Graphical Abstract

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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 Figure 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

Figure 1. (relative stereochemistry shown)

The structure of these alkaloids is 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 (eg. **6**, **7**, **8**).

As both the precursors (**5** and **8**) of Melicodine E also occur in the leaves, the interesting question arises as to whether **1-4** are artifacts formed by sunlight-induced [2+2]

cycloaddition within the leaves of the plant, or whether they are biosynthesized 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 synthesis of Melicodenines C-E (**1-3**) utilizing this route.

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

trans-3,4-Methylenedioxcinnamyl alcohol methyl ether **6** was synthesized in three steps starting from 3,4-methylenedioxybenzaldehyde. Treatment of the aldehyde with (carbethoxymethylene)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.

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Scheme. Synthesis of Melicodenine C (**1**, 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 a 300 W + 2 x 150 W (600 W total) floodlights (tungsten filament). This was based on a method that we had used successfully in previous work on the synthesis of related compounds.³ Irradiation for 24 hours led to the desired intermolecular cycloaddition product **1** in modest yield (22%) and with excellent chemo and regioselectivity. 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 RayonetTM reactor with either a quartz or glass tube at 300 nm. The reaction was carried out with one equivalent of **5** and three equivalents of the cinnamyl ether in acetonitrile for 72 hours. The yield of **1** obtained using the Rayonet reactor was 15% (34% after allowing for recovered **5**). Some isomerization of the cinnamyl ether (15% isomerized to the *Z*-isomer) was observed, as well as formation of small amounts of the [2+2] cycloaddition dimer of the *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** to **1**. Use of toluene as 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 AlCl₃ or transition metal-mediated reactions (such as [Ni(PPh₃)₂Cl₂] + Zn) were unsuccessful.⁴

Melicodenines D and E were synthesised from *N*-methylflindersine **5** and the cinnamyl derivatives **7** and **8** (both of which also occur naturally⁵) respectively, using the same general procedure as that outlined in the Scheme. The

yields for the final [2+2] cycloadditions were 11% and 10% (22% after allowing for recovered **5**), respectively. The cinnamyl ethers **7** and **8** (Figure 1) were prepared in 41% and 49% overall yields, respectively, via a three-step sequence analogous to that outlined for **6** in the Scheme.

Figure 2.

The ¹H and ¹³C NMR spectra of **1-3** were virtually identical to those reported by Oyama et al¹ for the natural products. An exception was the resonance reported for C-7 in Melicodenine E, for which Oyama et al¹ 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. 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 the *N*-methylflindersine being observed.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures and NMR spectra) associated with this article can be found in the online version, at doi:

References and notes

1. Nakashima, K.; Oyama, M.; Ito, T.; Akao, Y.; Witono, J. R.; Darnaedi, D.; Tanaka, T.; Murata, J.; Iinuma, M. *Tetrahedron*. **2012**, 68, 2421-2428.
2. Wang, X.; Lee, Y. R. *Synthesis* **2007**, 19, 3044-3050.
3. Avery, V.; Carroll, A. R.; Duffy, S.; Garavelas, A.; Jenkins, I. D.; Neve, J. E.; Le, P. V.; Leone, P. de A.; Nikolopoulos, G.;

- Pham, N.; Quinn, R. J.; Ripper, J. A.; Teague, S. J.; Wijesekera, H. P.; Williams, N. *unpublished data*.
4. Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, *6*, 3706-3713.
 5. Dictionary of Natural Products on DVD, CRC Press, Taylor and Francis, 2012.
 6. General procedure for the [2+2] cycloaddition reaction employed to synthesise Melicodenines C (**1**), D (**2**) & E (**3**): A solution of *N*-methylflindersine (**5**, 0.5 mmol) and one of the respective cinnamyl ethers (**6**, **7**, **8**) (3 equivalents) in acetonitrile (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 RayonetTM photochemical reactor at $\lambda = 300$ nm for 72 h, at room temperature. The solvent was evaporated under reduced pressure & 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**) and E (**3**).

Melicodenine C (**1**): Colourless oil; ¹H NMR (500 MHz, CDCl₃): 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, OCH₂O), 5.77 (d, $J = 1.5$ Hz, 1H, OCH₂O), 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); ¹³C NMR (125 MHz, CDCl₃): 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 (OCH₂O), 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 C₂₆H₂₈NO₅ [M]⁺ 434.1961, found 434.1981.

Melicodenine D (**2**): Colourless oil; ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): 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 C₂₇H₃₂NO₅ [MH]⁺ 450.2275, found 450. 2276.

Melicodenine E (**3**): Colourless oil; ¹H NMR (500 MHz, CDCl₃): 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, OCH₂O), 5.64 (d, $J = 1.3$ Hz, 1H, OCH₂O), 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-

Supporting Information

Total Synthesis of Melicodenine C, D and E

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General experimental details:

NMR spectra were acquired on a 500 MHz instrument in CDCl₃ as solvent (referenced to 7.26 ppm for ¹H and 77.0 ppm for ¹³C for CDCl₃). Coupling constants (*J*) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. High resolution mass spectra (HRMS) were obtained on a 4.7 T Fourier Transform Spectrometer. All reactions were performed under an atmosphere of argon unless otherwise indicated using anhydrous dichloromethane, acetonitrile and tetrahydrofuran. All other reagents and solvents were used as purchased from commercial suppliers unless otherwise noted. Reaction progress was monitored by thin layer chromatography (TLC) on aluminum backed silica gel plates, visualizing with UV light, and plates were developed using potassium permanganate or phosphomolybdic acid stains. Flash chromatography was performed using silica gel (230-400 mesh).

Preparation of compounds and spectral data:

N-methyl flindersine (6) :

To a stirred solution of 4-hydroxy-1-methyl-2(1*H*)-quinolone (2.627 g, 15 mmol) and 3-methyl-2-butenal (2.523g, 30 mmol) in acetonitrile (30 mL), Yb(OTf)₃ (0.93 g, 1.5 mmol) was added. The reaction mixture was refluxed for 16 h at 80°C. After completion of the reaction, the reaction mass was allowed to cool then evaporated under gravity, followed by flash column chromatography. The desired product (**6**) was separated as brown solid (2.055 g, 56.8%).

Brown Solid; ¹H NMR (500 MHz, CDCl₃) : δ 7.94 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.52 (td, *J* = 8.2, 1.2 Hz, 1H), 7.29 (m, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 9.9 Hz, 1H), 5.52 (d, *J* = 9.8 Hz, 1H), 3.68 (s, 3H), 1.51 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) : δ 160.9, 155.1, 139.3, 130.7, 126.2, 123.0, 121.6, 117.9, 116.0, 113.9, 105.8, 78.6, 29.2, 28.1. LRMS (ESI) : *m/z* 242 [M+H]⁺. HRMS (ESI): calcd for C₁₅H₁₅NO₂Na [M+Na]⁺ 264. 0995, found 264. 0994

(E)-ethyl 3-(benzo[d][1,3]dioxol-5-yl)acrylate (10) :

To a stirred solution of 1,3-benzodioxole-5-carbaldehyde (**9**) (1.05 g, 5 mmol) in anhydrous dichloromethane (15 mL) under argon, a solution of ethyl(triphenyl phosphoranylidene)acetate (3.657 g, 10.5 mmol) in dichloromethane (20 mL) was added. The reaction mixture was allowed to stir for 16 h. The reaction mass was quenched by addition of water and was extracted with excess dichloromethane and brine solution. The organic layer was separated, dried over MgSO_4 , evaporated under vacuum and subjected to flash column chromatography. The compound **10** was separated as white crystalline solid (1.263 g, 82%).

White crystalline solid; ^1H NMR (500 MHz, CDCl_3) : δ 7.57 (d, J = 16.0 Hz, 1H), 7.01 (d, J = 1.0 Hz, 1H), 6.98 (dd, J = 8.0, 2.9 Hz, 1H), 6.78 (dd, J = 7.8, 2.7 Hz, 1H), 6.24 (d, J = 15.9 Hz, 1H), 5.98 (s, 2H), 4.23 (q, J = 7.0 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) : δ 167.0, 149.4, 148.2, 144.1, 128.8, 124.2, 116.1, 108.4, 106.4, 101.4, 60.2, 14.2. LRMS (ESI) : m/z 221 $[\text{M}+\text{H}]^+$, 243 $[\text{M}+\text{Na}]^+$. HRMS (ESI): calcd for $\text{C}_{12}\text{H}_{12}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 243. 0627, found 243. 0623

(E)- 3-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (11) :

To a stirred solution of (E)-ethyl 3-(benzo[d][1,3]dioxol-5-yl)acrylate (**10**) (1.075 g, 4.88 mmol) in anhydrous THF (30 mL) at -78°C , diisobutyl aluminium hydride (1.0 M in toluene, 17.08 mL) was added via pressure equalizing dropping funnel. The reaction mixture was allowed to stir at -78°C for 2 h. The reaction was quenched slowly by drop wise addition of methanol (15 mL) and slowly the reaction mass was allowed to warm to 0°C . This reaction mass was added to 0.1N HCl solution (500 mL). The reaction mass allowed to stir overnight followed by extraction with excess ether. The organic layer was separated, dried over MgSO_4 , evaporated under vacuum and

subjected to flash column chromatography. The compound **11** was separated as white crystalline solid (0.704 g, 81%).

White crystalline solid; ^1H NMR (500 MHz, CDCl_3) : δ 6.92 (s, 1H), 6.81(d, J = 8.0 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.51 (d, J = 15.8 Hz, 1H), 6.19 (dt, J = 15.8, 5.8 Hz, 1H), 5.94 (s, 2H), 4.28 (d, J = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) : δ 147.9, 147.2, 131.1, 130.9, 126.6, 121.1, 108.2, 105.7, 101.0, 63.6. . HRMS (ESI): calcd for $\text{C}_{11}\text{H}_{12}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 231. 0627, found 231. 0621

(E)-5-(3-methoxyprop-1-enyl)benzo[d][1,3]dioxole (5a):

To a stirred solution of sodium hydride (60 %) (0.351 g, 8.788 mmol) in anhydrous THF (15 mL) at 0°C , a solution of (*E*)- 3-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (**11**) (0.783 g, 4.394 mmol) in THF (15 mL) was added. The reaction mixture was allowed to stir at room temperature for 2 h, followed by addition of methyl iodide (1.871 g, 13.18 mmol). The reaction mixture was allowed to stir for next 16 h. The reaction was quenched by adding water drop wise at 0°C . Further the reaction mass was evaporated under vacuum followed by extraction with ethyl acetate and brine solution. The organic layer was separated, dried over MgSO_4 , evaporated under vacuum and subjected to flash column chromatography. The compound **5a** was separated as yellow oil (0.792 g, 76.3 %).

Yellow oil; ^1H NMR (500 MHz, CDCl_3) : δ 6.93 (s, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.52 (d, J = 15.9 Hz, 1H), 6.11 (dt, J = 15.9, 6.1, 5.8 Hz, 1H), 5.95 (s, 2H), 4.06 (d, J = 6.0 Hz, 2H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) : δ 148.0, 147.2, 132.2, 131.2, 124.1, 121.1, 108.2, 105.8, 101.0, 73.1, 57.9. LRMS (ESI) : m/z 193 $[\text{M}+\text{H}]^+$, 215 $[\text{M}+\text{Na}]^+$.

(E)-ethyl 3-(3,4-dimethoxyphenyl)acrylate (13) :

To a stirred solution of 3,4-dimethoxy benzaldehyde (**12**) (0.83 g, 5 mmol) in anhydrous dichloromethane (15 mL) under argon, a solution of ethyl(triphenyl phosphoranylidene)acetate (2.09 g, 6 mmol) in dichloromethane (20 mL) was added. The reaction mixture was allowed to stir for 16 h. The reaction mass was quenched by addition of water and was extracted with excess dichloromethane and brine solution. The organic layer was separated, dried over MgSO₄, evaporated under vacuum and subjected to flash column chromatography. The compound **13** was separated as white crystalline solid (1.003 g, 85%).

White crystalline solid; ¹H NMR (500 MHz, CDCl₃) : δ 7.60 (d, *J* = 15.9 Hz, 1H), 7.07 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.03 (s, 1H), 6.84 (d, *J* = 8.1, 2.5 Hz, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 6H), 1.31 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) : δ 167.0, 151.0, 149.1, 144.3, 127.3, 122.4, 115.9, 111.0, 109.6, 60.2, 55.8, 55.7, 14.2. LRMS (ESI) : *m/z* 237 [M+H]⁺, 259 [M+Na]⁺. HRMS (ESI): calcd for C₁₃H₁₆O₄Na [M+Na]⁺ 259. 0940, found 259. 0933

(*E*)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol (14**) :**

To a stirred solution of (*E*)-ethyl 3-(3,4-dimethoxyphenyl)acrylate (**13**) (1.129 g, 4.78 mmol) in anhydrous THF (30 mL) at -78°C, diisobutyl aluminium hydride (1.0 M in toluene, 16.7 mL) was added via pressure equalizing dropping funnel. The reaction mixture was allowed to stir at -78°C for 2 h. The reaction was quenched slowly by drop wise addition of methanol (15 mL) and slowly the reaction mass was allowed to warm to 0°C. This reaction mass was added to 0.1N HCl solution (500 mL). The reaction mass allowed to stir overnight followed by extraction with excess ether. The organic layer was separated, dried over MgSO₄, evaporated under vacuum and subjected to flash column chromatography. The compound **14** was separated as colourless oil (0.742 g, 80%).

Colourless oil; ¹H NMR (500 MHz, CDCl₃) : δ 6.95 (d, *J* = 1.8 Hz, 1H), 6.93 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.55 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.25 (dt, *J* = 15.9, 5.8 Hz, 1H), 4.31 (d, *J* = 5.7 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) : δ 149.0, 148.9,

131.1, 129.7, 126.5, 119.7, 111.2, 108.9, 63.8, 55.9, 55.8. LRMS (ESI) : m/z 217 $[M+Na]^+$. .
 HRMS (ESI): calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217. 0835, found 217. 0832

(*E*)-1,2-dimethoxy-4-(3-methoxyprop-1-enyl)benzene (5b):

To a stirred solution of sodium hydride (60 %) (0.305 g, 7.64 mmol) in anhydrous THF (15 mL) at 0°C, a solution of (*E*)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol (**14**) (0.742 g, 3.82 mmol) in THF (15 mL) was added. The reaction mixture was allowed to stir at room temperature for 2 h, followed by addition of methyl iodide (1.626 g, 11.46 mmol). The reaction mixture was allowed to stir for next 16 h. The reaction was quenched by adding water drop wise at 0°C. Further the reaction mass was evaporated under vacuum followed by extraction with ethyl acetate and brine solution. The organic layer was separated, dried over $MgSO_4$, evaporated under vacuum and subjected to flash column chromatography. The compound **5b** was separated as colourless oil (0.477 g, 60%).

Colourless oil; 1H NMR (500 MHz, $CDCl_3$) : δ 6.95 (d, J = 1.1 Hz, 1H), 6.92 (dd, J = 8.1, 1.5 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.54 (d, J = 15.7 Hz, 1H), 6.15 (dt, J = 15.8, 6.2, 6.0 Hz, 1H), 4.07 (d, J = 6.1 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) : δ 149.2, 149.0, 132.5, 129.9, 124.1, 119.8, 111.3, 109.0, 73.3, 58.0, 56.0, 55.9. LRMS (ESI) : m/z 231 $[M+Na]^+$. HRMS (ESI): calcd for $C_{12}H_{16}O_3Na$ $[M+Na]^+$ 231. 0991, found 231. 0989

(*E*)-ethyl 3-(6-methoxybenzo[*d*][1,3]dioxol-5-yl)acrylate (16) :

To a stirred solution of 6-methoxybenzo[*d*][1,3]dioxole-5-carbaldehyde (3.964 g, 22 mmol) in anhydrous dichloromethane (30 mL) under argon, a solution of ethyl(triphenyl phosphoranylidene)acetate (9.197 g, 26.4 mmol) in dichloromethane (30 mL) was added. The reaction mixture was allowed to stir for 16 h. The reaction mass was quenched by addition of

water and was extracted with excess dichloromethane and brine solution. The organic layer was separated, dried over MgSO_4 , evaporated under vacuum and subjected to flash column chromatography. The compound **16** was separated as white crystalline solid (4.404 g, 80%).

White crystalline solid; ^1H NMR (500 MHz, CDCl_3) : δ 7.94 (d, J = 16.0 Hz, 1H), 6.95 (s, 1H), 6.49 (s, 1H), 6.26 (d, J = 16.2 Hz, 1H), 5.93 (s, 2H), 4.22 (q, J = 7.0 Hz, 2H), 3.80 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) : δ 167.4, 154.7, 150.3, 141.5, 139.1, 115.8, 115.5, 106.2, 101.5, 94.4, 59.9, 56.2, 14.2. LRMS (ESI) : m/z 273 $[\text{M}+\text{Na}]^+$. HRMS (ESI): calcd for $\text{C}_{13}\text{H}_{14}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 273.0733, found 273.0726

(E)- 3-(6-methoxybenzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (17) :

To a stirred solution of (*E*)-ethyl 3-(6-methoxybenzo[d][1,3]dioxol-5-yl)acrylate (**16**) (1.501 g, 6.0 mmol) in anhydrous THF (30 mL) at -78°C , diisobutyl aluminium hydride (1.0 M in toluene, 18.0 mL) was added via pressure equalizing dropping funnel. The reaction mixture was allowed to stir at -78°C for 2 h. The reaction was quenched slowly by drop wise addition of methanol (15 mL) and slowly the reaction mass was allowed to warm to 0°C . This reaction mass was added to 0.1N HCl solution (500 mL). The reaction mass allowed to stir overnight followed by extraction with excess ether. The organic layer was separated, dried over MgSO_4 , evaporated under vacuum and subjected to flash column chromatography. The compound **17** was separated as white solid (0.999 g, 80%).

White solid; ^1H NMR (500 MHz, CDCl_3) : δ 6.94 (s, 1H), 6.87 (d, J = 16.0 Hz, 1H), 6.51 (s, 1H), 6.18 (dt, J = 15.9, 6.0 Hz, 1H), 5.91 (s, 2H), 4.29 (dd, J = 6.0, 1.0 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) : δ 152.4, 147.9, 141.6, 126.8, 125.9, 118.3, 105.7, 101.2, 94.9, 64.2, 56.6. LRMS (ESI) : m/z 231 $[\text{M}+\text{Na}]^+$. HRMS (ESI): calcd for $\text{C}_{11}\text{H}_{12}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 231.0627, found 231.0621

(E)-5-methoxy-6-(3-methoxyprop-1-enyl)benzo[d][1,3]dioxole (5):

To a stirred solution of sodium hydride (60 %) (0.518 g, 12.96 mmol) in anhydrous THF (15 mL) at 0°C, a solution of (*E*)- 3-(6-methoxybenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (**9**) (1.35 g, 6.48 mmol) in THF (15 mL) was added. The reaction mixture was allowed to stir at room temperature for 2 h, followed by addition of methyl iodide (2.759 g, 19.44 mmol). The reaction mixture was allowed to stir for next 16 h. The reaction was quenched by adding water drop wise at 0°C. Further the reaction mass was evaporated under vacuum followed by extraction with ethyl acetate and brine solution. The organic layer was separated, dried over MgSO₄, evaporated under vacuum and subjected to flash column chromatography. The compound **10** was separated as brown oil (1.116 g, 77.5 %).

Brown oil; ¹H NMR (500 MHz, CDCl₃) : δ 6.95 (s, 1H), 6.86 (d, *J* = 15.9 Hz, 1H), 6.50 (s, 1H), 6.10 (dt, *J* = 16.0, 6.2 Hz, 1H), 5.91 (s, 2H), 4.07 (d, *J* = 6.3 Hz, 2H), 3.78 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) : δ 152.4, 147.9, 141.5, 127.2, 124.1, 118.4, 105.7, 101.1, 94.9, 73.5, 57.7, 56.6. LRMS (ESI) : *m/z* 245 [M+Na]⁺. HRMS (ESI): calcd for C₁₂H₁₄O₄Na [M+Na]⁺ 245. 0784, found 245.0779

General procedure for [2+2] photochemical cycloaddition reaction for synthesis of Melicodenine C(**1**), D(**2**) & E(**3**) :

A solution of N-methyl flindersine (**6**) and respective ethers (**5a**, **5b**, **5**) in 2 mL acetonitrile was purged with a gentle stream of argon in an ultrasonicator bath for 15 min and transferred in to a glass test tube or quartz test tube under argon atmosphere. This mixture was irradiated at room temperature at λ= 300 nm for 72 h (light source: Rayonet). The solvent was evaporated under reduced pressure & the remaining residue was purified by either by flash column chromatography or by reverse phase HPLC (C-18 betasil column), to give respective Melicodenine C, D & E(**1**, **2**, **3**).

Compound 1:

Colourless oil; $[\alpha]_D^{25} = +257.1$ (c 0.07, CHCl_3); ^1H NMR (500 MHz, CDCl_3) : δ 8.02 (dt, $J = 16.0, 6.2$ Hz, 1H) 6.95 (s, 1H), 6.86 (d, $J = 15.9$ Hz, 1H), 6.50 (s, 1H), 6.10 (dt, $J = 16.0, 6.2$ Hz, 1H), 5.91 (s, 2H), 4.07 (d, $J = 6.3$ Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) : δ 152.4, 147.9, 141.5, 127.2, 124.1, 118.4, 105.7, 101.1, 94.9, 73.5, 57.7, 56.6. LRMS (ESI) : m/z 434 $[\text{M}+\text{Na}]^+$. HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{28}\text{NO}_5$ $[\text{M}]^+$ 434.1961, found 434.1981

Compound 2:

Colourless oil; $[\alpha]_D^{25} = +440$ (c 0.035, CHCl_3); ^1H NMR (500 MHz, CDCl_3) : δ 8.03 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.50 (td, $J = 8.5, 1.5$ Hz, 1H) 7.21 (m, 2H), 6.63 (dd, $J = 8.1, 1.6$ Hz, 1H), 6.62 (d, $J = 8.1$ Hz, 1H), 3.89 (m, 1H), 3.76 (s, 3H), 3.70 (m, 1H), 3.44 (m, 2H), 3.32 (s, 3H), 3.31 (s, 3H), 3.23 (s, 3H), 2.68 (m, 1H), 2.62 (dd, $J = 8.8, 8.5$ Hz, 1H), 1.53 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) : δ 162.5, 155.3, 147.8, 147.3, 138.7, 132.5, 130.0, 122.8, 121.3, 121.2, 116.5, 113.5, 110.7, 110.2, 108.0, 76.6, 74.5, 59.0, 55.7, 55.0, 43.6, 41.7, 40.0, 32.8, 28.8, 25.1, 23.6. LRMS (ESI) : m/z 450 $[\text{M}+\text{H}]^+$. HRMS (ESI): calcd for $\text{C}_{27}\text{H}_{32}\text{NO}_5$ $[\text{M}]^+$ 450.2275, found 450.2276

Compound 3:

Colourless oil; $[\alpha]_D^{25} = +435.5$ (c 0.045, CHCl_3); ^1H NMR (500 MHz, CDCl_3) : δ 8.02 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.49 (td, $J = 7.5, 1.3$ Hz, 1H), 7.20 (m, 1H), 6.46 (s, 1H), 6.05 (s, 1H), 5.71 (d, $J = 1.3$ Hz, 1H), 5.64 (d, $J = 1.3$ Hz, 1H), 4.17 (dd, $J = 10.4, 8.2$ Hz, 1H), 3.86 (s, 3H), 3.80 (t, $J = 8.3$ Hz, 1H), 3.41 (m, 2H), 3.32 (s, 3H), 3.29 (s, 3H), 2.62 (m, 1H), 2.56 (dd, $J = 8.7, 8.3$ Hz, 1H), 1.52 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) : δ 162.5, 155.3, 153.7, 145.7, 140.2, 138.8, 129.9, 123.0, 121.5, 121.0, 116.5, 113.4, 107.5, 107.0, 100.4, 95.5, 76.2, 74.7, 59.0, 57.6, 42.5, 39.0, 36.6, 32.9, 28.8, 25.3, 23.7. LRMS (ESI) : m/z 464 $[\text{M}+\text{Na}]^+$. HRMS (ESI): calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 217. 0835, found 217. 0832

^1H & ^{13}C spectra of compounds: