Accepted Manuscript

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PII: S0040-4039(19)30392-2
DOI: https://doi.org/10.1016/j.tetlet.2019.04.044
Reference: TETL 50759

To appear in: *Tetrahedron Letters*

Received Date: 1 March 2019
Revised Date: 16 April 2019
Accepted Date: 25 April 2019

Please cite this article as: Szabó, T., Hazai, V., Volk, B., Simig, G., Milen, M., First total synthesis of the β-carboline alkaloids Trigonostemine A, Trigonostemine B and a new synthesis of Pityriacitrin and Hyrtiosulawesine, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.04.044

First total synthesis of the β-carboline alkaloids Trigonostemine A, Trigonostemine B and a new synthesis of Pityriacitrin and Hyrtiosulawesine

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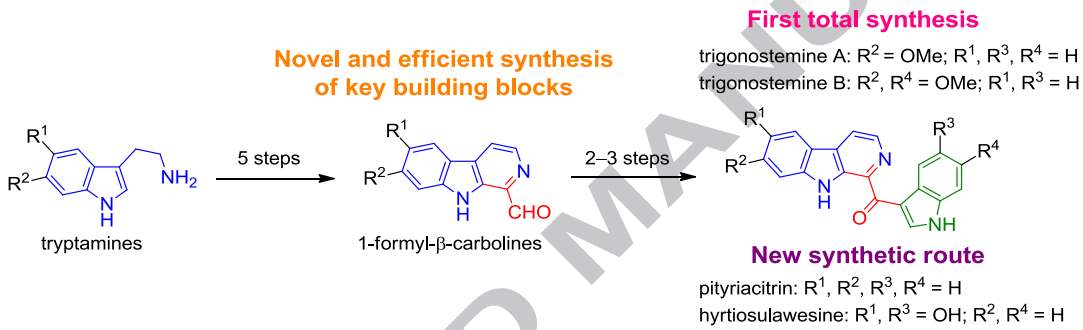
GRAPHICAL ABSTRACT



ABSTRACT

The total synthesis of four natural products, trigonostemine A, trigonostemine B, pityriacitrin, and hyrtiosulawesine was accomplished. The key intermediates, variously substituted 1-formyl-β-carbolines, were prepared in five steps *via* a novel synthetic approach using readily available starting materials. These formyl derivatives were then further transformed, providing a general route for the synthesis of the four title alkaloids. The method reported herein represents the first total synthesis of the two trigonostemines and a new pathway to pityriacitrin and hyrtiosulawesine.

KEYWORDS

Alkaloids, Total synthesis, β-Carbolines, Indole

INTRODUCTION

The β-carboline (**1**, 9*H*-pyrido[3,4-*b*]indole, Fig. 1) scaffold can be found in many natural products and synthetic compounds. Moreover, several representatives of this family show varied biological activities.[1–5]

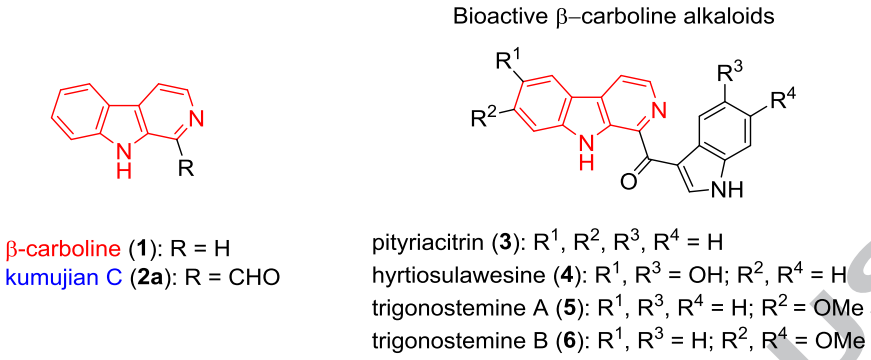
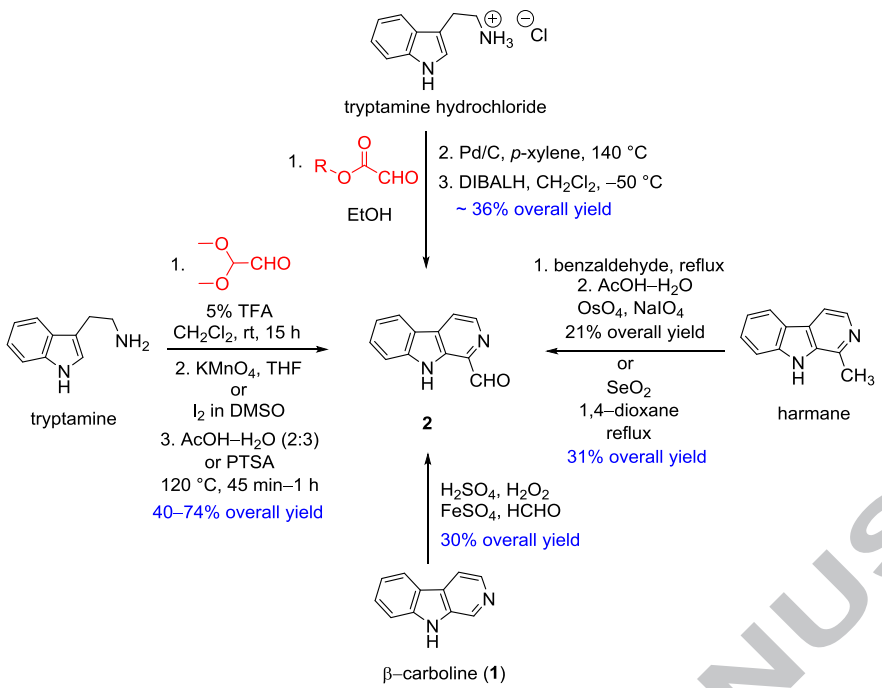


Figure 1. Structure of β-carboline (**1**) and alkaloids **2a**–**6**.

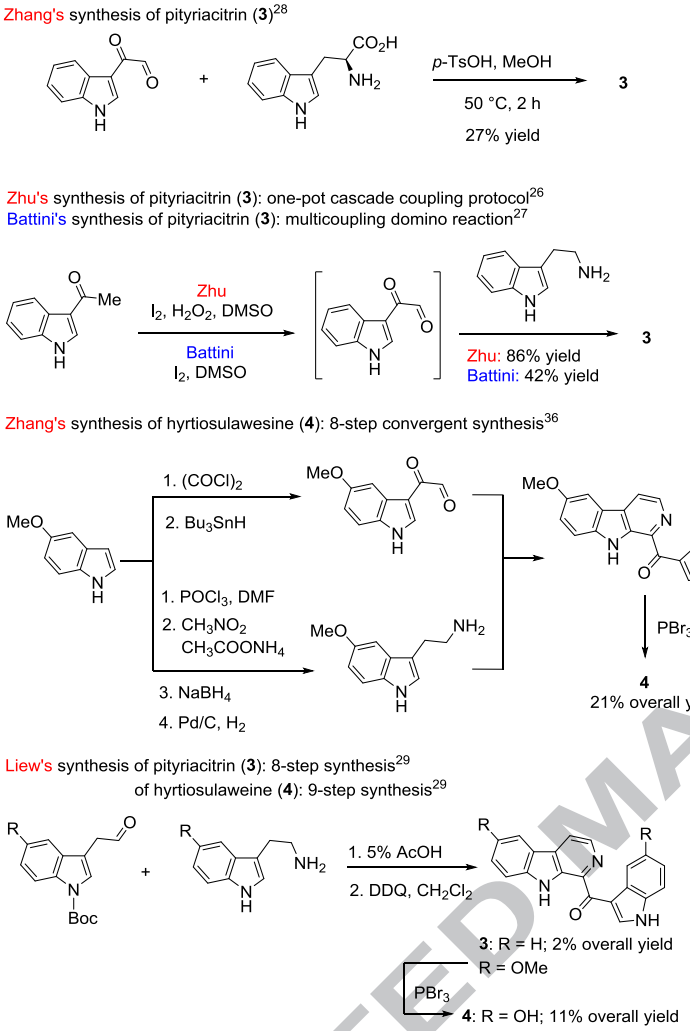
Kumujian C (1-formyl-9*H*-β-carboline, **2a**), as a natural member of this alkaloid family has been used as a building block for the synthesis of more complex compounds. Thanks to the synthetic potential of aldehyde **2a** and its derivatives, a number of syntheses have been described (Scheme 1).[5–8] Many syntheses start from tryptamine or its derivatives and build the β-carboline scaffold *via* a Pictet-Spengler reaction, followed by aromatization of the C-ring with a dehydrogenation catalyst or with an oxidizing agent, and construction of the aldehyde functional group at the C1 position in diverse overall yields.[9–18] Other synthetic methods are based on more complex and less available starting materials such as harmane or β-carboline (**1**).[19] These methods usually use difficult-to-handle or toxic reagents (e.g. OsO_4,[20] SeO_2[21] or H_2SO_4/H_2O_2[22]) and prepare this important building block with modest yields.



Scheme 1. Synthesis of 1-formyl-9*H*-β-carboline (**2**).

Pityriacitrin (**3**), trigonostemine A (**4**), trigonostemine B (**5**), and hyrtiosulawesine (**6**) are β-carboline alkaloids possessing an indol-3-carbonyl moiety at position 1 (Fig. 1) and were isolated from various sources.

Pityriacitrin (**3**) was first extracted from a marine bacterium of the genus *Paracoccus* in 1999;[23] later the same compound was isolated from the human pathogenic yeast *Malassezia furfur*.[24] Recently, pityriacitrin (**3**) was discovered as a secondary metabolite from the marine fungus *Dichotomomyces cejpii* F31-1.[25] Hitherto, four total syntheses of pityriacitrin (**3**) have been described in the literature (Scheme 2)[26–29] and the compound has also been tested for various biological activities.[28–30]



Scheme 2. Total syntheses of pityriacitrin (**3**) and hyrtiosulawesine (**4**).

Hyrtiosulawesine (**4**) was first isolated from an Indonesian specimen of the marine sponge *Hyrtios erectus*.[31] Ten years later, alkaloid **4** extracted from the Asian medicinal plant *Alocasia macrorrhiza* showed antiproliferative activity against human nasopharyngeal carcinoma epithelial.[32] Recently, hyrtiosulawesine (**4**) has been isolated from two different sources: a marine sponge *Ircinia sp.*[33] and from the roots of *Aristolochia cordigera*[34] which is a member of the birthwort family. The antimalarial activity of hyrtiosulawesine (**4**) was observed against chloroquine resistant[29] and 3D7[34] strains of the protozoan parasite *Plasmodium falciparum*. In addition, compound **4** exhibited antiphospholipase A2[35] and antioxidant activities.[29] The first total synthesis of hyrtiosulawesine (**4**) in eight steps was reported by Zhang and co-workers in 2010.[36] Four years later, Liew and co-workers described a new 9-step synthetic strategy for the preparation of compound **4** (Scheme 2).[29]

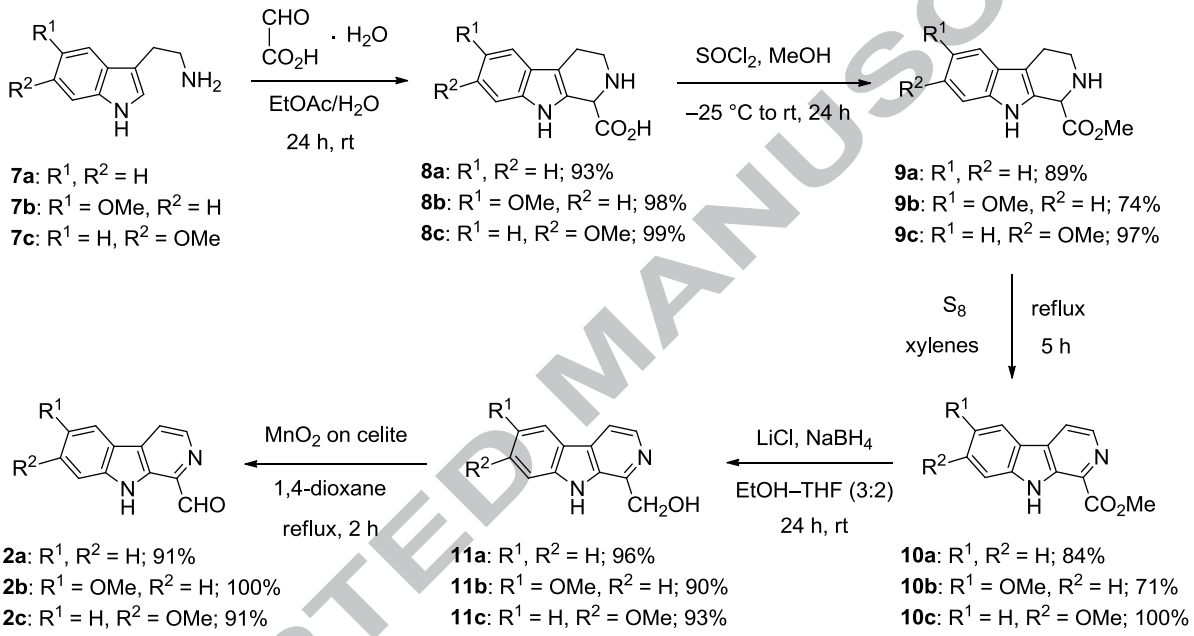
Trigonostemine A (**5**) and trigonostemine B (**6**) were isolated from plants that are members of the spurge family. In the literature they were originally extracted from the leaves of *Trigonostemon lii* along with twelve other β-carboline alkaloids.[37] Recently Wang and co-workers isolated alkaloids **5** and **6** from the ethanolic extract of the twigs of *Trigonostemon filipes*.[38] For comparison, compounds **5** and **6** exhibited a higher cytotoxic activity against various human cancer cell lines than the chemotherapy medication cisplatin.[36,37] To the best of our knowledge, the total synthesis of these promising alkaloids trigonostemine A (**5**) and trigonostemine B (**6**) have not been described.

In this paper, we report the synthesis of various β-carboline alkaloids with a remarkable pharmacological potential using a novel and efficient synthetic approach *via* well-known 1-formyl-β-carboline building blocks (**2**). A new and convenient synthetic route for pityriacitrin (**3**) and hyrtiosulawesine (**4**), as well as the first total synthesis of trigonostemine A (**5**) and B (**6**) are described below.

RESULTS AND DISCUSSION

Initially, the appropriate 1-formyl-9*H*-β-carboline key intermediates (**2a**–**c**) were prepared *via* a novel and practical synthetic route (Scheme 3). Although a number of syntheses have been described for the preparation of 1-formyl-9*H*-β-carboline (**2a**),[5–9] many of them use toxic or difficult-to-handle reagents and result in low yields,[18–22] while others could hardly be reproduced in our experiments.[12–17] Therefore, we developed an improved and efficient method for the construction of compounds **2a**–**c**. In the first step, the Pictet–Spengler reaction of tryptamines **7a**–**c** and glyoxylic acid monohydrate in an ethyl acetate−water biphasic system[39] gave tetrahydro-β-carboline-carboxylic acids (**8a**–**c**) in excellent yields under mild conditions (24-hour stirring at room temperature). This was followed by the esterification of compounds **8a**–**c** using a literature method (thionyl chloride, methanol).[40] During the addition of reagents, a low temperature (−25 °C) was used then the mixture was stirred for 24 hours at room temperature to give methyl esters **9a**–**c**. Compounds **9a**–**c** were used in the next step without further purification and characterization. Aromatization of the C-ring was carried out using elemental sulfur in xylene isomers[41] at reflux for 5 hours. The dehydrogenated compounds **10a**–**c** were synthesised in good yields (71–100%). Afterwards the ester group of

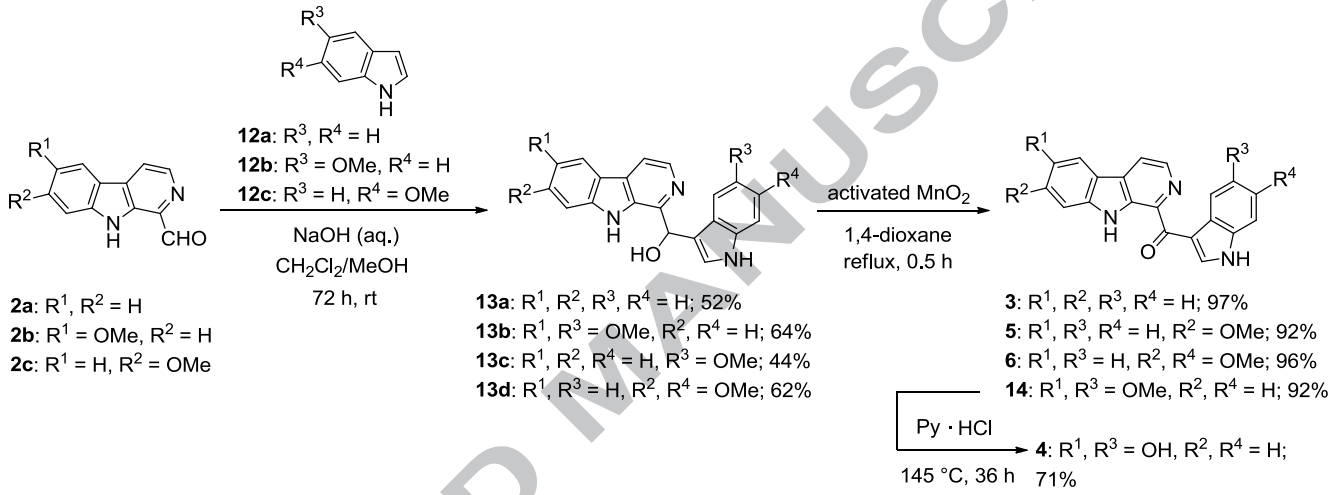
10a–**c** was reduced to give alcohols **11a**–**c** using lithium chloride-activated sodium borohydride[42] in an ethanol/tetrahydrofuran solvent system at room temperature for 24 hours. Finally, oxidation of the hydroxyl group in alcohols **11a**–**c** was achieved using MnO_2 on Celite® prepared by Attenburrow's method[43,44] in 1,4-dioxane at reflux, and aldehydes **2a**–**c** were isolated in excellent yields after stirring for 2 hours. The overall yield of the building blocks was 46–81%. It should be noted that compounds **2a**–**c** were obtained 10–20% lower yield when commercially available activated MnO_2 was used in the oxidation step.



Scheme 3. Synthesis of 1-formyl-9*H*-β-carbolines (**2a**–**c**).

Next, the preparation of alkaloids **3**–**6** took place from the synthesised 1-formyl-9*H*-β-carbolines (**2a**–**c**, Scheme 4). First, the appropriate 1-formyl-9*H*-β-carbolines (**2a**–**c**) were coupled with indole (**12a**) or substituted indole derivatives **12b**,**c** under basic conditions. Although the conversion was not complete with 1 equivalent of indoles, the corresponding products were selectively obtained and the formation of disubstituted products (containing 2 indole moieties)[45,46] was avoided. The isolated secondary alcohols (**13a**–**d**) were obtained in moderate yields and then oxidized to ketones using activated MnO_2 under the same conditions described for the preparation of 1-formyl-9*H*-β-carbolines (**2a**–**c**). This gave the desired natural products (**3**, **5**, **6**) were isolated in excellent yields (92–97%). An additional double *O*-demethylation step was required to obtain hyrtiosulawesine (**4**). The reaction with 1-dodecanethiol[47] in *N*-methyl-2-pyrrolidone in the presence of NaOH at 130 °C for 2 hours did

not result in the product, and only the starting material was detected in the reaction mixture. *O*-Demethylation with iodotrimethylsilane[48] in acetonitrile at 82 °C for 48 hours led to only trace amounts of **4**, and partially demethylated products were detected as well. The attempted demethylation of **14** with boron tribromide[36] in dichloromethane at room temperature for 72 hours gave partially demethylated derivatives as the main products, along with a minor amount of the target compound hyrtiosulawesine (**5**). Finally, the *O*-demethylation of **14** with pyridine hydrochloride[49] at 145 °C led to hyrtiosulawesine (**4**) selectively in good yield (71%) after 36 hours.



Scheme 4. Synthesis of β-carboline alkaloids **3**–**6**.

The overall yield of the synthesized alkaloids, calculated from tryptamines **7a**–**c**, was 31% for pityriacitrin (**3**), 33% for trigonostemine A (**5**), 48% for trigonostemine B (**6**) and 13% for hyrtiosulawesine (**4**) through a 7- or 8-step synthetic route. The NMR data of the synthesised alkaloids pityriacitrin (**3**, see ESI, Table S1) and hyrtiosulawesine (**4**, Table S2) are identical with the literature data. Similarly, the spectral data of trigonostemine A (**5**, Table S3) and trigonostemine B (**6**, Table S4) are the same as those described from natural sources.[37,38]

CONCLUSION

1-Formyl-9*H*-β-carboline intermediates (**2**) were synthesized in five steps starting from tryptamines **7** using simple reactions, readily available materials and easy-to-handle reactants. These were further transformed to four β-carboline alkaloids in 2 or 3 steps. While for trigonostemines **5** and **6**, this represents the first reported total synthesis, the methodology

could also be applied to the preparation of pytiriacitrin (**3**) and hyrtiosulawesine (**4**), representing a fundamentally new synthetic approach towards these two alkaloids.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge on the *Tetrahedron Letters* website at DOI:

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Highlights

- First reported synthesis of trigonostemine A and trigonostemine B
- New synthesis of pityriacitrin and hyrtiosulawesine
- An improved preparation of 1-formyl-β-carboline building blocks