hydrochloride (1): 1.22 g (88% yield); mp 175–177 °C dec; $[\alpha]^{20}_D$ +78.5° (c 1.9, H_2O), +96° (c 1, 2 N HCl); NMR (D_2O) δ 4.6 (d, 1 H, J = 6 Hz), 5.35–6.1 (m, 3 H). Anal. Calcd for $C_4H_8ClNO_2$: C, 34.4; H, 5.7; N, 10.0. Found: C, 34.9; H, 5.5; N, 9.9.

The vinylglycine hydrochloride (1) obtained above was proved to be optically pure as follows. A solution of 1 (275 mg, 2 mmol) in 20 mL of dry methanol saturated with HCl gas was refluxed for 4 h with the use of dry ice condenser. Evaporation left 250 mg (85% yield) of the hydrochloride 17 as an amorphous residue: $[\alpha]^{20}_D$ +81.4° (c 2, CH_3OH); NMR (free base, $CDCl_3$) δ 3.63 (s, 3 H), 3.95 (m, 1 H), 5.0–6.1 (m, 3 H). Anal. Calcd for $C_5H_{10}ClNO_2 \cdot {}^1/_3H_2O$: C, 38.1; H, 6.8; N, 8.9. Found: C, 38.0; H, 6.8; N, 8.7.

A solution of 200 mg of 17 in 10 mL of methanol was shaken with H_2 at 40 psi in the presence of $Pd/BaSO_4$ for 4 h. The catalyst was removed, the solvent was evaporated, and the residue was crystallized from acetone, affording methyl 2-aminobutanoate (14), identical in all respects with 14 obtained from hydrogenation of 11. Treatment of 14 with (+)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride gave ester amide 15 which showed a single peak, R_T = 13.2 min, on high-pressure LC as above.

L-2-[(*tert*-Butyloxy)carbonyl]amino]-3-butenoic Acid (18). A solution of L-vinylglycine hydrochloride (1; 275 mg, 2 mmol), di-*tert*-butyl dicarbonate (575 mg, 2.1 mmol), and sodium bicarbonate (335 mg, 4 mmol) in 12 mL each of dioxane and water was refluxed for 2 h. The dioxane was evaporated, and the aqueous solution was acidified with dilute hydrochloric acid and extracted with chloroform (3 × 15 mL). The combined chloroform extracts were washed with saturated sodium bicarbonate and then water, dried, and evaporated to give 450 mg (87% yield) of 18 as a colorless oil: NMR ($CDCl_3$) δ 1.46 (s, 9 H), 3.7 (m, 1 H), 4.73 (br d, 1 H), 5.1–6.05 (m, 3 H), 10.3 (s, 1 H); $[\alpha]^{20}_D$ +2.8° (c 4, CH_3OH). Anal. Calcd for $C_8H_{15}NO_4$: C, 53.7; H, 7.5; N, 7.0. Found: C, 53.5; H, 7.8; N, 6.7.

The optical purity of acid 18 was determined by hydrogenating a solution of 18 (200 mg, 1 mmol) in 10 mL of methanol with H_2 at 40 psi in the presence of 150 mg of 10% Pd/C for 16 h. The catalsyt was removed, the solvent was evaporated, and to the residue of 19 as a solution in 10 mL THF at −20 °C were added isobutyl chloroformate (137 μL, 1 mmol) and *N*-methylmorpholine (112 μL, 1 mmol). After the mixture was stirred for 10 min at −20 °C, (+)-α-phenylethylamine (130 μL, 1 mmol) was added and stirring continued for 20 min. Extraction in the usual way gave the L-2-[[(*tert*-butyloxy)carbonyl]amino]butanoyl-*d*-α-phenylethylamide (20) as a colorless oil in quantitative yield. The above procedure was repeated with acid 19 and (±)-α-phenylethylamine. The diastereomeric amides 20 from the latter reaction on high-pressure LC (10/1 hexane/ethyl acetate, 1.5 mL/min) showed two equal peaks (R_T = 9.6 and 11.1 min); the amide 20 from the former reaction showed only the single peak of R_T = 9.6 min.

Registry No. 1, 75266-38-5; 8, 2491-18-1; 9, 56762-93-7; 10, 75266-39-6; 11, 75266-40-9; 12, 60027-61-4; 13, 60027-55-6; 14, 56545-22-3; (±)-14, 7682-18-0; 15, 70363-18-7; (±)-15 (isomer 1), 75330-84-6; (±)-15 (isomer 2), 75330-85-7; 16, 72015-57-7; 17, 75266-41-0; 18, 75266-42-1; 19, 34306-42-8; 20 (isomer 1), 75266-43-2; 20 (isomer 2), 75266-44-3; benzyl choroformate, 501-53-1; (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4; (±)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 64312-89-6; di-*tert*-butyl dicarbonate, 691-64-5; (+)-α-phenethylamine, 3886-69-9; (±)-α-phenethylamine, 618-36-0.

Synthetic Studies toward Verrucarol. 1. Synthesis of the AB Ring System

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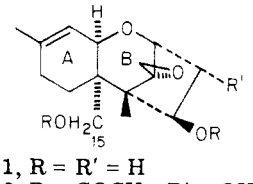
Received June 24, 1980

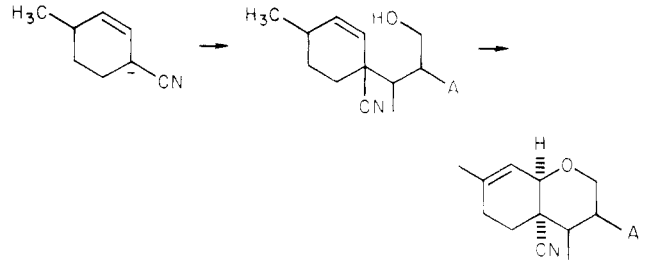
A synthetic route to the AB ring system of verrucarol is described. After two routes employing intramolecular cyclization failed, the Diels–Alder reaction of methyl coumalate and isoprene afforded bicyclic lactone 13. Transformation of 13 into hydroxy lactone 16 involved cuprate addition, hydroxylation, and oxidation. The conversion of 16 into desired keto alcohol 14 was accomplished by enol ether formation, reduction of the lactone and ester, and hydrolysis of the enol ether. The successful nine-step sequence proceeded in an overall yield of 7.9% from methyl coumalate.

Verrucarol (1) is the sesquiterpene portion of several macrocyclic dilactones which exhibit potent anticancer activity.[1] Certain derivatives of verrucarol are active in inhibiting viral infections.[2] Anguidin (2), a related compound, shows inhibitory activity against several cancers.[3] As a result of their biological activity and novel structures,



1, R = R′ = H
2, R = $COCH_3$; R′ = OH

Scheme I



verrucarol and related compounds have been the objects of intense synthetic activity. The total synthesis of trichodermol (15-deoxyverrucarol) has been reported by both Colvin[4] and Still.[5] Syntheses of certain precursors and aromatic analogues[6] have also been reported. Trost and

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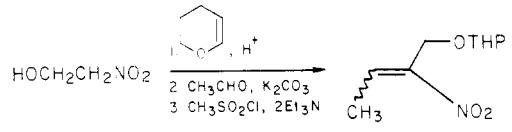
Rigby have communicated[7] a clever approach to the verrucarol ring system. Interestingly, Colvin has recently reported[8] that his trichodermol route cannot be used to prepare verrucarol.

Our initial synthetic strategy toward the A–B ring system of verrucarol is outlined in Scheme I.

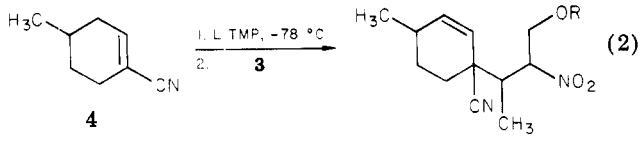
Key steps include the Michael addition of the anion of an unsaturated nitrile and an intramolecular etherification reaction. This etherification reaction must afford a cis ring junction. Additionally, the unspecified group A must serve as both an activator for Michael addition and a convenient precursor for a carbonyl group. Previous work in our laboratory indicated that Michael addition reactions of cyclic unsaturated nitriles with good Michael acceptors afforded variable yields of easily purified products. In accord with the restrictions on group A, we chose nitroalkene **3** to initiate our investigations. This compound can be conveniently prepared as depicted in eq 1. Although



(1)

3 (30% yield)

it can be stored at 0 °C for a few weeks, optimal results are achieved with freshly purified material. Deprotonation of nitrile **4**[9] with lithium 2,2,6,6-tetramethylpiperidide at −78 °C in tetrahydrofuran followed by addition of **3** and warming to 0 °C affords a 43% yield of adduct **5** (eq 2).

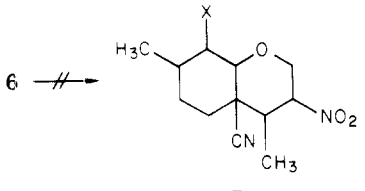


(2)

4

5, R = THP (43% yield)
6, R = H

No products arising from γ Michael addition were observed as evidenced by the crude NMR spectrum. Notably, no elimination of the tetrahydropyranyloxy group could be detected. Compound **5** was clearly a mixture of stereoisomers. However, each isomer should be convertible to the desired product. Acid-catalyzed removal of the alcohol protecting group afforded **6**. Several reaction conditions were studied for the transformation of alcohol **6** into ether **7** (eq 3). Both the selenoetherification method



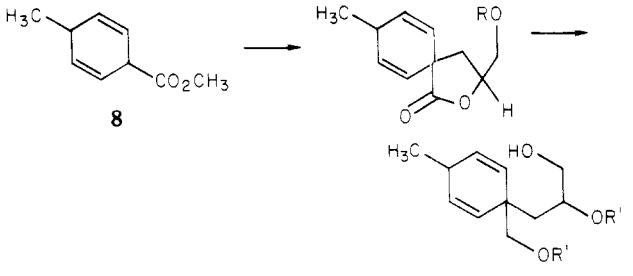
(3)

7

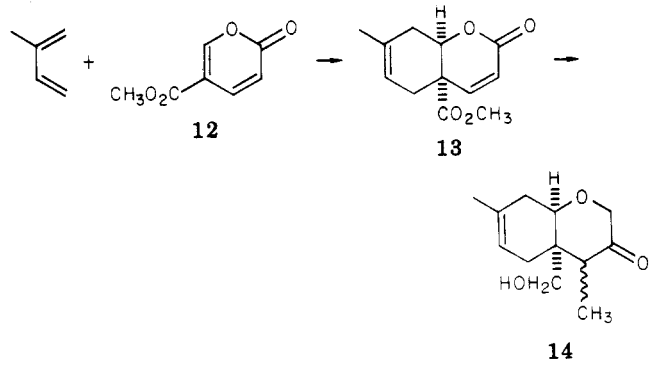
of Nicolaou[10] and oxymercuration with mercuric trifluoroacetate[11] led to recovery of **6**. Since the inductive effect of the nitrile could be deactivating the olefin toward electrophilic reactions, hydrolysis of the nitrile was considered. All attempts to convert the nitrile to an acid or aldehyde led to the destruction of starting materials. Alternatively, **6** could be brominated with *N*-bromosuccinimide in carbon tetrachloride to produce an unstable allylic bromide. Neither base-induced cyclization with DBN nor silver nitrate mediated cyclization afforded identifiable products. In view of the failure of **6** to cyclize, a modification of our initial plan was required. This modification is depicted in Scheme II. Reaction of the anion of ester **8**[12] with various epoxides led to the isolation of spiro lactones in excellent yield. The most direct route to **9** involved reaction of the anion of **8** with epoxide **10** to produce lactone **11** in 94% yield. Lithium aluminum hydride reduction of **11** afforded a diol which in turn could be benzolated and hydrolyzed to form **9** (R′ = PhCO; eq 4). Unfortunately, attempted cyclization of **9** with phenylselenyl chloride or mercuric trifluoroacetate again led to recovery of starting material. Preferential complexation with the benzoate may be responsible for the reluctance of **9** to cyclize.

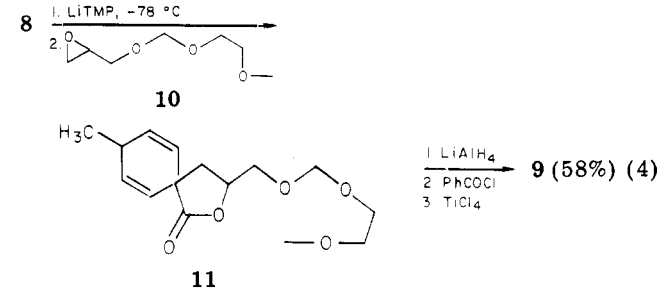
In view of problems encountered in forming the A–B ring system by intramolecular cyclization, a new strategy was devised which would unambiguously define the ring junction stereochemistry and also permit rapid access to a functionalized B ring. This plan is outlined in Scheme III. Although the Diels–Alder reaction of isoprene with readily available methyl coumalate[13] had been reported,[14]

Scheme II



Scheme III





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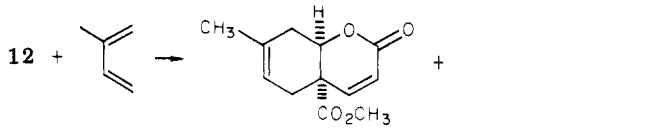
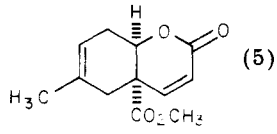
no assessment of the regiochemical purity of the adducts had been made. In our hands either the aluminum chloride catalyzed reaction at 23 °C or the thermally promoted reaction in benzene at 110 °C produced a mixture of regioisomers in a ratio of 85:15 **13a/13b** (eq 5), with the



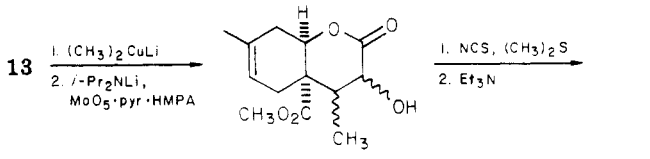
13a



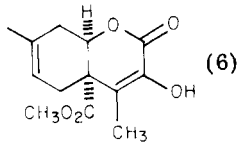
(5)

13b

expected regioisomer predominating. This ratio was determined by integration of the 400-MHz spectrum of the subsequent cuprate addition product. Experiments to optimize reaction conditions for the transformation of **13** to **14** were conducted on the mixture of isomers. Reaction of dimethylcopper lithium with the bicyclic lactone followed by hydroxylation according to the method of Vedejs[15] afforded hydroxy lactone **15** (eq 6). The low overall



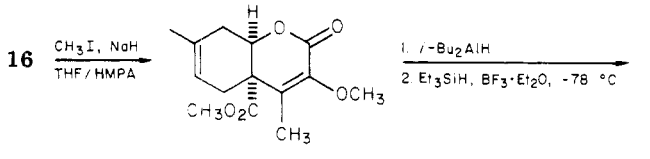
15



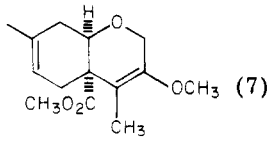
(6)

16 (100%)

yield from **12** (13%) is due to polymer formation in the Diels–Alder step. Oxidation of hydroxy lactone **15** with *N*-chlorosuccinimide (NCS) and dimethyl sulfide[16] in methylene chloride at −25 °C followed by addition of triethylamine produced lactone **16**. A variety of oxidation procedures (Jones,[1] pyridinium chlorochromate, pyridinium dichromate) gave inferior results. Exclusive O-methylation of **16** with sodium hydride and methyl iodide in THF–HMPA produced **17** (eq 7). A two-step sequence



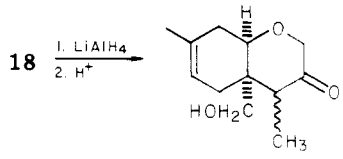
17 (72%)



(7)

18 (90%)

involving reduction of **17** to the lactol with diisobutylaluminum hydride followed immediately by reaction of the unstable lactol with triethylsilane and boron trifluoride etherate[17] provided allylic ether **18** in 90% yield. Lithium aluminum hydride reduction and acidic hydrolysis afforded keto alcohol **14** (eq 8). Compound **14** is produced by a



(8)

14 (93%)

nine-step route in 7.9% overall yield from methyl coumalate. Introduction of the requisite two-carbon bridge, isomerization of the trisubstituted olefin in ring A,[18] and transformation of the ketone in ring B into an epoxide[19] are necessary operations to complete the synthesis of verrucarol. Experiments designed to solve the remaining problems are under active investigation.[21]

Experimental Section

General Methods. Diethyl ether and THF were distilled from lithium aluminum hydride. All organic extracts were dried over Na_2SO_4. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian A60 or HA-100 instrument in $CDCl_3$ with absorptions recorded in parts per million downfield from internal Me_4Si. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer.

2-(2-Nitroethoxy)tetrahydropyran. To 2-nitroethanol (9.1 g, 100 mmol) in 50 mL of methylene chloride were added dihydropyran (13.8 mL, 150 mmol) and pyridinium *p*-toluenesulfonate (2.51 g, 10 mmol). This solution was stirred at room temperature under nitrogen for 2 h. After dilution with chloroform, the solution was then washed twice with H_2O, dried, and concentrated in vacuo. A fast silica gel column chromatography (4:1 ether–hexane) yielded 15.4 g (88%) of a pale yellow oil: IR (film) 1560, 1350 cm^{-1}; NMR ($CDCl_3$) δ 1.31–2.03 (m, 6 H), 3.37–4.30 (m, 4 H) 4.35–4.83 (m, 3 H).

3-Hydroxy-2-nitro-1-(2-tetrahydropyranyloxy)butane. To a solution of K_2CO_3 (2.28 g, 16 mmol) in 10 mL of a 1:1 ethanol–H_2O mixture at room temperature was added 2-(2-nitroethoxy)tetrahydropyran (5.26 g, 30 mmol) in 5 mL of ethanol. Freshly distilled acetaldehyde (1.85 mL, 35 mmol) in 5 mL of ethanol was then added dropwise. After being stirred for 30 min, the solution was neutralized with 1 N HCl. The solution was extracted twice with chloroform and dried. Filtration and removal of the solvent in vacuo gave 5.189 g (78.6%) of a mixture of diastereomers which can be used without further purification: IR (film) 3450, 1560, 1350 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (m, 3 H), 1.40–1.86 (m, 6 H), 3.37–4.40 (m, 6 H, with D_2O added, 5 H), 4.55–4.81 (m, 2 H).

2-Nitro-1-(2-tetrahydropyranyloxy)-2-butene (3). The crude 3-hydroxy-2-nitro-1-(2-tetrahydropyranyloxy)butane (2.19 g, 10 mmol) was stirred in 10 mL of methylene chloride at 0 °C under nitrogen. To this solution was added, all at once, mesityl chloride (0.77 mL, 10 mmol). After a few minutes, triethylamine (2.79 mL, 20 mmol) was added dropwise. Stirring was continued for 15 min. The solution was then diluted with methylene chloride and washed twice with H_2O and once with brine. After the solution was dried and concentrated in vacuo, silica gel chro-

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(21) A referee has noted that a similar strategy is outlined in the Ph.D. thesis of J. A. Thomas (*Diss. Abstr. Int. B* **1979**, *40*(2), 760).

matography (2:1 ether–hexane) yielded 865 mg (43%) of **3** as a viscous orange-red oil: IR (film) 1630, 1530, 1320 cm^{-1}; NMR ($CDCl_3$) δ 1.33–1.82 (m, 6 H), 2.01 (d, J = 8 Hz), 3.35–4.08 (m, 4 H), 4.55–4.71 (m, 1 H), 7.37 (q, 1 H, J = 8 Hz).

1-Cyano-4-methyl-1-cyclohexene (4). 4-Methylcyclohexanone (6.1 mL, 50 mmol) was added over a period of 30 min to an ice-cold solution of sodium bisulfite (7.8 g, 75 mmol) in 15 mL of H_2O. Then potassium cyanide (4.88 g, 75 mmol) in 10 mL of water was added slowly to the cooled mixture. The solution was allowed to warm to room temperature and stirred overnight. After the mixture was extracted three times with ether, dried, and concentrated in vacuo, 4.34 g (62%) of cyanohydrin was obtained and used without further purification. The crude cyanohydrin was stirred in pyridine (7 mL, 90 mmol) at 0 °C under nitrogen. Thionyl chloride (6.27 mL, 86 mmol) was then added dropwise. The solution was warmed to room temperature and stirred overnight. The mixture was then poured into 100 mL of H_2O, the pH adjusted to 4 with 1 N NaOH, and the mixture extracted three times with ether. After the mixture was dried and the solvent removed in vacuo, the residue was distilled to yield 2.72 g (78% from cyanohydrin) of **4** as a pale yellow oil: bp 118 °C (11 mm) [lit.[20] bp 98–100 °C (5 mm)]; IR (film) 3040, 2215, 1635 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (d, 3 H, J = 6 Hz), 1.21–2.50 (m, 7 H), 5.50–6.72 (m, 1 H).

1-Cyano-1-(4-hydroxy-3-nitro-2-butyl)-4-methyl-2-cyclohexane (6). To a stirred solution of 2,2,6,6-tetramethylpiperidine (0.93 mL, 5.5 mmol) in 5 mL of THF at 0 °C under nitrogen was added 2.52 mL (5.5 mmol) of a 2.1 M solution of *n*-butyllithium in hexane. After 15 min, **4** (600 mg, 5 mmol) was added dropwise in 5 mL of THF. The red solution was stirred for 30 min at 0 °C and then cooled to −78 °C. Compound **3** (1.01 g, 5 mmol) dissolved in 5 mL of THF was then added dropwise. After 5 min the solution was warmed to 0 °C and quenched with acetic acid (0.63 mL, 11 mmol). After dilution with ether, the solution was washed once with H_2O and brine, dried, and concentrated in vacuo. The crude product was then dissolved in 10 mL of 95% ethanol. A trace of *p*-toluenesulfonic acid was added and the solution refluxed for 4 h. After the mixture cooled, 15 mL of H_2O was added, and the mixture was extracted three times with ether. The extracts were dried and concentrated in vacuo. Silica gel chromatography (2:1 ether–hexane) yielded 512 mg (43%) of **6** as a mixture of diastereomers: IR (film) 3450, 2230, 1560, 1350 cm^{-1}; NMR ($CDCl_3$) δ 0.82–2.34 (m, 12 H), 3.08 (br s, 1 H, OH), 3.80–4.34 (m, 3 H), 5.33–5.71 (m, 1 H), 5.84–6.12 (m, 1 H); high-resolution mass spectrum, calcd for $C_{12}H_{18}N_2O_3$ m/e 238.131 73, found m/e 238.132 51.

1-(Carbomethoxy)-4-methyl-2,5-cyclohexadiene (8). To 200 mL of liquid ammonia were added 7.5 mL of H_2O, *p*-toluic acid (3.4 g, 25 mmol), and lithium (870 mg, 125 mmol). The lithium was added quickly over a period of approximately 3 min. The ammonia was allowed to evaporate over a period of several hours. H_2O (50 mL) was added and the pH adjusted to 4 with 3 N HCl. The mixture was extracted with ether three times, and the extracts were dried. Filtration and removal of solvent in vacuo yielded 3.09 g of crude material (mp 98–102 °C; lit.[12] mp 105–106 °C) which was dissolved in 50 mL of anhydrous methanol. Boron trifluoride etherate (3.2 mL) was added and the solution refluxed under nitrogen for 24 h. Upon cooling, the mixture was poured into 100 mL of H_2O and extracted three times with ether. The extracts were dried and evaporated in vacuo. A 2.82-g (74%) sample of **8** was obtained as white needles from silica gel chromatography (4:1 ether–hexane): mp 68–71 °C; IR (Nujol) 3040, 1735, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.01–1.23 (m, 3 H), 2.29–3.30 (m, 2 H), 3.78 (s, 3 H), 5.67–6.09 (br s, 4 H).

9,10-Epoxy-2,5,7-trioxadecane (10). Glycidol (1.33 mL, 20 mmol) and diisopropylethylamine (5.22 mL, 30 mmol) were mixed in 20 mL of methylene chloride at room temperature under nitrogen. (β-Methoxyethoxy)methyl chloride (3.42 mL, 30 mmol) in 20 mL of methylene chloride was then added dropwise. The solution was then stirred for 3 h. The mixture was diluted with ether and washed once with H_2O, 1 N HCl, and brine. The organic layer was dried and concentrated in vacuo to yield after silica gel chromatography (4:1 ether–hexane) 2.99 g (92%) of **10** as a clear oil: IR (film) 2835, 1095 cm^{-1}; NMR ($CDCl_3$) δ 2.40–2.89 (m, 2 H), 2.98–3.28 (m, 1 H), 3.37 (s, 3 H), 3.45–3.97 (m, 6 H), 4.84 (br s, 2 H).

1-Oxo-3-(2,4,7-trioxaoct-1-yl)-8-methyl-2-oxaspiro[4.5]-deca-6,10-diene (11). To a stirred solution of 2,2,6,6-tetramethylpiperidine (0.56 mL, 3.3 mmol) in 3 mL of THF at 0 °C under nitrogen was added 1.57 mL (3.3 mmol) of a 2.1 M solution of *n*-butyllithium in hexane. After 15 min, **8** (457 mg, 3 mmol) in 3 mL of THF was added dropwise. The solution was stirred 15 min at 0 °C and then cooled to −78 °C. A solution of **10** (487 mg, 3 mmol) in 3 mL of THF was then added dropwise. The solution was warmed to room temperature and stirred for 2 h. The solution was then quenched with acetic acid (0.38 mL, 6.6 mmol). The mixture was diluted with ether, washed once with H_2O and brine, dried, and concentrated in vacuo. Silica gel chromatography yielded 798 mg (94%) of **11** as a viscous oil. NMR indicated **11** to be a mixture of diastereomers: IR (film) 1770, 1670, 1095 cm^{-1}; NMR ($CDCl_3$) δ 1.01–1.25 (m, 7 H), 4.86 (br s, 2 H), 5.35–6.10 (m, 4 H); high-resolution mass spectrum, calcd for $C_{15}H_{22}O_5$ m/e 282.145 71, found m/e 282.146 89.

$LiAlH_4$ Reduction of 11. To a stirred solution of lithium aluminum hydride (144 mg, 3.8 mmol) in 3 mL of ether at 0 °C under nitrogen was added **11** (549 mg, 1.95 mmol) in 2 mL of ether. The solution was stirred for 30 min at 0 °C and then quenched by slow addition of 5 drops of H_2O, 5 drops of 1 N NaOH, and 0.4 mL of H_2O. After being stirred for 30 min, the solution was diluted with ether, filtered through Celite, and dried. Evaporation of solvent yielded 413 mg (74%) of a pale yellow oil: IR (film) 3410, 1070 cm^{-1}; NMR ($CDCl_3$) δ 0.97–1.19 (m, 3 H), 1.37–1.56 (m, 2 H), 1.90–2.12 (m, 1 H), 3.38 (s, 3 H), 3.52–4.10 (m, 9 H), 4.27 (br s, 2 H, OH), 4.85 (br s, 2 H), 5.34–6.15 (m, 4 H).

1-[(Benzoyloxy)methyl]-1-[2-(benzolyloxy)-4,6,9-trioxodec-1-yl]-4-methyl-2,5-cyclohexadiene. To a solution of the crude diol from **11** (413 mg, 1.44 mmol) and triethylamine (0.89 mL, 6.35 mmol) in 10 mL of methylene chloride under nitrogen was added benzoyl chloride (0.37 mL, 3.18 mmol). The mixture was refluxed 24 h, diluted with ether, washed twice with brine, and dried. Filtration and removal of solvent in vacuo yielded after silica gel chromatography (2:1 ether–hexane) 618 mg (87%) of the dibenzolated product as a yellow viscous oil: IR (film) 1715, 1260, 1090; NMR ($CDCl_3$) δ 0.95–1.15 (m, 3 H), 1.28–1.47 (m, 2 H), 1.92–2.15 (m, 1 H), 3.40 (s, 3 H), 3.49–3.90 (m, 9 H), 4.82 (br s, 2 H), 5.34–6.12 (m, 4 H), 7.29–8.41 (m, 10 H).

1-[(Benzoyloxy)methyl]-1-[2-(benzoyloxy)-3-hydroxyprop-1-yl]-4-methyl-2,5-cyclohexadiene (9). To a solution of the dibenzoylated MEM ether (306 mg, 0.62 mmol) in 10 mL of a 2:1 methylene chloride–hexane mixture at 0 °C under nitrogen was added dropwise a fivefold excess of titanium tetrachloride (0.34 mL, 3.1 mmol). The solution was stirred at 0 °C for 30 min followed by quenching with 1 mL of concentrated ammonium hydroxide. The mixture was stirred 30 min, diluted with methylene chloride and filtered through Celite. The organic layer was separated, dried, and concentrated in vacuo. Silica gel chromatography (2:1 ether–hexane) yielded 227 mg (90%) of **9** as a clear viscous oil: IR (film) 3440, 1710, 1260 cm^{-1}; NMR ($CDCl_3$) δ 0.95–1.12 (m, 3 H), 1.26–1.48 (m, 2 H), 1.92–2.15 (m, 1 H), 3.01 (br s, 1 H, OH), 3.37–3.94 (m, 5 H), 5.40–6.01 (m, 4 H), 7.42–8.99 (m, 10 H); high-resolution mass spectrum, calcd for $C_{25}H_{26}O_5$ m/e 406.178 01, found m/e 406.177 81.

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-7-methyl-2*H*-1-benzopyran-2-one (13). Method A. Aluminum chloride (67 mg, 5 mmol) was stirred in 5 mL of benzene at 0 °C under nitrogen. To this suspension was added, dropwise, methyl coumalate (750 mg, 5 mmol) in 5 mL of benzene. On addition of the coumalate, a sticky precipitate formed in large clumps; presumably this was an aluminum chloride–coumalate complex. This mixture was stirred 30 min at 0 °C, and then isoprene (2.5 mL, 25 mmol) was added all at once. The solution was allowed to warm to room temperature and stirred 48 h. A 10-mL sample of 1 N HCl was then added and the solution stirred vigorously for 30 min. The solution was diluted with ether and filtered through Celite, and the organic layer was separated, dried, and concentrated in vacuo. Silica gel chromatography (4:1 hexane–ether) yielded 723 mg of a mixture of the desired Diels–Alder product **13**, the 6-methyl regioisomer, and an undesired product. The last few fractions yielded 46 mg of Diels–Alder products free from this undesired material. This almost pure mixture of regioisomers exists as a viscous oil: IR (film) 1730, 1750 (sh), 1640, 1260 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (br s, 3 H), 1.85–2.97 (m, 4 H),

3.76 (s, 3 H), 4.81–5.06 (m, 1 H), 5.25–5.52 (m, 1 H), 5.99 (d, 1 H, J = 8 Hz), 6.89 (d, 1 H, J = 8 Hz). The acid-catalyzed reaction, however, produces large amounts of isoprene polymer. This can be avoided by conducting the reaction under thermal conditions.

Method B. Methyl coumalate (18.5 g, 120 mmol) and isoprene (36 mL, 360 mmol) in 80 mL of benzene were heated 48 h at 110 °C in a sealed tube. The solvent was removed in vacuo, and silica gel chromatography (4:1 hexane–ether) yielded 14.17 g of a mixture of products. Smaller amounts of the undesired product were also produced. The undesired material does not interfere in the subsequent conjugate addition. Since the tedious separation proved to be impractical for obtaining large amounts of **13**, the unknown compound was carried along with **13** into the next reaction.

(±)-(4α,4aβ,8aβ)-4a-(Carbomethoxy)-3,4,4a,5,8,8a-hexahydro-4,7-dimethyl-2*H*-1-benzopyran-2-one. Cuprous iodide (19.05 g, 100 mmol) was suspended in 200 mL of ether at 0 °C under N_2. Methyllithium–lithium bromide complex as a solution in ether was added slowly to the suspension until the initially formed yellow precipitate just disappears. The solution was then stirred for 5 min at 0 °C. A 14.17-g amount of the mixture of **13** and the unwanted materials dissolved in 50 mL of ether was then added slowly. The mixture was stirred for 30 min after the addition was completed. The bright yellow suspension was then poured slowly into 200 mL of a saturated ammonium chloride solution. The mixture was filtered through Celite and the organic layer separated. The aqueous layer was extracted two times with ether, and all the organic fractions were combined, dried, and evaporated in vacuo. Silica gel chromatography yielded 4.93 g (17.5% from methyl coumalate) of the conjugate addition product as white needles: mp 82–83.5 °C; IR (Nujol) 1735, 1640, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.00–1.10 (m, 3 H), 1.67 (br s, 3 H), 1.98–2.86 (m, 6 H), 3.72 (s, 3 H), 4.85–4.96 (m, 1 H), 5.20–5.42 (m, 1 H); high-resolution mass spectrum, calcd for $C_{13}H_{14}O_4$ m/e 222.089 20, found m/e 222.089 52. The 400-MHz proton NMR spectrum of this compound shows it to be a mixture of regioisomers (6- and 7-methyl). This was determined by integration of the olefinic proton at δ 5.20–5.42 which at 400 MHz separates into two multiplets: δ 5.33–5.42 (85%) and 5.20–5.28 (15%). The unidentified material from the Diels–Alder reaction apparently is destroyed in the reaction because no other product was ever isolated from this reaction.

(±)-(3α,4α,4aβ,8aβ)-4a-(Carbomethoxy)-3,4,4a,5,8,8a-hexahydro-3-hydroxy-4,7-dimethyl-2*H*-1-benzopyran-2-one and the C-3 Epimer (15). To diisopropylamine (1.55 mL, 11 mmol) in 10 mL of THF at −78 °C under N_2 was added 4.58 mL (11 mmol) of 2.4 M *n*-butyllithium solution in hexane. After 15 min, the product of the cuprate reaction (2.38 g, 10 mmol) in 5 mL of THF was added dropwise and the mixture was stirred for 10 min. Then the molybdenum peroxide reagent, MoO_5·pyr·HMPA (MoOPH; 6.51 g, 15 mmol), was added all at once. The solution quickly turned orange. The solution was stirred for 2 h at −78 °C and then warmed to 0 °C. On warming, the orange solution turned dark brown, and the yellow solid (undissolved MoOPH) gradually dissolved. After 15 min at 0 °C the solution turned light green, and all of the MoOPH had dissolved. A 15-mL amount of H_2O was added as was 15 mL of ether. The organic layer was separated and washed one time with 1 N HCl, saturated $NaHCO_2$ solution, and brine and then dried. Concentration in vacuo and silica gel chromatography yielded 2.86 g (75%) of **15** as a very oily white solid. Several attempts at recrystallization proved unsuccessful: IR (Nujol) 3460, 1735, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.13–1.21 (m, 3 H), 1.64 (m, 3 H), 1.90–2.60 (m, 4 H), 3.71 (m, 3 H), 3.91–4.13 (m, 1 H), 4.82–5.04 (m, 1 H), 5.20–5.45 (m, 1 H); no hydroxyl proton was observed.

(±)-4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-3-hydroxy-4,7-dimethyl-2*H*-1-benzopyran-2-one (16). *N*-Chlorosuccinimide (2.04 g, 15 mmol) was stirred in 40 mL of methylene chloride at 0 °C under N_2. Dimethyl sulfide (1.51 mL, 20.5 mmol) was added dropwise, and the solution was then cooled to −25 °C. The α-hydroxy lactone **15** (2.54 g, 10 mmol) dissolved in 10 mL of methylene chloride was then added dropwise and stirred for an additional 2 h at −25 °C. Triethylamine (2.09 mL, 15 mmol) in 2 mL of methylene chloride was then added slowly. The cooling bath was removed, and the solution was stirred for 5 min and then poured into 80 mL of ether. The solution was washed twice with 20% HCl solution and then dried. Silica gel chromatography (2:1 ether–hexane) yielded 2.51 g (~100%) of **16** as white crystals: mp 92–93 °C; IR (Nujol) 3480, 1740, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (br s, 3 H), 1.82 (s, 3 H), 2.10–2.43 (m, 4 H), 3.73 (s, 3 H), 4.89–5.11 (m, 1 H), 5.20–5.56 (m, 1 H), 5.72 (s, 1 H, OH).

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4,7-dimethyl-3-methoxy-4a,5,8,8a-tetrahydro-2*H*-1-benzopyran-2-one (17). Sodium hydride (396 mg, 16.5 mmol) was stirred in 15 mL of THF and hexamethylphosphoramide (2.61 mL, 15 mmol) at 0 °C under nitrogen. Compound **16** in 5 mL of THF was added and the solution stirred for 30 min. Methyl iodide (1.87 mL, 30 mmol) was then added all at once. The solution was stirred for 2 h at 0 °C and then poured into hexane, washed once with H_2O and then brine, and dried. Filtration and concentration in vacuo yielded 2.88 g (72%) of the O-methylated product **17** as a viscous oil: IR (film) 1740, 1690, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (br s, 3 H), 1.84 (s, 3 H), 2.10–3.03 (m, 4 H), 3.77 (s, 6 H), 4.92–5.06 (m, 1 H), 5.23–5.56 (m, 1 H).

(±)-(2α,4aβ,8aβ)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-2-hydroxy-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran and the C-2 Epimer. The enol ether lactone **17** (2.66, 10 mmol) was stirred in 10 mL of methylene chloride at −25 °C under nitrogen. Diisobutylaluminum hydride (10.68 mL, 11 mmol) as a 1.03 M solution in hexane was then added dropwise. After 1 h at −25 °C the solution was poured into 10 mL of 10% acetic acid solution. Chloroform (50 mL) was added, and the mixture was stirred for 2 h. The organic layer was separated, dried, and concentrated in vacuo to yield after chromatography (2:1 ether–hexane) 2.52 g (94%) of the lactol, an oily solid, as a mixture of diastereomers. Recrystallization (hexane) yielded only crystals which rapidly became oily again: mp 52–66 °C; IR (Nujol) 3430, 3020, 1730, 1690, 1210 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.68 (br s, 3 H), 2.06–2.99 (m, 4 H), 3.58–3.78 (m, 7 H), 4.58–4.76 (m, 1 H), 5.20–5.54 (m, 2 H; D_2O added, 1 H).

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran. The enol ether lactol (2.52 g, 9.4 mmol) was dissolved in 20 mL of methylene chloride at −78 °C along with triethylsilane (2.24 mL, 14.1 mmol). Boron trifluoride etherate (1.16 mL, 9.4 mmol) was added dropwise. Monitoring by TLC indicated an almost instantaneous reaction. A 500-mg sample of anhydrous potassium carbonate was added and then 2 mL of saturated sodium bicarbonate solution. The solution was then allowed to warm to 0 °C. If the solution was warmed before any base was added, the BF_3 apparently attacked other functionality in the molecule because no desired product was obtained. The solution was diluted with methylene chloride, washed several times with saturated sodium bicarbonate solution, dried, and concentrated in vacuo. Immediate silica gel chromatography (1:1 ether–hexane) yielded 2.27 g (96%) of **18** as a pale yellow oil: IR (film) 1740, 1690, 1210 cm^{-1}; NMR ($CDCl_3$) δ 1.02–1.75 (m, 6 H), 2.00–2.80 (m, 4 H), 3.52 (s, 3 H), 3.68 (s, 3 H), 3.95–4.29 (m, 2 H), 4.50–4.72 (m, 1 H), 5.16–5.53 (m, 1 H).

(±)-(4aα,8aα)-4a,5,8,8a-Tetrahydro-4a-(hydroxymethyl)-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran. Lithium aluminum hydride (380 mg, 10 mmol) was suspended in 10 mL of ether at 0 °C under nitrogen. To this suspension was added the enol ether ester **18** (1.25 g, 5 mmol) in 5 mL of ether. The solution was stirred for 30 min and then worked up by adding first 5 drops of H_2O and then 5 drops of 1 N NaOH followed by 0.5 mL of H_2O. The solution was stirred for 1 h and then diluted with ether, and the fluffy white precipitate was filtered off through Celite. The filtrate was dried and concentrated in vacuo to yield after silica gel chromatography (2:1 ether–hexane) 1.10 g (98%) of the alcohol as a very viscous oil: IR (film) 3450, 1690, 1090 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (br s, 3 H), 1.82–2.51 (m, 4 H), 3.57 (s, 3 H), 3.60–3.71 (m, 2 H), 3.83–3.99 (m, 1 H), 4.11–4.25 (m, 2 H), 4.41 (br s, 1 H, OH), 5.20–5.38 (m, 1 H).

(±)-(4α,4aα,8aα)-4a,5,6,8a-Tetrahydro-4a-(hydroxymethyl)-4,7-dimethyl-2*H*-1-benzopyran-3(4*H*)-one (14). The alcohol enol ether (1.10 g, 4.9 mmol) was stirred in 20 mL of aqueous THF with 5 drops of 3 N $HClO_4$ for 18 h at room temperature. The solution was diluted with an equal amount of ether, washed twice with a saturated sodium bicarbonate solution, and dried. Concentration in vacuo and silica gel chromatography

yielded 979 mg (95%) of the keto alcohol **14** as a very viscous oil: IR (film) 3460, 1715, 1100, 1060 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 6.5 Hz), 1.69 (br s, 3 H), 1.82 (br s, 1 H, OH), 1.89–2.84 (m, 4 H), 2.99 (q, 1 H, J = 6.5 Hz), 3.38–3.76 (m, 2 H), 4.08 (s, 2 H), 4.14–4.26 (m, 1 H), 5.24–5.36 (m, 1 H); high-resolution mass spectrum calcd for $C_{12}H_{18}O_3$ m/e 210.12558, found m/e 210.12577.

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Registry No. **3**, 75233-41-9; **4**, 41198-89-4; **5**, 75233-42-0; **6**, 75233-43-1; **8**, 75233-44-2; **9**, 75233-45-3; **10**, 75233-46-4; **11**, 75233-47-5; **12**, 6018-41-3; **13a**, 75233-48-6; **13b**, 75233-49-7; **14**, 75247-52-8; **15** (isomer 1), 75233-50-0; **15** (isomer 2), 75233-51-1; **16**, 75233-52-2; **17**, 75233-53-3; **18**, 75233-54-4; 4-methyl-1-(hydroxymethyl)-1-(2-hydroxy-4,6,9-trioxodec-1-yl)-2,5-cyclohexadiene, 75233-55-5; 1-[(benzoyloxymethyl)]-1-[(2-(benzoyloxy)-4,6,9-trioxodec-1-yl]-4-methyl-2,5-cyclohexadiene, 75233-56-6; (±)-(4α,4aβ,8aβ)-4a-(carbomethoxy)-3,4,4a,5,8,8a-hexahydro-4,7-dimethyl-2*H*-1-benzopyran-2-one, 75233-57-7; (±)-(4α,4aβ,8aβ)-4a-(carbomethoxy)-3,4,4a,5,8,8a-hexahydro-4,6-dimethyl-2*H*-1-benzopyran-2-one, 75233-57-7; (±)-(2α,4aβ,8aβ)-4a-(carbomethoxy)-4a,5,8,8a-tetrahydro-2-hydroxy-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran (isomer 1), 75233-58-8; (±)-(2α,4aβ,8aβ)-4a-(carbomethoxy)-4a,5,8,8a-tetrahydro-2-hydroxy-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran (isomer 2), 75233-59-9; (±)-(4aα,8aα)-4a,5,8,8a-tetrahydro-4a-(hydroxymethyl)-4,7-dimethyl-3-methoxy-2*H*-1-benzopyran, 75233-60-2; 2-(2-nitroethoxy)tetrahydropyran, 75233-61-3; 3-hydroxy-2-nitro-1-(2-tetrahydropyranyloxy)butane (isomer 1), 75233-62-4; 3-hydroxy-2-nitro-1-(2-tetrahydropyranyloxy)butane (isomer 2), 75281-72-0; 2-nitroethanol, 625-48-9; dihydropyran, 25512-65-6; 4-methylcyclohexanone, 589-92-4; 1-cyano-1-hydroxy-4-methylcyclohexane, 933-45-9; *p*-toluic acid, 99-94-5; 4-methyl-2,5-cyclohexadienecarboxylic acid, 20646-36-0; glycidol, 556-52-5; (β-methoxyethoxy)methyl chloride, 3970-21-6; benzoyl chloride, 98-88-4; isoprene, 78-79-5.

Synthetic Studies toward Verrucarol. 2. Synthesis of the AB Ring System

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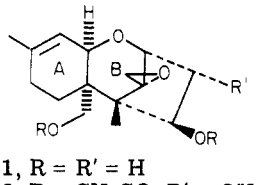
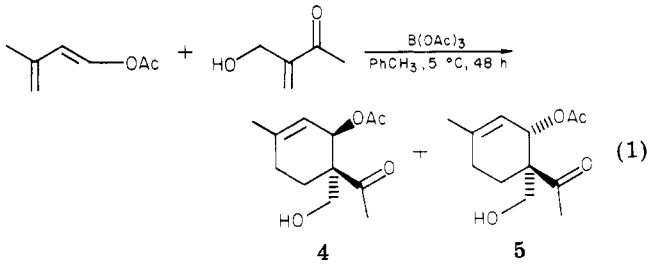
A route to the AB ring system of verrucarol is described. The successful scheme involved the formation of the A ring by a boron triacetate catalyzed Diels–Alder reaction. The second ring can be appended by an intramolecular Knoevenagel reaction to afford lactone **12b**. This lactone could be converted into the desired keto alcohol **3b** by reduction of the lactone and nitrile followed by an oxidation and Curtius degradation.

As indicated in the previous paper,[1] the biological activity and challenging structures of verrucarol (**1**) and



1, R = R′ = H
2, R = CH_3CO; R′ = OH

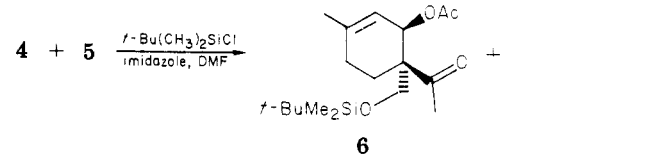
anguidin (**2**) have prompted considerable synthetic effort. Our initial successful preparation of a functionalized AB ring system for verrucarol involved a Diels–Alder reaction between isoprene and methyl coumalate followed by functional group modifications on the B ring. Although the ring-junction stereochemistry was unambiguously defined, our strategy mandated eventual isomerization of the trisubstituted olefin in ring A. In this paper an alternate strategy will be presented in which the trisubstituted olefin in ring A is regiospecifically introduced by a Lewis acid promoted Diels–Alder reaction. Subsequent transformations will afford ketol **3b**. The general plan is outlined in Scheme I. A Diels–Alder reaction between 1-acetoxy-3-methylbutadiene[2] and 3-(hydroxymethyl)-3-buten-2-one[3] afforded a mixture of diastereomeric acetoxy ketones **4** and **5** (3.5:1, eq 1). Stereochemistry was tentatively assigned



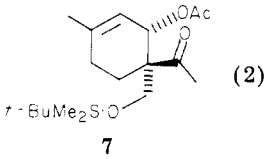
(1)

4 **5**

by comparison of the spectra of the silylated adducts **6** and **7** with the spectrum of **8**. Ketone **8** was the exclusive

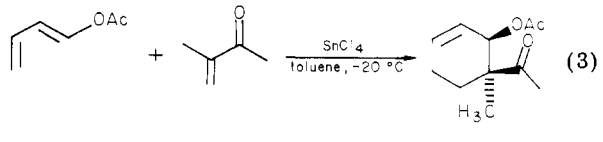


6



(2)

7



(3)

8

product from the tin tetrachloride catalyzed Diels–Alder reaction of 1-acetoxybutadiene and isopropenyl methyl

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