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Expedient synthesis of ialibinones A and B by manganese(III)-mediated oxidative free radical cyclisation

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ABSTRACT

The tricyclic natural products ialibinone A and ialibinone B were prepared as a 41:59 mixture in four steps starting from phloroglucinol. The synthetic sequence involved (i) acylation of phloroglucinol under Friedel–Crafts conditions, (ii) double prenylation using phase-transfer methodology, (iii) dearomatising methylation, and (iv) oxidative free radical cyclisation using manganese(III) acetate.

Recent years have witnessed sustained interest in the synthesis of members of the polyprenylated polycyclic acylphloroglucinol (PPAP) family of natural products.[1] This reflects both the synthetic challenge presented by the complex functionalised frameworks of these structures and the diverse biological properties that they possess.

Like several other groups, we have focused our attention on key representatives of this family possessing a core bicyclo[3.3.1]nonane structure, for example, clusianone (**1**), nemorosone (**2**) and garsubellin A (**3**), Figure 1.[2]

Total syntheses of **1**–**3** have employed diverse strategies for assembling the core structure, including malonyl dichloride enol ether annulation,[2,3] iodonium-induced cyclisation,[4] ring-closing metathesis[5] and dearomatising Michael addition.[6] Most recently, Shibasaki and co-workers described the synthesis of hyperforin using an aldol reaction to close the bicyclic core structure.[7]

These syntheses tend to involve many steps, and efforts to develop shorter biomimetic routes have also been described, most notably employing cationic cyclisations or by manganese(III)-mediated oxidative cyclisation.[8,9] This last approach appeared to us to be applicable to the synthesis of more unusual types of PPAP having a bicyclo[3.2.1]octane core, for example, enaimeone A (**4**), aissatone (**5**), epimeric takaneones A and B (**6**) and ialibinones A and B (**7**), Figure 2.[10–12]

In these cases, the key cyclisation step for assembling the core structure is required to proceed with complimentary regiochemist-

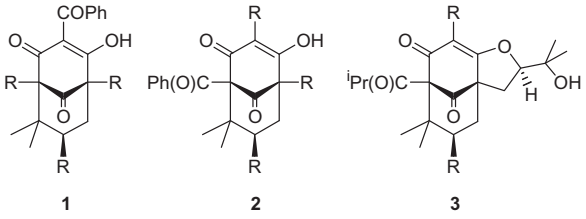

Figure 1. Bicyclo[3.3.1]nonane PPAP structures (R = prenyl).

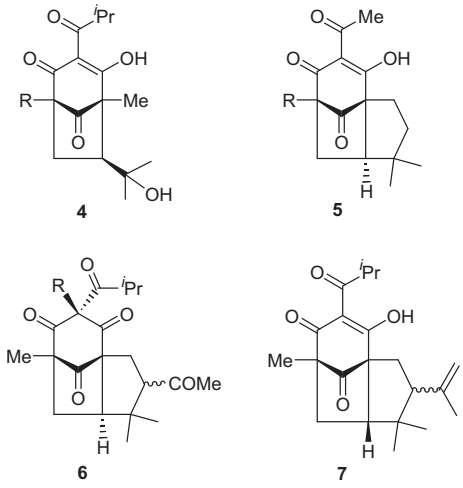

Figure 2. Bicyclo[3.2.1]octane PPAP structures (R = prenyl).

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ry, compared to the established methods for the [3.3.1] systems such as **1**–**3**. Here we describe a particularly rapid access to ialibinones A and B (**7**), using an oxidative cyclisation approach, which mimics the likely biosynthesis of these compounds.

The epimeric ialibinones A and B (**7**) were isolated, along with three other closely related substances, from the leaves of *Hypericum papuanum*, by Sticher and co-workers in 2000.[11] They feature an interesting tricyclic core which is very closely related to that in the takaneones A–C.[10c,13] They exhibit antibacterial activity against *Bacillus cerus*, *Staphylococcus epidermidis* and *Micrococcus luteus*, and are also cytotoxic against KB cell lines.[10a,11]

Owing to these intriguing properties, and their structural similarity to several of our previous PPAP targets, we elected to investigate a short total synthesis of ialibinones A and B (**7**). Our proposed synthesis is outlined in retrosynthetic form in Scheme 1.

Key to this approach is the aforementioned manganese(III)-mediated cyclisation, which we required to effect an oxidative free radical cascade, initiating at C-1 in intermediate **8**, and proceeding by two successive 5-*exo*-*trig* cyclisations to give **7**. Whilst this appeared eminently reasonable, we were mindful of the previous applications of the Mn(III) chemistry in the arena of PPAP construction, Scheme 2.[9,14]

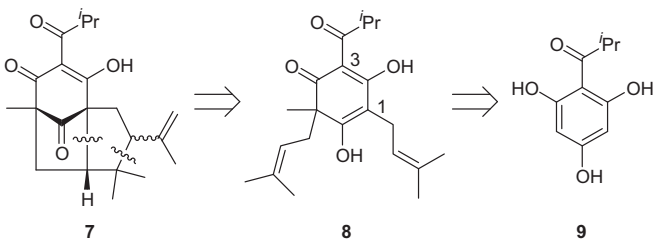
In the cyclisation of keto ester **10** to give a simple PPAP model **11**, Kraus and co-workers indicated that *less than 5% of the corresponding [3.2.1] system was produced.*[14a,b] Cyclisation of derivatives such as **12** was found to proceed via an apparent 8-*endo* mode of cyclisation, to give **13**, by initiation at C-3, although here the regioselectivity is controlled by partial O-methylation of the core ring.

With issues of regiocontrol being a remaining concern, we set about the preparation of the key intermediate **8**, Scheme 3.[15]

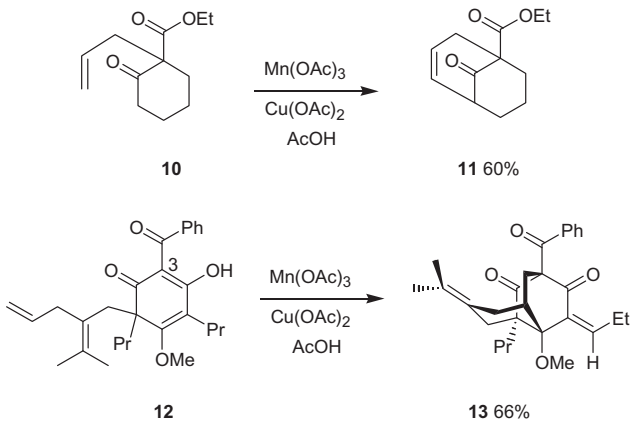
The bis-prenylated acylphloroglucinol **15** was prepared in two steps from phloroglucinol by Friedel–Crafts acylation (to give **9**) followed by double prenylation of the electron-rich benzene ring, Scheme 3.[16] At this point, our synthesis required regioselective addition of a methyl group with concomitant dearomatisation of the phloroglucinol core. After experimentation, we observed that treatment of **15** with sodium methoxide (5 equiv) and iodomethane (5 equiv) at −20 °C, followed by warming of the reaction mixture to 0 °C, gave **8** in a satisfactory yield of 70%. Since the methylated compound **8** was obtained as a complex mixture of tautomers, it was converted selectively into enol acetate **16**, by treatment with Ac_2O in pyridine, to facilitate the complete assignment of its ^1H and ^{13}C NMR spectra.[8,17,18] We were now in a position to investigate the key oxidative cyclisation, which was carried out using the classic Snider protocol,[14] Scheme 4.

Exposure of **8** to $Mn(OAc)_3$ (2 equiv) and $Cu(OAc)_2$ (1 equiv) in acetic acid led to a very rapid consumption of the starting material and formation of the target natural products, ialibinone A (**7a**) and ialibinone B (**7b**), as an inseparable mixture (by column chromatography) in 35% overall yield.[19]

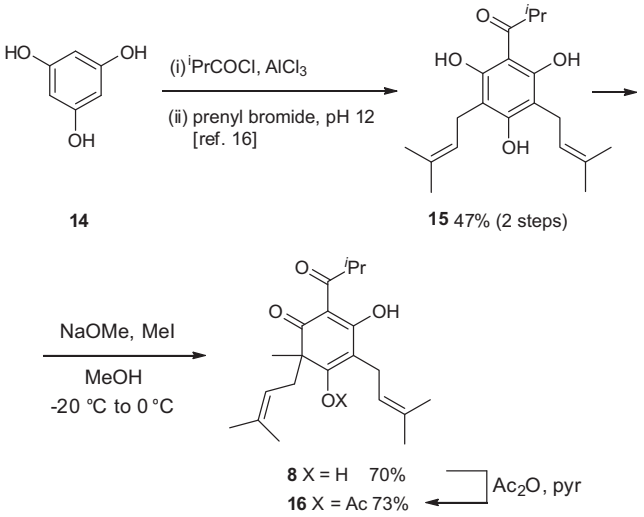
Full characterisation of our final product was hampered by the presence of two epimers—each of which exists in a mixture of tautomeric forms. The initial evidence for the formation of ialibinones



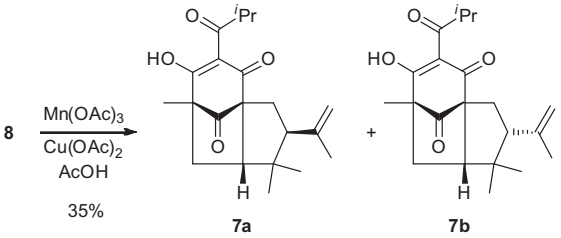
Scheme 1. Retrosynthesis of ialibinones A and B (**1**).



Scheme 2. PPAP synthesis using Mn(III)-mediated oxidative cyclisations.



Scheme 3. Synthesis of key intermediate **8**.



Scheme 4. Synthesis of ialibinone A (**7a**) and ialibinone B (**7b**).

A and B was provided by the ^{13}C NMR data of the mixture of **7a** and **7b** which closely matched that reported by Sticher and co-workers.[11] Two components in a ratio of 41:59 (subsequently determined to be **7a**:**7b**) were observed by analytical HPLC, indicating that the double cyclisation was very weakly diastereoselective. The mixture was subsequently separated by reversed-phase HPLC using a semi-prep C18(2) column to afford purified samples of **7a** and **7b**.[19] The separated epimers of **7** provided spectroscopic data in complete accord with those described previously, and in both cases, the major tautomeric isomer is apparently the one shown in Scheme 4.[20]

Given the established reactivity of compound **12** at C-3, we might have expected to observe product formation arising from

this mode of reaction with our acylphloroglucinol derivative **8**. However, we were unable to isolate any regioisomeric products from the reaction mixture, and the substantial mass loss presumably represents over-oxidation, which is a known issue in these processes.[14c] Interestingly, attempts to change the regioselectivity of the cyclisation by oxidation of acetate derivative **16** were unsuccessful, this compound being unreactive under the conditions used for compound **8**.

To conclude, we have described a facile access to ialibinones A and B, which are the first PPAP natural products having a core bicyclo[3.2.1]octane structure to be synthesised. In terms of bond formation, our synthesis can be considered biomimetic, although whether compounds such as ialibinones arise in Nature through radical or cationic intermediates is unclear. The *5-exo* mode of initial ring formation contrasts with that seen in the examples in Scheme 2, and it appears that the regiochemistry of initial bond formation and the ring size formed might be controllable by varying the substituent pattern in the starting material, and by the judicious use of enol derivatives. We are currently exploring these avenues in more detail.

Acknowledgements

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We also thank Graham D. Burns for assistance with HPLC.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.025.

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15. Despite our concerns regarding the regiocontrol of cyclisation, 5-exo-trig cyclisations are known, for example: Pettus, T. R. R.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12684–12685.
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18. Enol acetate **16** (from **15**): NaOMe (423 mg, 7.83 mmol) was added in one portion to a solution of acylphloroglucinol **15** (520 mg, 1.57 mmol) in MeOH (15 mL) at −20 °C. After 15 min, MeI (488 μL, 7.83 mmol) was added at −20 °C. The reaction mixture was allowed to warm to 0 °C and after 1 h, satd aq NH_4Cl solution (25 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (3 × 25 mL), brine (3 × 25 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the purification of the residue by flash column chromatography (10% EtOAc in petroleum ether) gave the methylated product **8** as a yellow oil (379 mg, 70%); selected data: R_f = 0.43 (20% EtOAc in petroleum ether); *m/z* (TOF ES-) 377.3 ([M+MeOH−H]$^-$, 38%), 345.3 (100, [M−H]$^-$); HRMS *m/z* (TOF ES-) found (M−H)$^-$ 345.2063. $C_{21}H_{29}O_4$ requires 345.2066. For the acetylation step, Ac_2O (414 μL, 4.38 mmol) and pyridine (442 μL, 5.47 mmol) were added to a solution of **8** (379 mg, 1.09 mmol) in acetone (12 mL). After 1 h, satd aq NH_4Cl solution (25 mL) was added and the work-up procedure of the previous step was repeated. The solvent was removed under reduced pressure and purification of the residue by flash column chromatography (5% EtOAc in petroleum ether) gave enol acetate **16** as a colourless oil (309 mg, 73%); R_f = 0.57 (20% EtOAc in petroleum ether); ν_{max}(film)/cm^{-1} 2971w, 2932m, 1778m (C=O), 1667 m (C=O), 1642s (C=O), 1535s, 1438s, 1366 m, 1186vs, 1153vs, 1091s, 883w; δ_H (300 MHz, $CDCl_3$) mixture of two tautomers: 1.11–1.18 (12H, m), 1.27 (3H, s), 1.40 (3H, s), 1.51–1.59 (12H, m), 1.65–1.71 (12H, m), 2.26 (3H, s), 2.27 (3H, s), 2.34 (dd, *J* 13.7, 7.5, 1H), 2.44 (dd, *J* 13.8, 7.4, 1H), 2.63 (app. td, *J* 14.0, 8.2, 2H), 2.83 (app. td, *J* 15.3, 7.3, 2H), 3.08 (dd, *J* 15.3, 6.9, 2H), 3.98 (septet, *J* 6.8, 1H), 4.11 (septet, *J* 6.8, 1H), 4.75–4.87 (2H, m), 4.94–5.05 (2H, m); δ_C (100 MHz, $CDCl_3$) mixture of two tautomers: 17.7, 17.8, 18.67, 18.71, 18.8, 19.0, 20.6, 22.3, 22.5, 23.3, 23.6, 25.66, 25.72, 25.74, 25.8, 35.6, 36.5, 37.8, 38.9, 48.9, 53.8, 108.1, 110.4, 117.4, 118.1, 120.1, 120.9, 124.7, 129.1, 132.1, 133.0, 135.2, 136.1, 157.2, 162.7, 166.8, 167.0, 183.3, 189.2, 195.6, 196.8, 208.7, 210.8 (1 resonance obscured); *m/z* (EI) 388 ([M]$^+$, 5%), 318 (70, [M−CO^{i}Pr+H]$^+$), 276 (88, [M−CO^{i}Pr-Ac+2H]$^+$), 234 (100); HRMS *m/z* (EI) found (M)$^+$ 388.2232. $C_{23}H_{32}O_5$ requires 388.2250.
19. Ialibinone A (**7a**) and ialibinone B (**7b**): Manganese(III) acetate dihydrate (379 mg, 1.41 mmol) and copper(II) acetate monohydrate (141 mg, 0.71 mmol) were added to a solution of **8** (245 mg, 0.71 mmol) in glacial AcOH (15 mL) at room temperature. After 30 min, the reaction mixture was diluted with petroleum ether (20 mL) and filtered through a short silica plug, eluting with 20% Et_2O in petroleum ether (60 mL). The solvent was removed under reduced pressure and purification of the residue by flash column chromatography (10% Et_2O in petroleum ether) gave a 41:59 mixture of ialibinone A (**7a**) and ialibinone B (**7b**) as a yellow oil (85 mg, 35%); R_f = 0.50 (20% EtOAc in petroleum ether). The mixture was separated by reversed-phase HPLC using a Phenomenex Luna C18(2) semi-prep column and MeCN–H_2O–TFA (70:29.95:0.05) as the eluent. The retention times (25 °C, flow rate: 3 mL/min) were as follows: ialibinone A (**7a**) 49.6 min; ialibinone B (**7b**) 53.4 min. After separation, the MeCN was removed under reduced pressure and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the title compounds as yellow oils (24 mg of **7a** and 36 mg of **7b**). Ialibinone A (**7a**): ν_{max}($CHCl_3$)/cm^{-1} 3382w br (O–H), 2969s, 2872 m, 1763s (C=O), 1668s (C=O), 1546s, 1458 m, 1321 m, 1216m, 1092w, 894m, 758s; δ_H (300 MHz, $CDCl_3$) mixture of two tautomers: 0.81–0.87 (3H, m, including [0.83 (s), 0.86 (s)]), 0.94–1.00 (3H, m, including [0.97 (s), 0.98 (s)]), 1.08–1.22 (6H, m, including [1.11 (d, *J* 6.8), 1.15 (d, *J* 6.8), 1.20 (d, *J* 6.8)]), 1.32–1.41 (3H, m, including [1.33 (s), 1.39 (s)]), 1.61–1.75 (1H, m), 1.75–1.79 (3H, m, including [1.76 (s), 1.78 (s)]), 2.00–2.57 (5H, m), 3.86–4.08 (1H, m, including [3.94 (sept, *J* 6.8), 4.01 (sept, *J* 6.8)]), 4.73–4.82 (1H, m), 4.89–4.97 (1H, m), OH resonance outside of the range; δ_C (100 MHz, $CDCl_3$) mixture of two tautomers: 12.4, 13.1, 18.5, 18.6, 19.0, 19.2, 23.56, 23.62, 24.38, 24.44, 24.9, 25.70, 25.74, 25.8, 33.4, 34.3, 34.4, 34.8, 42.8, 43.4, 54.5, 54.9, 55.5, 57.7, 61.3, 65.1, 67.9, 72.1, 109.4, 109.6, 113.45, 113.52, 143.2, 143.3, 191.0, 194.6, 200.1, 201.6, 206.1, 207.0, 207.6, 208.6; *m/z* (TOF ES-) 343.1 ([M−H]$^-$, 100%); HRMS *m/z* (TOF ES-) found (M−H)$^-$ 343.1906. $C_{21}H_{27}O_4$ requires 343.1909. Ialibinone B (**7b**): ν_{max}($CHCl_3$)/cm^{-1} 3326w br (O–H), 2969m, 2873m, 1759s (C=O), 1668s (C=O), 1548s, 1455m, 1324m, 1174w, 1094w, 891m, 757m; δ_H (300 MHz, $CDCl_3$) mixture of two tautomers: 0.54–0.61 (3H, m, including [0.57 (s), 0.58 (s)]), 0.93–1.00 (3H, m, including [0.95 (s), 0.97 (s)]), 1.08–1.22 (6H, m, including [1.13 (d, *J* 6.8), 1.14 (d, *J* 6.8), 1.18 (d, *J* 6.8)]), 1.29–1.40 (3H, m, including [1.31 (s), 1.38 (s)]), 1.70–1.91 (4H, m, including [1.77 (s), 1.79 (s), 1.86 (dd, *J* 12.4, 4.9)]), 2.03–2.32 (3H, m), 2.37–2.57 (2H, m), 3.92–4.14

(1H, m), 4.73–4.86 (1H, m), 4.92–5.02 (1H, m), OH resonance outside of the range; δ_C (100 MHz, $CDCl_3$) mixture of two tautomers: 12.4, 13.1, 16.4, 16.9, 18.7, 18.8, 18.85, 18.91, 23.7, 23.8, 24.2, 24.9, 27.2 (×2), 31.1, 32.7, 34.7, 35.0, 44.8, 45.1, 55.8, 58.14, 58.47, 58.6, 62.1, 66.2, 68.3, 72.4, 107.9, 108.0, 113.6, 113.8, 142.8, 143.0, 191.0, 193.6, 200.3, 201.7, 206.7, 207.3, 209.1, 209.6; *m/z* (TOF ES-) 343.1 ($[M-H]^-$, 100%); HRMS *m/z* (TOF ES-) found $(M-H)^-$ 343.1911. $C_{21}H_{27}O_4$ requires 343.1909.

20. Winkelmann et al. (Ref. 11) propose that there is a destabilising effect of the neighbouring five-membered ring system on the enolic hydroxy group relative to the methyl substituent.