Synthesis of the Drimane-related Sesquiterpenes Euryfuran, Confertifolin, and Valdiviolide

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trans-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalene-1(2*H*)-one (1) was converted into the drimane sesquiterpene euryfuran (5) in 59% yield. Euryfuran was then used as a starting material for the synthesis of two other drimane natural products, confertifolin and valdiviolide. The preparation of valdiviolide constitutes the first total synthesis of this molecule.

The readily available trimethyldecalone [1] (1) has recently been used as a starting material for various drimane-related natural products, including pallescensin A [2] and the potent insect antifeedant warburganal.[3,4] In this work we show how it can also be used as a precursor for three other drimanes.[5]

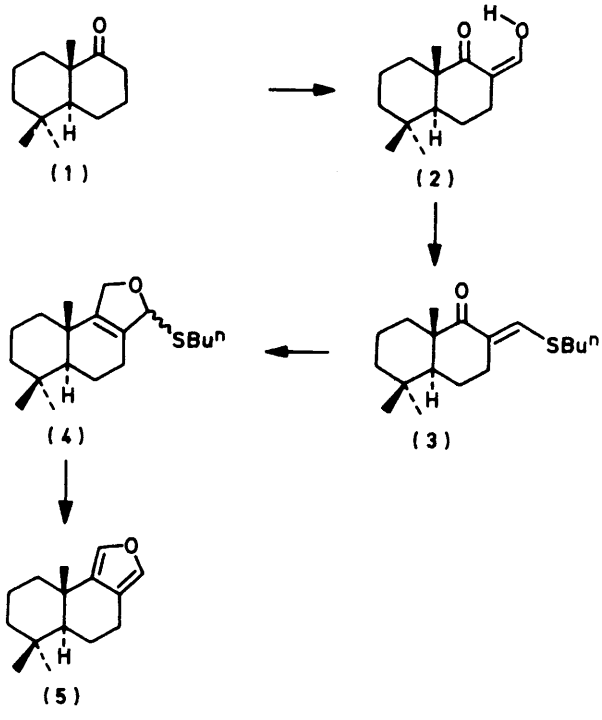
The first of these is euryfuran (5) which has recently been obtained from the nudibranchs [6] *Hypselodoris californensis* and *H. porterae*, and the sponges *Dysidea herbacea* [7] and *Eurysongia* sp.[6] Syntheses of the novel furanosesquiterpene (5) have been reported previously; however, the workers were unaware that it was a natural product.[8]

We reasoned that the mild reaction conditions associated with the furan annelation method reported by Spencer [9] could be used to achieve a highly efficient synthesis of the unstable euryfuran (5). Consequently, hydroxymethylenation of compound (1) using sodium hydride and ethylformate gave the enol (2) [10] after 12 h at room temperature. Compound (2) was subsequently converted into the butylthio derivative (3) by standard methods in 85% overall yield from (1). Treatment of compound (3) with an excess of dimethylsulphonium methylide at −78 °C for 10 min provided the unstable dihydrofuran (4) which, being kept at 35 °C for 12 h or, more conveniently, by brief treatment with mercury(II) sulphate, afforded a 70% yield of euryfuran (5) (Scheme). The sample was isolated by flash chromatography and was shown to be identical with the natural material.† The overall yield to euryfuran by this reaction sequence was therefore an excellent 59%.

Having established such an efficient route, it was attractive to investigate further chemistry of euryfuran (5) in anticipation of being able to prepare other natural products. For example, reaction of compound (5) with bromine in methanol led to the formation of the diacetal (6), in 92% yield, as a mixture of all stereoisomers. When compound (6) was treated with 10% hydrochloric acid in acetone a 75% yield of the sesquiterpene confertifolin (7) was isolated after crystallization; the product was again identical (^{1}H n.m.r., i.r., and t.l.c.) with the natural species.[8a,8d,11-13] ‡ In the crude reaction mixture we noticed that a small amount of the other regioisomer, isodrimenin (8), was also produced but this was not isolated.

The formation of confertifolin (7) from (6) is rationalised as a facile 1,4-elimination of methanol by loss of the more accessible proton and the sterically more congested methoxy group to afford 12-methoxyeuryfuran which would undoubtedly hydrolyse rapidly to give compound (7).

As no total synthesis of the drimane sesquiterpene valdiviolide (9) has yet been reported [13] we sought to achieve this by direct photo-oxidation of euryfuran (5). It was expected that singlet oxygen would preferentially add from the underside of (5) to give an endoperoxide which should collapse in the presence of base by removal of the less hindered proton, *i.e.* that on C-12, to produce regio- and stereo-selectively compound (9). In the event, when euryfuran (5) was photo-oxidised in the presence of 2,6-lutidine,[14] a 90% yield of a 2 : 1 mixture of valdiviolide (9) and 11-epivaldiviolide (10) was produced. Pure valdiviolide was obtained by crystallization and compared with an authentic sample isolated from *Drimys winteri* Forst.‡



Scheme.

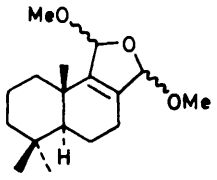
Experimental

M.p.s were determined with a Kofler hot-stage apparatus. ^{1}H N.m.r. spectra were obtained for solutions in $CDCl_3$ (Me_4Si as internal standard). Chromatography was carried out on silica gel (Merck Kieselgel 60 H). All solvents were dried and purified by standard techniques.

Preparation of the Butylthiomethylene Derivative (3).—The *trans*-trimethyldecalone (1) (4.5 g, 23 mmol), ethyl formate (2.5 g, 1.5 equiv.), sodium hydride (50% in oil; 1.44 g, 1.3

† We thank Professor D. J. Faulkner at the Scripps Institution, La Jolla, California for making these comparisons.

‡ We thank Professor K. H. Overton for kindly providing comparison samples of the natural material.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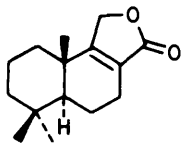
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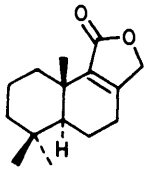
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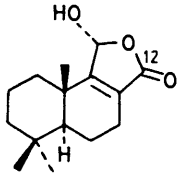
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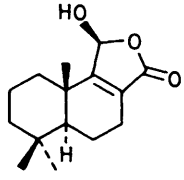
(10)

equiv.), and benzene (120 ml) were stirred rapidly at room temperature for 12 h. The reaction mixture was quenched by the addition of 5% hydrochloric acid (50 ml) and extracted with diethyl ether. Work-up in the usual manner gave compound (2) as an oil (4.63 g, 90%), $\nu_{max.}$ 2 960—2 840, 1 730, 1 700, 1 640, 1 590, 1 460, 1 330, 1 033, and 680 cm^{-1}; δ (60 MHz) 0.85 (3 H, s), 0.9 (3 H, s), 1.1 (3 H, s), 1.0—2.5 (11 H, m), 7.28 (1 H, m), and 8.4 (1 H, m). Treatment of the enol (2) (4.0 g, 18 mmol) with butane-1-thiol (2.88 ml, 1.5 equiv.) and toluene-*p*-sulphonic acid (50 ml) in benzene (50 ml) under Dean–Stark conditions for 4 h, followed by removal of excess of solvent and reagents under reduced pressure, gave an oil. Chromatography [silica gel H (130 g); diethyl ether–hexane (20 : 80)] gave 2-(*butylthiomethylene*)-3,4,4a,5,6,7,8,8a-*octahydro*-5,5,8a-*trimethylnaphthalen*-1(2H)-*one* (3) [4.5 g, 85% from (1)], m.p. 60—62 °C; $\nu_{max.}$ 2 960—2 850, 1 675, 1 550, 1 430, 1 300, 1 230, 1 140, and 810 cm^{-1}; δ (60 MHz) 0.9 (6 H, s), 1.08 (3 H, s), 0.9—2.8 (20 H, m), and 7.45 (1 H, m) (Found: C, 73.2; H, 10.3; S, 11.1. $C_{18}H_{30}OS$ requires C, 73.4; H, 10.25; S 10.9%).

Preparation of Euryfuran (5).—A solution of compound (3) (0.1 g, 0.34 mmol) in 1,2-dimethoxyethane (5 ml) was added dropwise to a mixture of dimethylsulphonium methylide [from trimethylsulphonium tetrafluoroborate (1.65 g) and n-butyllithium (3.8 ml; 2.65M) in 1,2-dimethoxyethane (40 ml) at −78 °C under argon. After 10 min, water (25 ml) was added and the mixture was worked up to afford the dihydrofuran (4) as an oil, $\nu_{max.}$ 2 980—2 860, 1 620, 1 460, 1 380, and 1 100 cm^{-1}; δ (60 MHz) *inter alia* 4.5 (2 H, m) and 5.7 (1 H, m). This oil, on being kept at 35 °C for 12 h or by brief treatment with mercury(II) sulphate (0.1 g) in 1,2-dimethoxyethane (2 ml), gave, after work-up and flash chromatography [silica gel H, (5 g); hexane], (5aα,9aβ)-4,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethylnaphtho[1,2-*c*]furan (euryfuran) (5) (52 mg, 70%) as an oil, $\nu_{max.}$ 2 960—2 850, 1 460, 1 430, 1 380, and 890 cm^{-1}; δ (250 MHz) 0.91 (3 H, s), 0.94 (3 H, s), 1.21 (3 H, s), 1.2—2.0 (9 H, m), 2.5 (1 H, dddd, *J* 2, 7.5, 11.5, and 16 Hz), 2.77 (1 H, ddm, *J* 6.5 and 16 Hz), and 7.05 (1 H, d, *J* 1.5 Hz) (Found: M^+, 218.1671. Calc. for $C_{15}H_{22}O$: *M*, 218.1671).

Preparation of Compound (6).—A solution of euryfuran (5) (15 mg, 0.069 mmol) in methanol (2 ml) at 0 °C was treated with a 0.05M solution of bromine in methanol (1.7 ml, 1.2 equiv.). After 30 min at room temperature the reaction mixture was diluted with water and extracted with diethyl ether to give *compound* (6) (18 mg, 92%) as an oil, $\nu_{max.}$ 2 960—2 840, 1 460, 1 370, and 1 190 cm^{-1}; δ (60 MHz) 0.9—1.2 (9 H, m), 1.0—2.4 (11 H, m), 3.3—3.5 (6 H, 8 × s), and 5.2—5.8 (2 H, m) (Found: M^+, 280.2046. $C_{17}H_{28}O_3$ requires *M*, 280.2038).

Preparation of Confertifolin (7).—A solution of compound (6) (15 mg, 0.53 mmol) in diethyl ether (0.1 ml) was added to a vigorously stirred mixture of 10% hydrochloric acid in acetone (2 ml). After 30 min at room temperature the reaction mixture was transferred to a mixture of aqueous sodium hydrogen carbonate and diethyl ether (20 ml). The ethereal extract was dried ($MgSO_4$) and evaporated to give a crude oil. Crystallization from hexane gave (5aα,9aβ)-4,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethylnaphtho[1,2-*c*]furan-3(1*H*)-one (confertifolin) (7) (9.5 mg, 75%), m.p. 120—123 °C (lit.,[12] 116—117 °C); $\nu_{max.}$ 2 960—2 840, 1 760, 1 670, 1 460, 1 380, 1 090, and 1 010 cm^{-1}; δ (250 MHz) 0.92 (3 H, s), 0.96 (3 H, s), 1.17 (3 H, s), 1.1—2.0 (8 H, m), 1.8 (1 H, ddm, *J* 7.5 and 13 Hz), 2.15 (1 H, dm, *J* 18 Hz), 2.4 (1 H, dm, *J* 18 Hz), 4.65 (1 H, ddd, *J* 2, 3.5, and 17,5 Hz), and 4.75 (1 H, ddd, *J* 3, 3.7 and 7 Hz) (Found: C, 76.65; H, 9.45%; M^+, 234. Calc. for $C_{15}H_{22}O_2$: C, 76.9; H, 9.45%; *M*, 234).

Preparation of Valdiviolide (9).—A solution of compound (2) (17 mg, 0.078 mmol) in t-butyl alcohol–2,6-lutidine (5 ml; 2 : 1) containing eosin (0.5 mg) was irradiated with an external 300-W quartz–halogen lamp for 4 h during which time oxygen was bubbled through the reaction mixture. The temperature in the reaction flask was maintained at 25 °C using an internal cold finger arrangement. Solvent was removed from the reaction mixture by evaporation under reduced pressure and the residue was subjected to column chromatography [silica gel H (4 g); diethyl ether–hexane (50 : 50)] to afford an oil (16 mg, 90%) as a 2 : 1 mixture of valdiviolide (9) and 11-epivaldiviolide (10). Crystallization from benzene gave pure valdiviolide, m.p. 160—168 °C {lit.,[15] [(+)-valdiviolide] 177—178 °C}; $\nu_{max.}$ 3 360, 2 980, 2 860, 1 765, 1 675, 1 460, 1 390, 1 150, 1 015, and 910 cm^{-1}; δ (250 MHz) 0.91 (3 H, s), 0.97 (3 H, s), 1.25 (3 H, s), 1.1—2.0 (9 H, m), 2.13 (1 H, m), 2.38 (1 H, m), 3.95 (1 H, s, OH), and 6.09 (1 H, m); *m/z* 250.1564 (M^+), 232, 217, 205, 203, 135, and 123 ($C_{15}H_{22}O_3$ requires *M*, 250.1569.)

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