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RCM-based approach to seven- and eight-member ring-fused β-carbolines ☆

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Dedicated to Dr. J. S. Yadav on his 60th birthday

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ABSTRACT

RCM-based new route to the synthesis of seven- and eight-member ring-fused β-carboline from Morita–Baylis–Hillman adduct or Barbier-allylation product of *N*-allyl-1-formyl-9*H*-β-carboline is described.

The β-carboline core occupies a privileged position in pharmaceuticals and natural products. In particular, the annulated β-carbolines are subunits of several compounds displaying anticancer and antitumor activities.[1] Recently, we have achieved considerable success in the synthesis of annulated β-carbolines by employing 1-formyl-9*H*-β-carboline in the Morita–Baylis–Hillman (MBH) cycloaddition or carbonyl-ene reactions.[2] We were keen to extend the use of this substrate for the development of a new general route to the synthesis of annulated β-carboline using RCM approach. Herein, we describe our studies in this direction.

A β-carboline unit annulated to a seven-member ring between C-1 and N-9 is represented by arborescidine C and D, maxonine, and adefoline class of alkaloids (Fig. 1) yet, no general routes for the synthesis of such a framework is present in the literature. In principle, an allyl group placed on the nitrogen of the indole-unit on one hand and another allyl chain originating from the formyl group at the C-1 would undergo ring-closing metathesis reaction to afford the desired framework. A retrosynthetic analysis demonstrating the rationale is outlined in Scheme 1. Recently, though Parez-Castells and co-workers have illustrated the use of RCM for generating diverse annulated β-carbolines,[3] the strategy envisaged by us is sufficiently different. As a consequence of our recent work on MBH chemistry of 1-formyl-9*H*-β-carbolines, the expertise to generate the starting material required for this study already existed in the laboratory.

Accordingly, we commenced our work with the preparation of MBH adducts (**2–6**) which was smoothly achieved via reaction between the aldehyde **1** and various alkenes (Scheme 2). Notably, in case of methyl vinyl ketone instead of the expected MBH adduct, we could isolate **7** in good yields as the sole product. With MBH adducts in hand we next investigated the RCM reaction with these

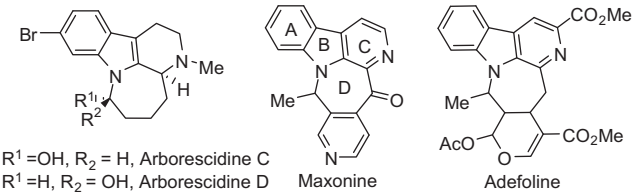
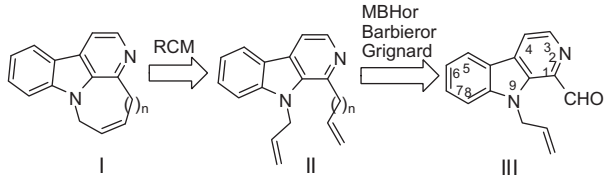


Figure 1. Examples of β-carboline-based alkaloids containing seven-member-fused ring.



Scheme 1. Retrosynthetic scheme for seven- and eight-member ring-fused β-carbolines.

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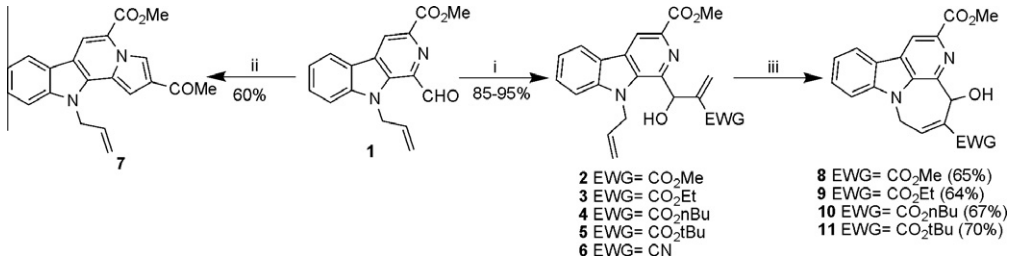
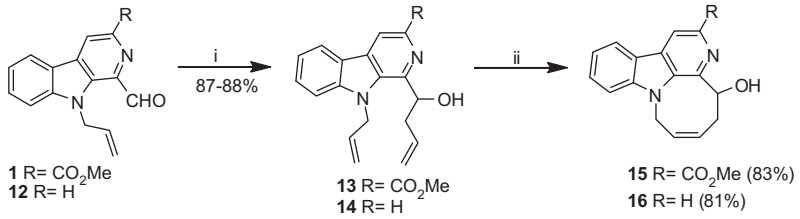


Scheme 2. Reagents and conditions: (i) CH_2=$CHCO_2Et$ or CH_2=CHCN, DABCO, neat rt, 24 h; (ii) CH_2=CHCOMe, DABCO, neat rt, 2 h; (iii) Grubb's II generation cat. (10 mol %), dry CH_2Cl_2, reflux, 3–6 h.



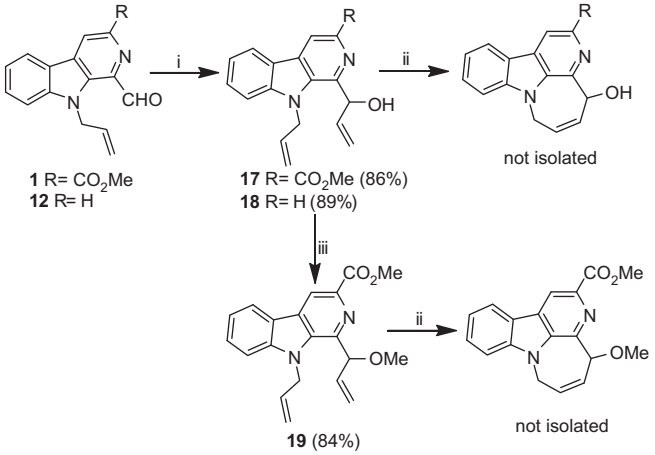
Scheme 3. Reagents and conditions: (i) CH_2=$CHCH_2Br$, In, THF/water (2:1), rt, 3 h; (ii) Grubb's II generation cat. (10 mol %), dry CH_2Cl_2, reflux, 12 h.

substrates. After screening a series of conditions for the purpose of optimization with **2**, it was discovered that **2** in the presence of 10 mol % of Grubb II generation catalyst in methylene chloride under heating at reflux for 3 h afforded the desired product (**8**) in 65% yields.[4] To evaluate the generality of the protocol, different MBH adducts were subjected to the RCM reaction. Except **6**, all substrates successfully yielded the corresponding annulated β-carbolines **9**–**11** in 64–70% yields. In case of **6** we failed to isolate the product as the reaction mixture produced several spots which were inseparable via column chromatography.

Next the scope of the strategy was evaluated with the substrates generated via Barbier type allylation of the formyl group with allyl bromide in substituted 1-formyl-9*H*-β-carboline.[5] Accordingly, the aldehydes **1** and **12** were treated with allyl bromide in the presence of indium under aqueous conditions to afford the corresponding products **13** and **14** in excellent yields (Scheme 3). Treating **13** and **14** with Grubbs II catalyst in methylene chloride under heating at reflux for 12 h, afforded the ring-closed products **15** and **16**, respectively, in 81–83% yields.

After the success of these reactions we next investigated similar substrates originating from Grignard reactions. Accordingly aldehydes **1** and **12** were treated with vinyl magnesium bromide in THF for 1 h to afford the Grignard products **17** and **18** in excellent yields (Scheme 4). Treating these substrates with Grubbs II catalyst, however failed to furnish the desired products even after 24 h of the reaction. Assuming that allyl alcohol interfered with the reaction, we transformed the hydroxyl group to methoxy group to generate another substrate **19**. Unfortunately even this compound failed to yield the desired RCM product.

In summary, we have exemplified the utility of the Morita–Baylis–Hillman and Barbier adducts of 1-formyl-9*H*-β-carboline for the synthesis of new annulated derivatives of β-carbolines via RCM reaction. However, allylic alcohols derived from the addition of vinyl Grignard reagent to this substrate failed to undergo the RCM illustrating the limitation of the protocol. Studies to explore the scope of this strategy to generate more diverse annulated β-carbolines are underway and will form the topic of our future communication.



Scheme 4. Reagents and conditions: (i) CH_2=CHMgBr, THF, −78 °C to rt, 1 h; (ii) Grubb's II generation cat. (10 mol %), dry CH_2Cl_2, reflux, 12 h; (iii) Ag_2O, MeI, rt, 18 h.

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Supplementary data

Supplementary data (experimental procedure, spectroscopic data, and copies of ^1H and ^{13}C NMR) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.087.

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4. *General procedure for the synthesis of* **8**, **9**, **10**, **11**, **15**, *and* **16** *as exemplified for* **8**. A mixture of methyl 9-allyl-1-(1-hydroxy-2-(methoxycarbonyl)allyl)-9*H*-pyrido-[3,4-*b*]indole-3-carboxylate (**2**) (0.35 g, 0.92 mmol) and Grubb's II generation catalyst (0.76 g, 0.09 mmol) in 50 mL dry methylene chloride was refluxed for 3 h. After completion of the reaction as monitored by TLC, the solvent was evaporated under reduced pressure to yield a gummy residue. Purification by silica-gel column chromatography [EtOAc/hexanes, 22:78; R_f = 0.43 (EtOAc/hexanes, 45:55)] afforded **8** as a white solid (0.22 g, 65%). *Dimethyl 4-hydroxy-4,7-dihydro-3,7a-diazacyclohepta[jk]fluorene-2,5-dicarboxylate* (**8**). Mp 129–130 °C; ν_{max} (KBr) = 1712 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, CO_2CH_3), 3.98 (s, 3H, CO_2CH_3), 5.09 (dd, 1H, J_1 = 8.6 Hz, J_2 = 14.6 Hz, NC*H*H), 5.60 (dd, 1H, J_1 = 5.6 Hz, J_2 = 14.5 Hz, NCH*H*), 6.37 (s, 1H, C*H*OH), 7.31–7.40 (m, 2H, =CH and ArH), 7.55 (d, 1H, J = 8.4 Hz, ArH), 7.66 (t, 1H, J = 7.3 Hz, ArH), 8.20 (d, 1H, J = 7.9 Hz, ArH), 8.82 (s, 1H, ArH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 47.5, 52.7, 53.0, 70.6, 104.3, 111.3, 118.9, 120.7, 121.6, 122.7, 130.0, 131.0, 134.2, 135.8, 136.8, 139.4, 141.9, 165.0, 166.0. MS (ES+): m/z = 353.1 [M+1]$^+$. Anal. Calcd for $C_{19}H_{16}N_2O_5$ (352.1059): C, 64.77; H, 4.58; N, 7.95. Found: C, 64.59; H, 4.83; N, 8.07. *5-Ethyl 2-methyl 4-hydroxy-4,7-dihydro-3,7a-diazacyclohepta[jk]fluorene-2,5-dicarboxylate* (**9**). The title compound was synthesized following the above described general procedure and after purification by column chromatography [EtOAc/hexanes, 20:80; R_f = 0.44 (EtOAc/hexanes, 45:55)] was obtained as a white solid (0.18 g from 0.30 g). Yield: 64%, mp 119–121 °C; ν_{max} (KBr) = 1713 ($CO_2C_2H_5$), 3376(OH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, 3H, J = 7.1 Hz, CH_2CH_3), 3.36 (br s, 1H, OH), 4.02 (s, 3H, CO_2CH_3), 4.26 (br s, 2H, OCH_2), 5.09 (dd, 1H, J_1 = 8.9 Hz, J_2 = 14.2 Hz, NC*H*H), 5.57 (dd, 1H, J_1 = 4.0 Hz, J_2 = 13.7 Hz, NCH*H*), 6.36 (s, 1H, C*H*OH), 7.29–7.40 (m, 2H, =CH and ArH), 7.55 (d, 1H, J = 7.6 Hz, ArH), 7.66 (d, 1H, J = 7.0 Hz, ArH), 8.20 (d, 1H, J = 7.7 Hz, ArH), 8.85 (s, 1H, ArH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 14.1, 52.1, 61.1, 70.1, 110.6, 118.1, 120.2, 120.8, 122.3, 128.9, 135.3, 135.7, 139.1, 141.1, 143.4, 165.4, 165.8. MS (ES+): m/z = 367.1 [M+1]$^+$. Anal. Calcd for $C_{20}H_{18}N_2O_5$ (366.1216): C, 65.57; H, 4.95; N, 7.65. Found: C, 65.85; H, 4.79; N, 7.43. *5-Butyl 2-methyl 4-hydroxy-4,7-dihydro-3,7a-diazacyclohepta[jk]-fluorene-2,5-dicarboxylate* (**10**). The title compound was synthesized following the above described general procedure and after purification by column chromatography [EtOAc/hexanes, 18:82; R_f = 0.47 (EtOAc/hexanes, 45:55)] was obtained as a white solid (0.17 g from 0.27 g). Yield: 67%, mp 148–149 °C; ν_{max} (KBr) = 1714 (CO_2nBu), 3316 (OH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3H, J = 7.3 Hz, CH_3), 1.35–1.43 (m, 2H, CH_2), 1.63–1.68 (m, 2H, CH_2), 3.55 (br s, 1H, OH), 3.98 (s, 3H, CO_2CH_3), 4.17–4.22 (m, 2H, OCH_2), 5.09 (dd, 1H, J_1 = 8.7 Hz, J_2 = 14.5 Hz, NC*H*H), 5.60 (dd, 1H, J_1 = 5.7 Hz, J_2 = 14.4 Hz, NCH*H*), 6.38 (s, 1H, C*H*OH), 7.28–7.40 (m, 2H, =CH and ArH), 7.55 (d, 1H, J = 8.2 Hz, ArH), 7.67 (t, 1H, J = 7.2 Hz, ArH), 8.19 (d, 1H, J = 7.7 Hz, ArH), 8.83 (s, 1H, ArH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 13.4, 18.6, 30.1, 39.8, 52.0, 64.7, 70.1, 110.5, 118.0, 120.2, 120.6, 122.2, 128.8, 135.3, 135.5, 135.8, 139.1, 141.1, 143.4, 165.4, 165.8. MS (ES+): m/z = 395.2 [M+1]$^+$. DART-HRMS (ESI+): calcd for $C_{22}H_{23}N_2O_5$ 395.1607; found 395.1579. *5-tert-Butyl 2-methyl 4-hydroxy-4,7-dihydro-3,7a-diazacyclohepta[jk]-fluorene-2,5-dicarboxylate* (**11**). The title compound was synthesized following the above described general procedure and after purification by column chromatography [EtOAc/hexanes, 18:82; R_f = 0.48 (EtOAc/hexanes, 45:55)] was obtained as a white solid (0.20 g from 0.30 g). Yield: 70%, mp 179–180 °C; ν_{max} (KBr) = 1711 (CO_2tBu) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 9H, 3 × CH_3) 3.63 (br s, 1H, OH) 3.97 (s, 3H, CO_2CH_3), 5.07 (dd, 1H, J_1 = 8.8 Hz, J_2 = 14.5 Hz, NC*H*H), 5.57 (dd, 1H, J_1 = 5.8 Hz, J_2 = 14.7 Hz, NCH*H*), 6.34 (s, 1H, C*H*OH), 7.19–7.23 (m, 1H, =CH), 7.37 (t, 1H, J = 7.1 Hz, ArH), 7.54 (d, 1H, J = 8.2 Hz, ArH), 7.66 (t, 1H, J = 8.1 Hz, ArH), 8.19 (d, 1H, J = 7.5 Hz, ArH), 8.82 (s, 1H, ArH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 27.7, 39.8, 52.1, 69.9, 81.1, 110.6, 118.0, 120.2, 120.7, 122.3, 128.9, 134.9, 135.3, 135.8, 140.3, 141.1, 143.6, 164.6, 165.8. MS (ES+): m/z = 395.1 [M+1]$^+$. DART-HRMS (ESI+): calcd for $C_{22}H_{23}N_2O_5$ 395.1607; found 395.1622. *Methyl 4-hydroxy-5,8-dihydro-4H-3,8a-diazacycloocta[jk]fluorene-2-carboxylate* (**15**). The title compound was synthesized following the above described general procedure and after purification by column chromatography [EtOAc/hexanes, 20:80; R_f = 0.45 (EtOAc/hexanes, 45:55)] was obtained as a white solid (0.31 g from 0.40 g). Yield: 83%, mp 215–216 °C; ν_{max} (KBr) = 1715 (CO_2CH_3) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.46–2.64 (m, 1H, C*H*H), 3.26–3.36 (m, 1H, CH*H*), 4.03 (s, 3H, CO_2CH_3), 4.78–4.90 (m, 1H, NC*H*H), 5.11–5.23 (m, 1H, NCH*H*), 5.73–5.95 (m, 2H, 2 × =CH), 6.13 (br s, 2H, CHOH), 7.31–7.39 (m, 1H, ArH), 7.52–7.69 (m, 2H, ArH), 8.17 (d, 1H, J = 7.9 Hz, ArH), 8.76 (s, 1H, ArH), ^{13}C NMR (50 MHz, DMSO-d_6): δ = 40.4, 40.7, 52.1, 71.3, 110.4, 117.1, 120.5, 120.6, 122.1, 124.0, 128.8, 129.3, 133.6, 134.8, 135.1, 141.5, 146.6, 165.7. MS (ES+): m/z = 309.1 [M+1]$^+$. Anal. Calcd for $C_{18}H_{16}N_2O_3$ (308.1161): C, 70.12; H, 5.23; N, 9.09. Found: C, 70.35; H, 5.42; N, 8.85. *5,8-Dihydro-4H-3,8a-diazacycloocta[jk]fluoren-4-ol* (**16**). The title compound was synthesized following the above described general procedure and after purification by column chromatography [EtOAc/hexanes, 20:80; R_f = 0.49 (EtOAc/hexanes, 40:60)] was obtained as a white solid (0.21 g from 0.30 g). Yield: 81%, mp 144–146 °C; ν_{max} (KBr) = 3372 (OH) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.39–2.57 (m, 1H, C*H*H), 3.22–3.35 (m, 1H, CH*H*), 4.72–4.84 (m, 1H, NC*H*H), 5.08–5.20 (m, 1H, NCH*H*), 5.74–5.92 (m, 2H, 2 × =CH), 6.16 (dd, 1H, J_1 = 4.6 Hz, J_2 = 11.4 Hz, C*H*OH), 7.23–7.31 (m, 1H, ArH), 7.46–7.64 (m, 2H, ArH), 7.88 (d, 1H, J = 5.3 Hz, ArH), 8.11 (d, 1H, J = 7.8 Hz, ArH), 8.35 (d, 1H, J = 5.3 Hz, ArH), ^{13}C NMR (50 MHz, DMSO-d_6): δ = 40.8, 41.0, 70.3, 110.0, 114.2, 119.5, 120.4, 121.7, 124.0, 128.3, 129.1, 133.1, 133.2, 136.5, 141.1, 146.6. MS (ES+): m/z = 251.2 [M+1]$^+$. Anal. Calcd for $C_{16}H_{14}N_2O$ (250.1106): C, 76.78; H, 5.64; N, 11.19. Found: C, 77.08; H, 5.76; N, 11.04.
5. *General procedure for the synthesis of* **13** *and* **14** *as exemplified for* **13**. To a stirred solution of methyl 9-allyl-1-formyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**1**) (0.60 g, 2 mmol) in a mixture of THF/H_2O (21.0 mL, 2:1 v/v)), allylbromide (0.26 mL, 3.0 mmol) and indium powder (0.34 g, 3.0 mmol) were added and the reaction was continued for 3 h. After completion of the reaction as monitored by TLC, THF was removed and to the residue water (20 mL) and ethyl acetate (50 mL) were added. Organic layer was partitioned and separated, dried, (Na_2SO_4) and evaporated under vacuum to furnish a yellow residue. After purification by column chromatography [EtOAc/hexanes, 18:82; R_f = 0.41 (EtOAc/hexanes, 40:60)] **13** was obtained as a white solid (0.31 g, 88%). *Methyl 9-allyl-1-(1-hydroxybut-3-enyl)-9H-β-carboline-3-carboxylate* (**13**). Mp 101–102 °C; ν_{max} (KBr) = 1714 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52–2.62 (m, 1H, C*H*H), 2.69–2.76 (m, 1H, CH*H*), 4.03 (s, 3H, CO_2CH_3), 4.76 (d, 1H, J = 17.2 Hz, =C*H*H), 5.02–5.28 (m, 6H, NCH_2, $=CH_2$, =CH*H* and CHO*H*), 5.37 (dd, 1H, J_1 = 3.4 Hz, J_2 = 8.3 Hz, C*H*OH), 5.98–6.07 (m, 2H, 2 × =CH), 7.38 (t, 1H, J = 7.5 Hz, ArH), 7.47 (d, 1H, J = 8.3 Hz, ArH), 7.61–7.66 (m, 1H, ArH), 8.21 (d, 1H, J = 7.8 Hz, ArH), 8.82 (s, 1H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.6, 47.4, 52.5, 69.8, 110.6, 117.1, 117.2, 117.6, 121.3, 121.7, 129.2, 130.4, 132.2, 134.6, 134.7, 135.9, 142.3, 145.2, 166.3. MS (ES+): m/z = 337.1 [M+1]$^+$. Anal. Calcd for $C_{20}H_{20}N_2O_3$ (336.1474): C, 71.41; H, 5.99; N, 8.33. Found C, 71.34; H, 5.76; N, 8.56. *1-(9-Allyl-9H-β-carbolin-1-yl)but-3-en-1-ol* (**14**): The title compound was synthesized following the above described general procedure and after purification by column chromatography [EtOAc/hexanes, 17:83; R_f = 0.43 (EtOAc/hexanes, 40:60)] was obtained as yellow oil (0.62 g from 0.60 g). Yield: 87%; ν_{max} (Neat) = 3405 (OH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46–2.56 (m, 1H, C*H*H), 2.69–2.75 (m, 1H, CH*H*), 4.76 (d, 1H, J = 16.8 Hz, =C*H*H), 4.97–5.24 (m, 6H, NCH_2, $=CH_2$, =CH*H* and CHO*H*), 5.36 (dd, 1H, J_1 = 3.3 Hz, J_2 = 8.2 Hz, C*H*OH), 5.93–6.07 (m, 2H, 2 × =CH), 7.32 (t, 1H, J = 7.5 Hz, ArH), 7.43 (d, 1H, J = 8.3 Hz, ArH), 7.60 (t, 1H, J = 7.2 Hz, ArH), 7.95 (d, 1H, J = 5.1 Hz, ArH), 8.16 (d, 1H, J = 7.7 Hz, ArH), 8.41 (d, 1H, J = 5.1 Hz, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.9, 47.3, 69.5, 110.2, 114.2, 117.0, 117.5, 120.4, 121.5, 121.6, 128.8, 130.4, 132.5, 132.9, 134.7, 137.2, 142.1, 145.2. MS (ES+): m/z = 279.2 [M+1]$^+$. Anal. Calcd for $C_{18}H_{18}N_2O$ (278.1419): C, 77.67; H, 6.52; N, 10.06. Found: C, 77.35; H, 6.72; N, 9.85.