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Tetrahedron Letters 49 (2008) 481–484
Tetrahedron Letters

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

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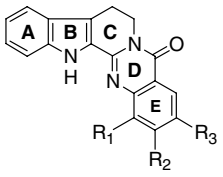
Received 10 October 2007; revised 13 November 2007; accepted 16 November 2007
Available online 22 November 2007

Abstract

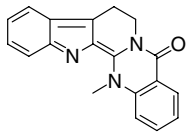
The quinazolinocarboline alkaloids including rutaecarpine (**1a**), euxylophoricine A (**1b**), and euxylophoricine C (**1c**) have been synthesized efficiently from the ring opened β-carboline derivative as key intermediate by a one-pot reductive-cyclization reaction. The key intermediate was prepared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

Keywords: Alkaloids; Rutaecarpine; One-pot reductive-cyclization

Rutaecarpine (**1a**)[1] isolated from the dried fruits of *Evodia 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]



1a : $R_1 = R_2 = R_3 = H$, Rutaecarpine
1b : $R_1 = H$; $R_2 = R_3 = OMe$, Euxylophoricine A
1c : $R_1 = H$; R_2 , R_3 = -O-CH_2-O- , Euxylophoricine C

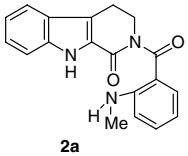


2 Dehydroevodiamine

Fig. 1. Rutaecarpine and its analogues.

Recently, Don et al.[9] reported that rutaecarpine derivatives selectively inhibited human CYP1A1, CYP1A2, and CYP2B1. Robinson and co-workers[10] 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.



2a

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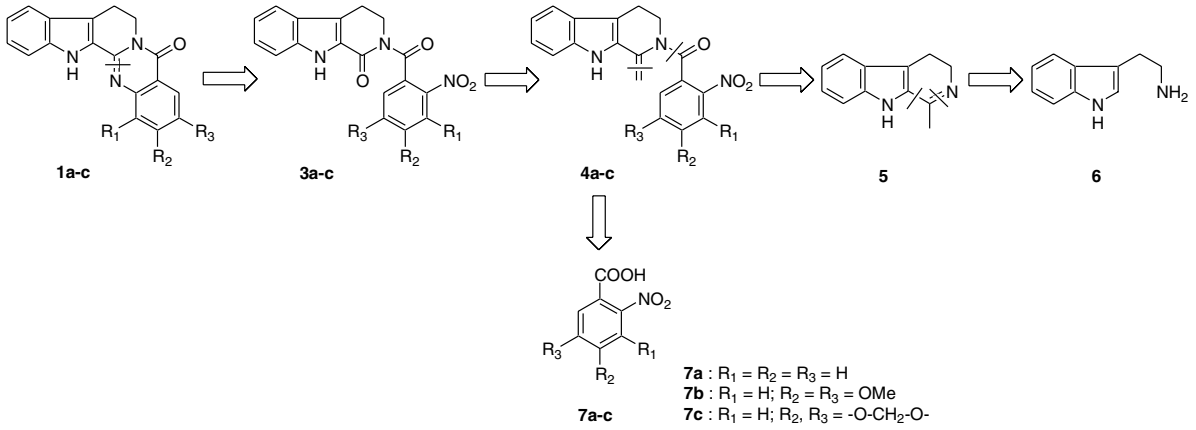
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.094

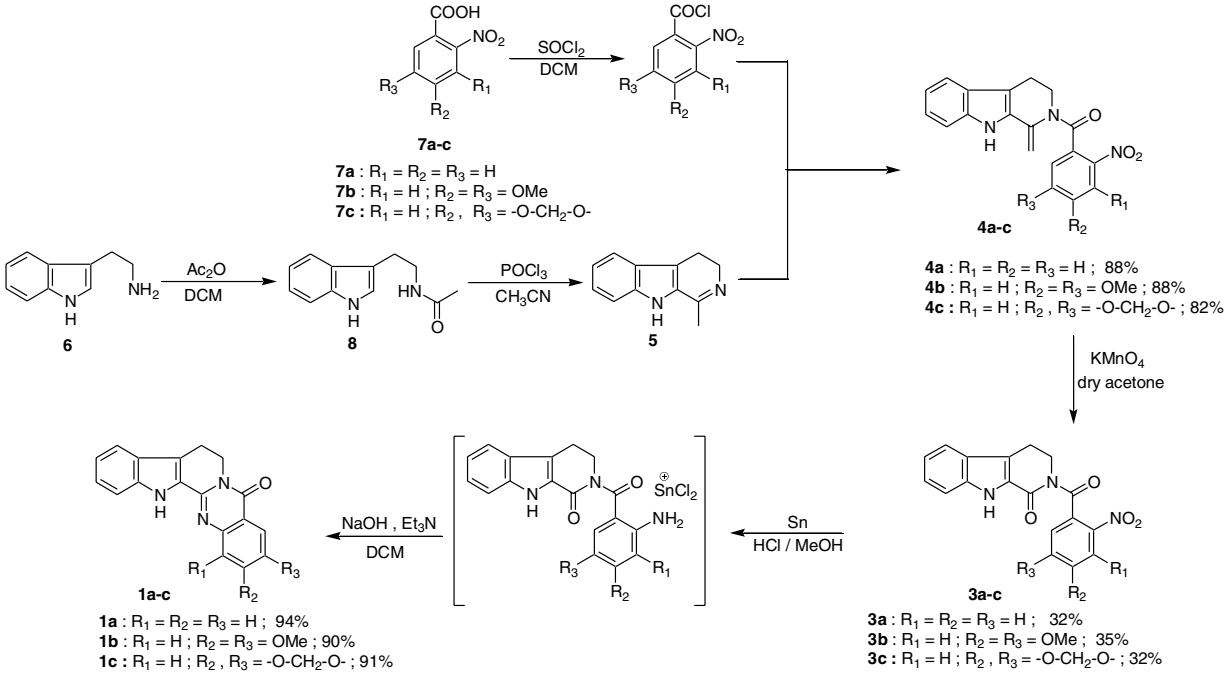
Our synthetic strategy for rutaecarpine alkaloids **1a**–**c** is to construct an intermediate similar to β-carboline **2a**. The retrosynthetic analysis is shown in Scheme 1. We envisage that the reverse cyclization to rutaecarpine alkaloids **1a**–**c** from the nitro-intermediate of the ring opened β-carboline derivatives can be carried out in a one-pot reaction via reductive-cyclization. Furthermore, the 2,3,4,9-tetrahydro-β-carbolin-1-one **3a**–**c** can be readily prepared from 1-methyl-4,9-dihydro-3*H*-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-3*H*-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 $POCl_3$ to give compound **5** in good yield. The reaction of compound **5** with various benzoly chloride derivatives, prepared from the corresponding benzoic acid derivatives **7a**–**c** with $SOCl_2$, 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

We thank National Science Council, R.O.C. for financial support (NSC82-0208-M110-066).

Supplementary data

The ^{1}H 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.

References and notes

1. Asahina, Y. *Acta Phytochim.* **1922**, *1*, 67.
2. Kamikado, T.; Murakoshi, S.; Tamura, S. *Agric. Biol. Chem.* **1978**, *42*, 1515.
3. Bergman, J. The Alkaloids. In *The Quinazolinocarboline alkaloids*; Brossi, A. R., Ed.; Academic Press: New York, 1983; Vol. 21, pp 29–54.
4. (a) Ikuta, A.; Urabe, H.; Nakamura, T. *J. Nat. Prod.* **1998**, *61*, 1012; (b) Ikuta, A.; Nakamura, T.; Urabe, H. *Phytochemistry* **1998**, *48*, 285.
5. Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 697.
6. Chen, A. L.; Chen, K. K. *J. Am. Pharm. Assoc.* **1933**, *22*, 716.
7. (a) King, C. L.; Kong, Y. C.; Wong, N. S.; Yeung, H. W.; Fong, H. H. S.; Sankawa, U. *J. Nat. Prod.* **1980**, *43*, 577; (b) Gillner, M.; Bergman, J.; Cambillau, C.; Gustafsson, J.-A. *Carcinogenesis* **1989**, *10*, 651; (c) Rannug, U.; Sjögren, M.; Rannug, A.; Gillner, M.; Toftgard, R.; Gustafsson, J. A.; Rosenkranz, H.; Klopman, G. *Carcinogenesis* **1991**, *12*, 2007; (d) Matsuda, H.; Yoshikawa, M.; Ko, S.; Iinuma, M.; Kubo, M. *Nat. Med.* **1998**, *52*, 203; (e) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66.
8. (a) Wang, G. J.; Shan, J.; Pang, P. K. T.; Yang, M. C. M.; Chou, C. J.; Chen, C. F. *J. Pharmacol. Exp. Ther.* **1996**, *270*, 1016; (b) Sheu, J. R.; Hung, W. C.; Wu, C. H.; Lee, Y. M.; Yen, M. H. *Br. J. Haematol.* **2000**, *110*, 110.
9. Don, M. J.; Lewis, D. F. V.; Wang, S. Y.; Tsai, M. W.; Ueng, Y. F. *Bioorg. Med. Chem. Lett.* **2003**, 2535.
10. Asahina, Y.; Manske, R. H. F.; Robinson, R. *J. Chem. Soc.* **1927**, 1708.
11. (a) Kametani, T.; Higa, T.; Loc, C. V.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186; (b) Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306; (c) Danieli, B.; Palmisano, G. *Heterocycles* **1978**, *9*, 803; (d) Kökösi, J.; Hermecz, I.; Szász, G.; Mészáros, Z. *Tetrahedron Lett.* **1981**, *22*, 4861; (e) Kaneko, C.; Chiba, T.; Kasai, K.; Miwa, C. *Heterocycles* **1985**, *23*, 1385; (f) Kökösi, J.; Hermecz, I.; Podanyi, B.; Szász, G.; Mészáros, Z. *J. Heterocycl. Chem.* **1985**, *22*, 1373; (g) Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. *Heterocycles* **1985**, *23*, 2803; (h) Hermecz, I.; Kökösi, J.; Horvath, A.; Vasavari, D. I.; Podanyi, B.; Szász, G.; Mészáros, Z. *J. Heterocycl. Chem.* **1987**, *24*, 1045; (i) Kökösi, J.; Szász, G.; Hermecz, I. *Tetrahedron Lett.* **1992**, *33*, 2995; (j) Hermecz, I.; Kökösi, J.; Vasavari, D. I.; Podanyi, B.; Szász, G. *Heterocycles* **1994**, *37*, 903; (k) Yang, L. M.; Chen, C. F.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 465; (l) Lee, S. H.; Kim, S. I.; Park, J. G.; Lee, E. S.; Jahng, Y. *Hetereocycles* **2001**, *55*, 1555; (m) Mohanta, P. K.; Kim, K. *Tetrahedron Lett.* **2002**, *43*, 3993; (n) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659; (o) Lee, E. S.; Park, J. G.; Jahng, Y. *Tetrahedron Lett.* **2003**, *44*, 1883; and references cited therein; (p) Chavan, S. P.; Sivappa, R. *Tetrahedron Lett.* **2004**, *45*, 997; (q) Mhaske, S. B.; Narshinha, P. A. *Tetrahedron* **2004**, *60*, 3417; (r) Harayama, T.; Hori, A.; Serban, G.; Morikami, Y.; Matsumoto, T.; Abe, H.; Takeuchi, Y. *Tetrahedron* **2004**, *60*, 10645; (s) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153; (t) Liu, J. F.; Lee, J.; Dalton, A. M.; Bi, G.; Yu, L.; Baldino, C. M.; McElory, E.; Brown, M. *Tetrahedron Lett.* **2005**, *46*, 1241; (u) Jeon, M. K.; Kim, D. S.; La, H. J.; Ha, D. C.; Gong, Y. D. *Tetrahedron Lett.* **2005**, *46*, 7477; (v) Hamid, A.; Elomri, A.; Daïch, A. *Tetrahedron Lett.* **2006**, *47*, 1777; (w) Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L. *Tetrahedron Lett.* **2006**, *47*, 9025; (x) Kshirsagar, U. A.; Mhaske, S. B.; Argade, N. P. *Tetrahedron Lett.* **2007**, *48*, 3243.
12. Bergman, J.; Bergman, S. *J. Org. Chem.* **1985**, *50*, 1246.
13. Naito, T.; Hirata, Y.; Miyato, O.; Ninomiya, I. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2219.
14. Yamada, F.; Yoshihiro, S.; Somei, M. *Heterocycles* **1968**, 2619.
15. *N-(2-Nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro-β-carboline* (**3a**): mp 109–111 °C ($MeOH/CH_2Cl_2$); IR ($CHCl_3$, cm^{-1}) 3457 (NH), 1684 (C═O), 1680 (C═O), 1530 (NO_2), 1347 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{13}N_3O_4$ 335.0890. *N-(4,5-Dimethoxy-2-nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro-β-carboline* (**3b**): mp 117–119 °C ($MeOH/CH_2Cl_2$); IR ($CHCl_3$, cm^{-1}) 3456 (NH), 1704 (C═O), 1684 (C═O), 1518 (NO_2), 1333 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{20}H_{17}N_3O_6$ 395.1126. *N-(4,5-Dimethylenedioxy-2-nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro-β-carboline* (**3c**): mp 111–113 °C ($MeOH/CH_2Cl_2$); IR ($CHCl_3$, cm^{-1}) 3464 (NH), 1674(C═O), 1669 (C═O), 1552 (NO_2), 1340 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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.