Synthetic Study towards Strictamine: The Oxidative Coupling Approach

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Abstract: A synthetic approach featuring a key intramolecular oxidative coupling of a dianion for the formation of the C7–C16 bond was exploited aiming at the synthesis of strictamine. Treatment of substituted tetrahydrocarboline with LHMDS at –78 °C followed by iodine at room temperature afforded a tetracyclic compound, a substructure of eburnane-type alkaloid, via the formation of the N_a–C16 bond.

Key words: strictamine, oxidative coupling, indole alkaloid, tetrahydro-β-carboline

Strictamine (**1**, Figure 1),[1] one of the constituents of *Rhazya* alkaloids, was first isolated in 1966 from the flowers of *Alstonis scholaris*, which has been used as folk medicine for its potent antitumor, anti-inflammatory, and antibiosis activities. The absolute configuration of strictamine was resolved with the aid of X-ray crystallography in 1977.[2] It is a representative member of the akuammiline family of alkaloid[3] that derives biosynthetically from geissoschizine (**2**) via C7–C16 bond formation.[4] Because of its inspiring molecular architecture and biological significance, considerable synthetic efforts have been made towards its synthesis.[5] However, no total synthesis has been reported to date. Herein we report our synthetic studies aiming at closing the ring E via formation of the C7–C16 bond by way of oxidative coupling of a dianion.

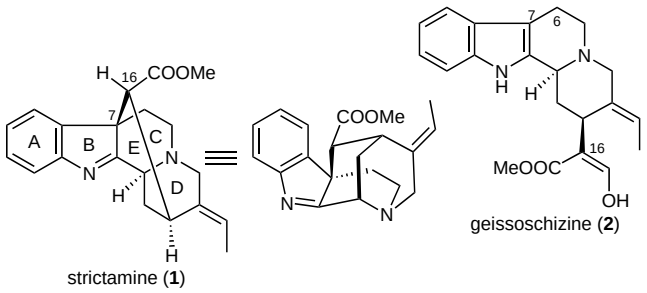
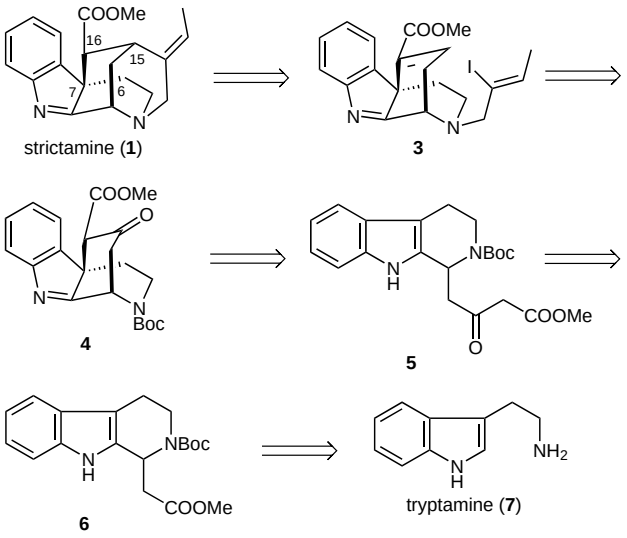


Figure 1 Strictamine and geissoschizine

From the retrosynthetic perspective, we expected that strictamine could be synthesized from vinyl iodide **3** by way of an intramolecular Michael addition or its synthetic equivalents (Scheme 1). Compound **3** would be derived from tetracycle **4**, which was thought to be accessible by an intramolecular oxidative coupling of β-keto ester **5**. Generation of **5** could be achieved from a known tetrahydro-β-carboline derivative **6**, easily available from tryptamine (**7**) through simple chemical reactions.



Scheme 1 Retrosynthetic analysis of strictamine (**1**)

The recent work from the groups of Baran,[6] Overman,[7] and Ma[8] has exposed the potency of oxidative dianion coupling in the total synthesis of indole alkaloids.[9] Thus, the direct intramolecular oxidative coupling to form the crucial C7–C16 bond of strictamine was expected to be an attractive strategy. On the other hand, since it has been suggested that a possible biosynthetic route to strictamine from geissoschizine would necessitate an oxidative coupling to form the C7–C16 bond,[10] the strategy proposed in Scheme 1 could be considered as biomimetic.

We initiated our synthesis by the preparation of β-keto ester **5**, which is the precursor for the planned oxidative coupling reaction (Scheme 2). Treatment of tryptamine (**7**) with methyl malonitrile under hydrogenation conditions according to Lévy,[11] followed by selective protection of the secondary amine (N_b) as the *N*-Boc carbamate provided tetrahydro-β-carboline **6** in 96% isolated yield. Hydrolysis of ester **6** delivered the corresponding carboxylic acid. The acid was then activated with CDI (1,1′-carbonyldiimidazole) to yield the imidazolide intermediate which, upon reaction with magnesium methyl malonate, afforded the desired β-keto ester **5** with 91% isolated yield.[12] We chose the N_b-Boc-protection based on the hypothesis that it could push the β-keto ester moiety to a pseudo-axial position to avoid the $A^{1,3}$ strain.[13] Such con-

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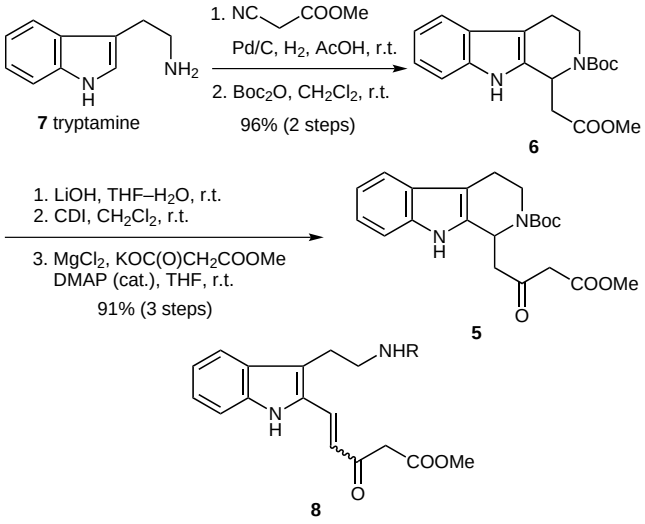
formational preference, conducive to the desired intramolecular oxidative coupling reaction, was indeed confirmed by X-ray structural analysis of **5** (Figure 2).



Scheme 2 Synthesis of the oxidative coupling precursor **5**

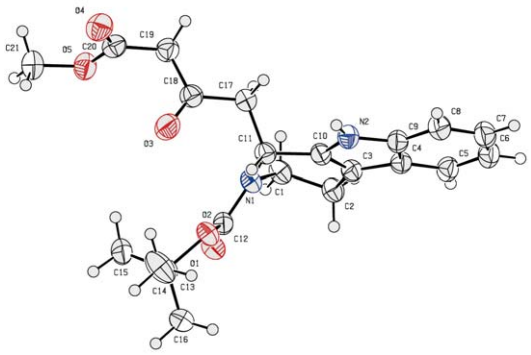
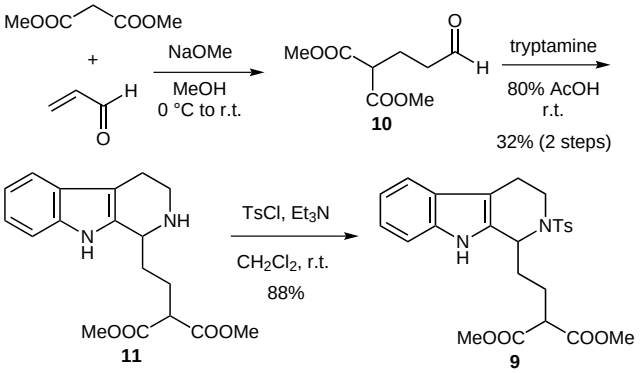


Figure 2 ORTEP drawing of **5** with 30% thermal ellipsoids

With compound **5** in hand, we began to test the pivotal oxidative coupling reaction. To our disappointment, no desired product resulting from the formation of C6–C17 bond could be found under different conditions varying the bases, the stoichiometries, the oxidants, and the temperature.[14] Similar results were obtained using *N*-tosyl and *N*-benzoyl derivatives. While complete degradation was observed in most of the cases, one byproduct **8** resulting from the retro-Michael reaction was isolated. The related process has in fact been elegant exploited for the synthesis of 2,3-disubstituted indoles.[15]

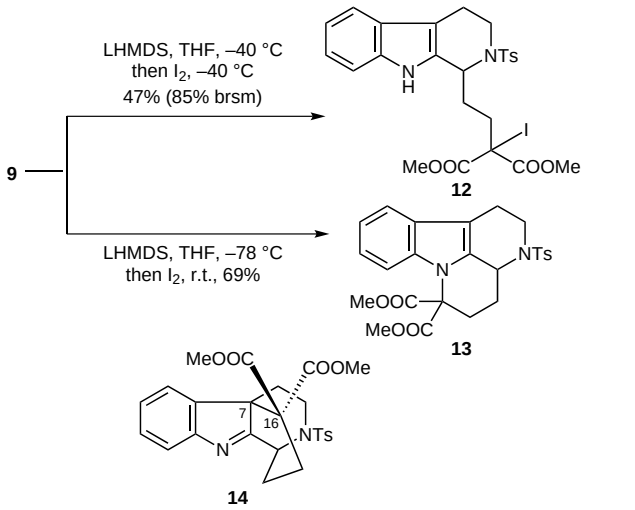
To examine the oxidative coupling reaction further, we next turned our attention to a dimethyl malonate derivative **9** that is devoid of the undesired β-elimination process. Michael addition of dimethyl malonate with acrolein afforded the dimethyl 2-(3-oxopropyl)malonate (**10**, Scheme 3).[16] Pictet–Spengler reaction of the tryptamine (**7**) with aldehyde **10** under acidic conditions furnished **11** in 32% yield over two steps.[17] N-Tosylation of the secondary amine (TsCl, Et_3N, CH_2Cl_2, r.t.) produced compound **9** in 88% yield.



Scheme 3 Synthesis of the oxidative coupling precursor **9**

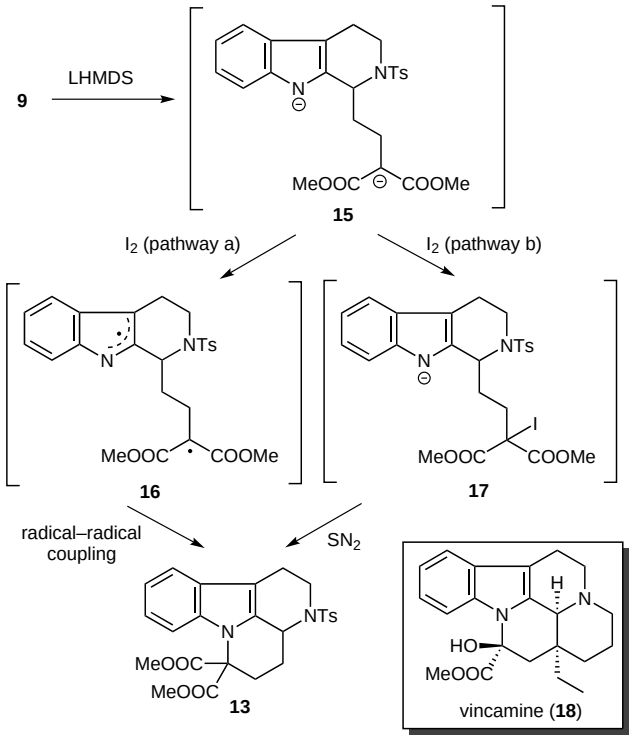
The intramolecular oxidative coupling of **9** was then examined. Since the oxidant played a major role in the oxidative coupling,[6] a variety of oxidants were screened.[14] While the degradation or the recovery of starting materials were two scenarios that we encountered in most of the cases, an iodination product **12** was isolated in 47% yield when iodine (1.0 equiv) was added as oxidant at –40 °C (Scheme 4). Interestingly, when iodine (1.0 equiv) was added at room temperature to the solution of the dianion generated in situ from **9**, a tetracyclic product **13** resulting from the formation of N_a–C16 bond was obtained in 49% yield at the expense of the desired tetracycle **14**.[18,19] The yield of **13** was increased to 69% when two equivalents of iodine were added. Hypervalent iodine reagent such as PIFA (iodobenzenebistrifluoroacetate) could also act as oxidant to afford compound **13** albeit with lower yield. We assumed that the failure to produce **14** from **9** via the formation of C6–C17 bond could not be attributed to the unfavorable geometric constraints as it was evidenced in the X-ray structure of related compound **5**. The outcome could rather be rationalized by invoking the excessive ring strain associated with the bridged ring system of **14**. Consequently, the alternative cyclization leading to ring-fused product **13** became predominant.

Two pathways could account for the formation of the tetracycle **13**.[20] One involved the radical–radical coupling of **16** generated by oxidation of the dianion **15** with I_2 (pathway a, Scheme 5).[21] The other implicated an S_N2 reaction of intermediate **17** (pathway b).[22] Treatment of a THF solution of **12** with LHMDS at –78 °C, followed by addition of iodine (1.0 equiv) at room temperature failed to produce tetracycle **13**. The result of this control experiment indicated that **12** could not be the intermediate en route to tetracycle **13**. It is known that the β-position of indole is generally involved in the bond-forming process under oxidative coupling conditions,[6f] the result shown here is, to the best of our knowledge, the first example wherein the C–N bond formation is preferred over the C–C bond formation under oxidative coupling conditions. Notwithstanding, the formation of **13** was not without interest.



Scheme 4 Oxidative coupling of **9**

Indeed, we expected that this novel cyclization could be applied to the synthesis of other natural product bearing the similar skeleton such as vincamine (**18**, Scheme 5),[23] which is a well-known alkaloid of eburnane type with a broad range of bioactivities.



Scheme 5 Possible mechanisms for the formation of **13**

In conclusion, an intramolecular oxidative coupling of tetrahydro-β-carboline derivatives was examined aiming at closing the ring E of strictamine via formation of C7–C16 bond. Under optimized conditions [LHMDS (2.2 equiv), –78 °C, then r.t., I_2 (2.0 equiv)], cyclization of **9** did occur leading to tetracycle **13** via the formation of N_a–C16 bond. Although not initially expected, we believed that this reaction could find application in the synthesis of eburnane type of alkaloids.[24]

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **Procedure for the Preparation of Compound 13**
To a solution of methyl malonate **9** (48.0 mg, 0.1 mmol) in THF (1.0 mL, 0.1 M) was added dropwise LHMDS (0.22 mL, 1.0 M in THF, 0.22 mmol) at –78 °C. After 10 min, the reaction mixture was warmed to r.t. and a solution of iodine (52.0 mg, 0.2 mmol) in THF (0.2 mL) was added. The reaction was stirred at r.t. for 10 min, and then quenched with $Na_2S_2O_3$ (aq). The aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2–acetone = 150:1) to yield **13** as a yellow foam (32.0 mg, 69%). IR (neat): 2925, 2854, 1739, 1454, 1229, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.2 Hz, 2 H), 7.38–7.36 (m, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.13–7.07 (m, 3 H), 4.46 (dd, *J* = 11.8, 4.2 Hz, 1 H), 3.90 (s, 3 H), 3.76 (ddd, *J* = 13.4, 4.4, 4.4 Hz, 1 H), 3.61 (s, 3 H), 3.50 (ddd, *J* = 13.4, 8.8, 3.6 Hz, 1 H), 2.94–2.89 (m, 1 H), 2.75–2.69 (m, 1 H), 2.66–2.61 (m, 1 H), 2.51–2.43 (m, 1 H), 2.41 (s, 3 H), 2.39–2.32 (m, 1 H), 2.04–1.94 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.5, 168.0, 143.8, 137.9, 136.7, 131.7, 130.1, 127.7, 127.3, 122.4, 120.7, 118.3, 112.6, 109.9, 68.4, 53.7, 53.2, 53.1, 44.7, 32.1, 27.4, 21.7, 21.3. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{25}H_{27}N_2O_6S$: 483.1590; found: 483.1598.
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