Intramolecular Photocycloaddition–Cyclobutane Fragmentation: Total Synthesis of (±)-Silphinene

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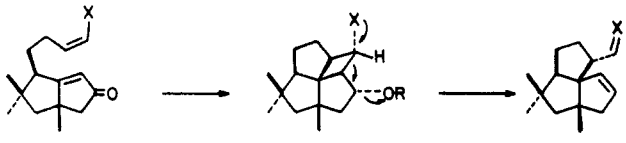
Abstract: A total synthesis of the triquinane sesquiterpene silphinene (**1**) has been accomplished in 12 steps in an overall yield of 22%. The key steps are an intramolecular photocycloaddition utilized to establish a quaternary center and an adjacent stereocenter followed by a Me_3SiI-induced cyclobutane cleavage of the fenestrane produced in the photocycloaddition.

Silphinene (**1**) was isolated in 1980 by Bohlmann and Jakupovic from the roots of *Silphium perfoliatum L.*[1,2] The structure of **1** was assigned on the basis of NMR studies of a number of oxidation products. As a part of a larger program directed toward the utilization of intramolecular [2 + 2] photocycloadditions in natural products synthesis,[3] particularly the total synthesis of angularly fused cyclopentanoids,[4] we embarked on the total synthesis of silphinene (**1**).[5] A combination of the strategically positioned methyl substituents and the double bond of **1** as well

1 2

as the opportunity to utilize a synthesis of silphinene to gain information regarding a similar synthetic approach to the structurally related fenestrane, laurenene (**2**),[6] made the endeavor attractive.

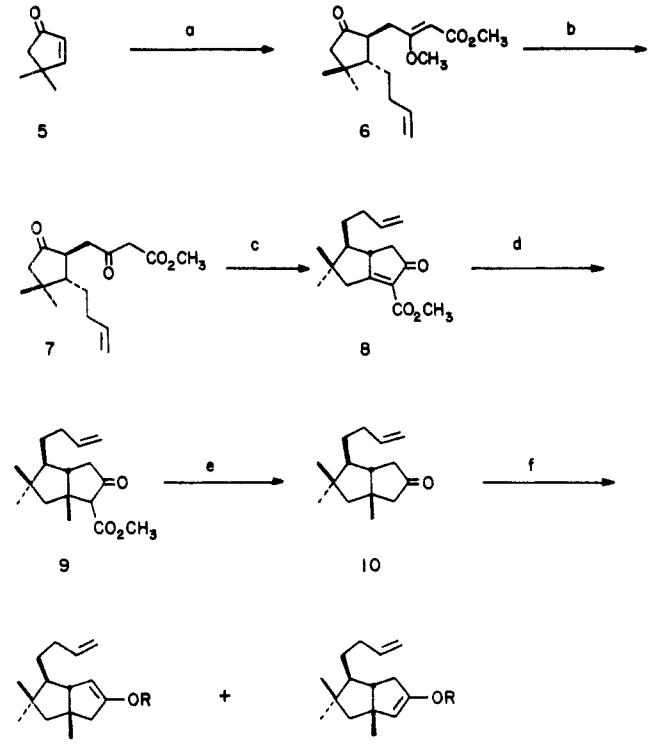
From the outset, our strategy was to take advantage of an intramolecular [2 + 2] photocycloaddition of a diquinane **3** to construct the functionalized fenestrane **4**. This key step would (1) close the final cyclopentane ring, (2) establish the stereochemistry of the incipient methyl group, and (3) strategically position functionality to allow regioselective introduction of the double bond by a selective cleavage of the cyclobutane. With this protocol in mind, the initial task was to construct diquinane (**3a**). It was felt that **3a** could serve as the precursor to various functionalized analogues such as **3b**.



3a X = H 4
3b X = OCH_3

Synthesis of Enone 3a. The desired enone **3a** was conveniently prepared from the readily available 4,4-dimethylcyclopent-2-en-3-one (**5**)[7] in an efficient seven-step sequence (Scheme I). Addition of **5** to a solution of $[Bu_3PCuI]_4$ and the Grignard reagent prepared from 4-bromo-1-butene followed by alkylation of the regiospecifically generated enolate with methyl 4-iodo-3-methoxycrotonate in the presence of HMPA produced the crystalline ketone **6** in 58% yield.[8] Production of trans-disubstituted cyclopentanones by this sequence is well precedented. Hydrolysis of the enol ether of **6** with 30% aqueous perchloric acid in dichloromethane provided the crude keto ester **7** which was im-

Scheme I[a]



12a R = Li 13a
12b R = $Si(CH_3)_3$ 13b

[a] (a) $CH_2{=}CHCH_2CH_2MgBr$, Bu_3PCuI, THF; then $ICH_2C(OCH_3)CHCO_2CH_3$, HMPA. (b) 30% $HClO_4$, CH_2Cl_2. (c) NaOMe, MeOH. (d) Me_2CuLi, Et_2O. (e) LiCl, H_2O, Me_2SO, heat. (f) ETSA, Bu_4NF, THF.

Table I

base	12b, %	13b, %
$(i\text{-Pr})_2NLi$	45	55
$(Me_3Si)_2NLi$	30	70
LTMP	65	35
$(Me_2PhSi)_2NLi$	80	20
ETSA, Bu_4NF	96	4

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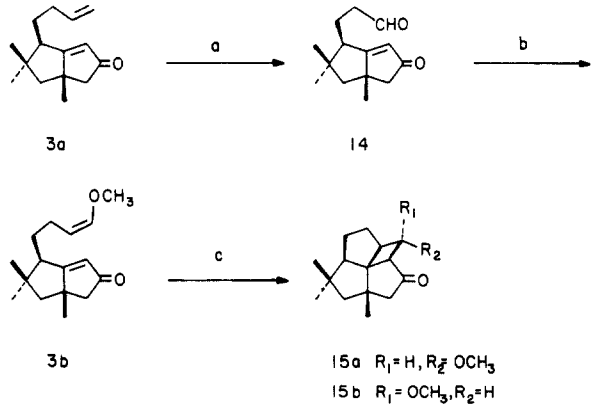
mediately cyclized by the action of freshly prepared sodium methoxide in methanol to give a 100% yield of ester **8** as a crystalline solid. Introduction of the angular methyl was accomplished by treating **8** with lithium dimethylcopper to provide the cis bicyclic ketone **9**. Removal of the carbomethoxyl with lithium chloride in wet Me_2SO at 100 °C gave the ketone **10** in 89% yield from **6**.[9] Thus, all that remained to complete the target **3a** was to introduce the remaining double bond.

On the basis of an analogous system **11** studied by Danishefsky in his synthesis of quadrone in which enolization occurred exclusively in the direction shown,[8] we anticipated that the double

bond in **3a** might be introduced by regioselective selenenylation of **10** through a regioselective formation of enolate **12a**. A study of several bases (see Table I) produced only modest selectivity for the desired enolate, and attempts to implement the selenenylation–elimination sequence produced only low yields (10%) of the desired enone **3a**. Use of sulfur-based reagents resulted in only slight improvements of the yields. However, regioselective formation of the trimethylsilyl enol ether followed by oxidation with palladium(II) acetate and *p*-benzoquinone in acetonitrile proved to be a practical method.[10]

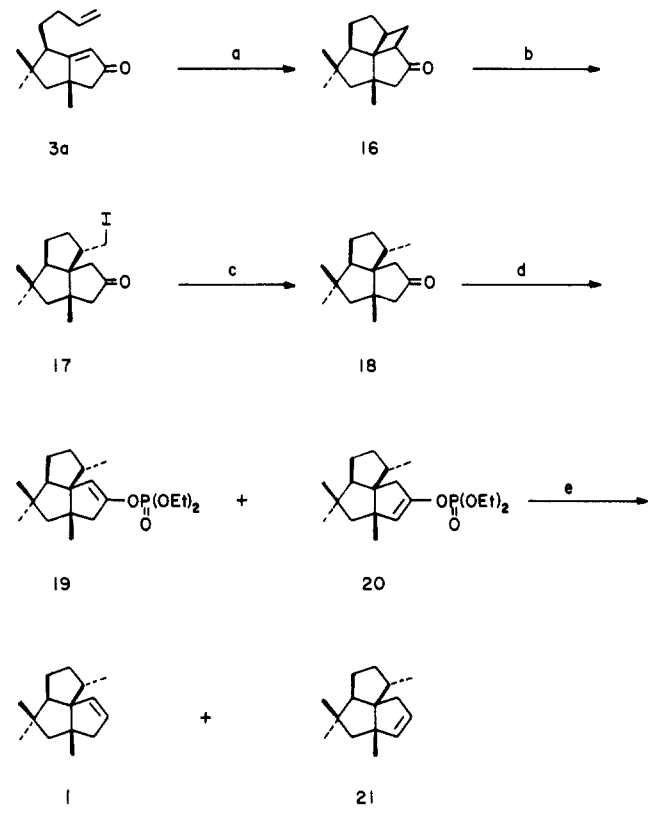
Surprisingly high selectivity was obtained in the formation of the silyl enol ether (**12b**:**13b** = 96:4) using ethyl (trimethylsilyl)acetate and tetrabutylammonium fluoride in THF (−78 to 25 °C).[11] This method was significantly more selective than the most selective dialkylamide base studied, $(Me_2PhSi)_2NLi$, **12b**:**13b** = 80:20.[12] An added advantage to this sequence was the ability to recycle the undesired enol ether by simple hydrolysis. Thus, enone **3a** was obtained in 89% yield from ketone **10**.

Functionalization of Enone 3a. Our initial plan was to utilize enol ether **3b** in the photocyclization step. This would provide the functionalized cyclobutane, which could undergo the proposed cleavage reaction. Oxidative cleavage of the terminal olefin of **3a** with osmium tetraoxide and sodium periodate gave somewhat varying yields of the aldehyde **14**, but this material could be obtained in reasonable quantities. However, attempts to prepare the enol ether **3b** by a Wittig reaction with (methoxymethylene)triphenylphosphorane led to very capricious results (yields from 0 to 80%, usually 10 to 20% accompanied by complete disappearance of aldehyde **14**).[13] Alternatives to this reagent ($Me_3SiCH_2CH_2OCH{=}PPh_3$,[14] p-$ClC_6H_4OCH{=}PPh_3$[15]) were



(a) $NaIO_4$, OsO_4, Et_2O, H_2O. (b) $Ph_3P{=}CHOCH_3$, THF. (c) $h\nu$, hexane.

Scheme II[a]



[a] (a) $h\nu$, hexane. (b) Me_3SiI, CH_3CN, reflux. (c) Bu_3SnH, C_6H_6, reflux. (d) LDA, 0.1 equiv, *t*-BuOH, THF, $(EtO)_2POCl$. (e) Li, CH_3NH_2.

attempted with equally poor results. Although **3b** underwent smooth photocycloaddition to fenestrane **15**, the difficulties encountered in the Wittig reaction prompted investigation of alternative routes.

We had previously carried out the photocycloaddition of enone 3a (Scheme II) to produce fenestrane (**16**), and it occurred to us that perhaps a direct cleavage of **16** might be possible. Attempted reductive cleavage of **16** with lithium in ammonia analogous to some cyclopropyl systems proved unsuccessful. Alternatively, exposure of ketone **16** to trimethylsilyl iodide (Me_3SiCl, NaI)[16] in refluxing acetonitrile resulted in smooth cleavage of the cyclobutane to provide iodo ketone **17** in 89% yield. Reduction of the carbon–iodine bond with tributyltin hydride gave 98% of ketone **18** with all the required stereocenters in place.

Since attempts to trap ketone **17** as its silyl enol ether in the cleavage reaction were unsuccessful, a study of the enolate formation of **18** was undertaken in hopes of selectively forming enol phosphate **19** as the direct precursor to silphinene. Enolization of **18** under kinetic conditions with LDA in THF at various temperatures gave approximately equal amounts of enol phosphates **19** and **20**. Thermodynamic enolization of **18** was accomplished by treatment of **18** with LDA and 0.1 equiv of *tert*-butyl alcohol in THF at reflux for 2 h. Quenching of the enolate with diethyl chlorophosphonate resulted in a 4.5:1 ratio of **19**:**20** in 78% yield.

Reduction of the enol phosphate[17] mixture with lithium in methylamine gave a 4.5:1 mixture of silphinene (**1**):isosilphinene (**21**) in 99% yield. Pure silphinene or isosilphinene could be obtained from this mixture by chromatography on silver nitrate impregnated silica gel. In summary, an efficient, regioselective synthesis of (±)-silphinene has been accomplished in 12 steps in

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an overall yield of 22%. An intramolecular photocycloaddition–fragmentation sequence served to establish two stereocenters with high selectivity.

Experimental Section

Materials and Methods. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from sodium benzophenone ketyl immediately prior to use. Dichloromethane, triethylamine, pyridine, tetramethylethylenediamine (TMEDA), and hexamethylphosphoramide (HMPA) were dried by distillation from calcium hydride immediately prior to use.

Infrared spectra were recorded on a Beckman IR 4210. Nuclear magnetic resonance spectra (NMR) were recorded either at 100 MHz on a Varian XL-100 or at 250 MHz on a Bruker WM-250 spectrometer.

Microanalyses were performed by Galbraith Labs. Melting points and boiling points were uncorrected.

Methyl (*Z*)-(1*R,2*R**)-β-Methoxy-3,3-dimethyl-5-oxo-2-(3-butenyl)cyclopentanecrotonate (6).** The Grignard reagent prepared from 4-bromo-1-butene (15.73 g, 120 mmol) and magnesium metal (3.36 g, 140 mmol) in dry THF (90 mL) was added via cannula to a solution of $[CuI(Bu_3P)]_4$ (3.97 g, 2.53 mmol) in dry THF (30 mL) at −50 °C, and the resulting solution was stirred with a mechanical stirrer for 20 min. The enone **5** (8.64 g, 78 mmol) was then added dropwise and the reaction was stirred for 2 h at −50 to −20 °C. Dry HMPA (92 mL) was added rapidly, followed immediately by methyl 4-iodo-3-methoxycrotonate (45 g, 176 mmol). The reaction solution was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and diluted with hexane. The organic layer was washed 4 times with water, dried over $MgSO_4$, and concentrated on a rotary evaporator. Purification by flash chromatography (200 g silica gel, 10% EtOAc/hexane) yielded **6** (13.3 g, 44.5 mmol, 58% yield, tan solid): mp 46–49 °C. ^1H NMR (250 MHz, $CDCl_3$): 0.91 (s, 3 H), 1.18 (s, 3 H), 1.37–1.78 (band, 3 H), 2.00–2.33 (m, 5 H), 2.94 (dd, 1 H), 3.48 (dd, 1 H), 3.61 (s, 3 H), 3.67 (s, 3 H), 4.90–5.06 (m, 2 H), 5.08 (s, 1 H)8 5.66–5.91 (m, 1 H). IR (neat): 1635, 1720, 1750 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.37; H, 9.08.

Methyl (3a*R,4*R**)-4-(3-butenyl)-2,3,3a,4,5,6-hexahydro-5,5-dimethyl-2-oxo-1-pentalenecarboxylate (8).** The enol ether **6** (13.1 g, 44.50 mmol) was subjected to acidic hydrolysis by stirring at room temperature in a mixture of 70% perchloric acid (40 mL), water (40 mL), and methylene chloride (300 mL). After 30 min, the organic layer was separated and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL). The solution was dried over $MgSO_4$ and then concentrated on a rotary evaporator. A solution of sodium methoxide was prepared by carefully adding NaH (1.9 g, 79 mmol) to methanol (150 mL) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C, and the neat hydrolysis product was added. After 45 min the reaction was quenched with saturated aqueous NH_4Cl, and the solvent was removed on a rotary evaporator. The residue was redissolved in diethyl ether and dried with $MgSO_4$. Purification by flash chromatography (100 g silica gel, 10% EtOAc/hexane) yielded compound **8** (11.67 g, 44.48 mmol, 100% yield, light yellow solid): mp 40–43 °C. ^1H NMR (250 MHz, $CDCl_3$): 1.05 (s, 3 H), 1.15 (s, 3 H), 1.20–1.73 (band, 3 H), 1.94–2.24 (band, 2 H), 2.30 (dd, 1 H), 2.80 (dd, 1 H), 2.86–2.99 (band, 3 H), 3.82 (s, 3 H), 5.05 (m, 2 H), 5.81 (m, 1 H). IR (neat): 1650, 1720, 1755 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_3$: 73.25; H, 8.45. Found: C, 73.32; H, 8.45.

Methyl 4-(3-Butenyl)octahydro-5,5,6a-trimethyl-2-oxopentalene-1-carboxylate (9). A solution of **8** (10.67 g, 40.7 mmol) in ether (50 mL) was added dropwise to a solution of lithium dimethylcuprate (64.8 mmol) in ether (80 mL) at 0 °C. After 15 min the reaction was quenched with saturated aqueous NH_4Cl. An amount of Celite approximately equal to that of the precipitated salts in the product mixture was thoroughly stirred into the solution, and all solids were then removed by vacuum filtration. The solids were extracted with ether (3 × 100 mL). The combined product solution and ethereal extracts were washed with 10% HCl (2 × 100 mL), dilute NH_4OH (2 × 100 mL), and saturated NaCl (2 × 100 mL). The solution was dried over $MgSO_4$ and concentrated on a rotary evaporator. Purification by flash chromatography (100 g of silica gel, 10% EtOAc/hexane) yielded compound **9** (10.08 g, 36.22 mmol, 89% yield, colorless oil). ^1H NMR (250 MHz, $CDCl_3$): 0.91 (s, 3 H), 0.95 (s, 3 H), 1.24 (s, 3 H), 1.70 (s, 2 H), 1.01–1.62 (band, 4 H), 2.02 (m, 3 H), 2.27 (dd, 1 H), 2.81 (dd, 1 H), 3.78 (s, 3 H), 5.01 (m, 2 H), 5.81 (m, 1 H). IR (neat): 1660, 1740 cm^{-1}.

4-(3-Butenyl)hexahydro-5,5,6a-trimethyl-2(1*H*)-pentalenone (10). A solution of **9** (8.07 g, 29 mmol) and LiCl (7.29 g, 0.17 mol) in a mixture of Me_2SO (140 mL) and water (4 mL) was heated to 145 °C and then immediately allowed to cool to room temperature. The solution was diluted with half-saturated NaCl (200 mL) and extracted with 1:1 ether/hexane (6 × 50 mL). The combined organic extracts were washed with saturated NaCl (2 × 50 mL) and dried over $MgSO_4$. Concentration on a rotary evaporator and purification by flash chromatography (60 g silica gel, 10% EtOAc/hexane) yielded **10** (6.11 g, 27.7 mmol, 96%, colorless oil). ^1H NMR (250 MHz, $CDCl_3$): 0.94 (s, 3 H), 1.04 (s, 3 H), 1.17 (s, 3 H), 1.20–1.62 (band, 4 H), 1.70 (s, 2 H), 2.10 (m, 3 H), 2.22 (s, 2 H), 2.52 (dd, 1 H), 4.98 (m, 2 H), 5.78 (m, 1 H). IR (neat): 1750 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.48; H, 10.91.

4-(3-Butenyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1*H*)-pentalenone (3a). The ketone **10** (1.54 g, 7.0 mmol) and ethyl (trimethylsilyl)acetate (2.53 g, 14.7 mmol) were dissolved in dry THF (15 mL) under nitrogen atmosphere. The resulting solution was cooled to −78 °C and a solution of 1.0 M Bu_4NF (0.2 mmol in 2 mL of THF) was added dropwise over a period of 30 min. The mixture was allowed to warm to room temperature and then stirred for 1 h. The solvent was removed on a rotary evaporator and the residue was redissolved in hexane and filtered through Celite. The hexane was removed on a rotary evaporator, and the mixture of silyl enol ether products was added to a solution of benzoquinone (1.51 g, 14 mmol) and $Pd(OAc)_2$ (1.55 g, 6.9 mmol) in dry acetonitrile (75 mL) under nitrogen atmosphere. After stirring overnight, the reaction mixture was then diluted with 1:1 ether/hexane (50 mL) and filtered through Celite. The solution was washed with 10% HCl (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and saturated aqueous NaCl (25 mL). The product solution was dried over $MgSO_4$ and concentrated on a rotary evaporator. Fractionation by flash chromatography (65 g of silica gel, 10% EtOAc/hexane) gave the desired enone **3a** (1.35 g, 6.2 mmol, 89% yield, colorless oil) and the starting ketone **10** (169 mg, 0.77 mmol, 11%). ^1H NMR (250 MHz, $CDCl_3$): 0.98 (s, 3 H), 1.18 (s, 3 H), 1.34 (s, 3 H), 1.70 (AB, 2 H), 1.54–1.86 (band, 2 H), 1.97–2.26 (band, 2 H), 2.38 (AB, 2 H), 2.48 (dd, 1 H), 5.06 (m, 2 H), 5.84 (m, 1 H), 5.88 (s, 1 H). IR (neat): 1760 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.85; H, 10.12.

Photocyclization of 3a. The enone **3a** (1.027 g, 4.7 mmol) was dissolved in 250 mL of hexane and irradiated (uranium filter, 450-W medium-pressure mercury lamp) for 4 h at room temperature. The solvent was removed on a rotary evaporator to give the cyclobutane **16** (970 mg, 4.44 mmol, 94% yield, colorless waxy solid, mp 62–65 °C). ^1H NMR (250 MHz, $CDCl_3$): 0.90 (s, 3 H), 1.05 (s, 3 H), 1.16 (s, 3 H), 1.58 (m, 2 H), 1.78 (AB, 2 H), 1.68–1.86 (band, 1 H), 1.91–2.19 (band, 5 H), 2.42 (AB, 2 H), 2.62 (m, 1 H). IR (neat): 1745 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found C, 82.40; H, 9.95.

9-(Iodomethyl)-2,2,4-trimethyltricyclo[6.3.0.0^{4,8}]undecan-6-one (17). A solution of the cyclobutane **16** (932 mg, 4.27 mmol) and NaI (7.52 g, 50.2 mmol) in dry acetonitrile (50 mL) was prepared under a nitrogen atmosphere. Trimethylsilyl chloride (6.5 mL, 51.2 mmol) was added and the reaction mixture was heated to reflux. After 2 days at reflux the mixture was cooled to room temperature and diluted with diethyl ether (100 mL). The solution was washed with 10% HCl, saturated aqueous $NaHCO_3$, 10% Na_2SO_4, and saturated NaCl. The solution was dried with $NaSO_4$ and the solvent removed on a rotary evaporator. Fractionation by flash chromatography (100 g of silica gel, 5% EtOAc/hexane) gave the desired iodo ketone **17** (1.051 g, 3.04 mmol, 71% yield) and cyclobutane **16** (133 mg, 0.61 mmol, 14%). ^1H NMR (250 MHz, $CDCl_3$): 1.02 (s, 3 H), 1.06 (s, 3 H), 1.16 (s, 3 H), 1.37–1.79 (band, 3 H), 1.83 (AB, 2 H), 2.09 (m, 1 H), 2.27 (AB, 2 H), 2.30 (AB, 2 H), 2.30–2.53 (band, 2 H), 2.92 (dd, 1 H), 3.37 (dd, 1 H). IR (neat): 1750 cm^{-1}. Anal. Calcd for $C_{15}H_{23}IO$: C, 52.03; H, 6.70; I, 36.65. Found: C, 52.15; H, 6.59; I, 36.73.

2,2,4,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undecan-6-one (18). A solution of the iodo ketone **17** (197 mg, 0.57 mmol) and Bu_3SnH (325 mg, 1.12 mmol) in dry benzene (10 mL) was heated to reflux under nitrogen atmosphere for 30 min. The benzene was then removed on a rotary evaporator and the residue redissolved in diethyl ether. The solution was washed with dilute aqueous KF, dried over $MgSO_4$, and filtered. The solvent was removed on a rotary evaporator, and the product was isolated by flash chromatography (15 g of silica gel, 10% EtOAc/hexane) to give the ketone **18** (124 mg, 0.56 mg, 98% yield, colorless oil). ^1H NMR (250 MHz, $CDCl_3$): 0.96 (s, 3 H), 1.00 (s, 3 H), 1.05 (s, 3 H), 1.11 (s, 3 H), 1.27 (m, 1 H), 1.51–1.75 (band, 2 H), 1.78 (s, 2 H), 1.90–2.18 (band, 3 H), 2.22 (AB, 2 H), 2.30 (AB, 2 H). IR (neat): 1740 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: 81.51; H, 10.74.

Synthesis of Silphinene (1). A solution of lithium diisopropylamide (1 M, 0.45 mmol) was added to a solution of the ketone **18** (99 mg, 0.45 mmol) in dry THF (2 mL) cooled to 0 °C. After 15 min, *t*-BuOH (3.38 mg, 0.046 mmol) in THF (0.45 mL) was added. The mixture was heated to reflux for 2 h. At this point the solution was allowed to cool to room temperature and then quenched with a solution of diethyl chlorophosphate (240 mg, 1.39 mmol), dry TMEDA (1 mL), and diethyl ether (2 mL). After stirring for 30 min, the mixture was diluted with ether and washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl. The solution was dried over $NaSO_4$, and the solvent was removed on a rotary evaporator. Fractionation via flash chromatography (15 g of silica

gel; 10% EtOAc/hexane + 25% EtOAc/hexane) yielded starting material (10 mg, 0.045 mmol) and a mixture (4.5:1) of the enol phosphates **19** and **20** (125 mg, 0.35 mmol, 78% yield). A solution of the enol phosphates (202 mg, 0.57 mmol) and *t*-BuOH (403 mg, 5.4 mmol) in THF (4 mL) was added dropwise to a solution of lithium metal (55 mg, 7.92 mmol) in dry refluxing methylamine (10 mL). The mixture was stirred for 30 min, after which the reaction was quenched with solid sodium benzoate and then saturated aqueous NH_4Cl. The solution was allowed to warm to room temperature and the methylamine allowed to evaporate. The remaining solution was diluted with pentane and washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried over $NaSO_4$ and filtered through a small amount of silica gel. The solvent was then removed cautiously on a rotary evaporator. A 4.5:1 mixture of silphinene (**1**) and isosilphinene (**21**) was obtained (115 mg, 0.56 mmol, 99% yield). Pure silphinene was isolated by column chromatography on 15% $AgNO_3$/silica gel eluted with 2% benzene/hexane. The NMR spectrum of the synthetic silphinene was identical with that of a comparison spectrum of authentic silphinene provided by Professor D. D. Sternbach.

Silphinene (**1**): ^{1}H NMR (250 MHz, $CDCl_3$) 0.82 (d, J = 6.0 Hz, 3 H), 0.93 (s, 3 H), 0.99 (s, 3 H), 1.08 (s, 3 H), 1.14–1.36 (band, 3 H), 1.67 (AB, 2 H), 1.77–2.08 (band, 3 H), 2.19 (ddd, J = 13.6 Hz, 2.4 Hz, 2.4 Hz, 1 H), 2.49 (ddd, J = 13.6 Hz, 2.4 Hz, 2.4 Hz, 1 H), 5.46 (m, 1 H), 5.60 (m, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) 16.43, 26.65, 27.40, 27.64, 30.95, 37.43, 38.58, 38.36, 49.22, 50.95, 58.33, 63.73, 72.83, 125.36, 138.41 Isosilphinene (2): ^{1}H NMR (250 MHz, $CDCl_3$) 0.87 (s, 3 H), 0.98 (s, 3 H), 0.99 (d, J = 6.0 Hz, 3 H), 1.02 (s, 3 H), 1.09–1.45 (band, 3 H), 1.58 (AB, 2 H), 1.61–1.97 (band, 3 H), 2.06 (d, J = 13.6 Hz, 1 H), 2.67 (d, 13.6 Hz, 1 H), 5.50 (s, 2 H,). ^{13}C NMR (200 MHz, $CDCl_3$) 17.04, 23.42, 26.97, 27.20, 27.93, 32.28, 37.00, 38.63, 41.12, 53.95, 57.87, 64.19, 67.92, 126.03, 142.62.

Acknowledgment. We gratefully acknowledge financial support from the National Institutes of Health (AI-20283), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of North Carolina for a Junior Faculty Development Award to M.T.C. Thanks are due to Lori D. Bredon and Dr. David H. Harris for assistance in recording 250-MHz NMR spectra. We also thank Professor Daniel D. Sternbach for providing authentic spectra of silphinene for comparison purposes.

Cationic Cyclopentaannelation: An Efficient Methylenomycin Synthesis

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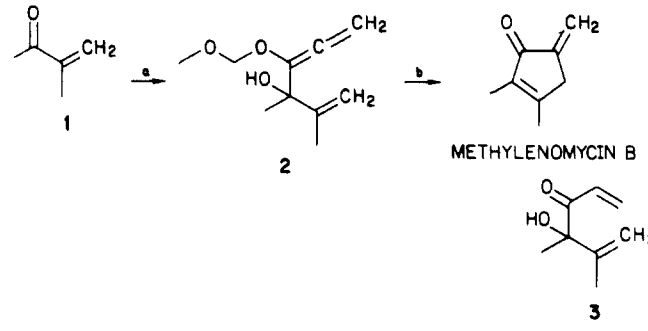
Received September 23, 1985

Abstract: A cationic cyclopentaannelation reaction which was discovered in our laboratories has been used for an extremely short and efficient synthesis of some methylenomycins. Methylenomycin B was prepared in two steps. (±)-Desepoxy-4,5-didehydromethylenomycin A and (±)-desdihydroxy-4,5-didehydroxanthocidin have also been prepared in order to demonstrate the scope and the efficiency of this unusual cyclization.

Cyclopentanoid antibiotics have been the focus of considerable synthetic activity in recent years. The isolation of methylenomycins A and B from a streptomycete strain and the elucidation of their structure in 1974[1] were followed by disclosure of their synthesis by several groups.[2] Xanthocidin, the most densely functionalized member of this class of compounds and a highly unstable molecule, was prepared by Smith through a very ingenious route in 1983.[3] The interest that the methylenomycins have elicited is due to their unusual structure and their promising profile of antibiotic and antineoplastic activity. Methylenomycin A is effective against Lewis lung carcinoma in mice.[4] Methylenomycin A and methylenomycin B are active against Gram-positive and Gram-negative bacteria and are cytotoxic in vitro in the KB assay.[1,5]

Scheme I.[a] Synthesis of Methylenomycin B



[a] (a) 4 equiv of α-lithio-α-(methoxymethyl)allene, THF/ether (1:1) −78 °C, 88%; (b) 3 equiv of $(CF_3CO)_2O$, 5 equiv of 2,6-lutidine, CH_2Cl_2, −20 °C, 74%.

A cationic cyclopentaannelation reaction which was discovered in our laboratories[6] appeared to offer an extremely direct method

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