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Total synthesis of the plant alkaloid racemic microthecaline A: first example of a natural product bearing a tricyclic quinoline-serrulatane scaffold

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The first total synthesis of racemic microthecaline A, a quinoline serrulatane alkaloid, isolated from the Australian desert plant *Eremophila microtheca* is described. The natural product was synthesized in ten steps, starting from ethyl 4-bromo-6-methoxy-8-methylquinoline-3-carboxylate in 8% overall yield.

Introduction

Isolation and characterization of the alkaloid (*R*)-microthecaline A was reported by Davis and co-workers from the Australian desert plant *Eremophila microtheca*.¹ The molecule is the first example of a natural product bearing the tricyclic quinoline-serrulatane scaffold and displayed moderate activity against 3D7 and Dd2 *Plasmodium falciparum* strains. Bioactive serrulatane based molecules are well known for their diverse activities including anti-tubercular, anti-inflammatory and inhibition of phagocytosis.² These properties along with interesting structural features have made serrulatane diterpenoids important targets in synthetic explorations. In a paper reported last year by Rajan Babu and coworkers they disclosed the use of stereoselective hydrovinylation *en route* to the synthesis of serrulatane diterpenes and several of their diastereomeric analogs.³ This paper attempted to address the installation of stereogenic centers on exocyclic locations adjacent to chiral centers and also developed the synthesis of various serrulatane diterpenoids. Aggarwal *et al.* in another paper have reported the synthesis of all diastereomers of erogorgiaene, a serrulatane diterpenoid *via* a lithiation–borylation methodology.⁴

Given our research interest in the area of fused quinoline based heterocycles,⁵ total synthesis of microthecaline A was undertaken. Key feature of its structure is the presence of a tetra-substituted 5,6-dihydro-4*H*-benzo[*de*]quinoline ring. While several reports are available in the literature for the synthesis of the aforementioned ring system, most of them disclose the synthesis in a fused ring format along with other aromatic rings.⁶ Very few examples reveal a stand-alone synthesis of this scaffold. In a recent paper AlCl₃ assisted

synthesis of 6-methyl-5,6-dihydro-1*H*-benzo[*de*]quinolin-2(4*H*)-one from 4-(but-3-en-1-yl)quinolin-2(1*H*)-one was reported by Xu *et al.*⁷ Kanai and co-workers have reported synthesis of these rings by reaction between methyl quinolines and styrenes using an *in situ* generated cobalt hydride catalyst.⁸ Li *et al.* in a separate paper have reported the formation of 2-methyl-6-phenyl-5,6-dihydro-4*H*-benzo[*de*]quinoline, in their attempt to carry out photo-induced methylation of heteroarenes.⁹ Ellman and co-workers have reported synthesis of 2,3-dihydro-1*H*-benzo[*kl*]acridine bearing the 5,6-dihydro-4*H*-benzo[*de*]quinoline unit in their attempt to synthesize unsymmetrical acridines and phenazines.¹⁰ In a recent paper by Kuhn and coworkers AlCl₃ mediated intramolecular α -alkylation was used for the synthesis of diverse tricyclic scaffolds starting from α,β -unsaturated lactones and lactams.¹¹ Most of the reported compounds represented either 4*a*,5,7,8,9,10-hexahydrophenanthridin-6(10*bH*)-one or 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-one type of ring system, except one example which showed the formation of 6-methyl-5,6-dihydro-1*H*-benzo[*de*]quinolin-2(4*H*)-one compound.

Results and discussion

Retrosynthetic analysis

For microthecaline A synthesis, construction of the 5,6-dihydro-4*H*-benzo[*de*]quinoline ring was crucial along with its C-3 appendage and other substituents. Accordingly, a retrosynthetic strategy was envisaged relying mainly on introduction of a pivotal cyclohexane ring by Friedel–Crafts reaction. The initial 5,6-dihydro-4*H*-benzo[*de*]quinoline ring system was supposed to be synthesized starting from ethyl 4-bromo-6-methoxy-8-methylquinoline-3-carboxylate and subsequent implementation of Heck coupling and Friedel–Crafts acylation. As per this strategy Wittig reaction followed by asymmetric reduction would generate the required C-6 chiral center with a substituted methyl group. Further systematic two fold implementation of partial reduction and Wittig/Wittig–Horner reaction, respectively would provide the methoxy-substituted

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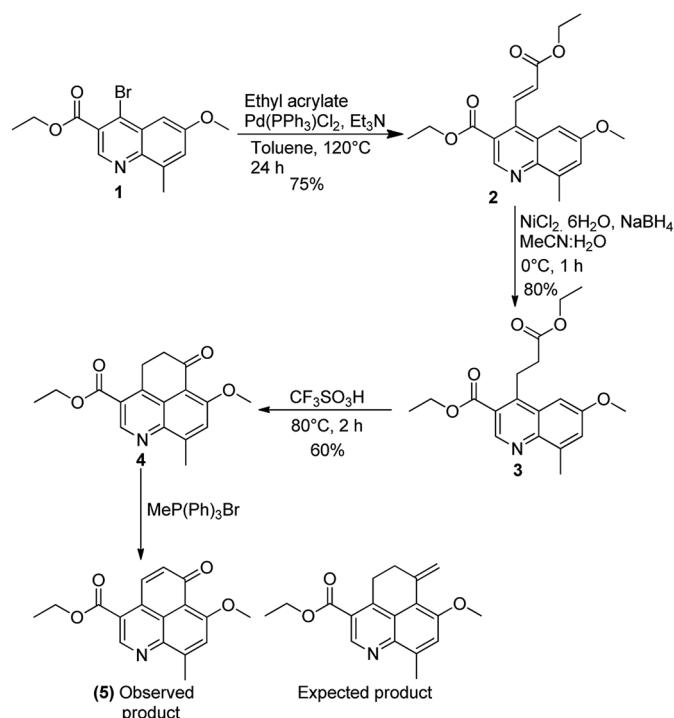
penultimate compound. The final step required demethylation to generate the target molecule (Scheme 1).

Synthetic strategy

Our synthetic efforts started with commercially available 4-methoxy-2-methylaniline which was converted to ethyl 4-bromo-6-methoxy-8-methylquinoline-3-carboxylate (**1**) using well established synthetic protocol.¹² Compound **1** was subjected to Heck coupling which yielded corresponding α,β -unsaturated ester (**2**) in 75% yield. On reaction with $\text{NiCl}_2\text{-NaBH}_4$ in $\text{CH}_3\text{CN-H}_2\text{O}$ as solvent system, compound **2** was converted to the corresponding reduced ester (**3**). Subsequent attempts to carry out Friedel–Crafts acylation on **2** in the presence of $\text{CF}_3\text{SO}_3\text{H}$ gave the tricyclic cyclohexanone moiety in 60% yield. At this juncture our repeated attempts (by using KO^tBu , NaO^tBu , NaH , $n\text{-BuLi}$) to generate ethyl 7-methoxy-9-methyl-6-methylene-5,6-dihydro-4*H*-benzo[*de*]quinoline-3-carboxylate (**4**) via Wittig reaction resulted in the formation of only α,β -unsaturated cyclohexanone derivative **5** instead of the expected product (**ESI**). This forced us to abandon the initially articulated route of asymmetric reduction of the terminal double bond (Scheme 2).

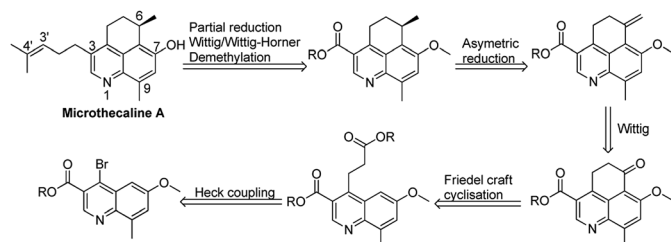
We subsequently carried out a Grignard reaction on the cyclohexanone carbonyl in **4** and the resulting tertiary alcohol (**6**) was treated with HCl to generate ethyl 7-methoxy-6,9-dimethyl-4*H*-benzo[*de*]quinoline-3-carboxylate. The rationale here was to attempt asymmetric reduction of the double bond to generate the appropriate chiral center. Several attempts to carry out elimination reaction using HCl , HBr , *p*-TSA (*p*-toluene sulfonic acid), PPTS (pyridinium-*p*-toluenesulfonate), TESiH (triethylsilane) and SiO_2 did not yield the desired compound ethyl 7-methoxy-6,9-dimethyl-4*H*-benzo[*de*]quinoline-3-carboxylate (**7**) (Scheme 3).

Our initial setbacks in obtaining the chiral center with appropriate stereochemistry forced us to follow a different approach and focus mainly on the synthesis of the racemic microthecaline A. Our revised method was also initiated from **1**, which when subjected to reductive Heck coupling (initial attempt with $\text{Pd}(\text{OAc})_2$ and *o*-tolylphosphine led to the formation of reductive Heck product and Heck product in 4 : 1 ratio, while reaction using $\text{PdCl}_2(\text{PPh}_3)_2$ as catalyst gave 9 : 1 ratio of the reductive Heck product and Heck product) yielded compound **8**. Subsequent reduction of ketonic carbonyl in **7** using NaBH_4 gave the corresponding tertiary alcohol (**9**) in 91% yield. Subjecting **9** to intramolecular Friedel–Crafts alkylation, by using well known route with $\text{FeCl}_3\text{-AgSbF}_6$ did not give the expected

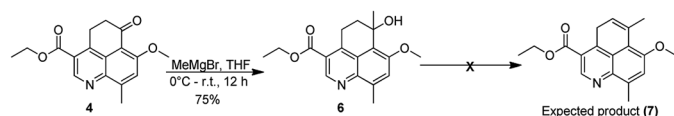


Scheme 2 Initial attempt to synthesize the tricyclic core and introduction of the chiral center.

product.¹³ This observation forced us to defer the intramolecular Friedel–Crafts alkylation step and instead chlorination of compound **9** was attempted with *N*-chlorosuccinimide in the presence of PPh_3 . The reaction was successful and gave compound **10** in 85% yield. Further, the available ester on quinoline ring was reduced with DIBAL-H (attempts to terminate the reaction at aldehyde stage failed) and compound **11** thus obtained was oxidized by Dess–Martin periodinane (DMP) to the corresponding aldehyde. It was not isolated and was directly used as a substrate for the Wittig–Horner reaction in the presence of NaH in THF to produce the α,β -unsaturated ester (**12**) in 70% yield. Subjecting compound **12** to the deferred intramolecular Friedel–Crafts alkylation step using AlCl_3 yielded the required tricyclic scaffold (**13**) in 68% yield. The compound was thoroughly characterized by $^1\text{H}/^{13}\text{C}$ and NOE experiments (**ESI**). Subsequent attempts were directed on installing the remaining C3 fragment on the side chain. It was carried out by reduction of the double bond in compound **13** to its corresponding saturated congener **14**, which was further reduced to the 1° alcohol (similar to our previous observation, attempts to terminate the reaction at aldehyde stage failed) **15**. Oxidation with DMP followed by treatment with the appropriate

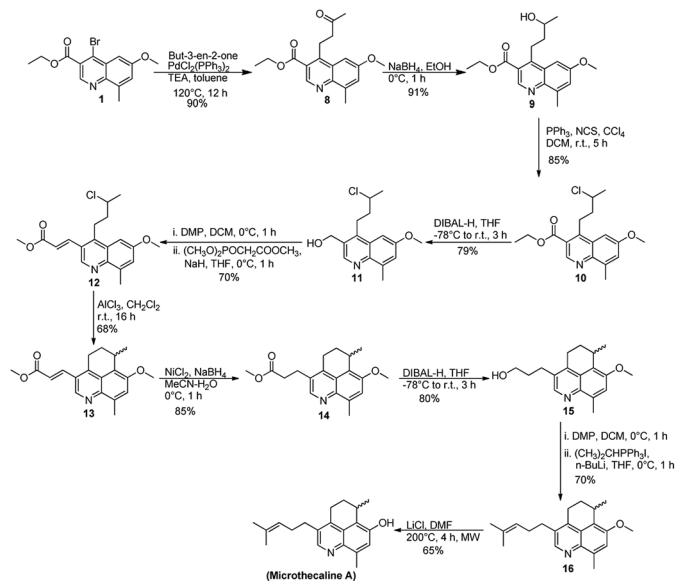


Scheme 1 Preliminary retrosynthetic analysis of microthecaline A.



Scheme 3 Grignard reaction on the tricyclic core and subsequent elimination attempts.





Scheme 4 Reactions which led to the final synthesis of (\pm)-microthecaline A.

ylide in the presence of *n*-BuLi led to the penultimate compound **16**. Final step of demethylation was attempted with various reagents such as BBr₃, HBr, HCl, NaSEt but was only successful with LiCl in DMF under microwave conditions and gave (\pm)-microthecaline A as a free base in 65% yield. The product obtained was thoroughly characterized and the spectroscopic data was found to be comparable with the literature values available for microthecaline A (ESI).¹ Given the importance of enantiomeric purity to evaluate the biological activity of the molecule, attempts are currently underway in our lab to develop a synthetic route for (*R*)-microthecaline A, the naturally occurring stereoisomer (Scheme 4).

Conclusion

In summary, we have developed the first total synthesis of quinoline serrulatane alkaloid (\pm)-microthecaline A in 8% total yield. Given the generic nature of the reactions incorporated in the synthetic route, we feel that diverse analogues of the aforesaid molecule can be prepared, if required.

Experimental

All the compounds and reagents required were purchased from commercial sources and were used without further purification. Solvents were dried and distilled using standard procedures, prior to use. Antonpaar-Monowave microwave synthesizer was used for reactions carried out under microwave conditions. ¹H NMR (500 MHz and 400 MHz) and ¹³C (125 MHz and 100 MHz) spectra were recorded in CDCl₃, DMSO-*d*₆ and CD₃OD using (CH₃)₄Si as internal standard. IR spectra were recorded as KBr plates on Shimadzu-IR Affinity instrument. Melting points were recorded on a Buchi-M565 melting point apparatus and are uncorrected.

(*E*)-Ethyl 4-(3-ethoxy-3-oxoprop-1-en-1-yl)-6-methoxy-8-methylquinoline-3-carboxylate (**2**)

To a stirred and de-gassed solution of **1** (1 g, 3.09 mmol) in dry toluene (20 mL) was added ethylacrylate (460 mg, 4.6 mmol), triethylamine (1.3 mL, 9.2 mmol) and PdCl₂(PPh₃)₂ (217 mg, 0.3 mmol). The reaction mixture was further de-gassed for 2 minutes in a seal-tube and the reaction mixture was then heated at 120 °C for 24 hours. On completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and filtered through Celite pad. The Celite pad was further washed with 50 mL of ethyl acetate (EtOAc). The organic layers were subsequently combined and evaporated to afford crude compound. Column chromatography was performed on the crude compound using silica and 30% EtOAc/hexanes as the mobile phase afforded compound **2** (796 mg, 75%) as a light yellow solid (mp 99–101 °C). ¹H NMR (400 MHz, CDCl₃) δ : 9.2 (s, 1H), 8.33–8.29 (dd, *J*₁ = 16.4 Hz, *J*₂ = 0.8 Hz, 1H), 7.33 (d, 1H), 7.17 (d, 1H), 6.16–6.12 (dd, *J*₁ = 16.4 Hz, *J*₂ = 1.2 Hz, 1H), 4.4–4.36 (q, 2H), 4.36–4.32 (q, 2H), 3.9 (s, 3H), 2.78 (s, 3H), 1.42–1.39 (t, 6H); ¹³C NMR (100 MHz, CDCl₃) δ : 166, 165.6, 158, 146.3, 144.5, 142.8, 142.4, 139.5, 126.3, 125.8, 123.9, 121.5, 103.8, 61.6, 60.9, 55.5, 18.4, 14.2, 14.1; ν_{\max} (KBr)/cm⁻¹: 3301, 1610; HRMS-ESI (+) *m/z*: calculated for C₁₉H₂₂NO₅ [M + H]⁺, 344.1492; found, 344.1473.

Ethyl 4-(3-ethoxy-3-oxopropyl)-6-methoxy-8-methylquinoline-3-carboxylate (**3**)

To a stirred solution of **2** (700 mg, 2.04 mmol) in MeCN : H₂O (9 : 1, 15 mL) at 0 °C was added NiCl₂·6H₂O (1.45 g, 6.1 mmol), followed by portion-wise addition of NaBH₄ (232 mg, 6.1 mmol). The reaction mixture was then allowed to stir at 0 °C for 1 hour. On completion, the reaction mixture was filtered through Celite pad, which was further washed with EtOAc (30 mL). The combined organic layers were then washed with water and saturated brine solution; it was subsequently dried with anhydrous Na₂SO₄ and evaporated to afford crude compound. Column chromatography of the crude compound using silica and elution with 30% EtOAc/hexanes provided **3** (560 mg, 80%) as a light yellow solid (mp 70–72 °C). ¹H NMR (400 MHz, CDCl₃) δ : 9.18 (s, 1H), 7.25 (s, 2H), 4.48–4.42 (q, 2H), 4.28–4.14 (q, 2H), 3.96 (s, 3H), 3.7–3.66 (t, *J* = 7.6 Hz, 2H), 2.77 (s, 3H), 2.76–2.72 (t, *J* = 7.6 Hz, 2H), 1.4–1.42 (t, *J* = 7.6 Hz, 3H), 1.27–1.23 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 172.8, 166.8, 158, 147.5, 146.8, 144.5, 139.8, 127.4, 122.2, 122, 100.1, 61.5, 60.7, 35.4, 34.3, 24.4, 18.4, 14.2, 14.1; ν_{\max} (KBr)/cm⁻¹: 3310, 1625; HRMS-ESI (+) *m/z*: calculated for C₁₉H₂₄NO₅ [M + H]⁺, 346.1649; found, 346.1638.

Ethyl 7-methoxy-9-methyl-6-oxo-5,6-dihydro-4H-benzo[de]quinoline-3-carboxylate (**4**)

A mixture of **3** (500 mg, 1.45 mmol) and trifluoromethanesulphonic acid (5 mL) were heated at 80 °C for 2 hours. On completion, the reaction mixture was cooled to room temperature, diluted with ice cold water and quenched with saturated NaHCO₃ solution. The resulting aqueous solution was



then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄ evaporated to afford crude compound, which was chromatographed on silica by eluting with 65% EtOAc/hexanes to give **4** (260 mg, 60%) as light yellow solid (mp 148–150 °C). ¹H NMR (400 MHz, CDCl₃) δ: 9.2 (s, 1H), 7.56 (s, 1H), 4.49–4.44 (q, 2H), 4.19 (s, 3H), 3.82–3.78 (t, *J* = 7.4 Hz, 2H), 2.88 (s, 3H), 2.9–2.86 (t, *J* = 7.4 Hz, 2H), 1.47–1.42 (q, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 196.9, 166.2, 157.4, 147.8, 146.4, 143.8, 142.3, 128.4, 122.9, 118.9, 114.3, 61.6, 56.7, 39.2, 26.9, 19.4, 14.3; ν_{max} (KBr)/cm⁻¹: 3255, 1710; HRMS-ESI (+) *m/z*: calcd for C₁₇H₁₈NO₄ [M + H]⁺, 300.123; found, 300.122.

Ethyl 7-methoxy-9-methyl-6-oxo-6H-benzo[de]quinoline-3-carboxylate (**5**)

To a stirred suspension of KO^tBu (112 mg, 1 mmol) in dry THF (10 mL) was added dropwise methyltriphenylphosphonium bromide (358 mg, 1 mmol) in THF at 0 °C (reaction mixture turned to light red) and stirred for 30 min at same temperature. To this compound **4** (250 mg, 0.83 mmol) dissolved in dry THF was added and the resulting reaction mixture was allowed to stir for 1 hour at 0 °C. The reaction mixture was then diluted with water and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and evaporated to afford the crude compound, which was chromatographed on SiO₂ by eluting with 50% EtOAc/hexanes to give ethyl 7-methoxy-9-methyl-6-oxo-6H-benzo[de]quinoline-3-carboxylate (**5**) (180 mg, 73%) as light yellow solid (mp 148–150 °C). ¹H NMR (400 MHz, CDCl₃) δ: 9.32 (s, 1H), 8.67 (d, *J* = 10.2 Hz, 1H), 7.56 (s, 1H), 6.89 (d, *J* = 10.2 Hz, 1H), 4.53 (d, *J* = 7.1 Hz, 2H), 4.22 (s, 3H), 2.94 (s, 3H), 1.72 (s, 1H), 1.49 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 182.72, 165.82, 163.48, 149.32, 147.31, 142.44, 135.66, 134.20, 133.59, 124.29, 123.14, 118.60, 113.30, 62.12, 56.93, 19.45, 14.29; HRMS-ESI (+) *m/z*: calcd for C₁₇H₁₆NO₄ [M + H]⁺, 298.1074; found, 298.1065.

Ethyl 6-hydroxy-7-methoxy-6,9-dimethyl-5,6-dihydro-4H-benzo[de]quinoline-3-carboxylate (**6**)

To a stirred solution of **4** (100 mg, 0.33 mmol) in dry THF (5 mL) was added a solution of 1 M methylmagnesium bromide (0.5 mL, 0.5 mmol) in THF at 0 °C and the reaction mixture was allowed to stir at room temperature for 12 hours. The reaction was then quenched with NH₄Cl solution, diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine solution, dried with Na₂SO₄ and evaporated to afford the crude compound. Column chromatography on silica by eluting with 30% EtOAc/hexanes to give **6** (80 mg, 75%) as brown gummy solid. ¹H NMR (400 MHz, CDCl₃) δ: 9.17 (s, 1H), 7.45 (s, 1H), 5.06 (s, 1H), 4.47–4.41 (m, 2H), 4.08 (s, 3H), 3.91–3.83 (m, 1H), 3.17–3.08 (m, 1H), 2.81 (s, 3H), 2.27–2.09 (m, 1H), 1.64 (s, 3H), 1.46–1.42 (t, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 166.8, 153.1, 148, 147.3, 143.3, 138.2, 125.6, 124.8, 121.4, 118.2, 71.2, 61.4, 56.6, 36.5, 27.8, 25.9, 18.8, 14.4; ν_{max} (KBr)/cm⁻¹: 3315, 1690; HRMS-ESI (+) *m/z*: calcd for C₁₈H₂₂NO₄ [M + H]⁺, 316.1543; found, 316.1539.

Ethyl 6-methoxy-8-methyl-4-(3-oxobutyl)quinoline-3-carboxylate (**8**)

To a stirred and de-gassed solution of **1** (5 g, 15.4 mmol) in dry toluene was added but-3-en-2-one (2.5 mL, 30.9 mmol) followed by TEA (8.7 mL, 61.2 mmol) and PdCl₂(PPh₃)₂ (1 g, 1.54 mmol). The reaction mixture was further de-gassed for 2 min in a seal-tube and the reaction mixture was then heated at 120 °C for 24 hours. On completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and filtered through Celite pad. The Celite pad was washed with EtOAc (3 × 50 mL). The combined organic layers were evaporated to afford crude compound, which was then chromatographed using SiO₂ by eluting with 30% EtOAc/hexanes to give **8** (4.38 g, 90%) as white solid (mp 79–81 °C). ¹H NMR (400 MHz, CDCl₃) δ: 9.13 (s, 1H), 7.31 (d, *J* = 4 Hz, 1H), 7.2 (d, 1H), 4.46–4.41 (q, 2H), 3.92 (s, 3H), 3.62–3.58 (t, *J* = 8 Hz, 2H), 2.91–2.87 (t, *J* = 8 Hz, 2H), 2.77 (s, 3H), 2.21 (s, 3H), 1.45–1.41 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 207.3, 166.2, 158, 148.4, 146.7, 144.4, 139.2, 127.4, 123.3, 123, 100.1, 61.4, 55.4, 43.6, 29.9, 23.2, 18.4, 14.2; ν_{max} (KBr)/cm⁻¹: 3411, 2972, 1720; HRMS-ESI (+) *m/z*: calcd for C₁₈H₂₂NO₄ [M + H]⁺, 316.1543; found, 316.1538.

Ethyl 4-(3-hydroxybutyl)-6-methoxy-8-methylquinoline-3-carboxylate (**9**)

To a stirred solution of **8** (2.5 g, 7.93 mmol) in EtOH (25 mL) at 0 °C was added NaBH₄ (361 mg, 9.52 mmol) portion wise and the reaction mixture was stirred for 1 hour. On completion, the reaction was quenched with ice cold water, EtOH evaporated and the compound precipitated in water was filtered and dried to get **9** (2.26 g, 91%) as white solid (mp 113–115 °C). ¹H NMR (400 MHz, CDCl₃) δ: 9.14 (s, 1H), 7.34–7.33 (d, *J* = 2.4 Hz, 1H), 7.3 (d, *J* = 1 Hz, 1H), 4.47–4.42 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 3.9–3.8 (m, 1H), 2.77 (s, 3H), 2.51–2.5 (d, *J* = 4 Hz, 2H), 1.98–1.83 (m, 2H), 1.45–1.42 (t, *J* = 7.2 Hz, 3H), 1.25–1.24 (d, *J* = 6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 167.7, 157.7, 149.7, 146.8, 144.4, 139.6, 127.9, 123.2, 122.7, 100.9, 67.1, 63.5, 55.4, 39.3, 25.1, 23.5, 19.4, 14.2; ν_{max} (KBr)/cm⁻¹: 3310, 2970, 1710; HRMS-ESI (+) *m/z*: calcd for C₁₈H₂₄NO₄ [M + H]⁺, 318.17; found, 318.1695.

Ethyl 4-(3-chlorobutyl)-6-methoxy-8-methylquinoline-3-carboxylate (**10**)

To a stirred solution of **9** (1 g, 3.15 mmol) in CH₂Cl₂ : CCl₄ (1 : 1, 20 mL) at room temperature was added PPh₃ (1.23 g, 4.75 mmol) followed by *N*-chlorosuccinimide (503 mg, 3.78 mmol) and the reaction mixture was stirred for 5 hours. On completion of the reaction, the solvent was removed under reduced pressure to afford crude compound, which was further chromatographed on SiO₂ by eluting with 60% EtOAc/hexanes to give **10** (898 mg, 85%) as white solid (mp 64–66 °C). ¹H NMR (500 MHz, CDCl₃) δ: 9.13 (s, 1H), 7.38–7.37 (d, *J* = 2.5 Hz, 1H), 7.29 (s, 1H), 4.46–4.44 (q, *J* = 7 Hz, 2H), 4.3–4.26 (m, 1H), 3.94 (s, 3H), 3.6–3.5 (m, 1H), 2.76 (s, 3H), 2.23–2.19 (m, 1H), 2.1–2 (m, 1H), 1.62–1.6 (d, *J* = 6.5 Hz, 3H), 1.45–1.42 (t, *J* = 7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ: 166.9, 157.9, 148.6, 146.7, 144.5, 139.6, 127.9, 123.6, 122.8, 100.3, 61.3, 59.5, 55.5, 40.3, 26.3, 25.3, 18.4, 14.3;



ν_{\max} (KBr)/ cm^{-1} : 3450, 2960, 1736; HRMS-ESI (+) m/z : calcd for $\text{C}_{18}\text{H}_{23}\text{ClNO}_3$ [$\text{M} + \text{H}$] $^+$, 336.1361; found, 336.1351.

(4-(3-Chlorobutyl)-6-methoxy-8-methylquinolin-3-yl)methanol (11)

To a stirred solution of **10** (700 mg, 2.08 mmol) in dry THF (10 mL) at -78°C dropwise addition of 1 M DIBAL-H (3.13 mL, 3.13 mmol) in hexane was carried out. The reaction mixture was then warmed to room temperature and stirred for 3 hours. On completion, the reaction was quenched with aqueous NH_4Cl solution and further extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine solution, dried with Na_2SO_4 and evaporated under reduced pressure. The resulting crude compound was chromatographed on SiO_2 by eluting with 50% EtOAc/hexanes to give **11** (480 mg, 79%) as white solid (mp $143\text{--}145^\circ\text{C}$). ^1H NMR (500 MHz, CDCl_3) δ : 8.64 (s, 1H), 7.26 (s, 1H), 7.23 (s, 1H), 4.87 (s, 2H), 4.25–4.21 (m, 1H), 3.93 (s, 3H), 3.43–3.37 (m, 1H), 3.24–3.18 (m, 1H), 2.75 (s, 3H), 2.13–2.01 (m, 2H), 1.59–1.58 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 157.6, 147.6, 144.6, 143.6, 139.4, 130.5, 128.1, 121.8, 99.6, 61.5, 59.1, 55.5, 40.4, 25.3, 25.2, 18.5; ν_{\max} (KBr)/ cm^{-1} : 3231, 1614; HRMS-ESI (+) m/z : calcd for $\text{C}_{16}\text{H}_{21}\text{ClNO}_2$ [$\text{M} + \text{H}$] $^+$, 294.1255; found, 294.1247.

(E)-Methyl 3-(4-(3-chlorobutyl)-6-methoxy-8-methylquinolin-3-yl)acrylate (12)

To a stirred solution of **11** (450 mg, 1.53 mmol) in CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (813 mg, 1.91 mmol) portion wise at 0°C and the reaction mixture was left to stir at same temperature for 1 hour. On completion, the resulting mixture was filtered through Celite pad, which was further washed with CH_2Cl_2 (50 mL). The collected organic layers were then combined and further washed with aqueous NaHCO_3 , water, brine and dried with anhydrous Na_2SO_4 . The dried organic layer was then evaporated under reduced to afford aldehyde (1.53 mmol) compound as gummy oil, which was directly used for the next step.

To a stirred suspension of trimethylphosphonoacetate (0.37 mL, 2.3 mmol) in dry THF (25 mL) at 0°C was added 60% NaH (92 mg, 2.3 mmol) in small portions. After 10 minutes a solution of aldehyde (1.53 mmol) in dry THF was added and the reaction mixture was left to stir at 0°C for 1 h. On completion, the reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and evaporated to afford crude compound. The resulting crude product was chromatographed on SiO_2 by eluting with 30% EtOAc/hexanes to give **12** (373 mg, 70%) as gummy solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9 (s, 1H), 8.14–8.1 (d, $J = 15.6$ Hz, 1H), 7.34 (s, 2H), 6.84–6.8 (d, $J = 14.4$ Hz, 1H), 4.4 (m, 1H), 3.91 (s, 3H), 3.77 (s, 1H), 3.35–3.39 (m, 2H), 2.67 (s, 3H), 2.02–2.01 (m, 1H), 1.88 (m, 1H), 1.56–1.54 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.9, 157.6, 144.8, 144.5, 143.7, 139.9, 139.4, 127.7, 125.5, 122.6, 120.5, 100.1, 59.5, 55.4, 51.8, 40.2, 25.3, 25.1, 18.3; ν_{\max} (KBr)/ cm^{-1} : 3416, 2915, 1715; HRMS-ESI (+) m/z : calcd for $\text{C}_{19}\text{H}_{23}\text{ClNO}_3$ [$\text{M} + \text{H}$] $^+$, 348.1361; found, 348.1354.

(E)-Methyl 3-(7-methoxy-6,9-dimethyl-5,6-dihydro-4H-benzo[de]quinolin-3-yl)acrylate (13)

To a stirred solution of **12** (400 mg, 1.15 mmol) in dry DCM (20 mL) at 0°C was added AlCl_3 (306 mg, 2.3 mmol) and the reaction mixture was stirred at room temperature for 16 hours. On completion, it was quenched with aqueous NH_4Cl solution and extracted with DCM (3×75 mL). The combined organic layers were further washed with brine, dried with Na_2SO_4 and evaporated under reduced pressure to afford the crude compound. Pure product was obtained by performing column chromatography on silica gel and eluting with 25% EtOAc/hexanes to give **13** (276 mg, 68%) as white solid (mp $128\text{--}130^\circ\text{C}$). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 9 (s, 1H), 8.06–8.03 (d, $J = 16$ Hz, 1H), 7.54 (s, 1H), 6.79–6.76 (d, $J = 16$ Hz, 1H), 3.94 (s, 3H), 3.51 (m, 1H), 3.2–3.1 (m, 2H), 2.7 (s, 3H), 2–1.98 (m, 1H), 1.88–1.83 (m, 1H), 1.16–1.15 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ : 166.4, 152.3, 144.6, 143.2, 141.7, 139.2, 135.6, 123.8, 123.5, 123.3, 120, 117.5, 56.2, 51.5, 27.2, 25.4, 20.8, 18.9, 17.9; ν_{\max} (KBr)/ cm^{-1} : 3410, 2970, 1711; HRMS-ESI (+) m/z : calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_3$ [$\text{M} + \text{H}$] $^+$, 312.1594; found, 312.1584.

Methyl 3-(7-methoxy-6,9-dimethyl-5,6-dihydro-4H-benzo[de]quinolin-3-yl)propanoate (14)

To a stirred solution of **13** (250 mg, 0.8 mmol) in MeCN : H_2O (9 : 1, 10 mL) at 0°C was added $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (571 mg, 2.41 mmol), followed by portion wise addition of NaBH_4 (91 mg, 2.41 mmol). The reaction mixture was then left to stir at same temperature for 1 hour. On completion, the reaction mixture was filtered through Celite pad, which was further washed with EtOAc (40 mL). The combined organic layers were then washed with water, brine, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude compound was chromatographed on silica gel by eluting with 30% EtOAc/hexanes to give **14** (213 mg, 85%) as gummy solid. ^1H NMR (500 MHz, CDCl_3) δ : 8.58 (s, 1H), 7.28 (s, 1H), 3.95 (s, 3H), 3.69 (s, 3H), 3.61–3.59 (m, 1H), 3.14–3.11 (t, $J = 8$ Hz, 2H), 2.69–2.6 (m, 2H), 2.03–1.93 (m, 2H), 1.22–1.2 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 172.9, 152.2, 147.9, 141.7, 141.3, 135.8, 128.6, 125.1, 123.1, 116, 56.2, 51.8, 34.5, 27.8, 26.1, 25.7, 21.2, 19.2, 18.6; ν_{\max} (KBr)/ cm^{-1} : 2950, 1714; HRMS-ESI (+) m/z : calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_3$ [$\text{M} + \text{H}$] $^+$, 314.1751; found, 314.1747.

3-(7-Methoxy-6,9-dimethyl-5,6-dihydro-4H-benzo[de]quinolin-3-yl)propan-1-ol (15)

Compound **14** (200 mg, 0.63 mmol) converted to **15** (white gummy solid, 145 mg, 80%) by following the same procedure as that of compound **12**. ^1H NMR (500 MHz, CDCl_3) δ : 8.59 (s, 1H), 7.27 (s, 1H), 3.95 (s, 3H), 3.74–3.72 (t, $J = 6.2$ Hz, 2H), 3.61–3.59 (m, 1H), 3.08–2.98 (m, 2H), 2.9–2.87 (t, $J = 7.7$ Hz, 2H), 2.78 (s, 3H), 2.03–1.86 (m, 4H), 1.22–1.21 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 152.1, 148.4, 141.3, 141.2, 135.5, 130.1, 125.2, 123.1, 115.8, 62, 56.2, 33.2, 27.9, 26.6, 26, 21.1, 19.2, 18.6; ν_{\max} (KBr)/ cm^{-1} : 3385, 2910, 1621; HRMS-ESI (+) m/z : calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_2$ [$\text{M} + \text{H}$] $^+$, 286.1802; found, 286.1795.



7-Methoxy-6,9-dimethyl-3-(4-methylpent-3-en-1-yl)-5,6-dihydro-4H-benzo[de]quinolines (16)

Compound **15** (130 mg, 0.45 mmol) was converted to the corresponding aldehyde (0.45 mmol) by using the same procedure as that for the conversion of compound **10** to its corresponding aldehyde. To a stirred solution of isopropyltriphenylphosphonium iodide (295 mg, 0.68 mmol) in dry THF (10 mL) was added 1.6 M BuLi (0.42 mL, 0.68 mmol) in THF at 0 °C. After 5–10 minutes, a solution of aldehyde (0.45 mmol) in dry THF was introduced to it and the resulting mixture was allowed to stir at 0 °C for 1 hour. On completion, the reaction was quenched with aqueous NH₄Cl solution and extracted with EtOAc (3 × 25 mL). The combined organic layers were then washed with brine, dried with anhydrous Na₂SO₄ and evaporated to afford the crude compound. Chromatographic purification of the crude compound on SiO₂ by eluting with 25% EtOAc/hexanes led to the pure product **16** (98 mg, 70%) as a gummy solid. ¹H NMR (500 MHz, CD₃OD) δ: 8.41 (s, 1H), 7.38 (s, 1H), 5.21–5.18 (q, 1H), 3.94 (s, 3H), 3.59–3.56 (m, 1H), 3.14–3 (m, 2H), 2.83–2.8 (m, 2H), 2.83–2.8 (m, 2H), 2.71 (s, 3H), 2.34–2.31 (t, *J* = 7.25 Hz, 2H), 2.04–2.0 (m, 1H), 1.88–1.87 (m, 1H), 1.64 (s, 3H), 1.41 (s, 3H), 1.2–1.18 (d, *J* = 7 Hz, 3H); ¹³C NMR (125 MHz, CD₃OD) δ: 153.8, 149.4, 143.4, 141.9, 136.1, 133.7, 131.8, 126.5, 124.3, 124.2, 117.4, 31.3, 29.8, 28.9, 27.4, 25.9, 22.3, 19.5, 18.9, 17.5; ν_{\max} (KBr)/cm⁻¹: 2931, 1620; HRMS-ESI (+) *m/z*: calcd for C₂₁H₂₈NO [M + H]⁺, 310.2165; found, 310.2152.

6,9-Dimethyl-3-(4-methylpent-3-en-1-yl)-5,6-dihydro-4H-benzo[de]quinolin-7-ol [(±)-Microthecaline A]

To a stirred solution of **16** (70 mg, 0.22 mmol) in DMF (5 mL) was added LiCl (47 mg, 1.1 mmol) in closed vessel and the reaction mixture was then irradiated in a microwave at 200 °C for 4 h. The reaction mixture was then cooled to room temperature and diluted with water. It was further extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with water, brine, dried with anhydrous Na₂SO₄. The dried layer was evaporated under reduced pressure to afford the crude compound, which was further chromatographed on silica gel by eluting with 40% EtOAc/hexanes to give the free base of (±)-microthecaline A (43 mg, 65%) as a white solid (mp 78–80 °C). ¹H NMR (400 MHz, CD₃OD) δ: 8.35 (s, 1H), 7.12 (s, 1H), 5.23–5.19 (t, *J* = 7.4 Hz, 1H), 3.57–3.54 (m, 1H), 3.14–3.09 (m, 1H), 3.06–3.01 (m, 1H), 2.86–2.79 (m, 2H), 2.63 (s, 3H), 2.37–2.3 (m, 2H), 2.07–2.02 (m, 1H), 1.94–1.88 (m, 1H), 1.65 (s, 3H), 1.43 (s, 3H), 1.23–1.22 (d, *J* = 4.8 Hz, 3H); ¹³C NMR (100 MHz, CD₃OD) δ: 151.5, 148.3, 143, 141.8, 135.5, 133.6, 131.5, 127.1, 124.2, 121.9, 121.2, 31.3, 29.9, 28.5, 27.4, 25.9, 22.3, 19.3, 18.5, 17.5; ν_{\max} (KBr)/cm⁻¹: 2924, 1628; HRMS-ESI (+) *m/z*: calcd for C₂₀H₂₆NO [M + H]⁺, 296.2009; found, 296.2001.

Conflicts of interest

There are no conflicts to declare.

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