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Synthesis of melicodenines C, D and E

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ABSTRACT

A synthesis of the unusual cyclobutane-quinolinone alkaloids melicodenines C, D and E by intermolecular [2+2] cycloaddition is described.

Oyama et al. recently reported the isolation of a series of novel quinolinone alkaloids, the melicodenines C–F (**1–4**, relative stereochemistry shown in Fig. 1) from the leaves of *Melicope denhamii*, a rutaceous shrub found in Borneo and the Solomon Islands that has been used in indigenous medicine.[1]

The structures of these alkaloids are unusual in that they contain a cyclobutane ring that appears to have been formed by a [2+2] cycloaddition reaction between two different natural products, *N*-methylflindersine (**5**) and a cinnamyl derivative (e.g., **6**, **7** or **8**).

As both the precursors (**5** and **8**) of melicodenine E also occur in the leaves, the interesting question arises as to whether **1–4** are artefacts formed by sunlight-induced [2+2] cycloaddition within the leaves of the plant, or whether they are biosynthesised by enzyme-catalysed reactions. This question remains unanswered, however, as all four compounds are racemic, it seems more likely that they are formed via the [2+2] cycloaddition route. We now report the first syntheses of melicodenines C–E (**1–3**) utilising this route.

Melicodenine C (**1**) was synthesised as outlined in Scheme 1. *N*-Methylflindersine (**5**) was prepared by the method of Lee and Wang[2] utilising a tandem Knoevenagel-electrocyclic reaction. Commercially available 4-hydroxy-1-methyl-2(1*H*)-quinolone and 3-methyl-2-butenal were treated with ytterbium triflate as the catalyst in refluxing acetonitrile to afford the desired *N*-methylflindersine (**5**) as a yellowish brown solid in 57% yield.

trans-3,4-Methylenedioxycinnamyl alcohol methyl ether (**6**) was synthesised in three steps starting from 3,4-methylenedioxybenzaldehyde. Treatment of the aldehyde with (carboethoxymethylene) triphenylphosphorane [ethyl (triphenylphosphoranylidene)acetate] in anhydrous dichloromethane afforded the corresponding cinnamyl ester which was reduced with diisobutylaluminium hydride at low temperature followed by methylation to give the required cinnamyl derivative **6** in 50% overall yield.

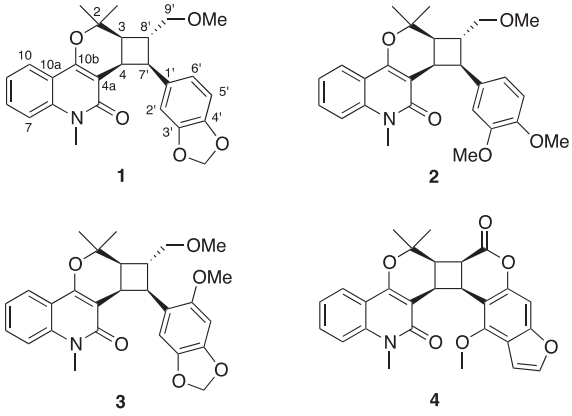

Figure 1. Melicodenines C–F (**1–4**, relative stereochemistry shown).

In order to achieve the desired [2+2] cycloaddition reaction, we initially tried dissolving **5** and **6** in dichloromethane in a 250 mL jacketed round-bottom flask, evaporating the mixture to give a thin film over the walls of the flask, then circulating cooling water through the jacket whilst irradiating the flask with one 300 W and two 150 W (600 W total) floodlights (tungsten filament). This was based on a method that we had used successfully in previous

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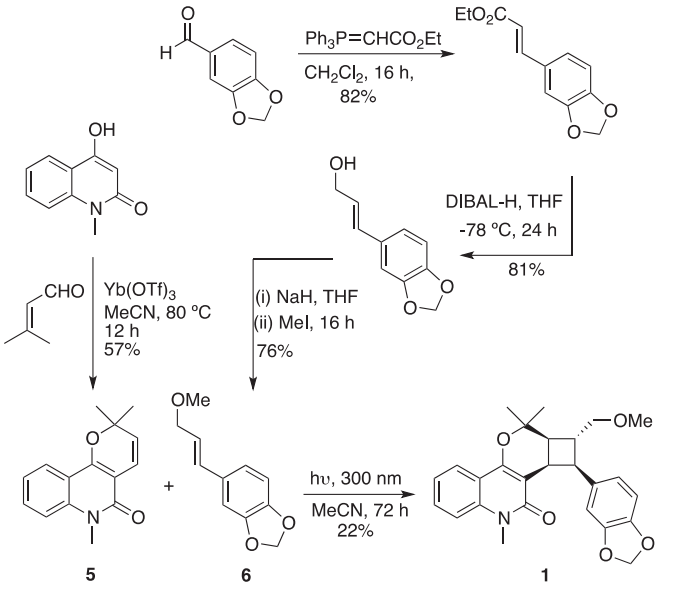

Scheme 1. Synthesis of melicodenine C (**1**, relative stereochemistry shown).

work in the synthesis of related compounds.[3] Irradiation for 24 h led to the desired intermolecular cycloaddition product **1** in modest yield (22%) and with excellent chemo and regioselectivities. Irradiation for longer periods did not result in any significant improvement in the yield. Subsequent reactions were carried out in acetonitrile solution using a conventional Rayonet reactor with either a quartz or glass tube at 300 nm. The reaction was carried out with 1 equiv of **5** and 3 equiv of the cinnamyl ether in acetonitrile for 72 h. The yield of **1** obtained using the Rayonet reactor was 15% (34% after allowing for recovered **5**). Some isomerisation of the cinnamyl ether (15% isomerised to the *Z*-isomer) was observed, as well as the formation of small amounts of the [2+2] cycloaddition dimer of *N*-methylflindersine. Changing the solvent to acetone, or addition of a sensitiser (benzophenone) did not appear (by LCMS) to have any significant effect on the conversion of **5** into **1**. Use of toluene as the solvent however, did appear (by LCMS) to give a slight improvement in the conversion, but this was not further investigated. Attempts at thermal [2+2] cycloaddition employing $AlCl_3$ or transition metal mediated reactions[4] (such as $[Ni(PPh_3)_2Cl_2]$ + Zn) were unsuccessful.

Melicodenines D and E were synthesised from *N*-methylflindersine (**5**) and the cinnamyl derivatives **7** and **8** (both of which also occur naturally[5]), respectively, using the same general procedure as that outlined in Scheme 1. The yields for the final [2+2] cycloadditions were 11% (**2**) and 10% (**3**) (22% after allowing for recovered **5**), respectively. The cinnamyl ethers **7** and **8** (Fig. 2) were prepared in 41% and 49% overall yields, respectively, via a three-step sequence analogous to that outlined for **6** in Scheme 1.

The ^1H and ^{13}C NMR spectra of **1–3** were virtually identical to those reported by Oyama et al.[1] for the natural products. An exception was the resonance reported for C-7 in melicodenine E, for which Oyama et al.[1] report a chemical shift of 107.1 ppm. This appears to be a typographical error as C-7 in melicodenines C and D occurs at 113.7 and 113.6 ppm, respectively. The chemical shifts for C-7 in (synthetic) **1–3** were 113.6, 113.5 and 113.4 ppm, respectively.

In conclusion, melicodenines C–E have been synthesised in modest yields by an intermolecular [2+2] cycloaddition strategy.[6] This provides confirmation of the structures and the relative stereochemistry assigned by Oyama et al. to the natural products. The [2+2] cycloaddition was regioselective, possibly as a result of a π-stacking interaction between the aryl group of the cinnamyl ether and the quinolinone ring. This would explain why the aryl group in the cinnamyl ether and the quinolinone of the *N*-methylflindersine are on the same face of the cyclobutane ring. The reaction was also chemoselective, with only [2+2] cycloaddition between the cinnamyl ether and the disubstituted double bond of *N*-methylflindersine being observed.

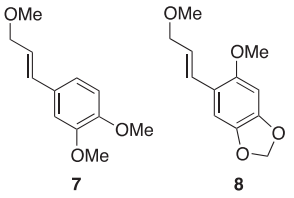

Figure 2.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.087.

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6. General procedure for the [2+2] cycloaddition reaction employed to synthesise melicodenines C (**1**), D (**2**) and E (**3**): A solution of *N*-methylflindersine (**5**) (0.5 mmol) and one of the respective cinnamyl ethers (**6**, **7** or **8**) (3 equiv) in MeCN (2 mL) was purged with a gentle stream of argon in an ultrasonic bath for 15 min and transferred to either a glass or quartz test tube under an atmosphere of argon. The mixture was irradiated using a Rayonet photochemical reactor at λ = 300 nm for 72 h, at room temperature. The solvent was evaporated under reduced pressure and the remaining residue was purified either by flash column chromatography or by reverse phase HPLC (C-18 betasil column), to give the respective melicodenines C (**1**), D (**2**) or E (**3**).
*Melicodenine C (**1**):* Colourless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 8.02 (dd, *J* = 8.04, 1.3 Hz, 1H, H-10) 7.50 (td, *J* = 7.7. 1.2 Hz, 1H, H-8), 7.22 (m, 2H, H-7,9), 6.48 (d, *J* = 8.2 Hz, 1H, H-5′), 6.48 (d, *J* = 1.5 Hz, 1H, H-2′), 6.38 (dd, *J* = 7.9, 1.5 Hz, 1H, H-6′), 5.80 (d, *J* = 1.4 Hz, 1H, OCH_2O), 5.77 (d, *J* = 1.5 Hz, 1H, OCH_2O), 3.85 (dd, *J* = 8.5, 8.3 Hz, 1H, H-4), 3.69 (dd, *J* = 9.5, 8.8 Hz, 1H, H-7′), 3.43 (dd, *J* = 10.0, 4.1 Hz, 1H, H-9′a), 3.41 (dd, *J* = 10.0, 4.1 Hz, 1H, H-9′b), 3.36 (s, 3H, 6-Me), 3.31 (s, 3H, 9′-OMe), 2.64 (m, 1H, H-8′), 2.60 (m, 1H, H-3), 1.52 (s, 3H, 2-Me), 1.18 (s, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6 (C-5), 155.5 (C-10b), 146.7 (C-3′), 145.8 (C-4′), 138.8 (C-6a), 133.9 (C-1′), 130.1 (C-8), 123.0 (C-10), 121.3 (C-6′), 121.2 (C-9), 116.6 (C-10a), 113.6 (C-7), 109.1 (C-2′), 107.6 (C-4a), 107.2 (C-5′), 100.5 (OCH_2O), 76.5 (C-2), 74.3 (C-9′), 59.0 (9′-OMe), 44.0 (C-7′), 41.6 (C-3), 40.1 (C-8′), 33.1 (C-4), 28.9 (6-Me), 25.2 (2-Me), 23.8 (2-Me). LRMS (ESI): *m*/*z* 434 $[MH]^+$. HRMS (ESI): Calcd for $C_{26}H_{28}NO_5$ $[MH]^+$: 434.1961. Found: 434.1981.
*Melicodenine D (**2**):* Colourless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 8.1, 1.5 Hz, 1H, H-10), 7.50 (td, *J* = 8.5, 1.5 Hz, 1H, H-8) 7.21 (m, 2H, H-7,9), 6.63 (dd, *J* = 8.1, 1.6 Hz, 1H, H-6′), 6.62 (d, *J* = 8.1 Hz, 1H, H-5′), 6.28 (d, *J* = 1.5 Hz, 1H, H-2′), 3.89 (m, 1H, H-4), 3.76 (s, 3H, 3′OMe), 3.70 (m, 1H, H-7′), 3.44 (m, 2H, H-9′), 3.32 (s, 3H, 9′-OMe), 3.31 (s, 3H, 6-Me), 3.23 (s, 3H, 4′-OMe), 2.68 (m, 1H, H-8′), 2.62 (dd, *J* = 8.8, 8.5 Hz, 1H, H-3), 1.53 (s, 3H, 2-Me), 1.19 (s, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5 (C-5), 155.3 (C-10b), 147.8 (C-4′), 147.3 (C-3′), 138.7 (C-6a), 132.5 (C-1′), 130.0 (C-8), 122.8 (C-10), 121.3 (C-9), 121.2 (C-6′), 116.5 (C-10a), 113.5 (C-7), 110.7 (C-2′), 110.2 (C-5′), 108.0 (4a), 76.6 (C-2), 74.5 (C-9′), 59.0 (9′-OMe), 55.7 (3′-OMe), 55.0 (4′-OMe), 43.7 (C-7′), 41.7 (C-3), 40.0 (C-8′), 32.8 (C-4), 28.8 (6-Me), 25.1 (2-Me), 23.6 (2-Me). LRMS (ESI): *m*/*z* 450 $[MH]^+$. HRMS (ESI): Calcd for $C_{27}H_{32}NO_5$ $[MH]^+$: 450.2275. Found: 450. 2276.

Melicodenine E (**3**)*:* Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (dd, J = 8.2, 1.5 Hz, 1H, H-10), 7.49 (td, J = 7.5, 1.3 Hz, 1H, H-8), 7.20 (m, 1H, H-9), 6.46 (s, 1H), 6.05 (s, 1H, H-6′), 5.71 (d, J = 1.3 Hz, 1H, OCH_2O), 5.64 (d, J = 1.3 Hz, 1H, OCH_2O), 4.17 (dd, J = 10.4, 8.2 Hz, 1H, H-7′), 3.86 (s, 3H, 2′-OMe), 3.80 (t, J = 8.3 Hz, 1H, H-4), 3.41 (m, 2H, H-9′), 3.32 (s, 3H, 6-Me), 3.29 (s, 3H, 9′-OMe), 2.62 (m, 1H, H-8′), 2.56 (dd, J = 8.7, 8.3 Hz, 1H, H-3), 1.52 (s, 3H, 2-Me), 1.17 (s, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5 (C-5), 155.3 (C-10b), 153.7 (C-2′), 145.7 (C-4′), 140.2 (C-5′), 138.8 (C-6a), 129.9 (C-8), 123.0 (C-10), 121.5 (C-1′), 121.0 (C-9), 116.5 (C-10a), 113.4 (C-7), 107.5 (C-4a), 107.0 (C-6′), 100.4 (OCH_2O), 95.5 (C-3′), 76.2 (C-2), 74.7 (C-9′), 59.0 (9′-OMe), 57.6 (2′-OMe), 42.5 (C-3), 39.0 (C-8′), 36.6 (C-7′), 32.9 (C-4), 28.8 (6-Me), 25.3 (2-Me), 23.7 (2-Me). LRMS (ESI): m/z 464 $[MH]^+$. HRMS (ESI): Calcd for $C_{27}H_{29}NO_6Na$ $[M+Na]^+$: 486.1887. Found: 486.1902.