4, 38.2, 34.9, 27.4, 25.3, 23.2, 19.3; IR (neat) 3406, 3086, 3012, 2948, 2864, 1639, 1454, 1374, 1245, 1105, 1018, 997, 973, 916. Anal. Calcd for $C_{12}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.24; H, 11.04.

Preparation of Ethynyl Cyclobutanol 25. A solution of ketone **13** (130 mg, 0.73 mmol) in THF (3 mL) was added dropwise to a suspension of lithium acetylide ethylenediamine complex (747 mg, 90% pure, 7.30 mmol) in THF (4 mL) at rt. Upon completion of the addition, the reaction mixture was quenched at 0 °C with ice-cold saturated NH_4Cl solution. The resulting solution was diluted with ether (70 mL), washed with H_2O (3 × 20 mL) and then with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue, consisting of an approximately 1:1 mixture of **13** and **25**, was added to lithium acetylide again. Flash chromatography on silica gel (19:1 hexane/EtOAc) provided 7 mg of recovered **13** and 116 mg (83% based on recovered **13**) of **25** as a 2:1 mixture of epimers: ^{1}H NMR (major) 2.62 (s, 1), 2.19–1.76 (series of m, 3), 2.11 (d, 1, J = 12.4), 1.94 (d, 1, J = 12.4), 1.73–1.52 (m, 3), 1.51–1.30 (m, 3), 1.23–1.09 (m, 1), 1.13 (s, 3), 0.98 (d, 3, J = 6.4); (minor) 2.14 (d, 1, J = 13.0), 1.82 (d, 1, J = 13.0), 1.16 (s, 3), 0.98 (d, 3, J = 6.4); ^{13}C NMR (major) 87.8, 73.5, 67.9, 65.4, 53.6, 44.9, 44.7, 41.1, 38.5, 35.4, 29.9, 27.9, 22.0, 19.2; (minor) 85.0, 74.1, 69.6, 65.6, 58.0, 45.3, 41.7, 40.2, 38.4, 34.8, 27.2, 25.3, 23.0, 19.2; IR (neat) 3413, 3307, 2948, 2865, 2107, 1454, 1428, 1374, 1213, 1067, 1046, 976, 940. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.05; H, 10.25.

Oxidation of Vinyl Cyclobutanol 24 with $PdCl_2(C_6H_5CN)_2$.[17,18] $PdCl_2(C_6H_5CN)_2$ (30 mg, 0.078 mmol) was added to a solution of **24** (16 mg, 0.078 mmol) in THF (0.5 mL). The reaction was stirred for 1 h at rt and quenched by addition of H_2O (3.0 mL). The resulting aqueous solution was extracted with ether (2 × 5 mL). The combined ether layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Benzonitrile, which coeluted with the product on chromatography, was removed by repeated azeotropic distillation with benzene under reduced pressure. Chromatography on silica gel (49:1 hexane/EtOAc) gave 12 mg (75%) of an 8:2:10:1 mixture of **12**, **26**, and the two diastereomers of **27**, respectively.

A similar reaction carried out using 5 mol % of $PdCl_2(C_6H_5CN)_2$ and benzoquinone (2 equiv) at reflux for 2 d gave 64% of a 30:5:10:1 mixture of **12**, **26**, and the two diastereomers of **27**, respectively.

Partial data for **26**: ^{1}H NMR 6.90 (q, 1, J = 1.4), 1.74 (d, 1, J = 1.4); ^{13}C NMR 164.4, 138.9.

Oxidation of Ethynyl Cyclobutanol 25 with Mn(III). $Mn(Pic)_3$ (512 mg, 1.47 mmol) was added to a solution of **25** (100 mg, 0.49 mmol) in degassed DMF (12 mL) at rt. The reaction mixture was heated to 100 °C for 3 h and cooled to rt, and H_2O (12 mL) was added. The resulting solution was extracted with ether (2 × 30 mL). The combined ether layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel (49:1 hexane/EtOAc) to provide 58 mg (58%) of pure **12**: ^{1}H NMR 5.93 (d, 1, J = 0.8), 5.26 (d, 1, J = 0.8), 2.39 (d, 1, J = 19.0), 2.13 (d, 1, J = 19.0), 1.96–1.85 (m, 2), 1.84–1.75 (m, 2), 1.73–1.56 (m, 4), 1.46–1.33 (m, 2), 1.04 (d, 3, J = 6.5), 1.02 (s, 3); ^{13}C NMR 208.1, 156.4, 115.7, 64.8, 62.4, 49.6, 47.3, 44.6, 37.5, 37.2, 35.7, 29.6, 22.8, 19.6; IR (neat) 2948, 2867, 1725, 1633, 1454, 1405, 1377, 1313, 1277, 1262, 1229, 1121, 932; $[\alpha]^{23}_D$ = +62.1° (*c* 1.2, $CHCl_3$).

Hydrogenation of Methylenecyclopentanone 12. A mixture of **12** (20 mg, 0.098 mmol) and 10% Pd/C (4 mg) in ether (4 mL) was stirred at rt under H_2 (1 atm) for 1 h. The solution was filtered through a thin layer of silica gel to remove

Pd/C and concentrated under reduced pressure to afford 20 mg (99%) of an inseparable 10:1 mixture of the diastereomers of **27**: ^{1}H NMR (major) 2.47 (dq, 1, J = 2.0, 6.9), 2.18 (dd, 1, J = 2.0, 19.4), 2.06 (d, 1, J = 19.4), 1.86−1.45 (m, 8), 1.38−1.24 (m, 1), 1.20−1.10 (m, 1), 1.17 (s, 3), 1.04 (d, 3, J = 6.9), 1.00 (d, 3, J = 6.5) (minor) 2.18 (d, 1, J = 19.0), 2.10 (d, 1, J = 19.0), 1.10 (s, 3), 1.07 (d, 3, J = 7), 1.01 (d, 3, J = 6.5); ^{13}C NMR (major) 218.3, 63.4, 62.6, 53.6, 51.0, 49.4, 46.5, 44.7, 37.9, 35.9, 35.2, 29.3, 23.1, 19.1, 10.4 (minor) 63.4, 50.9, 49.9, 44.4, 40.1, 36.8, 29.7, 28.5, 24.3, 20.0, 12.4; IR (neat) 2946, 2866, 1740, 1460, 1407, 1376, 1176.

Preparation of Allylic Alcohol 28. A solution of **12** (55 mg, 0.27 mmol) in THF (2 mL) was added dropwise to MeLi (0.96 mL of 1.4 M in ether, 1.35 mmol) at −78 °C over 15 min. Upon completion of the addition, the reaction mixture was quenched with saturated NH_4Cl solution. The resulting solution was extracted with ether (2 × 20 mL). The combined ether layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel (19:1 hexane/EtOAc) to give 27 mg of unreacted **12** followed by 28 mg (47%; 93% based on recovered **12**) of **28** as a 2:1 mixture of epimers: ^{1}H NMR (major) 5.05 (s, 1), 4.96 (s, 1), 1.92−1.20 (m, 10), 1.37 (s, 3), 1.19−0.92 (m, 2), 1.14 (s, 3), 1.01 (d, 3, J = 6.5); (minor) 5.03 (s, 1), 4.92 (s, 1), 1.39 (s, 3), 1.01 (d, 3, J = 6.5), 0.99 (s, 3); ^{13}C NMR (major) 171.7, 104.6, 79.2, 67.4, 64.0, 52.2, 50.7, 43.0, 39.1, 37.1, 37.0, 28.8, 28.5, 24.4, 19.7; (minor) 171.0, 104.0, 78.7, 66.7, 64.5, 53.8, 49.5, 42.8, 40.2, 36.1, 30.2, 28.4, 24.5, 19.6 (one carbon not observed); IR (neat) 3406, 3075, 2950, 2867, 1746, 1648, 1461, 1375, 1166, 893.

Preparation of (−)-Silphiperfol-6-ene (10). Na (58 mg, 2.54 mmol) was added to a solution of **28** (28 mg, 0.127 mmol) in EtOH (0.1 mL), pentane (1.0 mL), and NH_3 (4.0 mL) at −78 °C. The reaction mixture was allowed to warm to −33 °C under a Dewar condenser. The blue color disappeared after 3 h. NH_3 was then allowed to evaporate slowly. The resulting mixture was diluted with pentane (20 mL), washed with H_2O (3 × 5 mL) and brine (2 × 5 mL), dried ($MgSO_4$), and filtered through a short column of silica gel with pentane as eluent. Pentane was removed under reduced pressure at 0 °C to provide 18 mg (69%) of pure (−)-Silphiperfol-6-ene as a volatile colorless oil: ^{1}H and ^{13}C NMR and IR spectra are identical to those described in literature;[4−6] $[\alpha]^{23}_D$ = −69.9° (c 0.74, $CHCl_3$); {lit.[4] $[\alpha]^{25}_D$ = −92.8° (c 0.80, $CHCl_3$); lit.[6a] $[\alpha]^{23}_D$ = −34.2° (c 3.05, $CHCl_3$); lit.[6b] $[\alpha]^{21}_D$ = −74.06° (c 1.01, $CHCl_3$); lit.[6c] $[\alpha]_D$ = −79°}.

We also carried the mixture of *ent*-**14a**, *ent*-**14b**, and *epi-ent*-**14a** through the above sequence to obtain a 13:1 mixture of *ent*-silphiperfol-6-ene and *ent*-9-*epi*-silphiperfol-6-ene:[7] the spectral data of the major component are identical to those of **10**; $[\alpha]^{23}_D$ = +68.9° (c 1.32, $CHCl_3$). Partial data for *ent-epi*-silphiperfol-6-ene: ^{1}H NMR 2.07 (br s, 2). This absorption has been reported in the ^{1}H NMR spectrum of *epi*-silphiperfol-6-ene.[5b,6b]

Preparation of Dienyl Triflate 29. A solution of **12** (26 mg, 0.13 mmol) in THF (1 mL) was added slowly to a solution of KHMDS (0.38 mL of 0.5 M in toluene, 0.19 mmol) in THF (1 mL) at −78 °C. The mixture was stirred for 10 min and solid *N*-phenyltrifluoromethanesulfonimide (64 mg, 0.18 mmol) was added. The resulting mixture was stirred at −78 °C for 30 min, quenched by addition of saturated NH_4Cl, and extracted with ether (2 × 10 mL). The combined ether layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica (199:1 hexane/EtOAc) to give 36 mg of **29** (85%): ^{1}H NMR 5.88 (d, 1, J = 1.3), 4.99 (s, 1), 4.88 (d, 1, J = 1.3), 1.89−1.64 (m, 5), 1.61−1.25 (m, 5), 1.09 (s, 3), 1.00 (d, 3, J = 6.3); ^{13}C NMR 155.1, 131.3, 101.8, 64.7, 63.5, 55.0, 41.5, 37.0, 35.7, 33.2, 27.8, 21.9, 19.2 (2 C were not observed); IR (neat) 2952, 2869, 1615, 1460, 1426, 1248, 1213, 1143, 1072, 1044, 894, 878; $[\alpha]^{23}_D$ = −35.5° (c 1.5, $CHCl_3$).

Preparation of Methyl Cantabradienate (11). A solution of **29** (26 mg, 0.077 mmol) and Et*i*-Pr_2N (16 mg, 0.12 mmol) in THF (2 mL) and MeOH (1 mL) was purged for 5 min with CO. $Pd(Cl)_2(PPh_3)_2$ (17 mg of 98%, 0.023 mmol) was added and the mixture was heated to reflux for 24 h with CO being bubbled through the solution. The reaction mixture was cooled to rt, diluted with ether (20 mL), washed with 1 N HCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was treated with a freshly prepared solution of diazomethane in ether to convert any carboxylic acid to the methyl ester. Excess diazomethane was quenched with HOAc. The reaction mixture was diluted with ether (20 mL) and worked up as described above. The residue was chromatographed on silica gel (99:1 hexane/EtOAc) to give 10 mg (53%) of pure (−)-methyl cantabradienate (**11**) as a yellow oil: ^{1}H NMR 6.68 (d, 1, J = 1.4), 5.63 (s, 1), 4.96 (d, 1, J = 1.4), 3.77 (s, 3), 1.87−1.78 (m, 2), 1.75−1.65 (m, 3), 1.59−1.25 (m, 5), 1.04 (s, 3), 0.98 (d, 3, J = 6.1); ^{13}C NMR 164.6, 159.1, 157.2, 133.4, 104.8, 66.0, 64.9, 57.5, 51.3, 41.7, 37.1, 36.0, 33.5, 28.2, 21.0, 19.2; IR (neat) 2949, 2865, 1726, 1632, 1600, 1456, 1436, 1350, 1247, 1203, 1065, 1047, 883; $[\alpha]^{23}_D$ = −56.7° (c 0.45, $CHCl_3$) {lit.[7] $[\alpha]^{24}_D$ = −22.3° (c 0.5, $CHCl_3$)}. The ^{1}H NMR and ^{13}C NMR spectra are identical to those of the natural product.[23]

Acknowledgment. We are grateful to the National Institutes of Health for generous financial support.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **10**−**13**, **22**, **28**, and **29** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.