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Synthesis of a Cancer Growth-Inhibiting Diterpene—Stereoselective Formal Synthesis of (+)-Aphidicolin

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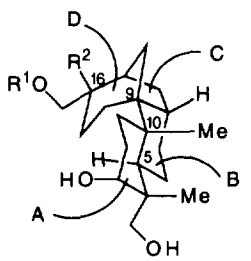
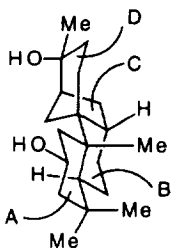
Abstract: Stereoselective formal synthesis of the diterpene tetraol (+)-aphidicolin (**1**) is described employing as key steps the cycloisomerization of the enyne **9** to provide the bicyclo[3.2.1]octane derivative **8** and the intramolecular Diels-Alder reaction of the triene **7** to form the aphidicolane-type ring system. This route is, in principal, highly stereocontrolled and extremely efficient.

Introduction

The structure of a tetracyclic diterpenoid antibiotic, aphidicolin (**1**), isolated from *Cephalosporium aphidicola*[1] and later found to occur in *Nigrospora sphaerica*,[2] was reported in 1972 by Hesp and his co-workers[1,3] and shortly thereafter, several related diterpenes (e.g. stemodin (**4**)) isolated from *Stemodia maritima* were described.[4,5] The relationship between aphidicolin (**1**) and stemodin (**4**) is a topographical one[6] (i.e. identical ring system but epimeric at C-9 and C-12). The fusion of the five-membered C ring to B in stemodin (**4**) is *cis*, however, in contrast to the *trans* fusion in aphidicolin (**1**).



R^1 = H, R^2 = OH; Aphidicolin (**1**)
R^1 = $COCH_2NH_2 \cdot HCl$, R^2 = OH;
Aphidicolin-17-glycinate HCl salt (**2**)
R^1 = H, R^2 =F; 16-Fluoroaphidicolin (**3**)



Stemodin (**4**)

The novel tetracyclic carbon skeleton of **1** incorporates 8 stereogenic centers and a spiro fused bicyclo[3.2.1]octane moiety which comprises the C and D rings. Not only is C-9 spiro center chiral, it is also next to another quaternary center, C-10. The presence of these two adjacent chiral quaternary centers makes this region of aphidicolin (**1**) quite crowded.

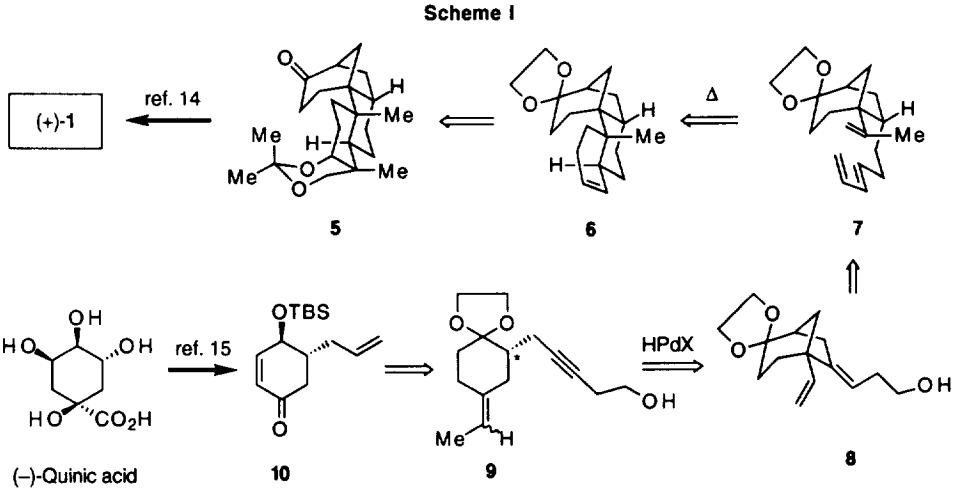
Little is known about the substantial biological activity of stemodin (**4**) itself, however, aphidicolin (**1**) displays marked activity against Herpes simplex.[7] In addition to its antifeedant property,[8] aphidicolin (**1**) inhibits DNA replication and growth of several human and murine neoplastic cells.[9] The poor water solubility of **1** prevented its parenteral administration, but recent report of enhanced antitumor activity associated with the more water-soluble compounds such as aphidicolin-17-glycinate HCl salt (**2**)[10] and 16-fluoroaphidicolin (**3**),[11] synthesized as pro-drug, might revive interest in aphidicolin (**1**) and its analogues as a potential anticancer compound.

During the intervening years since 1972, when the structures of aphidicolin (**1**) and stemodin (**4**) were established, numerous total syntheses for **1** and **4** were reported so far.[12] However, with a few exceptions[12h,12j,12k,12l,12n,12o,13] most of the synthetic studies toward the unusual carbon framework envisaged the ABC + D or ABD + C sequence for forming the ring system. Our group has previously been involved in developing a *de novo* synthesis of these unusual natural products.[12j,12o,13] We have reported recently a formal total synthesis of (±)-aphidicolin (**1**) employing a Heck reaction and an intramolecular Diels-Alder reaction.[12k] After experimentation, however, it was found that the enantioselective construction of CD ring part of **1** can be successfully achieved using palladium catalyzed cycloisomerization under mild conditions in place of the Heck reaction.[12l] In this paper we would like to describe the details of the enantioselective total synthesis of (+)-aphidicolin (**1**).

Synthetic Plan

Since the ketone **5** has already been converted into the natural product **1** by Smith III,[14] the synthesis of **5** completes the task. The novel synthetic strategy contemplated for the present enantioselective approach to (+)-**1** is shown in **Scheme 1**. Access to **5** is provided through the intramolecular Diels-Alder reaction of the triene **7** followed by photosensitized oxygenation of the resulting olefin **6**. The triene **7** is in turn available from the bicyclo[3.2.1]octane derivative **8**, obtainable from the enyne **9** using a palladium catalyzed cycloisomerization reaction. Finally, regioselective introduction of diene and yne portions into the enone **10**[15] was expected to give rise to **9**.

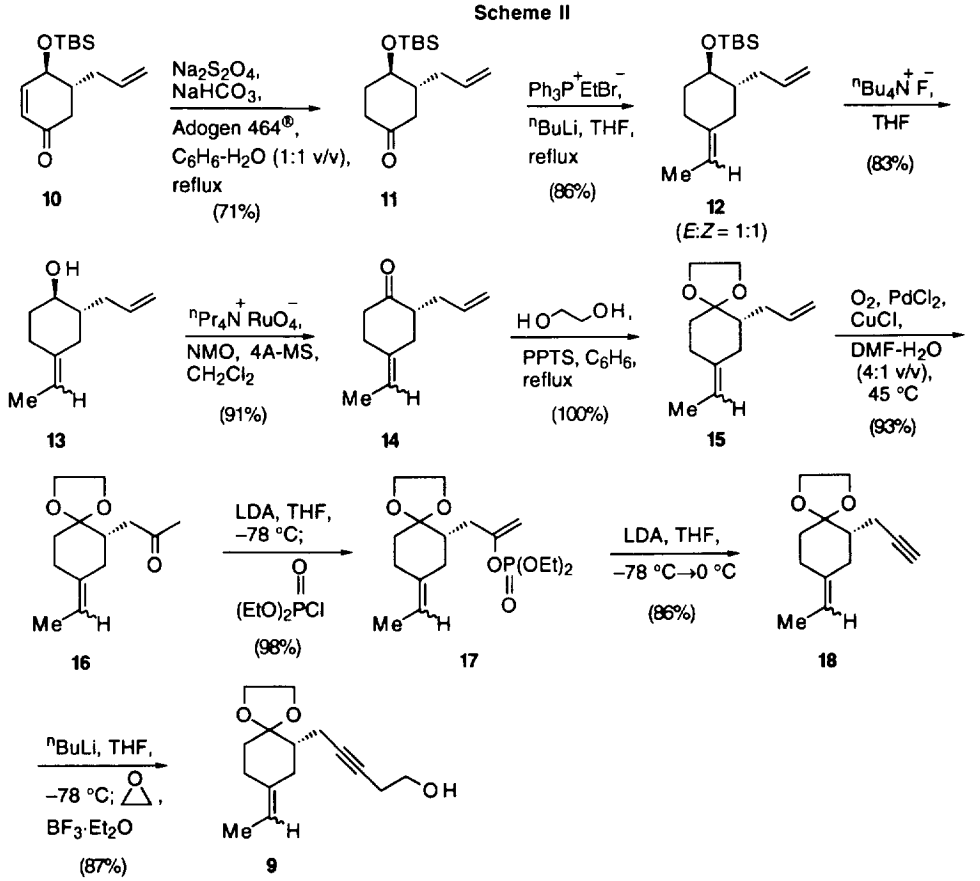
Scheme I



Results and Discussion

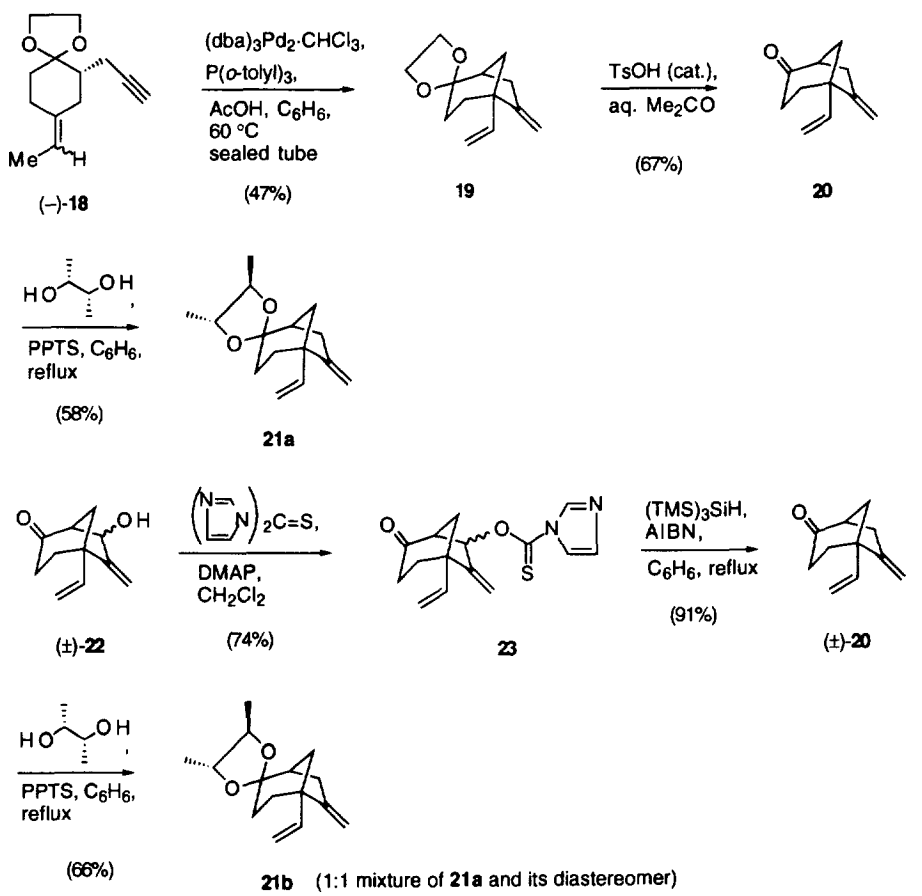
Preparation of the Enyne 9. To prepare the palladium catalyzed cycloisomerization precursor **9**, the readily available optically pure enone **10**, prepared from (–)-quinic acid by means of Overman's protocol,[15] was converted to **9**, as shown in **Scheme II**. Namely, chemoselective reduction of the enone **10** with sodium hydrosulfite[16] in the presence of Adogen 464® and sodium hydrogen carbonate in an equivolume mixture of benzene and water provided the ketone **11** (71%), which was subjected to Wittig reaction ($Ph_3P^+EtBr^-$, ^nBuLi, THF), affording the ethylidene derivative **12** in 86% yield as a 1 : 1 mixture of *E* and *Z* stereoisomers. Stereoselection in this step was of no consequence, since both double bond isomers were converted to the bicyclo[3.2.1]octane compound **8** in good yield upon palladium catalyzed cycloisomerization process. Deprotection (83%) of the TBS group of **12**, followed by oxidation[17] with tetrapropylammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine *N*-oxide (NMO) and 4A-molecular sieves (4A-MS) in dichloromethane furnished, in 91% yield, the ketone **14**, which was transformed into the compound **15** after ketalization (100%). Subsequent conversion to the ketone **16** was accomplished in 93% yield through regioselective Wacker oxidation[18] of **15** with palladium (II) chloride and copper (I) chloride in aqueous DMF under oxygen atmosphere at 45 °C. Several approaches were then explored for introducing the enyne functionality of the side chain. The ultimately successful route is summarized in **Scheme II**.

Scheme II



Treatment of **16** with LDA under kinetic conditions, followed by trapping of the resulting enolate with diethyl chlorophosphate provided the enol phosphonate **17** in 98% yield. When **17** was subjected to basic treatment with LDA, the desired product **18** was obtained in 86% yield. Alkylation of lithium salt of the acetylene **18** was conducted with ethylene oxide by means of Kotsuki's procedure[19] to give rise to **9** in 87% yield. In order to confirm no epimerization in the ketalization process (**14**→**15**), ketalization of the ketone **20**, prepared from (–)-**18** *via* palladium catalyzed cycloisomerization (47%) followed by deprotection (67%), with (2R, 3R)-butanediol was performed. Care was taken with this ketalization to minimize accidental kinetic resolution of the ketal diastereomers. **21a** was appeared to be > 99% pure by direct comparison of its ^{1}H NMR spectrum with that of a diastereomeric mixture synthesized from racemic **20** {prepared from (±)-**22** by means of thioimidazolide formation (74%) followed by radical reduction (91%)} and (2R, 3R)-butanediol (**Scheme III**).

Scheme III

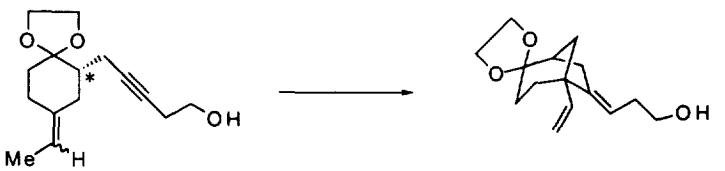


Palladium Catalyzed Cycloisomerization Reaction to Form the C and D Rings of (+)-Aphidicolin. Representative examples of palladium catalyzed cycloisomerization reaction of the enyne **9** are shown in **Table I**. By following Trost's representative protocol,[20] the first attempt to cyclize **9** was performed

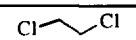
in 1,2-dichloroethane employing 10 mol % of $Pd(OAc)_2$ as catalyst and 10 mol % of *N,N'*-bis(benzylidene)ethylenediamine (BBEDA) as ligand and resulted in formation of the desired bicyclo[3.2.1]octane compound **8** in low yield along with inseparable impurities. Changing the solvent from 1,2-dichloroethane to benzene with the mixed reactant system had a slight effect on the yield, producing **8** (19%). Switching to tris(dibenzylideneacetone)dipalladium(0)chloroform adduct ($(dba)_3Pd_2{\cdot}CHCl_3$) as catalyst further enhanced the yield to 46%. After careful investigation of this reaction, the following procedure was found to be optimal: 5 mol % of AcOH was added to a solution of 2.5 mol % of $(dba)_3Pd_2{\cdot}CHCl_3$, 5 mol % of tri-*o*-tolylphosphine (TOTP) and **9** in benzene and the resulting mixture was heated at 60 °C in a sealed tube for 15 h. This condition resulted in formation of the desired compound **8** in 76% yield.

Table I

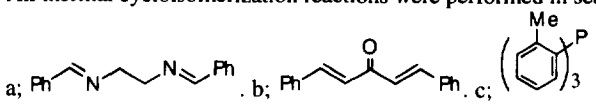
Palladium Catalyzed Cycloisomerization Reaction of the Enyne **9**



9 **8**

entry	catalyst (mol %)	ligand (mol %)	additive (mol %)	solvent	temp. (°C)	time (h)	yield (%)
1	$Pd(OAc)_2$ (10)	BBEDA[a] (10)	——		50	> 168	low
2	$Pd(OAc)_2$ (5)	BBEDA (6)	——	C_6H_6	60	72	19
3	$(dba)_3Pd_2{\cdot}CHCl_3$[b] (5)	Ph_3P (20)	AcOH (40)	C_6H_6	50	9	46
4	$(dba)_3Pd_2{\cdot}CHCl_3$ (2.5)	TOTP[c] (5)	AcOH (5)	C_6H_6	60	15	76

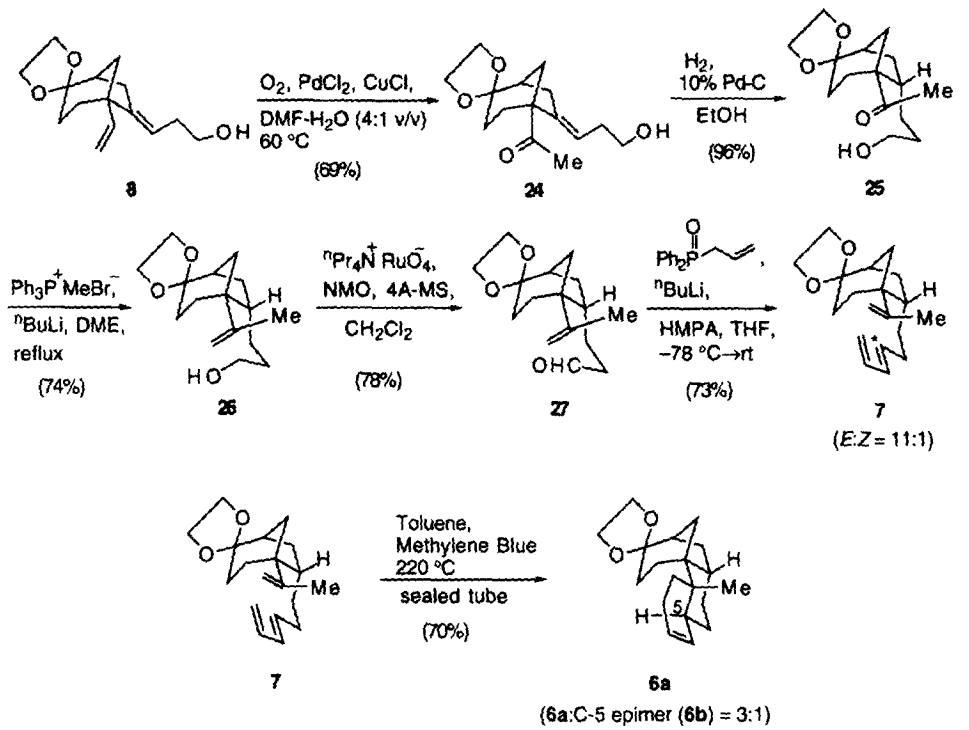
All thermal cycloisomerization reactions were performed in sealed tube.



Preparation of the Triene 7. Having found conditions for the preparation of **8**, the CD ring system of (+)-aphidicolin (**1**), we were now positioned to synthesize the triene **7**. When **8** was subjected to Wacker oxidation, the desired methyl ketone **24** was obtained in 69% yield. Catalytic hydrogenation of **24** in the presence of 10% palladium-charcoal in EtOAc caused reduction of the carbonyl function of **24**, and only the diol product was obtained. Changing the solvent from EtOAc to EtOH had a remarkable effect on chemoselectivity, furnishing the keto alcohol **25** (96%). Wittig olefination (74%) of **25** provided the olefinic alcohol **26**, which was oxidized with TPAP to give the corresponding aldehyde **27** in 78% yield. Subsequent transformation into the triene **7** was accomplished in 73% yield by means of Yamamoto's method.[21] The *E/Z* ratio (11 : 1) of **7** was determined by integration of the resonances due to the olefinic proton in the NMR spectra of reaction mixture. Since separation of the double bond isomers was difficult, this crude product was used directly in the next step. The intramolecular Diels-Alder reaction was performed by heating a mixture of **7**

and a small amount of methylene blue[22] in toluene at 220 °C for 190 h in a sealed tube. This afforded the desired pentacyclic compounds **6** in 70% yield as a 3 : 1 diastereomeric mixture at C-5.

Scheme IV

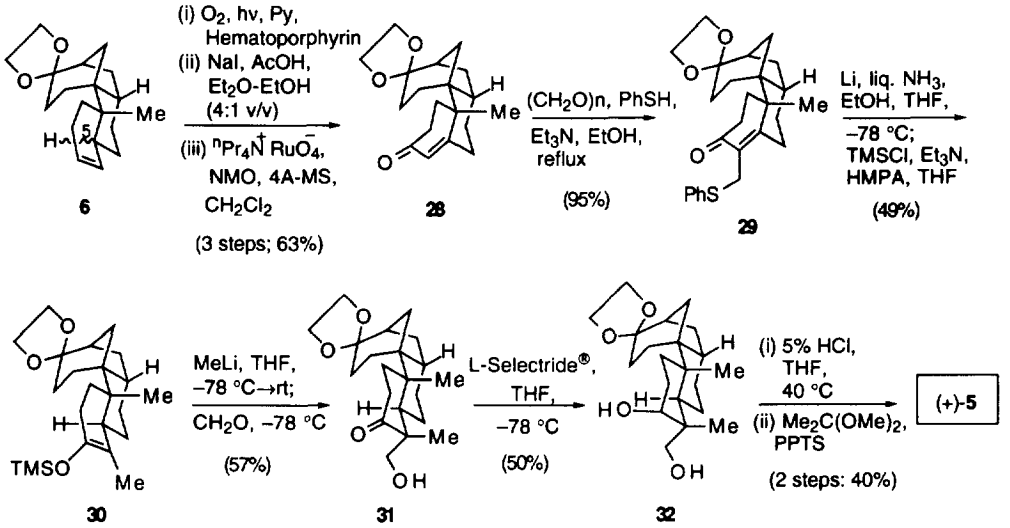


Completion of a Total Synthesis of (+)-Aphidicolin (1). With efficient access to **6** and our previous experience[12j,12k,12l] with the photosensitized oxygenation of **6**, the completion of a total synthesis of (+)-**1** seemed imminent. Consecutive irradiation of **6** in pyridine in the presence of hematoporphyrin under oxygen atmosphere with a halogen lamp, reductive work-up of the resulting hydroperoxides with NaI in the presence of AcOH in a 5 : 1 mixture of Et_2O and EtOH and oxidation with TPAP gave, in 63% overall yield, the enone **28**, which displays the same spectra with those provided by Iwata and his co-workers in a total synthesis of (±)-aphidicolin (**1**).[12h] An important advantage of the present strategy is that each diastereomers **6a** and **6b**, isomeric only at C-5, yields the same product **28**. Subsequent elaboration of **28** into (+)-**5** was then achieved by applying the known technique.[12d,12h] Conversion of **28** to (+)-**5** was then accomplished *via* the reaction sequence summarized in **Scheme V**.

The Petrow reaction[23] (95%) of **28** was conducted with thiophenol, paraformaldehyde and Et_3N in refluxing EtOH to give rise to the phenyl thiomethyl enone **29**, which was then subjected to Birch reduction (Li/liq. NH_3) followed by trapping of the corresponding lithium enolate with TMSCl to furnish the silyl enol ether **30**. The aldol functionality next was installed by the general method of Stork,[24] **30** was treated with MeLi, and the resulting lithium enolate was subjected to react with gaseous formaldehyde to give the aldol **31** in 57% yield. Hydride reduction of **31** with L-Selectride® afforded, in 50% yield, the diol **32**, which was converted to (+)-**5**

by hydrolysis with 5% HCl, followed by protection (2,2-dimethoxypropane, PPTS) in 40% overall yield. The ^1H NMR and IR spectra of synthetic **5** were agreement with those reported.[12h,14] Since (+)-**5** has been converted to (+)-aphidicolin (**1**),[14] the present preparation of **5** constitutes an alternative enantioselective total synthesis of (+)-**1**.

Scheme V



Conclusion

An enantioselective total synthesis of (+)-aphidicolin, a cancer growth-inhibiting diterpene, has been accomplished. Our synthesis features enantioselective preparation of the CD ring system of aphidicolin employing palladium catalyzed cycloisomerization reaction and stereoselective construction of the AB-*trans* ring juncture using intramolecular Diels-Alder reaction. An important advantage of the present strategy is that each diastereoisomers, produced by the above thermal reaction, yields the same desired product. Our methodology should prove an efficient tool in the syntheses of aphidicolin analogues, such as aphidicolin-17-glycinate HCl salt or 16-fluoroaphidicolin.

Experimental Section

General. Unless otherwise noted, nonaqueous reactions were carried out under argon in rigorously dried glassware. Materials were obtained from commercial supplier and used without further purification except when otherwise noted. Anhydrous solvents were freshly distilled as follows: Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and Et_2O were distilled under argon from sodium benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2), acetonitrile (MeCN), pyridine and Et_3N were distilled under argon from CaH_2 and used immediately. Toluene and benzene (C_6H_6) were distilled under argon from phosphorus pentoxide (P_2O_5). Dimethylformamide (DMF) was distilled under argon from $MgSO_4$ prior to use.

Diisopropylamine, hexamethylphosphoramide (HMPA), *t*-BuOH and EtOH were distilled under argon and used immediately. The concentration of commercially available n-butyllithium in n-hexane was checked by titration by using diphenylacetic acid.[25] Unless otherwise noted, reagents and solvents were added by syringe, and organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through Celite, and concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Chromatography was carried out using Merck 60 (230–400 mesh) or Cica 60 (spherical/40–100 μm) silica gel according to the procedure described by Still.[26] Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). IR spectra were recorded as films on NaCl plates unless otherwise noted. ^1H NMR spectra were measured as $CDCl_3$ solutions at 300 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative internal $CHCl_3$. *J* values are in hertz.

(3*R*,4*R*)-4-*tert*-Butyldimethylsiloxy-3-(2-propenyl)cyclohexanone (11). To a stirred solution of the enone **10** (3.89 g, 14.6 mmol) in an equivolume mixture of benzene and H_2O (80 mL) were added $NaHCO_3$ (15.5 g, 148 mmol), Adogen 464® (1.2 mL) and $Na_2S_2O_4$ (6.00 g, 34.5 mmol) at ambient temperature, whereupon it was refluxed. After 15 min, an additional $Na_2S_2O_4$ (6.90 g, 39.6 mmol) was added, and the resulting mixture was continued to reflux for 3 h. After separation, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O and saturated NaCl solution, and evaporated to leave an oil, which was chromatographed. Elution with a 12 : 1 mixture of n-hexane-EtOAc gave **11** (2.78 g, 71%) as a colorless oil: $[\alpha]^{25}_D$ –7.36 (c 1.60, $CHCl_3$). IR ($CHCl_3$) 1720 cm^{-1}. ^1H NMR δ 0.11 (3H, s), 0.17 (3H, s), 0.93 (9H, s), 1.92–2.28 (4H, m), 2.38–2.65 (2H, m), 2.76 (1H, dd, *J* = 14.6 and 6.0), 2.83 (1H, dd, *J* = 11.6 and 11.6), 2.97 (1H, ddd, *J* = 12.1, 4.0 and 2.1), 3.92–3.98 (1H, m), 5.02–5.13 (2H, m), 5.60–5.76 (2H, m). ^{13}C NMR (75 MHz) δ –4.9, –4.7, –4.4, 18.0, 25.6, 25.7, 26.0, 31.4, 36.9, 37.1, 37.4, 42.2, 44.3, 70.2, 117.0, 135.0, 135.3, 210.5. Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.52. Found: C, 67.25; H, 10.52.

(1*R*,2*R*)-1-*tert*-Butyldimethylsiloxy-4-ethylidene-2-(2-propenyl)cyclohexane (12). To a stirred suspension of ethyltriphenylphosphonium bromide (6.31 g, 17.0 mmol) in THF (60 mL) was added n-butyllithium (10% n-hexane solution, 10.9 mL, 17.0 mmol) at room temperature, whereupon it was refluxed for 1.5 h. After cooling the mixture to 25 °C, a THF solution of the ketone **11** (2.28 g, 8.51 mmol) was added dropwise at ambient temperature, then the resulting mixture was refluxed for an additional 2 h. After successive addition of Et_2O and saturated NH_4Cl solution, the resulting mixture was extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried, and evaporated to yield an oil, which was chromatographed. Elution with n-hexane afforded the diene **12** (2.06 g, 86%) as a colorless oil: $[\alpha]^{25}_D$ +12.77 (c 1.37, $CHCl_3$). IR ($CHCl_3$) 1635 cm^{-1}. ^1H NMR δ 0.05 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.20–2.01 (6H, m), 1.27–2.59 (3H, m), 3.39–3.51 (1H, m), 4.95–5.06 (2H, m), 5.08–5.22 (1H, m), 5.67–5.86 (1H, m). Anal. Calcd for $C_{17}H_{32}OSi$: C, 72.79; H, 11.50. Found: C, 72.67; H, 11.57.

(1*R*,2*R*)-4-Ethylidene-2-(2-propenyl)cyclohexanol (13). To a stirred solution of **12** (14.9 mg, 53.0 μmol) in THF (0.5 mL) was added n-$Bu_4N^+F^-$ (1.0 mol solution in THF, 0.08 mL, 80.0 μmol) at rt, whereupon it was continued to stir for 12 h. After addition of saturated NaCl solution, the resulting mixture was extracted with Et_2O. The organic layer was dried and evaporated to afford an oil, which was

chromatographed. Elution with a 5:1 mixture of n-hexane-EtOAc gave the alcohol **13** (7.3 mg, 83%) as a colorless oil: $[\alpha]^{25}_D$ +42.62 (c 1.37, $CHCl_3$). IR ($CHCl_3$) 3350 cm^{-1}. ^1H NMR δ 1.20–1.89 (4H, m), 1.58 (3H, d J = 6.6), 1.90–2.12 (2H, m), 2.16–2.29 (1H, m), 2.35–2.48 (1H, m), 2.52–2.64 (1H, m), 3.40–3.54 (1H, m), 5.00–5.24 (3H, m), 5.76–5.94 (1H, m). HRMS *m/z*: Calcd for $C_{11}H_{18}O$, 166.1358. Found 166.1331 (M^+).

(2*R*)-4-Ethylidene-2-(2-propenyl)cyclohexanone (14). To a stirred suspension of **13** (1.42 g, 8.55 mmol), 4A-MS (4.30 g), and NMO (1.50 g, 12.8 mmol) in CH_2Cl_2 (18 mL) was added TPAP (150 mg, 0.428 mmol) at 0 °C, whereupon it was stirred at 0 °C for 5 min, and at rt for 1 h. After filtration through Celite, the filtrate was concentrated to furnish an oil, which was chromatographed. Elution with a 15 : 1 mixture of n-hexane-EtOAc gave rise to the ketone **14** (1.28 g, 91%) as a colorless oil: $[\alpha]^{25}_D$ –17.48 (c 1.22, $CHCl_3$). IR ($CHCl_3$) 1700 cm^{-1}. ^1H NMR δ 1.64 (1.5H, s), 1.66 (1.5H, s), 1.98–2.82 (9H, m), 4.99–5.12 (2H, m), 5.34–5.48 (1H, m), 5.67–5.82 (1H, m). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.34; H, 9.83.

(2*R*)-4-Ethylidene-2-(2-propenyl)cyclohexanone Ethylene Acetal (15). A solution of **14** (15.0 mg, 91.5 μmol), ethylene glycol (0.5 mL) and PPTS (6.9 mg, 28.0 μmol) in C_6H_6 (1 mL) was refluxed under a Dean-Stark water separator for 2.5 h. After removal of the solvent, the residue was chromatographed. Elution with a 20:1 mixture of n-hexane-EtOAc yielded **15** (19.0 mg, 100%) as a colorless oil: $[\alpha]^{25}_D$ +36.82 (c 6.57, $CHCl_3$). IR 1640 cm^{-1}. ^1H NMR δ 1.30–2.53 (9H, m), 1.59 (3H, d, J = 5.9), 3.92–4.02 (4H, m), 4.95–5.07 (2H, m), 5.13–5.28 (1H, m), 5.67–5.86 (1H, m). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.01; H, 9.60.

(2*R*)-4-Ethylidene-2-(2-oxopropyl)cyclohexanone Ethylene Acetal (16). The reactor was charged with $PdCl_2$ (34.5 mg, 0.195 mmol), CuI (75.9 mg, 0.974 mmol), H_2O (20 mL) and DMF (2 mL) and the mixture was stirred at 45 °C for 41 h under oxygen, whereupon a DMF solution (2.0 mL) of the olefin **15** (135 mg, 0.649 mmol) was added dropwise at rt, and then the resulting mixture was stirred at 45 °C for 5 h under oxygen. Saturated NaCl solution was added, then the mixture was extracted with EtOAc. The organic layer was dried and evaporated to leave an oil, which was chromatographed. Elution with a 4:1 mixture of n-hexane-EtOAc afforded the ketone **16** (135 mg, 93%) as a colorless oil: $[\alpha]^{25}_D$ –27.32 (c 1.36, $CHCl_3$). IR 1710 cm^{-1}. ^1H NMR δ 1.40–1.68 (2H, m), 1.57 (1.5H, d, J = 1.5), 1.60 (1.5H, br s), 1.70–1.81 (1H, m), 1.92–2.07 (1H, m), 2.10–2.47 (5H, m), 2.13 (1.5H, s), 2.14 (1.5H, s), 2.54–2.67 (1H, m), 3.90–3.98 (4H, m), 5.14–5.31 (1H, m). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.81; H, 8.90.

(2*R*)-4-Ethylidene-2-(2-diethoxyphosphoryloxy-2-propenyl)cyclohexane Ethylene Acetal (17). To a stirred solution of LDA, prepared from diisopropylamine (0.72 mL, 5.14 mmol) and n-butyllithium (10% n-hexane solution, 3.3 mL, 5.14 mmol) in THF (20 mL) was added dropwise a THF solution (20 mL) of **16** (959 mg, 4.28 mmol) at –78 °C, whereupon it was continued to stir at the same temperature for 50 min. After addition of diethyl chlorophosphate (0.86 mL, 5.99 mmol) at –78 °C, the resulting mixture was stirred at –78 °C for 80 min, and at 0 °C for 10 min. H_2O was added at 0 °C, then the mixture was extracted with EtOAc. The organic layer was dried and evaporated to give an oil, which was chromatographed. Elution with Et_2O

furnished the enol phosphonate **17** (1.38 g, 98%) as a colorless oil: $[\alpha]^{25}_D$ +9.69 (c 1.09, $CHCl_3$). IR 1280 cm^{-1}. ^1H NMR δ 1.10–1.55 (2H, m), 1.35 (3H, d, *J* = 7.3), 1.36 (3H, d, *J* 7.3), 1.58 (3H, d, *J* = 8.3), 1.58–1.81 (1H, m), 1.94–2.22 (4H, m), 2.30–2.42 (1H, m), 2.52 (1H, br d, *J* = 11.0), 3.92–4.00 (4H, m), 4.10–4.22 (4H, m), 4.47–4.53 (1H, m), 4.86–4.91 (1H, m), 5.14–5.30 (1H, m). Anal. Calcd for $C_{17}H_{29}O_6P$: C, 56.66; H, 8.11. Found: C, 56.47; H, 8.16.

(2*R*)-4-Ethylidene-2-(2-propynyl)cyclohexanone Ethylene Acetal (18). To a stirred solution of LDA, prepared form diisopropylamine (0.11 mL, 0.785 mmol) and n-butyllithium (10% n-hexane solution, 0.49 mL, 0.764 mmol), in THF (2 mL) was added dropwise a THF solution (1.5 mL) of **17** (113 mg, 0.345 mmol) at –78 °C, whereupon it was continued to stir at the same temperature for 45 min, and 0 °C for 0.5 h. After addition of H_2O (3 mL), the resulting mixture was extracted with EtOAc, then the organic layer was washed with saturated NaCl solution, dried, and evaporated to yield an oil, which was chromatographed. Elution with an 8:1 mixture of n-hexane-EtOAc gave rise to the acetylene **18** (61.1 mg, 86%) as a colorless oil: $[\alpha]^{25}_D$ –17.58 (c 1.46, $CHCl_3$). IR 3290, 2110 cm^{-1}. ^1H NMR δ 1.36–1.52 (1H, m) 1.59 (1.5H, br d, *J* = 6.7), 1.63 (1.5H, br d, *J* = 7.0), 1.67–1.78 (1H, m), 1.83–2.22 (5H, m), 2.32–2.72 (3H, m), 3.92–4.01 (4H, m), 5.22–5.33 (1H, m). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.71; H, 8.84.

(2*R*)-4-Ethylidene-2-(5-hydroxy-2-pentynyl)cyclohexane Ethylene Acetal (9). To a stirred solution of **18** (1.07 g, 5.19 mmol) in THF (40 mL) was added n-butyllithium (10% n-hexane solution, 4.3 mL, 6.75 mmol) at –78 °C, whereupon it was continued to stir at the same temperature for 1.5 h. After addition of ethylene oxide (*ca.* 1 mL) at –78 °C, $BF_3{\cdot}Et_2O$ (0.83 mL, 0.75 mmol) was added, then the resulting mixture was stirred at –78 °C for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution at the same temperature, then the resulting solution was allowed to warm to rt. After extraction with EtOAc, the organic layer was washed with saturated NaCl solution, dried, and evaporated to afford an oil, which was chromatographed. Elution with a 3:2 mixture of n-hexane-EtOAc furnished **9** (1.13 g, 87%) as a colorless oil: $[\alpha]^{25}_D$ –13.52 (c 0.77, $CHCl_3$). IR 3430 cm^{-1}. ^1H NMR δ 1.35–1.52 (1H, m), 1.59 (1.5H, d, *J* = 7.0), 1.60–1.91 (2H, m), 1.62 (1.5H, d, *J* = 7.7), 1.94–2.22 (4H, m), 2.33–2.48 (4H, m), 3.63–3.73 (2H, m), 3.91–4.01 (4H, m), 5.20–5.32 (1H, m). HRMS m/z: Calcd for $C_{15}H_{22}O_3$, 250.1569. Found 250.1571 (M^+).

Ketal (21a). A mixture of the enyne **18** (61.3 mg, 0.298 mmol), TOTP (4.5 mg, 14.9 μmol), $(dba)_3Pd_2{\cdot}CHCl_3$ (7.7 mg, 7.45 μmol) and AcOH (17.3 μl, 0.301 μmol) in C_6H_6 (3 mL) was heated at 60 °C for 17 h in a sealed tube. After removal of the solvent, the residue was chromatographed. Elution with a 10:1 mixture of hexane-EtOAc gave the *exo*-olefin **19** (29.0 mg, 47%) as a colorless oil: ^1H NMR δ 1.50–1.98 (6H, m), 2.13–2.22 (1H, m), 2.41–2.50 (2H, m), 3.80–4.10 (4H, m), 4.73–4.78 (1H, m), 4.90–4.94 (1H, m), 5.05 (1H, dd, *J* = 11.4 and 1.5), 5.07 (1H, dd, *J* = 16.9 and 1.5) and 5.89 (1H, dd, *J* = 16.9 and 11.4).

To a stirred solution of the ketal **19** (11.3 mg, 54.9 μmol) in a 1:1 mixture of Me_2CO-H_2O (1 mL) was added $TsOH{\cdot}H_2O$ (0.5 mg, 2.63 μmol), whereupon it was continued to stir at rt for 4 h. After addition of saturated $NaHCO_3$ solution, the resulting mixture was extracted wtih Et_2O. The ethereal layer was washed with saturated NaCl solution, dried and evaporated to afford an oil, which was chromatographed. Elution with a 10:1 mixture of hexane-EtAOc furnished the ketone **20** (5.9 mg, 67%) as a colorless oil: IR 1715 cm^{-1}. ^1H

NMR δ 1.80–1.91 (3H, m), 2.00–2.19 (1H, m), 2.26–2.58 (3H, m), 2.67–2.82 (2H, m), 4.95–4.98 (1H, m), 5.06–5.10 (1H, m), 5.11 (1H, dd, J = 17.6 and 1.1), 5.16 (1H, dd, J = 9.5 and 1.1) and 5.95 (1H, dd, J = 17.6 and 9.5). HRMS m/z: Calcd for $C_{11}H_{14}O$, 162.1045. Found: 162.1089 (M^+).

A mixture of the ketone **20** (5.9 mg, 36.9 μmol), (2R,3R)-(–)-butanediol (20.0 μl, 0.223 μmol) and PPTS (0.5 mg, 1.99 μmol) in C_6H_6 (2 mL) was refluxed for 2 h. After removal of the solvent, the residue was chromatographed. Elution with a 15:1 mixture of hexane-EtOAc gave rise to the ketal **21a** (5.0 mg, 58%) as a colorless oil: ^{1}H NMR δ 1.23 (3H, d, J = 5.5), 1.25 (3H, d, J = 5.9), 1.46–1.56 (1H, m), 1.59–1.80 (4H, m), 1.87 (1H, br d, J = 12.0), 2.14–2.21 (1H, m), 2.44–2.50 (2H, m), 3.61–3.72 (2H, m), 4.72–4.76 (1H, m), 4.88–4.93 (1H, m), 5.04 (1H, dd, J = 17.9 and 1.5), 5.05 (1H, dd, J = 10.3 and 1.5) and 5.88 (1H, dd, J = 17.9 and 10.3). HRMS m/z: Calcd for $C_{15}H_{22}O_2$, 234.1620. Found: 234.1632 (M^+).

Ketal (21b). A mixture of the alcohol **22** (120 mg, 0.682 mmol), 1,1'-thiocarbonyldiimidazole (203 mg, 1.02 mmol) and DMAP (124 mg, 1.02 mmol) in CH_2Cl_2 (7 mL) was stirred at rt for 1 h. After removal of the solvent, the residue was chromatographed. Elution with a 1:1 mixture of hexane-EtOAc provided the thioimidazolide **23** (144.2 mg, 74%) as a colorless oil: IR 1720 and 1230 cm^{-1}. A mixture of **23** (56.5 mg, 0.196 mmol), tris(trimethylsilyl)silane (70.0 μl, 0.216 mmol) and AIBN (3.2 mg, 19.6 μmol) in degassed C_6H_6 (2 mL) was refluxed for 9 h. After removal of the solvent, the residue was chromatographed. Elution with a 15:1 mixture of hexane-EtOAc afforded (±)-**20** (28.4 mg, 91%) as a colorless oil. The ketal **21b** (27.3 mg, 66%; 1:1 mixture of **21a** and its diastereomer) was prepared from the above ketone **20** (28.4 mg, 0.178 mmol) and (2R,3R)-butanediol (80 μl, 0.888 mmol) in the presence of PPTS (0.5 mg, 1.99 mmol) by means of the same procedure described previouly. ^{1}H NMR δ 1.20–1.28 (6H, m), 1.46–2.01 (6H, m), 2.12–2.21 (1H, m), 2.42–2.51 (2H, m), 3.52–3.70 (2H, m), 4.72–4.76 (1H, m), 4.88–4.92 (1H, m), 4.97–5.10 (2H, m) and 5.82–5.96 (1H, m).

(1*S*,5*R*)-5-Ethenyl-6-(3-hydroxypropylidene)bicyclo[3.2.1]octan-2-one Ethylene Acetal (8). A mixture of the enyne **9** (255 mg, 1.02 mmol), $(dba)_3Pd_2{\cdot}CHCl_3$ (26.4 mg, 25.5 μmol), TOTP (15.5 mg, 51.0 μmol) and AcOH (3.0 μL, 51.0 μmol) in C_6H_6 (10 mL) was heated at 60 °C in a sealed tube for 15 h. After removal of the solvent, the residue was chromatographed. Elution with a 3:2 mixture of n-hexane-EtOAc provide **8** (193 mg, 76%) as a colorless oil: $[\alpha]^{25}_D$ –81.88 (c 1.02, $CHCl_3$). IR 3400 cm^{-1}. ^{1}H NMR δ 1.47–1.92 (4H, m), 2.20–2.55 (7H, m), 3.64 (2H, t, J = 6.6), 3.83–4.04 (4H, m), 5.04 (1H, dd, J = 17.6 and 1.5), 5.05–5.13 (1H, m), 5.07 (1H, dd, J = 11.0 and 1.5), 5.84 (1H, dd, J = 17.6 and 11.0). ^{13}C NMR (75 MHz) δ 29.7, 32.9, 33.9, 41.6, 41.9, 48.9, 62.2, 64.2, 64.6, 111.0, 112.4, 116.9, 143.7, 148.5. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86; H, 8.81.

(1*S*,5*S*)-5-Acetyl-6-(3-hydroxypropylidene)bicyclo[3.2.1]octan-2-one 2,2-Ethylene Acetal (24). The reactor was charged with $PdCl_2$ (287 mg, 1.62 mmol), CuCl (632 mg, 8.10 mmol), H_2O (10 mL) and DMF (20 mL), and the mixture was stirred at 60 °C for 10 h under oxygen, whereupon a DMF solution (20 mL) of **8** (1.15 g, 4.60 mmol) was added dropwise at rt, then the resulting mixture was stirred at 60 °C for 11 h under oxygen. Saturated NaCl solution (10 mL) was added, then the resulting solution was extracted with Et_2O. The organic layer was dried, and evaporated to give an oil, which was chromatographed. Elution with a 3:2 mixture of n-hexane-EtOAc yielded the ketone **24** (845 mg, 69%) as a colorless oil: $[\alpha]^{25}_D$ –92.57 (c

1.44, $CHCl_3$). IR 1690 cm^{-1}. ^1H NMR δ 1.35–1.41 (1H, m), 1.54–1.70 (2H, m), 1.79–1.87 (1H, m), 1.97 (1H, br d, J = 11.0), 2.04–2.13 (1H, m), 2.13 (3H, s), 2.25–2.35 (3H, m), 2.45–2.50 (2H, m), 3.60–3.69 (2H, m), 3.83–4.03 (4H, m), 5.00–5.10 (1H, m). ^{13}C NMR (75 MHz) δ 25.1, 29.5, 31.8, 32.9, 33.1, 39.6, 42.8, 59.9, 62.1, 64.4, 64.7, 110.5, 118.6, 145.6, 210.4. HRMS *m/z*: Calcd for $C_{15}H_{22}O_4$, 266.1518. Found 266.1507 (M^+).

(1*S*,5*S*,6*S*)-5-Acetyl-6-(3-hydroxypropyl)bicyclo[3.2.1]octan-2-one 2,2-Ethylene Acetal (25). A mixture of **24** (14.2 mg, 53.4 μmol) and 10% palladium-charcoal (17.0 mg) in EtOH (0.5 mL) was stirred at rt under hydrogen for 5 h. After filtration through Celite, the filtrate was evaporated and then the residue was chromatographed. Elution with a 2:1 mixture of benzene-acetone furnished **25** (13.7 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ –19.25 (c 0.27, $CHCl_3$). IR ($CHCl_3$) 3440, 1690 cm^{-1}. ^1H NMR δ 1.29–1.91 (11H, m), 1.96–2.04 (1H, m), 2.05–2.24 (1H, m), 2.15 (3H, s), 3.64 (2H, t, J = 6.0), 3.80–4.02 (4H, m). ^{13}C NMR (75 MHz) δ 26.2, 26.4, 26.6, 29.4, 31.9, 32.5, 40.5, 42.8, 43.2, 57.1, 62.7, 64.1, 64.7, 111.0, 212.9. HRMS *m/z*: Calcd for $C_{15}H_{24}O_4$, 268.1675. Found 268.1680 (M^+).

(1*S*,5S,6*S*)-6-(3-Hydroxypropyl)-5-methylethenylbicyclo[3.2.1]octan-2-one Ethylene Acetal (26). To a suspension of methyltriphenylphosphonium bromide (1.16 g, 3.25 mmol) in DME (10 mL) was added dropwise n-butyllithium (10% n-hexane solution, 2.1 mL, 3.25 mmol) at rt, whereupon it was refluxed for 2.5 h. After cooling the mixture to rt, a DME solution (10 mL) of the ketone **25** (174 mg, 0.649 mmol) was added dropwise at ambient temperature, then the resulting mixture was stirred at rt for 7 h. Saturated NH_4Cl solution (20 mL) was added, and the resulting solution was extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried, and evaporated to leave an oil, which was chromatographed. Elution with a 6:1 mixture of benzene-acetone furnished **26** (128 mg, 74%) as a colorless oil: $[\alpha]^{25}_D$ –2.32 (c 0.74, $CHCl_3$). IR 3400 cm^{-1}. ^1H NMR δ 1.20–1.90 (9H, m), 1.73 (3H, s), 1.90–2.18 (3H, m), 3.59–3.69 (2H, m), 3.80–4.01 (4H, m), 4.73 (1H, br d, J = 1.1), 4.80 (1H, br dd, J = 1.5 and 1.1). ^{13}C NMR (75 MHz) δ 20.4, 26.4, 29.0, 30.0, 32.5, 33.1, 41.1, 42.8, 43.1, 48.8, 63.3, 64.1, 64.7, 110.5, 111.7, 149.8. HRMS *m/z*: Calcd for $C_{16}H_{26}O_3$, 266.1882. Found 266.1868 (M^+).

(1*S*,5*S*,6*S*)-5-Methylethenyl-2-spiro(2,5-dioxolane)bicyclo[3.2.1]octane-6-propanal (27). To a stirred suspension of **26** (34.5 mg, 0.130 mmol), NMO (35.5 mg, 0.303 mmol) and 4A-MS (65 mg) in CH_2Cl_2 (1.5 mL) was added TPAP (2.3 mg, 6.55 μmol) at rt, whereupon it was continued to stir at the same temperature for 1 h. After filtration through Celite, the filtrate was concentrated to leave a crude product, which was chromatographed. Elution with a 20:1 mixture of benzene-acetone gave rise to **27** (26.6 mg, 78%) as a colorless oil: $[\alpha]^{18}_D$ –2.94 (c 1.16, $CHCl_3$). IR ($CHCl_3$) 1720 cm^{-1}. ^1H NMR δ 1.20–1.35 (2H, m), 1.44–1.87 (7H, m), 1.73 (3H, s), 1.90–2.16 (3H, m), 2.33–2.59 (2H, m), 3.79–4.01 (4H, m), 4.76 (1H, br d, J = 0.7), 4.83 (1H, br dd, J = 1.5 and 1.5), 9.76 (1H, t, J = 1.5). ^{13}C NMR (75 MHz) δ 20.2, 22.6, 28.8, 30.0, 32.7, 41.1, 42.5, 42.7, 43.5, 48.7, 64.1, 64.7, 110.9, 111.4, 149.3, 202.5. HRMS *m/z*: Calcd for $C_{16}H_{24}O_3$, 264.1725. Found 264.1724 (M^+).

(1*S*,5*S*,6*S*,E)-6-(3,5-Hexadienyl)-5-methylethenylbicyclo[3.2.1]octan-2-one Ethylene Acetal (7). To a stirred solution of allyldiphenylphosphine oxide (45.5 mg, 0.202 mmol) and HMPA (0.07

mL, 0.404 mmol) in THF (0.5 mL) was added dropwise n-butyllithium (10% n-hexane solution, 0.13 mL, 0.202 mmol) at –78 °C, whereupon it was continued to stir at the same temperature for 0.5 h. A THF solution (1 mL) of **27** (26.6 mg, 0.101 mmol) was added at –78 °C, then the resulting mixture was stirred at –78 °C for 10 min, at 0 °C for 0.5 h, and at rt for 2 h. Saturated NH_4Cl solution was added at 0 °C, whereupon the mixture was extracted with Et_2O. The organic layer was washed with saturated NaCl solution, dried, and evaporated to provide an oil, which was chromatographed. Elution with a 20:1 mixture of n-hexane-EtOAc gave rise to the triene **7** (21.1 mg, 73%) as a colorless oil: $[\alpha]^{25}_D$ –7.96 (c 0.47, $CHCl_3$). IR 1640 cm^{-1}. ^1H NMR δ 1.24–1.41 (2H, m), 1.48–1.83 (6H, m), 1.73 (3H, m), 1.91–2.25 (6H, m), 3.80–4.01 (4H, m), 4.72 (1H, br s), 4.80 (1H, dq, *J* = 1.1 and 1.1), 4.95 (1H, br d, *J* = 10.6), 5.08 (0.917H, dd, *J* = 16.8 and 1.1), 5.18 (0.083H, br d, *J* = 16.0), 5.69 (1H, dt, *J* = 14.7 and 7.3), 5.96–6.11 (1H, m), 6.30 (0.917H, ddd, *J* = 16.8, 10.6 and 10.6), 6.56–6.71 (0.083H, m). HRMS *m/z*: Calcd for $C_{19}H_{28}O_2$, 288.2090. Found 288.2084 (M^+).

(5*S*,8*S*,9*S*,12*S*)-3,4-Didehydro-17,18,19-trisnoraphidicolin-16-one Ethylene Acetal (6). A mixture of **7** (70.0 mg, 0.243 mmol) and methylene blue (0.5 mg, catalytic amount) in toluene (2.5 mL) was heated at 220 °C in a sealed tube for 190 h. After removal of the solvent, the residue was chromatographed. Elution with a 3:1 mixture of n-hexane-EtOAc furnished **6** (49.9 mg, 70%) as a 3:1 mixture of diastereomers as a colorless oil: $[\alpha]^{25}_D$ +8.55 (c 0.73, $CHCl_3$). IR 2950 cm^{-1}. ^1H NMR δ 0.83 (0.75H, s), 0.87 (2.25H, s), 1.19–2.25 (18H, m), 2.34–2.49 (1H, m), 3.80–4.03 (4H, m), 5.32–5.69 (2H, m). HRMS *m/z*: Calcd for $C_{19}H_{28}O_2$, 288.2090. Found 288.2079 (M^+).

(8*S*,9*S*,12*S*)-4,5-Didehydro-17,18,19-trisnoraphidicolin-3,16-dione 16,16-Ethylene Acetal (28). A stirred solution of **6** (181 mg, 0.628 mmol) and hematoporphyrin (37.6 mg, 62.8 μmol) in pyridine (15 mL) was irradiated by 700-W halogen lamp through a Pyrex® filter with oxygen bubbling for 190 h. Active charcoal (150 mg) and Et_2O (20 mL) were added, whereupon the resulting mixture was stirred at rt for 8 h. After filtration through Celite, the filtrate was evaporated (< 35 °C) to leave a crude material. To a stirred solution of the above product in a mixture of Et_2O (50 mL) and EtOH (12 mL) were added NaI (2.18 g, 14.9 mmol) and AcOH (10 drops) at ambient temperature, then the resulting mixture was continued to stir at rt for 24 h. After addition of Et_2O, the organic layer was washed with saturated $Na_2S_2O_3$ solution and saturated NaCl solution, dried, and evaporated to give an oil, which was taken up in CH_2Cl_2 (6 mL). TPAP (11.0 mg, 31.4 μmol), NMO (114 mg, 94.2 μmol) and 4A-MS (314 mg) were added, whereupon the resulting mixture was stirred at rt for 1 h. After filtration through Celite, the filtrate was concentrated to provide a crude product, which was chromatographed. Elution with a 15:1 mixture of n-hexane-EtOAc furnished the enone **28** (119 mg, 63%) as a colorless oil: $[\alpha]^{25}_D$ +91.57 (c 0.375, $CHCl_3$). IR 1660 cm^{-1}. ^1H NMR δ 1.27 (3H, s), 1.28–1.41 (2H, m), 1.45–2.06 (8H, m), 2.15–2.22 (1H, m), 2.26–2.56 (7H, m), 3.79–4.02 (4H, m), 5.82 (1H, br s). ^{13}C NMR (75 MHz) δ 18.4, 25.4, 27.8, 29.2, 30.5, 30.7, 34.1, 34.5, 34.6, 39.3, 42.8, 43.7, 47.1, 64.1, 64.7, 111.5, 126.7, 170.6, 199.2. HRMS *m/z*: Calcd for $C_{19}H_{26}O_3$, 302.1882. Found 302.1893. (M^+).

(8*S*,9*S*,12*S*)-4,5-Didehydro-4-phenylthiomethyl-17,18,19-trisnoraphidicolin-3,16-dione 16,16-Ethylene Acetal (29). To a stirred solution of **28** (95.0 mg, 0.315 mmol), paraformaldehyde (425

mg), and Et_3N (0.75 mL, 5.36 mmol) in EtOH (4 mL) was added thiophenol (0.90 mL, 8.82 mmol) at ambient temperature, whereupon it was refluxed for 48 h. After cooling the mixture to rt, the mixture was diluted with Et_2O. The organic layer was washed with 1N NaOH solution (5 mL × 2) and saturated NaCl solution. The aqueous layer was extracted with CH_2Cl_2, and then the combined organic layers were dried, and evaporated to afford an oil, which was chromatographed. Elution with a 20:1 mixture of benzene-acetone provided the sulfide **29** (127 mg, 95%) as a colorless oil: $[\alpha]^{22}_D$ +34.41 (c 0.585, $CHCl_3$). IR 1660 cm^{-1}. ^1H NMR δ 1.19–1.98 (11H, m), 1.22 (3H, s), 2.06–2.50 (7H, m), 3.79–4.01 (6H, m), 7.17–7.29 (3H, m), 7.36–7.41 (2H, m). ^{13}C NMR (75 MHz) δ 18.8, 25.4, 27.5, 29.2, 29.4, 29.7, 30.6, 34.2, 34.6, 38.6, 43.4, 43.6, 47.5, 64.0, 64.6, 111.4, 126.6, 128.7, 131.1, 131.4, 136.4, 166.9, 196.6. HRMS *m/z*: Calcd for $C_{26}H_{32}O_3S$, 424.2072. Found 424.2071 (M^+).

(5*S*,8*S*,9*S*,12*S*)-3,4-Didehydro-3-trimethylsiloxy-17,18-dinoraphidicolin-16-one Ethylene Acetal (30). To a stirred solution of lithium (16.0 mg, 2.31 mmol) in anhydrous liquid ammonia (10 mL) were added dropwise a THF solution (5 mL) of **29** (127 mg, 0.300 mmol) and t-BuOH (51 μL) at –78 °C. After 15 min, the mixture was treated with isoprene (5 drops) at –78 °C, whereupon ammonia was allowed to evaporate, and the residue was dried under reduced pressure. To a stirred solution of the crude product in THF (10 mL) were added dropwise HMPA (1.4 mL) and the supernatant liquid from a mixture of TMSCl (1.4 mL) and Et_3N (1.4 mL) at –78 °C, whereupon it was stirred at rt for 1 h. After addition of Et_2O, the organic layer was washed with saturated $NaHCO_3$ solution (10 mL × 2) and saturated NaCl solution, dried, and evaporated to leave a crude product, which was chromatographed on Florisil®. Elution with a 15:1 mixture of n-hexane-Et_2O gave the silyl enol ether **30** (57.0 mg, 49%) as a colorless oil: $[\alpha]^{24}_D$ +2.31 (c 1.43, $CHCl_3$). IR 1670 cm^{-1}. ^1H NMR δ 0.16 (6H, s), 0.17 (3H, s), 0.88 (3H, s), 0.94–2.51 (19H, m), 1.52 (3H, br s), 3.79–4.02 (4H, m). HRMS *m/z*: Calcd for $C_{23}H_{38}O_3Si$, 390.2590. Found 390.2590 (M^+).

(4*R*,5*S*,8*S*,9*S*,12*S*)-17-Noraphidicolin-3,16-dione 16,16-Ethylene Acetal (31). To a stirred solution of **30** (28.0 mg, 71.8 μmol) in THF (1 mL) was added methyllithium (1.06 mol solution in Et_2O, 85 μL, 89.7 μmol) at –78 °C, whereupon it was allowed to warm to rt. After 1 h of stirring at the same temperature, the mixture was re-cooled to –78 °C with stirring, and then treated with gaseous formaldehyde *via* a stream of nitrogen. After 10 min, a 0.1% solution of AcOH in THF (0.1 mL) was added, whereupon the resulting mixture was allowed to warm to rt and treated with a buffer solution (2 mL) of NH_4Cl and NH_4OH. After 1 h of stirring, the mixture was diluted with Et_2O, then the organic layer was washed with NaCl solution, dried and evaporated to yield an oil, which was chromatographed. Elution with a 2:3 mixture of n-hexane-EtOAc afforded **31** (14.3 mg, 57%) as a colorless oil: $[\alpha]^{24}_D$ –0.90 (c 0.29, $CHCl_3$). IR 3450 and 1690 cm^{-1}. ^1H NMR δ 1.01 (3H, s), 1.17 (3H, s), 1.20–2.00 (15H, m), 2.09–2.20 (2H, m), 2.25–2.38 (2H, m), 2.58–2.73 (1H, m), 3.36 (1H, br dd, J = 11.2 and 6.8), 3.66 (1H, dd, J = 11.2 and 3.8), 3.79–4.01 (4H, m). HRMS *m/z*: Calcd for $C_{21}H_{32}O_4$, 348.2301. Found: 348.2253 (M^+).

(3*R*,4*R*,5*S*,8*S*,9*S*,12*S*)-17-Noraphidicolin-16-one Ethylene Acetal (32). To a stirred solution of **31** (5.0 mg, 14.4 μmol) in THF (0.5 mL) was added dropwise L-Selectride® (1.0 mol solution in THF, 0.06 mL, 60.0 μmol) at –78 °C, whereupon it was continued to stir at the same temperature for 3 h. After successive addition of EtOH (0.05 mL), 15% NaOH solution (0.07 mL) and 30% H_2O_2 (0.07 mL), the resulting mixture

was stirred at rt for 3 h. The mixture was extracted with CH_2Cl_2, then the organic layer was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried, and evaporated to afford an oil, which was chromatographed. Elution with a 3:4 mixture of n-hexane-EtOAc furnished the diol **32** (2.5 mg, 50%) as a colorless oil: $[\alpha]^{24}_D$ –9.40 (c 0.125, $CHCl_3$). IR 3400 cm^{-1}. ^1H NMR δ 0.70 (3H, s), 0.99 (3H, s), 1.20–2.18 (21H, m), 2.42 (1H, dd, J = 12.5 and 3.5), 3.37 (1H, br d, J = 10.9), 3.43–3.52 (1H, m), 3.66–3.70 (1H, m), 3.80–4.00 (4H, m). HRMS *m/z*: Calcd for $C_{20}H_{31}O_4$, 335.2223. Found: 335.2202 (M^+ –15).

(3*R*,4*R*,5*S*,8*S*,9*S*,12*S*)-3,18-Isopropylidenedioxy-17-noraphidicolan-16-one (5). To a stirred solution of **32** (2.5 mg, 7.14 μmol) in THF (1 mL) was added 5% HCl solution (0.5 mL) at ambient temperature, whereupon it was continued to stir at 40 °C for 5 h. After extraction with EtOAc, the organic layer was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried, and evaporated to give a product, which was used in the next reaction without purification. A mixture of the above material and PPTS (10 mg) in 2,2-dimethoxypropane (1 mL) was stirred at rt for 1 h. After addition of Et_2O, the organic layer was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried, and evaporated to afford a crude product, which was chromatographed. Elution with a 5:1 mixture of n-hexane-EtOAc provided **5** (1.0 mg, 40%) as a colorless oil: $[\alpha]^{20}_D$ –13.88 (c 0.05, $CHCl_3$) (lit.[14] $[\alpha]^{20}_D$ –21.3 (c 0.80, $CHCl_3$). IR 1720 cm^{-1}. ^1H NMR δ 0.74 (3H, s), 0.80–2.40 (18H, m), 1.08 (3H, s), 1.43 (6H, s), 2.60–2.68 (1H, m), 3.10–3.30 (2H, m), 3.60–3.70 (1H, m). HRMS m/z: Calcd for $C_{21}H_{31}O_3$, 331.2273. Found: 331.2285 (M^+ –15).

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