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Abstract
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.

Disciplines
Chemistry | Inorganic Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

Comments
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yielded 979 mg (95%) of the keto alcohol 14 as a very viscous oil: IR (film) 3460, 1715, 1100, 1060 cm\(^{-1}\); NMR (CDCl\(_3\) 5.105 (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\(_{20}\)O\(_4\), m/e 210.1258, found m/e 210.1277.

Acknowledgment. We thank the National Institutes of Health for generous financial assistance.

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, 75233-50-0; 15 (isomer 1), 75233-51-1; 15 (isomer 2), 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-
[benzoyloxy)methyl]-1-[(2-(benzoyloxy)-4,6,9-trioxodec-1-yl)-4-
methyl-2,5-cyclohexadiene, 75233-56-6; (±)-(4a,4aβ,8aβ)-4a-(carbo-
methoxy)-3,4,4a,5,8,8a-hexahydro-4,7-dimethyl-2H-1-benzopyran-2-
one, 75233-57-7; (±)-(4a,4aβ,8aβ)-4a-(carboxytoxy)-3,4,4a,5,8,8a-
hexahydro-4,6-dimethyl-2H-1-benzopyran-2-one, 75233-58-8; (±)-
(2a,4aβ,8aβ)-4a-(carboxytoxy)-4a,5,8,8a-tetrahydro-4,7-
dimethyl-3-methoxy-2H-1-benzopyran, 75233-59-9; (±)-
(4a,4aβ,8aβ)-4a,5,8,8a-tetrahydro-4,7-
dimethylymethoxy-2H-1-benzopyran, 75233-60-2; 2-(2-nitroethoxy)teta-
ratropyran, 75233-61-3; 3-hydroxy-2-nitro-1-(2-tetrahydropropyral-
onyloxy)butane (isomer 1), 75233-62-4; 3-hydroxy-2-nitro-1-(2-tetra-
hydrorxopyranyloxy)butane (isomer 2), 75238-72-0; 2-nitroethanol,
629-48-9; dihydroxpyrane, 25512-63-6; 4-methylcyclohexanone, 589-
92-4; 1-cyano-1-hydroxy-4-methylcyclohexane, 893-45-9; p-toluic
acid, 99-94-5; 4-methyl-2,5-cyclohexadienecarboxylic acid, 20646-36-
0; glycidol, 556-52-5; (5-methoxystyryl)methyl chloride, 3970-21-6;
benzyl chloride, 98-88-4; isoprene, 78-79-5.

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

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Received June 24, 1980

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 ac-
activity and challenging structures of verrucarol (1) and
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 de-
dined, 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 transforma-
tions will afford ketol 3b. The general plan is outlined in
Scheme I. A Diels–Alder reaction between 1-acetoxy-3-
methylbutadiene6 and 3-(hydroxymethyl)-2-buten-2-one3 af-
forded a mixture of diastereomeric acetoxy ketones 4 and
5 (3.5:1, eq 1). Stereochemistry was tentatively assigned

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125-17
(3) Gault, H.; Germann, L. A. C. R. Heb. Seances Acad. Sci. 1933,
197, 650-1.
This compares closely to the value for Hz at 6.325 which represents the allylic methine proton. This compares closely to the value for 6 (J = 4.5 Hz at 6.523) but differs significantly from the corresponding signal for 7 at 6.412. Freshly prepared boron triacetate proved to be the Lewis acid catalyst of choice for obtaining an optimal yield of 4. Other catalysts such as aluminum chloride, tin tetrachloride, and boron trifluoride etherate afforded inferior yields or showed lower selectivity. Interestingly, the thermal reaction (115 9C, 24 h) gave a 2:1 ratio where 5 predominated. Boron triacetate does not catalyze the reaction of acetoxybutadiene and isopropenyl methyl ketone. In addition to 4 and 5, variable amounts of diene resulting from acetate elimination were obtained. Silylation was accomplished by the method of Corey.8

Saponification of the acetate was conducted under mild conditions (K2CO3, CH3OH, 0 9C; eq 4) in order to avoid epimerization by a process which would involve an initial retro aldol condensation followed by realdolization. Hydroxy ketone 10 (which could be conveniently separated from 9 at this point in the sequence) has been converted into an equal mixture of 9 and 10 with a catalytic amount of benzyltrimethylammonium hydroxide. Attempted epimerization of ketone 10 with triphenylphosphine, diethyl azodicarboxylate, and formic acid6 led to recovery of starting materials. The reaction of 9 with acid chlorides and pyridine afforded esters of benzyltrimethylammonium hydroxide. Attempted epoxidation using a modification of a reduction procedure developed by Doyle and co-workers.7 Reduction of 12a with diisobutylaluminum hydride (DIBAL) afforded an unstable lactol which could be reduced to allylic ether 13 with triethylamine and boron trifluoride etherate at -78 9C (eq 6). Notably, no olefin migration was observed as evidenced by the NMR of the crude product. Removal of the alcohol protecting group with tetrabutylammonium fluoride8 produced alcohol 14 in 85% yield. Examination of molecular models indicated that the conformation of 14 that was most consistent with the observed coupling constants had the hydroxymethyl group in close proximity to the olefin in ring B.26 Therefore, directed epoxidation using the method of Sharpless8 was attempted and proved to be highly selective. No other products were isolated. In support of the selectivity and identity of epoxide 15 (eq 7) the regioisomeric epoxide was synthesized by a four-step sequence starting from 12a. Acetylation with acetic anhydride and triethylamine afforded 16 in 70% yield. Unfortunately, all attempts to convert epoxide 16 to a ketone failed. Epoxide isomerization11 (BF3.Et2O, PhH;12 lithium perchlorate in refluxing benzene;13 NaI, Me2SO;14 (eq 10) strongly affected a mixture of stereoisomers of which 8 was the major isomer.

(4) Run by Hirohiko Sugimoto. In this case the thermal reaction afforded a mixture of stereoisomers of which 8 was the major isomer.
(10) (a) MCPBA, CH2Cl2, 0 9C; (b) DIBAL, PhCH3, -78 9C; (c) pTSA, CH3OH; (d) BF3.Et2O, Et2SiH, CH2Cl2, -78 9C.
Verrucarol

SnCl4, toluene, 0 °C(15) led to decomposition of 16. Alternatively, 3 could be approached from an α-hydroxy ketone by reductive elimination. This plan would also permit regioselective formation of an enol acetate or enol silyl ether. Acid-catalyzed opening of the epoxide 16 to a diol(18) followed by attempted oxidation [N-chlorosuccinimide, dimethyl sulphide;17 N-bromosuccinimide in aqueous dioxane;18 dimethyl sulfoxide (Me2SO), dicyclocHexylcarbodiimide, iind various acids;19 Me2SO, acetic anhydride20] failed to yield the desired hydroxy ketone. In all cases unreacted diol was recovered.

As a consequence of our failure to transform epoxide 16 into the desired ketone 3, cyanide ester 11b was synthesized and cyclized to provide 12b in 75% yield from 9. The corresponding diester 11c failed to cyclize. Cyanolactone 12b could be reduced to a cyanolactol by using DIBAL in toluene at -78 °C which in turn could be reduced to 17 with boron trifluoride etherate and triethylsilane (eq 8). A minor product isolated in the conversion of 12b to 17 was aldehyde 18. The DIBAL reduction of 17 provided 18 in 94% yield.

Aldehyde 18 was oxidized to acid 19 in 80% yield using sodium chlorite in aqueous tert-butyl alcohol21 with 2-methyl-2-buten as a chlorine scavenger (eq 9). A more direct route to acid 19 would involve saponification. However, nitrite 17 proved to be resistant to a variety of hydrolysis procedures.22 Acid 19 could be transformed into the desired hydroxy ketone 3 by Curtius degradation23 and desilylation24 in 75% yield. As an additional proof of structure, hydroxy ketone 3 was converted into ether 20 (eq 10) by cyclization with phenylselenyl chloride24 followed by reductive deselenylation. Ether 20 could then be compared with the products obtained by the same reaction sequence on isomeric hydroxy ketone 21.25 The cis ring junction in 21 had been unambiguously defined by the synthetic approach. Both comparison of the δH NMR and 13C NMR spectra and coinjection on capillary gas chromatography indicated that the products obtained by both routes were identical.

The hydroxy ketone 3 is available in 11 steps in 10.4% overall yield. The conversion of 3 into verrucarol requires the introduction of a functionalized two-carbon bridge and the transformation of the ketone into an epoxide. Schemes to accomplish this goal are under active investigation.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether, THF, benzene, and toluene were distilled from LiAlH4 prior to usage. Dichloromethane was distilled from P2O5. All organic extracts were dried over Na2SO4, except where otherwise noted. Melting points were determined on a Fisher-Price apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on either a Hitachi Perkin-Elmer R-20B 60-MHz or a Varian HA-100 100-MHz instrument. Carbon-13 NMR spectra were determined on a JEOl FX-9Q Fourier transform spectrometer. Both proton and carbon chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

cis-1-[(tert-Butyldimethylsiloxy)methyl]-2-hydroxy-4-methyl-3-cyclohexenyl]-1-ethanone (9). Boron trichloride (76 g, 405 mmol) was added in one portion to a rapidly stirred solution of 3-(hydroxymethyl)-3-buten-2-one (27 g, 270 mmol), 1-acetoxy-3-methylbutadiene (37.5 g, 300 mmol), and hydroquinone (2 g) in 600 mL of dry toluene cooled to 0 °C. The resulting suspension was stirred at 5 °C for 2 days. The mixture mixture was heated to 35 °C and the catalyst destroyed by slow addition of aqueous bicarbonate with vigorous stirring. When the mixture had assumed a bright yellow-orange color, it was transferred to a separatory funnel and partitioned between water (500 mL) and ether (1 L). The organic layer was washed with water (2 × 200 mL), bicarbonate (2 × 250 mL), and brine (100 mL). Drying and removal of the solvents afforded 46.2 g of a bright orange oil, which was estimated to be a 3:1 mixture of compounds 4 and 5 by NMR and TLC data. After dissolution of the crude mixture of diastereomers in dry N,N-dimethylformamide (100 mL), tert-butyl(dimethylsilyl)chloroethane (46.5 g, 308 mmol) and imidazole (81.6 g, 1200 mmol) were added.

(b) Hall, J. H.; Gisler, M. Ibid. 1978, 43, 5783.
(25) This experiment was performed on the mixture of regioisomers described in the previous paper. The regioisomeric ethers obtained by the selenenylation-deselenenylation procedure were completely separable under the VPC conditions described in the Experimental Section.
(26) As noted by a referee, several conformations of the cis-cadacalin ring are possible. It may be that steric factors control the site of epoxidation.
The mixture was stirred at 45 °C for 4.5 h and then partitioned between hexanes (600 mL) and water (150 mL). The organic layer was washed with water (100 mL) and brine (100 mL) and dried. Removal of the solvents yielded 68 g of silylated material.

The crude mixture of acetates was dissolved in dry methanol (500 mL) and cooled to 0 °C. Potassium carbonate (99 g, 0.70 mol) and the mixture was stirred for 15 min. The reaction was judged complete by TLC analysis (4–5 h), it was acidified with 6 N HCl (pH 3), and the methanol was removed under reduced pressure. The residue was taken up in ether (500 mL) and washed with water (150 mL), 1 N HCl (150 mL), bi-carbonate (150 mL), and brine (100 mL). The ether layer was dried, the solvents were removed, and the residue was recrystallized (silica gel, 30.1 hexanes–EtOAc) to afford two major substances. The undesired diastereomer 10: R (31 hexane–EtOAc) 0.35; 83 g (10%); IR (film) 3450, 2980, 2860, 1715, 1265, 1105 cm⁻¹; 100-MHz NMR (CDCl₃) δ 0.10 (6, H, 8.8 s, 9 H), 0.93 (s, 9 H), 1.45 (br s, 3 H), 1.8–2.0 (m, 4 H, 2.22 (s, 3 H), 2.60 (br s, 1 H, OH), 3.76, 3.92 (AB q, J = 10 Hz, 2 H), 4.68 (m, 1 H), 5.00 (m, 1 H); 90-MHz ¹³C NMR (CDCl₃) δ 6.57, 18.14, 22.89, 24.00, 25.82, 27.44, 27.77, 56.87, 65.17, 67.70, 123.49, 137.28. Major isomer 9: 27.4 g (33%); R (31 hexane–EtOAc) 0.21; IR (film) 3440, 1715 cm⁻¹; 100-MHz NMR (CDCl₃) δ 0.10 (6, H, 8.8 s, 9 H), 1.70 (m, 3 H), 1.97 (m, 2 H), 2.04 (br s, 1 H, OH), 3.05 (s, 1 H), 3.14 (AB q, J = 11 Hz, 2 H), 4.16 (m, 1 H), 5.52 (m, 1 H), collapses to d, J = 5 Hz, on irradiation at 1.70); 90-MHz ¹³C NMR (CDCl₃) δ 18.14, 21.10, 23.02, 25.81, 27.50, 27.89, 56.25, 65.48, 68.06, 122.96, 173.73, 213.104; high-resolution mass spectrum calculated for C₁₆H₃₀O₃Si 318.1963, found m/e 318.1964, 54.5; m/e 298.1963 found m/e 298.1964.

**cis-cis-1,1’-[[3-(tert-Butyldimethylsiloxy)methyl]-4,4-bromoacetoxy-1]ethylamine** (11a). To a 0 °C solution of alcohol 9 (2.25 g, 7.6 monol) and dry pyridine (1.45 mL, 18 mmol) in dichloromethane (11 mL) was added a solution of bromoacetyl bromide (1.45 mL, 15.1 mmol) in dry THF (13 mL) dropwise over a period of 10 min. The resulting suspension was stirred for a further 30 min and then poured into 200 mL of ether. The organic layer was washed with water (30 mL), 1 N HCl (2 X 20 mL), bicarbonate (2 X 20 mL), and brine (20 mL). Drying and removal of the solvents afforded a quantitative yield of bromoacetate 11a: IR (film) 2880, 2860, 2870, 1740, 1715, 1275, 1105, 835, 770 cm⁻¹; 100-MHz NMR (CDCl₃) δ (6, H, 0.98 (s, 9 H), 1.72 (m, 2 H), 2.0–2.2 (m, 4 H, 2.17 (s, 3 H), 3.43, 3.72 (AB q, J = 10 Hz, 2 H), 3.73 (a, 2 H), 5.27 (br d, J = 5 Hz, 1 H), 5.0 (m, 1 H), collapses to d, J = 5 Hz, on irradiation at 1.72); high-resolution mass spectrum calculated for C₁₆H₂₃BrSi (parent ion = 37) e 361.047, found m/e 361.0465.

**cis-cis-1,1’-[[3-(tert-Butyldimethylsiloxy)methyl]-4,7-dimethyl-4,5,5,8a-tetrahydro-2H-1-benzopyran-2-one** (12a). Bromoacetate 11a (1.694 g, 4.04 monol) and trimethyl phosphate (1.42 mL, 16 mol) were heated together at 90–95 °C under nitrogen for 12 h. After the mixture cooled to room temperature, the excess phosphate was removed under vacuum (~1 mm, 10 h, room temperature), affording the crude phosphonate: high-resolution mass spectrum calculated for C₁₆H₂₅O₃Si m/e 448.2046, found m/e 448.2047.

The crude phosphonate was dissolved in 16 mL of anhydrous THF and the mixture was added dropwise to a suspension of potassium hydride (penta wased) in 5 mL of anhydrous THF at 0 °C under nitrogen. Upon completion of hydrogen evolution, the heating bath was removed and the solution of the mixture was poured into ice–water. The aqueous layer was extracted with ether (5 X 50 mL), and the combined ether layers were washed with water (15 mL) and brine (15 mL). Drying and removal of the solvents gave an oil, which was chromatographed (silica gel, 10 g, 1:1 hexanes–EtOAc), affording 1.604 g (67%) of a pale yellow oil: R (31 hexane–EtOAc) 0.28; IR (film) 2980, 2970, 2725 cm⁻¹; 100-MHz NMR (CDCl₃) δ (6, H, 0.88 (s, 9 H), 1.71 (br s, 3 H), 1.8–1.96 (m, 1 H), 1.20 (d, J = 1.6 Hz, 3 H), 3.67, 3.05 (AB q, J = 9 Hz, 2 H), 4.94 (m, 1 H), 5.44 (m, 1 H), 5.84 (q, J = 1.6 Hz, 1 H); 90-MHz ¹³C NMR δ 18.19, 18.625, 22.878, 25.224, 26.565, 27.288, 42.143, 55.533, 75.919, 119.187, 119.720, 138.800, 160.355, 163.707; high-resolution mass spectrum calculated for C₁₆H₂₅O₃Si m/e 422.1965, found m/e 422.1967;
The cyanoacetate (2.2 g, 80 mmol) and 1,5-diazobicyclo-[4.3.0]non-5-ene (1.0 mL, 8 mmol) were heated to reflux in benzene (150 mL) with azotropic removal of water. After 30 min, the solution was cooled, diluted with ether (500 mL), and washed with 1 N HCl (200 mL). The organic layer was washed with bicarbonate (15 mL), water (300 mL), and brine (100 mL). Drying and removal of the solvents afforded a crude solid which was recrystallized from 50:1 hexanes–EtOAc, yielding 18.15 g (52.3 mmol) of light yellow crystals (mp 145–146 °C). Chromatography (SiO₂, 10:1 hexanes–EtOAc) of the mother liquors afforded a further 2.81 g (7.7 mmol) of crystals (60 mmol overall yield from lactone 12b).

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Synthesis and Properties of 2'-Deoxy-2'-thiocytidine

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In order to assess the significance of the 2'-position of nucleosides, the nucleoside analogue 2'-deoxy-2'-thiocytidine was synthesized by using 2,2'-anhydro-1,1-D-arabinosylcytosine and PS₅ as starting materials. Several thiophosphorylated derivatives were also obtained as synthetic intermediates and characterized by NMR spectroscopy and elemental analysis. The main stable intermediate was 2'-deoxy-2'-thiocytidine, 2',3'-diphosphorodithioate which was subjected to iodine oxidation, alkaline hydrolysis, and finally, a dephosphorylation step, yielding the title compound 2'-S-dCyd, or its disulfide. According to NMR and ORD data, the 2'-carbon of the nucleoside is in the endo orientation, and the rotation of the cytosine moiety is restricted. The most outstanding chemical property of 2'-S-dCyd is the lability of the glycosidic bond, owing to an intramolecular displacement reaction. The rate of decomposition could be conveniently studied by ORD spectroscopy as a function of pH, ionic strength, and temperature. Slightly different first-order kinetics were observed for the nucleoside and its 2' phosphate.

In the past decade numerous 2'-substituted nucleoside analogues have been prepared for the study of structure–function relationships in nucleic acids. Of these analogues, only the 2'-amino and thio substituents possess the capacity to hydrogen bond as hydrogen donors. Since only one analogue, 2'-deoxy-2'-thiodenosine was prepared, but the free nucleoside was too labile to be isolated. We have concentrated our efforts on the synthesis of the cytidine analogue 2'-deoxy-2'-thiocytidine because of its expected stability and biological activity. Our attempts to obtain 2'-S-dCyd in a manner analogous to Imazawa’s method by reacting anhydro-araC' with thioacetate were not successful, and only cytosine was formed. We found it necessary to introduce a thio nucleophile as a 3' neighboring group which could then react selectively with the 2'-carbon. The use of a thiophosphorylated precursor allowed the introduction of cis 3'-O, 2'-S substitution without the use of blocking groups. The conditions for the hydrolysis and oxidation of the phosphorodithioate esters were mild and yielded a stable disulfide of 2'-S-dCyd. This convenient storage form, in turn, could be quantitatively reduced to the thiol by using d-mercaptoethanol.

In our first attempt we used dithiophosphate as a thiophosphorylating agent, but the lability of this compound made it unsuitable for large-scale preparation of 2'-S-dCyd. In the same communication we also noted the felicitous peculiarity of anhydro-araC chemistry which features a reversal in the customary reactivities of the 5' and 3' OH groups. This becomes understandable in view of the X-ray diffraction data which reveal an interaction

(1) F. Rottman and K. Heinlein, Biochemistry, 7, 2934–2939 (1968).
(11) Abbreviations: 2'-S-dCyd, 2'-deoxy-2'-thiocytidine; 2'-S-dCyd-2',5'-P and 2'-S-dCyd-2',2'-PS are the corresponding cyclic phosphorothioate and phosphorodithioate; anhydro-araC, 2',2'-anhydro-1,3-D-arabinosylcytosine.