Synthesis of cleviolide and the scobinolides

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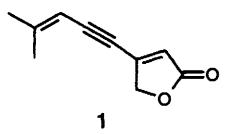
1 PERKIN

The palladium-catalysed cross-coupling reaction of 4-tributylstannylfuran-2(5*H*)-one 3 with 1-iodo-4-methylpent-3-en-1-yne 4a gives the natural product cleviolide; from this substance may be prepared both (*Z*)- and (*E*)-isomers of scobinolide.

Many natural products contain a furanone ring.[1] We recently reported that 3- and 4-tributylstannylfuran-2(5*H*)-ones act as precursors for direct attachment of furanones to aryl halides: we report here in full[2] the details of our investigations into the synthesis of the furanone-containing natural products cleviolide and (*E*)- and (*Z*)-scobinolide using 4-tributylstannylfuran-2(5*H*)-one.

In 1981, a trio of monoterpene lactones was isolated from *Senecio Clevelandii* by Bohlmann *et al.*[3] One of these compounds, cleviolide **1**, was the first example of an acetylenic



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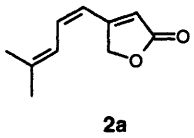
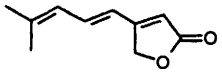


2a

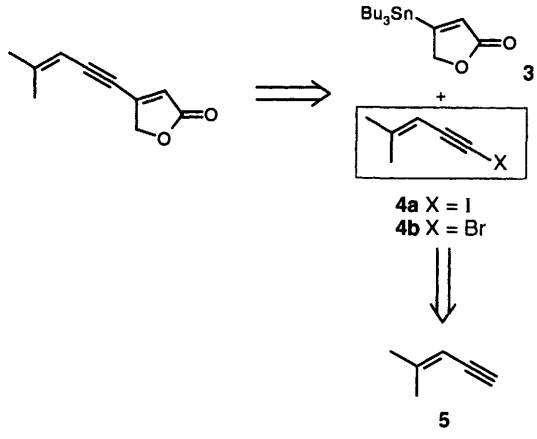


2b

monoterpene to be isolated. Also isolated were the analogous compounds **2a** and **2b** which contained an alkenic bond in place of the alkynic bond of cleviolide; Bohlmann named these compounds *cis*- and *trans*-dihydrocleviolide, but they were later renamed (*Z*)- and (*E*)-scobinolide respectively by Gadir *et al.*, who had independently isolated the compounds from *Psathyrella scobinacea*.[4] At the time we commenced our study, no existing syntheses of cleviolide were reported, although Gadir *et al.* had published details of their non-selective synthetic route to the scobinolides, which was encumbered by the need for repeated chromatographic separation of the mixture of stereoisomers produced during the synthesis. Furthermore, only (*E*)-scobinolide was fully characterized during the study.[4] We sought to employ stannylfuranone **3** to allow unambiguous preparation of both isomers of scobinolide from cleviolide, thereby allowing the first complete characterization of (*Z*)-scobinolide.

Our proposed synthetic strategy was that outlined in Scheme 1. We predicted that (*Z*)-scobinolide would be obtained by catalytic hydrogenation of cleviolide and we presumed that equilibration of the (*Z*)-alkene to the thermodynamically more stable (*E*)-isomer would be facile. The synthetic strategy therefore was simplified: if we could design and execute a synthesis of cleviolide, the scobinolides would be within our reach.

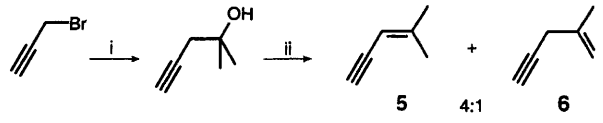
Disconnection of the furanone-acetylene linkage gives, on one side, a 1-halogeno-4-methylpent-3-en-1-yne **4**, and, on the other, furanone **3**. Given that we had an efficient synthetic route to **3**, the problem was further simplified to the stage that we



Scheme 1

considered we would be able to prepare these highly unsaturated furanone natural products if we could prepare the (previously unreported) iodide **4a** or bromide **4b**. In turn, we envisaged that **4a** and **4b** would be prepared from the corresponding terminal alkyne **5**.

The synthetic sequence commenced with reaction of prop-2-ynyl bromide with aluminium foil and $HgCl_2$, followed by acetone, which furnished 2-methylpent-4-yn-2-ol in 61% yield (Scheme 2).[5] Treatment of this alcohol with phosphorus oxychloride in pyridine effected dehydration in 69% yield.[6] Unfortunately, the desired conjugated enyne **5** was present as the major isomer in a 4:1 ratio with deconjugated isomer **6**. These compounds, as might be expected, possessed extremely similar physical properties, which similarity precluded routine separation. Furthermore, no variation in reaction conditions could change the product ratio of this reaction. We were, however, able to prepare a mixture of isomeric alkynyl iodides by deprotonation and subsequent iodination of the mixture of **5** and **6**, thereby establishing the viability of our synthetic route. However, we were never able to prepare significant quantities of pure **5** by this reaction, and an alterative was sought.



Scheme 2 *Reagents*: i, Al foil, THF, $HgCl_2$(cat), then acetone, Et_2O, 61%; ii, $POCl_3$, 69%

The Corey alkynylation reaction[7] was next examined. Thus, commercially available 3-methylbut-2-enal (senecialdehyde) was reacted with 2 equiv. of a reagent prepared from zinc, carbon tetrabromide and triphenylphosphine. This reaction

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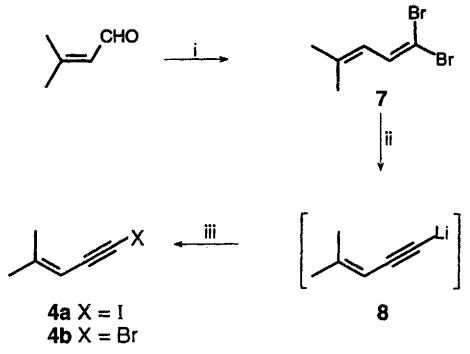
produced 1,1-dibromo-4-methylpenta-1,3-diene **7** in 97% yield, and of >95% purity after filtration through a short column of flash silica gel. Treatment of **7** with 2 equiv. of butyllithium in THF gave acetylide anion **8**; treatment of this anion with iodine gave the required iodoalkyne **4a** in 92% crude yield (Scheme 3).

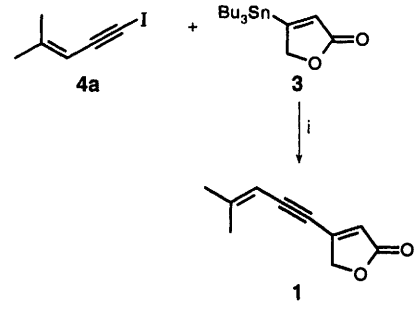


Scheme 3 *Reagents and conditions*: i, CBr_4, PPh_3, Zn, CH_2Cl_2, O °C to room temp., 97%; ii, BuLi (2 equiv.), THF, −78 °C; iii, I_2 or Br_2, −78 °C, 92% (for **4a**), 18% (for **4b**)

This slightly unstable compound was not purified, but was used crude in the subsequent reaction. Reaction of acetylide **8** with 1 equiv. of elemental bromine gave the highly unstable alkynyl bromide **4b**, in 18% yield after flash column chromatography.

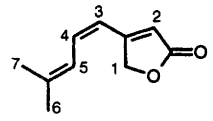
With the required subunits of cleviolide now available in good yield, we attempted to execute palladium-catalysed cross-coupling reactions of iodide **4a** with stannylfuranone **3a**. Bromide **4b** was judged too unstable to survive the predicted reaction conditions. Thus, $Cl_2(PPh_3)_2Pd$ (2 mol%) was added to a refluxing toluene solution of 1 equiv. of both iodide **4a** and furanone **3**. This reaction delivered cleviolide in 24% yield after column chromatography: the synthetic sample possessed physical data virtually identical to those previously reported for the natural product.[3] In addition, the ^{13}C NMR spectrum of our product (the same data for natural cleviolide were unreported) correlated with that predicted for cleviolide. The infrared spectral data of synthetic cleviolide reinforced our surmise that the reaction had produced the desired product, having a split peak (due to Fermi resonance) typical of a 4-substituted furan-2(5*H*)-one in the carbonyl stretching region. There was one discrepancy between our data and those reported by Bohlmann *et al.*: in the ^1H NMR spectrum of synthetic cleviolide the resonance of the acyclic alkenic proton appeared as a broad singlet at δ 5.48, not at δ 5.99 as reported.[3]

Various attempts to improve the yield of the cross-coupling reaction were made; the best yield of cleviolide obtained was 37% for the coupling using the same catalyst but performing the reaction in dry DMF at room temperature using 5% hydroquinone as a radical scavenger (to avoid polymerization of the iodoenyne) (Scheme 4). Since our previous work on the Stille-



Scheme 4 *Reagents and conditions*: i, $Cl_2(PPh_3)_2Pd$, DMF, hydroquinone, room temp., 37%

Table 1 Proton NMR data for (*Z*)-scobinolide **2a**

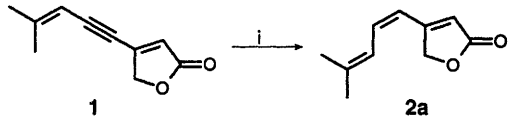


	δ_H/ppm (pattern, *J*/Hz)		
Position	Ref. 4[a]	This work[b]	Ref. 3[b]
1	4.90 (br s)	5.00 (d, *J* 1.1)	5.01 (d, *J* 1.5)
2	5.70 (s)	5.98 (br s)	5.87 (br s)
3	6.10 (d, *J* 11.5)	5.98 (d, *J* 11.9)	5.87 (br d, *J* 11.5)
4	6.70 (dd, *J* 11.5, 11.5)	6.69 (dd, *J* 11.9, 11.9)	6.58 (dd, *J* 11.5, 11.5)
5	6.15 (d, *J* 11.5)	6.09 (dd, *J* 11.9, 1.1)	5.98 (d, *J* 11.5)
6	1.90 (br s)	1.92 (s)	1.92 (s)
7	1.90 (br s)	1.88 (s)	1.87 (s)

[a] Spectrum recorded at 300 MHz in $CDCl_3$. [b] Spectrum recorded at 400 MHz in $CDCl_3$.

coupling of aryl iodides with **3** required excess iodide to allow efficient reaction, we presume that this yield represents the best we can achieve. Given that **4a** is not commercially available, the use of 2 equiv. of **4a** in the coupling reaction was not thought an efficient process.

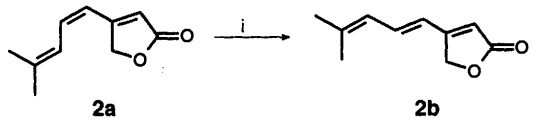
At first, partial catalytic hydrogenation of cleviolide was not successful: using a variety of Lindlar catalysts only starting material was recovered. When pyridine-poisoned palladium–barium sulfate[8] was used, cleviolide was selectively reduced to produce (*Z*)-scobinolide **2a** which was obtained analytically pure in quantitative yield after routine column chromatography (Scheme 5). Compound **2a** was stable indefinitely when stored



Scheme 5 *Reagents and conditons*: i, H_2, Pd–$BaSO_4$, pyridine (cat), toluene, room temp., 100%

at −20 °C, but gradually turned brown upon standing at room temperature for one day. The spectral data exhibited by the compound are shown in Table 1. Our compound's data showed overall agreement with those for the isolated material reported by Bohlmann:[3] we observed identical chemical shifts for three of the seven resonances and the remaining four all differed from Bohlmann's by the same chemical shift difference ($\Delta\delta$ 0.11 ppm). The ^1H NMR spectral data exhibited by our compound showed less agreement (Table 1) with the only other ^1H NMR data for **2a**, those reported by Gadir *et al.* who accomplished the only other synthesis of (*Z*)-scobinolide to date.[4]

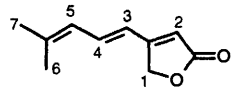
The synthesis of (*E*)-scobinolide was from its (*Z*)-configured counterpart, by treatment of the latter with a sub-stoichiometric (*ca.* 0.5 mol%) amount of iodine in dichloromethane[9] at room temperature, under which conditions isomerization occurred in quantitative yield (Scheme 6).



Scheme 6 *Reagents and conditons*: i, I_2 (0.5 mol%), CH_2Cl_2, room temp., 100%

Direct comparison of spectral data for (*E*)-scobinolide with Bohlmann's data for the isolated compound was not possible

Table 2 Proton NMR data for (*E*)-scobinolide **2b**



Position	δ_H/ppm (pattern, *J*/Hz) Ref. 4[a]	This work[b]
1	5.02 (br s)	5.01 (br s)
2	5.87 (s)	5.86 (br s)
3	6.36 (d, *J* 15.5)	6.36 (d, *J* 15.6)
4	6.75 (dd, *J*, 11.0, 15.5)	6.75 (dd, *J* 11.0, 15.6)
5	5.99 (d, *J* 11)	5.99 (br d, *J* 11.0)
6	1.88 (s)	1.85 (s)
7	1.90 (s)	1.88 (s)

[a] Spectrum recorded at 300 MHz in $CDCl_3$. [b] Spectrum recorded at 400 MHz in $CDCl_3$.

since the ^1H NMR spectral data for the isolated material were recorded in a mixed solvent. However, all the data exhibited by our compound agreed with the proposed structure and showed agreement with the data previously reported for (*E*)-scobinolide (Table 2).[4]

Conclusion

The palladium-catalysed cross-coupling reaction of stannylfuranone **3a** with 1-iodo-4-methylpent-3-en-1-yne **4a** has allowed the first synthesis of cleviolide and also allowed unambiguous preparation and characterization of (*Z*)- and (*E*)-scobinolide.

Experimental

General

All organic solvents were distilled prior to use and all reagents were purified by standard procedures. Light petroleum refers to the fraction with the boiling range 40–60 °C. Diethyl ether, THF and DME were distilled from sodium benzophenone ketyl, toluene from sodium, dichloromethane, triethylamine, diisopropylamine and acetonitrile from calcium hydride and pyridine and diisopropylethylamine from potassium hydroxide.

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer. Mass spectra were recorded on a VG9090 mass spectrometer or on a Fisons Autospec machine. ^1H and ^{13}C NMR spectra were recorded on JEOL GX-270 and EX-400 spectrometers. Unless otherwise stated, deuteriochloroform was used as solvent and tetramethylsilane was used as the internal standard. Chemical shifts (δ) in ^1H NMR spectra are expressed as ppm downfield from tetramethylsilane, and in ^{13}C NMR relative to the internal solvent standard. Coupling constants (*J*) are quoted in Hz.

Reactions involving chemicals or intermediates sensitive to air and/or moisture were performed under a nitrogen atmosphere in flame- or oven-dried apparatus. Flash column chromatography was performed using Merck kieselgel 60 or Fluka kieselgel 60 silica. Analytical thin layer chromatography (TLC) was performed on pre-coated Merck kieselgel 60 F_{254} aluminium-backed plates and were visualized under UV conditions at 254 nm, and by staining with an acidic ammonium molybdate spray.

4-Methylpent-3-en-1-yne 5 and 4-methylpent-4-en-1-yne 6[5]

A solution of phosphoryl chloride (6.31 ml, 67 mmol) in pyridine (10 ml) was added dropwise to a solution of 2-methylpent-4-yn-2-ol (8.83 g, 90.2 mmol) in pyridine (15 ml) under nitrogen: the addition was performed in such a manner that the reaction mixture temperature was maintained at less then 20 °C with water bath cooling (25 min required for complete addition). After stirring for a further 30 min much white solid had precipitated. Fractional distillation of the reaction mixture through a Vigreux column afforded a clear colourless liquid, bp 74–79 °C (760 mmHg) (4.96 g, 69%), shown to be a 4:1 mixture of *alkynes* **5** and **6**. Compound **5**: $\delta_H(CDCl_3)$ 5.25 (1 H, br s, vinylic), 2.95 (1 H, br s, ≡CH), 1.90 (3 H, s, Me), 1.80 (3 H, s Me); compound **6**: $\delta_H(CDCl_3)$ 5.0 (1 H, br s, vinylic), 4.80 (1 H, br s, vinylic), 2.90 (2 H, br s, CH_2), 2.10 (1 H, br s, ≡CH), 1.80 (3 H, s, Me); ν_{max}(neat)/cm^{-1} 3080, 3028, 2978, 2913, 2101 (C≡C), 1629 (C=C), 1437; $\delta_C(CDCl_3)$ 150.5, 135.8, 123.6, 111.8, 104.2, 81.7, 79.0, 70.4, 27.1, 24.6, 21.9, 20.8; *m/z* 80 (M^+, 60%), 79 (53), 77 (27), 59 (100), 43 (54), 39 (38).

1,1-Dibromo-4-methylpenta-1,3-diene 7

Carbon tetrabromide (7.91 g, 23.85 mmol), triphenylphosphine (6.26 g, 23.85 mmol) zinc dust (1.56 g, 23.85 mmol) were placed in a dry 250 ml round-bottomed flask under a nitrogen atmosphere. The flask was cooled to 0 °C and dichloromethane (100 ml) was added to the mixture of solids, giving a green suspension. The reaction mixture was allowed to warm to room temperature and was then stirred for 24 h, after which time it was pink in colour. 3-Methylbut-2-enal (1.00 g, 11.93 mmol) was then added *via* syringe and the mixture stirred for a further 2 h. The now purple suspension was transferred to a large conical flask, pentane (400 ml) added and the resultant solution was filtered. The residue was dissolved in dichloromethane (50 ml) and then further pentane (200 ml) added. This was also filtered and the combined filtrates were concentrated to a colourless oil. This was triturated with pentane (10 ml) and passed through a short silica column to remove triphenylphosphine oxide. After removal of solvent *in vacuo*, *diene* **7** was obtained as a colourless oil (2.75 g. 97%); ν_{max}(neat)/cm^{-1} 3036, 2971, 2909, 2854, 1638 (C=C), 1569 (C=C), 1437, 1262, 859, 773; $\delta_H(CDCl_3)$ 7.08 (1 H, d, *J* 10.5, Br_2CCH), 5.84 (H, br d, *J* 10.5, Me_2CCH), 1.79 (3 H, br s, Me), 1.74 (3 H, br s, Me); $\delta_C(CDCl_3)$ 140.8, 133.6, 122.2, 88.5, 26.3, 19.3 (HRMS: found M^+, 237.9008. $C_6H_8Br_2$ requires *M*, 237.8992); *m/z* 240 (57.5%), 242, 80, 79, 77, 39.

1-Iodo-4-methylpent-3-en-1-yne 4a

A solution of 1,1-dibromo-4-methylpenta-1,3-diene (352 mg, 1.47 mmol) in tetrahydrofuran (5 ml) under a nitrogen atmosphere was cooled to −78 °C and butyllithium (2.5 M; **1.17 ml,** 2.94 mmol) was added dropwise. The clear ochre solution was stirred at −78 °C for 75 min and then a solution of iodine (390 mg, 1.54 mmol) in tetrahydrofuran (2.5 ml) was added dropwise. Rapid decolorization was observed. After warming to room temperature the mixture was partitioned between water (10 ml) and Et_2O (10 ml). The organic phase was washed with water (10 ml) and saturated aqueous Na_2SO_3 (10 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give *iodoalkyne* **4a** as an orange oil (278 mg, 92%); ν_{max}(neat)/cm^{-1} 2972, 2931, 2909, 2851, 2155 (C≡C), 1758, 1625 (C=C), 1444, 1378, 1107; $\delta_H(CDCl_3)$ 5.36 (1 H, br s, CH), 1.91 (3 H, br s, Me), 1.80 (3 H, br s, Me); $\delta_C(CDCl_3)$ 151.6, 105.6, 92.5, 24.5, 21.0, 5.3 (HRMS: found M^+, 205.9612. C_6H_7I requires *M*, 205.9595; *m/z* 206 (100%), 164, 83, 77, 43.

1-Bromo-4-methylpent-3-en-1-yne 4b

A solution of 1,1-dibromo-4-methylpenta-1,3-diene (692 mg, 2.88 mmol) in tetrahydrofuran (15 ml) under nitrogen was cooled to −78 °C and butyllithium (2.5 M; **2.31 ml, 5.77 mmol)** was added dropwise. The clear ochre solution which resulted was stirred at −78 °C for 75 min and then a solution of bromine (0.15 ml, 2.88 mmol) in THF (5 ml) was added dropwise. The solution was stirred (5 min) and allowed to warm gradually to room temperature, by which time it was pale orange in colour. The reaction mixture was partitioned between diethyl ether (15 ml) and water (15 ml) and the aqueous layer extracted with

diethyl ether (20 ml). The combined organic phases were washed with 5% aqueous sodium sulfite (20 ml), water (20 ml) and brine (20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil (474 mg). Column chromatography (pentane) afforded *bromoalkyne* **4b** as a colourless oil (84 mg, 18%); $\delta_H(CDCl_3)$ 5.25 (1 H, br s, vinylic), 1.95 (3 H, s, Me), 1.85 (3 H, s, Me); $\delta_C(CDCl_3)$ 150.8, 104.7, 78.3, 49.9, 24.7, 21.0.

Cleviolide [4-(4′-methylpent-3′-en-1′-yn-1′-yl)furan-2(5*H*)-one] 1[3]

Dichlorobis(triphenylphosphine) palladium(II) (*ca.* 7 mg, 2 mol%) was added to a solution of 4-(trimethylstannyl)furan-2(5*H*)-one **3**[10] (160 mg, 0.429 mmol) and 1-iodo-4-methylpent-3-en-1-yne (117 mg, 0.568 mmol) in DMF (5 ml) containing hydroquinone (2 mg, 5 mol%) under nitrogen. The yellow solution was stirred at room temperature for 70 min by which time it had gone black in colour and TLC showed complete consumption of the stannane. After removal of the DMF *in vacuo*, the residue was dissolved in Et_2O (5 ml) and stirred with aqueous potassium fluoride (8 M; **5 ml) for 4 h. The layers were separated** and the organic phase washed with water (5 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Column chromatography (Et_2O–light petroleum, 1:1; R_f 0.46) furnished pure *cleviolide* as colourless crystals, recrystallized from light petroleum (25.5 mg, 37%), mp 63.5 °C (lit.,[3] 64 °C); $\nu_{max}(CCl_4)/cm^{-1}$ 2977, 2938, 2190 (C≡C), 1782 (C=O), 1746 (C=O), 1596 (C=C), 1141, 1045; $\delta_H(CDCl_3)$ 6.09 (1 H, t, *J* 1.90, 3-H), 5.48 (1 H, br s, 3′-H), 4.80 (2 H, d *J* 1.90, 5-H), 1.95 (3 H, s, Me), 1.90 (3 H, s, Me); $\delta_C(CDCl_3)$ 173.6 (C), 155.2 (C), 147.8 (C), 120.5 (CH), 104.1 (CH), 104.0 (C), 81.7 (C), 73.0 (CH_2), 25.3 (CH_3), 21.6 (CH_3) (HRMS: found M^+, 162.0688. $C_{10}H_{10}O_2$ requires *M*, 162.0681; *m/z* 162 (M^+, 100%), 133 (10), 104 (52), 103 (14), 84 (18).

(*Z*)-Scobinolide [(2′*Z*)-4-(4′-methylpenta-1′,3′-dien-1′-yl)furan-2(5*H*)-one][3] 2a

Cleviolide (28 mg, 0.173 mmol), as a solution in toluene (3 ml), was added to a suspension of palladium(0) on barium sulfate (2 mg) in toluene (1 ml), poisoned by the addition of pyridine (2 drops) followed by stirring (5 mins). The mixture was vigorously stirred under a hydrogen atmosphere and the uptake of gas monitored. After 1 h, uptake had ceased and the reaction mixture was filtered and the solvent removed *in vacuo*. The pure product was obtained by column chromatography (light petroleum–diethyl ether, 1:1, R_f 0.29) to give pure (Z)-*Scobinolide* as colourless crystals from light petroleum (28.3 mg, 100%), mp 70 °C (Found: C, 73.57; H, 7.06%. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37%); $\nu_{max}(CCl_4)/cm^{-1}$ 2964, 2932, 1782 (C=O), 1756 (C=O), 1611 (C=C), 1149; $\delta_H(CDCl_3)$ 6.69 (1 H, dd, *J* 11.9, 11.9, 2′-H), 6.09 (1 H, dd, *J* 11.9, 1.1, 3′-H), 5.98 (1 H, d, *J* 11.9, 1′-H), 5.98 (1 H, br s, 3-H), 5.00 (2 H, d, *J* 1.1, 5-H), 1.92 (3 H, s, Me), 1.88 (3 H, s, Me); $\delta_C(CDCl_3)$ 174.1, 162.0, 146.2, 134.7, 121.5, 115.8, 115.5, 72.7, 27.0, 18.5 (HRMS: found M^+, 164.0830. $C_{10}H_{12}O_2$ requires *M*, 164.0837); *m/z* 164 (M^+, 100%), 121 (27), 105 (91), 91 (64), 78 (31), 28 (39).

(*E*)-Scobinolide [(2*E*)-4-(4′-methylpenta-1′,3′-dien-1-yl)furan-2(5*H*)-one][3] 2b

Iodine (0.5 mol%) was added to a solution of (*Z*)-scobinolide (18 mg, 0.11 mmol) in CH_2Cl_2 (1 ml). After 3 days at room temperature complete isomerization of the double bond had occurred; the solution was filtered through Celite and concentrated *in vacuo*. The pure product was obtained by column chromatography (light petroleum–diethyl ether, 1:1, R_f 0.27) to give (E)-*scobinolide* as colourless crystals from light petroleum (18 mg, 100%), mp 137–139 °C (lit.,[4] 114–115 °C); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1782 (C=O), 1749 (C=O), 1621 (C=C), 1152, 1037; $\delta_H(CDCl_3)$ 6.75 (1 H, dd, *J* 11.0, 15.6, 2′-H), 6.36 (1 H, d, *J* 15.6, 3-′H), 5.99 (1 H, br d, *J* 11.0, 1′-H), 5.86 (1 H, br s, 3-H), 5.01 (2 H, br s, 5-H), 1.88 (3 H, s, Me), 1.85 (3 H, s, Me); $\delta_C(CDCl_3)$ 174.3, 162.7, 144.8, 133.8, 124.6, 119.5, 113.6, 70.5, 26.6, 19.0 (HRMS: found M^+, 164.0845. $C_{10}H_{12}O_2$ requires *M*, 164.0837); *m/z* 164 (M^+, 75%), 105 (85), 91 (78), 59 (74), 43 (100).

Acknowledgements

We acknowledge the financial support of the EPSRC and Nuffield Foundation.

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Paper 6/03897B
Received 4*th June* 1996
Accepted 21*st August* 1996