Furanosesquiterpenoids: Total Synthesis of Pallescensins 2, F, and G

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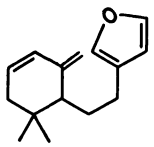
Oxidation of the synthetic pallescensin 1 with *m*-chloroperbenzoic acid, followed by treatment of the resulting epoxide with lithium diethylamide, afforded 3-[2-(2-furyl)ethyl]-4,4-dimethyl-2-methylenecyclohexanol (**6**). The alcohol **6** was dehydrated with refluxing hexamethylphosphoric triamide to give pallescensin 2. Oxidation of **6** with pyridinium chlorochromate, followed by intramolecular cyclization with 85% phosphoric acid, afforded 5,5a,6,7,8,9,9a,10-octahydro-6,6-dimethyl-4*H*-benzo[5,6]cyclohepta[1,2-*b*]furan-9-one. This was converted into the corresponding α,β-unsaturated ketone (**10**) *via* an α-phenylseleno ketone. Reduction of **10** with lithium aluminium hydride, followed by dehydration with hexamethylphosphoric triamide at 200—210 °C, afforded pallescensin G, which was further isomerized to pallescensin F.

Pallescensins 2, F, and G, have recently been isolated from the marine sponge *Disidea pallescens* by Cimino *et al.*[1] On the basis of spectroscopic studies, they deduced the structures of pallescensins 2, F, and G, to be **1**, **2**, and **3**, respectively. To confirm the validity of these unique structures, we have attempted the total syntheses of **1**, **2**, and **3**, starting from pallescensin 1 (**4**)[2] which was prepared from α-cyclocitral in our laboratory.



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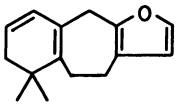

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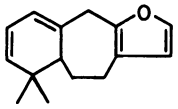

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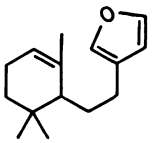

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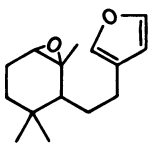
Oxidation of **4** with *m*-chloroperbenzoic acid in dichloromethane at 0—5 °C afforded the corresponding epoxide (**5**) which, without purification, was treated with lithium diethylamide[3] in refluxing tetrahydrofuran to give 3-[2-(2-furyl)ethyl]-4,4-dimethyl-2-methylenecyclohexanol (**6**) in 49% yield from **4**. The structure of **6** was supported by its ^{1}H NMR spectrum, which showed broad singlet signals at δ 2.66 (1H) due to a hydroxyl group and at δ 4.71 (1H) and 5.22 (1H) due to an *exo*-methylene group. Dehydration of **6** with refluxing hexamethylphosphoric triamide[4] under a stream of nitrogen afforded the desired 3-[2-(6,6-dimethyl-2-methylene-3-cyclohexenyl)ethyl]furan (**1**) in 89% yield. The ^{1}H NMR spectrum of the synthetic **1** was identical with that of natural pallescensin 2.

Our next effort was directed toward the syntheses of **2** and **3**. Oxidation of **6** with pyridinium chlorochromate in dichloromethane at room temperature afforded the corresponding α,β-unsaturated ketone (**7**) in 80% yield. The IR spectrum of **7** showed a conjugated carbonyl absorption band at 1690 cm^{-1} and its ^{1}H NMR spectrum showed two doublet signals at δ 4.91 (1H, J=2 Hz) and 5.69 (1H, J=2 Hz) due to an *exo*-methylene group. These spectral data suggested the structure of **7** to be 3-[2-(2-furyl)ethyl]-4,4-dimethyl-2-methylenecyclohexanone. Intramolecular cyclization of **7** with 85% phosphoric acid in tetrahydrofuran at room temperature afforded a single tricyclic ketone[5] (**8**) in 79% yield. The ^{1}H NMR spectrum of **8** showed a *gem*-dimethyl group at δ 1.01 (3H, s) and 1.03 (3H, s) and a furan moiety at δ 5.92 (1H, d, J=2 Hz) and 6.97 (1H, d, J=2 Hz). The presence of a non-conjugated carbonyl group (IR: 1705 cm^{-1}) and the chemical shifts of two furan protons suggested the structure of **8** to be 5,5a,6,7,8,9,9a,10-octahydro-6,6-dimethyl-4*H*-benzo-[5,6]cyclohepta[1,2-*b*]furan-9-one. In the present study, the stereochemistry of the ring juncture in **8** has remained unsettled. Treatment of **8** with benzeneselenenyl bromide[6] in tetrahydrofuran at −70 °C in the presence of lithium diisopropylamide under a stream of nitrogen afforded the corresponding α-phenylseleno ketone (**9**) in 80% yield. The ketone **9** in tetrahydrofuran was then treated with 30% hydrogen peroxide at room temperature to give an α,β-unsaturated ketone (IR: 1670 cm^{-1}), 5,5a,6,9,9a,10-hexahydro-6,6-dimethyl-4*H*-benzo[5,6]cyclohepta[1,2-*b*]furan-9-one (**10**), in 69% yield. The ^{1}H NMR spectrum of **10** showed two doublet signals at δ 5.79 (1H, J=10 Hz) and 6.50 (1H, J=10 Hz) due to two olefinic protons, supporting the presence of a disubstituted olefinic moiety. Reduction of **10** with lithium aluminium hydride in ether at 0—5 °C, followed by heating of the resulting alcohol (**11**) with hexamethylphosphoric triamide at 200—210 °C under a stream of nitrogen, afforded the desired 5,5a,6,10-tetrahydro-6,6-dimethyl-4*H*-benzo[5,6]cyclohepta[1,2-*b*]-furan (**3**) in 51% yield from **10**. The structure of **3** was supported by its ^{1}H NMR spectrum, which showed signals at δ 0.99 (3H) and 1.06 (3H) due to a *gem*-dimethyl group, at δ 5.4 (1H) and 5.73 (2H) due to three olefinic protons, and at δ 6.12 (1H) and 7.18 (1H) due to two furan protons. Isomerization of **3** with refluxing hexamethylphosphoric triamide under a stream of nitrogen afforded an isomer (**2**) in 75% yield. The ^{1}H NMR spectrum of **2** showed a *gem*-dimethyl group at δ 1.03 (6H), four methylene groups at δ 2.03 (2H), 2.47 (4H), and 3.37 (2H), two olefinic protons at δ 5.52 (1H) and 5.74 (1H), and two furan protons at δ 5.97 (1H) and 7.02 (1H). These spectral data,

especially the presence of signals due to four methylene groups and two olefinic protons, suggested the structure of **2** to be the desired 5,6,7,10-tetrahydro-6,6-dimethyl-4*H*-benzo[5,6]cyclohepta[1,2-*b*]furan. The ^{1}H NMR spectra of the synthetic **2** and **3** were also in good agreement with those[1] of natural pallescensins F and G.



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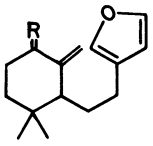
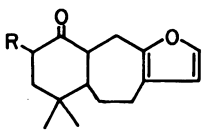
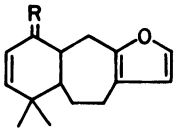


6 R = H,OH
7 R = O



8 R = H
9 R = SePh



10 R = O
11 R = H,OH

Experimental

The melting point is uncorrected. The IR spectra were measured in chloroform and the ^{1}H NMR spectra in carbon tetrachloride at 90 MHz, with tetramethylsilane as an internal standard, unless otherwise stated. The chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, dd: double doublet, t: triplet, dt: double triplet, m: multiplet, dm: doublet of multiplet. Column chromatography was performed using Merck silica gel (0.063—0.200 mm).

3-[2-(2,6,6-Trimethyl-2-cyclohexenyl)ethyl]furan (Pallescensin 1) (**4**). Pallescensin 1 was prepared from (±)-α-cyclocitral by the known procedure.[2]

3-[2-(2-Furyl)ethyl]-4,4-dimethyl-2-methylenecyclohexanol (**6**). A solution of **4** (412 mg) and 85% *m*-chloroperbenzoic acid (420 mg) in dichloromethane (6.0 ml) was stirred at 0—5 °C for 1 h and then diluted with ether. The solution was washed successively with 10% aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated *in vacuo* to give a crude epoxide (**5**); ^{1}H NMR (60 MHz): 0.83 (3H, s) and 0.90 (3H, s) (-C(CH$_3$)$_2$), 1.30 (3H, s, -OCCH$_3$), 6.23 (1H, bs), 7.18 (1H, bs), and 7.26 (1H, t, J=2 Hz) (furan protons).

A solution of the crude **5** in dry tetrahydrofuran (2.0 ml) was added to a solution of lithium diethylamide which was prepared from butyl lithium in hexane [1.6 M (1 M=1 mol dm^{-3}): 6.0 ml] and diethylamine (1.0 ml) in dry tetrahydrofuran (4.0 ml) at room temperature for 30 min. The mixture was refluxed for 3 h, cooled, and diluted with ether. The solution was washed successively with aqueous ammonium chloride and brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (Merck, 0.063 mm: 40 g), usingether–benzene (1: 9) as the eluent, to give **6** (215 mg: 49% from **4**); IR: 3610, 3450 br cm^{-1}; ^{1}H NMR (60 MHz): 0.73 (3H, s) and 0.96 (3H, s) (-C(CH$_3$)$_2$), 2.66 (1H, bs, -OH), 3.88 (1H, m, $W_{1/2}$=16 Hz, -CHOH), 4.71 (1H, bs) and 5.22 (1H, bs) (-C=CH$_2$), 6.18 (1H, bs), 7.12 (1H, bs), and 7.27(1H, t, J=2 Hz) (furan protons). Found: C, 76.75; H, 9.73%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

3-[2-(6,6-Dimethyl-2-methylene-3-cyclohexenyl)ethyl]furan (Pallescensin 2) (**1**). A solution of **6** (200 mg) in hexamethylphosphoric triamide (2.0 ml) was refluxed for 1.5 h under a stream of nitrogen. The solution was cooled, poured into dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (20 g), using hexane as the eluent, to give **1** (164 mg: 89%); ^{1}H NMR: 0.84 (3H, s) and 0.97 (3H, s) (-C(CH$_3$)$_2$), 4.71 (1H, bs) and 4.87 (1H, bs) (-C=CH$_2$), 5.57 (1H, dm, J=10 Hz, -CH=CH-C=), 5.99 (1H, bd, J=10 Hz, -CH=CH-C=), 6.14 (1H, bs), 7.10 (1H, bs), and 7.23 (1H, t, J=2 Hz) (furan protons). Found: C, 83.00; H, 9.35%. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32%. The ^{1}H NMR spectrum of the synthetic **1** was identical with that of natural pallescensin 2.

3-[2-(2-Furyl)ethyl]-4,4-dimethyl-2-methylenecyclohexanone (**7**). A mixture of **6** (165 mg) and pyridinium chlorochromate (230 mg) in dichloromethane (4.0 ml) was stirred at room temperature for 3 h, poured into aqueous sodium carbonate, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (15 g), using ether–benzene (2: 98) as the eluent, to give **7** (132 mg: 80%); IR: 1690 cm^{-1}; ^{1}H NMR: 1.01 (3H, s) and 1.08 (3H, s) (-C(CH$_3$)$_2$), 4.91 (1H, d, J=2 Hz) and 5.69 (1H, d, J=2 Hz) (-C=CH$_2$), 6.17 (1H, bs), 7.12 (1H, bs), and 7.26 (1H, t, J=2 Hz) (furan protons). Found: C, 77.27; H, 8.79%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

5,5a,6,7,8,9,9a,10-Octahydro-6,6-dimethyl-4H-benzo-[5,6]cyclohepta[1,2-b]furan-9-one (**8**). A solution of **7** (368 mg) in tetrahydrofuran (2.0 ml) was added to a mixture of 85% phosphoric acid (16 ml) and tetrahydrofuran (30 ml). The mixture was stirred at room temperature for 10 h, diluted with ice-water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporared *in vacuo*. The crude product was purified by column chromatography on silica gel (40 g), using ether–benzene (2 : 98) as the eluent, to give **8** (292 mg: 79%); IR: 1705 cm^{-1}; ^{1}H NMR: 1.01 (3H, s) and 1.03 (3H, s) (-C(CH$_3$)$_2$), 5.92 (1H, d, J=2 Hz) and 6.97 (1H, d, J=2 Hz) (furan protons). Found: C, 77.48; H, 8.78%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

5,5a,6,7,8,9,9a,10-Octahydro-6,6-dimethyl-8-phenylseleno-4H-benzo[5,6]cyclohepta[1,2-b]furan-9-one (**9**). A solution of **8** (67 mg) in dry tetrahydrofuran (1.0 ml) was added at −70 °C to a solution of lithium diisopropylamide [prepared from butyl lithium in hexane (1.6 M: 0.450 ml) and diisopropylamine (0.100 ml) in dry tetrahydrofuran (2.0 ml) at −70 °C] under a stream of nitrogen. The solution was stirred at the same temperature for 10 min and then a solution of benzeneselenenyl bromide (170 mg) in dry tetrahydrofuran (1.0 ml) was added. The mixture was stirred at −70 °C for 10 min more, poured into ice–dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (10 g), using benzene as the eluent, to give **9** (89 mg: 80%). This was recrystallized from methanol; mp 115- 117 °C; IR: 1700 cm^{-1}; ^{1}H NMR: 0.99 (6H, s, -C(CH$_3$)$_2$), 4.18 (1H, dd, J=8 and 12 Hz, C$_6$H$_5$SeCH-), 5.98 (1H, d, J=2 Hz) and 7.01 (1H,d, J=2 Hz) (furan protons), 7.0—7.6 (5H, m, C$_6$H$_5$Se-). Found:

C, 65.27; H, 6.40%. Calcd for $C_{21}H_{24}O_2Se$: C, 65.11; H, 6.24%.

*5,5a,6,9,9a,10-Hexahydro-6,6-dimethyl-4H-benzo[5,6]cyclohepta-[1,2-b]furan-9-one (**10**).* A solution of **9** (165 mg) and 30% hydrogen peroxide (0.09 ml) in tetrahydrofuran (4.0 ml) was stirred at room temperature for 1.5 h and then diluted with aqueous sodium hydrogencarbonate. The mixture was extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (5 g), using ether–benzene (1:99) as the eluent, to give **10** (68 mg: 69%); IR: 1670 cm^{-1}; ^1H NMR: 1.09 (3H, s) and 1.19 (3H, s) ($-\dot{C}(CH_3)_2$), 5.79 (1H, d, $J=10$ Hz) and 6.50 (1H, d, $J=10$ Hz) ($-CH=CHCO-$), 5.98 (1H, d, $J=2$ Hz) and 7.03 (1H, d, $J=2$ Hz) (furan protons); MS (*m/e*): 230 (M^+).

5,5a,6,10-Tetrahydro-6,6-dimethyl-4H-benzo[5,6]cyclohepta[1,2-b]furan (Pallescencin G) (3). A mixture of **10** (68 mg) and lithium aluminium hydride (15 mg) in dry ether (2.0 ml) was stirred at 0—5 °C for 30 min. The mixture was poured into ice–dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude alcohol (**11**); IR: 3590, 3430br cm^{-1}; ^1H NMR: 0.93 (3H, s) and 0.98 (3H, s, $-\dot{C}(CH_3)_2$), 2.40 (1H, bs, –OH), 3.72 (1H, bd, $J=10$ Hz, $-\dot{C}\underline{H}OH$) 5.28 (1H, d, $J=10$ Hz) and 5.42 (1H, d, $J=10$ Hz) ($-CH=CH-$), 5.99 (1H, d, $J=2$ Hz) and 7.03 (1H, d, $J=2$ Hz) (furan protons).

The crude alcohol **11** was heated with hexamethylphosphoric triamide (2.0 ml) at 200—210 °C for 1 h under a stream of nitrogen. The mixture was cooled, poured into ice–dilute hydrochloric acid, and extracted with ether. The ether extract was washed successively with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (10 g), using hexane–benzene (1 : 1) as the eluent, to give **3** (32 mg: 51% from **10**); ^1H NMR ($CDCl_3$): 0.99 (3H, s) and 1.06 (3H, s) ($-\dot{C}(CH_3)_2$), 3.41 (1H, d, $J=17$ Hz) and 3.67 (1H, d, $J=17$ Hz) ($=\dot{C}CH_2\dot{C}=$), 5.4 (1H, m) and 5.73 (2H, m) (olefinic protons), 6.12 (1H, d, $J=2$ Hz) and 7.18 (1H, d, $J=2$ Hz) (furan protons); MS (*m/e*): 214 (M^+). The ^1H NMR spectrum of the synthetic **3** was in good agreement with that of natural pallescensin G.

5,6,7,10-Tetrahydro-6,6-dimethyl-4H-benzo[5,6]cyclohepta[1,2-b]furan (Pallescensin F) (2). A solution of **3** (22.0 mg) in hexamethylphosphoric triamide (2.0 ml) was refluxed for 1 h under a stream of nitrogen. After the same work-up as described for the preparation of **3**, the crude product was chromatographed on silica gel (5 g), using hexane–benzene (1 : 1) as the eluent, to give **2** (16.4 mg: 75%); ^1H NMR: 1.03 (6H, s, $-\dot{C}(CH_3)_2$), 2.03 (2H, dd, $J=4$ and 2 Hz, $=CHC\underline{H}_2\dot{C}-$), 2.47 (4H, s, $-CH_2CH_2-$), 3.37 (2H, bs, $=\dot{C}CH_2\dot{C}=$), 5.52 (1H, dt, $J=10$ and 4 Hz) and 5.74 (1H, dt, $J=10$ and 2 Hz) ($-CH=CH\dot{C}=$), 5.97 (1H, d $J=2$ Hz) and 7.02 (1H, d, $J=2$ Hz) (furan protons); MS (*m/e*): 214 (M^+). The ^1H NMR spectrum of the synthetic **2** was in good agreement with that of natural pallescensin F.

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References

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2) T. Matsumoto and S. Usui, *Chem. Lett.*, **1978**, 105.

3) J. K. Crandall and L. C. Lin, *J. Org. Chem.*, **33**, 2375 (1968).

4) R. S. Monson, *Tetrahedron Lett.*, **1971**, 567; R. S. Monson and D. N. Priest, *J. Org. Chem.*, **36**, 3826 (1971).

5) When the cyclization was carried out with 85% phosphoric acid in dichloromethane at room temperature, a mixture of **8** and its other isomer (**8a**) (*ca.* 3 : 7) was obtained in 33% yield. The ^1H NMR spectrum of **8a** showed a *gem*-dimethyl group at δ 1.04 (3H, s) and 1.25 (3H, s) and a furan moiety at δ 5.96 (1H, d, $J=2$ Hz) and 7.04 (1H, d, $J=2$ Hz).