TOTAL SYNTHESIS OF THE STRUCTURE PROPOSED FOR PICRASIDINE-H (DIMERIC 4-METHOXY-β-CARBOLINE ALKALOID)[1]

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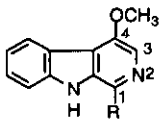
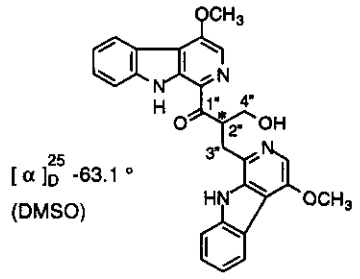
Abstract - Total synthesis of the reported structure of naturally occurring picrasidine-H (dimeric 4-methoxy-β-carboline alkaloid) was accomplished. However, the synthesized compound was not identical with the natural product. Our precise considerations revealed that the reported structure of picrasidine-H had been incorrectly characterized.

Recently 4-methoxy-β-carbolines (**1, Figure 1**), a new class of β-carboline alkaloids, have been isolated[2] from Simarubaceae plants. We have been interested in their potential biological activities [3] and have synthesized[4,5] some of representatives (**1a, b, c**), leading to a new general synthetic method of **1**. Picrasidine-H (**2**)[6], an optically active dimeric alkaloid isolated from *Picrasma quassioides* Bennet (*Simarubaceae*), has an unique structure in this family, which includes an aliphatic linkage connecting two aromatic parts and an asymmetric center on the active methine. In this paper, we report our effort for the total synthesis of picrasidine-H on the basis of our synthetic methodology.[4,5]



1a R=CH_2CH_3 (crenatine)
1b R=$COCH_3$
1c R=CO_2CH_3



$[\alpha]_D^{25}$ -63.1 °
(DMSO)

Picrasidine-H (**2**)

Figure 1

Claisen condensation of the 1-methoxycarbonyl compound [5] (**1c**) with ethyl acetate, using lithium hexamethyldisilazide (LHMDS) as a base gave requisite C_3-unit compound (**3**) in a good yield (**Scheme 1**). To synthesize the remaining C_1-unit compound (**4**), the ester (**1c**) was reduced to the alcohol with $LiAlH_4$ in a good yield, and then chlorinated with thionyl chloride to give relatively stable benzyl chloride

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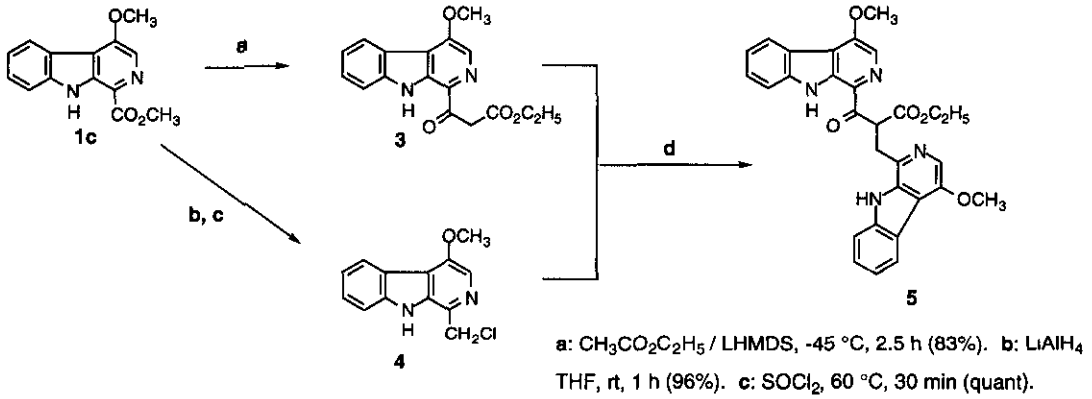
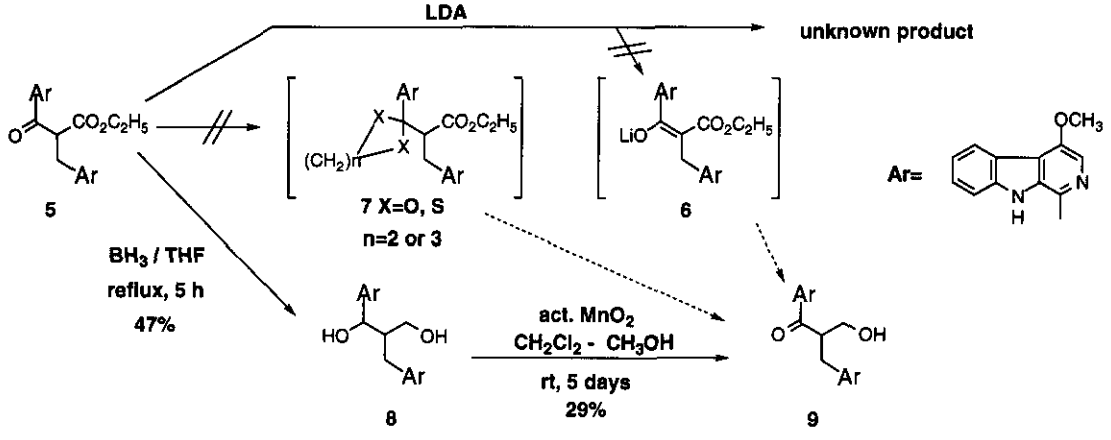
This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.

(**4**) in quantitative yield. The corresponding benzyl bromide prepared with triphenylphosphine dibromide [$(C_6H_5)_3PBr_2$] was too unstable to isolate. The coupling reaction of the C_3-unit (**3**) and C_1-unit compounds (**4**) in the presence of magnesium ethoxide proceeded at room temperature by adding potassium iodide to give the dimer (**5**) in a good yield. The ^{1}H-NMR spectrum revealed that the dimer (**5**) existed in complete keto-form.



Scheme 1

Chemical discrimination of the two carbonyl groups in **5** was required to obtain the target compound (**2**). Thus, to accomplish the selective reduction of the ester carbonyl of the enolate anion (**6**), LDA was added to a solution of **5** at -78 °C. However, the reaction resulted in the formation of an unknown product. Next, ketalization of **5** was attempted, but the reaction of **5** with ethylene glycol or propanedithiol did not proceed (**Scheme 2**). We intended to discriminate the two oxygen functional groups at the stage of the diol (**8**) by selective oxidation of the benzylic position. Reduction of **5** with $LiAlH_4$ or DIBAL gave only a trace amount of the diol (**8**) on the TLC. However, reduction with BH_3[7] in THF gave the diol (**8**) in 47% yield as the main product. Selective benzylic oxidation[8] of the diol (**8**) was achieved by use of activated MnO_2 to give the desired keto alcohol (**9**), the target structure corresponding to **2**.



Scheme 2

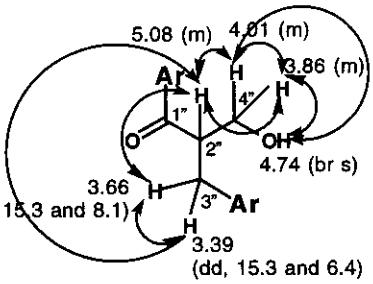
Although the synthetic sample (**9**) is the structure proposed for picrasidine-H (**2**), the Rf values on the TLC and spectrums were completely different from those of the natural product (**Table**). In the EIMS spectrum, our synthetic sample was unstable at the reported measurement conditions; [6] it (**9**) showed a characteristic *retro*-aldol peak (450) originating from the β-keto alcohol, whereas the natural product showed a stable M^+ ion peak (480). In the ^{1}H-NMR spectra, the aliphatic three carbon unit (C2", C3", and C4"-positions) of our synthetic samples (**5, 8, 9**) was confirmed by the H-H COSY, C-H COSY, and NOESY spectra for each compound (**Figure 2**). Therefore, the structure of our synthetic sample was confirmed to be **9** (corresponding to the structure proposed for picrasidine-H).

Table

Our Synthetic Sample ≠ Natural Product [6]

mp	192-194 °C (decomp)	218-220 °C (decomp)
TLC Rf (CH_2Cl_2:MeOH=10:1)	0.41	0.54
IR (KBr) ν_{max} cm^{-1}	3430, 3200, 1660	3420, 3200, 1660
MS (EI)	450 (M^+-HCHO, 6%)	480 (M^+, 52%)
	225 (Ar-CO^+, base peak)	255 (base peak)
MS (FAB)	481 $(M+H)^+$	——
^{1}H-NMR (DMSO-d_6) δ		
2"	5.08	4.23
3"	3.39, 3.66	3.82, 4.37
4"	3.86, 4.01	3.84
^{13}C-NMR (DMSO-d_6) δ		
1"	201.9	200.4
2"	46.4	40.1
3"	31.4	38.3
4"	62.7	65.6

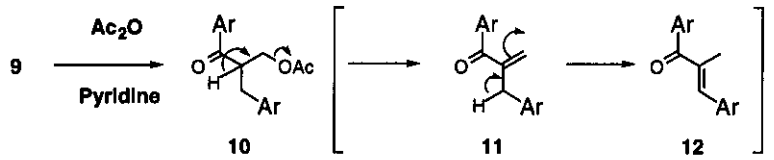
H-H COSY Observation



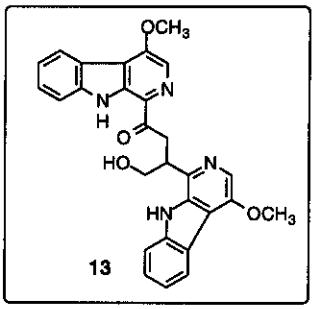
9

Figure 2

This finding has prompted us to reinvestigation of the real structure of natural picrasidine-H. We found following two problems about the structure determination in the literature: [6] i) They reported[6] that treatment of the natural product with Ac_2O in pyridine at room temperature gave a stable mono-acetate described as **10**. On the other hand, acetylation of our synthetic sample under the same condition gave rise to decomposition of the product (should be **10**) during work up. We considered that the acetate (**10**) would be degraded according to **Scheme 3**, having an eliminative acetoxy group on the β-position of the carbonyl group. It is strange that a stable β-acetoxy ketone (**10**) could be isolated from the natural product. ii) In the ^{1}H-NMR spectrum of the natural product, the methylene proton signals of 3.82 ppm (C-3"position) and 3.84 ppm (C-4"position) were too close to discriminate by selective decoupling. Thus the structure of picrasidine-H cannot be identified as **2** from the NMR data.



Scheme 3



We speculated that the structure of natural picrasidine-H is **13**, a regio isomer of the hydroxymethyl group of the reported structure (**2**). The structure (**13**) for picrasidine-H provides reasonable explanations for all above irrationality. We started to synthesize **13** for obtaining the final solution.

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