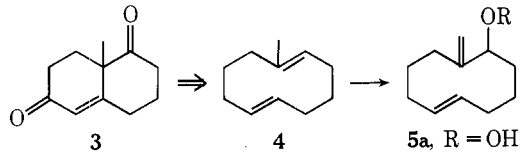
oxygen at the trisubstituted double bond (C-4,5) faster than at the exocyclic double bond (C-8,15), thus exclusively generating 4-methylene-5-hydroperoxy derivative.[4a] Germacrene (2) was reported to react with singlet oxygen at the isopropylidene double bond much faster than the endocyclic double bonds, giving specifically the 7-hydroperoxy derivative.[4b]

We have studied the dye-sensitized photooxygenation of *trans,trans*-1-methylcyclodeca-1,6-diene (**4**), because it has two transannularly interacting double bonds which are suitable for a cycloaddition reaction, and because the two double bonds have different substitution patterns which are capable of revealing the regiospecificity of the "ene" reaction. The diene 4 was readily synthesized from 9-methyloctalin-1,6-dione (**3**) according to literature procedures.[5] A methanol solution of 4 was irradiated in the presence of Methylene Blue at 10° for 4.5 hr while pure oxygen was bubbled through. The disappearance of 4 was monitored by taking aliquots and analyzing them on TLC. A single produce **5a** isolated in 55% yield showed a positive peroxide test with starch–iodine and gave an alcohol **5b** upon reduction with aqueous methanolic sodium sulfite.



3 4 5a, R = OH
b, R = H

Analysis by TLC, GC, and NMR spectrum clearly indicated that alcohol **5b** was homogenous and free from other possible isomers. A thorough search for the transannular cycloaddition products proved futile. It is interesting to note that the hydroperoxidation is completely regiospecific in spite of the fact that four other positions are also available for the "ene" reaction. A qualitative reactivity order of the double bonds toward the singlet oxygen "ene" reaction appears to be the following: isopropylidene > endocyclic trisubstituted olefin > endocyclic disubstituted olefin > isopropenyl > *exo*-methylene.[4] Although there is no straightforward explanation for the exclusive formation of the *exo*-methylene *sec*-hydroperoxide over the other possible endocyclic *tert*-hydroperoxide products, the observed regiospecificity should be of considerable value in synthetic design.[6]

Experimental Section

The NMR spectra were recorded on a Jeol JNM-MH 100 spectrometer. Ir spectra were recorded on a Perkin-Elmer Model 421 grating spectrophotometer. Mass spectral data were obtained on a Hitachi RMU-6 spectrometer. Gas chromatograms were run on a Varian Model 2700 using the columns 5 ft × 0.125 in, 10% OV-101 on Anakrom C.D. and 5 ft × 0.125 in, 10% FFAP on Anakrom C.D. Microanalysis was performed by Dr. R. C. Rittner at Olin Laboratory, New Haven, Conn.

***trans,trans*-1-Methylcyclodeca-1,6-diene (4)** was prepared from 1-methyloctalin-1,6 dione (**3**)[7] according to literature procedures[5] in ca. 35% overall yield: NMR ($CDCl_3$) δ 1.0–2.0 (m, 4 H), 1.64 (s, 3 H), 2.0–2.6 (m, 8 H), 5.0–5.5 (m, 3 H).

2-Methylenecyclodeca-*trans*-6,7-enol (5b). A solution of diene **4** (266 mg, 1.77 mmol) and Methylene Blue (10 mg) in methanol (20 ml) at 10° was irradiated with a 275-W sun lamp while pure oxygen was bubbled through the solution. After 4.5 hr, the solution was poured into cold water and extracted with ether. The extract was washed thoroughly with water, dried (Na_2SO_4), and evaporated at room temperature to give crude hydroperoxide **5a.** Pure **5a** (oil, 180 mg, 55% yield) was obtained by a thick layer chromatography (2 mm SiO_2, developed in 40% ether in hexane): NMR ($CDCl_3$) δ 1.0–2.4 (m, 12 H), 4.36 (br, 1 H), 5.18 (s, 1 H), 5.28 (s, 1 H), 5.42 (m, 2 H).

Stirring a solution of **5a** in methanol (20 ml) and 10% sodium sulfite in water (20 ml) for 5 hr at room temperature, followed by an extractive work-up with ether, gave pure alcohol **5b** in quantitative yield: oil, homogeneous by TLC (SiO_2) and GC (OV 101, 140°); ir 3600, 3080, 3030, 1640, 1448, 1345, 980, 910 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.4 (m, 12 H), 4.08 (br, 1 H), 4.98 (s, 1 H) 5.18 (s, 1 H), 5.36 (m, 2 H); MS *m/e* 166 (M^+), 148, 134, 124, 120.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.52; H, 10.84. Found: C, 79.33; H, 10.77

Acknowledgment. We wish to thank the National Science Foundation (Grant GP33505X) for support of this work.

Registry No.—**3,** 20007-72-1; **4,** 13304-33-1; **5a,** 54814-44-7; **5b,** 54814-45-8.

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(7) Purchased from Aldrich Chemical Co.

Synthesis of Three Substituted Aminochloropropanes

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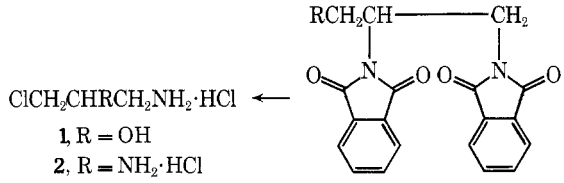
In the course of a study of male antifertility agents it became necessary to synthesize several aminochloropropanes. Because of the proximity of mutually interactive functional groups in such molecules, the instability of the products was a problem that had to be overcome. One of these, 1-amino-3-chloro-2-propanol hydrochloride (**1**), had very interesting properties and its pharmacology has been reported elsewhere.[1,2]

The synthesis of 1,2-diamino-3-chloropropane dihydrochloride (**2**) has been reported by Philippi[3] via the following sequence. 2,3-Dibromopropanol on fusion with potassium phthalimide gave 2,3-bisphthalimidopropanol (**3**).



1, R = OH
2, R = NH_2·HCl

3, R = OH
4, R = Cl

Phosphorus pentachloride converted **3** to **4,** which gave **2** on hydrolysis. Although part of the sequence has been repeated in the literature[4] but without proof of structure of the products, in our hands dehydrobromination occurred on the first step, yielding phthalimide and potassium bro-

mide as the only recovered solids. If epibromohydrin were formed during the hydrogen bromide elimination and not permitted to escape, there would be a danger of getting 1,3-bisphthalimido-2-propanol.[5] A less equivocal path was adopted by us wherein ethyl acetamidocyanoacetate (**5**) was reduced to the alcohol **6** with sodium borohydride. Hydrogenation over Raney nickel in acetic anhydride gave **7**.

$NCCH(NHCOCH_3)R \longrightarrow$

5, R = $CO_2C_2H_5$

6, R = CH_2OH

$CH_3CONHCH_2CH(NHCOCH_3)CH_2O_2CCH_3 \longrightarrow$

7

$CH_2(NHR)CHCH_2OH \longrightarrow CH_2(NHR)CHCH_2Cl$

8, R = H·HCl

9, R = CO_2CH_2Ph

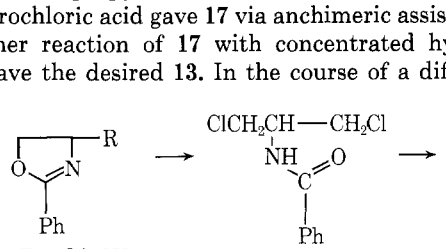
10, R = CO_2CH_2Ph

11, R = H·HBr

2, R = H·HCl

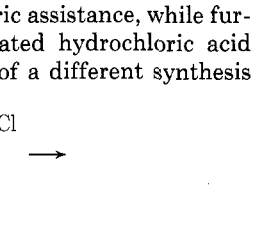
This triacetate had been previously reported,[4] via the phthalimido approach discussed above, but ours had a different melting point. Attempts at a selective hydrolysis of the ester linkage of **7** failed and it was totally hydrolyzed to **8**. Carbobenzoxylation of **8** gave **9** while triphenylphosphine–carbon tetrachloride converted that alcohol to the chloride **10**. Hydrogen bromide in acetic acid on **10** gave **11**, whose structure was confirmed by NMR. After two precipitations from concentrated hydrochloric acid–ethanol, **11** was converted to **2**, demonstrating that the covalent chloride had not been displaced during the hydrogen bromide treatment. The melting point of our **2**, 220–223°, was close to that cited by Philippi, 218–219°. On the other hand, Gabriel[6] prepared 1,3-diamino-2-chloropropane dihydrochloride by the following scheme. 1,3-Dichloro-2-propanol and potassium phthalimide gave 1,3-bisphthalimido-2-propanol; next phosphorus pentachloride and then hydrolysis gave 1,3-diamino-2-chloropropane dihydrochloride (**12**). Even if epichlorohydrin were an intermediate, this scheme would give the structure Gabriel assigned to it. Since Gabriel's melting point was 216°, Philippi's compound could also be, and probably is, **12**.

The second aminochloropropane prepared was 2-amino-3-chloropropanol hydrochloride (**13**). Methyl 2-phenyl-2-oxazoline-4-carboxylate[7] (**14**) was reduced with sodium borohydride to the alcohol **15**. Thionyl chloride converted the alcohol to a chloride and opened the ring to give *N*-2-(1,3-dichloropropyl)benzamide (**16**). Treatment with dilute hydrochloric acid gave **17** via anchimeric assistance, while further reaction of **17** with concentrated hydrochloric acid gave the desired **13**. In the course of a different synthesis



14, R = CO_2CH_3

15, R = CH_2OH



16

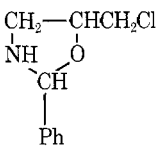
$ClCH_2CHNH_2CH_2OR \cdot HCl$

17, R = COPh

13, R = H

that had one step in common with ours, Berger et al.[8] prepared **16** in low yield and also noted its conversion to **17** by the anchimeric effect.

Finally we wanted to obtain the two enantiomers of our active compound **1**. There are a number of syntheses of racemic **1** in the literature;[9] however, the yields are poor and they do not lend themselves to large scale-ups. Carter and Bhattacharyya[10] reported the reaction of epichlorohydrin with concentrated ammonium hydroxide and benzaldehyde to give **18** in 67% yield. Their structure was based on an



18

$PhCH{=}NCH_2CHOHCH_2Cl$

19

earlier assignment by Bergmann.[11] On preparing **18** and taking an ir spectrum, an imine band was seen at 6.08 μ, indicating that Carter and Bhattacharyya's and Bergmann's compound was probably the Schiff base **19**. Hydrolysis of **19** gave **1** in high yield, thus achieving a simple two-step preparation. Originally we resolved **1** using dibenzoyl-*d*-tartaric acid,[1] but a better resolution was achieved with (+)-10-camphorsulfonic acid.

To determine the absolute configuration of (+)-**1**, it was converted to the free base and condensed with acetone to form a Schiff base, which was reduced without purification to **20**. Dukes and Smith[12] had previously determined the

(+)-**1** $\xrightarrow{CH_3COCH_3}$ $\xrightarrow{NaBH_4}$ (+)-$(CH_3)_2CHNHCH_2CHOHCH_2Cl$

20

absolute configuration of **20**; thus (+)-**1** had the *R* configuration.

Experimental Section

Melting points were determined with a standardized Mel-Temp apparatus. NMR spectra were recorded on a Varian HA-100.

2-Acetamido-3-hydroxypropionitrile[13] (6). To a stirred slurry of 100 g (0.59 mol) of ethyl acetamidocyanoacetate (**5**) in 1 l. of ethanol was added 60 g (1.59 mol) of $NaBH_4$ over a 20-min period. Occasional cooling was used to maintain a 50–55° temperature throughout the addition. Then the reaction was stirred at ambient temperature for 3 hr and cooled in an ice bath and 132 ml of 12 *N* HCl in 500 ml of ethanol was added over a 20-min period. An inorganic precipitate was filtered off and the filtrate was concentrated under vacuum. Three portions of ethanol were added, followed by concentration under vacuum each time to remove water. The residue was leached with 800 ml of acetone and the insolubles were discarded. Concentrating the acetone solution left an oil which on seeding gave 66.5 g of orange crystals. Recrystallization from ethanol gave 28.5 g (38%) of solid, mp 108–110°.

This reaction proved to be erratic and in 13 runs yields varied from 0 to 51%.

An analytical sample was recrystallized twice from ethanol to give mp 111–112°.

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.87. Found: C, 46.92; H, 6.14; N, 22.14.

2,3-Bis(acetamido)propyl Acetate (7). 2-Acetamido-3-hydroxypropionitrile (33.5 g, 0.26 mol), 18.0 g of Raney Ni (prewashed with ethanol three times and then with acetic anhydride three times), 61 g of anhydrous sodium acetate, and 280 ml of acetic anhydride were hydrogenated in a Parr shaker in two portions at 33–40°. When the theoretical amount of hydrogen had been taken up, the mixture was filtered and the filtrate was concentrated under vacuum to give a yellow oil. On crystallization from ethyl acetate–benzene–ether, 48 g of oily crystals, mp 90–95°, were obtained. Recrystallizations from ethyl acetate gave 26 g (46%) of colorless crystals: mp 130–132°; NMR (DMSO-d_6) 2-NAc (6 H) δ 1.85 (s), OAc (3 H) 2.04 (s), CH_2N (2 H) 3.19 (m), CHN and CH_2O (3 H) 4.00 (m), 2-NH (2 H) 7.84 (m).

An analytical sample was recrystallized twice from benzene–cyclohexane to give mp 132–133° (lit.[4] mp 146° for a compound claimed, but not proven, to be **7**).

Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.88; H, 7.47; N, 13.04.

2,3-Diaminopropanol Dihydrochloride (8). After 130 g (0.60 mol) of **7** was refluxed in 1.3 l. of 6 *N* HCl for 45 min, the solution

was permitted to stand overnight. It was next concentrated at 70° (25 mm) to dryness and the residue was slurried with ethanol. Upon standing, crystals were collected, 70 g (71%), mp 162–163°, and recrystallized from aqueous ethanol to obtain 50 g (51%) of light tan crystals, mp 184–186°.

Anal. Calcd for $C_3H_{12}Cl_2N_2O$: C, 22.10; H, 7.42; Cl, 43.49; N, 17.18. Found: C, 22.09; H, 7.51; Cl, 43.30; N, 17.28.

***N,N'*-Dicarbobenzoxy-2,3-diaminopropanol (9)** was prepared by a method of Bergmann and Zervas,[14] yield 62%, mp 109–110° (ethanol).

Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.50; H, 6.09; N, 7.65.

***N,N'*-Dicarbobenzoxy-1,2-diamino-3-chloropropane (10).** A solution of 36.0 g (0.10 mol) of *N,N'*-dicarbobenzoxy-2,3-diaminopropanol in 170 ml of alumina-dried chloroform and 112 ml of carbon tetrachloride was warmed while 53.5 g (0.2 mol) of triphenylphosphine was added. After the exothermic reaction subsided, the solution was refluxed for 2 hr. The solvent was removed under vacuum, and the resulting yellow oil was taken up in 1 l. of hot 60% aqueous ethanol. Seeding and cooling to 0° gave 27.5 g (73%) of colorless crystals, mp 119–120°. A sample was recrystallized from ethanol for analysis, mp 120–121°.

Anal. Calcd for $C_{19}H_{21}ClN_2O_4$: C, 60.55; H, 5.62; Cl, 9.41; N, 7.44. Found: C, 60.51; H, 5.64; Cl, 9.28; N, 7.39.

1,2-Diamino-3-chloropropane Dihydrobromide (11) and Dihydrochloride (2). *N,N'*-Dicarbobenzoxy-1,2-diamino-3-chloropropane (**10**, 30 g, 0.08 mol) was dissolved in 300 ml of glacial acetic acid and saturated with HBr at 0°. After standing for 1 hr, the precipitate which had formed was collected, washed with ether, and air dried to give 19 g (81%) of **11**, mp 210–212° dec. A NMR spectrum confirmed the structure: CH_2N^+ (2 H) δ 3.23 (d), J = 6 Hz, CHN^+ (1 H) 3.96 (m), CH_2Cl (2 H) 4.08 (m), 2-NH_3^+ (6 H) 8.49 (s).

Anal. Calcd for $C_3H_{11}Br_2ClN_2$: C, 13.32; H, 4.10; Br, 59.10; Cl, 13.11; N, 10.36. Found: C, 13.58; H, 4.13; Br, 58.79; Cl, 12.57; N, 10.72.

To ensure that the covalent chlorine had not been lost, the 19 g of hydrobromide **11** was dissolved in 210 ml of warm 12 *N* HCl, filtered, and diluted with 800 ml of ethanol. Cooling overnight gave 13 g of damp crystals, mp 219–222° dec, which were dissolved in 100 ml of hot 12 *N* HCl and diluted with 300 ml of ethanol. Again cooling gave a precipitate which was collected and dried to obtain 11.5 g (79%) of colorless, crystalline **2**, mp 220–223° dec.

Anal. Calcd for $C_3H_{11}Cl_3N_2$: C, 19.85; H, 6.11; Cl, 58.60; N, 15.44. Found: C, 19.72; H, 6.13; Cl, 58.67; N, 15.52.

2-Phenyl-4-hydroxymethyl-2-oxazoline (15). A solution of 50.0 g (0.24 mol) of methyl 2-phenyl-2-oxazoline-4-carboxylate[7] in 670 ml of ethanol was cooled to 5–10° while 33.4 g (0.88 mol) of $NaBH_4$ was added portionwise. After stirring at room temperature for 1.5 hr, 85 ml of water was added and stirring was continued for 1.5 hr more. The reaction was then diluted to 3 l. with water, saturated with salt, and extracted three times with 500 ml of ether. On combining the extracts, they were dried ($MgSO_4$) and concentrated to give 42.2 g (99%) of colorless crystals, mp 85–87°, whose NMR agreed with the structure.

A sample was recrystallized for analysis from ethyl acetate–cyclohexane, mp 83–86°.

Anal. Calcd for $C_{10}H_{11}NO_2 \cdot \frac{1}{4}C_2H_5OH$: C, 66.82; H, 6.68; N, 7.42. Found: C, 66.89; H, 6.30; N, 7.78.

***N*-2-(1,3-Dichloropropyl)benzamide (16).** Over a 10-min period, 24.0 g (0.135 mol) of **15** was added to 120 ml of $SOCl_2$ at 5° with stirring. After stirring for 30 min at room temperature, the mixture was refluxed for 1 hr. Next the mixture was concentrated under vacuum, ethanol was added, and the mixture was reconcentrated to flush out excess $SOCl_2$. A gray solid was obtained which was recrystallized from benzene–hexane to give 18.7 g (65%) of **16**, mp 107–108°. Recrystallizing a sample for analysis from the same system gave mp 112–113°. The structure was confirmed by NMR.

Anal. Calcd for $C_{10}H_{11}NOCl_2$: C, 51.74; H, 4.78; Cl, 30.55; N, 6.04. Found: C, 51.71; H, 4.79; Cl, 31.38; N, 5.92.

1-Chloro-2-amino-3-propyl Benzoate Hydrochloride (17). After a solution of 18.0 g (0.078 mol) of *N*-2-(1,3-dichloropropyl)benzamide (**16**) in 455 ml of 50% ethanol–water and 23.1 ml of 12 *N* HCl was refluxed for 30 min, the solvent was removed under vacuum. The residue was flushed with ethanol to give 18 g (92%) of colorless crystals, mp 180–182°. Recrystallization from ethanol gave 14 g of crystals (72%), mp 190–191° (lit.[8] mp 184–185°), which were identified by NMR.

Anal. Calcd for $C_{10}H_{13}Cl_2NO_2$: C, 48.02; H, 5.24; Cl, 28.35; N, 5.60. Found: C, 47.94; H, 5.38; Cl, 28.53; N, 5.59.

2-Amino-3-chloropropanol Hydrochloride (13). 1-Chloro-2-amino-3-propyl benzoate hydrochloride (**17**, 7.0 g, 0.028 mol) was dissolved in 245 ml of 6 *N* HCl preheated to 85°. After stirring and maintaining the temperature for 10 min, the solution was refluxed for 0.5 hr. Then the solution was chilled in ice and extracted four times with 400-ml portions of ether. On concentrating the aqueous layer under vacuum at 60°, a yellow oil was obtained, which was flushed several times with ethanol. Three days under high vacuum left 1.88 g of intractable oil which would not give a correct analysis but whose structure was confirmed by NMR: CHN^+ (1 H) δ 3.46 (m), CH_2O (2 H) 3.71 (d), CH_2Cl (2 H) 3.93 (d), OH (1 H) 4.92 (s), NH_3^+ (3 H) 8.56 (s).

(±)-1-Amino-3-chloro-2-propanol Hydrochloride (1). (±)-1-Benzalimino-3-chloro-2-propanol[10] (6.3 g, 0.032 mol) was stirred with 30 ml of 2 *N* HCl for 1 hr. After the mixture was extracted with three 10-ml portions of benzene to remove the benzaldehyde, the aqueous portion was concentrated at 40° (25 mm) to obtain an oil. Flushing with ethanol gave crystals which were collected, washed with ether, and dried to give 4.6 g (98%) of product, mp 101–102° (lit.[9a] mp 103–104°).

Resolution of (±)-1-Amino-3-chloro-2-propanol Using (+)-10-Camphorsulfonic Acid. A solution of 584 g (4.00 mol) of (±)-1-amino-3-chloro-2-propanol hydrochloride in 1 l. of methanol at 40° was neutralized with a second solution of 392 g (4.00 mol) of potassium acetate in 1.3 l. of methanol. After cooling, 1.1 l. of ether was added and the precipitate was filtered off. Then the filtrate was concentrated under vacuum and 930 g (4.00 mol) of (+)-10-camphorsulfonic acid in 1.0 l. of ethanol was added. Cooling and seeding with (−)-1-amino-3-chloro-2-propanol (+)-10-camphorsulfonic acid salt gave the first precipitate. A fractional crystallization from ethanol was then carried out. As the (−)-amine salt became pure, the rotation approached $[\alpha]^{25}D$ +5.2°, mp 118–119°, while pure (+)-1-amino-3-chloro-2-propanol (+)-10-camphorsulfonate had $[\alpha]^{25}D$ +23.1°, mp 118–120°.

Anal. Calcd for $C_{13}H_{24}ClNO_5S$ [(−)-1 salt]: C, 45.67; H, 7.08; Cl, 10.37; N, 4.10; S, 9.38; Found: C, 45.78; H, 7.07; Cl, 10.67; N, 4.12; S, 9.19.

Apparently the solubility of the salts was so similar that whichever one was in excess would come out of the mother liquor. To convert back to the hydrochloride salt, the camphorsulfonate was slurried in 5 ml of tetrahydrofuran/g of salt while HCl was bubbled in until about 20% excess (by weight) had been added. The solution was then cooled to 0° and 5 ml of ether/g of salt was added. The hydrochloride from (−)-1-amino-3-chloro-2-propanol (+)-camphorsulfonic acid salt, $[\alpha]^{25}D$ +5.23° (*c* 2, water), was pure in one recrystallization at 1 g/7 ml ethanol–HCl, with constants of mp 144–146°, $[\alpha]^{25}D$ −23.6° (*c* 2.18, water). Yields up to 69% were obtained.

(+)-1-Chloro-3-isopropylamino-2-propanol hydrochloride (20) was prepared from (+)-1 and acetone following the general procedure of Billman and Diesing[15] to give the free base of **20**, bp 40° (0.1 mm), which was immediately converted to the hydrochloride, yield 39%, mp 105–107°. A sample was recrystallized for analysis and rotation from 2-propanol–ether–HCl(g), mp 107–108.5°, $[\alpha]^{25}D$ +33.6° (*c* 2.3, ethanol) [lit.[11] mp 106°, $[\alpha]^{25}D$ +25.9° (*c* 2, ethanol)]. The structure was confirmed by NMR.

Anal. Calcd for $C_6H_{15}Cl_2NO$: C, 38.31; H, 8.04; Cl, 37.70; N, 7.45. Found: C, 38.58; H, 8.13; Cl, 37.28; N, 7.21.

Acknowledgments. Microanalyses were performed by Mr. L. M. Brancone and staff. Spectra and rotations were determined by Mr. W. Fulmor and staff, while Mr. G. O. Morton interpreted the NMR spectra.

Registry No.—(±)-1 HCl, 34839-12-8; (−)-1 HCl, 54798-66-2; (−)-1 (+)-10-camphorsulfonic acid salt, 54798-67-3; (+)-1 (+)-10-camphorsulfonic acid salt, 54868-32-5; **2**, 54798-68-4; **5**, 4977-62-2; **6**, 54832-65-4; **7**, 54798-69-5; **8**, 52393-59-6; **9**, 54798-70-8; **10**, 54798-71-9; **11**, 54798-72-0; **13**, 54798-73-1; **14**, 55044-06-9; **15**, 15263-48-6; **16**, 23546-99-8; **17**, 23551-84-0; (±)-**19**, 54798-75-3; **20** HCl, 54831-47-9; **20** free base, 54831-48-0; (+)-10-camphorsulfonic acid, 3144-16-9.

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Total Synthesis of (±)-4-Deoxydamsin. Structure Correlation of Pseudoguaianolide Sesquiterpenes

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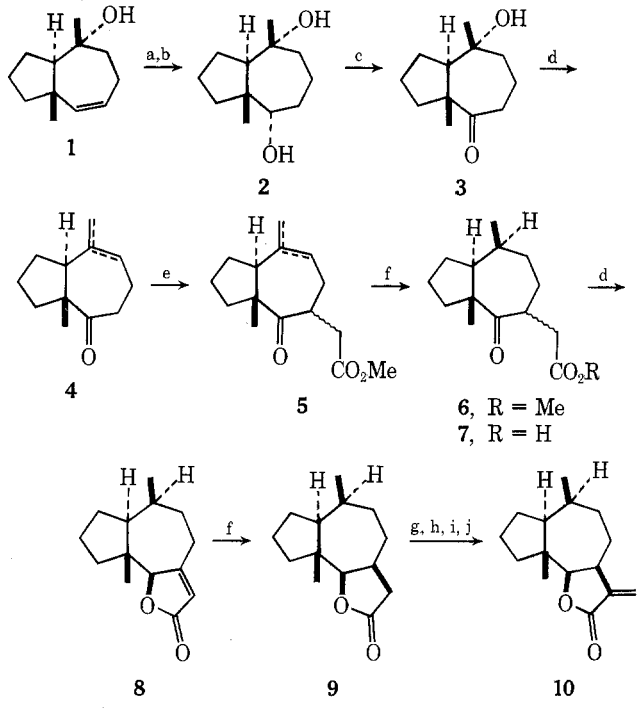
The pseudoguaianolides are a widespread class of nonisoprenoid hydroazulene lactones containing an array of functional and chiral centers which challenge present-day synthesis methodology and design.[1] Initial structure assignments based on chemical degradations erroneously classified these natural products as guaiazulene derivatives.[2] Their identity as a separate family of rearranged "pseudo" guaiazulenes was revealed by nuclear magnetic resonance (NMR), which showed the presence of a quaternary methyl grouping.[3] Stereochemical details were subsequently elucidated by NMR studies and single-crystal X-ray analysis.[1]

Despite the increasing variety of reported synthetic approaches to hydroazulenes, none of the pseudoguaianolides have yet been synthesized.[4,5] Attempts to date have failed to develop the necessary stereochemical control of the cycloheptane substituents.[5] In this report we describe a scheme for construction of the pseudoguaianolide skeleton with complete stereochemical control of the five commonly encountered chiral centers.

Our synthetic plan centered about the hydroazulenol **1**, an intermediate which we prepared via 1,6-cyclodecadienol solvolysis.[6] This intermediate with its propitious arrangement of substituents and functional groups seemed well suited for further elaboration to a pseudoguaianolide derivative for several reasons. Foremost, the rigidity imposed upon the hydroazulene system by the trans ring fusion simplifies conformational analysis, thus permitting realistic stereochemical predictions. In addition, the angular methyl grouping serves as a stereochemical directing group for the introduction of proximate chiral centers. The only real disadvantage of hydroazulenol **1** as a pseudoguaianolide precursor is its lack of functionality in the cyclopentane ring. Thus we could not expect to prepare the natural sesquiterpenes, at least initially. Nonetheless we felt that the aforementioned stereochemical problems were of sufficient intrinsic interest to justify work on the synthesis of 4-deoxypseudoguaianolides.

Our first objective was to incorporate a properly oriented fused γ-butyrolactone at the double bond position of hydroazulenol **1** (Chart I). Toward this end the double bond

Chart I[a]



1 2 3 4 5 6, R = Me 7, R = H 8 9 10

[a] a, *m*-$ClC_6H_4CO_3H$; b, $LiAlH_4$; c, H_2CrO_4, acetone; d, Ac_2O, NaOAc; e, LiICA, $BrCH_2CO_2Me$; f, H_2/PtO_2; g, NaH, HCO_2Et; h, $NaBH_4$; i, TsCl; j, C_5H_5N.

was epoxidized with *m*-chloroperoxybenzoic acid and the crude epoxide was reduced with lithium aluminum hydride to the diol **2**. Oxidation with Jones reagent[7] afforded the desired ketone intermediate **3**. However, attempted alkylation of the corresponding enolate with methyl bromoacetate proceeded poorly. Thinking that steric factors might be responsible for this result, we decided to examine the alkylation of unsaturated ketones related to ketol **3**.

Dehydration with thionyl chloride in pyridine led to a mixture of three double-bond isomers (25% exo, 60% trisubstituted, and 15% tetrasubstituted). However with acetic anhydride–sodium acetate only the trisubstituted (**4**) and exo olefins (60:40) were formed. Previous results have indicated that the dehydration of tertiary alcohols with sodium acetate–acetic anhydride proceeds via the acetate, which subsequently undergoes a pyrolytic cis elimination.[8] Accordingly, the isolation of only the trisubstituted olefin **4** and the corresponding exo isomer is unexpected. However, molecular models show that eclipsing of a tertiary acetate carbonyl grouping with the ring fusion hydrogen introduces severe steric strain in the transition state leading to the tetrasubstituted olefin. The corresponding transition states leading to olefin **4** and its exo isomer appear relatively strain free. Thus steric factors may block this elimination pathway.

Alkylation of unsaturated ketone **4** (40% exo isomer) with methyl bromoacetate afforded the keto esters **5** as an apparent mixture of epimers and double-bond isomers in high yield. Hydrogenation of this mixture gave the saturated keto ester **6** as an epimeric mixture. Keto ester **6** could also be prepared by reordering these steps. However, this variation suffered from two drawbacks. In the first place, hydrogenation of enone **4** took place at the ketone carbonyl