Efficient Synthesis of the Spiroacetal Core of Paecilospirone via Oxidative Radical Cyclisation

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Abstract: The spiroacetal core of the microtubule assembly inhibitor paecilospirone has been prepared using two separate oxidative cyclisation methods.

Key words: paecilospirone, microtubule, spiroacetal, oxidative radical cyclisation, DDQ

Paecilospirone (**1**) is a novel bisbenzannulated spiroacetal isolated from *Paecilomyces sp.* collected at Yap island, Micronesia that has been shown to inhibit microtubule assembly (Figure 1).[1,2] To date, no other natural products have been described that contain the spiro[chroman-2,1′(3′*H*)-isobenzofuran] core and no total syntheses of **1** have been reported. The novel chemical scaffold embedded in **1** provides the opportunity for development of a flexible synthetic route to the natural product and analogues thereof in order to probe their promising biological activity. Paecilospirone is structurally related to the rubromycin family of natural products that exhibit antimicrobial and anticancer properties.[3]

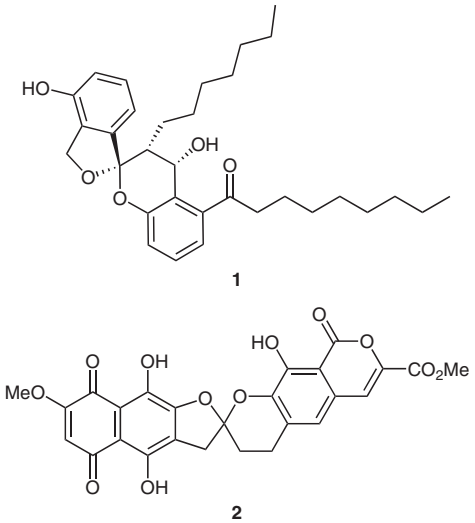
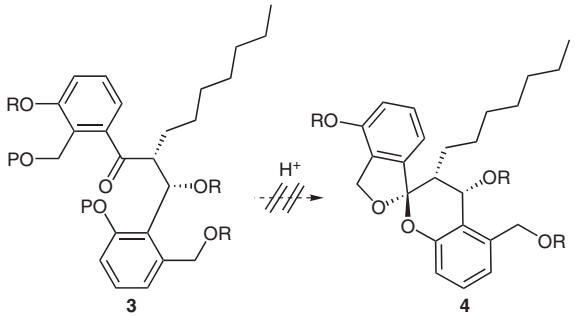


Figure 1 Paecilospirone (**1**) and γ-rubromycin (**2**)

Spiroacetals are commonly synthesised by acid-catalysed cyclisation of a dihydroxyketone precursor, forming the thermodynamic products favoured by maximum anomeric stabilisation and minimum steric interactions.[4] Despite the prevalence of this method, it is not always practical for the synthesis of acid-sensitive substrates and some spiroacetals exist in the nonanomeric form.[5] This research group has focused on the total synthesis of paecilospirone via acid-induced deprotection–cyclisation of a diprotected dihydroxyketone of type **3**; however, undesired elimination of the sensitive β-hydroxy group (protected or unprotected) during the spirocyclisation event has significantly hampered this route to date. Indeed, no advanced spiroacetal intermediates (e.g., **4**) have been successfully prepared using this classical approach (Scheme 1).[6]



Scheme 1 Problematic acid-catalysed formation of the spiroacetal core of paecilospirone[6]

Synthetic studies towards the paecilospirone spiroacetal ring system are scarce and the only report to date by Pettus and co-workers involves an elegant inverse electron-demand [4+2] cycloaddition of a 1,3-dihydroisobenzofuran enol ether with an *ortho*-quinone methide.[7] Herein we report our own efforts towards the synthesis of the bisbenzannulated spiroacetal core of **1** that provides a viable alternative to the troublesome acid-catalysed cyclisation encountered in our laboratory.

Our research group has a long-standing interest in the synthesis of spiroacetals using the oxidative radical cyclisation of cyclic ethers containing a hydroxyalkyl side chain.[8] Thus, we were interested in extending this methodology toward the synthesis of the spiroacetal framework of **1**, mindful of the fact that participation of benzylic alcohols in this type of reaction had not been explored previously.

Our key retrosynthetic disconnection of the paecilospirone core **5** makes use of an oxidative radical cyclisation of benzylic alcohol **6** to form the C8–O bond of the isobenzofuran moiety. Benzylic alcohol **6** should be ac-

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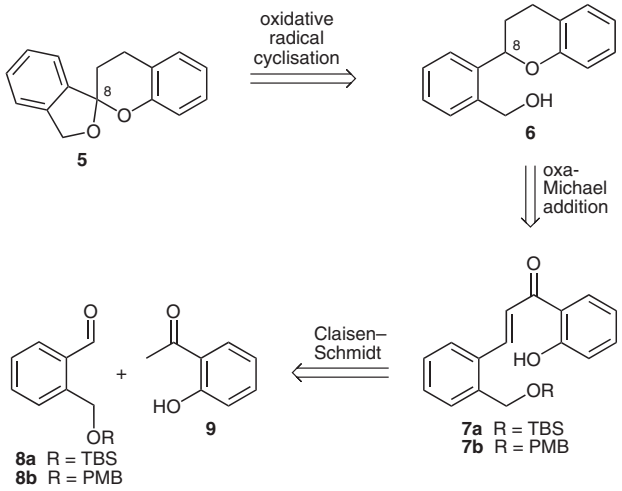
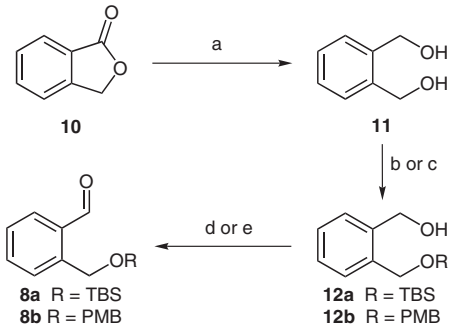
cessible from the corresponding chalcone **7a** or **7b**, prepared by Claisen–Schmidt condensation of an appropriately protected aldehyde **8a** or **8b** with commercially available 2′-hydroxyacetophenone **9**, respectively (Scheme 2).



Scheme 2 Retrosynthetic analysis of paecilospirone spiroacetal core **5**

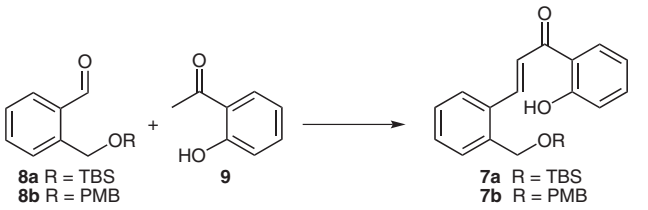
Thus, the synthesis of the benzaldehyde coupling partners **8a** and **8b** was initiated. Simple reduction of phthalide **10** with lithium aluminium hydride gave diol **11** which underwent smooth monoprotection with TBSCl or PMBCl, affording the desired alcohols **12a** and **12b**, respectively. PCC oxidation of **12a** and **12b** gave **8a** and **8b**, respectively, with Swern oxidation of **12b** affording aldehyde **8b** in higher yield than the PCC protocol (Scheme 3).



Scheme 3 Preparation of aldehydes **8a** and **8b**. *Reagents and conditions*: (a) $LiAlH_4$, Et_2O–THF, r.t., 97%; (b) NaH, TBSCl, THF, 84% (**12a**); (c) NaH, PMBCl, DMF, cat. NaI, 80% (**12b**); (d) PCC, CH_2Cl_2, 70% (**8a**) or 70% (**8b**); (e) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N, 97% (**8b**).

With aldehydes **8a** and **8b** in hand, the Claisen–Schmidt condensation[9,10] to form chalcone **7a** or **7b** was investigated. Although numerous examples detailing the condensation between benzaldehydes and acetophenones exist in the literature,[11–13] this transformation proved troublesome to achieve in practice. Initial attempts resulted in complex product mixtures only containing approximately 3–10% of the desired chalcone **7a** or **7b** (Table 1, entries 1–8).

Table 1 Claisen–Schmidt Condensation



Entry	Substrate	Solvent	Base (equiv)	Conditions	Yield (%)
1	**8a**	PhMe	piperidine (0.2)	110 °C, 24 h	–[a]
2	**8a**	PhMe	piperidine (2)	110 °C, 40 h	–[a]
3	**8a**	EtOH	piperidine (2)	80 °C, 40 h	–[a]
4	**8a**	EtOH	KOH (5)	r.t., 5 h	–[a]
5	**8a**	EtOH	KOH (5)	80 °C, 40 h	–[a]
6	**8b**	PhMe	piperidine (2)	110 °C, 40 h	–[a]
7	**8b**	EtOH	piperidine (2)	80 °C, 30 h	–[a]
8	**8b**	THF	NaH (3)	r.t. to 50 °C, 2 h	–[a]
9	**8b**	THF	NaH (3)	r.t., 2 h	69
10	**8b**	THF	NaH (3)	r.t., 16 h	80

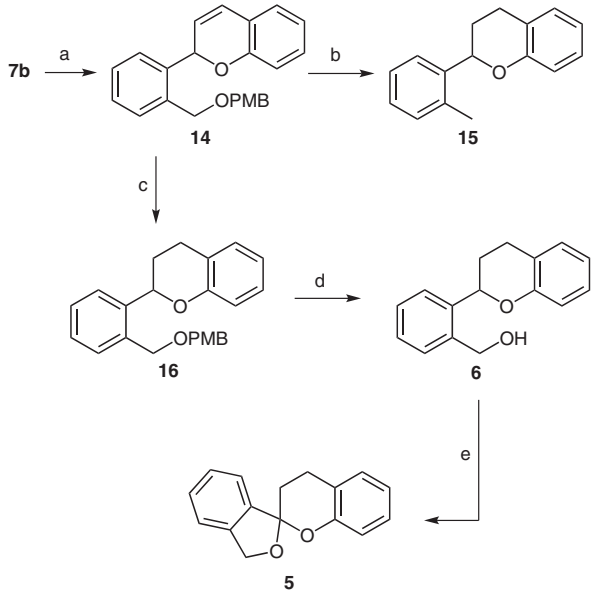
[a] Inseparable complex mixture containing 3–10% **7a** or **7b**.

These initial results suggested that the desired chalcones **7a**,**b** decomposed at elevated temperatures and conducting the condensation under ambient conditions would provide more positive results. Thus, exposure of 2′-hydroxyacetophenone **9** and aldehyde **8b** to sodium hydride in THF at room temperature for two hours afforded **7b** in good yield (entry 9). The yield of **7b** was increased to a pleasing 80% by employing an extended reaction time (entry 10).

Next, the intramolecular conjugate addition of chalcone **7b** was investigated (Scheme 4). Somewhat disappointingly, the cyclisation of chalcone **7b** to the desired chromene **14** via ketone reduction and intramolecular oxa-Michael addition using sodium borohydride initially halted at the intermediate allylic alcohol. Thus, the cyclisation was driven to completion by adjustment of the reaction mixture pH by addition of dilute acetic acid at this intermediate stage, gratifyingly affording chromene **14** in excellent yield.

Initial attempts to reduce the double bond in **14** by hydrogenation over 10% palladium on carbon in ethyl acetate somewhat surprisingly afforded *o*-tolylchroman **15** as the sole product, presumably via reductive cleavage of the PMB group at the proximal benzylic methylene. In contrast, palladium on carbon deactivated with ethylenediamine, Pd/C(en),[14] cleanly effected the desired reduction to chroman **16**, that then underwent uneventful deprotection with DDQ to give the key oxidative radical cyclisation substrate **6**. Gratifyingly, irradiating a cyclohexane

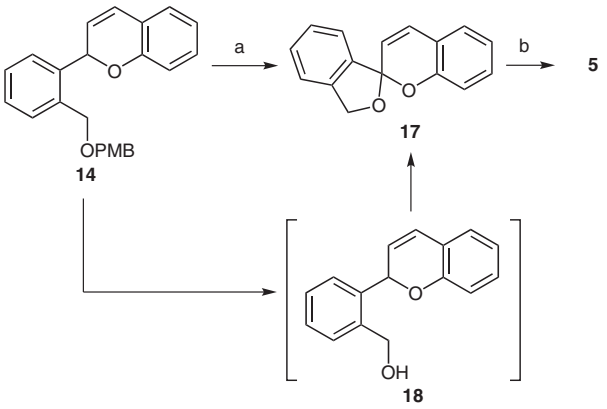
solution of **6** with iodobenzene diacetate and iodine at room temperature furnished spiroacetal **5** in 61% yield (Scheme 4).[15] To the best of our knowledge, this is the first reported example of spiroacetal ring-system formation achieved by the oxidative radical cyclisation of a benzylic alcohol.



Scheme 4 Synthesis of spiroacetal **5** via oxidative radical cyclisation. *Reagents and conditions*: (a) $NaBH_4$, THF–EtOH, 60 °C, 10 min, then 50% AcOH, 16 h, 88%; (b) 10% Pd/C, H_2, EtOAc, 22%; (c) 10% Pd/C(en), H_2, EtOAc, 78%; (d) DDQ, CH_2Cl_2–H_2O, 95%; (e) *hν*, $PhI(OAc)_2$, I_2, cyclohexane, r.t., 2 h, 61%.

A complementary route to spiroacetal **5** from chromene **14** was also investigated (Scheme 5). Interestingly, in the presence of an excess of DDQ (3 equiv) the expected alcohol **18** was not observed. Instead, spiroacetal **17** was directly formed as the only product.[16] It appears that additional resonance stabilisation of the benzylic position due to the double bond is sufficient to favour further oxidation and spiroacetal formation, possibly through the intermediacy of alcohol **18**. This appears to be the first incidence of oxidative cyclisation to form a spiroacetal ring system mediated by DDQ and is a useful addition to existing methods for spiroacetal synthesis. Furthermore, the double bond in **17** serves as a useful synthetic handle when considering a total synthesis of **1**. Finally, spiroacetal **17** was smoothly hydrogenated over the deactivated catalyst Pd/C(en) in two hours at room temperature, affording spiroacetal **5** in 88% yield.

In summary, the oxidative radical cyclisation approach to spiroacetal synthesis has been extended to the use of benzylic alcohol substrates, further increasing the scope of this methodology. It is therefore envisaged that oxidative radical cyclisation will be applicable to future synthetic studies towards the total synthesis of paecilospirone and analogues thereof. The concomitant DDQ-mediated PMB deprotection and cyclisation of **14** to spiroacetal **17** is also notable, presenting an interesting alternative to existing



Scheme 5 Concomitant PMB deprotection–spiroacetal formation using DDQ. *Reagents and conditions*: (a) DDQ, CH_2Cl_2–H_2O, 1.5 h, 95%; (b) 10% Pd/C(en), H_2, EtOAc, 88%.

methods for spiroacetal formation. As the reaction conditions for DDQ deprotection are suitably mild for late-stage transformations, this method has potential to be applied to late-stage spiroacetal formation in complex synthetic targets. The application of this new spiroacetalisation methodology toward the total synthesis of **1** is ongoing and will be reported in due course.

Acknowledgment

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(15) **Spiroacetal 5**

Iodine (67 mg, 0.26 mmol) and iodobenzene diacetate (84 mg, 0.26 mmol) were added to a solution of benzyl alcohol **6** (30 mg, 0.13 mmol) in cyclohexane (5 mL), and the reaction mixture was irradiated with a 60 W desk lamp. After stirring for 1 h at r.t., the reaction mixture was diluted with hexane–EtOAc (1:1, 20 mL total) and shaken with sat. aq $Na_2S_2O_3$ (4 mL) until colourless. The mixture was washed with brine, extracted with EtOAc, and the aqueous layer was further extracted with EtOAc. The combined organic phases were then dried over anhyd $MgSO_4$ and the solvent removed in vacuo. Purification via flash column chromatography using hexane–EtOAc (9:1) as eluent afforded the title compound **5** (18 mg, 0.076 mmol, 61%) as a pale yellow oil. R_f = 0.40 (2:1, hexane–EtOAc). IR: 2923, 2868, 1656, 1582, 1487, 1456, 1373, 1232, 1110, 1004, 904, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.21 (1 H, ddd, *J* = 13.2, 5.6, 2.0 Hz, CH_2, $PhCH_2CH_2$), 2.45 (1 H, td, *J* = 13.2, 5.6 Hz, CH_2, $PhCH_2CH_2$), 2.88 (1 H, ddd, *J* = 16.0, 5.6, 2.0 Hz, CH_2, $PhCH_2CH_2$), 3.29 (1 H, ddd, *J* = 16.0, 13.6, 6.0 Hz, CH_2, $PhCH_2CH_2$), 5.05 (1 H, d, *J* = 12.4 Hz, CH_2, $PhCH_2O$), 5.30 (1 H, d, *J* = 12.4, CH_2, $PhCH_2O$), 6.79 (1 H, dd, *J* = 8.0, 1.2 Hz, Ar, PhH), 6.90 (1 H, td, *J* = 3.6, 0.8 Hz, Ar, PhH), 7.10 (1 H, t, *J* = 7.6 Hz, Ar, PhH), 7.15 (1 H, d, *J* = 7.6 Hz, Ar, PhH), 7.33 (1 H, dt, *J* = 7.2, 0.8 Hz, Ar, PhH), 7.38–7.44 (3 H, m, Ar, PhH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (CH_2, $PhCH_2CH_2$), 30.2 (CH_2, $PhCH_2CH_2$), 71.7 (CH_2, $PhCH_2O$), 108.2 (q, spiroacetal), 117.1 (CH, Ar), 120.8 (CH, Ar), 121.3 (CH, Ar), 121.7 (q, Ar), 122.0 (CH, Ar), 127.4 (CH, Ar), 127.9 (CH, Ar), 129.1 (CH, Ar), 129.4 (CH, Ar), 140.0 (2 × q, 2 × Ar), 153.2 (q, Ar). MS (ESI^+): *m/z* (%) = 239(100) [MH^+]. HRMS: *m/z* calcd for $C_{16}H_{15}O_2$ [M + H]$^+$: 239.1072; found: 239.1075.

(16) **Spiroacetal 17**

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (67 mg, 0.30 mmol) was added to a solution of compound **14** (70 mg, 0.20 mmol) in CH_2Cl_2–H_2O (9:1, 3.3 mL total). The dark green reaction was stirred for 90 min at r.t. and then filtered through cotton wool. The reaction mixture was washed with brine, extracted with EtOAc, and the aqueous layer was further extracted with EtOAc. The combined organic phases were then dried over anhyd $MgSO_4$ and the solvent removed in vacuo. Purification by flash column chromatography using hexane–EtOAc (9:1) afforded the title compound **17** (45 mg, 0.19 mmol, 95%) as a yellow oil. R_f = 0.59 (2:1, hexane–EtOAc). IR: 2854, 1611, 1512, 1486, 1456, 1246, 1033, 820, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.05 (1 H, d, *J* = 12.4 Hz, CH_2, $PhCH_2O$), 5.33 (1 H, d, *J* = 12.4 Hz, CH_2, $PhCH_2O$), 5.87 (1 H, d, *J* = 9.6 Hz, PhCH=C*H*), 6.90 (2 H, t, *J* = 10.0 Hz, PhC*H*=CH, PhH), 6.98 (1 H, t, *J* = 7.6 Hz, Ar, PhH), 7.20–7.22 (2 H, m, Ar, PhH), 7.34 (1 H, dt, *J* = 7.6, 0.8 Hz, Ar, PhH), 7.39–7.40 (2 H, m, Ar, PhH), 7.42–7.46 (1 H, m, Ar, PhH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 71.8 (CH_2, $PhCH_2O$), 107.7 (q, spiroacetal), 116.6 (CH, Ph*C*H=CH), 119.7 (q, Ar), 121.1 (CH, PhCH=*C*H), 121.2 (CH, Ar), 121.5 (CH, Ar), 123.2 (CH, Ar), 126.9 (CH, Ar), 127.0 (CH, Ar), 128.1 (CH, Ar), 129.6 (CH, Ar), 129.6 (CH, Ar), 139.7 (q, Ar), 140.2 (q, Ar), 151.5 (q, Ar). MS (ESI^+): *m/z* (%) = 237(100) [MH^+]. HRMS: *m/z* calcd for $C_{16}H_{13}O_2$ [M + H]$^+$: 237.0910; found: 237.0915.