Tetrahedron Letters 56 (2015) 434–436

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A biomimetic method to synthesise indolo[3,2-*a*]carbazoles

Li-na Liang [a,b], Tian-yun Fan [b], Tao Huang [b], Chen Yan [b], Mei Xu [b], Sheng Liu [b,*]

[a] Guizhou University, Guiyang 550000, PR China
[b] The Key Laboratory of Chemistry for Natural Products of Guizhou Province, Chinese Academy of Sciences, Guiyang 550002, PR China

ARTICLE INFO

Article history:
Received 27 September 2014
Revised 25 November 2014
Accepted 28 November 2014
Available online 5 December 2014

Keywords:
Indolo[3,2-*a*]carbazoles
Biomimetic synthesis
Transamination
Aromatic cyclisation

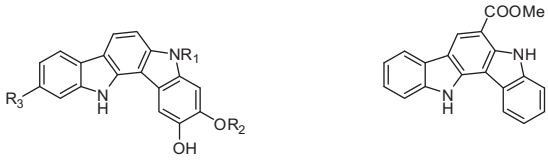
ABSTRACT

A simple and biomimetic synthetic strategy for indolo[3,2-*a*]carbazoles has been developed. Our approach involved the efficient conversion of 2-(3′-indolyl)tryptophan derivatives into the corresponding α-keto esters and the subsequent aromatic cyclisation of these intermediates to construct the characteristic heteroaryl-condensed carbazole core.

© 2014 Elsevier Ltd. All rights reserved.

Since early 2000, several indolo[3,2-*a*]carbazoles were successively isolated from marine organisms (Fig 1).[1] These natural carbazoles have received less attention compared to their isomeric form, indolo[3,2-*b*]carbazoles, which have demonstrated diverse biological activities and been intensely studied.[2] These compounds have not been thoroughly studied presumably not only because of their limited access from natural sources and lack of reported significant biological activities but also due to the lack of efficient methods for their synthesis. To the best of our knowledge, to date the only synthetic study towards natural indolo[3,2-*a*]carbazoles was focused on constructing the skeleton of ancorinazole, which was reported by Bergman and co-workers.[3] This approach followed their earlier work,[4] via a modified Vilsmeier reaction to generate 2,3′-biindoles before the condensation of the biindole with dimethylaminoacetaldehyde diethyl acetal to successfully furnish the corresponding indolo[3,2-*a*]carbazole. Moreover, indolo[3,2-*a*]carbazole derivatives have also been assembled by using electrophilic substrates ranging from 1,2-diones, propargyl ethers and nitrostyrenes to react with indoles or 2,3′-biindoles under acid-promoted conditions.[5]

Concerning the development of novel synthesis strategies for indole alkaloids, we considered that all natural indolo[3,2-*a*]carbazole alkaloids could be assembled by a unified biomimetic synthetic strategy. Scheme 1 depicts our retrosynthetic analysis, where indolo[3,2-*a*]carbazole **1** could be obtained by decarboxylation from esters **2**, which represent racemosin B and its derivatives with different substitutions. Compound **2** containing a latent



1x. ancorinazole, $R_1 = R_2 = SO_3Na$, $R_3 = H$
1y. $R_1 = H$, $R_2 = SO_3Na$, $R_3 = Br$
1z. $R_1 = R_2 = H$, $R_3 = Br$,

2a. racemosin B

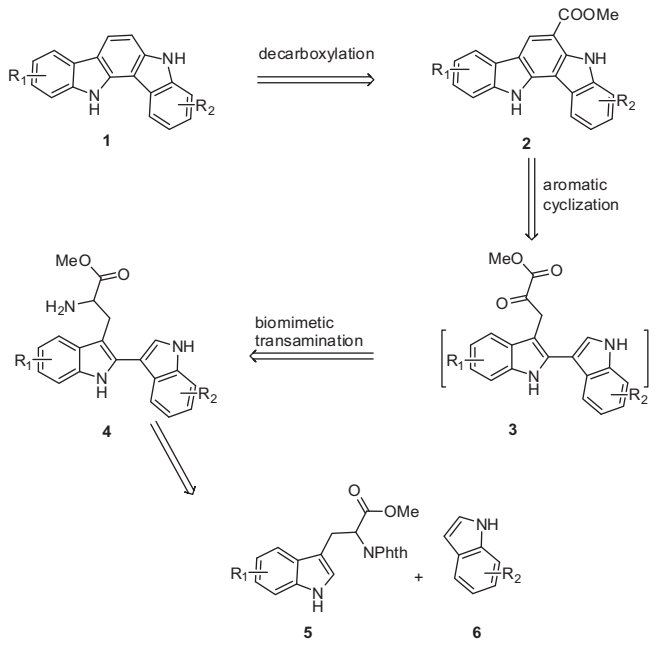
Figure 1. Natural indolo[3,2-*a*]carbazole alkaloids.

indole 3-pyruvic acid ester unit might be rapidly produced via a biomimetic transamination/aromatic cyclisation sequence from precursor **4**. Further disconnection provided two basic fragments: *N*-phthaloyl-2-indolyl tryptophan ester **5** and indole **6**. The main challenge in our plan was the adoption of a non-enzymatic transamination to form the key keto intermediate **3**. Although a transamination reaction has been developed[6] and served as a critical step in the synthesis of several natural products,[7] few examples have focused on its application in constructing carbazoles. If realised, it would not only provide a novel synthesis route to indolo[3,2-*a*]carbazoles but also allow us to further apply this strategy to other types of indole alkaloids containing the latent indole 3-pyruvic acid ester unit.

Intrigued by the above considerations, a synthesis study towards indolo[3,2-*a*]carbazoles was initiated (Scheme 2). We chose racemosin B (**2a**) as the first target because *N*-phthaloyl-2-indolyl tryptophan methyl ester **7a** was an intermediate in our recent work towards gliocladin C.[8] The deprotection of the Phth

* Corresponding author. Tel./fax: +86 851 5416876.
E-mail address: lsheng@126.com (S. Liu).

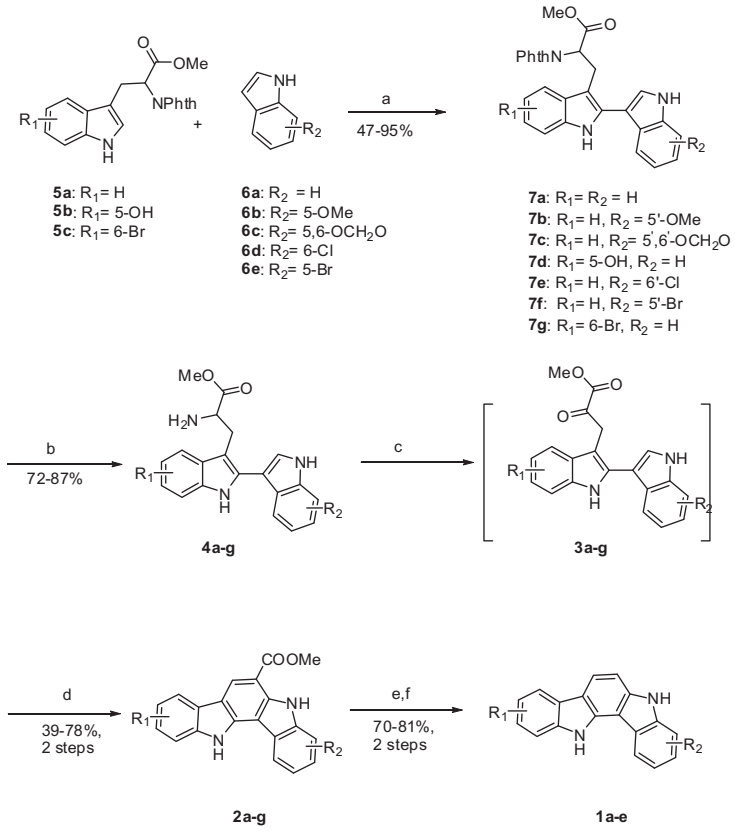
http://dx.doi.org/10.1016/j.tetlet.2014.11.136
0040-4039/© 2014 Elsevier Ltd. All rights reserved.



Scheme 1. Biomimetic retrosynthetic analysis towards indolo[3,2-*a*]carbazoles.

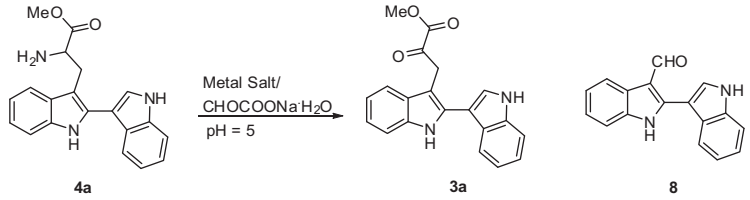
group would provide a free amine **4a** for the further optimisation of biomimetic transamination conditions. At the outset of screening, two reported conditions adopting catalysts such as isonicotinaldehyde/DBU and copper(II) ions/sodium glyoxylate have been examined.[6] Both attempts were unsuccessful, and we determined that the implementation of the latter condition in air afforded 2,3′-biindole-3-carbaldehyde **8**[4] as a major product (Table 1). Further investigation determined that the desired keto intermediate **3a** was formed in the reaction system; however, it rapidly decomposed to **8** through an autooxidation process, which has also been discussed by Barry B. Snider and coworkers.[9] Moreover, our study showed that copper(II) ions could significantly accelerate the above oxidative decomposition. Combining with the adoption of sodium glyoxylate, several other metal ions had also been tested in a parallel screening. It was found that both a catalytic amount of nickel ions and zinc ions could promote the demanding transformation effectively with no by-product **8** being detected. Attempts to purify this unstable keto ester were inefficient because decomposition was concomitant. However, we were able to circumvent this problem by a modified procedure: the crude intermediate **3a** was extracted from the aqueous reaction mixture and directly subjected to next TFA promoted aromatic cyclisation in heat dioxane.[10] To our delight, ester **2a** (racemosin B) was furnished in a 78% yield (two steps). Compound **2a** was then hydrolysed. Subsequent decarboxylation of the corresponding acid occurred at 300 °C, yielding a final product **1a**, which represents the basic core of natural indolo[3,2-*a*]carbazole alkaloids.[4]

Further assembled compounds **7b–g** with several different tryptophan and indole fragments[8,11] smoothly delivered compounds **2b–g** through the continuation of the synthesis following the above established procedure. Notably, α-keto ester **3c** (R_2 = 5′,6′-OCH_2O–) was active; it was formed in situ and cyclised to give indolo[3,2-*a*]carbazole ester **2c** in one pot during the transamination step. Previous decarboxylative condition was adaptable for the preparation of indolo[3,2-*a*]carbazoles **1a–e**. However, for **2f** and **2g** because debromination concurrently happened in the high-heat process, our attempts to deliver the corresponding brominated indolo[3,2-*a*]carbazoles failed.



Scheme 2. Reagents and conditions: (a) *t*-BuOCl, Et_3N, THF, then indole, $BF_3{\cdot}Et_2O$; (b) $N_2H_4{\cdot}H_2O$, CH_2Cl_2/MeOH; (c) for **3a–b**, **2c**, **3d–g**: $ZnSO_4$, $CHOCOONa{\cdot}H_2O$, MeCN/acetate buffer; (d) for **2a–b**, **2d–g**: TFA, 1,4-dioxane, 100 °C; (e) NaOH, MeOH/H_2O/DMSO; (f) for **1a–e**, **2d–g**: 300 °C, neat.

Table 1
Optimisation of transamination conditions of **4a**[a]



4a **3a** **8**

Entry	Metal salts	Time (min)	Yield[b]
1	$CuSO_4$	30	**8**, 85%[c]
2	$ZnSO_4$	30	**3a**, 94%
3	$NiCl_2$	30	**3a**, 90%
4	$FeSO_4$	120	**3a**, 23%
5	$FeCl_3$	120	ND
6	$CaCl_2$	120	ND
7	$MgSO_4$	120	ND
8	$Al_2(SO_4)_3$	120	ND

[a] A mixture of compound **4a** (34 mg, 0.10 mmol), metal salt (0.05 mmol), $CHOCOONa·H_2O$(114 mg, 1.0 mmol) in 1 mL of MeCN and 1 mL of buffer (pH = 5, containing 165 mg sodium acetate and 30 μL acetic acid) was stirred at 25 °C in air.
[b] Entries 2–4, yields determined by ^1H NMR of the crude extraction of reaction mixtures.
[c] Isolated yield.

In conclusion, we have developed a general approach to construct the heteroaromatic system of natural indolo[3,2-*a*]carbazoles. The operational simplicity combined with the adoption of eco-friendly reagents makes this method remarkable. Furthermore because the latent indole 3-pyruvic acid esters are substructures found in a variety of indole alkaloids, the methodology described herein can be applied to other natural targets.

Acknowledgments

The work was financially supported by the NSFC (No. 21462013), Qiankehe [2011] 3002, QKH-JZ [2010]2219 and the West Light Foundation of the Chinese Academy of Sciences.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.136.

References and notes

1. (a) Meragelman, K. M.; West, L. M.; Northcote, P. T.; Pannell, L. K.; McKee, T. C.; Boyd, M. R. *J. Org. Chem.* **2002**, *67*, 6671–6677; (b) Liu, D.-Q.; Mao, S.-C.; Zhang, H.-Y.; Yu, X.-Q.; Feng, M.-T.; Wang, B.; Feng, L.-H.; Guo, Y.-W. *Fitoterapia* **2013**, *91*, 15–20; (c) Russell, F.; Harmody, D.; McCarthy, P. J.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod.* **2013**, *76*, 1989–1992.
2. Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193–3328.
3. Wahlström, N.; Bergman, J. *Tetrahedron Lett.* **2004**, *45*, 7273–7275.
4. Janosik, T.; Bergman, J. *Tetrahedron* **1999**, *55*, 2371–2380.
5. (a) Nair, V.; Nandialath, V.; Abhilash, K. G.; Suresh, E. *Org. Biomol. Chem.* **2008**, *6*, 1738–1742; (b) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Nagase, Y.; Miyamura, T.; Shirakawa, E. *J. Am. Chem. Soc.* **2008**, *130*, 15823–15835; (c) Dupeyre, G.; Lemoine, P.; Ainseba, N.; Micheland, S.; Cachet, X. *Org. Biomol. Chem.* **2011**, *9*, 7780–7790.
6. (a) Ohta, S.; Okamoto, M. *Synthesis* **1982**, *9*, 756–758; (b) Papanikos, A.; Rademann, J.; Meldal, M. *J. Am. Chem. Soc.* **2001**, *123*, 2176–2181.
7. (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203; (b) Liu, S.; Cui, Y. M.; Nan, F. J. *Org. Lett.* **2008**, *10*, 3765–3768.
8. Sun, M.; Hao, X.-Y.; Liu, S.; Hao, X.-J. *Tetrahedron Lett.* **2013**, *54*, 692–694.
9. Barykina, O. V.; Snider, B. B. *Org. Lett.* **2010**, *12*, 2664–2667.
10. Tholander, J.; Bergman, J. *Tetrahedron* **1999**, *55*, 6243–6260.
11. Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964–11975.