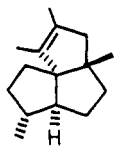
Total Synthesis of (-)-Silphiperfol-6-ene and (-)-5-Oxosilphiperfol-6-ene

Leo A. Paquette,* Richard A. Roberts,[1] and Gary J. Drtina

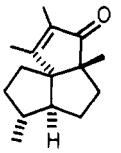
Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received March 14, 1984. Revised Manuscript Received May 15, 1984*

Abstract: The angular triquinane sesquiterpene (-)-silphiperfol-6-ene (**1**) has been synthesized in efficient fashion from (*R*)-(+)-pulegone. Assignment of absolute stereochemistry to one of these architecturally unusual molecules is thereby made possible for the first time. The pyridine chlorochromate oxidation of **1** to (-)-5-oxosilphiperfol-6-ene (**2**) has previously been reported. As a result, the present work also constitutes a formal total preparation of the correct enantiomer of **2**.

Silphiperfol-6-ene (**1**), an architecturally unusual tricyclic sesquiterpene, was isolated in 1980 from the roots of *Silphium perfoliatum*.[2] Shortly thereafter, the related ketone **2** was characterized as a constituent of the stems of *Espeletiopsis quacharaca*.[3] Because of our interest in the synthesis of angular triquinanes,[4,5] as well as a desire to affirm the structural assignments,[6] we undertook to devise an efficient and enantioselective approach to these substances. The realization of this goal has secured the original formulations and established the absolute stereochemistries of **1** and **2** to be as shown in the formulas.



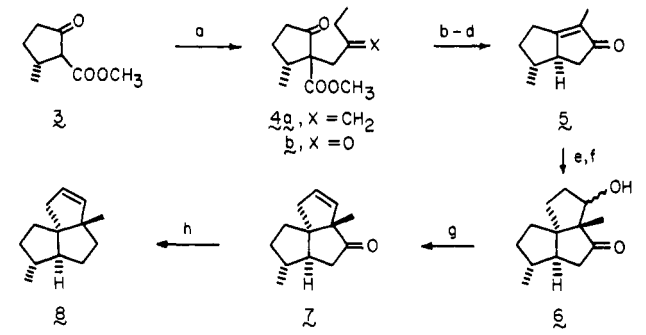
1



2

Keto ester **3** ($[\alpha]^{20}_D$ +68.9° (neat)), which is readily available from (*R*)-(+)-pulegone,[7] was alkylated with 1-(tosyloxy)-2-ethyl-2-propene.[8] This electrophile delivers the same product via either S_N2 or S_N2' attack (Scheme I). Furthermore, although tosylates frequently induce substantial O-alkylation under these circumstances, this product (if formed) also reverts to **4a** (66% isolated) by [3,3] sigmatropic rearrangement.[9] To facilitate ring closure,[10] **4a** was ozonized and cyclized prior to decarboxylation. This sequence proceeded with 44% overall efficiency to deliver a 1:1 mixture of **5** ($[\alpha]^{20}_D$ +77.81° (*c* 11.2, $CHCl_3$)) and its epimer which were readily separated by HPLC on silica gel. Preliminary stereochemical assignments, based upon the deshielded position of the α-methyl group in **5** (δ 1.20) relative to that in its epimer (δ 0.62),[11] were substantiated by equilibration of the latter to **5**

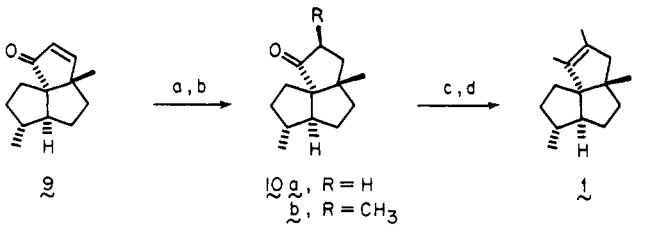
Scheme I[a]



3 **4a**, X = CH_2; **b**, X = O **5** **6** **7** **8**

[a] (a) NaH, catalyst KH, $CH_3CH_2C(=CH_2)CH_2OTs$, toluene, reflux, 8 h; 10% HCl. (b) O_3, CH_3OH, -78 °C; Me_2S. (c) NaH, toluene, reflux, 18 h; 10% HCl. (d) LiI·$3H_2O$, DMF, reflux, 18 h, 10% HCl. (e) $(C_4H_7O_2)CH_2CH_2MgBr$ ($C_4H_7O_2$ = 1,3-dioxan-2-yl), CuBr·Me_2S, THF, -78 °C (10 h) → 0 °C (2 h); NH_4Cl (H_2O). (f) HCl, aqueous THF, 20 °C, 72 h. (g) See text. (h) K_2CO_3, $H_2NNH_2 \cdot H_2O$, diethylene glycol, 130-200 °C (7 h); 10% HCl.

Scheme II[a]



9 **10a**, R = H; **b**, R = CH_3 **1**

[a] (a) H_2, Pd-C, C_2H_5OH. (b) KH, THF; $(C_2H_5)_3B$; CH_3I; H_2O_2, NaOH, H_2O. (c) CH_3Li, Et_2O, -78 °C. (d) $POCl_3$, py, 20 °C, 3 days.

and sequential sodium-liquid ammonia/Wolff-Kishner reduction of this ketone to deliver a symmetric 2,6-dimethylbicyclo[3.3.0]octane.[12] The indicated base-promoted isomerization serves as an efficient vehicle for ultimate utilization of all the cyclization product, although some loss of chirality may be incurred in this maneuver (see below).

Marfat-Helquist annulation[13,14] of **5** led to the aldol **6** (72%), which was best dehydrated by thermolysis of the *p*-tolyl thionocarbonate (72%)[15] or treatment with triphenylphosphine dibromide followed by DBU (55%). Wolff-Kishner deoxygenation of **7**

(1) Continental Oil Company Fellow, 1982.
(2) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.
(3) Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M. *Phytochemistry* **1980**, *19*, 2399.
(4) (a) Isocomene: Paquette, L. A.; Han, Y.-K *J. Org. Chem.* **1979**, *44*, 4014; *J. Am. Chem. Soc.* **1981**, *103*, 1835. (b) Silphinene: Leone-Bay, A.; Paquette, L. A. *J. Org. Chem.* **1982**, *47*, 4173; *J. Am. Chem. Soc.* **1983**, *105*, 7352. (c) Pentalene: Annis, G. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4504; **1983**, *105*, 7358.
(5) Reviews: Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41; **1984**, *119*, 1.
(6) The difficulties associated with assigning structure in this triquinane area solely on the basis of NMR spectroscopy are best exemplified by senoxydene [Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 1747] which has been incorrectly formulated [Paquette, L. A.; Galemmo, R. A., Jr; Springer, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 6975. Tsunoda, T.; Kabasawa, V.; Itô, S.; Kodama, M. *Tetrahedron Lett.* **1984**, 773.
(7) Marx, J. N.; Naman, L. R. *J. Org. Chem.* **1975**, *40*, 1602 and references cited therein.
(8) Prepared by $LiAlH_4$ reduction and tosylation of 2-ethyl-2-propenal [Green, M. B.; Hickinbottom, W. S. *J. Chem. Soc.* **1957**, 3262].
(9) Jefferson, A.; Scheinmann, F. *Q. Rev.* **1968**, *22*, 391.
(10) Klipa, D. K.; Hart, H. *J. Org. Chem.* **1981**, *46*, 2815.
(11) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.
(12) A symmetric hydrocarbon can arise only if both methyl groups are alpha, since the reduction conditions used were equilibrating.
(13) Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 4217.
(14) The more stable magnesium cuprate from 2-(2-bromoethyl)-1,3-dioxane was utilized: Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560. Stowell, J. C.; Keith, D. *Synthesis* **1979**, 132.
(15) Gerlach, H. *J. Chem. Soc., Chem. Commun.* **1972**, 1215.

0002-7863/84/1506-6690$01.50/0

($[\alpha]^{20}_D$ +298.97° (*c* 2.9, $CHCl_3$)) provided **8** in 72% yield.

With this hydrocarbon in hand, our plan for introduction of the remaining functionality called first for allylic oxidation. Success was realized with sodium chromate in $HOAc/Ac_2O$ solution,[16] although **9** (64%; $[\alpha]^{20}_D$ +16.53 (*c* 13.0, $CHCl_3$)) was accompanied by a small amount of the transposed enone (Scheme II). Subsequent catalytic reduction of **9** to **10** proceeded in straightforward fashion (100%). Of the several protocols available for α-monomethylation of this saturated ketone, that involving condensation of the potassium enoxyborate[17] proved most expedient. Thus, addition of **10a** to a suspension of KH in THF followed by treatment with $(C_2H_5)_3B$ generated the reactive intermediate. Introduction of CH_3I and ultimate hydrolysis with alkaline hydrogen peroxide afforded stereoisomerically pure **10b** (56%; $[\alpha]^{24}_D$ +23.64 (*c* 4.9, $CHCl_3$)). Steric considerations lead us to assume that the methyl group is β oriented.

Addition of methyllithium to **10b** in cold (−78 °C) tetrahydrofuran solution effected conversion to the tertiary alcohol (94%) without undue complication due to enolization. Upon exposure to phosphorus oxychloride in pyridine at 20 °C, (−)-**1** was obtained in 86% yield. Suitable spectral correlation (IR, ^1H NMR) was made with the natural product.[18] The optical rotation, while not at the maximum value earlier cited,[19,20] unequivocally establishes the absolute configuration to be as represented. Since the origin of the stereogenic center associated with the secondary group was preordained in (*R*)-(+)-pulegone, the remaining stereocenters are readily defined.

The pyridine chlorochromate oxidation of **1** to **2** has previously been reported.[3] As a result, this work also constitutes a formal total synthesis of 5-oxosilphiperfol-6-ene.

In summation, the first enantiospecific synthesis of two naturally occurring angular triquinanes has been achieved. The possible utilization of several of the intermediates in effecting a total synthesis of retigeranic acid (the triquinane segment of which possesses the same absolute stereochemistry as **1** and **2**) is currently being addressed.

Experimental Section

All optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter and are expressed in g/100 mL. Infrared spectra were recorded on a Perkin-Elmer Model 467 instrument. Proton magnetic resonance spectra were recorded with Varian EM-390, Bruker WP-200, and Bruker WM-300 spectrometers. Carbon spectra were recorded with a Bruker WP-80 spectrometer. Mass spectra were determined on AEI-MS9 and Kratos MS 25 spectrometers at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

2-Ethyl-2-propen-1-ol *p*-Toluenesulfonate. In a dry 2-L three-necked flask equipped with a mechanical stirrer, condenser, and addition funnel was placed sodium hydride (50% dispersion in mineral oil, 16.8 g, 0.35 mol) and anhydrous ether (600 mL). To the suspension was added 2-ethyl-2-propen-1-ol (30 g, 0.35 mol) in ether (100 mL) in dropwise fashion at room temperature. The mixture was stirred for 4 h, after which was added a solution of *p*-toluenesulfonyl chloride (66.5 g, 0.35 mol) in ether (400 mL) at 0 °C. The mixture was stirred at 0 °C for 4 h and at room temperature for 12 h. Water was added until all the solids had dissolved. The layers were separated, and the aqueous layer was extracted with ether. The combined organic phases were washed with water and brine prior to drying. Removal of the solvent gave a crude oil which was purified by HPLC (silica gel; elution with 3% ethyl acetate in petroleum ether) to provide pure tosylate (67.2 g, 80%): IR (neat, cm^{-1}) 1650, 1600, 1180; ^1H NMR ($CDCl_3$) δ 7.52 (ABq, *J* = 8 Hz, 4 H), 4.90 (m, 2 H), 4.45 (s, 2 H), 2.41 (s, 3 H), 2.02 (q, *J* = 7 Hz, 2 H), 1.00 (t, *J* = 7 Hz, 3 H); *m/z* calcd (M^+) 240.0820, obsd 240.0827.

(+)-Methyl 1-(2-Ethylallyl)-2-methyl-5-oxocyclopentanecarboxylate (4a). A solution of **3** (59.5 g, 0.38 mol) in dry toluene (150 mL) was added dropwise to a stirred suspension of sodium hydride (50% oil dispersion, 18.4 g, 0.38 mol) and potassium hydride (catalytic amount) in toluene (600 mL). The reaction mixture was stirred at the reflux temperature for 2 h, cooled, and treated in a slow stream with a solution of the tosylate (96.8 g, 0.40 mol) in toluene (200 mL). After being heated at reflux for 18 h, the sludge was cooled to 0 °C and 10% hydrochloric acid was added. Extraction with ether provided an organic solution that was washed with water and brine prior to drying and concentration. Purification of the residue by HPLC on silica gel (elution with 12% ethyl acetate in petroleum ether) gave **4a** (56.2 g, 66%) as predominantly one isomer: IR (CCl_4, cm^{-1}) 1750, 1730; ^1H NMR ($CDCl_3$) δ 4.84 (br s, 1 H), 4.70 (br s, 1 H), 3.64 (s, 3 H), 2.80–1.70 (m, 9 H), 0.98 (d, *J* = 6 Hz, 3 H), 0.95 (t, *J* = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) ppm 216.5, 171.2, 147.0, 113.8, 63.4, 51.9, 39.0, 37.7, 36.7, 30.2, 28.0, 15.5, 12.2; $[\alpha]^{20}_D$ +78.6° (*c* 12.1, $CHCl_3$).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.62; H, 9.06.

(+)-Methyl 1-(2-Oxobutyl)-2-methyl-5-oxocyclopentanecarboxylate (4b). A solution of **4a** (0.35 g, 1.56 mmol) in methanol (25 mL) was cooled to −78 °C and exhaustively ozonized. The solution was flushed with nitrogen for 30 min to remove excess ozone, treated with dimethyl sulfide (2 mL), and allowed to warm to room temperature where it was stirred for 1 h. The solvent was removed, and the residual oil was taken up in ether. The ethereal solution was washed with water and brine before drying. Removal of the solvent and purification by MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether) gave diketo ester **4b** (0.28 g, 79%): IR (CCl_4, cm^{-1}) 1746, 1726, 1714; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3 H), 3.10 (m, 2 H), 2.75–1.75 (m, 7 H), 1.22–0.85 (m, 6 H); *m/z* calcd (M^+) 210.1256, obsd 210, 1259; $[\alpha]^{20}_D$ +23.9° (*c* 11.3, $CHCl_3$).

(−)-Methyl 2,4,5,6-Tetrahydro-1,4-dimethyl-2-oxo-3a(3*H*)-pentalenecarboxylate. A 50-mL two-necked flask equipped with a condenser and addition funnel was charged with sodium hydride (50% dispersion in mineral oil, 0.2 g, 4.2 mmol). The dispersion was washed three times with dry toluene (5 mL) to remove the oil. Toluene (20 mL) was added and the mixture heated to reflux. To the boiling mixture was added keto ester **4b** (0.15 g, 0.66 mmol) in toluene (5 mL) in dropwise fashion over a 30-min period. After continued heating at reflux for 18 h, the reaction mixture was cooled, quenched carefully with water, and acidified with 10% hydrochloric acid solution. The product was extracted with ether, washed with water and brine, and dried. Evaporation of the solvent and purification by MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether) gave the enone ester (0.090 g, 66%): IR (cm^{-1}) 1735, 1705, 1665; ^1H NMR ($CDCl_3$) δ 3.80, 3.65 (2 s, 3 H), 3.40–1.90 (m, 7 H), 1.70 (br s, 3 H), 1.20, 0.75 (2 d, *J* = 6 Hz, 3 H); *m/z* calcd (M^+) 208.1099, obsd 208.1096; $[\alpha]^{20}_D$ −30.9° (*c* 7.6, $CHCl_3$).

(+)-*cis*-4,5,6,6a-Tetrahydro-3(*R),6-dimethyl-2(1*H*)-pentalenone (5).** To a solution of lithium iodide trihydrate (0.25 g, 1.33 mmol) in dimethylformamide (10 mL) was added the keto ester (0.090 g, 0.43 mmol) in dimethylformamide (1 mL). The resulting mixture was heated at reflux for 18 h, cooled, poured onto water, and acidified with 10% hydrochloric acid solution. The product was extracted into ether, and the combined ether extracts were washed with water and brine prior to drying. Removal of the solvent and purification by MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether) gave a 1:1 mixture of the α- (i.e., **5**) and β-methyl isomers (0.055 g total, 85%). For preparative purposes, this mixture was not separated until after equilibration as follows.

The residue from a much larger run was taken up in toluene (1000 mL) and an aqueous solution of potassium hydroxide (118 g in 2000 mL containing 5 mL of 40% tetra-*n*-butylammonium hydroxide solution) was added. The mixture was stirred vigorously and heated at reflux for 72 h. After cooling, the layers were separated and the aqueous layer was extracted with ether (2 × 500 mL). The combined organic extracts were washed with brine and dried. After removal of the solvent, the residue was vacuum distilled to give bicyclic enone **5** and its epimer (90 g, 60%): bp 74–78 °C (0.1 torr). Analysis of the product by vapor phase chromatography (12 ft × 0.25 in. 15% SE-30 on 60/80 mesh Chromosorb G, 140 °C) showed the two enones to be present in a 4.8:1 ratio, respectively.

For **5**: IR (neat, cm^{-1}) 1710, 1665; ^1H NMR ($CDCl_3$) δ 2.70–1.80 (m, 6 H), 1.70 (s, 3 H), 1.68–1.30 (m, 2 H), 1.20 (d, *J* = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) ppm 210.3, 183.6, 131.8, 51.4, 40.3, 40.1, 34.3, 25.3, 18.4, 8.1; *m/z* calcd (M^+) 150.1045, obsd 150.1040; $[\alpha]^{20}_D$ +77.8° (*c* 9.42, $CHCl_3$).

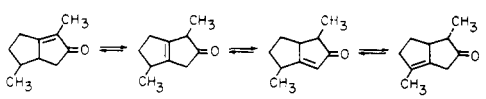
(16) (a) Marshall, J. A.; Johnson, P. C. *J. Org. Chem.* **1970**, *35*, 192. (b) Marshall, J. A.; Brady, S. F. *Ibid.* **1970**, *35*, 4068.

(17) Negishi, E.; Chatterjee, S. *Tetrahedron Lett.* **1983**, 1341.

(18) We thank Prof. Bohlmann for making copies of the original spectra available to us.

(19) Natural **1**: $[\alpha]^{24}_D$ −92.8° (*c* 0.8, $CHCl_3$).[2]

(20) The loss of optical purity may arise during the equilibration of **5** according to the following scheme:



In support of this suggestion, quantities of **5** obtained from different runs exhibited nonidentical optical rotations.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.40. Found: C, 79.83; H, 9.46.

For the β-methyl epimer: IR ($CDCl_3$, cm^{-1}) 1700, 1660; ^1H NMR ($CDCl_3$) δ 3.10–1.90 (m, 8 H), 1.70 (br s, 3 H), 0.62 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) ppm 211.6, 182.6, 132.7, 48.1, 37.2, 33.7, 32.4, 23.4, 13.7, 8.5; m/z calcd (M^+) 150.1045, obsd 150.1040; $[\alpha]^{20}_D$ −123.1° (c 11.2, $CHCl_3$).

1β,3aα,4β,6aα-Octahydro-1,4-dimethylpentalene. In a 100-mL three-necked flask equipped with a dry ice condenser, addition funnel, and nitrogen inlet, sodium metal (250 mg, 10.9 mg-at) was added to liquid ammonia (30 mL) at −78 °C. To the blue mixture was added a solution of racemic **5** (0.5 g, 3.31 mmol) and *tert*-butyl alcohol (0.25 g, 3.38 mmol) in tetrahydrofuran (10 mL) over a period of 10–20 min. The reaction mixture was stirred for an additional 30 min. Excess solid ammonium chloride was added to discharge the blue color. The ammonia was allowed to evaporate, and the residue was partitioned between ether and water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine and concentrated. The residual oil was taken up in acetone (5 mL) at 0 °C, and Jones reagent (5 mL) was added. The mixture was stirred for 5 min before addition of excess isopropyl alcohol. The resulting mixture was concentrated and the residue was partitioned between ether and water. The organic layer was washed with 5% sodium bicarbonate solution, dried, and evaporated. The crude ketone so obtained (300 mg) was taken up in diethylene glycol (5 mL). Hydrazine hydrate (95%, 0.35 mL) and potassium hydroxide (0.35 g) were added, and the mixture was heated at reflux for 4 h. Excess hydrazine and water were distilled until the bath temperature reached 240 °C. Heating was continued for an additional 4 h. After cooling, water (10 mL) was added, and the distillate and pot residue were extracted with pentane. The organic phases were washed with 10% hydrochloric acid solution and brine and dried. The solvent was carefully removed via fractional distillation until 3–4 mL of solution remained. Preparative vapor phase chromatography (6 ft × 0.25 in. 5% SE-30 on 60/80 mesh Chromosorb G, 95 °C) gave the symmetrical hydrocarbon: ^1H NMR ($CDCl_3$) δ 2.05–1.10 (m, 12 H), 0.90 (d, J = 6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) ppm 52.3, 42.2, 35.6, 31.4, 19.8; m/z calcd (M^+) 138.1409, obsd 138.1406.

(+)-(3α,3aβ,5aα,6α,8aα)-Octahydro-3-hydroxy-3a,6-dimethylcyclopenta[*c*]pentalen-4(5*H*)-one (6). To a mixture of magnesium turnings (12.0 g, 0.49 mg-at) in tetrahydrofuran (60 mL) was added a solution of 2-(2-bromoethyl)-1,3-dioxane (64.5 g, 0.33 mol) in tetrahydrofuran (75 mL) in dropwise fashion. Reaction was initiated with a crystal of iodine and momentary heating. The rate of addition was moderated to maintain a reflux temperature. After the addition was complete, the mixture was heated at reflux for 30 min, cooled to −78 °C, and diluted with tetrahydrofuran (130 mL). A solution of copper bromide–dimethyl sulfide complex (16.9 g, 0.083 mol) in dimethyl sulfide (200 mL) was introduced over a 15 min period. The mixture was stirred for 1 h prior to addition of a solution of **5** (20.0 g, 132 mmol) in tetrahydrofuran (50 mL) over a 4 h period. The solution was stirred at −78 °C for 12 h, allowed to warm to 0 °C, and stirred for an additional 8 h. Treatment with basic ammonium chloride solution (pH 8) was followed by extraction with ether. The combined organic extracts were washed with brine and dried. Evaporation of the solvent gave the addition product, which was taken up in acetone (1300 mL). Water (150 mL) and concentrated hydrochloric acid (17 mL) were added, and the resulting mixture was stirred at room temperature for 72 h, concentrated, and extracted with ether. The extracts were washed with saturated sodium bicarbonate solution and brine before drying. Evaporation of the solvent and purification by HPLC on silica gel (elution with 20% ethyl acetate in petroleum ether) gave **6** (20 g, 72%) as the anticipated mixture of isomers: $[\alpha]^{20}_D$ +59.1° (c 5.3, $CHCl_3$).

The less polar isomer had the following spectral properties: IR (CCl_4, cm^{-1}) 3450, 1725; ^1H NMR ($CDCl_3$) δ 3.82 (t, J = 6 Hz, 1 H), 3.10–2.80 (m, 1 H), 2.75–1.20 (m, 12 H), 1.10–0.90 (m, 6 H); m/z calcd (M^+) 208.1463, obsd 208.1459. The more polar compound had the following spectral properties: IR (CCl_4, cm^{-1}) 3450, 1725; ^1H NMR ($CDCl_3$) δ 4.05 (t, J = 5 Hz, 1 H), 3.00–1.40 (m, 13 H), 1.10–0.90 (m, 6 H); m/z calcd (M^+) 208.1462, obsd 208.1459.

(+)-(3aβ,5aα,6α,8aα)-1,3a,5a,6,7,8-Hexahydro-3a,6-dimethylcyclopenta[*c*]pentalen-4(5*H*)-one (7). A. Dehydration by Thionocarbonate Pyrolysis. To a solution of the less polar adol **6** (0.139 g, 0.666 mmol) in dry pyridine (10 mL) was added *O*-4-methylphenyl chlorothioformate (0.15 mL) and the mixture was allowed to stir overnight. After additon of water, the mixture was extracted with ether. The ether extracts were washed with 10% hydrochloric acid solution and brine prior to drying. Evaporation of the solvent and purification by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) gave the thionocarbonate (0.174 g, 73%): ^1H NMR ($CDCl_3$) δ 7.15, 6.95 (ABq, J = 8 Hz, 4 H), 5.65–5.50 (m, 1 H), 2.32 (s, 3 H), 2.30–1.40 (m, 12 H), 1.20–1.00 (m, 6 H). The thionocarbonate was pyrolyzed at 180 °C for 1 h under reduced pressure (24 torr). After dissolution in ether, the reaction mixture was washed with 10% sodium hydroxide solution and brine, and dried. Evaporation of the solvent and purification by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) gave **7** (0.080 g, 99%). The overall yield was 72%: IR (neat, cm^{-1}) 1730; ^1H NMR ($CDCl_3$) δ 5.80–5.76 (m, 1 H), 5.37–5.34 (m, 1 H), 2.75–2.50 (m, 3 H), 2.00–1.30 (m, 7 H), 1.08 (d, J = 6 Hz, 3 H), 1.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 220.3, 135.5, 131.6, 65.7, 59.9, 53.8, 49.6, 43.9, 43.3, 35.0, 34.2, 20.5, 16.4; $[\alpha]^{20}_D$ +299.0° (c 2.9, $CHCl_3$).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.89; H, 9.46.

B. Dehydration with Triphenylphosphine Dibromide. To a solution of triphenylphosphine dibromide prepared from triphenylphosphine (1.26 g, 4.81 mmol) and bromine (0.25 mL, 4.87 mmol) in dichloromethane (15 mL) was added **6** (0.5 g, 2.40 mmol) at 0 °C. The reaction mixture was allowed to stir overnight at room temperature before being poured into ice water. The product was extracted into dichloromethane, washed with 5% sodium hydroxide solution and brine, and dried. The solution was concentrated in vacuo and the residue was triturated with petroleum ether and vacuum filtered. After removal of the solvent, the oil obtained was found to be a mixture of bromo ketone and olefin **7** (1:1 by ^1H NMR). The mixture was dissolved in benzene (30 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3 mL) was added. The solution was heated at reflux for 24 h before cooling. The solution was washed with 10% hydrochloric acid solution and brine and dried. Purification by MPLC on silica gel (elution with 6% ethyl acetate in petroleum ether) provided pure **7** (0.25 g, 55%).

(3α,3aα,5aβ,8aα)-1,2,3,3a,4,5,5a,8-Octahydro-3,5a-dimethylcyclopenta[*c*]pentalene (8). A mixture of **7** (1.0 g, 5.21 mmol) in diethylene glycol (1 mL) containing potassium carbonate (0.6 g) and hydrazine hydrate (1 mL) was heated at reflux (ca. 150 °C) for 3 h. A short path still was placed atop the flask and the pot temperature was raised to 200 °C. The distillate was immediately taken up in ether and the pot residue heated at 200 °C for an additional 4 h. After cooling, the residue was diluted with water and extracted with ether. The combined ether phases were washed with 10% hydrochloric acid solution and brine prior to drying. The solvent was carefully removed on a rotary evaporator without heat to give pure **8** (0.70 g, 72%). Vapor phase chromatographic analysis showed the presence of only one peak (6 ft × 0.25 in. 5% SE-30, 130 °C): ^1H NMR ($CDCl_3$) δ 5.60–5.50 (m, 1 H), 5.40–5.20 (m, 1 H), 2.50–2.40 (m, 2 H), 1.80–1.10 (m, 10 H), 1.02 (d, J = 6 Hz, 3 H), 0.95 (s, 3 H); m/z calcd (M^+) 176.1565, obsd 176.1558.

Anal. Calcd for $C_{13}H_{20}$: C, 88.56; H, 11.44. Found: C, 88.44; H, 11.37.

(+)-(3aβ,5aα,6α,8aα)-4,5,6a,6,7,8-Hexahydro-3a,6-dimethylcyclopenta[*c*]pentalen-1(3a*H*)-one (9). To hydrocarbon **8** (0.70 g, 3.98 mmol) in a mixture of acetic anhydride (7 mL) and acetic acid (11 mL) at 0 °C was added sodium chromate (3.4 g, 20.8 mmol). The orange solution was allowed to warm to room temperature and stirred for 24 h during which time the orange color gradually turned green. The solution was diluted with water and neutralized with solid sodium bicarbonate before extraction with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and brine prior to drying. Evaporation of the solvent and purification by MPLC on silica gel (elution with 7% ethyl acetate in petroleum ether) gave **9** (0.482 g, 64%): IR (CCl_4, cm^{-1}) 1692; ^1H NMR ($CDCl_3$) δ 7.28 (d, J = 6 Hz, 1 H), 6.07 (d, J = 6 Hz, 1 H), 2.00–1.20 (m, 10 H), 1.12 (s, 3 H), 0.98 (d, J = 6 Hz, 3 H); m/z calcd (M^+) 190.1308, obsd 190.1303; $[\alpha]^{20}_D$ +16.5° (c 13.0, $CHCl_3$).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.05; H, 9.54. Found: C, 81.95; H, 9.57.

A small quantity of the regioisomeric enone was also isolated: IR (CCl_4, cm^{-1}) 1710; ^1H NMR ($CDCl_3$) δ 7.44 (d, J = 5.5 Hz, 1 H), 5.96 (d, J = 5.5 Hz, 1 H), 2.05–1.20 (m, 10 H), 1.03 (s, 3 H), 1.00 (d, J = 6 Hz, 3 H); m/z calcd (M^+) 190.1308, obsd 190.1303.

(3aβ,5aα,6α,8aα)-Octahydro-3a,6-dimethylcyclopenta[*c*]pentalen-1-(3a*H*)-one (10a). A solution of **9** (252 mg, 1.32 mmol) in 95% ethanol (50 mL) containing 5% palladium on charcoal (30 mg) was hydrogenated at 45 psi for 1 h. After removal of the catalyst by filtration through Celite, the filtrate was concentrated in vacuo to afford pure **10a** (256 mg, 100%): ^1H NMR ($CDCl_3$) δ 2.36–1.29 (m, 14 H), 1.03 (s, 3 H), 0.99 (d, J = 6.3 Hz, 3 H); m/z calcd (M^+) 192.1514, obsd 192.1530.

C-Methylation of 10a. A solution of **10a** (135 mg, 0.702 mmol) in dry tetrahydrofuran (2 mL) was added to a suspension of potassium hydride (150 mg, 0.920 mmol of a 24.6g suspension in mineral oil previously rinsed with pentane) in tetrahydrofuran (5 mL). After being stirred at room temperature for 30 min, the mixture was cooled to 0 °C and triethylborane (1.15 mL of 1 M solution in tetrahydrofuran) was added. The mixture was stirred for 15 min prior to the introduction of methyl

iodide (100 μL, 1.606 mmol). After 60 min at 0 °C, hydrogen peroxide (30%, 0.5 mL) and aqueous sodium hydroxide (3 M, 0.5 mL) were added, and stirring was continued for 15 min prior to dilution with ether and water. The aqueous phase was extracted with ether, and the combined organic layers were washed with 10% hydrochloric acid and saturated sodium bicarbonate solution prior to drying. Concentration left an oil that was purified by MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether) to give 81 mg (56%) of **10b** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.12–2.05 (m, 1 H), 1.86–1.18 (series of m, 12 H), 1.05 (d, J = 7.1 Hz, 3 H), 1.032 (s, 3 H), 0.97 (d, J = 6.1 Hz, 3 H); m/z calcd (M^+) 206.1671, obsd 206.1674; $[\alpha]^{24}_D$ +23.6° (c 4.9, $CHCl_3$).

(−)-Silphiperfol-6-ene (1). Methyllithium (330 μL of 1.19 M in ether, 0.39 mmol) was added to a solution of **10b** (54 mg, 0.262 mmol) in dry tetrahydrofuran (10 mL) at −78 °C. After 1 h, saturated ammonium chloride solution (2 mL) was added, and the resulting mixture was allowed to warm to room temperature. Concentration in vacuo afforded a residue that was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried, and evaporated to furnish 55 mg (94%) of the tertiary alcohol: ^{1}H NMR ($CDCl_3$) δ 2.06–1.03 (series of m, 14 H), 1.03 (s, 3 H), 0.99 (d, J = 6.6 Hz, 3 H), 0.98 (s, 3 H), 0.87 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) ppm 82.6, 69.9, 55.6, 47.3, 46.2, 44.0, 42.7, 42.1, 35.7, 31.0, 28.8, 25.9, 20.3, 19.2, 13.6; m/z calcd (M^+) 222.1984, obsd 222.1955; $[\alpha]^{27}_D$ −7.2° (c 16.0, $CHCl_3$).

Freshly distilled phosphorus oxychloride (41 μL, 0.440 mmol) was added to a solution of the above alcohol (73 mg, 0.328 mmol) in dry pyridine (2 mL), and the resulting mixture was stirred at room temperature for 3 days. Ice water (50 mL) was added, and the product was extracted into pentane (4 × 25 mL). The combined extracts were washed with 10% hydrochloric acid (3 × 15 mL), saturated sodium bicarbonate solution (15 mL), and brine (15 mL) prior to drying. Concentration in vacuo gave a yellow oil, which was purified by chromatography on silica gel (pentane elution). There was isolated 45 mg (67%) of (−)-**1**. Elution with ethyl acetate returned 16 mg of unreacted alcohol. The corrected yield of silphiperfol-6-ene is therefore 86%: IR ($CDCl_3$, cm^{-1}) 1450, 1380; ^{1}H NMR ($CDCl_3$) δ 2.20 and 1.95 (ABd, J = 16 Hz, 2 H), 1.9–1.1 (series of m, 12 H), 1.54 (m, 3 H), 1.52 (m, 3 H), 0.99 (s, 3 H), 0.96 (d, J = 6.5 Hz, 3 H); m/z calcd (M^+) 204.1878, obsd 204.1903; $[\alpha]^{23}_D$ −34.2° (c 3.05, $CHCl_3$).

Acknowledgment. We are pleased to acknowledge the support of this investigation by the National Institutes of Health through Grant GM-28468.

Registry No. 1, 74284-56-3; **2**, 77887-60-6; **4a**, 92269-51-7; **4b**, 92269-52-8; **5** (isomer 1), 92269-53-9; **5** (isomer 2), 92269-54-0; **6** (isomer 1), 92269-55-1; **6** (isomer 2), 92418-26-3; **7**, 92269-56-2; **8**, 92269-57-3; **9**, 92269-58-4; **10a**, 92269-59-5; **10b**, 92269-60-8; $CH_3CH_2C(=CH_2)CH_2OTs$, 92269-61-9; 2-(2-bromoethyl)-1,3-dioxane, 33884-43-4; 2-ethyl-2-propen-1-ol, 4435-54-5; methyl 2,4,5,6-tetrahydro-1,4-dimethyl-2-oxo-3a(3*H*)-pentalenecarboxylate, 92269-62-0; 1,3a,4,6a-octahydro-1,4-dimethylpentalene, 92269-63-1.

Effective Control of Regioselectivity by a Bridgehead Substituent in the Di-π-methane Rearrangement of Dibenzobarrelenes and Benzonorbornadienes

Leo A. Paquette* and Elliott Bay

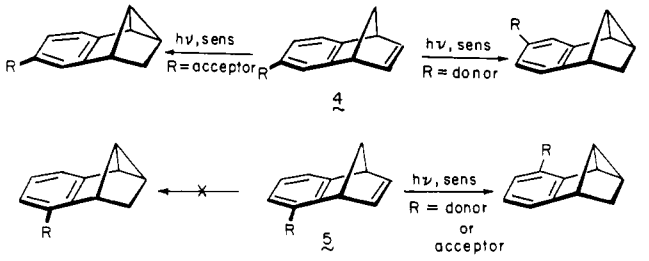
Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received March 28, 1984*

Abstract: The triplet-state photoisomerizations of eight bridgehead monosubstituted benzonorbornadienes are described. Six of the examples underwent di-π-methane rearrangement with a highly regioselective or fully regiospecific preference for proximal bond reorganization. In the bromo example, a 50:50 distribution of the two possible photoisomers was observed. When the substituent group was deuterium, a substantial preference for distal rebonding was encountered (k_H/k_D = 1.27). This finding prompted a companion investigation of two benzobarrelenes isotopically substituted at one of their bridgehead sites. The k_H/k_D values noted for the last two substrates are of comparable magnitude and in the same direction. A synopsis of the regiochemical consequences of bridgehead substitution in various doubly channeled di-π-methane substrates reveals the existence of two entirely different preferred reaction modes. This is taken to be a reflection of the operation of two different mechanistic pathways involving product-determinative aryl–vinyl bridging on the one hand and direct 1,2-aryl migration on the other.

The present investigation was initiated with the idea of studying the role of a functional group on the bridgehead carbon of benzonorbornadiene where this substituent is varied in its effective ability to withdraw or donate electron density. Because the ring system is a dual-channel di-π-methane substrate having two competitive isomerization pathways open to fit, the controlling effect of the R group in **1** following triplet sensitization can be easily determined by simple ^{1}H analysis of the **2**/**3** ratio.

1 **2** **3**

This interest was prompted by previous investigations involving meta- (**4**)[1] and ortho-substituted derivatives (**5**)[2] which revealed that electronic perturbation of aryl sites exerts a major impact on the product-forming steps of the rearrangement. Dramatic



regioselectivities have also been noted when the vinyl double bond is forced to carry a cyano[3] or methyl group.[4] Because of its role

(1) (a) Paquette, L. A.; Cottrell, D. M.; Snow, R. A.; Gifkins, K. B.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 3275. (b) Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *Ibid.* **1977**, *99*, 3723. (c) Hahn, R. C.; Johnson, R. P. *Ibid.* **1977**, *99*, 1508.

(2) (a) Santiago, C.; Houk, K. N.; Snow, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 7443. (b) Snow, R. A.; Cottrell, D. M.; Paquette, L. A. *Ibid.* **1977**, *99*, 3734.

(3) (a) Paquette, L. A.; Ku, A. Y.; Santiago, C.; Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 5972. (b) Ku, A. Y.; Paquette, L. A.; Rozeboom, M. D.; Houk, K. N. *Ibid.* **1979**, 101, 5981.

0002-7863/84/1506-6693$01.50/0