HETEROCYCLES, Vol. 72, 2007, pp. 175 - 179. © The Japan Institute of Heterocyclic Chemistry
Received, 11th December, 2006, Accepted, 22nd January, 2007, Published online, 23rd January, 2007. COM-06-S(K)43

DIASTEREOSELECTIVE CONSTRUCTION OF INDOLO[2,3-*a*]QUINOLIZIDINE SKELETON BY CYCLOADDITION REACTION OF 3,4-DIHYDRO-β-CARBOLINES WITH γ,δ-UNSATURATED β-KETOESTERS

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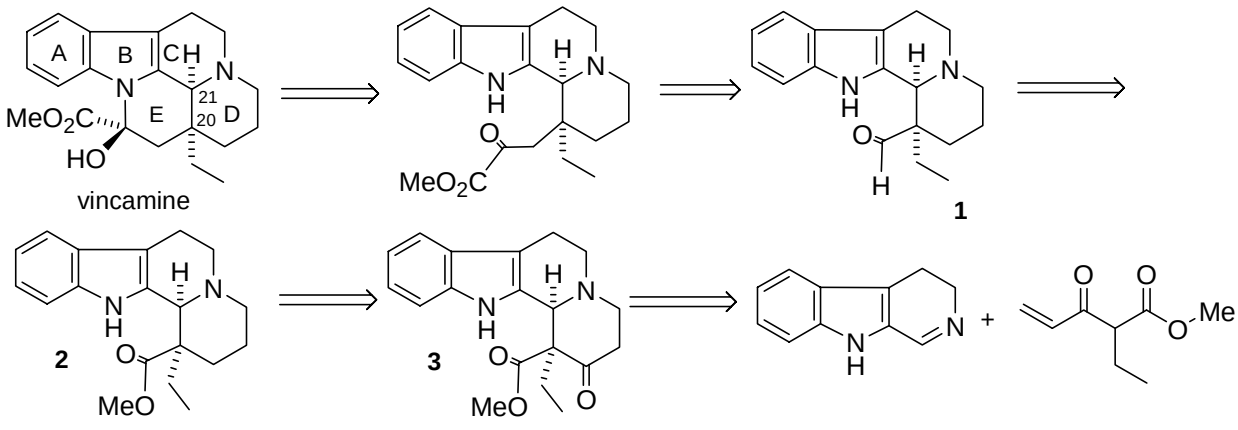
Abstract – Cycloaddition reaction of 3,4-dihydro-β-carboline derivatives with γ,δ-unsaturated-β-ketoesters afforded octahydroindolo[2,3-*a*]quinolizidines in one step. The reaction was applied to the synthesis of a potential precursor of Eburnamine-Vincamine alkaloids in a highly diastereoselective manner.

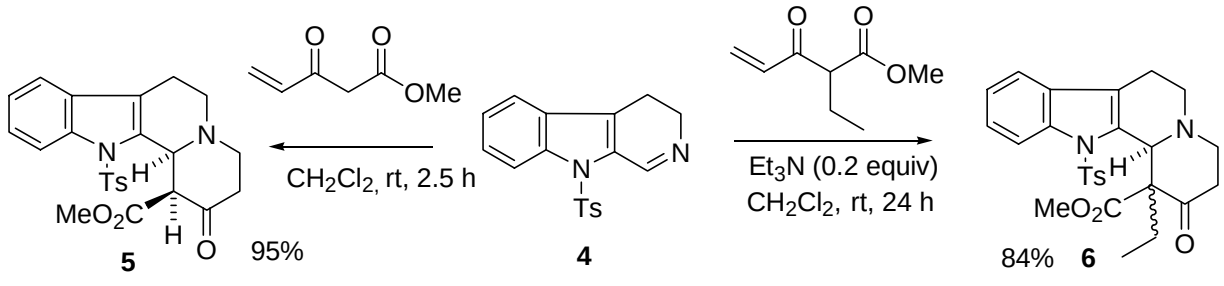
Eburnamine-vincamine alkaloids exhibit a variety of physiological activities.[1] Among these alkaloids, vincamine, which has potent pharmacological activity[2] including cerebroprotective activity caused by a dilation of brain arteries, is a major alkaloid and has been the target of many synthetic studies.[1] Several strategies for the synthesis of the eburnamine-vincamine alkaloids were reported.[3] In the principal strategies, tetracyclic intermediates having octahydroindolo[2,3-*a*]quinolizine skeleton were synthesized followed by the formation of the fifth ring E. Thus, stereoselective construction of a D/E ring junction is a crucial step for the synthesis. Retrosynthetic pathway of vincamine is outlined in Scheme 1. An



Scheme 1

aldehyde (**1**) was first synthesized by Oppolzer et al.,[4] and it was converted to vincammine in six steps. Since then the aldehyde (**1**) has been a key intermediate in many vincamine syntheses. Langlois et al. accomplished the synthesis of (±)-vincamine from **1** in two steps,[5] and the synthesis of (+)-vincamine via intermediates (**1**) and (**2**) has been achieved by Rapoport et al. using L-aspartic acid as a starting material.[3c] Thus the chiral aldehyde (**1**) is an important intermediate for the synthesis of (+)-vincamine, but reported method to obtain the chiral **1** required tedious many steps. We thought if the compound (**1**) or (**2**) was synthesized stereo selectively in short steps, more practical synthetic route would be established. In the course of our research for the synthesis of 1-substituted 1,2,3,4-tetrahydro-β-carboline derivatives,[6] we have found that 3,4-dihydro-β-carboline reacts with γ,δ-unsaturated-β-ketoesters to give cycloaddition products which contain octahydroindolo[2,3-*a*]quinolizidine skeleton, therefore we have investigated the reaction with α-ethyl-γ,δ-unsaturated-β-ketoester to obtain **3** which would lead to the intermediate (**2**) for the synthesis of vincamine. In this paper we described these results.

Firstly, We investigated the reaction of 9-tosyl-3,4-dihydro-β-carboline (**4**)[7] with α-unsubstituted γ,δ-unsaturated-β-ketoesters (Scheme 2). When the reaction was carried out with methyl 3-oxo-4-pentenoate, a cycloaddition product (**5**) was obtained in 95% yield as a single diastereomer.[8] Compound (**5**) is thought to be a thermodynamically controlled product, because there is an acidic hydrogen at α position of both carbonyl groups. The reaction with methyl 2-ethyl-3-oxo-4-pentenoate



Scheme 2

also proceed to give cycloaddition product (**6**) in high yield in the presence of Et_3N (0.2 equiv), though diastereoselectivity was low. With these results in hand, the cycloaddition reaction employing 3-(*S*)-benzyl 3,4-dihydro-β-carboline-3-carboxylate 4-toluenesulfonic acid salt (**7**)[9] was next examined to synthesize the optically active indolo[2,3-*a*]quinolizidine derivative (Table). As compound (**7**) was insoluble in CH_2Cl_2, the reaction was carried out in more polar DMF solution to give a trace amount of **8** as a single diastereomer.[10] When DMF/H_2O=1 solvent was used, yield rise up to 38%. The compound (**7**) was unstable under a basic condition to give some degradation products, thus the cycloaddition

reaction was carried out in the presence of buffer solution. As a result, the yield of **8** was up to 67% when 1.2 equivalent of pH 7.4 phosphate buffer was added.

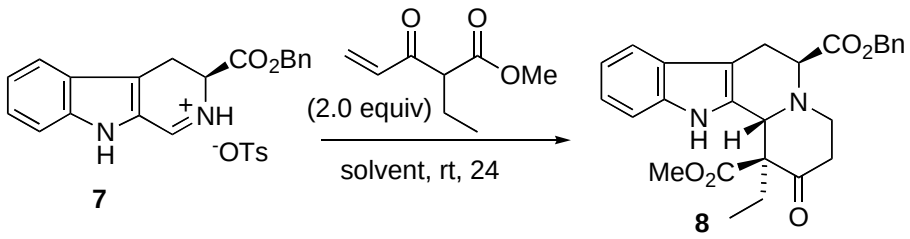


Table 1

Entry	Solvent	Additive (equiv)	Yield(%)
1	DMF	-	trace
2	DMF/H_2O=1	-	38
3	H_2O	-	trace
4	DMF/H_2O=1	Et_3N (1.0)	38
5	DMF/H_2O=1	pH 7.4 phosphate buffer (1.2)	67
6	DMF/H_2O=1	pH 7.4 phosphate buffer (2.4)	66
7	DMSO/H_2O=1	pH 7.4 phosphate buffer (1.2)	38
8	MeOH/H_2O=1	pH 7.4 phosphate buffer (1.2)	38
9	THF/H_2O=1	pH 7.4 phosphate buffer (1.2)	66
10 *	DMF/H_2O=1	pH 7.4 phosphate buffer (1.2)	73

* 8.0 equivalent of methyl 2-ethyl-3-oxo-4-pentenoate was used

Among aqueous polar solvents, the DMF/H_2O solvent gave the best yield (entries 5-9), and **8** was obtained in 73% yield as a single diastereomer using 8.0 equivalent of 2-ethyl-3-oxo-4-pentenoate (entry 10).

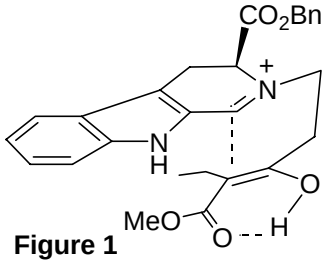
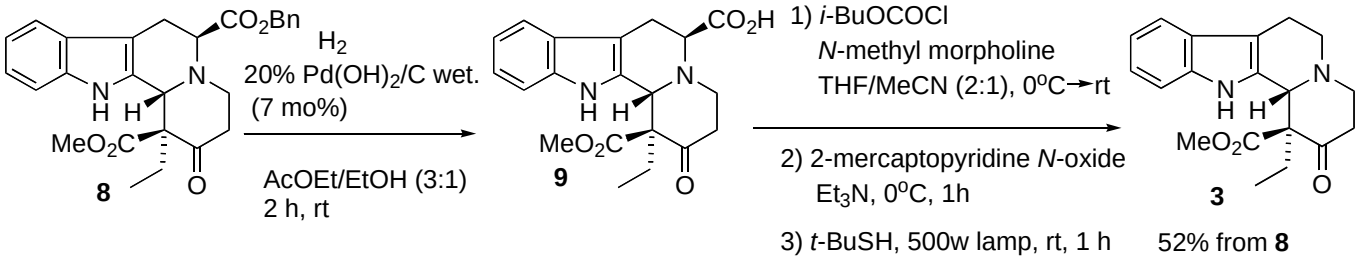


Figure 1

A plausible reaction mechanism is thought as follows. Conjugate addition of ß-carboline (**7**) to 2-ethyl-3-oxo-4-pentenoate is thought to occur to form iminium salt, then intramolecular Mannich-type reaction proceeded to give **8**.[11] In this case, the geometry of the enol moiety was considered to be *Z* form because of the hydrogen bond between ester carbonyl and enol hydroxyl group. The addition of enolate to iminium carbon was thought to occur from the face opposite to the benzyloxycarbonyl group (Figure 1). Compound (**8**) thus obtained was subjected to the debenzyloxycarbonylation reaction,[12] and catalytic debenzylation using Pd $(OH)_2$/C (1 atm H_2) followed by Barton-Crich decarboxylation[13] afforded **3** in 52% yield from **8** as a single stereo isomer (Scheme 3).

In conclusion we found that cycloaddition reactions of 3,4-dihydro-β-carbolines with γ,δ-unsaturated-β-ketoesters proceeded to give octahydroindolo[2,3-*a*]quinolizidines in one step and the construction of two adjacent stereogenic carbons at C-20 and C-21 positions was demonstrated by use of 3,4-dihydro-β-carboline derived from L-tryptophan. Although the compound is the epimer of **3** at C-21,



Scheme 3

an acid-catalyzed epimerization of indolo[2,3-*a*]quinolizidines including compound (**2**) at C-21 position was reported.[3c, 14] Thus the present method is capable of preparing the compound (**2)** and all other stereoisomers by using both enantiomers of tryptophan. Syntheses of eburnamine-vincamine alkaloids and related compounds using the present method are now under investigation.

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8. Relative configuration of compound **5** was determined by NOE experiment.
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10. Relative configuration of compound **8** was determined by NOE experiment.
11. There is a possibility that the cycloaddition product **8** was obtained by Diels-Alder-type reaction.

But we thought that Michael addition followed by Mannich-type reaction gave the product **8**, because the cycloaddition reaction was promoted in the presence of a base which abstracts the proton of iminium salt **7**. Further, Martin *et al*. reported[12] that the reaction of **7** with 1-[(trimethylsilyl)oxy]butadiene or vinyl ketene acetals gave Mannich-type addition products and not Diels-Alder-type cycloaddition products.

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