Stereoselective Olefin Cyclization Mediated by the Selenyl Group; Direct Formation of a Selenyl Caparrapi Oxide †

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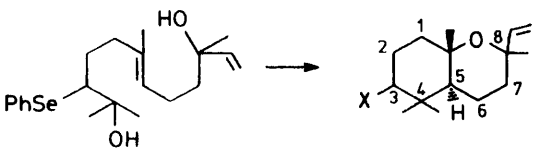
By acid-catalysed cyclization of 10-phenylseleno-3,7,11-trimethyldodeca-1,6-diene-3,11-diol (1), 3β-phenylselenocaparrapi oxide (5) was obtained stereoselectively as a mixture with its C-8 epimer, together with 5-(1,5-dimethyl-1-phenylselenohex-4-enyl)-2-methyl-2-vinyltetrahydrofuran (6).

THE biogenetic-type synthesis of polycyclic carbon frameworks through polyolefin cyclization has been widely studied.[1] The observation of bromine-containing natural products in marine organisms [2] has stimulated investigation into the use of bromonium-ion-initiated polyolefin cyclization [3] to incorporate bromine atoms into cyclic systems. As a continuation of our work [4] on olefin cyclization mediated by phenylseleniranium ions, we have studied the acid-catalysed cyclization of the β-hydroxy-selenide (1); the direct formation of bicyclic compounds such as (3) (3β-bromocaparrapi oxide and its 8-epimer) from nerolidol has not been observed [3a,5] or has been detected only in low yield.[6]



(1) (2) X = SePh (3) X = Br

SCHEME 1

The β-hydroxy-selenide (1) was prepared by treatment of nerolidol with *m*-chloroperbenzoic acid followed by reaction of the resulting epoxide (4) with phenylselenide anion generated *in situ* by reduction of diphenyl diselenide with sodium borohydride. Then a solution of (4) in dichloromethane containing trifluoroacetic acid was stirred for 5 min at 0 °C to afford the bicyclic compound (5) [*m/z* 376/378 (M^+)] and the monocyclic compound (6) [*m/z* 376/378 (M^+)] as diastereoisomeric mixtures in 21 and 48% yield, respectively.

Although the stereochemistry at the selenium-bearing carbon atom of (5) was easily deduced by the appearance of an axial proton signal as a broad doublet of doublets (*J* 4 and 12 Hz) at δ 3.0 in the n.m.r. spectrum, full confirmation of the structure of compound (5) was obtained by treatment with tri-n-butyltin hydride [7] to yield a *ca.* 1 : 1 mixture of the bicyclic ethers (7) and (8) in 77.3% yield. Since the separation of compounds (7) and (8) was difficult, the mixture was treated with bromine to give a mixture of compounds, (9) and (8), which were easily separated on a silica gel column. The selective bromination of (7) occurs because an equatorial vinyl group is more reactive than an axial vinyl group. After the separation of two C-9 epimers of (9), each of them was subjected to reductive elimination of bromine by zinc powder, to regenerate (7). Caparrapi oxide (7) and its C-8 epimer (8) thus obtained were identical with authentic samples in their n.m.r. spectra.[8] Thus the stereochemical course of the cyclization of the β-hydroxy-selenide (1) giving the bicyclic ether (5) was confirmed.

The structure of the monocyclic compound (6) was confirmed by oxidative elimination of the phenylselenyl group giving compounds (10) [*m/z* 220 (M^+)] and (11) [*m/z* 220 (M^+)]. The signal due to the 1′-methyl group of compound (6) was not observed in the n.m.r. spectra of (10) and (11). In the case of compound (10), additional olefinic proton signals were observed at δ 4.68 and 4.93 as broad singlets, and the C-3′ methylene protons of compound (11) resonated at δ 2.6 as a triplet, *J* 8 Hz. These facts strongly suggested structures (10) and (11), implying that compound (6) has the phenylselenyl group at C-1′.

The formation of compounds (5) and (6) can be rationalized in terms of phenylseleniranium ion intermediates as shown in Scheme 3.

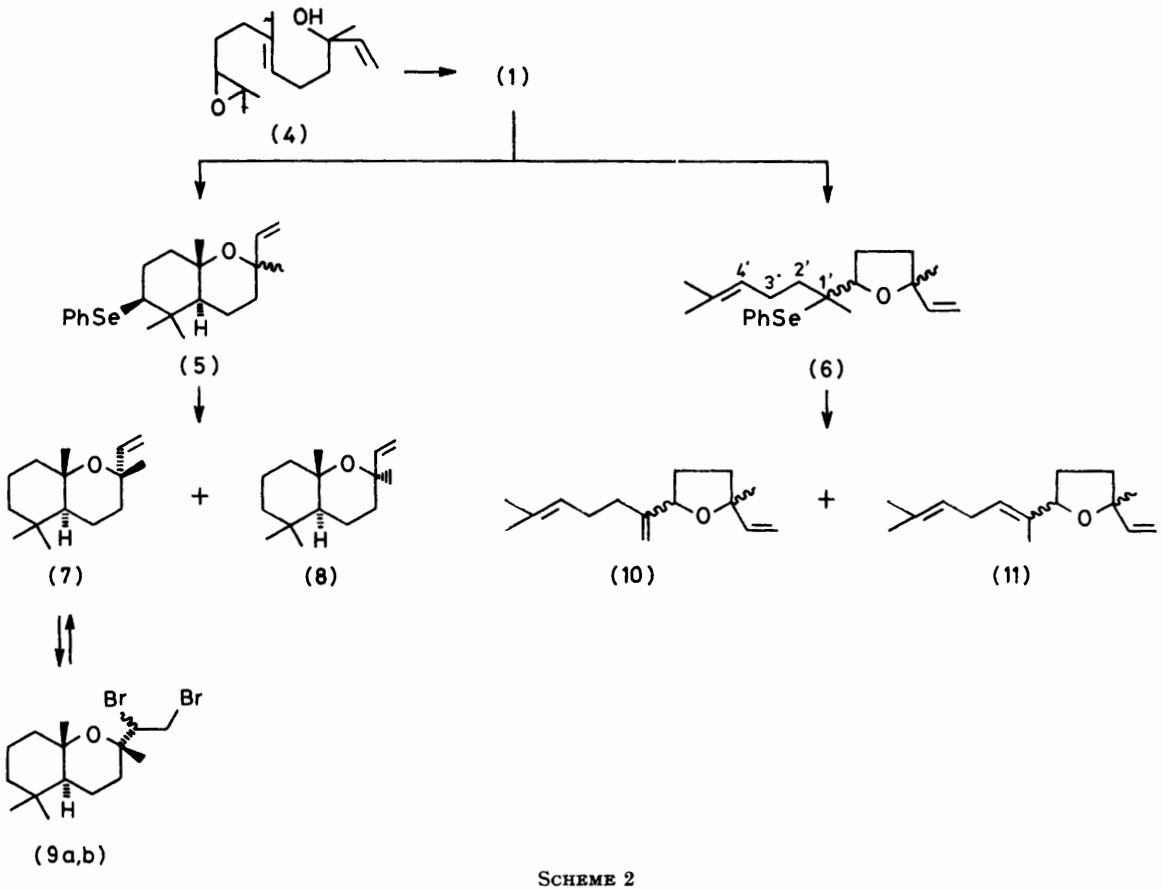
Thus the stereoselective formation of compound (5) *via* acid-actalysed cyclization of the β-hydroxy-phenylselenide (1) is confirmed; the compound (5) thus obtained is a potential intermediate for the preparation of the brominated derivative (3) by a known procedure [9] for the conversion of carbon–selenium bonds into carbon–halogen linkages.

EXPERIMENTAL

I.r. spectra were obtained with a Hitachi 260-10 spectrometer, n.m.r. spectra with a JEOL PMX-60 instrument (tetramethylsilane as internal reference), and mass spectra with a Hitachi M-52G and a JEOL JMX-01SG-2 spectrometer. M.p.s were determined with a Yanoco micro apparatus. All products described were homogeneous on t.l.c.

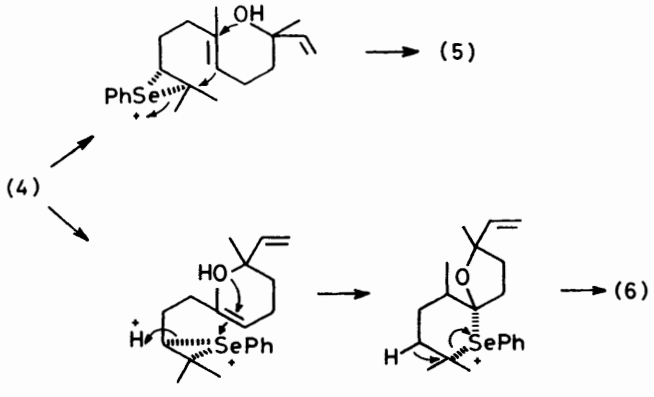
3,7,11-Trimethyl-10-phenylselenododeca-1,6-diene-3,11-diol (1).—To a stirred solution of nerolidol (5.5 g, 24.8 mmol) in dichloromethane (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml) was added *m*-chloro-

† Caparrapi oxide is named systematically as (2α,4aα,8aβ)-2,5,5,8a-tetramethyl-2-vinylhexahydrochroman. The terpenoid numbering system used in the present paper is shown in structure (2).



SCHEME 2

perbenzoic acid (70% purity) (6.3 g, 25.6 mmol). After stirring for 20 h at room temperature, the dichloromethane layer was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent afforded a crude product which was chromatographed on silica gel (200 g) using hexane–ethyl acetate (4 : 1 v/v) as eluant to



SCHEME 3

give 10,11-epoxynerolidol (10,11-epoxy-3,7,11-trimethyldodeca-1,6-dien-3-ol) (4) (4.0 g, 68%) as a colourless oil.

To a suspension of diphenyl diselenide (5.22 g, 16.7 mmol) in ethanol (60 ml) was added sodium borohydride (0.95 g, 25.1 mmol) in small portions with stirring at 0 °C under nitrogen. After stirring for 30 min, a solution of the epoxide (4) (6.62 g, 27.8 mmol) in ethanol (20 ml) was added and the mixture was stirred for 14 h at room temperature. It was then evaporated and the residue was poured into saturated aqueous sodium chloride (100 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent afforded a yellow oil, which was chromatographed on silica gel (300 g) using hexane–ethyl acetate (9 : 1 v/v) as eluant to give the *selenide* (1) (6.8 g, 62%) as a colourless oil (Found: C, 63.8; H, 8.15. $C_{12}H_{32}O_2Se$ requires C, 63.8; H, 8.15%); $\nu_{max.}$ ($CHCl_3$) 3 600 cm^{-1} (OH); δ (CCl_4) 1.20 (6 H, s, 2 × Me), 1.30 (3 H, s, Me), 1.57br (3 H, s, Me), 3.0 (1 H, dd, *J* 11 and 3 Hz, H-10), 4.83—6.07 (4 H, m, olefinic), and 7.07—7.67 (5 H, m, aromatic); *m/z* 394/396 (M^+).

Reaction of the Hydroxy-selenide (1) *with Acid Catalyst.*— To a solution of the selenide (1) (6.3 g, 15.9 mmol) in dry dichloromethane (100 ml) at 0 °C was added trifluoroacetic acid (7 ml) under nitrogen. After stirring for 5 min at 0 °C, the mixture was poured into water (50 ml). The dichloromethane layer was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, and dried (Na_2SO_4). Evaporation afforded a crude product which was chromatographed on silica gel (150 g) using hexane–benzene (4 : 1 v/v) as eluant to give 5-(1,5-*dimethyl*-1-*phenylselenohex*-4-*enyl*)-2-*methyl*-2-*vinyltetrahydrofuran* (6) (2.887 g, 48%); elution with hexane–benzene (2 : 1 v/v) then gave the mixture (5) of 3β-*phenylselenocaparrapi oxide* and its C-8 epimer (1.263 g, 21%). Compound (6) (Found: C, 66.6; H, 8.1. $C_{21}H_{30}OSe$ requires C, 66.85; H, 8.0%) showed δ (CCl_4) 1.22 (3 H, s, 2-Me), 1.62br (6 H, s, CMe_2),

3.73—4.17 (1 H, m, H-5), 4.77—6.2 (4 H, m, olefinic), and 7.03—7.7 (5 H, m, aromatic). Compound (5) (Found: C, 66.65; H, 8.25. $C_{21}H_{30}OSe$ requires C, 66.85; H, 8.0%) showed δ ($CDCl_3$) 0.83, 0.88, 1.12, 1.18, 1.23, 1.27, and 1.32 (each s, 4 × Me), 3.0br (1 H, dd, *J* 4 and 12 Hz, H-3), 4.78—6.32 (3 H, m, olefinic), and 7.17—7.7 (5 H, m, aromatic); *m/z* 376/378 (M^+).

Reduction of the C-8 Epimers (5) *with tri-n-Butyltin Hydride*.—To a stirred solution of (5) (426 mg, 1.13 mmol) in benzene (30 ml) was added tri-n-butyltin hydride (985 mg, 3.39 mmol). After refluxing for 15 h, the mixture was diluted with ether and then washed with aqueous 5% sodium hydroxide and saturated aqueous sodium chloride, and dried (Na_2SO_4). Removal of the solvent afforded a crude product which was chromatographed on silica gel (20 g) using hexane–benzene (2 : 1 v/v) as eluant to give a mixture of ethers (7) and (8) (194 mg, 77.3%) as a colourless oil, δ ($CDCl_3$) 0.73, 0.78, 0.85, 0.88, 1.13, 1.22, and 1.28 (each s, 4 × Me), and 4.77—6.3 (3 H, m, olefinic); *m/z* 222 (M^+).

Bromination of the Ethers (7) *and* (8).—To a solution of the mixture of (7) and (8) (132 mg, 0.595 mmol) in dichloromethane (10 ml) was added a 0.17N-solution of bromine in dichloromethane (1.43 ml) at 0 °C. After stirring for 10 min at 0 °C, evaporation at room temperature gave crude products, which were chromatographed on silica gel (3 g) using hexane–benzene (95 : 5 v/v) as eluant to give one C-9 *epimer* (9a) of the dibromide (9) (54 mg) as a colourless powder, m.p. 77.5—79 °C; elution with hexane–benzene (9 : 1 v/v) then afforded the other *epimer* (9b) (41 mg). Further elution with hexane–benzene (4 : 1 v/v) gave 8-epi-*caparrapi oxide* (8) (46 mg) as a colourless oil. Compound (9a) (Found: C, 46.85; H, 6.75. $C_{15}H_{26}Br_2O$ requires C, 47.15; H, 6.85%) showed δ ($CDCl_3$) 0.77 (3 H, s, Me), 0.89 (3 H, s, Me), 1.26 (3 H, s, Me), 1.33 (3 H, s, Me), and 3.43—4.48 (3 H, m, $CHBr{-}CH_2Br$); *m/z* 365 ($M^+ - 17$)/367 ($M^+ - 15$)/369 ($M^+ - 13$). Compound (9b) (Found: C, 46.9; H, 7.0%) showed δ ($CDCl_3$) 0.77 (3 H, s, Me), 0.9 (3 H, s, Me), 1.28 (3 H, s, Me), 1.5 (3 H, s, Me), and 3.58—4.43 (3 H, m, $CHBr{-}CH_2Br$); *m/z* 365 ($M^+ - 17$)/367 ($M^+ - 15$)/369 ($M^+ - 13$). Compound (8) (Found: M^+, 222.1995. $C_{15}H_{26}O$ requires *M*, 222.1984) showed δ ($CDCl_3$) 0.73 (3 H, s, Me), 0.88 (3 H, s, Me), 1.13 (3 H, s, Me), 1.22 (3 H, s, Me), 4.9 (1 H, dd, *J* 11 and 2 Hz, olefinic), 4.95 (1 H, dd, *J* 18 and 2 Hz, olefinic), and 6.07 (1 H, dd, *J* 18 and 11 Hz, olefinic); *m/z* 222 (M^+).

Caparrapi Oxide (7).—(*a*) To a stirred suspension of the dibromide (9a) (45 mg, 0.118 mmol) and zinc powder (100 mg) in ether (2 ml) was added acetic acid (two drops) at 0 °C. After stirring for 1 h at room temperature, zinc powder was filtered off. The filtrate was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, and dried (Na_2SO_4). Evaporation afforded a crude product which was chromatographed on silica gel (1 g) using hexane–benzene (4 : 1 v/v) as eluant to give the *product* (7) (15 mg, 57%) as a colourless oil (Found: M^+, 222.1940. $C_{15}H_{26}O$ requires *M*, 222.1981); δ ($CDCl_3$) 0.78 (3 H, s, Me), 0.85 (3 H, s, Me), 1.28 (6 H, s, 2 × Me), 4.9 (1 H, dd, *J* 10 and 2 Hz, olefinic), and 5.13 (1 H, dd, *J* 16 and 10 Hz, olefinic); *m/z* 222 (M^+).

(*b*) Caparrapi oxide (7) was also obtained from the dibromide (9b) by the procedure just described, in 62% yield as a colourless oil.

Oxidation of the Tetrahydrofuran Derivative (6).—To a stirred solution of (6) (254 mg, 0.674 mmol) in tetrahydrofuran (1 ml) at 0 °C was added 30% hydrogen peroxide (1 ml). After stirring for 15 min at the same temperature, the mixture was diluted with water (5 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation afforded a crude product, which was chromatographed on silica gel (10 g) using hexane–benzene (4 : 1 v/v) as eluant to give 2-*methyl*-5-(5-*methyl*-1-*methylenehept*-4-*enyl*)-2-*vinyltetrahydrofuran* (10) (52 mg, 35.1%); elution with hexane–benzene (3 : 1 v/v) furnished 2-*methyl*-5-(1,5-*dimethylhepta*-1,4-*dienyl*)-2-*vinyltetrahydrofuran* (11) (41 mg, 27.7%). Compound (10) (Found: M^+, 220.1791. $C_{15}H_{24}O$ requires *M*, 220.1826) showed δ (CCl_4) 1.23 (3 H, s, Me), 1.57 and 1.63br (each 3 H, s, 2 × Me), 4.07—4.43 (1 H, m, H-5), 4.68br (1 H, s, =C*H*H), 4.93br (1 H, s, =CH*H*), 4.9—5.17 (1 H, m, H-4'), 4.87 (1 H, dd, *J* 10 and 2 Hz, CH=C*H*H), 5.07 (1 H, dd, *J* 18 and 2 Hz, CH=CH*H*), and 5.78 (1 H, dd, *J* 18 and 10 Hz, C*H*=CH_2). Compound (11) (Found: M^+, 220.1805. $C_{15}H_{24}O$ requires *M*, 220.1826) showed δ (CCl_4), 1.23 (3 H, s, Me), 1.57br (6 H, s, 2 × Me), 1.63br (3 H, s, Me), 2.6 (2 H, distorted t, *J* 8 Hz, C=C–CH_2–C=C), 4.0—4.4 (1 H, m, H-5), and 4.6—6.17 (5 H, m, olefinic).

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