Organic & Biomolecular Chemistry

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Constructions of tetrahydro-γ-carboline skeletons *via* intramolecular oxidative carbon–carbon bond formation of enaminest

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 1929

Received 9th January 2013,
Accepted 3rd February 2013

DOI: 10.1039/c3ob00039g

www.rsc.org/obc

Jinglei Lv, Ji Li, Daisy Zhang-Negrerie, Siyun Shang, Qingzhi Gao, Yunfei Du* and Kang Zhao*

The synthetically and biologically important 4-methyl and 4-methoxy tetrahydro-γ-carboline compounds were readily synthesized in high yields from an aryl amine and a 5-amino-3-oxo-pentanoate derivative through a series of reactions of enamination, oxidative annulation, deprotection/lactamization and the final reduction reaction of the carbonyl group. The underpinning strategy involves the oxidative C(sp^2)–C(sp^2) bond formation realized by either $Pd(OAc)_2$/$Cu(OAc)_2$ or a hypervalent iodine reagent.

The tetrahydro-γ-carboline framework (**A**) occupies an increasingly important position in organic synthesis because of its frequent presence in many novel pharmaceutical agents as well as natural products. Numerous designed medical agents, especially those with specific effects on human cardiovascular and nervous systems, *e.g.*, dimebon (**I**),[1] second-generation histone deacetylase 6 inhibitors (**II**),[2] pyridoindole benzodiazepine antipsychotic agents (**III**),[3] potential c-met inhibitors (**IV**),[4] antagonists of the 5-HT_6 and H_1 receptors (**V**),[5] novel NO-mimetic neuroprotective and procognitive agents (**VI**),[6] all contain the tetrahydro-γ-carboline skeleton in their chemical structures. Furthermore, some natural products, such as horsfiline (**VII**), can also be synthesized starting from tetrahydro-γ-carboline compounds by known methods (Fig. 1).[7]

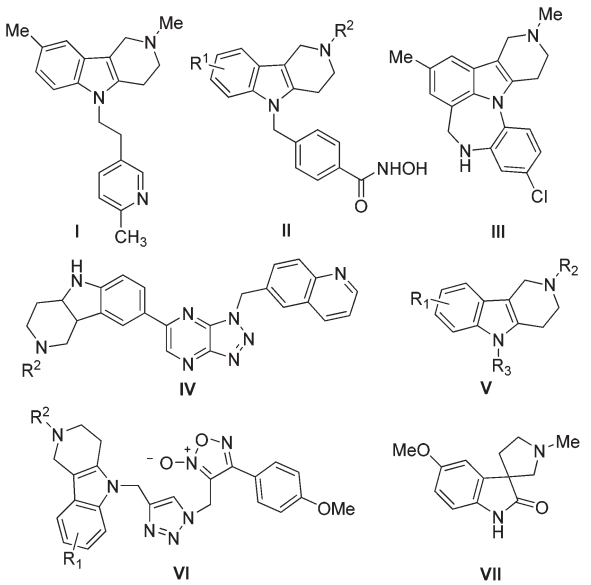


Fig. 1 Pharmaceutical agents containing the tetrahydro-γ-carboline skeleton or natural products that can be synthesized from tetrahydro-γ-carboline compounds.

A literature survey indicates that there are only a few strategies so far developed for the construction of the tetrahydro-γ-carboline skeleton, among which the most commonly used approach involves the reactions between a substituted phenylhydrazine derivative and a 4-piperidinone derivative, a method known as the Fischer indole synthesis (Fig. 2, path a).[8] Besides, the skeleton can also be assembled *via* a condensation reaction between an isotryptamine and an aldehyde followed by a subsequent iso-Pictet–Spengler reaction (Fig. 2, path b).[9] A third method is through the treatment of substituted 2-fluorophenyl imines with LDA possibly through a benzyne intermediate (Fig. 2, path c), as reported by

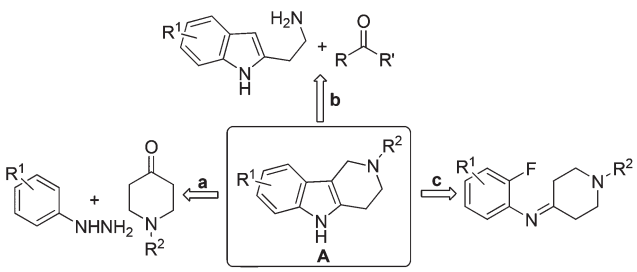
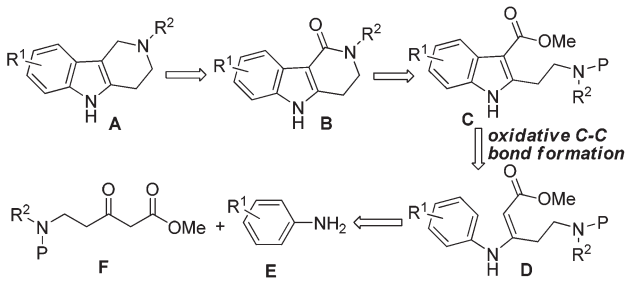


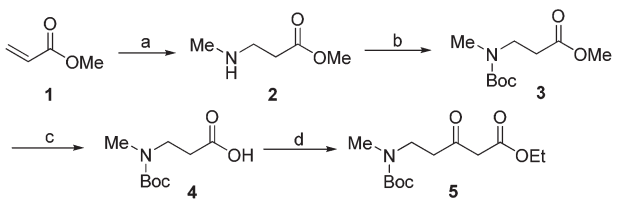
Fig. 2 Existing approaches for the construction of the tetrahydro-γ-carboline skeleton.

Tianjin Key Laboratory for Modern Drug Delivery and High-Efficiency, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072, P. R. China. E-mail: duyunfeier@tju.edu.cn, kangzhao@tju.edu.cn; Fax: +86-22-27404031; Tel: +86-22-27404031

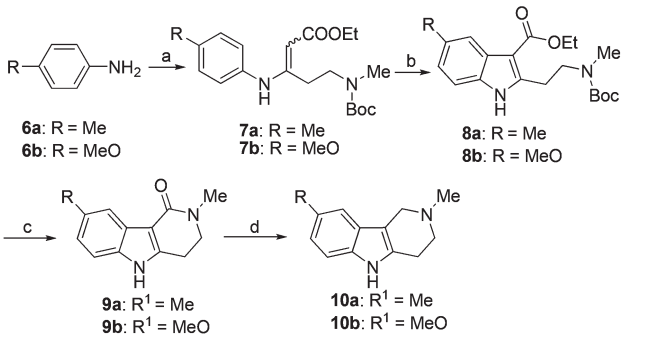
†Electronic supplementary information (ESI) available: NMR data. See DOI: 10.1039/c3ob00039g



Scheme 1 Retrosynthetic analysis.



Scheme 2 Preparation of intermediate **5**. [a]*Reagents and conditions*: (a) $MeNH_2$, EtOH, −10 °C, 86%; (b) $(Boc)_2O$, TEA, CH_2Cl_2, 94%; (c) (1) NaOH, EtOH–H_2O; (2) HCl (1 M); 95%; (d) CDI, $MgCl_2$, $KOCOCH_2CO_2Et$, MeCN, 92%.



Scheme 3 Synthesis of tetrahydro-γ-carbolines from aryl amines and 5-amino-3-oxopentanoate **5**. [a]*Reagents and conditions*: (a) **5**, CH_3CO_2H, 95% (**7a**), 94% (**7b**); (b) Method A: $Pd(OAc)_2$ (10%), $Cu(OAc)_2$, K_2CO_3, DMF, 80 °C, 89% (**8a**), 90% (**8b**); Method B: $PhI(OAc)_2$, DCE, 60 °C, 52% (**8a**), 50% (**8b**); (c) (1) TFA, DCM; (2) $NaHCO_3$, H_2O; (3) NaOH, MeOH, reflux, 92% (**9a**), 95% (**9b**); (d) $LiAlH_4$, THF, reflux, 85% (**10a**), 88% (**10b**).

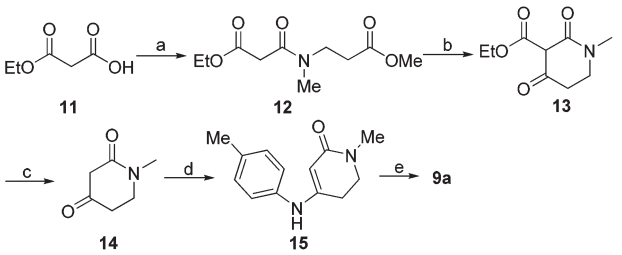
Kudzma.[10] However, with this method, the *ortho*-fluoro substituent in the imine substrates is essential for the cyclization to occur. In this communication, we report a new strategy for the construction of the tetrahydro-γ-carboline framework from the readily available arylamine and 5-amino-3-oxopentanoate derivatives.

Our synthetic strategy of the target tetrahydro-γ-carboline (**A**) was designed based on the retrosynthetic analysis shown in Scheme 1. We envisaged that the tetrahydro-γ-carboline skeleton could be obtained by the reduction of the carbonyl group in lactam **B**, which was expected to be easily prepared from the indole intermediate **C** through deprotection and the subsequent lactamization. The construction of the key indole skeleton of **C** was foreseen to be realized through $C(sp^2)$–$C(sp^2)$ bond formation in the enamine **D** by either the palladium-catalyzed oxidative annulation,[11] such as the method developed by Glorius,[11a,b] or the hypervalent iodine reagent-mediated direct oxidative carbon–carbon bond formation, developed in our laboratory.[12] The synthesis of the enamine intermediate **D** was expected from the reaction of arylamine **E** and an N-protected 5-amino-3-oxopentanoate **F** through a condensation reaction.

Scheme 2 shows the synthesis of compound **5**, a specific example of intermediate **F** where the protecting group is *tert*-butoxy carbonyl (Boc). Although a new compound, compound **5** can be prepared from the readily available starting materials through a series of well-known reactions. The synthesis starts with an aza-Michael addition[13] of methylamine to methyl acrylate at low temperature, affording *N*-methyl-β-alanine ester **2** in 86% yield. Treatment of intermediate **2** with Boc_2O in the presence of TEA[14] conveniently furnishes the *N*-Boc protected *N*-methyl-β-alanine ester **3**, which yields its corresponding carboxylic acid **4** in an excellent yield of 95% after hydrolysis in aqueous hydroxide solution.[15] Intermediate **4** then undergoes a condensation reaction, according to the method described by Challenger,[16] with potassium monomethyl malonate salt in the presence of CDI and magnesium chloride, to afford β-keto ester **5** in 92% yield. Consisting of simple reaction steps of extremely high yields, the above synthetic procedures afford the key β-keto ester compound **5** in an overall 71% yield, and can be applied to the preparation of this class of compounds as a straightforward and efficient approach.

With the key intermediate **5** prepared, the construction of the tetrahydro-γ-carboline skeleton was tested by using the synthetic protocol shown in Scheme 3. Two particular substituted anilines, namely **6a** and **6b**, were chosen as the arylamine since the corresponding tetrahydro-γ-carboline compounds have been widely used for the synthesis of important pharmaceutical agents[1–3] and natural products.[7] As a first step, solvent-free acid-catalyzed enamination of 5-amino-3-oxopentanoate **5** with the *N*-aryl-enamine (**6a** or **6b**) gave the enamine intermediates **7**, a mixture of *trans* and *cis* isomers, in excellent yields (95% for **7a** and 94% for **7b**).[11a,b,12,17] Then the oxidative annulation of *N*-aryl-enamine compound **7** was attempted by two established methods, with the first one being the application of Glorius's method[11a,b] for indole synthesis through palladium(II)-catalyzed oxidative cyclization of *N*-aryl enamines. This method proved to be an ideal approach since the desired indole intermediates **8a** and **8b** were obtained in 89% and 90% yields, respectively. We also applied our own transition metal-free approach, *i.e.*, the hypervalent iodine reagent as the oxidant, to test the feasibility of this transformation. The desired indole products **8a** and **8b** were found to be achieved in 52% and 50% yields, respectively.[18]

Removal of the Boc protective group in **8**, prior to the intramolecular lactamization reaction (step c), was realized by using TFA with the subsequent neutralization with aqueous $NaHCO_3$. After unsuccessful attempts to obtain the desired lactam products of **9** by using the published procedures in previous literature,[19,20] specifically, through treating **8** with $NaHCO_3$ in DCM at room temperature, we conducted a series



Scheme 4 An alternative synthetic protocol. [a]*Reagents and conditions*: (a) **2**, DCC, CH_2Cl_2, rt, 91%; (b) EtONa, EtOH, 80 °C, 84%; (c) 5% HCl (aq.), 80 °C, 58%; (d) **6a**, AcOH, rt 92%; (e) Method A: $Pd(OAc)_2$ (10%), $Cu(OAc)_2$, K_2CO_3, DMF, 80 °C, 66%; Method B: $PhI(OAc)_2$, DCE, −20 °C to −60 °C, 0%.

of screening tests of the various conditions/parameters including the types of bases, the reaction temperature and the solvent. To our delight, we found that the use of sodium hydroxide in methanol at reflux temperature could furnish the desired lactam **9a** or **9b** in 92% or 95% yields, respectively. Finally, lactams **9a** and **9b** underwent smooth carbonyl reduction by using $LiAlH_4$ in THF to give the target compound, tetrahydro-γ-carboline **10a** and **10b**, respectively, in satisfactory yield.[21]

We also tested an alternative synthetic protocol in which the lactamization occurs before the formation of the indole ring (Scheme 4). The enamination of **14** with arylamine **6a** afforded the enamine intermediate **15** in 92% yield,[17] and the oxidative $C(sp^2)$–$C(sp^2)$ bond formation in **15** was again realized by using Glorius's method, but with a lower yield of 66% in comparison to the case of intermediate **7**.[11a,b] However, this method suffers a significant disadvantage as the crucial intermediate, 1-methylpiperidine-2,4-dione (**14**), is not readily available and its preparation by the known methods[22] proved to be less efficient with an overall yield of only 38% starting from methylamine and methyl acrylate. Furthermore, the oxidative annulation of **15** was also tested by our own transition metal-free approach,[12] but afforded an inseparable complex mixture even at lower temperature.

Both methods of the transition metal and the hypervalent iodine reagent can convert various *N*-aryl enamine substrates into their corresponding indole products through oxidative C–C bond formation, with the requirement that the *N*-aryl enamine compound bear one or more electron-withdrawing groups such as cyano, ester or acyl groups, as their presence is essential for keeping the enamine configuration of the substrates. However, the hypervalent iodine reagent was also found to be applicable to the synthesis of 3-nitroindole from the *N*-aryl β-nitroenamine compound. On comparing the two methods, the transition metal method offers the advantage of tolerating a variety of substituents on the aromatic ring of the *N*-aryl enamine reactant, including nitro, cyano, amide, hydroxyl and trifluoromethyl groups. Furthermore, the oxidative annulation of cyclic *N*-aryl enamines was found to be achieved exclusively by the former method while our metal-free approach proved to be ineffective for this class of cyclic substrates.[23]

In conclusion, we have demonstrated a new approach to construct the synthetically and biologically important 4-methyl and 4-methoxy tetrahydro-γ-carboline compounds from the readily available 5-amino-3-oxopentanoate derivatives and substituted anilines. The most crucial step is the oxidative annulation, which can be realized by either Pd-catalyzed or $PhI(OAc)_2$-mediated C–C bond oxidative formation, with the former method furnishing the cyclized product in better yields. It can be envisaged that by starting off with different arylamines, this method provides convenient access to a variety of tetrahydro-γ-carboline derivatives containing different substituents on the phenyl ring.

Acknowledgements

Y. Du acknowledges the National Natural Science Foundation of China (#21072148) and the Cultivation Foundation (B) for Young Faculty of Tianjin University (TJU-YFF-08B68) for financial support.

Notes and references

1 (*a*) A. V. Ivachtchenko, E. B. Frolov, O. D. Mitkin, V. M. Kysil, A. V. Khvat, I. M. Okun and S. E. Tkachenko, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3183; (*b*) M. Gao and M. Wang, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2529; (*c*) P. R. Bharadwaj, G. Verdile, R. K. Barr, V. Gupta, J. W. Steele, M. L. Lachenmayer, Z. Yue, M. E. Ehrlich, G. Petsko and S. Ju, *J. Alzheimers Dis.*, 2012, **32**, 949.

2 (*a*) K. V. Butler, J. Kalin, C. Brochier, G. Vistoli, B. Langley and A. P. Kozikowski, *J. Am. Chem. Soc.*, 2010, **132**, 10842; (*b*) J. H. Kalin, K. V. Butler, T. Akimova, W. W. Hancock and A. P. Kozikowski, *J. Med. Chem.*, 2012, **55**, 639.

3 (*a*) S. Gore, S. Baskaran and B. König, *Org. Lett.*, 2012, **14**, 4568; (*b*) L. Zhang, W. Meier, E. Wats, T. D. Costello, P. Ma, P. O. Ensinger, J. M. Rodgers, I. C. Jacobson and P. Rajagopalan, *Tetrahedron Lett.*, 1995, **36**, 8387; (*c*) Rajagopalan and Parthasarathi, WO1994003455, PCT/US1993/006823, 1994.

4 L. Ye, Y. Tian, Z. Li, J. Zhang and S. Wu, *Helv. Chim. Acta*, 2012, **95**, 320.

5 A. Bridoux, J. Pommery, N. Pommery and J. P. Henichart, *Bioorg. Med. Chem.*, 2010, **18**, 3910.

6 I. T. Schiefer, L. VandeVrede, M. Fa', O. Arancio and G. R. J. Thatcher, *J. Med. Chem.*, 2012, **55**, 3076.

7 (*a*) S. L. Bascop, B. Sapi, J. Y. Laronze and J. Lévy, *Heterocycles*, 1994, **38**, 725; (*b*) J. A. Murphy, R. Tripoli, T. A. Khan and U. W. Mali, *Org. Lett.*, 2005, **7**, 3287; (*c*) B. M. Trost and M. K. Brennan, *Org. Lett.*, 2006, **8**, 2027; (*d*) V. J. Reddy and C. J. Douglas, *Org. Lett.*, 2011, **13**, 3288.

8 (*a*) C. A. Harbert, J. J. Plattner, W. M. Welch, A. Weissman and B. K. Koe, *J. Med. Chem.*, 1980, **23**, 635; (*b*) K. V. Butler, J. Kalin, C. Brochier, G. Vistoli, B. Langley and A. P. Kozikowski, *J. Am. Chem. Soc.*, 2010, **132**, 10842;

(*c*) C. Sheng, X. Che, W. Wang, S. Wang, Y. Cao, J. Yao and W. Zhang, *Eur. J. Med. Chem.*, 2011, **46**, 1706.

9 (*a*) V. Vecchietti, G. D. Clarke, R. Colle, G. Giardina, G. Petrone and M. Sbacchi, *J. Med. Chem.*, 1991, **34**, 2624; (*b*) D. Robaa, C. Enzensperger and J. Lehmann, *J. Med. Chem.*, 2010, **53**, 2646; (*c*) Y. Lee, R. S. Klausen and E. N. Jacobsen, *Org. Lett.*, 2011, **13**, 5564.

10 L. V. Kudzma, *Synthesis*, 2003, **11**, 1661.

11 (*a*) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2008, **47**, 7230; (*b*) J. J. Neumann, S. Rakshit, T. Dröge, S. Würtz and F. Glorius, *Chem.–Eur. J.*, 2011, **17**, 7298; (*c*) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 4572; (*d*) A. B. Gamble and P. A. Keller, *Chem. Commun.*, 2010, **46**, 4076.

12 W. Yu, Y. Du and K. Zhao, *Org. Lett.*, 2009, **11**, 2417.

13 D. R. Howton, *J. Org. Chem.*, 1945, **10**, 277.

14 (*a*) Y. Özlü, D. E. Cladingboe and P. J. Parsons, *Tetrahedron Lett.*, 1991, **50**, 2183; (*b*) S. Vassis, G. Karigiannis, G. Balayiannis, M. Militsopoulou, P. Mamos, G. W. Francis and D. Papaioannou, *Tetrahedron Lett.*, 2001, **42**, 1579; (*c*) K. M. Brinner, J. M. Kim, H. Habashita, I. Y. Gluzman, D. E. Goldberg and J. A. Ellman, *Bioorg. Med. Chem.*, 2002, **10**, 3649; (*d*) S. Varghese, D. Gupta, T. Baran, A. Jiemjit, S. D. Gore, R. A. Casero and P. W. Woster, *J. Med. Chem.*, 2005, **48**, 6350.

15 K. Ryuichi, K. Yasuhiko, T. Yukio, F. Toshio, K. Takashi, T. Shozo and F. Masahiro, WO2003016275, PCT/JP2002/008108, 2003.

16 M. Birch, S. Challenger, J. P. Crochard, D. Fradet, H. Jackman, A. Luan, E. Madigan, N. McDowall, K. Meldrum, C. M. Gordon, M. Widegren and S. Yeo, *Org. Process Res. Dev.*, 2011, **15**, 1172.

17 (*a*) C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.*, 1948, **70**, 2402; (*b*) Y. Abe, H. Kayakiri, S. Satoh, T. Inoue, Y. Sawada, N. Inamura, M. Asano, I. Aramori, C. Hatori, H. Sawai, T. Oku and H. Tanaka, *J. Med. Chem.*, 1998, **41**, 4062; (*c*) Q. Dai, W. Yang and X. Zhang, *Org. Lett.*, 2005, **7**, 5343; (*d*) M. Zhao, F. Wang and X. Li, *Org. Lett.*, 2012, **14**, 1412.

18 For an intramolecular S_N2'-type cyclization mechanism for this $PhI(OAc)_2$-mediated oxidative cyclization of *N*-aryl enamines, see ref. 12.

19 M. B. Bertrand, J. D. Neukom and J. P. Wolfe, *J. Org. Chem.*, 2008, **73**, 8851.

20 J. Zhang, C. Xiong, W. Wang, J. Ying and V. J. Hruby, *Org. Lett.*, 2002, **4**, 4029–4032.

21 T. Yasuhara, K. Nishimura, M. Yamashita, N. Fukuyama, K. I. Yamada, O. Muraoka and K. Tomioka, *Org. Lett.*, 2003, **5**, 1123.

22 J. R. Allen, M. P. Bourbeau, N. Chen, E. Hu, R. Kunz and S. Rumfelt, WO2010057121, PCT/US2009/064637, 2010.

23 For our previous work describing the reactions of $ArI(OAc)_2$ with the cyclic N-substituted 3-aminocyclohex-2-enones, analogs of enamine **15**, which afforded the *N*-arylated α-iodo β-enaminones, see: Y. Chen, T. Ju, J. Wang, W. Yu, Y. Du and K. Zhao, *Synlett*, 2010, 231.

