Total Synthesis of (±)-Aphidicolin and (±)-β-Chamigrene†[1,2]

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Total syntheses of (±)-chamigrene and (±)-aphidicolin are described. Both approaches are based on the spiroannelation of related α-methylene ketones through first hetero-Diels–Alder condensation and then Claisen rearrangement of the derived allyl vinyl ethers. A central feature of the (±)-aphidicolin synthesis is the rearrangement of the intermediate ((trimethylsilyl)methyl)cyclobutanone **16** to the aphidicolane bicyclo[3.2.1]octane ring system.

Earlier[4] a report from these laboratories presented the results of an investigation of an approach to the total synthesis of the aphidicolin[5] stemodinone[6] class of tetracyclic diterpenes that entailed the development of a Claisen rearrangement based spiroannelation sequence. In this work subsequent use of a solvolytic π-route for the formation of the bicyclo[3.2.1]octane portion of the molecule led to the construction of the basic carbon skeleton of the aphidicolane ring system. With this work[4] as a basis, this synthetic scheme has been refined so as to provide an efficient process for the total synthesis of (±)-aphidicolin (**34**)[7] itself and amplified to include a total synthesis of the sesquiterpene, (±)-β-chamigrene (**22**).[8]

Spiroannelation of the α-methylene ketone **5** entails the Claisen rearrangement of the allyl vinyl ether **8c** and directly generates the desired endocyclic olefinic ketone **10** for the (±)-β-chamigrene (**22**) synthesis (Scheme I). A similar series of operations applied to the dicyclic α-methylene ketone **1** led,[4] however, to the corresponding tricyclic endocyclic olefinic ketone which provided a tetracyclic endocyclic olefinic ketone after π-route solvolysis of a subsequent β-ring contracted intermediate. The endocyclic location of this double bond makes it difficult to foresee a method for the introduction of the C16,C17 diol system required in the aphidicolin (**34**) molecule. Therefore, while the newly developed spiroannelation sequence[4] was well suited to the (±)-β-chamigrene (**22**) synthesis, some modification in the scheme seemed in order for the (±)-aphidicolin (**34**) work.

For the (±)-β-chamigrene (**22**) synthesis, the spiroannelation sequence required the monocyclic α-methylene ketone **5**. This was prepared in good yield from the endocyclic olefin **3** by photosensitized oxygenation in the same manner as that used earlier[9] for the preparation of the dicyclic analogue **1** (Scheme I). The yield of this α-methylene ketone **5** based on the concentration of the olefin **3** present belies somewhat the complexity of the synthesis, for it was not possible to prepare the starting olefin **3** as a pure substance in good yield. Generation of the olefin **3** by dehydration of the corresponding tertiary alcohol invariably led to a mixture of the three olefins shown. Brief treatment with thionyl chloride/pyridine led predominantly to the exocyclic isomer **2** and more vigorous conditions produced the rearranged material **4**. Since neither of the isomers **2** or **4** underwent the photosensitized oxygenation process, a mixture of the three olefins **2**, **3**, and **4** that was rich in the endocyclic isomer **3** was used directly. Recovered olefins **2** and **4** could then be partially recycled to the original ternary mixture after treatment with iodine. After one such cycle of recovered olefins, the yield of the α-methylene ketone **5** was 62%.

While the hetero-Diels–Alder reaction between the α-methylene ketone **5** and methyl methacrylate was fraught with the same problems experienced earlier[4] due to polyacrylate formation, the adduct **8a** was isolable in satisfactory yield and then efficiently converted to the corresponding vinyldihydropyran **8c**. Rearrangement of this allyl vinyl ether **8c** *in the presence* of quinoline led to the desired spiro ketone **10**. It was interesting to note[10] that *in the absence* of the base, and even when scrupulously base washed glassware was used, the sole product from this rearrangement was the bicyclic ketone **11**. While the mechanism of the latter transformation is not clear, the bicyclic ketone **11** could arise through equilibration of the enol ether double bond between the pyran and the cycloheptane rings and then rapid Claisen-type rearrangement of the less hindered cycloheptyl enol ether. Other pathways that entail dissociation–recombination of the hetero-Diels–Alder adduct cannot be excluded.

An alternate, more direct preparation of the spiro ketone **10** by Diels–Alder reaction of the α-methylene ketone **5** with isoprene under Lewis acid catalysis (dimethylaluminum chloride[11]) proved to be more effective than the above sequence when the adduct **10** was formed in 69% yield. While the observed regioisomer **10** was expected to predominate,[12] it is noteworthy that none of the alternate regioisomer was detected in the reaction mixture (^{1}H NMR).

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(3) Postdoctoral Fellow of the National Institute of General Medical Sciences, DHEW, 1979–1980.

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(11) Karras, M.; Snider, B. B. *J. Am. Chem. Soc.* **1980**, *102*, 7951–7953.

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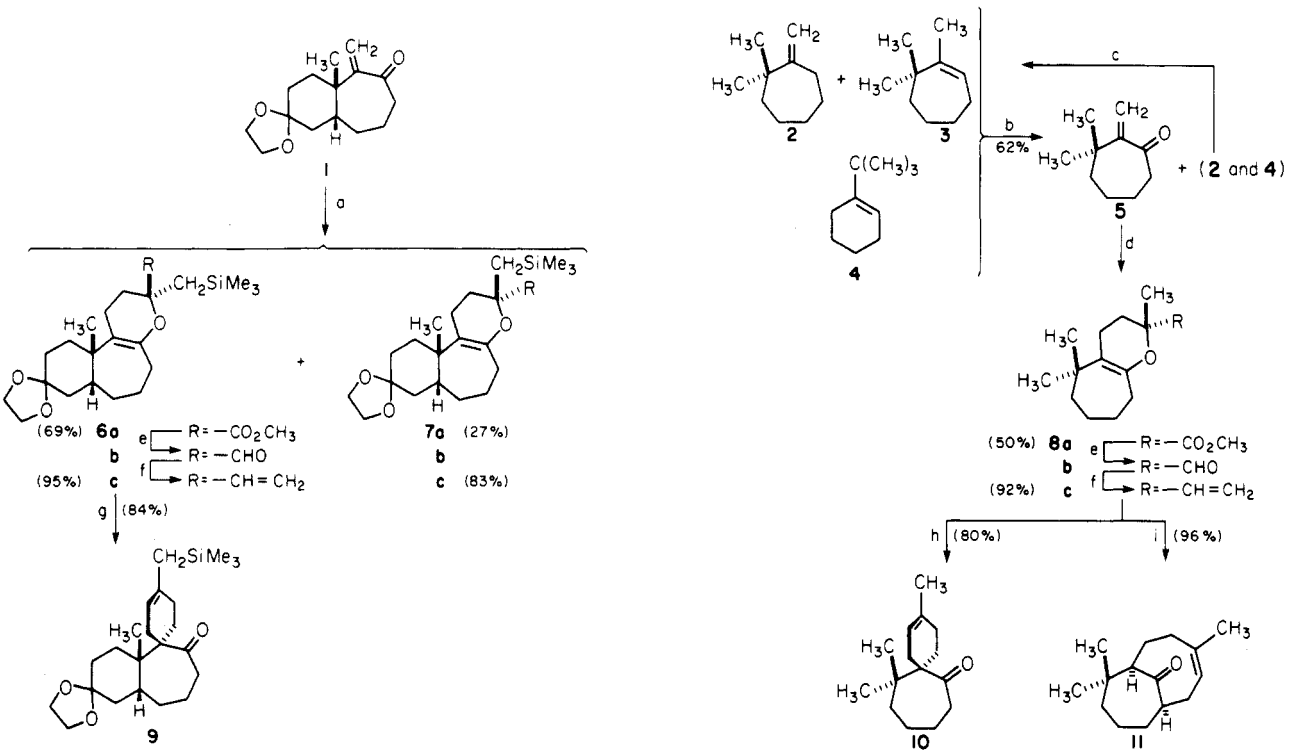
Scheme I. Spiroannelation of α-Methylene Cycloheptanones 1 and 5[a]



[a] a, $CH_2=C(CO_2CH_3)CH_2SiMe_3$, 125 °C, sealed tube, hydroquinone; b, *hν*, sens., pyr/EtOAc, O_2; Ac_2O; c, I_2, 120 °C; d, $CH_2=C(CO_2CH_3)CH_3$, xylene, hydroquinone, 195 °C; e, D/BAL, Et_2O or DME, −78 °C; f, $(C_6H_5)_3P=CH_2$, THF; g, 150 °C; 7.5 h; h, 170 °C; 4 h, quinoline; i, 165 °C, 2 h.

This direct Diels–Alder reaction, however, proved to be restricted to the unfunctionalized, monocyclic α-methylene ketone **5**, for condensation of the dicyclic α-methylene ketone ketal **1** with isoprene under the same conditions led to *none* of the corresponding spiro ketone. The lability of the ketal function in the presence of Lewis acids and the severe steric hindrance to both faces of the exocyclic methylene groupling probably account for the lack of success of this process.

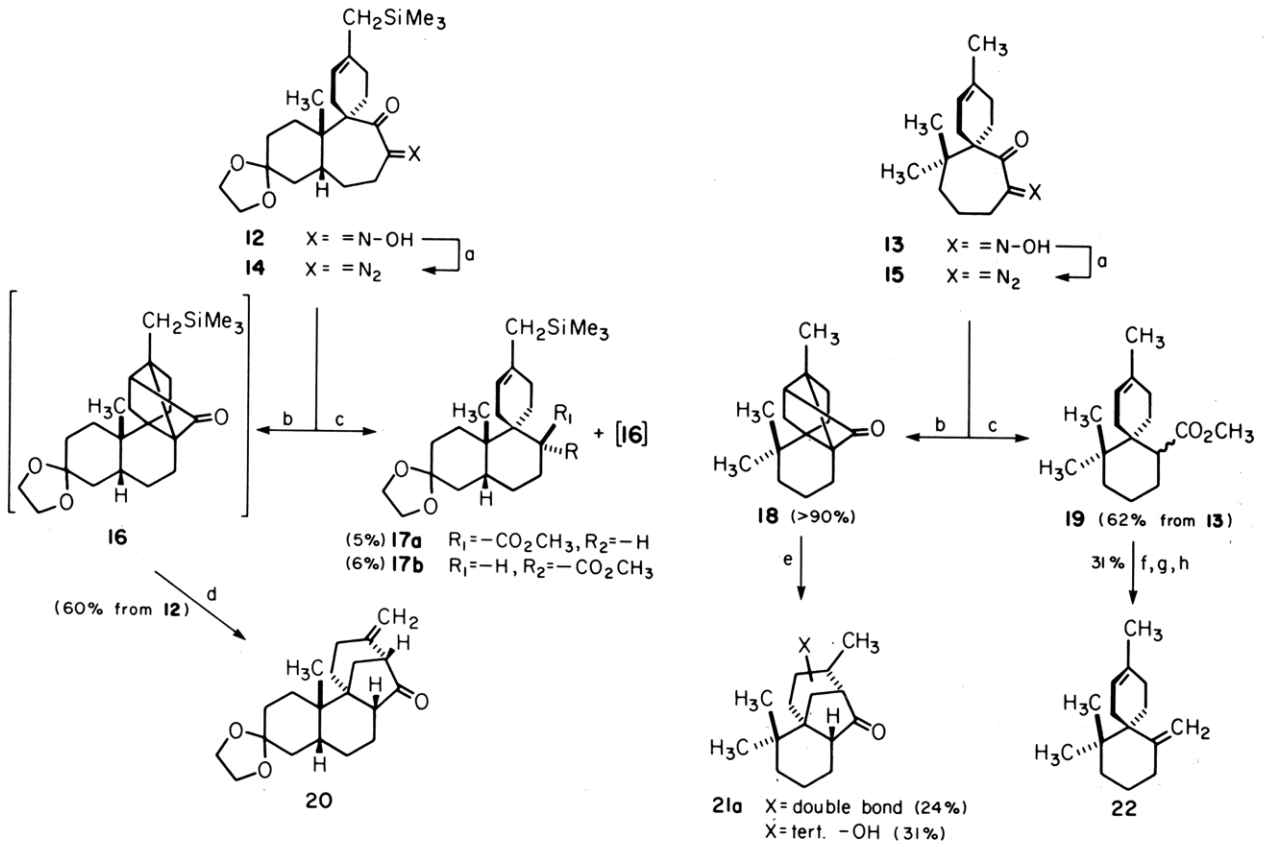
For the (±)-aphidicolin (**34**) synthesis, some modification of intermediates was necessary so that the ultimate π-route cyclization would generate a substrate that was suitable for the introduction of the C16,C17-diol system. An obvious solution to this problem was the preparation of an intermediate that on π-route cyclization would generate an exocyclic rather than endocyclic double bond. Subsequent hydroxylation would then directly provide the desired C16,C17-diol array. The opportunity to effect such a transformation suggested itself as a result of the work of Fleming[13] and Andersen[14] who showed that the use of an allyltrimethylsilane in similar π-route ring closures resulted exclusively in the formation of the exocyclic double bond isomer. In order to take advantage of this observation, a π-route substrate bearing a (trimethylsilyl)methyl substituent in the olefinic ring in place of the previous methyl group[4] was required. This condition translates then to the use of methyl ((trimethylsilyl)-methyl)acrylate rather than methyl methacrylate in the hetero-Diels–Alder reaction with the α-methylene ketone **1**. This acrylate was conveniently prepared in good yield and on large scale by adaptation of the methodology developed by Helquist[15] (see Experimental Section).

The results of the condensation of this heterodienophile with the α-methylene ketone **1** were similar to those experienced earlier[4] with the parent methyl methacrylate in that the stereochemical outcome of the reaction at the newly formed chiral center at C3 was temperature dependent. Lower reaction temperatures were found to favor the desired adduct **6a** (Scheme I). Even still both isomers **6a** and **7a** were formed but readily separated by chromatography. While conversion of these esters **6a** and **7a** individually to their corresponding vinyldihydropyran derivatives **6c** and **7c** was uneventful, the subsequent Claisen rearrangement of these allyl vinyl ethers proved novel. The "aphidicolin" isomer **6c** rearranged quite smoothly at 150 °C to the desired spiro ketone **9**, but the "stemodinone" isomer **7c** would *not* produce the corresponding spiro ketone. On heating the latter isomer **7c** at lower temperatures, it was recovered unchanged, while harsher treatment, even for brief periods, led to numerous decomposition products and none of the expected spiro ketone. Such behavior is almost certainly a function of the trimethylsilyl substituent, for the corresponding des-(trimethylsilyl)vinyldihydropyran derivative rearranged[4] to a spiro ketone quite smoothly. However, since it was not possible to obtain a defined reaction product from this latter rearrangement, it is not clear how this substituent alters the course of the reaction. While this result precludes the use of this scheme for the synthesis of the stemodinone series of diterpenes, this was of secondary interest, and the scheme for aphidicolin was unaffected. Indeed, the intermediates in the latter process predominate throughout in any case.

The next stage in these syntheses was the contraction of the seven-membered rings to be desired cyclohexanecarboxylic acid derivates (Scheme II). For the synthesis

(13) Fleming, I.; Pearce, A.; Snowden, R. L. *J. Chem. Soc., Chem. Commun.* **1976**, 182–183.
(14) Sarkar, T. K.; Andersen, N. H. *Tetrahedron Lett.* **1978**, 3513–3516.
(15) Yu, L. C.; Helquist, P. *Tetrahedron Lett.* **1980**, *21*, 951–954.

Scheme II. Ring Contraction of Spiroketones 9 and 10 and the Synthesis of β-Chamigrene (22)[a]

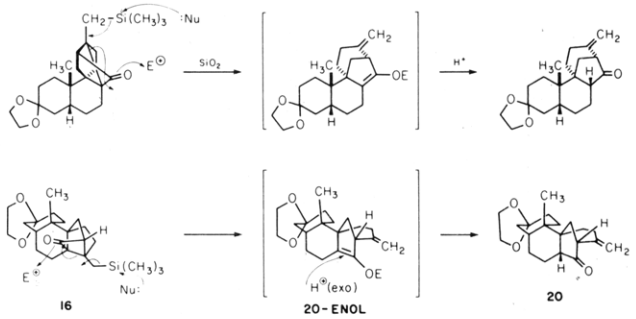


[a], NH_2Cl, THF; b, $h\nu$, Et_2O, −73 or 0 °C; c, $h\nu$, $NaOCH_3/CH_3OH$, −66 or −90 °C; d, SiO_2 gel, petroleum ether/Et_2O; e, pTsOH·H_2O, $HCCl_3$; f, $LiAlH_4$, Et_2O; g, (*o*-NO_2)C_6H_5SeCN, (*n*-Bu)$_3P$, THF; h, 90% TBHP, CH_2Cl_2.

of (±)-β-chamigrene (**22**), this process followed closely the precedence set earlier,[4] and the esters **19** were obtained in satisfactory yield from the spiro ketone **10** through photolysis of the derived diazo ketone **15**. To complete this synthesis, all that was required was the conversion of the ester function in the spirane **19** to an exocyclic methylene. This process proved to be somewhat difficult due to the rearrangement of cationic intermediates and the steric hindrance at the ring carbon observed earlier.[4] Finally, the elimination of the selenoxide derivative[16] provided the desired natural product, but the yield in this final process was unsatisfying. The physical properties (with the exception of optical activity) of the synthetic (±)-β-chamigrene (**22**) are in full agreement with those published[8] for the natural substance.

Application of the same ring contraction procedure to the spiro ketone **9** for the (±)-aphidicolin (**34**) synthesis took an unexpected, but very rewarding, turn (Scheme II). Formation of the diazo ketone **14** through the oximino ketone **12** proceeded in the now familiar fashion, i.e., only a 50% conversion to the oximino ketone **12** could be realized, as no oximination could be realized under equilibrating enolate formation conditions. Photolysis of the diazo ketone **14**, even in the presence of excess nucleophile ($NaOCH_3$), led to only meager production of the expected esters **17a** and **17b**. The infrared spectral properties of the crude photolysis product indicated that the major product of the reaction was the cyclobutanone derivative **16**. This system had been encountered earlier[4] in the dessilyl series, but this earlier experience suggested that its formation could be avoided under the photolysis conditions used here. Indeed, in the absence of added nucleophile, and in an inert solvent medium, the cyclobutanone **16** was the sole product. Unlike the previously prepared[4] dessilylcyclobutanone derivative, which was quite stable toward standard isolation and purification procedures, the silylcyclobutanone derivative **16** could *not* be purified from its crude reaction product state; rearrangement to a new ketone **20** took place even on brief chromatography on silica gel!

Scheme III. Cyclobutanone Rearrangement



Mechanistic considerations suggested that this (mild acid catalyzed) rearrangement product was indeed the desired bicyclo[3.2.1]octane system **20**, which had been formed in a manner as indicated in Scheme III. The spectral properties (^1H NMR, IR) of the ketone **20** were in full agreement with this proposal, and subsequent transformation that led to (±)-aphidicolin (**34**) confirmed this conclusion. Thus, the inclusion of the trimethylsilyl group in the synthetic scheme not only had assured the formation of an exocyclic C16,C17-double bond but had also shortcut the π-route approach to the bicyclo[3.2.1]-

(16) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

octane construction. The fact that the cyclobutanone derivatives **16** is formed with such great facility in the trimethylsilyl series is intriguing.

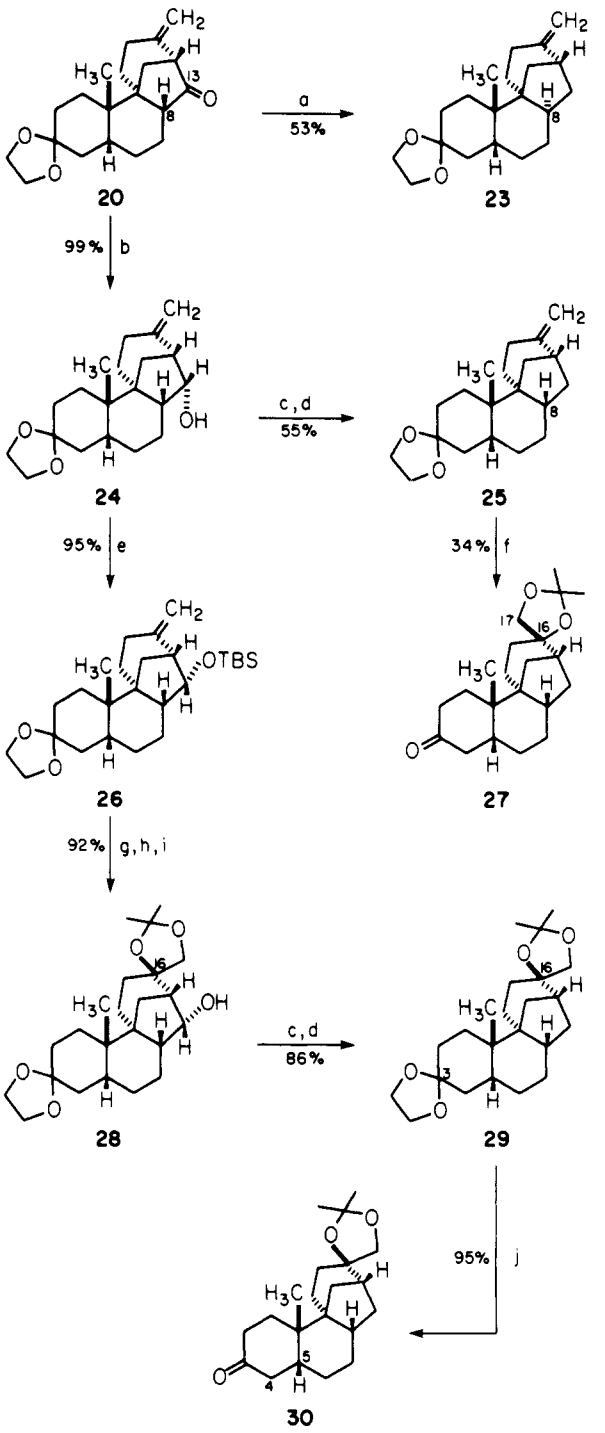
This experience with the rearrangement of the (trimethylsilyl)cyclobutanone **20** led to a reinvestigation of the previously prepared[4] dessilyl analogue. In this earlier report[4] the structure of this substance was incorrectly presented as the alternate fused cyclobutanone system, and thanks are due a referee for calling this to attention. Careful analysis of the high-field (500 MHz) ^{1}H NMR spectrum of this dessilylcyclobutanone derivative clearly revealed a proton adjacent to the carbonyl which had a chemical shift of 2.5 ppm (d of d, J = 2 and 2 Hz). In accord with this structure and by analogy to the trimethylsilyl series above, the dessilylcyclobutanone derivative *did* rearrange to the (now) expected bicyclo[3.2.1]-octane system under the influence of *p*-toluenesulfonic acid in boiling benzene. This rearrangement was, however, not nearly as facile as that encountered for the (trimethylsilyl)cyclobutanone **16** and was not even complete after 40 h of this vigorous acid treatment. As would be expected, the double bond in the bicyclo[3.2.1]octane product was endocyclic.

A similar reaction sequence was then explored in the (±)-β-chamigrene (**22**) series (Scheme II) in order to ascertain whether cyclobutanone formation was a function of the more rigid tricyclic "aphidicolin" system. Photolysis of the diazo ketone **15** in ether solution led in excellent yield to the cyclobutanone derivative **18** and demonstrated the relatively general formation of this ring system. Again it was shown that acid treatment of such fused cyclobutanone systems generates the bicyclo[3.2.1]octane array when the ketone **18** was converted into a mixture of the olefin **21a** and the alcohol **21b** with *p*-toluenesulforic acid monohydrate in hot chloroform. The ease and efficiency with which these bicyclo[3.2.1]octane ring systems can be generated may prove useful for the construction of other natural products (cedrene/cedrol?).

While the basic tetracyclic ring skeleton for (±)-aphidicolin (**34**) is formed in a very efficient manner as a result of this rearrangement, there still remained the cosmetic modifications of functionality and stereochemistry before the synthesis was completel. These modifications turned out to be no less challenging than the foregoing construction of the basic skeleton.

First, attention was paid to the removal of the C13-carbonyl and then hydroxylation of the exocyclic double bond in the ketone **20** (Scheme IV). Direct Wolff–Kishner reduction afforded the ketal **23** but in less than satisfactory yield. As well, ^{1}H NMR spectra of this product **23** suggested that epimerization had taken place at C8. In order to circumvent such an epimerization and increase the overall yield of the reduction product, the deoxygenation of the readily available alcohol **24** through its derived phosphorodiamidate derivative[17] was pursued.[18] This procedure is known[19] to obviate any possible epimerization adjacent to the alcohol function, and the overall yields are usually high. Unfortunately, due to the ease of exocyclic olefin reduction, even in lithium/methylamine solution,[18] the latter expectation was not realized. However, the ketal **25** that was formed proved conclusively that epimerization

Scheme IV. Stereochemical Control of the Hydroxylation of Exo-Olefinic Ketone **20**[a]



[a] a, $N_2H_4 \cdot H_2O$, $N_2H_4 \cdot 2HCl$, TEG; KOH; b, D/BAL, THF, −78 °C; c, *n*-BuLi, DME/TMEDA, Me_2NPOCl_2; Me_2NH; d, $MeNH_2$, THF, *t*-BuOH, Li; NH_4Cl; e, TBSCl, imidazole, DMF; f, OsO_4, MNO, acetone/H_2O/*t*-BuOH; acetone, H_3O^+; g, OsO_4, Pyr; $NaHSO_3$; h, $CH_3C(OCH_3)_2CH_3$, *p*-TsOH·H_2O; i, TBAF, THF; j, Py H^+OTs^-, acetone.

at C8 had taken place during the Wolff–Kishner reduction, for the two ketals **23** and **25** were distinctly different substances.

A further drawback to this sequence became apparent when hydroxylation and then acetonide formation of the ketal **25** led to the ketone acetonide **27**. Comparison of the signal due to the C17 methylene in the ^{1}H NMR spectrum of the ketone acetonide **27** to that due to this position in the spectrum reported[5] for the corresponding

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(18) Ireland, R. E.; Beslin, P.; Giger, R.; Hengartner, U.; Kirst, H. A.; Maag, H. *J. Org. Chem.* **1977**, *42*, 1267–1276.

(19) Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1962**, 1091–1096.

Table I. ^{1}H NMR Chemical Shift Data

compd	C17-CH_2, ppm
aphidicolin diacetonide[5]	3.49, 3.71
16-*epi*-aphidicolin diacetonide[5]	3.69, 3.81
diketal **29**	3.45, 3.69
ketone acetonide **30**	3.48, 3.72
ketone acetonide **27**	3.72, 3.82

aphidicolin derivative suggested that the chirality at C16 was epimeric to that of the natural product (see Table I). Thus, osmium tetroxide hydroxylation of the ketal **25** had occurred from the apparently less hindered α-face of the molecule.[7c]

In order to modify this result, as well as make the deoxygenation process more efficient, the hydroxylation step was included before removal of the C13-oxygen function. To this end, the α-oriented, C13-hydroxyl group was blocked with the bulky *tert*-butyldimethylsilyl grouping so as to increase the steric hindrance toward α-face attack during hydroxylation. Osmium tetroxide hydroxylation of the olefin **26** was now quite efficient and gave a single diol, and then acetonide, as the only product. Removal of the C13-hydroxyl function through reduction of its derived phosphorodiamidate[17] was now not complicated by overreduction, and the overall yield was correspondingly more favorable. That the ultimate diketal **29** did indeed possess the natural chirality at the crucial C16-position was apparent from the signal due to the C17-methylene group in the ^{1}H NMR spectrum (Table I). Thus, the oxygen function at C13 that was the ancillary result of the cyclobutanone rearrangement had serendipidously proved invaluable for the control of the stereochemical outcome of the crucial exocyclic olefin hydroxylation, and completion of this stage of the synthesis by exchange diketalization of the C3-ketal readily gave the tricyclic ketone **30**. The ^{1}H NMR signal due to the C17-methylene of this ketone acetonide **30** even more closely resembled that of the natural (+)-aphidicolin derivative (Table I).

With the ketone **30** in hand, the final obstacle to be overcome was the incorporation of the A ring substitution at C4 and the epimerization of the hydrogen at C5. Earlier work[4] had shown that the latter result could be obtained through lithium/ammonia reduction of the derived C4-(5)-α,β-unsaturated 3-ketone system. The A/B cis ring fusion in the ketone **30** assured the introduction of the conjugated double bond in the desired C4(5)-position and subsequent chemical reduction suggested that the intermediate enolate anion formed could be used to introduce a substituent at the C4-position. As attractive as this plan is, there still remained a problem—namely, how to introduce *two unlike* substituents at the C4-position. Several reaction sequences were explored on model systems with uniformly unrewarding results before the very efficient and potentially quite general pathway shown in Scheme V was applied.

While the amine-based Mannich condensation invariably attacked the ketone **30** at the C6-position, the thiol-based Mannich condensation, explored much earlier by Petrow,[19] was known to result in substitution at the vinylic C4-position. Advantage was thus taken of this reaction for the introduction of the C4-methyl group *and* the preservation of the intermediate enolate anion formed during the subsequent lithium/ammonia reduction. It seems reasonable to propose that the reduction of the unsaturated ketone **32** proceeds through the C4-*exo*-methylene ketone, which is formed when the initially produced enolate anion ejects phenyl mercaptide as a leaving group. Subsequent reduction of this new α,β-unsaturated ketone and then trapping of the resulting enolate anion with trimethylsilyl chloride leads to the observed silyl enol ether **33**. This procedure then introduces one of the required substituents at the C4-position *and* preserves the regiospecifically formed enol derivative that can be used to introduce the second, *unlike* C4-substituent.

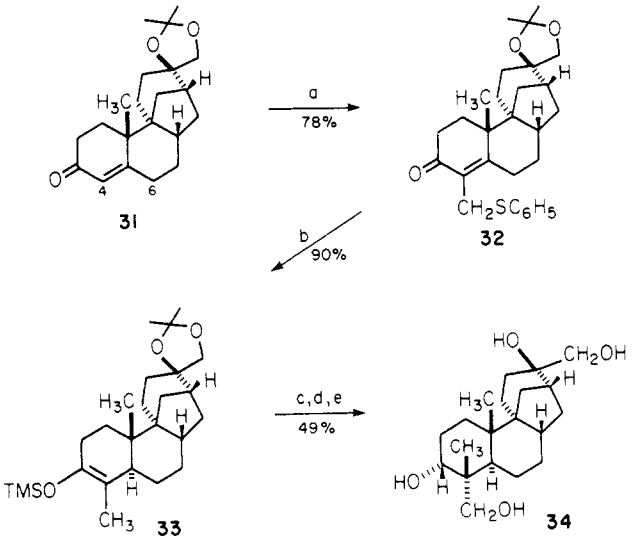
Completion of the (±)-aphidicolin (**34**) synthesis then followed well-established procedures. The enolate anion regenerated from the silyl enol ether **33** was formylated,[20] the C3-ketone reduced, and finally the acetonide at C16,C17 was cleaved. The racemic material prepared in this fashion had the same physical and spectral properties (except optical rotation) as those of an authentic sample of (±)-aphidicolin, which was kindly provided by Dr. B. Hesp.[21] Further refinement of this synthetic sequence and, in particular, the utilization of the scheme for the preparation of unnatural analogues are underway.

Experimental Section[22]

I. (±)-β-Chamigrene Series. 2,3,3-Trimethylcycloheptene (3), 1,1-Dimethyl-2-methylenecycloheptane (2), and 1-*tert*-Butylcyclohexene (4). To a stirred solution of 1.65 g (10.6 mmol) of 1,2,2-trimethylcycloheptanol[23] in 50 mL of pyridine at −45 °C (bath temperature) was added 3 mL (41 mmol) of thionyl chloride dropwise over 5 min. The reaction mixture was stirred for an additional 1 h at −45 to −50 °C and then poured into 200 mL of ice water. The resulting mixture was extracted with ether (3 × 100 mL), and the combined organic extracts were washed with 5% aqueous hydrochloric acid (4 × 50 mL), saturated aqueous sodium bicarbonate (1 × 50 mL), and then water (1 × 50 mL). The resulting solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on 40 g of silica gel with 250 mL of *n*-pentane to afford 1.40 g (77%) of a mixture of olefins **2**, **3**, and **4**[24] in the approximate ratio of 3:2:1, as judged by VPC (10% SE-30, 100 °C). This olefin

(20) Stork, G.; D'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114–7116.
(21) A sample of authentic (+)-aphidicolin was kindly provided by Dr. B. Hesp (ICI-Americas, Wilmington, DE).
(22) All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded with a Varian T-60, a Varian A-60, or a Varian EM390 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane (δ_{Me_4Si} 0.0) as an internal standard. Gas-liquid phase chromatographic (VPC) analyses were determined on a Hewlett-Packard 5750 gas chromatograph using helium carried gas at a flow rate of 60 mL/min. All analytical VPC was conducted on a 5 ft × 0.125 in. column packed with 4% SE-30 on 60–80 mesh Chromosorb WAS DMCS. Preparative layer chromatography (PTLC) was carried out on precoated PLC plates with a 20 × 20 × 2 mm layer of silica gel 60F-254 on glass plates manufactured by E. Merck. Alumina used for chromatography refers to the grade I, neutral variety manufactured by M. Woelm made up to grade II or III as indicated by addition of 3% or 6% water prior to use. Silica gel columns used the 0.005–0.2 mm silica gel manufactured "for column chromatography" by E. Merck. Preparative medium-pressure column chromatography was performed by using $^1/_2$ × 20 in. or 2 × 20 in. glass columns with fittings supplied by Chromatronix, Inc., and an instrument minipump supplied by Milton Roy Co. The columns were packed with silica gel H "for tlc acc. to Stahl" (10–40) manufactured by E. Merck. Ether and petroleum ether were degassed under water aspirator vacuum prior to use. "Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran were distilled from lithium aluminum hydride, *tert*-butyl alcohol, pyridine, and benzene were distilled from calcium hydride, dichloromethane and iodomethane were distilled from phosphorus pentoxide, and methanol was distilled from magnesium turnings. "Ether" refers to anhydrous diethyl ether which was supplied by Mallinckrodt. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction, bp 35–60 °C, which was supplied by J. T. Baker Co., and was not further purified. All water used in the reactions and workups was distilled water. Brine refers to a saturated aqueous solution of sodium chloride. All reaction flasks and syringes were dried for at least 12 h in an oven (at 140 °C) and cooled in a desiccator over anhydrous calcium sulfate prior to use. All reactions (except for photooxygenations and hydrogenations) were run under an atmosphere of argon, and at the beginning of all reactions, the solutions were degassed. Mass spectral analyses were performed by Beth Irwin, UCLA, Los Angeles, California. Microanalyses were performed by Spang Microanalytical Laboratory.
(23) Christl, M.; Roberts, J. D. *J. Org. Chem.* **1972**, *37*, 3443–3452.
(24) Servis, K. L.; Bowler, D. J.; Ishii, C. *J. Am. Chem. Soc.* **1975**, *97*, 73–80.

Scheme V. Conversion of the Ketone 30 to (±)-Aphidicolin (34)[a]



[a] a, $(CH_2O)_x$, C_6H_5SH, NEt_3, EtOH; b, Li, NH_3(l), *t*-BuOH, THF; TMSCl, NEt_3, THF; c, MeLi, THF, −78 °C; HCHO (g); 10% HOAc/THF; d, L-Selectride, THF, −78 °C; e, 10% aqueous HCl, CH_3OH.

mixture was routinely used for subsequent transformations without separation. An analytically pure sample of endocyclic olefin **3** was prepared by preparative VPC (10% SE-30, 90 °C): IR ($CHCl_3$) nondescript; ^1H NMR ($CDCl_3$) δ 1.07 (s, 6 H, *gem*-CH_3), 5.45 (br t, 1 H, J = 7 Hz, vinyl).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.97; H, 12.84.

An analytically pure sample of exocyclic olefin **2** was prepared as described below.

1,1-Dimethyl-2-methylenecycloheptane (2). To a stirred suspension of 19.8 g (55.4 mmol) of methyltriphenylphosphonium bromide in 60 mL of THF at −78 °C was added 24.7 mL (56.8 mmol) of a 2.3 M solution of *n*-butyllithium in hexane. The reaction mixture was warmed to room temperature and stirred for 30 min. A solution of 2.0 g (14.3 mmol) of 2,2-dimethylcycloheptanone in 7 mL of THF was then added, and the reaction mixture was stirred an additional 13 h. The reaction mixture was then heated under reflux for 7.5 h after TLC indicated that some starting material remained. The reaction mixture was then cooled and 5 mL of methanol was added. The resulting white suspension was filtered through a short pad of silica gel with ether, and the resulting 2.5 g of yellow oil was chromatographed on 50 g of silica gel with *n*-pentane to afford 1.6 g (81%) of exocyclic olefin **2** as a colorless oil. Analytically pure olefin was obtained by preparative VPC (10% SE-30, 100 °C): IR ($CHCl_3$) 3095 (=CH_2), 1631 cm^{-1} (C=C), ^1H NMR ($CDCl_3$) δ 1.08 (s, 6 H, 2 × CH_3), 2.05–2.20 (m, 2 H, allylic), 4.70, 4.77 (2 d, 2 × 1 H, J = 2 Hz, vinyl).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.74; H, 13.10.

3,3-Dimethyl-2-methylenecycloheptanone (5). A solution of 8.6 g (62 mmol) of the olefin mixture **2**, **3**, and **4** (27% olefin **3** by VPC at 90 °C) prepared as described above, 50 mg of hematoporphyrin dihydrochloride, 10 mL of pyridine, and 25 mL of ethyl acetate was irradiated for 2 h with a 650-W tungsten filament lamp in a Pyrex jacket cooled by tap water while oxygen was bubbled through the solution. The solution was added to 30 mL of acetic anhydride and stirred 2 h at room temperature. The brown mixture was carefully poured into an ice cold, stirred solution of saturated aqueous sodium carbonate (300 mL). Additional solid sodium carbonate was added in portions over 20 min until gas evolution had ceased, and the solution was saturated. This mixture was then extracted with ether (4 × 500 mL), and the combined organic layers were washed with brine (2 × 50 mL) and then concentrated under reduced pressure. The crude product was diluted with 100 mL of *n*-heptane and again concentrated under reduced pressure (azeotropic removal of pyridine) to provide 9.4 g of brown oil. Chromatography of this oil on 250 g of Florisil with petroleum ether provided 5.1 g of recovered olefin (a mixture of **2** and **4** by ^1H NMR) and subsequent elution with 1:1 petroleum ether:ether afforded 2.36 g (92% yield based on olefin **3** present) of the desired enone **5**. A portion of this material was rechromatographed on Florisil and then evaporatively distilled at 100–110 °C (ca. 45 mm) to obtain analytically pure α-methylene ketone **5**; R_f 0.30 (10:1 petroleum ether:ether); IR (neat) 1687 (C=O), 1608 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.13 (s, 6 H, 2 × CH_3), 2.35–2.60 (m, 2 H, allylic), 5.08, 5.27 (2 s, 2 H, vinyl).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.09; H, 10.54.

Equilibration of Olefin Mixture with Iodine. To 0.89 g (6.4 mmol) of olefin mixture (recovered from photooxygenation; approximately a 3:1 ratio of olefin **2** and *tert*-butylcyclohexene (**4**)) at 120 °C was added 7 mg (0.028 mmol) of freshly sublimed iodine with stirring. After 30 min, the reaction mixture was cooled and 5 mL of 10% aqueous sodium thiosulfate was added. The resulting mixture was extracted with *n*-pentane (3 × 75 mL) and the combined organic layers were concentrated under reduced pressure to a brown oil. Chromatography of this oil on 20 g of silica gel with *n*-pentane afforded 0.82 g (92%) of a colorless oil, shown by NMR and VPC (10% SE-30, 90 °C) to be a mixture of olefins **2**, **3**, and **4** in the approximate ratio 41:36:23. Material prepared in this manner was used for the photooxygenation procedure without further purification.

2,5,5-Trimethyl-3,4,6,7,8,9-hexahydrocyclohepta[*b*]pyran-2-carboxylic Acid, Methyl Ester (8a). A solution of 10.2 g (67 mmol) of enone **5**, 102 g (1 mol) of methyl methacrylate, and 100 mg of hydroquinone in 100 mL of xylenes was sealed in a 750-mL teflon-lined autoclave (Berghof) after bubbling argon through the solution. The reaction mixture was heated to 195 °C over 2 h and then maintained at 195 °C for an additional 69 h. The autoclave was cooled and ca. 200 mL of an amber, free flowing liquid was removed and slowly added to 1500 mL of rapidly stirred ether in an open flask. This served to precipitate polymeric material as a flocculent white solid. The solution was decanted and concentrated under reduced pressure at 45 °C to afford 185 g of amber liquid. The polymer was then dissolved in 150 mL of chloroform and slowly added to 1500 mL of rapidly stirred ether as before. Decantation and concentration of the solution under reduced pressure afforded an additional 28 g of yellow oil which was combined with the main fraction. Removal of xylenes by distillation under reduced pressure (ca. 50 mm), followed by filtration of the pot residue through silica gel with ether and then concentration of the eluent under reduced pressure, afforded 49 g of yellow oil. The material was divided into two portions and each was purified by flash chromatography (5 × 25 cm, 20:1 petroleum ether:ether) to afford a total of 8.5 g (50%) of Diels–Alder adduct as a colorless oil: R_f 0.44 (10:1 petroleum ether:ether); IR (neat) 1752, 1730 (C=O), 1660 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.97, 1.02 (2 s, 6 H, *gem*-CH_3), 1.41 (s, 3 H, C2 CH_3), 3.67 (s, 3 H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 20.3, 23.4, 24.4, 25.3, 27.0, 29.1, 30.7, 31.4, 35.9, 39.8, 51.4, 75.6, 111.7, 148.7, 174.2. Analytically pure material was prepared by rechromatography as above of a portion of the ester, followed by evaporative distillation at 125–135 °C (ca. 45 mm).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.52; H, 9.63.

Further elution provided 3.9 g (46%) of recovered enone.

2-Ethyl-2,5,5-trimethyl-3,4,6,7,8,9-hexahydrocyclohepta-[*b*]pyran (8c). To a stirred solution of 106 mg (0.42 mmol) of the ester **8a** in 3 mL of hexane at −78 °C was added dropwise over 1.5 min 1.5 mL (0.75 mmol) of a 0.5 M solution of diisobutylaluminum hydride (DiBAL-H) (Aldrich) in 1:1 hexane:dimethoxyethane. After stirring for 45 min at −78 °C, another 0.2 mL (0.10 mmol) of the 0.5 M DiBAL-H in hexane:DME was added. The reaction mixture was treated with 1 mL of methanol 5 min later and then warmed to room temperature. The gelatinous reaction mixture was then diluted with 20 mL of ether and 5 mL of a 0.5 M aqueous sodium potassium tartrate solution. The organic layer was removed, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (1 × 10 mL), dried ($MgSO_4$), and then concentrated under reduced pressure to afford 104 mg of crude aldehyde **8b** as an oil: IR (neat) 2820, 2725 (–CHO), 1740 (C=O), 1660 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.96, 1.01 (2 s, 2 × 3 H, *gem*-dimethyl),

1.20 (s, 3 H, C2 CH_3), 9.45 (d, 1 H, J = 2 Hz, CHO). This material was used directly for the following experiment.

To a suspension of 1.25 g (3.5 mmol) of methyltriphenylphosphonium bromide in 10 mL of THF at room temperature was added dropwise 1.4 mL (3.1 mmol) of a 1 M solution of *n*-butyllithium in hexane. After 1 h, the crude aldehyde in 2 mL of THF was added. The reaction mixture was stirred 5 h and then filtered through a short pad of silica gel with 300 mL of 1:1 petroleum ether:ether. The filtrate was concentrated under reduced pressure and immediately purified by flash chromatography (3 × 20 cm, 50:1 petroleum ether:ether) to afford 85 mg (92% from **8a** of the allyl vinyl ether) of **8c** as a colorless oil: R_f 0.80 (20:1 petroleum ether:ether); IR ($CHCl_3$) 1691 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.98, 1.03 (2 s, 2 × 3 H, *gem*-dimethyl), 1.23 (s, 3 H, C2 CH_3), 2.15–2.40 (m, 2 H, allylic), 4.95 (dd, 1 H, J = 1.8, 10.2 Hz, vinyl), 5.05 (dd, 1 H, J = 1.8, 16.8 Hz, vinyl), 5.72 (dd, 1 H, J = 10.2, 16.8 Hz, vinyl). Analytically pure material was obtained by rechromatography of a portion of the olefin followed by evaporative distillation at 55–65 °C (0.25 mm).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.57; H, 10.91.

3,12,12-Trimethylspiro[5.6]-2-dodecen-7-one (10). A. By Claisen Rearrangement of 8c in Quinoline. A stirred solution of 114 mg (0.52 mmol) of the allyl vinyl ether **8c** in 10 mL of quinoline was heated at 170 °C for 4 h. The cooled reaction mixture was then diluted with 300 mL of ether and washed with 5% aqueous hydrochloric acid (2 × 100 mL), saturated aqueous sodium bicarbonate (1 × 50 mL), and then brine (1 × 50 mL). The ethereal solution was dried ($MgSO_4$) and concentrated under reduced pressure to provide 174 mg of black oil, which was purified by flash chromatography (3 × 15 cm, 40:1 petroleum ether:ether) to afford 91 mg (80%) of spiro ketone **10** as a colorless oil which soon crystallized: mp 68–70 °C, R_f 0.32 (20:1 petroleum ether:ether); IR (neat) 1695 (C=O), 1402, 1382 cm^{-1} (*gem*-dimethyl); ^1H NMR (500 MHz, $CDCl_3$) δ 0.85, 0.87 (s, 2 × 3 H, *gem*-dimethyl), 1.55 (s, 3 H, allylic CH_3):, 5.38 (dd, 1 H, J = 6.2, 5.1 Hz, vinyl); ^{13}C NMR ($CDCl_3$) δ 22.3, 22.9, 23.4, 24.2, 25.1, 26.1, 27.8, 28.4, 35.8, 39.7, 40.7, 56.1, 120.1, 133.9, 214.8; mass spectrum (16 eV), *m/e* (intensity) 220 (100), 205 (20), 164 (22), 149 (95), 138 (19), 136 (53). Analytically pure material, mp 68–70 °C, was prepared by crystallization from *n*-pentane:ether.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.60; H, 10.90.

B. 3,6,6-Trimethylbicyclo[4.5.1]dodec-2-en-12-one (11). After 3 cycles of freezing and thawing, 89 mg (0.40 mmol) of the allyl vinyl ether **8c** was sealed in a base-washed and flame-dried Pyrex ampoule and heated at 165 °C for 2 h. The tube was cooled and then the contents were removed with ether. Concentration under reduced pressure afforded 85 mg (96%) of the bicyclic ketone **11** as a pale yellow oil: R_f 0.23 (20:1 petroleum ether:ether); IR (neat) 1710 (C=O), 1395, 1375 cm^{-1} (*gem*-dimethyl); ^1H NMR (500 MHz, $CDCl_3$) δ 0.82, 0.92 (2 s, 2 × 3 H, *gem*-dimethyl), 1.67 (s, 3 H, allylic CH_3), 2.87 (dd, 1 H, J = 12.5, 4.0 Hz, C7 methyne), 5.38 (br t, 1 H, J = 9 Hz, vinyl); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.1, 22.4, 25.1, 29.2, 29.3, 30.4, 32.5, 33.9, 46.4, 55.3, 56.1, 122.6, 139.5, 217.4; mass spectrum (16 eV), *m/e* (intensity) 220 (100), 205 (20), 187 (6), 151 (15), 138 (31). A portion of the material was rechromatographed and evaporatively distilled at 80–85 °C (0.25 mm) to afford analytically pure material.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.82; H, 10.94.

In many runs this procedure provided a mixture of spiro ketone **10** and bicyclic ketone **11** in variable proportions.

B. By Diels–Alder Reaction with Isoprene. To a stirred solution of 4.31 g (28.3 mmol) of the enone **5** and 8.5 mL (84.9 mmol) of isoprene in 20 mL of dichlormethane at −10 °C was added 19 mL (ca. 33.9 mmol) of a 25% solution of dimethylaluminum chloride in hexane over 5 min. The solution was then warmed to room temperature and stirred 4 h. The reaction mixture was then poured into 100 ml of ice water, and the resulting mixture was extracted with ether (3 × 500 mL). The ethereal extracts were combined, then washed with brine (1 × 50 mL), and then dried ($MgSO_4$). Concentration under reduced pressure afforded 6.27 g of oily crystals which were purified by flask chromatography (7 × 15 cm, 20:1 petroleum ether:ether) to provide 4.33 g (69%) spiro ketone **10** as colorless crystals. This material was identical by mp, TLC, and 500 MHz ^1H NMR with material prepared via the Claisen rearrangement of the allyl vinyl ether **8c**.

Preparation of α-Oximino Ketone 13. To a stirred solution of 166 mg (0.75 mmol) of the spiro ketone **10** in 10 mL of THF at 0 °C was added 0.6 mL (1.43 mmol) of a 2.38 M solution of *n*-butyllithium in hexane. The reaction mixture was then warmed to room temperature and stirred for 20 min before the addition of 0.6 mL (4.5 mmol) of isoamyl nitrite. The resulting solution was stirred for 4 h and then acidified to ca. pH 4 with 10 mL of 1% aqueous hydrochloric acid solution. The reaction mixture was then extracted with ether (3 × 100 mL) and the combined organic layers were washed with brine (1 × 25 mL) and dried ($MgSO_4$). Concentration under reduced pressure afforded an oil which was purified by flash chromatography (3 × 25 cm, 6:1 petroleum ether:ether) to afford 63 mg (40%) of the starting spiro ketone **10**. Further elution with 3:1 petroleum ether:ether provided 84 mg (45%) of the α-oximino ketone **13** as a pale yellow solid: R_f 0.11 (3:1 petroleum ether:ether); IR ($CDCl_3$) 3590 (s), 3300 (br) (–OH), 1700 (C=O), 1625 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.93 (s, 6 H, *gem*-dimethyl), 5.25 (s, 1 H, $w_{1/2}$ = 9 Hz, vinyl). A portion of this material was recrystallized from ether:petroleum ether to afford analytically pure material: mp 152–154 °C dec.

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 72.18; H, 9.24.

11-Carbomethoxy-3,7,7-trimethylspiro[5.5]undec-2-ene (19). An ethereal solution of chloramine was prepared just prior to use by the addition of 2.3 mL (35 mmol) of a 15 M aqueous solution of ammonium hydroxide to a stirred solution of 50 mL (36 mmol) of 5.25% aqueous sodium hypochlorite solution in 50 mL of ether at 0 °C. To a stirred solution of 426 mg (1.70 mmol) of the oximinoketone **13** and 0.42 mL (1.68 mmol) of 4 N aqueous sodium hydroxide solution in 35 mL of ether at 10 °C was added 25 mL (ca. 4 mmol) of the ethereal chloramine solution over 3 min. After 30 min, another 9 mL (ca. 1.5 mmol) of the chloramine solution was added, and the reaction mixture was stirred for an additional 80 min. The mixture was then diluted with 25 mL of water and extracted with ether (3 × 200 mL). The combined organic layers were washed with brine (1 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 481 mg of the crude diazo ketone **15** as a yellow solid: R_f 0.75 (3:1 petroleum ether:ether); IR ($CHCl_3$) 2085 (N_2), 1615 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.90, 0.95 (2 s, 2 × 3 H, *gem*-dimethyl), 5.33 (br d 1 H, $w_{1/2}$ = 9 Hz, vinyl). This material was used directly in the following experiment without further purification.

A solution of 481 mg of the above diazo ketone **15** and 584 mg (10.8 mmol) of sodium methoxide in 25 mL of methanol was photolyzed under argon for 1 h at −90 to −85 °C (liquid nitrogen–methanol bath) with a Hanovia medium-pressure mercury-vapor lamp and a Pyrex filter. The reaction mixture was maintained at −85 °C for 3 min and then warmed to room temperature over 30 min. The yellow solution was then poured into 50 mL of ice water and this mixture was then extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with brine (1 × 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 394 mg of yellow oil. The crude product was purified by flash chromatography (3 × 20 cm, 20:1 petroleum ether:ether) to afford 244 mg (57% from **13**) of ester **19** as a pale yellow oil. Mixed fractions afforded an additional 21 mg of ester for a total yield of 265 mg (62% from oximinoketone **13**): R_f 0.60 (10:1 petroleum ether:ether); IR ($CDCl_3$) 1723 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.85, 0.93 (2 s, 2 × 3 H, *gem*-dimethyl), 2.62 (dd, 1 H, J = 5, 14 Hz, >CH–CO_2), 3.57 (s, 3 H, ester), 5.33 (m, 1 H, $w_{1/2}$ = 9 Hz, vinyl); ^{13}C NMR ($CDCl_3$) δ 20.9, 22.9, 23.3, 25.6, 26.0, 28.5, 29.6, 37.3, 39.2, 47.4, 51.0, 122.0, 132.0, 176.9; mass spectrum (70 eV), *m/e* (intensity) 250 (6), 218 (15), 135 (49), 133 (18), 44 (46), 40 (100). Analytically pure material was prepared by rechromatography and evaporative distillation at 70–80 °C (1 mm) of a portion of the material. This material later crystallized: mp 77–80 °C.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.76; H, 10.45.

11-(Hydroxymethyl)-3,7,7-trimethylspiro[5.5]undec-2-ene. To a stirred solution of 141 mg (0.56 mmol) of the ester **19** in 10 mL of ether at 0 °C was added 80 mg (2.1 mmol) of lithium aluminum hydride. The ice bath was removed, and the reaction

mixture was stirred for 1.5 h at room temperature. Excess reagent was quenched by the addition of 80 μL of water, followed by 80 μL of 4 N aqueous sodium hydroxide solution, and 320 μL of water. The resulting mixture was dried ($MgSO_4$) and filtered, and then the filtrate was concentrated under reduced pressure to afford 119 mg (96%) of the corresponding alcohol as a colorless oil which crystallized upon standing. This material was generally used for subsequent transformations without additional purification. Analytically pure material was obtained by recrystallization from ether: mp 84–85 °C; R_f 0.27 (4:1 petroleum ether:ether); IR ($CHCl_3$) 3640, 3480 (OH), 1395, 1370 cm^{-1} (*gem*-dimethyl); ^1H NMR ($CDCl_3$) δ 0.82, 0.85 (2 s, 2 × 3 H, *gem*-dimethyl), 3.4–3.85 (m, 3 H, $-CH_2O$), 5.30 (m, 1 H, $w_{1/2}$ = 8 Hz, vinyl); mass measured molecular ioin calcd for $C_{15}H_{26}O$, 222.1985; found, 222.1980.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.13; H, 11.80.

(±)-β-Chamigrene (22). A. Preparation of the Selenide. When the procedure of Grieco and co-workers[16] was followed, a stirred solution of 40 mg (0.18 mmol) of the above alcohol and 184 mg of (0.81 mmol) *o*-nitrophenyl selenocyanate in 0.4 mL of THF at room temperature was treated dropwise with 0.253 mL (0.85 mmol) of tri-*n*-butylphosphine. The reaction mixture was stirred 1 h and then purified, without additional workup, by flash chromatography (3 × 15 cm, 100:1 petroleum ether:ether) to afford 48 mg (66%) of the selenide as a yellow oil: R_f 0.36 (25:1 petroleum ether:ether); ^1H NMR (CCl_4) δ 0.90, 0.95 (2 s, 2 × 3 H, *gem*-dimethyl), 2.5–3.3 (m, 2 H, CH_2–Se), 5.33 (m, 1 H, $w_{1/2}$ = 7 Hz, vinyl), 7.1–8.3 (m, 4 H, *o*-nitrophenyl). This material was used directly for subsequent experiments.

Prior to elution of the desired selenide, there was obtained 12 mg of an oil which was shown by TLC and VPC (10% SE-30, 160 °C) to be a mixture of olefins formed by cyclization of the *exo*-methylene group with the ring double bond. This material was discarded.

B. Elimination of the Selenide. To a stirred solution of 41 mg (0.10 mmol) of the above selenide in 0.5 mL of dichloromethane at room temperature was added 310 μL (3 mmol) of a 90% *tert*-butyl hydroperoxide solution. The reaction mixture was stirred for 24 h at room temperature, then diluted with 29 mL of *n*-pentane, and washed with brine (2 × 1 mL). The resulting solution was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the resulting oil on 10 g of silver nitrate impregnated silica gel (25% w/w) with *n*-pentane afforded 10 mg (49%) of (±)-β-chamigrene (**22**) with ^1H NMR and IR in excellent agreement with published data.[8] Analytically pure material was prepared by preparative VPC (10% SE-30, 160 °C), followed by evaporative distillation at 80–90 °C (1.2 mm) [lit.[8] bp 110–113 °C (13 m)].

Anal. Calcd for $C_{15}H_{24}$: C, 88.33; H, 11.67. Found: C, 88.04; H, 11.62.

Preparation of Cyclobutanone 18. A yellow solution of 62 mg (0.25 mmol) of the diazo ketone **15** in 5 mL of ether was photolyzed for 2 h at 0 °C in the apparatus previously described. The now colorless solution was then warmed to room temperature and concentrated under reduced pressure to afford 55 mg (>90%) of crude cyclobutanone **18** as a colorless oil which crystallized upon standing. A portion of the material was purified by flash chromatography (2 × 20 cm, 25:1 petroleum ether:ether) followed by crystallization from *n*-pentane at −10 °C to afford analytically pure material: mp 47.5–49.0 °C; R_f 0.62 (9:1 petroleum ether:ether); IR ($CHCl_3$) 1755 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.82, 0.87 (2 s, 2 × 3 H, *gem*-dimethyl), 1.01 (s, 3 H, CH_3), 2.47 (br d, 1 H, J = 2.5 Hz, methyne).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.29; H, 9.97.

Rearrangement of Cyclobutanone 18 with *p*-Toluenesulfonic Acid. To a solution of 21 mg of the cyclobutanone **18** in 0.5 mL of deuteriochloroform in an NMR tube was added ca. 1 mg of *p*-toluenesulfonic acid monohydrate. The disappearance of resonances attributed to cyclobutanone **18** and the development of new resonances were monitored by ^1H NMR, and the rearrangement was judged complete after 5 days at room temperature. The reaction mixture was then diluted with 10 mL of chloroform, washed with saturated aqueous sodium bicarbonate (1 × 1 mL) and brine (1 × 1 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 34 mg of an oil. This was purified by flash chromatography (2 × 15 cm, 9:1 *n*-pentane:ether) to afford 5 mg (24%) of rearranged ketone **21a** as a colorless oil. Rechromatography and evaporative distillation at 95–105 °C (0.8 mm) provided analytically pure material: R_f 0.29 (9:1 petroleum ether:ether); IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.93, 1.00 (2 s, 2 × 3 H, *gem*-dimethyl), 2.1–2.4 (m, 3 H, 2 allylic and —CH—C=O), 2.60 (br d, 1 H, J = 5 Hz, allylic α-keto), 5.28 (m, 1 H, $w_{1/2}$ = 9 Hz, vinyl).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.50; H, 10.07.

Further elution with ether provided 7 mg (31%) of keto alcohol **21b**. This material was filtered through a short pad of silica gel with 2:1 *n*-pentane:ether and evaporatively distilled at 105–115 °C (0.6 mm) to afford analytically pure material: R_f 0.18 (2:1 petroleum ether:ether); IR ($CHCl_3$) 3605 (s), 3450 (br) (–OH), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.93, 0.98 (2 s, 2 × 3 H, *gem*-dimethyl), 1.29 (s, 3 H, $-O-C-CH_3$).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.98; H, 10.18.

II. (±)-Aphidicolin Series. Methyl 3-(Dimethylamino)-2-((trimethylsilyl)methyl)propionate. To a solution of diisopropylamine (31 mL, 0.22 mol) in 400 mL of dry tetrahydrofuran at 0 °C under argon was added 94 mL (0.216 mol) of a 2.30 M *n*-butyllithium in hexane solution dropwise over 20 min. After stirring for 25 min, the resulting solution of lithium diisopropylamide was cooled to −78 °C and a solution of methyl 3-(dimethylamino)propionate (**1**) (26.2 g, 0.2 mol) in tetrahydrofuran (65 mL) was added dropwise over 30 min. After 45 min, a solution of (iodomethyl)trimethylsilane (45 g, 0.21 mol) and dry hexamethylphosphoric triamide (38.2 mL, 0.22 mol) was added over 20 min. After 15 min, the reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. The resulting pale yellow reaction mixture was quenched with 100 mL of saturated ammonium chloride and then poured into 800 mL of ether. The organic layer was separated and washed with water (2 × 250 mL). The aqueous fractions were combined and extracted with ether (3 × 150 mL). The organic fractions were combined and washed with water (2 × 200 mL) and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a pale yellow liquid. This material was combined with that obtained from two similar runs and distilled to give the amino ester as a colorless liquid (90.4 g, 69%) which contains small amounts of unknown impurities that do not interfere with subsequent reactions. An analytically pure sample was obtained by distillation: bp 95–97 °C (16 mmHg); IR 1730 (C=O), 840 ($SiMe_3$) cm^{-1}; ^1H NMR δ −0.13 (s, 9 H, $Si(CH_3)_3$), 0.65 (m, 2 H, CH_2Si), 2.03 (s overlapping m, 7 H, $(CH_3)_2N$ and $CHCO_2$), 2.43 (m, 2 H, CH_2N), 3.48 (s, 3 H, CO_2CH_3).

Methyl α-((Trimethylsilyl)methyl)acrylate. To a solution of 33.3 g (0.153 mol) of the above amino ester in 500 mL of anhydrous methanol was added 114 mL (1.8 mol) of methyl iodide. After stirring for 5 min, the solution was allowed to stand in the dark for 48 h. The solvent was removed at reduced pressure and the solid residue washed with ether to afford the corresponding salt (43.3 g, 78%) as a dark yellow solid which was used in the following reaction without further purification.

To a stirred suspension of this salt (43.3 g, 0.12 mol) in 250 mL of dry benzene under argon was added 1,5-diazabicyclo-[4.3.0]non-5-ene (34.5 g, 0.28 mol). After heating at reflux for 2 h, the mixture was cooled and washed with 1 N hydrochloric acid (3 × 100 mL) and brine. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure and the residue was distilled to give the acrylate as a colorless liquid (16.9 g, 81%). An analytically pure sample was obtained by distillation bp 101 °C (75 mmHg); IR 1720 (C=O), 1625 (C=C), 855 ($SiMe_3$) cm^{-1}; ^1H NMR δ −0.03 (s, 9 H, $Si(CH_3)_3$), 1.77 (br s, 2 H, CH_2Si), 3.68 (s, 3 H, CO_2CH_3), 5.25 (m, 1 H, vinyl), 5.92 (d, 1 H, J = 1.5 Hz, vinyl).

Anal. Calcd for $C_8H_{16}O_2Si$: C, 55.77; H, 9.36. Found: C, 55.59; H, 9.26.

9,9(8*H*)-(Ethylenedioxy)-11a-methyl-3-((trimethylsilyl)-methyl)-1,2,3,5,6,7,7a*β*,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-*b*]pyran-3-carboxylic Acid Methyl Ester (6a) and 9,9(8*H*)-(Ethylenedioxy)-11a*β*-methyl-3*β*-((trimethylsilyl)-methyl)-1,2,3,5,6,7,7a*β*,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-*b*]pyran-3*α*-carboxylic Acid Methyl Ester (7a). A

mixture of 1.42 g (5.68 mmol) of the α-methylene ketone **1** and 4.90 g (28.4 mmol) of methyl ((trimethylsilyl)methyl)acrylate (stabilized with 0.3 hydroquinone) in a base-washed (NH_4OH), flame-dried (under vacuum) glass tube was degassed and sealed under vacuum. The tube was then placed in a 125 °C oil bath and heated at 125 °C for 39 h. The tube was cooled and its contents (a freely flowing, pale yellow liquid) were applied directly to a silica gel column (120 g). Elution with cyclohexane:ethyl acetate (9:1) gave unreacted acrylate, which could be recovered in usable condition by distillation, and 2.13 g (89%) of a 7:3 mixture (by ^1H NMR) of esters **6a** and **7a**.

These esters could be efficiently separated by medium-pressure liquid chromatography on silica gel using petroleum ether:ether (6:1). For example, 4.75 g of a 7:3 mixture of esters **6a** and **7a** gave 3.26 g (69%) of ester **6a** as a colorless oil and 1.30 g (27%) of ester **7a** as a colorless solid.

An analytical sample of ester **6a** was prepared by evaporative distillation and that of ester **7a** by recrystallization from *n*-hexane.

For ester **6a**: R_f 0.37 (petroleum ether:ether, 2:1); evaporative distillation ~160 °C (0.005 mmHg); IR 1745, 1725 (C=O), 1650 (C=C), 860, 840 ($SiMe_3$) cm^{-1}; ^1H NMR δ −0.02 (s, 9 H, $Si(CH_3)_3$), 0.96 (s, 3 H, CH_3), 1.12 (s, 2 H, CH_2Si), 3.60 (s, 3 H, CO_2CH_3), 3.86 (s, 4 H, OCH_2CH_2O).

Anal. Calcd for $C_{23}H_{38}O_5Si$: C, 65.36; H, 9.06. Found: C, 65.27; H, 9.14.

For ester **7a**: R_f 0.29 (petroleum ether:ether, 2:1); mp 86–88 °C (*n*-hexane); IR 1745, 1725 (C=O), 1660 (C=O), 865, 845 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.03 (s, 9 H, $Si(CH_3)_3$), 1.07 (s, 3 H, CH_3), 3.68 (s, 3 H, CO_2CH_3), 3.88 (s, 4 H, OCH_2CH_2O).

Anal. Calcd for $C_{23}H_{38}O_5Si$: C, 65.36; H, 9.06. Found: C, 65.25; H, 9.13.

9,9(8*H*)-(Ethylenedioxy)-11aβ-methyl-3α-((trimethylsilyl)methyl)-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-*b*]pyran-3β-carbaldehyde (6b). To a solution of 3.36 g (7.95 mmol) of ester **6a** in 250 mL of dry ether at −78 °C under argon was added dropwise 24.0 mL of a 1.0 M solution of diisobutylaluminum hydride in hexane. The solution was stirred at −78 °C for 50 min, cautiously quenched with 24 mL of anhydrous methanol, and allowed to warm to room temperature. after 1.5 h, 300 mL of ether was added and the resulting solution washed with 1 N sodium bicarbonate (4 × 100 mL). The aqueous washes were combined and extracted with ether (2 × 100 mL). The combined etheral extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent at reduced pressure gave a quantitative yield of aldehyde **6b**, as a nearly colorless oil, which was used in the following reaction without further purification.

An analytical sample of aldehyde **6b** was prepared by chromatography on silica gel followed by evaporative distillation: R_f 0.42 (petroleum ether:ether, 2:1); evaporative distillation ~170 °C (0.005 mmHg); IR 1730 (C=O), 1640 (C=O), 855, 840 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.02 (s, 9 H, $Si(CH_3)_3$), 0.98 (s, 2 H, CH_2Si), 1.02 (s, 3 H, CH_3), 3.90 (s, 4 H, OCH_2CH_2O), 9.52 (s, 1 H, CHO).

Anal. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.46; H, 9.32.

9,9(8*H*)-(Ethylenedioxy)-11aβ-methyl-3α-((trimethylsilyl)methyl)-3β-vinyl-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-*b*]pyran (6c). To a stirred suspension of 5.70 g (15.9 mmol) of methyltriphenylphosphonium bromide in 120 mL of dry tetrahydrofuran at −78 °C under argon was added dropwise 6.70 mL (15.8 mmol) of a 2.36 M *n*-butyllithium in hexane solution. After stirring for 5 min, the cold bath was removed, and the mixture was warmed to room temperature. After 1.5 h, the resulting orange-red solution was cooled to −78 °C and a solution of aldehyde **6b** (3.12 g, 7.95 mmol) in 35 mL of tetrahydrofuran was added over 5 min. After stirring at −78 °C for 5 min, the mixture was warmed to room temperature and stirred for 26 h. The reaction was quenched with 50 mL of 1 N sodium bicarbonate solution and added to 500 mL of ether. The resulting solution was washed with 1 N sodium bicarbonate (2 × 125 mL). The aqueous layers were extracted with ether (2 × 100 mL) and the combined organic fractions were washed with brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (petroleum ether:ether, 10:11) to afford olefin **6c** as a nearly colorless oil (2.94 g, 95%). An analytically pure sample was obtained by evaporative distillation at ~165 °C and 0.005 mmHg: R_f 0.31 (petroleum ether:ether, 6:1); IR 1645 (C=C), 865, 845 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.03 (s, 9 H, $Si(CH_3)_3$), 0.89, 1.10 (2 d, 2 × 1 H, J = 13.5 Hz, CH_2Si), 1.06 (s, 3 H, CH_3), 3.90 (s, 4 H, OCH_2CH_2O), 4.94 (dd, 1 H, J = 1.8, 10.5 Hz, vinyl), 4.99 (dd, 1 H, J = 1.8, 17.3 Hz, vinyl); mass spectrum calcd for $C_{23}H_{38}O_3Si$, 390.259; found, 390.259.

9,9(8*H*)-(Ethylenedioxy)-11aβ-methyl-3β-((trimethylsilyl)methyl)-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-*b*]pyran-3α-carbaldehyde (7b). To a solution of 150 mg (0.35 mmol) of ester **7a** in 10 mL of dry ether at −78 °C under argon was added dropwise 2.13 mL of a 1.0 M solution of diisobutylaluminum hydride in hexane. The solution was stirred at −78 °C for 6 h, cautiously quenched with 1.0 mL of anhydrous methanol, and allowed to warm to room temperature. After 1 h, 70 mL of ether was added and the resulting solution washed with 1 N sodium bicarbonate (4 × 20 mL) and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (petroleum ether:ether, 4:1) to afford aldehyde **7b** as a colorless oil: 130 mg (93%); R_f 0.32 (petroleum ether:ether, 2:1); IR 1730 (C=O), 1655 (C=C), 860, 840 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.03 (s, 9 H, $Si(CH_3)_3$), 0.85, 1.01 (2 d, 2 × 1 H, J = 15 Hz, CH_2Si), 1.07 (s, 3 H, CH_3), 3.88 (s, 4 H, OCH_2CH_2O), 9.53 (s, 1 H, CHO).

An analytical sample of aldehyde **7b** was obtained by evaporative distillation (~170 °C, (0.005 mmHg)].

Anal. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.21; H, 9.14.

9,9(8*H*)-(Ethylenedioxy)-11aβ-methyl-3β-((trimethylsilyl)methyl)-3α-vinyl-1,2,3,5,6,7,7aα,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-*b*]pyran (7c). To a stirred suspension of 0.34 g (0.95 mmol) of methyltriphenylphosphonium bromide in 6 mL of dry tetrahydrofuran at −78 °C under argon was added dropwise 0.41 mL (0.95 mmol) of a 2.30 M *n*-butyllithium in hexane solution. After stirring for 5 min, the cold bath was removed and the mixture warmed to room temperature. After 1 h, the resulting orange solution was cooled to −78 °C and a solution of aldehyde **7b** (186 mg, 0.47 mmol) in 3 mL of tetrahydrofuran was added dropwise. After stirring at −78 °C for 5 min, the mixture was warmed to room temperature and stirred for 20 h. The reaction was quenched with 5 mL of 1 N sodium bicarbonate solution and added to 80 mL of ether. The resulting solution was washed with 1 N sodium bicarbonate (3 × 20 mL) and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (petroleum ether:ether, 10:1) to afford olefin **7c** as a colorless oil: 166 mg (89%); R_f 0.20 (petroleum ether:ether, 9:1); IR 1655 (C=C), 860, 838 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.03 (s, 9 H, $Si(CH_3)_3$), 1.00 (s, 2 H, CH_2Si), 1.09 (s, 3 H, CH_3), 3.89 (s, 4 H, OCH_2CH_2O), 4.86–5.79 (m, 3 H, vinyl); mass spectrum calcd for $C_{23}H_{38}O_3Si$, 390.259; found, 390.260.

2,2(1*H*)-(Ethylenedioxy)-4aβ-methyl-4′-((trimethylsilyl)methyl)-3,4,4a,8,9,9aβ-hexahydrospiro[5*H*-benzocycloheptane-5,1′-cyclohex-3β-en]-6(7*H*)-one (9). A base-washed (NH_4OH), flame-dried (under vacuum) glass tube containing olefin **6c** was sealed under vacuum and then placed in a preheated oil bath (150 °C). After $7^1/_2$ h, the tube was cooled and opened. A total of 9.31 g (23.8 mmol) of olefin **6c** was treated in this fashion (3 separate tubes). Recrystallization of the combined material from petroleum ether:ether gave **9** as a colorless solid (7.85 g, 84%). An analytically pure sample was obtained by recrystallization of a portion of this material from petroleum ether:ether: R_f 0.40 (petroleum ether:ether, 1:1); mp 153–156 °C (petroleum ether: ether); IR 1685 (C=O), 850 ($SiMe_3$) cm^{-1}; ^1H NMR δ −0.07 (s, 9 H, $Si(CH_3)_3$), 1.07 (s, 3 H, CH_3), 3.82 (m, 4 H, OCH_2CH_2O), 5.22 (br d, 1 H, J = 6.0 Hz, vinyl).

Anal. Calcd for $C_{23}H_{38}O_3Si$: C, 70.72; H, 9.80. Found: C, 70.77; H, 9.91.

2,2(1*H*)-(Ethylenedioxy)-7-(hydroxyimino)-4aβ-methyl-4′-((trimethylsilyl)methyl)-3,4,4a,8,9,9aβ-hexahydrospiro-[5*H*-benzocycloheptane-5,1′-cyclohex-3β-en]-6(7*H*)-one (12). To a solution of ketone **9** (790 mg, 2.02 mmol) in 50 mL of dry tetrahydrofuran at −78 °C under argon was added dropwise 0.88 mL (2.02 mmol) of a 2.30 M *n*-butyllithium in hexane solution. After stirring at −78 °C for 1 h and at 0 °C for 0.5 h, 1.10 mL (8.1 mmol) of freshly distilled isoamylnitrite was added. After stirring

for 10 min, the mixture was warmed to room temperature, stirred for 4 h, and then quenched with 15 mL of water. The resulting mixture was adjusted to pH 6 by the addition of 1% sulfuric acid, diluted with 50 mL of water, and then extracted with ether (3 × 50 mL). The combined ether layers were washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the crystalline residue chromatographed on silica gel (petroleum ether:ether, 5:4) to afford starting ketone **9** (396 mg, 50%) and oximino ketone **12** (360 mg, 42%, 85% based on recovered **9**) as colorless solids.

An analytically pure sample was obtained by recrystallization from ether:chloroform: R_f 0.20 (petroleum ether:ether, 1:1); mp 217–218 °C dec (ether:chloroform); IR 3580, 3280 (OH), 1695 (C=O), 1630 (C=N) cm^{-1}; ^1H NMR δ −0.03 (s, 9 H, $Si(CH_3)_3$), 1.12 (s, 3 H, CH_3), 3.85 (m, 4 H, OCH_2CH_2O), 5.07 (s, 1 H, $w_{1/2}$ = 9 Hz, vinyl).

Anal. Calcd for $C_{23}H_{37}NO_4Si$: C, 65.83; H, 8.88; N, 3.34. Found: C, 65.89; H, 8.95; N, 3.22.

7-Diazo-2,2(1*H*)-(ethylenedioxy)-4aβ-methyl-4′-((trimethylsilyl)methyl)-3,4,4a,8,9,9aβ-hexahydrospiro[5*H*-benzocycloheptane-5,1′-cyclohex-3β-en]-6(7*H*)-one (14). To a solution of 375 mg (0.89 mmol) of oximino ketone **12** in 50 mL of tetrahydrofuran at 5 °C was added 8.9 mL (35.6 mmol) of 4 M aqueous sodium hydroxide anol 2.9 mL (43.5 mmol) of 15 M aqueous ammonium hydroxide. After stirring for 3 min, 7.50 mL (5.25 mmol) of a 5.25% aqueous sodium hypochlorite (Chlorox) solution was added dropwise over 5 min. After stirring for 1 h at 5 °C and at room temperature for 4 h, 200 mL of water was added and the resulting mixture extracted with ether (3 × 100 mL). The combined ether extracts were washed with brine (2 × 70 mL) and dried over an equal mixture of anhydrous potassium carbonate and anhydrous sodium sulfate. The solvent was removed at reduced pressure to give a quantitative yield of diazo ketone **14** as a bright yellow oil which was used without further purification. The spectral data on this material is as follows: R_f 0.29 (petroleum ether:ether, 1:1); IR 2080 (N_2), 1670 (C=O), 1615 (C=N), 850 ($SiMe_3$) cm^{-1}.

Methyl 6,6(5*H*)-(Ethylenedioxy)-8aβ-methyl-4′-((trimethylsilyl)methyl)-1,2,3,4,4aβ,7,8,8a-octahydrospiro[naphthalene-1,1′-cyclohex-3β-ene]-2β-carboxylate (17a) and Methyl 6,6(5*H*)-(Ethylenedioxy)-8aβ-methyl-4′-((trimethylsilyl)methyl)-1,2,3,4,4aβ,7,8,8a-octahydrospiro[naphthalene-1,1′-cyclohex-3β-ene]-2α-carboxylate (17b). A solution of diazo ketone **14** (~0.54 mmol) and 20 mL (13 mmol) of a 0.65 M sodium methoxide in methanol solution in anhydrous methanol (60 mL) at −66 °C under an argon atmosphere was irradiated for 1 h with a Hanovia 450-W medium-pressure mercury-vapor lamp in a Pyrex jacket. After the photolysis was complete, the reaction mixture was maintained at −70 °C for 1 h and then warmed to room temperature. After 1 h the mixture was diluted with water (200 mL) and extracted with ether (4 × 100 mL). The organic fractions were combined and washed with brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give a crude mixture in which the desired esters **17a** and **17b** were minor products (<10%) and the cyclobutanone **16** was the major identifiable product.

Chromatography of the above material no silica gel (petroleum ether:ether, 3:1) gave ester **17a** (11 mg, 4.8%), ester **17b** (14 mg, 6.1%), a 1:1 mixture of ester **17b** and cyclobutanone **16** (34.5 mg), and impure ketone **20** (20 mg). Rechromatography of impure **20** on silica gel (petroleum ether:ethyl acetate, 3:1) gave **20** as a colorless solid, mp 147–149 °C (44 mg, 26%).

An analytical sample of ester **17a** was obtained by evaporative distillation (~145 °C (0.001 mmHg)): R_f 0.46 (petroleum ether:ether, 1:1); mp 97–99 °C (evaporative distillation and resolidification); IR ($CHCl_3$) 1725 (C=O), 855 ($SiMe_3$) cm^{-1}; ^1H NMR δ −0.02 (s, 9 H, $Si(CH_3)_3$), 0.97 (s, 3 H, CH_3), 3.60 (s, 3 H, OCH_3), 3.87 (m, 4 H, OCH_2CH_2O), 5.22 (m, 1 H, vinyl).

Anal. Calcd for $C_{24}H_{40}O_4Si$: C, 68.53; H, 9.58. Found: C, 68.74; H, 9.71.

An analytical sample of ester **17b** was obtained by evaporative distillation (~145 °C (0.001 mm Hg)): R_f 0.39 (petroleum ether:ether, 1:1); mp 105–108 °C (evaporative distillation and resolidication); IR ($CHCl_3$) 1725 (C=O), 855 ($SiMe_3$) cm^{-1}; ^1H NMR δ −0.02 (s, 9 H, $Si(CH_3)_3$), 1.00 (s, 3 H, OCH_2CH_2O), 5.03 (m, 1 H, vinyl).

Anal. Calcd for $C_{24}H_{40}O_4Si$: C, 68.53; H, 9.58. Found: C, 68.68; H, 9.58.

Cyclobutanone (16). A solution of diazo ketone **14** (~0.89 mmol) in anhydrous ether at −73 °C under an argon atmosphere was irradiated for 1 h with a Hanovia 450-W medium-pressure mercury-vapor lamp in a Pyrex jacket. After the photolysis was complete, the mixture was maintained at −73 °C for 15 min and then warmed to room temperature. After 1 h the resulting solution was filtered through a small pad of anhydrous magnesium sulfate. The solent was removed by reduced pressure to give a crude mixture in which cyclobutanone **16** is the major component. The spectral data on this material: R_f 0.38 (petroleum ether:ethyl acetate, 3:1); IR 1755 (C=O), 850 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.02 (s, 9 H, $Si(CH_3)_3$), 0.63 (s, 2 H, CH_2Si), 0.92 (s, 3 H, CH_3), 2.5 (br s, 1 H, C12–H), 3.90 (s, 4 H, OCH_2CH_2O).

(±)-3,3-(Ethylenedioxy)-5-*epi*-18,19-dinoraphidicolan-16-en-13-one (20). The crude cyclobutanone **16** (~0.89 mmol) was added to a stirred suspension of silica gel (20 g) in petroleum ether:ether (1:1, 70 mL). After stirring for 62 h, the mixture was filtered through a small pad of anhydrous magnesium sulfate using additional ether to wash the silica gel. The filtrate was concentrated at reduced pressure to give a pale yellow oil which was combined with that obtained from a separate experiment (~0.77 mmol) and then chromatographed on silica gel (petroleum ether:ether, 5:1) to give the ketone **20** as a colorless solid (315 mg, 60% from oximino ketone **12**). Recrystallization of a portion of this material from ethyl acetate:hexane gave an analytically pure sample: R_f 0.24 (petroleum ether:ethyl acetate, 3:1); mp 149–150 °C (ethyl acetate:hexane); IR 1730 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR δ 1.02 (s, 3 H, CH_3), 2.95 (d, 1 H, J = 5.1 Hz, C12–H), 3.88 (s, 4 H, OCH_2CH_2O), 4.58 (m, 2 H, vinyl).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.97; H, 8.92.

(±)-3,3-(Ethylenedioxy)-5,8-di-*epi*-18,19-dinoraphidicolan-16-ene (23). To a solution of ketone **20** (60 mg, 0.19 mmol) in triethylene glycol (23 mL) at room temperature under argon was added 99% hydrazine hydrate (1.10 mL, 22.6 mmol) followed by hydrazine dihydrochloride (318 mg, 3.02 mmol). The resulting mixture was heated at 130 °C for 3 h and then cooled to 100 °C. After the addition of 2.2 g of potassium hydroxide, the mixture was heated to 180 °C and the volatiles were removed with a stream of argon. After 6 h, the mixture was cooled, diluted with water (200 mL), and extracted with benzene (4 × 90 mL). The combined organic fractions were washed with water (6 × 50 mL) and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (petroleum ether:ether, 6:1) to give **23** as a colorless oil which partially crystallizes upon storage in the cold (30.4 mg, 53%): R_f 0.30 (petroleum ether:ether, 6:1); IR ($CHCl_3$) 1655 (C=C) cm^{-1}; ^1H NMR δ 1.00 (s, 3 H, CH_3), 3.88 (m, 4 H, OCH_2CH_2O), 4.33 (m, 1 H, vinyl), 4.41 (m, 1 H, vinyl).

An analytical sample was obtained by evaporative distillation (~125 °C (0.001 mmHg)).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.40, H, 9.95.

(±)-3,3-(Ethylenedioxy)-13-hydroxy-5-*epi*-18,19-dinoraphidicolin-16-ene (24). To a solution of 422 mg (1.33 mmol) of ketone **20** in 50 mL of dry tetrahydrofuran at −78 °C under argon was added dropwise 8.0 mL (8.0 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane. After 1 h, 300 mL of ether was added, and the resulting solution was washed with 1 N sodium bicarbonate (4 × 50 mL). The aqueous washes were combined and extracted with ether (2 × 75 mL). The ether fractions were combined, washed with brine, and dried ($MgSO_4$). The solvent was removed at reduced pressure to give the alcohol **24** as a colorless solid (423 mg, 99%). Recrystallization of a portion of this material from ethyl acetate:hexane gave an analytically pure sample: R_f 0.28 (petroleum ether:ether, 1:1), mp 138–139 °C (ethyl acetate/hexane); IR 3620, 3500 (OH), 1655 (C=C) cm^{-1}; ^1H NMR δ 0.95 (s, 3 H, CH_3), 2.86 (m, 1 H, C12–H), 3.88 (s, 4 H, OCH_2CH_2O), 4.31 (dd, 1 H, J = 7.2, 10.5 Hz, C13–H), 4.56 (m, 1 H, vinyl), 4.64 (m, 1 H, vinyl).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.56; H, 9.53.

(±)-3,3-(Ethylenedioxy)-5-*epi*-18,19-dinoraphidicolane and (±)-3,3-(Ethylenedioxy)-5-*epi*-18,19-dinoraphidicolan-16-ene

(25). To a solution of alcohol **24** (100 mg, 0.31 mmol) in 1,2-dimethoxyethane:*N,N,N',N'*-tetramethylethylenediamine (4:1, 5 mL) at room temperature under argon was added dropwise 0.19 mL (0.47 mmol) of a 2.50 M *n*-butyllithium in hexane solution. After stirring for 10 min, 0.20 mL (1.69 mmol) of *N,N*-dimethylphosphoramidic dichloride was added. After stirring for 45 min, the reaction mixture was cooled to 0 °C and 3 mL of anhydrous dimethylamine was added. The resulting mixture was stirred at 0 °C for 1.5 h, diluted with water (50 mL), and extracted with ether (4 × 40 mL). The combined organic fractions were washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure to give the corresponding phosphorodiamidate as a nearly colorless oil which was used without further purification.

To a solution of the crude phosphoradiamidate (~0.31 mmol) in dry tetrahydrofuran (6 mL) and methylamine (30 mL, freshly distilled from lithium) containing *tert*-butyl alcohol (0.60 ml, 6.36 mmol) under argon was added lithium wire (50 mg, 7.20 mmol). The reaction mixture turned blue in approximately 3 min. After 25 min, the blue color was discharged and an additional portion of lithium wire (21 mg, 3.04 mmol) and *tert*-butyl alcohol (0.20 mL, 2.12 mmol) was added. The resulting blue mixture was maintained at reflux temperature (dry ice condenser) for an additional 35 min and then carefully quenched with solid ammonium chloride. After the methylamine evaporated, the residue was partitioned between ether and water. The organic layer was washed with water and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (petroleum ether:ether, 10:1) to give over-reduction product (7.3 mg, 7.7%), mixed fractions containing both this product and the olefin **25** (8.1 mg, 8.5%), and olefin **25** (52.3 mg, 55%) as colorless oils.

An analytical sample of the over-reduced product was obtained by evaporative distillation (~120 °C (0.001 mmHg): R_f 0.30 (petroleum ether:ether, 6:1); IR ($CHCl_3$) nondescript.

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.95; H, 10.56.

An analytical sample of the olefin **25** was obtained by evaporative distillation (~115 °C (0.001 mmHg)); R_f 0.26 (petroleum ether:ether, 6:1); IR ($CHCl_3$) 1655 (C=C) cm^{-1}; ^1H NMR δ 0.94 (s, 3 H, CH_3), 2.62 (m, 1 H, C12–H), 3.87 (s, 4 H, OCH_2CH_2O), 4.30 (m, 1 H, vinyl), 4.40 (m, 1 H, vinyl).

Anal. Calcd $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.54; H, 10.00.

(±)-16α,17-(Isopropylidenedioxy)-5-*epi*-18,19-dinoraphidicolan-3-one (27). To a solution of olefin **25** (15 mg, 0.049 mmol) in acetone (0.5 mL) and water (0.2 mL) was added 4-methylmorpholine 4-oxide hydrate (12 mg, 0.089 mmol) followed by 5 μL (0.01 equiv) of a 0.1 M solution of osmium tetraoxide in *tert*-butyl alcohol. After stirring at room temperature for 24 h, the mixture was added to a slurry of sodium hydrosulfite (0.80 g), Florisil (4 g), acetone (8 mL), and water. The resulting mixture was filtered and the filtrate was acidified to pH 1 by using 10% aqueous HCl. After stirring for 1 h, the resulting mixture was extracted with ether (3 × 50 mL). The combined ether fractions were washed with water, 1 N sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue chromatographed on silica gel (petroleum ether:ether, 1:1) to give **27** as a colorless solid (5.7 mg, 34%): R_f 0.20 (petroleum ether:ether, 1:1); IR ($CHCl_3$) 1707 (C=O) cm^{-1}; ^1H NMR δ 0.92 (s, 3 H, CH_3), 1.34, 1.41 (2 s, 2 × 3 H, CH_3CCH_3), 3.72, 3.82 (2 d, 2 × 1 H, J = 8.25 Hz, CCH_2O). This material was not further purified.

(±)-13α-((*tert*-Butyldimethylsilyl)oxy)-3,3-(ethylenedioxy)-5-*epi*-18,19-dinoraphidicolan-16-ene (26). To a solution of alcohol **24** (322 mg, 1.01 mmol) in 4 mL of dry dimethylformamide under argon was added 1.54 g (22.6 mmol) of imidazole and 1.57 g (10.4 mmol) of *tert*-butyldimethylsilyl chloride. After stirring at room temperature for 6 days, the mixture was added to 150 mL of ether and the resultant solution washed successively with 1 N sodium bicarbonate, water, 1 N sodium bicarbonate, and brine. After drying ($MgSO_4$), the solvent was removed at reduced pressure and the residue was chromatographed on silica gel using petroleum ether:ether (7:1) to afford the silyl ether **26** as a colorless oil (415 mg, 95%).

An analytical sample was obtained by evaporative distillation: R_f 0.40 (petroleum ether:ether, 2:1); evaporative distillation ~125 °C (0.002 mmHg); IR 1655 (C=C) cm^{-1}; ^1H NMR δ −0.03, 0.00 (2 s, 2 × 3 H, CH_3SiCH_3), 0.84 (s, 9 H, $SiC(CH_3)_e$), 0.93 (s, 3 H, C10–CH_3), 3.89 (s, 4 H, OCH_2CH_2O), 4.29 (dd, 1 H, J = 6.7, 9.8 Hz, C13–H), 4.40 (m, 1 H, vinyl), 4.48 (m, 1 H, vinyl).

Anal. Calcd for $C_{26}H_{44}O_3Si$: C, 72.17; H, 10.25. Found: C, 72.14; H, 10.36.

(±)-13α-((*tert*-Butyldimethylsilyl)oxy)-16β,17-dihydroxy-3,3-(ethylenedioxy)-5-*epi*-18,19-dinoraphidicolane. To a solution of silyl ether **26** (513 mg, 1.18 mmol) in 30 mL of dry pyridine under argon was added a solution of 1.0 g (3.93 mmol) of osmium tetraoxide in 20 mL of pyridine. After stirring for 21 h, the resulting dark mixture was cooled to 0 °C and a solution of 3.5 g of sodium bisulfite in 30 mL of water was added. After stirring for 5 min, the cold bath was removed and after 75 min the resultant mixture was added to 300 mL of ethyl acetate and 150 mL of water. The aqueous layer was separated and extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with water (3 × 50 mL) and brine. After drying ($MgSO_4$), the solvent was removed at reduced pressure with the aid of a cyclohexane azeotrope to remove pyridine affording the corresponding diol as a colorless foam (538 mg, 97%) which was used in the subsequent reaction without further purification. The spectral data for this material: R_f 0.19 (cyclohexane:ethyl acetate, 1:1); IR 3570, 3430 (OH) cm^{-1}; ^1H NMR δ 0.08 (s, 6 H, CH_3SiCH_3), 0.92 (s, 9 H, $SiC(CH_3)_3$), 0.94 (s, 3 H, C10–CH_3), 3.62 (br s, 2 H, CCH_2O), 3.88 (s, 4 H, OCH_2CH_2O), 4.34 (d, 1 H, J = 7.0, 10.5 Hz, C13–H).

(±)-13α-((*tert*-Butyldimethylsilyl)oxy)-3,3-(ethylenedioxy)-16β,17-(isopropylidenedioxy)-5-*epi*-18,19-dinoraphidicolane. To a solution of the above crude diol (538 mg, 1.15 mmol) in 40 mL of 2,2-dimethoxypropane under argon was added several small crystals of *p*-toluenesulfonic acid monohydrate. After stirring for 30 min, the mixture was neutralized with 1 N sodium bicarbonate and then added to ether (300 mL). The resulting solution was washed with 1 N sodium bicarbonate and brine. After drying ($MgSO_4$), the solvent was removed at reduced pressure and the residue chromatographed on silica gel using cyclohexane:ethyl acetate (9:1) to give the corresponding acetonide as a colorless oil (561 mg, 96%).

An analytically pure sample was obtained by evaporative distillation: R_f 0.45 (petroleum ether:ether, 1:1); evaporative distillation ~180 °C (0.002 mmHg); IR nondescript; ^1H NMR δ 0.08 (s, 6 H, $Si(CH_3)_2$), 0.92 (s, 9 H, $SiC(CH_3)_3$), 0.94 (s, 3 H, C10–CH_3e, 1.34 (s, 6 H, CH_3CCH_3e, 3.68, 3.79 (2 d, 2 × 1 H, J = 8.25 Hz, CCH_2O), 3.88 (s, 4 H, OCH_2CH_2O), 4.28 (dd, J = 6.8, 10.5 Hz, C13–H).

Anal. Calcd for $C_{29}H_{50}O_5Si$: C, 68.73; H, 9.94. Found: C, 68.77; H, 9.81.

(±)-3,3-(Ethylenedioxy)-13α-hydroxy-16β,17-(isopropylidenedioxy)-5-*epi*-18,19-dinoraphidicolane (28). To a solution of the above silyl ether (370 mg, 0.73 mmol) in 30 mL of dry tetrahydrofuran under argon was added 2.90 g (11 mmol) of tetrabutylammonium fluoride. After stirring at room temperature for 47 h, the reaction mixture was diluted with 300 mL of ether and the resultant solution was washed with water (3 × 40 mL) and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue was chromatographed on silica gel (cyclohexane:ethyl acetate, 2:1) to give alcohol **28** (285 mg, 99%) as a colorless oil.

An analytically pure sample was obtained by evaporative distillation: R_f 0.35 (cyclohexane:ethyl acetate, 1:1); evaporative distillation ~165 °C (0.001 mmHg); IR 3650, 3500 (OH) cm^{-1}; ^1H NMR δ 0.93 (s, 3 H, C10–CH_3), 1.33 (s, 6 H, CH_3CCH_3), 3.66, 3.94 (2 d, 2 × 1 H, J = 9.0 Hz, CCH_2O), 3.82 (s, 4 H, OCH_2CH_2O), 4.30 (dd, 1 H, J = 7.0, 10.5 Hz, C13–H).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 70.31; H, 9.19.

(±)-3,3-(Ethylenedioxy)-16β,17-(isopropylidenedioxy)-5-*epi*-18,19-dinoraphidicolane (29). To a solution of alcohol **28** (212 mg, 0.54 mmol) in 1,2-dimethoxyethane:*N,N,N',N'*-tetramethylethylenediamine (4:1, 8 mL) at room temperature under argon was added 0.47 mL (1.08 mmol) of a 2.30 M *n*-butyllithium in hexane solution. After stirring for 10 min, 0.32 mL (2.7 mmol) of *N,N*-dimethylphosphoramidic dichloride was added. After

stirring for 4 min, the reaction mixture was cooled to 0 °C and 6 mL of anhydrous dimethylamine was added. The resulting mixture was stirred at 0 °C for 1.5 h, diluted with water (50 mL), and extracted with ether (4 × 40 mL). The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure to give the derived phosphorodiamidate as a nearly colorless oil which was used without further purification.

To a solution of this crude phosphorodiamidate (0.54 mmol) in dry tetrahydrofuran (6 mL) and methylamine (30 mL, freshly distilled from lithium) containing *tert*-butyl alcohol (1.0 mL, 10.8 mmol) under argon was added lithium wire (85 mg, 12.2 mmol). The reaction mixture turned blue in approximately 2 min. After 10 min, the blue color was discharged and an additional portion of lithium wire (42 mg, 6.05 mmol) and *tert*-butyl alcohol (0.4 mL, 4.3 mmol) was added. The resulting blue mixture was maintained at reflux (dry ice condenser) for 1.5 h and then carefully quenched with solid ammonium chloride. After the methylamine evaporated, the residue was partitioned between ether and water. The organic layer was washed with water and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure and the residue was chromatographed on silica gel (petroleum ether:ether, 3:1) to give di-ketal **29** (175 mg, 86%) as a colorless oil which very slowly crystallizes upon storage.

An analytically pure sample was obtained by evaporative distillation: R_f 0.38 (petroleum ether:ether, 1:1); evaporative distillation ~140 °C (0.002 mmHg); IR nondescript; ^{1}H NMR δ 0.96 (s, 3 H, C10–CH_3), 1.30, 1.37 (2 s, 2 × 3 H, CH_3CCH_3), 3.45, 3.69 (2 d, 2 × 1 H, J = 8.25 Hz, CCH_2O), 3.87 (s, 4 H, OCH_2CH_2O).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.43; H, 9.49.

(±)-16β,17-(Isopropylidenedioxy)-5-*epi*-18,19-dinoraphidicolan-3-one (30). A solution of 148 mg (0.39 mmol) of diketal **29** and 56 mg (0.22 mmol) of pyridinium *p*-toluenesulfonate in 25 mL of reagent grade acetone under argon was heated at reflux. After 7 h, the solvent was removed at reduced pressure and the residue was dissolved in dichloromethane (70 mL). The resultant solution was washed with water and brine. After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure to give the ketone ketal **30** as a colorless solid. Recrystallization of a portion of this material from ethyl acetate/hexane gave an analytically pure sample: R_f 0.24 (petroleum ether:ether, 1:1); mp 132–133 °C (ethyl acetate:hexane); IR 1710 (C=O) cm^{-1}; ^{1}H NMR δ 0.91 (s, 3 H, C10–CH_3), 1.32, 1.38 (2 s, 2 × 1 H, J = 8.25 Hz, CCH_2O).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.94; H, 9.68.

(±)-16β,17-(Isopropylidenedioxy)-18,19-dinoraphidicol-4-en-3-one (31). To a stirred solution of 54 mg (1.3 mmol) of potassium hydride in 4 mL of dry THF under argon in an ice water bath was added a solution of 223.7 mg (0.673 mmol) of the ketone ketal **30** in 3 mL of dry THF. The resulting mixture was stirred at room temperature for 18 h and then cooled in a dry ice:acetone bath. It was treated with 1.0 mL of the supernatant centrifugate from a mixture of 1.0 mL of trimethylchlorosilane and 1.0 mL of dry triethylamine. Cooling was discontinued, and the mixture was stirred at room temperature for 1 h, then treated with 5 mL of saturated aqueous $NaHCO_3$, and diluted with 60 mL of ether. The organic phase was washed with two 20-mL portions of saturated aqueous $NaHCO_3$ and 20 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvents under reduced pressure gave an oil which was dissolved in 14 mL of dry acetonitrile under argon. In one portion, 252 mg (1.12 mmol) of Pd(OAc)$_2$ was added. After stirring at room temperature for 24 h, the reaction mixture was diluted with 60 mL of ether. The organic phase was washed with two 20-mL portions of 10% aqueous $Na_2S_2O_3$ and 20 mL of saturated aqueous NaCl. The combined aqueous phase was extracted with two 20-mL portions of dichloromethane. The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 25 g of silica gel with 40% ether in pentane provided 200.5 mg (90%) of the enone **31**. A small amount (10 mg) of the isomeric enone was also obtained. An analytically pure sample of this material was obtained after recrystallization of a portion from petroleum ether:ether: mp 121–122 °C (petroleum ether:ether); IR ($CHCl_3$) 1655 (C=O), 1620 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3 H, C10–CH_3), 1.29, 1.37 (2 s, 2 × 3 H, CH_3CCH_3), 3.47, 3.71 (2 d, 2 × 1 H, J = 8.25 Hz, CCH_3O), 5.72 (s, 1 H, vinyl).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.28; H, 9.04.

(±)-16β,17-(Isopropylidenedioxy)-4-((phenylthio)methyl)-18,19-dinoraphidicol-4-en-3-one (32). To a stirred solution of 200.5 mg (0.607 mmol) of the enone **31** in 3.6 mL of dry ethanol under argon were added 810 mg (27 mmol) of dry paraformaldehyde, 1.4 mL (10 mmol) of dry triethylamine, and 1.75 mL (17 mmol) of dry thiophenol. The resulting mixture was heated at 90 °C for 5 h and then diluted with 60 mL of ether. The organic phase was washed with two 20-mL portions of cold 1 N aqueous NaOH and 20 mL of saturated aqueous NaCl. The combined aqueous phase was extracted with two 20-mL portions of dichloromethane. The combined organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 25 g of silica gel with 35% ether in pentane gave 215 mg (78%) of the (phenylthio)methyl enone **32**.

An analytically pure sample was obtained by evaporative distillation 200–220 °C (0.002 mmHg); IR ($CHCl_3$) 1660 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 3 H, C10–CH_3), 1.32, 1.39 (2 s, 2 × 3 H, CH_3CCH_3), 3.51, 3.74 (2 d, 2 × 1 H, J = 8 Hz, CCH_2O), 3.87 (s, 2 H, $CH_2SC_6H_5$).

Anal. Calcd for $C_{28}H_{36}O_3S$: C, 74.30; H, 8.02; S, 7.08. Found: S, 74.13; H, 7.90; S, 7.08.

(±)-16β,17-(Isopropylidenedioxy)-3-(trimethylsiloxy)-18-noraphidicol-3-ene (33). To a stirred solution of 0.5 cm (3 mmol) of lithium wire in 20 mL of anhydrous liquid ammonia under argon was added a solution of 195.5 mg (0.43 mmol) of the enone **32** and 0.075 mL of *tert*-butyl alcohol in 3 mL of dry THF. After stirring for 10 min, the reaction mixture was treated with 0.3 mL of isoprene, then ammonia was allowed to evaporate. The residue was dried under reduced pressure and then suspended in 10 mL of dry THF under argon at −78 °C. It was treated with 1.5 mL of the supernatant centrifugate from a mixture of 1.5 mL of trimethylchlorosilane and 1.5 mL of dry triethylamine. Cooling was discontinued and the mixture was stirred at room temperature for 1 h, then treated with 5 mL of saturated aqueous $NaHCO_3$, and diluted with 60 mL of ether. The organic phase was washed with two 20-mL portions of cold saturated aqueous $NaHCO_3$ and 20 mL of saturated aqueous NaCl and then dried ($MgSO_4$). After removal of the solvents, chromatography of the residue on 50 mL of Florisil with 4% ether in pentane afforded 162.4 mg (90%) of the silyl enol ether **33**.

An analytically pure sample of this material was obtained by evaporative distillation 160–170 °C (0.002 mmHg); IR ($CHCl_3$) 1670 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 9 H, $Si(CH_3)_3$), 0.88 (s, 3 H, C10–CH_3), 1.33, 1.41 (2 s, 2 × 3 H, CH_3CCH_3), 1.52 (s, 3 H, C4–CH_3), 3.51, 3.74 (2 d, 2 × 1 H, J = 8 Hz, CCH_2O).

Anal. Calcd for $C_{25}H_{42}O_3Si$: C, 71.72; H, 10.11. Found: C, 71.90, H, 10.12.

(±)-16β,17-(Isopropylidenedioxy)aphidicolan-3-one. To a stirred solution of 33.4 mg (0.08 mmol) of the silyl enol ether **33** in 1 mL of dry THF at −78 °C under argon was added 0.06 mL (0.1 mmol) of a 1.6 M solution of methyllithium in ether. Cooling was discontinued, and the resulting mixture was stirred at room temperature for 1 h. The solution was recooled in a dry ice:acetone bath and treated with dry gaseous formaldehyde (150 °C heating of dry paraformaldehyde) via a stream of argon. After stirring for 10 min, 0.1 mL of a 10% solution of acetic acid in THF was added. After an additional minute, the reaction mixture was treated with 2 mL of aqueous NH_3/NH_4Cl (pH 7–8) and then diluted with 30 mL of ether. The organic phase was washed with 15 mL of aqueous NH_3/NH_4Cl (pH 7–8) and 15 mL of saturated aqueous NaCl. The combined aqueous phase was extracted with two 30-mL portions of dichloromethane. The combined organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 20 mL of Florisil with 70% ether in pentane afforded 24 mg (80%) of the keto alcohol.

An analytical sample was obtained after rigorous vacuum drying of rechromatographed material: IR ($CHCl_3$) 1700 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.0, 1.17 (2 s, 2 × 3 H, C4 and C10–CH_3's), 1.33, 1.41 (2 s, 2 × 3 H, CH_3CCH_3), 3.37, 3.67 (2 dd,

2 × 1 H, J = 7 Hz, 11.5 Hz, CCH_2OH), 3.54, 3.76 (2 d, 2 × 1 H, J = 8.5 Hz, CCH_2O).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.12; H, 9.82.

(±)-16β,17-(Isopropylidenedioxy)aphidicolin. To a stirred solution of 18 mg (0.05 mmol) of the above keto alcohol in 1 mL of dry THF at −78 °C under argon was added 0.2 mL (0.2 mmol) of a 1 M solution of L-Selectride (Aldrich) in THF. After stirring for 2 h, cooling was discontinued. The reaction mixture was treated with 0.1 mL of ethanol, 0.15 mL of 15% aqueous NaOH, and 0.15 mL of 30% aqueous H_2O_2. After stirring at room temperature for 3 h, it was diluted with 30 mL of dichloromethane. The organic phase was washed with 20 mL of saturated aqueous $NaHCO_3$ and 15 mL of saturated aqueous NaCl. The combined aqueous phase was extracted with two 2-mL portions of dichloromethane. The combined organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 15 g of silica gel with 2% methanol:10% ethyl acetate in dichloromethane gave 12 mg (67%) of the expected diol.

Analytically pure material was obtained by recrystallization of this material from ether:hexane: mp 192–195 °C; IR ($CHCl_3$) 3440 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.70, 0.98 (2 s, 2 × 3 H, C4 and C10–CH_3's), 1.34, 1.42 (2 s, 2 × 3 H, CH_3CCH_3), 3.37, 3.47 (2 d, 2 × 1 H, J = 11 Hz, CCH_2OH), 3.54, 3.76 (2 d, 2 × 1 H, J = 8 Hz, CCH_2O), 3.67 (dd, 1 H, J = 2, 3 Hz, C3–H).

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 72.95; H, 10.21.

(±)-Aphidicolin (34). To a stirred solution of 21.2 mg (0.056 mmol) of the above diol in 4 mL of methanol was added 0.2 mL of 10% aqueous HCl. After 24 h, excess solid $NaHCO_3$ and K_2CO_3 were added. The resulting mixture was stirred for 1 h and then filtered. Removal of solvent under reduced pressure and chromatography of the residue on 10 g of silica gel with 8% methanol in dichloromethane afforded 17.2 mg (91%) of (±)-aphidicolin (**34**).

The analytically pure sample was obtained after crystallization of this material from ethyl acetate: mp 220–225 °C; IR (Nujol mull) 3500, 3300 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.70, 1.0 (2 s, 2 × 3 H, C4 and C10–CH_3's), 3.36, 3.46 (2 d, 2 × 1 H, J = 11 Hz, CH_3CCH_2OH), 3.37, 3.45 (2 d, 2 × 1 H, J = 11 Hz, $COCCH_2OH$), 3.67 (dd, 1 H, J = 2, 3 Hz, C3–H).

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 70.81; H, 9.87.

Registry No. (±)-**1**, 78310-39-1; **2**, 88802-63-5; **3**, 88802-64-6; **4**, 3419-66-7; **5**, 88802-65-7; (±)-**6a**, 78310-40-4; (±)-**6b**, 78310-41-5; (±)-**6c**, 78310-42-6; (±)-**7a**, 78391-97-6; (±)-**7b**, 88852-71-5; (±)-**7c**, 88852-72-6; (±)-**8a**, 88802-66-8; (±)-**8b**, 88802-67-9; (±)-**8c**, 88802-68-0; (±)-**9**, 78310-43-7; (±)-**10**, 88825-34-7; (±)-**11**, 88802-69-1; (±)-**12**, 78310-44-8; (±)-**13**, 88802-70-4; (±)-**14**, 78310-54-0; (±)-**15**, 88802-71-5; **16**, 78331-38-1; (±)-**17a**, 88802-72-6; (±)-**17b**, 88852-73-7; **18**, 88802-73-7; **19**, 88802-74-8; (±)-**20**, 78310-45-9; (±)-**21a**, 88802-75-9; **21b**, 88802-76-0; (±)-**22**, 15401-86-2; (±)-**23**, 88852-74-8; (±)-**24**, 78310-56-2; (±)-**25**, 88852-75-9; (±)-**26**, 78310-46-0; (±)-**27**, 88852-76-0; (±)-**28**, 78310-57-3; (±)-**29**, 78331-40-5; (±)-**30**, 78310-48-2; (±)-**31**, 88802-77-1; (±)-**32**, 88802-78-2; (±)-**33**, 88802-79-3; (±)-**34**, 69926-98-3; (±)-1,2,2-trimethylcycloheptanol, 88802-80-6; 2,2-dimethylcycloheptanone, 7228-52-6; 11-(hydroxymethyl)-3,7,7-trimethylspiro[5.5]undec-2-ene, 88802-81-7; 11-(*o*-nitrophenylselenomethyl)-3,7,7-trimethylspiro[5.5]undec-2-ene, 88802-82-8; *o*-nitrophenyl selenocyanate, 51694-22-5; methyl (±)-3-(dimethylamino)-2-[(trimethylsilyl)methyl)]propionate, 88802-83-9; methyl 3-(dimethylamino)propionate, 3853-06-3; methyl α-[(trimethysilyl)-methyl]acrylate, 78310-52-8; (±)-13α-[(*tert*-butyldimethylsilyl)-oxy]-16β,17-dihydroxy-3,3-(ethylenedioxy)-5-*epi*-18,19-dinor-aphidicolane, 78331-39-2; (±)-13α-[(*tert*-butyldimethylsilyl)-oxy]-3,3-(ethylenedioxy)-16β,17-(isopropylidenedioxy)-5-*epi*-18,19-dinoraphidicolane, 78310-47-1; (±)-16β,17-(isopropylidenedioxy)aphidicolan-3-one, 78310-59-5; (±)-16β,17-(isopropylidenedioxy)aphidicolin, 78310-60-8.

Synthesis of Dihydromauritine A, a Reduced Cyclopeptide Alkaloid

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The synthesis of the strained 14-membered cyclopeptide alkaloid derivative dihydromauritine A has been accomplished from L-proline via an S_N2 displacement and three amide bond forming steps. The nucleophilic displacement involved a β-bromopyrroline methyl ester and the thallium salt of Boc-phenylalanyltyramide to generate an aryloxy ether. Reduction of the pyrroline double bond with dimethylamine–borane resulted in a 60:40 ratio of trans:cis β-substituted proline derivatives. The critical cyclization step was accomplished by amide bond formation using an active ester derivative. Macrocyclic ring formation proceeded in similar yields when carried out at 90 °C in pyridine or at 25 °C with the acylation catalyst 1-hydroxybenzotriazole. Surprisingly, no stereoselectivity was observed in the cyclization step, and both proline diastereomers were formed in equal amounts. The introduction of the dipeptide side chain *N*,*N*-dimethylalanylvaline was carried out most easily by using dicyclohexylcarbodiimide/hydroxybenzotriazole activation to afford dihydromauritine A with configuration 8*S*,9*S*,5*S* and its stereoisomer with configuration 8*R*,9*R*,5*S*. This is the first synthesis of a 14-membered dihydrocyclopeptide alkaloid containing a non-proline internal amino acid.

Cyclopeptide alkaloids are macrocyclic molecules of various ring sizes including 13-, 14-, or 15-membered rings, 14-membered rings being the most common.[1]

Since the discovery of the first cyclopeptide alkaloid by Goutarel and Païs in 1963,[2] the field of cyclopeptide alkaloids has grown rapidly, and several reviews have been published on this subject.[1,3-5] Although they occur in many different parts of a plant, difficulties in isolation have resulted in limited supplies of these products. Several

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