

One-pot reductive-cyclization as key step for the synthesis of rutaecarpine alkaloids

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Abstract

The quinazolinocarboline alkaloids including rutaecarpine (**1a**), euxylophoricine A (**1b**), and euxylophoricine C (**1c**) have been synthesized efficiently from the ring opened β -carboline derivative as key intermediate by a one-pot reductive-cyclization reaction. The key intermediate was prepared from tryptamine (**6**) following Bischler–Napieralski cyclization, benzylation, and oxidative cleavage of the exocyclic double bond.

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Rutaecarpine (**1a**)¹ isolated from the dried fruits of *Evo-dia rutaecarpa* and callus tissue cultured from the stem of *Phellodendron amurense*^{2–5} has been used in China and Japan as traditional medicine for remedy such as headache, dysentery, cholera, worm infections, and postpartum.⁶ Rutaecarpine (**1a**) and its analogues, euxylophoricine A (**1b**), euxylophoricine C (**1c**), and dehydroevodiamine (**2**) (Fig. 1) were also found to possess anti-stomachic, anti-emetic, anti-nociceptive, anti-inflammatory, anti-pyretic, analgesic, astringent, anti-hypertensive, uterotonic, cyclooxygenase (COX-2) inhibitory, and agonist TCDD-receptor

activities.⁷ Furthermore, rutaecarpine (**1a**) can also suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in endothelial cells.⁸

Recently, Don et al.⁹ reported that rutaecarpine derivatives selectively inhibited human CYP1A1, CYP1A2, and CYP2B1. Robinson and co-workers¹⁰ reported the first total synthesis of rutaecarpine and since then several routes to it and its derivatives have been developed.¹¹

The generalized approach toward the synthesis of rutaecarpine (**1a**) and various analogues involved the late construction of the indole skeleton (A, B rings) by the widely used Fischer indole synthesis through an acid-catalyzed or thermal sigmatropic rearrangement of an *N*-aryl hydrazone. On the other hand, the quinazolinocarboline backbone of dehydroevodiamine (**2**) has been reported to give the ring opened β -carboline derivative **2a** upon the addition of water.¹² Furthermore, the pseudobase has been proposed as a likely but never isolated or observed intermediate.

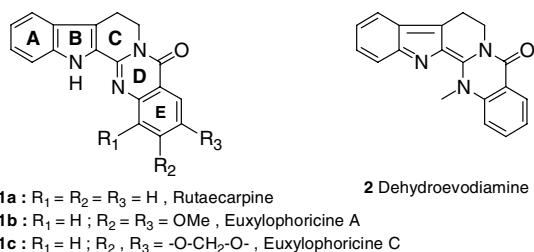
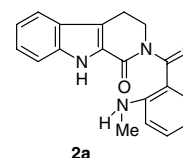


Fig. 1. Rutaecarpine and its analogues.



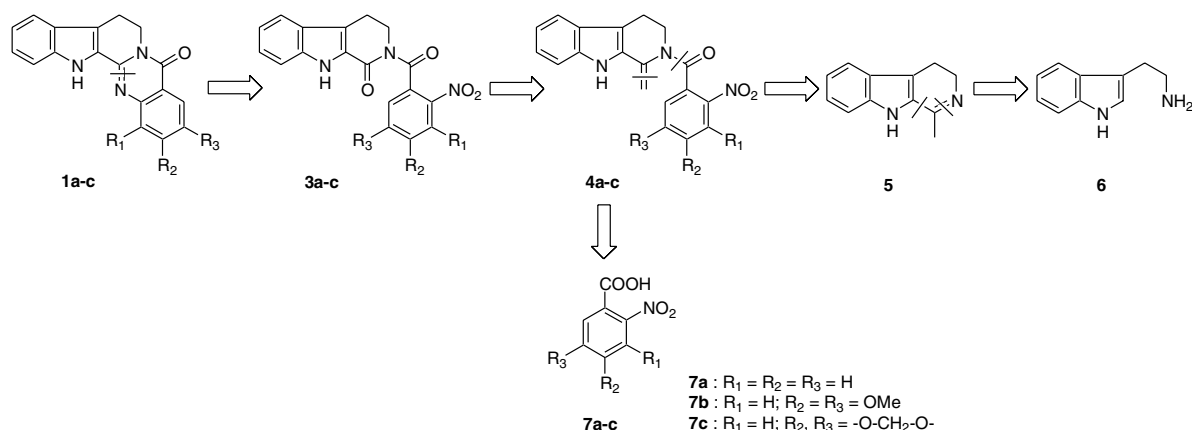
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Our synthetic strategy for rutaecarpine alkaloids **1a–c** is to construct an intermediate similar to β -carboline **2a**. The retrosynthetic analysis is shown in Scheme 1. We envisage that the reverse cyclization to rutaecarpine alkaloids **1a–c** from the nitro-intermediate of the ring opened β -carboline derivatives can be carried out in a one-pot reaction via reductive-cyclization. Furthermore, the 2,3,4,9-tetrahydro- β -carboline-1-one **3a–c** can be readily prepared from 1-methyl-4,9-dihydro-3H- β -carboline (**5**) in two steps that involved the isomerization of the endocyclic double bond to the exocyclic double bond,¹³ followed by an oxidative cleavage of the double bond to give the requisite carbonyl group.¹⁴ It is also of interest to investigate the biological activities of these ring opened β -carboline derivatives synthesized. To our knowledge, no approach involving the

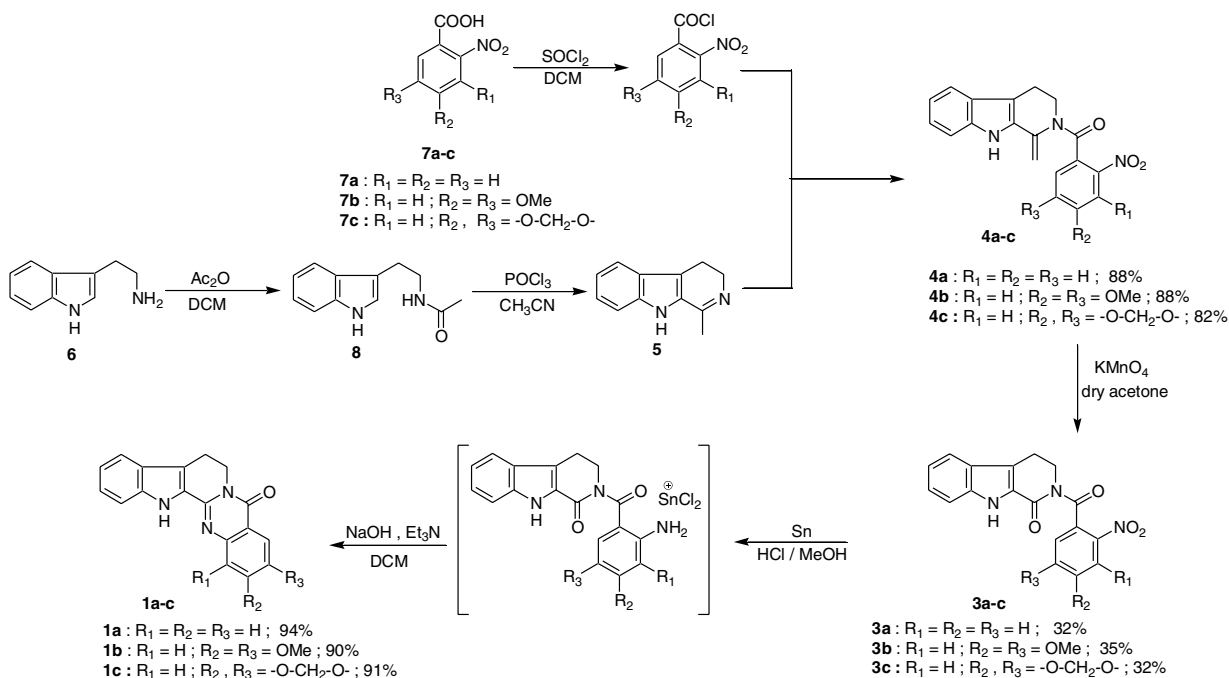
construction of a β -carboline C, D, E rings first, followed by the construction of the quinazolinone ring has been reported.

The 1-methyl-4,9-dihydro-3H- β -carboline (**5**) can be prepared from commercially available tryptamine (**6**). Treatment of tryptamine (**6**) with acetic anhydride gave the N-acetylated product **8** and subsequent Bischler–Napieralski cyclization in POCl₃ to give compound **5** in good yield. The reaction of compound **5** with various benzoyl chloride derivatives, prepared from the corresponding benzoic acid derivatives **7a–c** with SOCl₂, afforded the requisite intermediates **4a–c** for the synthesis of rutaecarpine alkaloids (Scheme 2).

We first attempted to oxidatively cleave the exocyclic double bond of **4a–c** under ozonolysis condition, but was



Scheme 1. Retrosynthetic analysis of **1a–c**.



Scheme 2. Total synthesis of **1a–c**.

unsuccessful. The use of potassium permanganate for the oxidative cleavage of the exocyclic double bond successfully gave the desired 2,3,4,9-tetrahydro- β -carbolin-1-one derivatives **3a–c**.¹⁵

We have obtained the ring open β -carboline intermediates **3a–c** in three steps from tryptamine (**6**). A one-pot reaction was sorted for the formation of the quinazolinone ring. This involved the reduction of the nitro- to the amino-group, followed by an in situ condensation of the free amino group with the ring amide to form the quinazolinone ring. It was found that the treatment of **3a–c** with tin in HCl/MeOH followed by basic workup can afford rutaecarpine analogue alkaloids **1a–c**¹⁶ in a one-pot reaction.

In conclusion, a simple procedure for the preparation of rutaecarpine analogue alkaloids **1a–c** and their ring opened β -carboline derivatives has been reported. The one-pot reductive-cyclization reaction for the construction of the quinazolinone ring is noteworthy.

Acknowledgment

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Supplementary data

The ¹H NMR spectra of **1a–c**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.094.

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- N*-(2-Nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro- β -carboline (**3a**): mp 109–111 °C (MeOH/CH₂Cl₂); IR (CHCl₃, cm⁻¹) 3457 (NH), 1684 (C=O), 1680 (C=O), 1530 (NO₂), 1347 (NO₂); ¹H NMR (300 MHz, CDCl₃) δ 3.21 (t, *J* = 6.0 Hz, 2H), 4.56 (br, 2H), 7.16–7.21 (m, 1H), 7.25–7.27 (m, 1H), 7.33–7.39 (m, 2H), 7.49–7.55 (m, 1H), 7.71–7.83 (m, 2H), 8.19 (dd, *J* = 1.2, 8.4 Hz, 1H), 8.76 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 20.51, 44.01, 112.58, 120.93, 120.98, 123.99, 124.67 (2C), 125.16, 126.83, 126.88, 129.12, 134.09, 135.29, 138.62, 144.60, 160.03, 168.22; LRMS *m/z* (%) 335 (M⁺, 35.6%), 289 (M⁺–46, 91.6%), 185 (M⁺–150, 51.9%), 184 (M⁺–151, 45.8%), 56 (M⁺–179, 67.3%), 150 (M⁺–85, 50.4%), 129 (M⁺–206, 100%), 128 (M⁺–207, 85.5%); HRMS *m/z* (%) 335.0893 (M⁺, 65.5%), calcd for C₁₈H₁₃N₃O₄ 335.0890. *N*-(4,5-Dimethoxy-2-nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro- β -carboline (**3b**): mp 117–119 °C (MeOH/CH₂Cl₂); IR (CHCl₃, cm⁻¹) 3456 (NH), 1704 (C=O), 1684 (C=O), 1518 (NO₂), 1333 (NO₂); ¹H NMR (300 MHz, CDCl₃) δ 3.22 (t, *J* = 6.3 Hz, 2H), 3.94 (s, 3H), 3.95 (s, 3H), 4.57 (t, *J* = 6.3 Hz, 2H), 6.87 (s, 1H), 7.18 (t, *J* = 6.9 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 6.9 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.68 (s, 1H), 8.81 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 20.53, 44.11, 56.36, 56.54, 106.73, 108.55, 112.49, 121.00, 121.04, 124.70, 124.76, 125.32, 126.95, 129.65, 137.60, 138.58, 148.74, 154.02, 160.05, 168.10; LRMS *m/z* (%) 395 (M⁺, 0.1%), 350 (M⁺–45, 2.37%), 349 (M⁺–46, 100%), 136 (M⁺–259, 39.1%), 129 (M⁺–266, 32.6%), 128 (M⁺–267, 26.7%), 93 (M⁺–302, 25.3%); HRMS *m/z* (%) 395.1124 (M⁺, 10.6%), calcd for C₂₀H₁₇N₃O₆ 395.1126. *N*-(4,5-Dimethylenedioxy-2-nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro- β -carboline (**3c**): mp 111–113 °C (MeOH/CH₂Cl₂); IR (CHCl₃, cm⁻¹) 3464 (NH), 1674 (C=O), 1669 (C=O), 1552 (NO₂), 1340 (NO₂); ¹H NMR (300 MHz, CDCl₃) δ 3.22 (t, *J* = 6.3 Hz, 2H), 4.57 (t, *J* = 6.3 Hz, 2H), 6.14 (s, 2H), 6.75 (s, 1H), 7.19–7.21 (m, 1H), 7.30–7.40 (m, 2H), 7.64 (s, 1H), 7.65 (d, *J* = 3.6 Hz, 1H), 8.68 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 20.57, 44.10, 103.46, 104.81, 106.16, 112.46, 121.12, 121.17, 124.73, 124.86, 125.31, 127.09, 131.98, 138.52, 139.26, 148.11, 152.71, 159.98, 167.62; LRMS *m/z* (%) 379

- (M^+ , 80.4%), 129 (M^+ –250, 63.59%), 120 (M^+ –259, 71%), 55 (M^+ –324, 98.9%), 44 (M^+ –335, 100%); HRMS m/z (%) 379.0788 (M^+ , 16.3%), calcd for $C_{19}H_{13}N_3O_6$ 379.0784.
16. Rutaecarpine (**1a**): mp 254–255 °C (MeOH/ CH_2Cl_2); IR ($CHCl_3$, cm^{-1}) 3463 (NH), 1676 (C=O); 1H NMR (300 MHz, $CDCl_3$) δ 3.24 (t, J = 6.9 Hz, 2H), 4.59 (t, J = 6.9 Hz, 2H), 7.19 (t, J = 8.4 Hz, 1H), 7.34 (dt, J = 1.2, 6.8 Hz, 1H), 7.41–7.67 (m, 2H), 7.63–7.73 (m, 3H), 8.32 (dd, J = 1.2, 7.8 Hz, 1H), 9.27 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.68, 41.12, 112.07, 118.33, 120.08, 120.62, 121.37, 125.58, 125.64, 126.19, 126.61, 127.23, 134.32 (2C), 138.27, 144.95, 147.52, 161.59; LRMS m/z (%) 287 (M^+ , 79.2%), 286 (M^+ –1, 100%); HRMS m/z (%) 287.1055 (M^+ , 38.9%), calcd for $C_{18}H_{13}N_3O$ 287.1054. Euxylophoricine A (**1b**): mp 293–295 °C (MeOH/ CH_2Cl_2); IR ($CHCl_3$, cm^{-1}) 3461 (NH), 1663 (C=O); 1H NMR (300 MHz, $CDCl_3$) δ 3.23 (t, J = 7.0 Hz, 2H), 3.98 (s, 3H), 4.01 (s, 3H), 4.59 (t, J = 7.0 Hz, 2H), 7.06 (s, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.33 (dd, J = 7.8, 8.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.66 (s, 1H), 9.22 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.69, 41.10, 56.22, 56.35, 106.41, 107.12, 111.97, 114.50, 117.64, 119.99, 120.62, 125.36, 125.73, 127.35, 138.13, 143.68, 143.99, 148.76, 154.98, 160.90; LRMS m/z (%) 347 (M^+ , 100%), 332 (M^+ –25, 22.7%), 128 (M^+ –219, 13.4%), 55 (M^+ –292, 48.6%), 43 (M^+ –304, 74.6%); HRMS m/z (%) 347.1265 (M^+ , 100%), calcd for $C_{20}H_{17}N_3O_3$ 347.1264. Euxylophoricine C (**1c**): mp 307–308 °C (MeOH/ CH_2Cl_2); IR ($CHCl_3$, cm^{-1}) 3469 (NH), 1663 (C=O); 1H NMR (300 MHz, $CDCl_3$) δ 3.27 (t, J = 6.9 Hz, 2H), 4.57 (t, J = 6.9 Hz, 2H), 6.10 (s, 2H), 7.03 (s, 1H), 7.18 (t, J = 6.9 Hz, 1H), 7.36 (t, J = 6.9 Hz, 1H), 7.44 (d, J = 6.9 Hz, 1H), 7.63 (d, J = 6.9 Hz, 1H), 7.64 (s, 1H), 9.07 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.88, 41.89, 102.53, 104.29, 105.96, 111.97, 116.10, 117.64, 120.00, 120.60, 125.38, 125.70, 127.24, 138.11, 143.81, 143.58, 147.10, 153.42, 160.87; LRMS m/z (%) 331 (M^+ , 100%), 330 (M^+ –1, 94%); HRMS m/z (%) 331.0957 (M^+ , 37.1%), calcd for $C_{19}H_{13}N_3O_3$ 331.0957.