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Synthesis of tetrahydro-β-carbolines, β-carbolines, and natural products, (±)-harmicine, eudistomin U and canthine by reductive Pictet Spengler cyclization

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ABSTRACT

Reductive Pictet Spengler cyclization was used for the synthesis of naturally occurring β-carbolines, eudistomin U, and canthine. Other biologically important β-carbolines as well as tetrahydro-β-carboline, such as (±)-harmicine were also synthesized using the same strategy.

Introduction

β- Carboline alkaloids constitute a large group of natural and synthetic indole alkaloids. The interest of chemists in the development of new methods for the synthesis of β-carboline alkaloids is mainly due to their broad spectrum of biological effects[1a-c] and presence in pharmaceuticals.[1d]

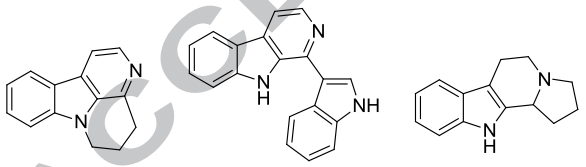


Figure 1. Structures of β-carbolines and tetrahydro-β-carboline alkaloids.

The Pictet Spengler condensation[2] is one of the most important strategies available for the synthesis of tetrahydro-β-carbolines (THβCs) which further can be dehydrogenated to β-carboline alkaloids. After the discovery of Pictet Spengler reaction, various Bronsted acids[3a], Lewis acids[3b], enzymes[3c], microwave reaction conditions[3d] etc. were used for this reaction.

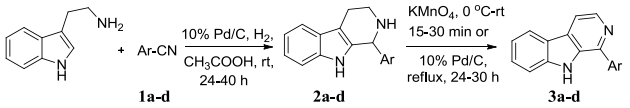
While targeting polyfunctional compounds, difficulty in the preparation of the polyfunctional aldehydes, use of corrosive CF_3COOH, and lower yields of the reactions, confines the scope of classical Pictet Spengler reaction. Literature survey revealed[4] an interesting modification for the synthesis of THβCs by reductive Pictet Spengler cyclization using nitrile and tryptamine in presence of hydrogenation conditions.

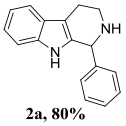
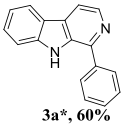
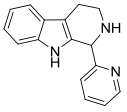
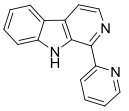
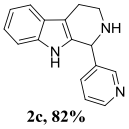
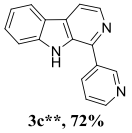
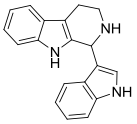
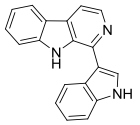
In this paper, we report the synthesis of biologically active, three natural products, eudistomin U (**3d**), canthine (**8**), harmicine (**10**) and three other unnatural β-carbolines, **3a-c** using reductive Pictet Spengler cyclization.

Results and discussion

The reductive Pictet Spengler cyclization[4-6] where nitrile is used instead of an aldehyde was visualized for the synthesis of natural and unnatural THβCs and β-carbolines. Thus, reaction of tryptamine with benzonitrile (**1a**) in presence of 10% Pd/C in acetic acid under hydrogen atmosphere, at room temperature resulted[7] in THβC **2a** (Table 1). Similar reaction using 2-cyanopyridine and 3-cyanopyridine furnished THβCs **2b** and **2c** respectively. Subsequently, THβC **2a** was dehydrogenated[8a] using $KMnO_4$, to produce β-carboline **3a** while compounds **2b** and **2c** were aromatized[8b] to **3b** and **3c** using 10% Pd/C in good yield. The same strategy using indole-3-carbonitrile furnished THβC **2d**, which on aromatization using 10% Pd/C resulted into the formation of eudistomin U (**3d**). For aromatization of **2a**, the use of Pd/C was avoided due to the reported[9] possibility of breakage of the ring during the dehydrogenation. All the synthesized compounds were characterized using spectral data and comparison with reported[10a-g] values.

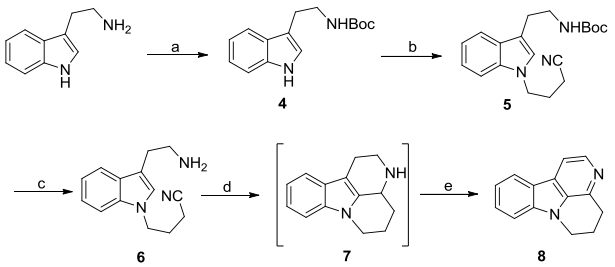
Table 1. Reductive Pictet Spengler reaction of tryptamine with nitriles **1a-d** and further dehydrogenation



Entry	Nitrile	THβC	β-Carboline
1	 **1a**	 **2a, 80%**	 **3a*, 60%**
2	 **1b**	 **2b, 80%**	 **3b**, 80%**
3	 **1c**	 **2c, 82%**	 **3c**, 72%**
4	 **1d**	 **2d, 85%**	 **3d**, 80%**

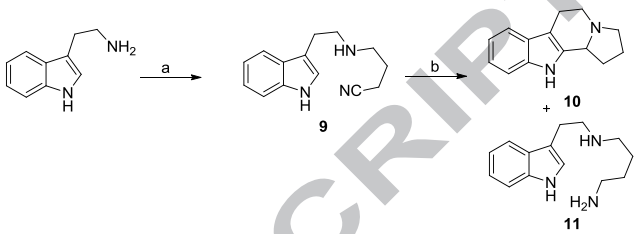
* aromatization using $KMnO_4$. ** aromatization using 10% Pd/C

For the synthesis of other target molecules, such as canthine and harmicine, use of aliphatic nitriles was envisioned. Thus, amino group of trypatamine was protected using $(Boc)_2O$ to give *N*-Boc compound **4** in 94% yield (Scheme 1). Treatment of compound **4** with 4-bromobutyronitrile in THF in presence of NaH gave selectively *N*-substituted[11a,b] compound **5**. Further, Boc group was deprotected using conc. HCl in ethanol to get amine **6** (crude compound 95%). Being an amine, it was difficult to purify using chromatographic separation. After removing ethanol on rotary evaporator, pH of the reaction mixture was adjusted to 11-12 by 5M NaOH and it was extracted with dichloromethane to obtain an oily product. It showed ^{1}H NMR consistent with the structure of amine **6** and its HRMS confirmed (M+H) 228.1498 for molecular formula $C_{14}H_{18}N_3$. Thus, it was used for further transformation without purification. Subsequently, stirring the compound **6** in acetic acid under hydrogen atmosphere, furnished an oily product by intramolecular reductive Pictet Spengler reaction. The efforts to purify the product by column chromatography, gave a complex mixture indicating the instability of this oily product. Therefore, it was used as such for the further reaction of aromatization using 10% Pd/C which furnished canthine **8** in 60% yield starting from compound **5**.



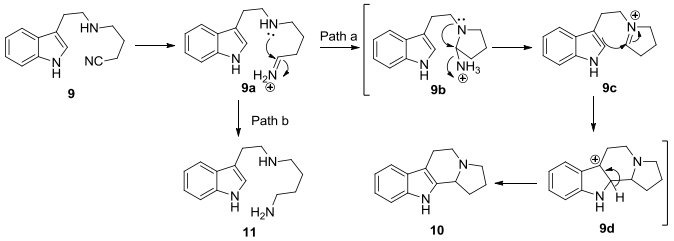
Scheme 1. Synthesis of canthine. Reagents and conditions: a) Et_3N, $(Boc)_2O$, Dioxane, rt, 3 h, 94%; b) 4-bromobutyronitrile, NaH, THF, rt, overnight, 92%; c) conc. HCl, EtOH, 50 °C, 2 h, 90% (crude compound); d) 10% Pd/C, H_2, CH_3COOH, 24 h, rt; e) 10% Pd/C, Toluene, reflux, 24 h, 60% (starting from compound **5**).

In order to synthesize harmicine, trypatamine was treated with 4-bromobutyronitrile which gave compound **9** with the preferential monosubstitution[12] at primary nitrogen (Scheme 2). Further intramolecular reductive Pictet Spengler reaction gave harmicine **10** (55%), along with reduced product **11** (40%).



Scheme 2. Synthesis of harmicine. Reagents and conditions: a) 4-bromobutyronitrile, K_2CO_3, EtOH, reflux, 6 h, 95%; b) 10% Pd/C, H_2, CH_3COOH, rt, 40 h, **10** (55%), **11** (40%).

According to the reported[3,4] mechanism of reductive Pictet Spengler reaction, in the present case, initially the nitrile group was hydrogenated to protonated imine **9a** under acetic acid condition. Further cyclization (might be assisted by Pd catalyst), loss of ammonia and Pictet Spengler reaction furnished compound **10**. This was accompanied with the hydrogenation of protonated imine in compound **9a** to get compound **11** as shown in Scheme 3.



Scheme 3. Possible Mechanism of the formation of **10** and **11**.

Conclusion

Reductive Pictet Spengler reaction has been used successfully for the synthesis of naturally occurring biologically active tetrahydro-β-carbolines, harmicine (**10**), β carbolines, eudistomin U (**3d**), canthine (**8**) and some pharmacologically important β-carbolines **3a**, **3b**, and **3c**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version.

References and notes

1) (a) de Freitas, Carla S.; Lucilia, K.; de Oliveira, Cecilia M. A.; Queiroz, Luiz H. K.; Santana, Mabio J.; Schuquel, I. T.; Delprete, P. G.; da Silva, Roosevelt A.; Quintino, G. O.; da Silva Neto, Benedito R. *Planta Medica* **2014**, *80*, 1746; (b) Hao, C.; Pengchao, G.; Meng, Z.; Wei, L.; Zhang, J. *New Journal of Chemistry* **2014**, *38*, 4155; (c) Takahiro, M.; Shotaro, H.; Shusaku, S.; Toshiyuki, W.; Takashi, M.; Hiroyuki, M.; Ikuro, A. *Chemistry & Biology* **2015**, *22*, 898; (d) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Current Medicinal Chemistry*, **2007**, *14*, 479.
2) Cox, E.D.; Cook, J. M. *Chem. Rev*. **1995**, *95,* 1797.
3) (a) Saito, A.; Numaguchi, J.; Hanzawa, Y. *Tetrahedron Lett*. **2007**, *48*, 835; (b) Srinivasan, N.; Ganesan, A. *Chem. Commun.* **2003**, 916; (c) Maresh, J. J.; Giddings, L. A.; Friedrich, A; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stockigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 710; (d) Mesangeau, C.; Yous, S.; Peres, B.; Lesieur, D.; Besson, T. *Tetrahedron Lett*. **2005**, *46*, 2465.
4) Diker, K.; Maindreville, M. D.; Levy, J. *Tetrahedron Lett*. **1995**, *36*, 2497.
5) Diker, K.; Biach, K. E.; Maindreville, M. D.; Levy, J. *J. Nat. Prod.* **1997**, *60,* 791.
6) Pouilhes, A.; Duval-Lungulescu, M.; Lambel, S.; Leonce, S.; Langlois, Y. *Tetrahedron Lett*. **2001**, *42*, 8297.
7) General procedure for reductive Pictet Spengler reaction: To a solution of tryptamine (1 mmol) in 10 mL of glacial acetic acid was added appropriate nitrile (1.5 mmol) and 10% Pd/C (0.2 mmol) in one portion. The mixture was hydrogenated at room temperature under balloon pressure for 24-40 h. The reaction was monitored by TLC. The catalyst was removed by filtration through celite and washed with dichloromethane. The resulting solution was made basic with aqueous NH_3 and then extracted with dichloromethane. The combined organic layers were dried on Na_2SO_4 and solvent was evaporated. The residue was purified by chromatography on activated neutral aluminium oxide using dichloromethane: methanol as an eluent to give tetrahydro-*β*-carboline.
8) General procedure for aromatization of TH*β*C to *β*-carboline: (a) To a solution of TH*β*C (1 mmol) in acetone was added $KMnO_4$ (4 mmol) cautiously (exothermic reaction) in portions at ice-water cooling and solution was stirred for 15-30 min. The reaction was monitored by TLC, then filtered on celite, washed with acetone, concentrated on rotary evaporator and purified by using column chromatography on silica gel using pet ether: ethyl acetate as an eluent to give *β*-carboline. (b) 10% Pd/C (5-7 mmol) was added to the appropriate TH*β*C (1 mmol) in toluene and heated to reflux for 24-30 h. The reaction was monitored by TLC. After completion of reaction, mixture was filtered while hot and evaporated on rotary evaporator. The residue was dissolved in methanol and chromatographed on silica gel using pet ether: ethyl acetate as an eluent to give corresponding *β*-carboline.
9) Hadjaz, F.; Yous, S.; Lebegue, N.; Berthelot, P.; Carato, P. *Tetrahedron* **2008**, *64*, 10004.
10) (a) Kulkarni, A.; Abid, M.; Torok, B.; Huang, X. *Tetrahedron Lett.* **2009**, *50*, 1791; (b) Handy, S.; Wright, M. *Tetrahedron Lett*. **2014**, *55*, 3440; (c) Tan, C.; Lai, S.; Wu, S.; Hu, S.; Zhou, L.; Chen, Y.; Wang, M.; Zhu, Y.; Lian, W.; Peng, W.; Ji, L.; Xu, A. *J. Med. Chem*. **2010**, *53*, 7613; (d) Espinoza-Moraga , M.; Petta, T.; Vasquez-Vasquez. M.; Laurie, V. F.; Moraes, L. A. B.; Santos, L. S. *Tetrahedron: Asymmetry* **2010**, *21*, 1988; (e) Shi, B.; Cao, R.; Fan, W.; Guo, L.; Ma, Q.; Chen, X.; Zhang, G.; Qiu, L.; Song, H.; *Eur. J. Med Chem.* **2013**, *60*, 10; (f) Wendlandt, A. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 506; (g) Yamaguchi, A. D.; Mandal, D.; Yamaguchi, J.; Itami, K. *Chem. Lett*. **2011**, *40*, 555.
11) (a) Mouchumi, B.; Burkhard, K. *Chem. Commun.* **2012**, *48*, 7489; (b) Chavez-Acevedo, L.; Miranda, L. D. *Organic & Biomolecular Chemistry*, **2015**, *13*, 4408.
12) Chu UB.; Vorperian SK.; Satyshur K.; Eickstaedt K.; Cozzi NV.; Mavlyutov T.; Hajipour AR.; Ruoho AE. *Biochemistry*, **2014**, *53*, 2956.

Graphical Abstract

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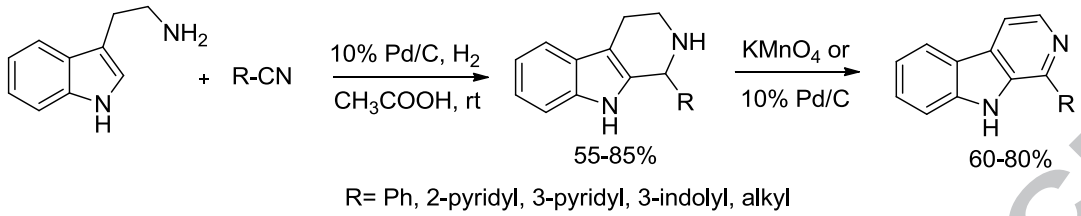

R= Ph, 2-pyridyl, 3-pyridyl, 3-indolyl, alkyl