A stereoselective synthesis of platyphyllide

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The norsesquiterpene lactone, platyphyllide has been synthesized in 8 steps in 23% overall yield *via* the Diels–Alder adduct of 2-(4-methylpent-3-enyl)furan with dimethyl acetylenedicarboxylate, the 3-substituted phthalic diester, and an *o*-formylbenzamide. An intramolecular ene reaction established the skeleton, and the final step involved inversion of configuration at the benzylic site.

Platyphyllide (**1**) is a levorotatory norsesquiterpene lactone isolated from *Senecioneae* species (family Compositae). Since its structural elucidation[1] in 1977, several reports of the synthesis of platyphyllide have appeared.[2] Unfortunately, all these routes suffer from the generation of a mixture of stereoisomers. Our interest in platyphyllide was related to occidol 2[3] which is also a tetralin derivative.

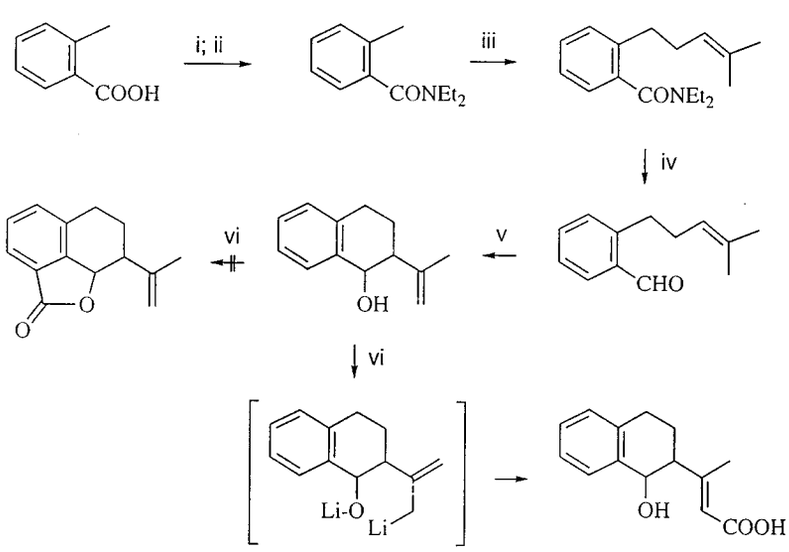
Our initial approach is summarized in Scheme 1.[4] The intention of pursuing an aromatic carboxylation as directed by the hydroxy group[5] of an α-tetralol intermediate was thwarted by the preferential deprotonation of the isopropenyl group. Accordingly, our tactics[6] were changed while still retaining the operation of an intramolecular ene reaction[7] to establish the tetralin system. In this key step two adjacent stereogenic centers were created.

The tactical change was also prompted by our recent fascination in exploiting the symmetry aspect in synthesis design.[8] In other words, we wished to elaborate a 3-substituted phthalic ester which, because of its local symmetry, can be obtained from the 2-substituted furan and an acetylenedicarboxylic ester by a Diels–Alder reaction followed by deoxygenative aromatization. The steric perturbation by the 3-substituent should then permit a selective transformation initially at the unflanked ester group, followed by the other ester group which was destined to become a formyl residue.

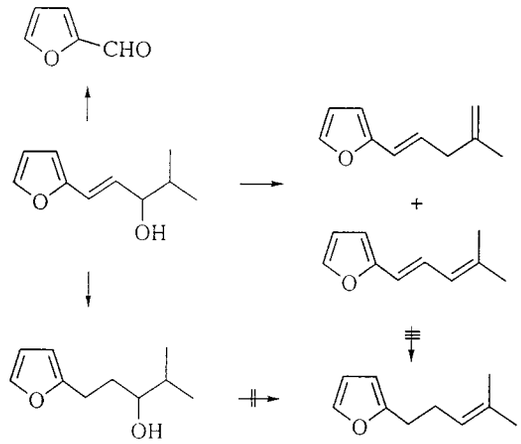
Our work started with the preparation of 2-(4-methylpent-3-enyl)furan (**3**). Whereas Scheme 2 summarizes our failed efforts, the compound was successfully secured in three steps involving the Feist–Benary furan synthesis by condensing methyl 3-oxo-7-methyloct-6-enoate[9] and chloroacetaldehyde in the presence of pyridine as the key step.[10] Saponification of the ester **4** and decarboxylation of the resulting acid **5** furnished the required furan **3**.

The Diels–Alder reaction of **3** with dimethyl acetylenedicarboxylate was best conducted in CH_2Cl_2 at reflux for 5 days. Under these conditions a 95% yield of the adduct **6** was obtained. At a higher temperature (*e.g.*, 110 °C in a sealed tube) the ene reaction adduct **7** was predominant. Heating the two components at 100 °C without solvent resulted in polymerization. In ether, the reaction either failed (25 °C, 20 h) or gave only a 50% yield (reflux, 7 days).

Aromatization of **6** without affecting the ester groups was accomplished on exposure to low-valent titanium species[11] produced from $TiCl_4$, $LiAlH_4$ and Et_3N. At this point we examined several possibilities for manipulation of **8** towards the target molecule. Thus, the straightforward reduction of the diester with $LiAlH_4$ to afford the diol **9** was followed by the rather undesirable nonregioselective oxidation. Manganese dioxide oxidation in refluxing CH_2Cl_2 furnished lactones **10a** and **10b** in a ratio of 3 : 1; the Fetizon oxidation also showed the same preference while PCC oxidation gave the lactones in a 2 : 3 ratio. When we subjected lactone **10a** to Weinreb's reagent[12]



Scheme 1 *Reagents and conditions*: (i) $SOCl_2$; (ii) Et_2NH; (iii) LDA, $Me_2C{=}CHCH_2Cl$; (iv) *i*-BuAlH/*n*-BuLi; (v) 200 °C; (vi) *n*-BuLi–TMEDA; CO_2.



Scheme 2

to obtain the amide alcohol **11a**, we entered a cul-de-sac unwittingly because the subsequent reoxidation of the benzylic alcohol to the aldehyde with MnO_2 was attained by a competing lactonization to return a portion of the material to **10a**. This complication led us to hydrolyze the diester **8** selectively, and convert the half-ester **12** to the amide ester **13** and thence to **11b**. It was estimated that this molecule having larger alkyl groups on the nitrogen atom, would be less prone to lactonization (by virtue of changing the relative orientation of the OH and C=O groups). We were glad to be able to obtain the amide aldehyde **14** by Swern oxidation of **11b** in 70% yield. The low reaction temperature definitely contributed to this final success.

Having in our possession the key intermediate **14**, we investigated the intramolecular ene reaction. After several unfruitful attempts at using Lewis acids to catalyze the cyclization, we conducted the thermal process in sealed vessels using toluene as solvent. From a reaction at 200 °C in a sealed glass tube we detected the formation of platyphyllide **1** and its diastereomer **15** in a ratio of 28 : 72. However, in a Teflon vessel (within a resealable stainless steel bomb) only **15** was produced. The difference between the two reactions may be attributed to the favored transition state **A** in which the aldehyde and the amide groups were oriented such as to minimize dipole–dipole interaction. On the other hand, the silicon atoms of the glass surface may have provided a binding site for the oxygen atoms of both groups, and reaction of molecules in such a bound state **B** would lead to the platyphyllide precursor. The products result from the subsequent lactonization.

We were rather pleased to observe the stereoselective formation of one lactone in the specified reaction conditions, even though an additional step or steps would be required to convert **15** to the target **1**. To that end we tried a Mitsunobu reaction to invert the configuration of the benzylic carbon. Relactonization did not take place under standard conditions probably due to steric hindrance in the formation of the phosphonium intermediate. This forced us to attempt other options such as mesylation after cleavage of the lactone. On acidification of the NaOMe treated lactone, in an attempt to isolate the hydroxy ester intermediate, platyphyllide **1** was detected. This finding led us to investigate the process more thoroughly, which resulted in establishing a procedure for the conversion of **15** to **1** in 84% yield. Because the benzylic cation was readily generated and the relactonization was under thermodynamic control (with 1,2-asymmetric induction by the isopropenyl group) the synthesis was rendered stereoselective.

Experimental

2-(4-Methylpent-3-enyl)furan (3)

A mixture of methyl 3-oxo-7-methyloct-6-enoate (10.0 g, 0.154 mol) and chloroacetaldehyde (50% aq. solution, 12.8 g, 0.231 mol) in pyridine (27 mL) was stirred and warmed at 50 °C under nitrogen for 24 h. The cooled product was diluted with ether (200 mL), washed with 10% HCl, water and brine. After drying over Na_2SO_4 the solution was evaporated *in vacuo*, to give an essentially pure ester **4** (8.0 g). ν (film) 1745 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 1.46 (3H, s), 1.56 (3H, s), 2.24 (2H, q, $J = 7.2$ Hz), 2.9 (2H, t, $J = 7.2$ Hz), 3.7 (3H, s), 5.05 (1H, t, $J = 7.2$ Hz), 6.51 (1H, d, $J = 1.5$ Hz), 7.12 (1H, d, $J = 1.5$ Hz); δ_C ($CDCl_3$, 75 MHz) 17.2 (q), 25.4 (q), 26.4 (t), 26.5 (t), 50.8 (q), 110.5 (d), 112.8 (s), 122.7 (d), 132.3 (s), 140.0 (d), 162.4(s), 164.0 (s); HRMS (*m*/*z*) 208.1099 (208.1095 calcd. for $C_{12}H_{16}O_3$).

The above ester **4** (8.0 g) was refluxed with sodium hydroxide (4.34 g, 0.109 mol) in water (36 mL) for 2 h, cooled, washed with ether (2 × 50 mL) and slowly acidified with 10% HCl. The carboxylic acid **5** (5.48 g, 52%) was obtained by extractive workup with dichloromethane. Mp 68–69 °C; ν (film) 3306–2350, 1680 cm^{-1}; δ_H 1.45 (3H, s), 1.56 (3H, s), 2.25 (2H, m), 2.93 (2H, t, $J = 7.2$ Hz), 5.03 (1H, t, $J = 7.2$ Hz), 6.56 (1H, d, $J = 1.5$ Hz), 7.12 (1H, d, $J = 1.5$ Hz), 12.44 (1H, br s); δ_C 17.4 (q), 25.6 (q), 26.6 (t), 27.9 (t), 111.0 (d), 113.0 (s), 122.8 (d), 133.0 (s), 140.5 (d), 164.0 (s), 170.0 (s); HRMS (*m*/*z*) 194.0935 (194.0939 calcd. for $C_{11}H_{14}O_3$).

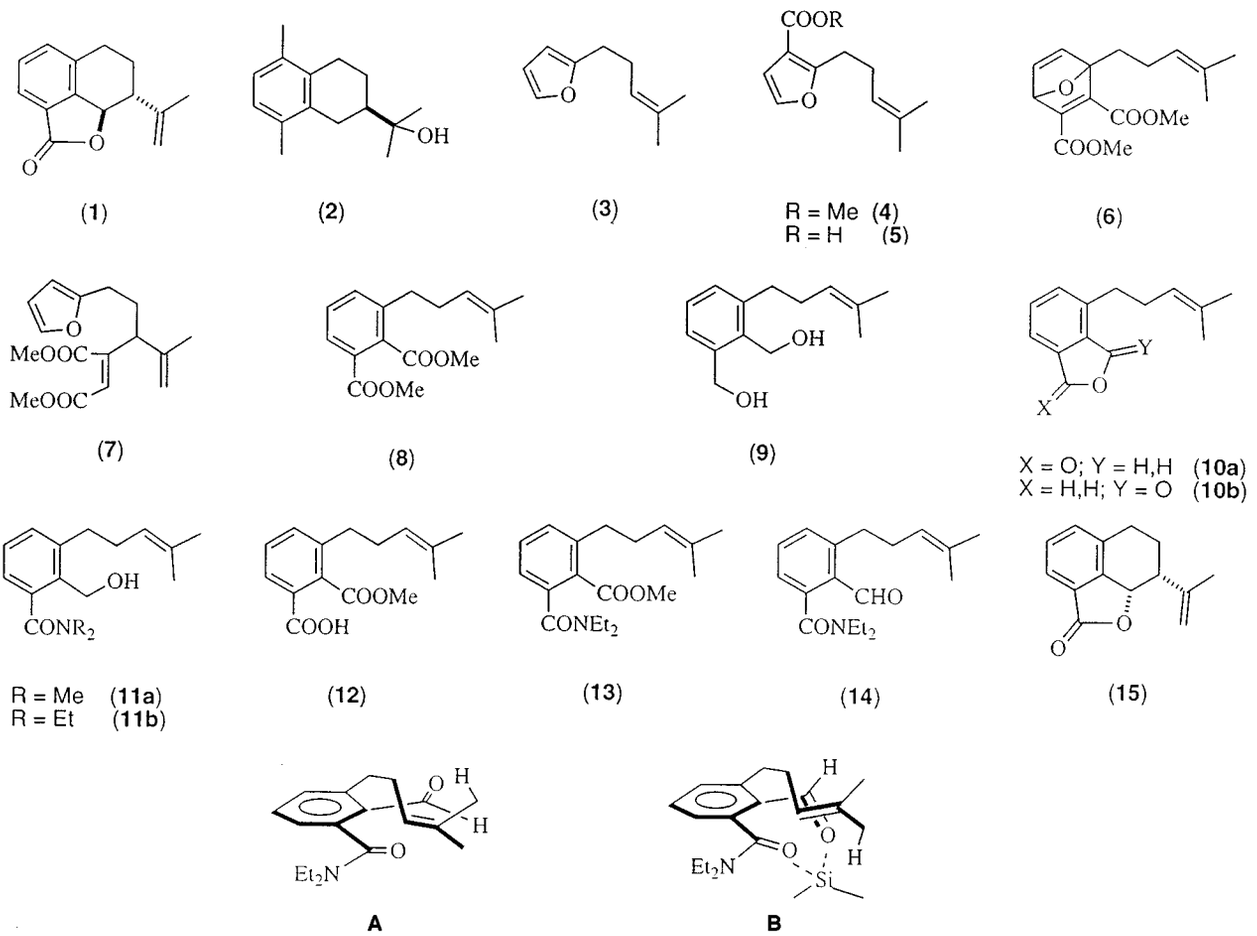
Decarboxylation of the acid **5** (9.69 g, 0.05 mol) was accomplished by heating with copper powder (0.64 g, 0.01 mol) and quinoline (12.9 g, 0.1 mol) for 2 h. The cooled mixture was filtered, diluted with dichloromethane and washed with 10% HCl. Drying, concentration, silica gel chromatography, and evaporative distillation (75 °C/3 Torr) led to the isolation of **3** (6.75 g, 90%). ν (film) 1598 cm^{-1}; δ_H 1.40 (3H, s), 1.50 (3H, s), 2.14 (2H, q, $J = 7.5$ Hz), 2.45 (2H, t, $J = 7.5$ Hz), 4.98 (1H, t, $J = 7.5$ Hz), 5.75 (1H, s), 6.03 (1H, s), 7.04 (1H, s); δ_C 17.7 (q), 25.6 (q), 26.6 (t), 28.2 (t), 104.7 (d), 110.0 (d), 123.5 (d), 132.4 (s), 140.7 (d), 156.1 (s).

Dimethyl 1-(4-methylpent-3-enyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (6)

Furan **3** (6.75 g, 0.045 mol) was mixed with dimethyl acetylenedicarboxylate (6.39 g, 0.045 mol) and dichloromethane (30 mL), and was refluxed for 5 days, cooled, and the solvent removed. The residue was chromatographed over silica gel using 1 : 9 EtOAc–hexane as eluent to give 6 (11.89 g, 90.5%). ν (film) 1712, 1639 cm^{-1}; δ_H 1.54 (3H, s), 1.65 (3H, s), 2.07–2.15 (4H, m), 3.75 (3H, s), 3.81 (3H, s), 5.09 (1H, t, $J = 4$ Hz), 5.60 (1H, d, $J = 2.1$ Hz), 6.95 (1H, d, $J = 5.4$ Hz), 7.12 (1H, dd, $J = 5.4$, 2.1 Hz); δ_C 17.3 (q), 23.2 (t), 25.5 (q), 28.7 (t), 51.7 (q), 83.0 (d), 97.1 (s), 123.2 (d), 132.0 (s), 144.1 (d), 144.9 (d), 151.1 (s), 155.8 (s), 164.7 (s), 164.7 (s); HRMS (*m*/*z*) 292.1302 (292.1305 calcd. for $C_{16}H_{20}O_5$).

Dimethyl 3-(4-methylpent-3-enyl)phthalate (8)

The low-valent titanium reagent was prepared by sequential, dropwise addition of titanium(IV) chloride (3 mL, 0.0274 mol) and then triethylamine (0.86 mL, 0.00617 mol) in THF (5 mL) to an ice-cooled, stirred suspension of lithium aluminium hydride (0.52 g, 0.0137 mol) in dry tetrahydrofuran (30 mL), which was then heated at 65 °C for 0.5 h, recooled to room temperature and treated with a solution of **6** (2.0 g, 0.00685 mol) in tetrahydrofuran (10 mL). After 24 h at room temperature the reaction mixture was poured into water (150 mL), and extracted with dichloromethane (3 × 50 mL). The crude product was chromatographed over silica gel (eluent: 1 : 9 EtOAc–hexane) to afford the phthalate **8** (2.1 g, 99%). ν (film) 1731, 1594 cm^{-1}; δ_H 1.43 (3H, s), 1.57 (3H, s), 2.16 (2H, m), 2.51 (2H, t, $J = 9$ Hz), 3.76 (3H, s), 3.82 (3H, s), 5.03 (1H, t, $J = 4.8$ Hz), 7.25–7.28 (2H, m), 7.72 (1H, dd, $J = 6.75$, 2.1 Hz); δ_C 17.3 (q), 25.5 (q), 29.7 (t), 33.3 (t), 52.1 (q), 122.9 (d), 127.4 (d), 127.6 (s), 128.6 (d), 132.3 (s), 133.6 (d), 134.9 (s), 139.6 (s), 165.8 (s), 169.2 (s); HRMS (*m*/*z*) 276.1361 (276.1356 calcd. for $C_{16}H_{20}O_4$).



2-(Methoxycarbonyl)-3-(4-methylpent-3-enyl)benzoic acid (12)

Diester **8** (6.38 g, 0.023 mol) was heated with sodium hydroxide (1.85 g, 0.046 mol) in 80% aqueous methanol (100 mL) under reflux for 3 h. The cooled mixture was washed with ether (2 × 50 mL), acidified with 10% HCl, and extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated to give the pure half-ester **12** (5.39 g, 89%). *ν* (film) 3687–2225, 1729, 1600 cm^{-1}; δ_H 1.52 (3H, s), 1.66 (3H, s), 2.27 (2H, m), 2.62 (2H, t, J = 9.9 Hz), 3.90 (3H, s), 5.11 (1H, t, J = 6 Hz), 7.37–7.91 (3H, m); δ_C 17.5 (q), 25.7 (q), 29.8 (t), 33.4 (t), 52.5 (q), 123.0 (d), 127.5 (s), 128.4 (d), 128.9 (d), 132.7 (s), 134.6 (d), 135.4 (s), 139.9 (s), 169.5 (s), 170.8 (s); HRMS (*m/z*) 262.1202 (262.1200 calcd. for $C_{15}H_{18}O_4$).

Methyl 2-[(diethylamino)carbonyl]-6-(4-methylpent-3-enyl)-benzoate (13)

The half-ester **12** (200 mg, 0.76 mmol) was treated with thionyl chloride (0.6 mL, 7.6 mmol) and *N,N*-dimethylformamide (4 drops) at room temperature. After stirring for 0.5 h, the excess thionyl chloride was removed in a rotary evaporator. The residue was co-evaporated with some toluene, dissolved in dry tetrahydrofuran (5 mL), and treated with diethylamine (0.32 mL, 3.04 mmol). The mixture was left at room temperature for 17 h, concentrated *in vacuo*, and purified by silica gel column chromatography (eluent: 4:6 EtOAc–hexane) to furnish the ester amide **13** (210 mg, 87%). *ν* (film) 1735, 1729, 1629 cm^{-1}; δ_H 0.87 (3H, t, J = 7.2 Hz), 0.95 (3H, t, J = 7.2 Hz), 1.34 (3H, s), 1.48 (3H, s), 2.20 (2H, m), 2.72 (2H, t, J = 8.7 Hz), 3.20 (2H, q, J = 7.2 Hz), 3.48 (2H, q, J = 7.2 Hz), 3.78 (3H, s), 5.08 (1H, t, J = 7.2 Hz), 7.05–7.32 (3H, m); δ_C 12.5 (q), 13.7 (q), 17.6 (q), 25.7 (q), 30.2 (t), 34.0 (t), 38.7 (t), 43.0 (t), 52.0 (q), 123.4 (d), 123.8 (d), 129.7 (d), 130.2 (d), 130.5 (s), 132.4 (s), 137.5 (s), 142.0 (s), 168.1 (s), 170.2 (s); HRMS (*m/z*) 317.1985 (317.1984 calcd. for $C_{19}H_{27}NO_3$).

N,N-Diethyl-2-(hydroxymethyl)-3-(4-methylpent-3-enyl)benzamide (11b)

A solution of the ester amide **13** (1.57 g, 0.00495 mol) in dry tetrahydrofuran (10 mL) was dropwise added to a stirred suspension of lithium aluminium hydride (0.28 g, 0.007425 mol) in tetrahydrofuran (40 mL) at 0 °C. After 1 h, the reaction mixture was quenched with saturated Na_2SO_4 solution (5 mL), filtered, and evaporated *in vacuo*. Silica gel chromatography (eluent: 4:6 EtOAc–hexane) provided the amide alcohol **11b** (1.2 g, 84%). *ν* (film) 3500–3280, 1612 cm^{-1}; δ_H 1.07 (3H, t, J = 6.9 Hz), 1.28 (3H, t, J = 6.9 Hz), 1.51 (3H, s), 1.65 (3H, s), 2.26 (2H, m), 2.75 (2H, m), 3.20 (2H, d, J = 6.3 Hz), 3.53 (2H, dd, J = 6.3, 3.3 Hz), 4.40–4.69 (2H, m), 5.15 (1H, t, J = 6.3 Hz), 6.99–7.24 (3H, m); δ_C 12.8 (q), 14.1 (q), 17.7 (q), 25.8 (q), 30.2 (t), 33.1 (t), 39.3 (t), 43.4 (t), 59.7 (t), 123.4 (d), 123.5 (d), 127.9 (d), 130.8 (d), 132.3 (s), 136.3 (s), 137.6 (s), 142.4 (s), 171.9 (s); HRMS (*m/z*) 289.2034 (289.2035 calcd. for $C_{18}H_{27}NO_2$).

2-[(Diethylamino)carbonyl]-6-(4-methylpent-3-enyl)benzaldehyde (14)

To the reagent prepared 15 min previously from oxalyl chloride (0.6 mL, 6.8 mmol) and dimethyl sulfoxide (1.2 mL, 17.7 mmol) in dichloromethane (5 mL) at −78 °C was added a solution of the amide alcohol **11b** (840 mg, 2.91 mmol) in dry dichloromethane (5 mL), and after 30 min, triethylamine (0.4 mL, 2.62 mmol). The cooling bath was removed 10 min later to allow the reaction mixture to attain room temperature, when it was quenched with water (5 mL). Extractive workup with dichloromethane and silica gel chromatography (eluent: 4:6 EtOAc–hexane) provided the amide aldehyde **14** (600 mg, 72%). *ν* (film) 2753, 1697, 1629 cm^{-1}; δ_H 0.99 (3H, t, J = 7.2 Hz), 1.23

(3H, t, J = 7.2 Hz), 1.46 (3H, s), 1.66 (3H, s), 2.22 (2H, m), 2.93–3.06 (4H, m), 3.52 (2H, q, J = 7.2 Hz), 5.08 (1H, t, J = 6 Hz), 7.05–7.43 (3H, m); δ_C 12.4 (q), 13.7 (q), 17.5 (q), 25.6 (q), 30.4 (t), 33.0 (t), 38.8 (t), 42.7 (t), 122.7 (d), 124.6 (d), 130.4 (d), 131.3 (d), 132.9 (d), 133.0 (s), 140.5 (s), 145.4 (s), 169.7 (s), 190.5 (s); HRMS (*m*/*z*) 287.1893 (287.1879 calcd. for $C_{18}H_{25}NO_2$).

(8*SR*,8a*RS*)-8-Isopropenyl-6,7,8,8a-tetrahydro-2*H*-naphtho-[1,8-*bc*]furan-2-one (15)

A solution of the amide aldehyde **14** (200 mg, 0.7 mmol) in dry toluene (1 mL) was deoxygenated, placed in a Teflon vessel inside a resealable stainless steel bomb, and heated at 200 °C for 15 h. After removal of the solvent from the cooled reaction mixture *in vacuo*, the product was isolated by silica gel chromatography (eluent: 25 : 75 EtOAc–hexane) and provided the lactone **15** (130 mg, 65%). ν (film) 1762, 1643 cm^{-1}; δ_H 1.49 (3H, s), 2.11–2.18 (2H, m), 2.73–2.82 (1H, m), 2.90–2.97 (1H, m), 3.14–3.17 (1H, m), 4.00 (1H, s), 4.50 (1H, s), 5.41 (1H, d, J = 6 Hz), 7.28–7.38 (2H, m), 7.56 (1H, d, J = 7.5 Hz); δ_C 23.0 (t), 24.0 (q), 24.8 (t), 40.8 (d), 79.3 (d), 113.1 (t), 122.7 (d), 124.9 (s), 129.6 (d), 131.9 (d), 134.0 (s), 141.6 (s), 147.0 (s), 170.2 (s); HRMS (*m*/*z*) 214.0991 (214.0990 calcd. for $C_{14}H_{14}O_2$).

(8*SR*,8a*SR*)-8-Isopropenyl-6,7,8,8a-tetrahydro-2*H*-naphtho-[1,8-*bc*]furan-2-one {platyphyllide} (1)

A solution of the lactone **15** (130 mg, 0.6 mmol) was refluxed with sodium methoxide (from sodium, 140 mg, 6 mmol) in methanol (5 mL) for 30 min. On cooling, the mixture was treated dropwise with concentrated sulfuric acid to the point past neutralization and left to stand for another 30 min. The reaction mixture was evaporated to dryness and extracted with dichloromethane. The crude product was purified by silica gel chromatography (eluent: 25 : 75 EtOAc–hexane) to afford platyphyllide **1** (110 mg, 84%). ν (film) 1762, 1643 cm^{-1}; δ_H 1.84 (3H, s), 1.86–1.97 (1H, m), 2.10–2.24 (2H, m), 2.79–2.88 (1H, m), 3.11 (1H, dd, J = 12, 7.8 Hz), 4.95 (2H, s), 5.17 (1H, d, J = 12 Hz), 7.33–7.64 (3H, m); δ_C 20.7 (q), 26.0 (t), 26.7 (t), 46.3 (d), 80.3 (d), 112.5 (t), 122.9 (d), 124.9 (s), 129.8 (d), 132.0 (d), 133.5 (s), 144.0 (s), 148.7 (s), 170.0 (s); HRMS (*m*/*z*) 214.0988 (214.0990 calcd. for $C_{14}H_{14}O_2$).

Acknowledgements

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