A FIRST TOTAL SYNTHESIS OF (±)-AMBININE

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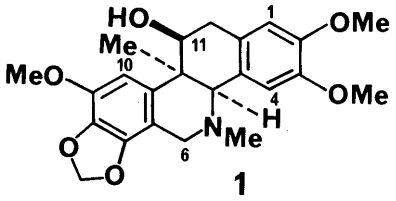
A first total synthesis of (±)-ambinine (**1**) was completed using the 13-methylprotoberberine (**10**), a plausible biogenetic precursor, which could be prepared *via* the isoquinolone derivative (**8**).

KEYWORDS ambinine; *cis*-hexahydrobenzo[*c*]phenanthridine; first total synthesis; protoberberine; 2,3,7,8,9-pentaoxygenated benzo[*c*]phenanthridine; isoquinolone

Ambinine (**1**),[1] isolated from *Corydalis ambigua* Cham. in 1984, has a *cis*-10b-methylhexahydrobenzo[*c*]-phenanthridine skeleton with a 2,3,7,8,9-pentaoxygenated substitution pattern on two aromatic rings, as shown by its spectral data. This alkaloid is the first benzo[*c*]phenanthridine alkaloid having a penta oxy functionality at 2,3,7,8, and 9 positions on its two aromatic rings, although several 2,3,7,8,10-pentaoxygenated alkaloids[2] have been isolated.

Recently we completed a biomimetic synthesis[3] of corynoline (**2**), a *cis*-10b-methylhexahydrobenzo[*c*]-phenanthridine alkaloid from a protoberberine alkaloid, corysamine (**3**). The unusual substitution pattern of **1** strongly prompted us to apply our biomimetic procedure to a synthesis of **1** even though its structure has recently been established by an X-ray analysis[4] during our synthesis. In this communication we describe a first total synthesis of (±)-ambinine (**1**).



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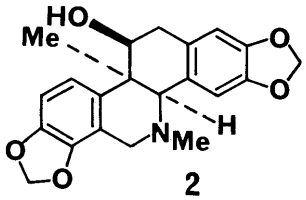

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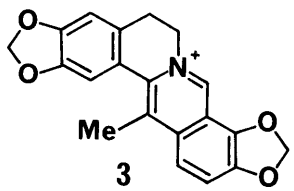

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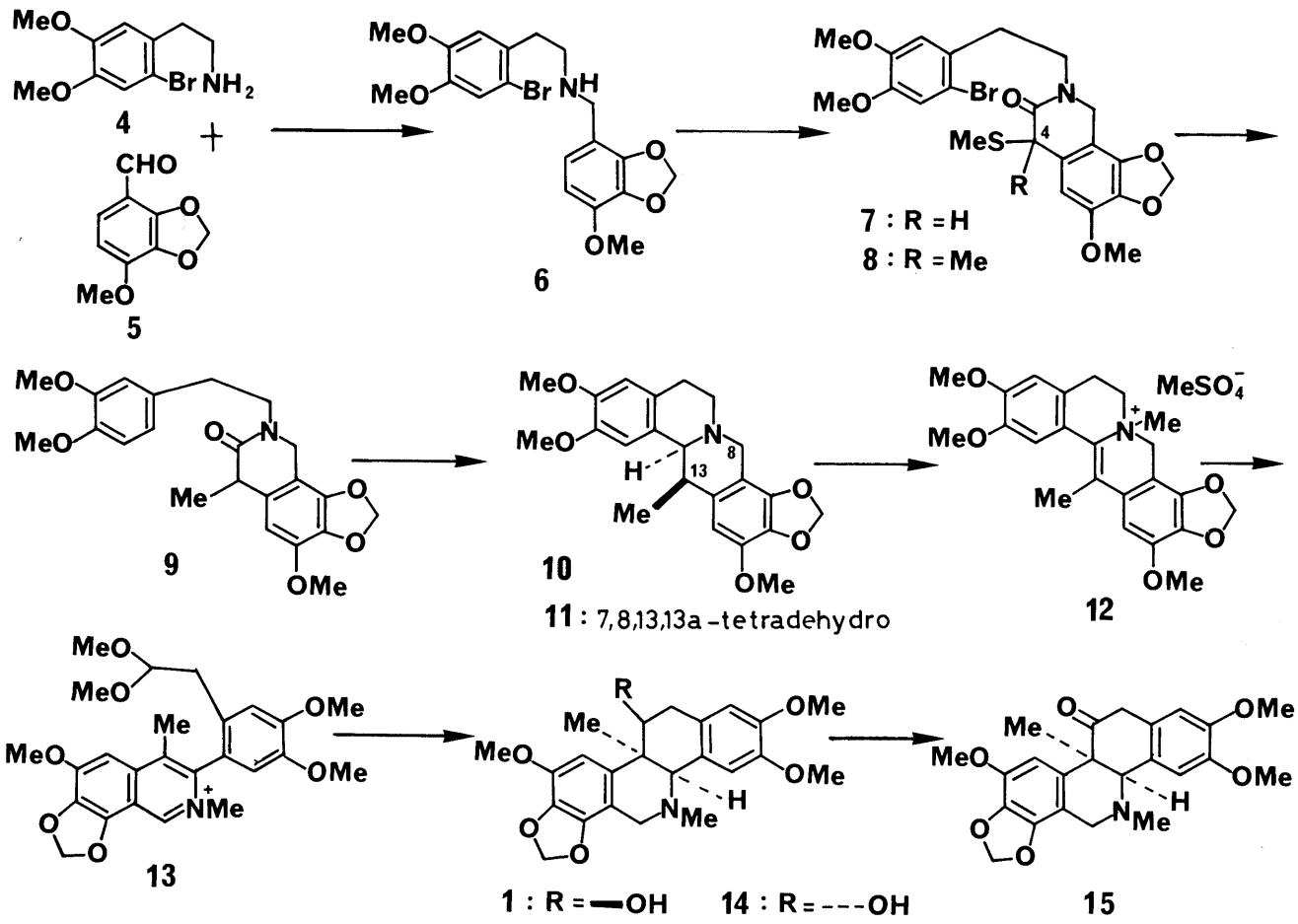
Condensation of the bromo-amine (**4**)[5] with the aldehyde (**5**),[6] followed by reduction with sodium borohydride ($NaBH_4$) afforded the amine (**6**: 95%), which was converted into the isoquinoline (**7**) in 90% yield by treatment with α-chloro-α-methylthioacetyl chloride.[7,8] Introduction of the methyl group at the C-4 position in **7** was realized by consecutive exposure to lithium diisopropylamide and methyl iodide to give **8** in 75% yield. Desulfurization of **8** with Raney-Ni easily occurred with concomitant removal of the bromine atom to provide **9** (90%). The Bischler-Napieralski reaction of **9** with $POCl_3$ in toluene gave, after reduction with $NaBH_4$, the 13-methyltetrahydroprotoberberine (**10**)[9] in 59% yield. The 13-methyl derivative (**10**) was then dehydrogenated with iodine to furnish the corresponding quarternary salt (**11**: 87%). Thus, the significant precursor (**11**) for our synthesis of **1** was prepared through α-chloro-α-methylthioacetyl chloride-mediated isoquinolone formation,[8] followed by methylation at the C-4 position as key steps. This provides a new general synthesis of 13-methylprotoberberine alkaloids.

The protoberberine (**11**) was reduced with lithium aluminum hydride and then N-methylated with dimethyl sulfate to give the methosulfate (**12**: 95%). The final and most crucial stage in our synthesis[3] was carried out as follows. A successful transformation of **12** into (±)-**1** was initiated by the selective C_6-N bond cleavage with 25% potassium hydroxide-methanol at refluxing temperature, followed by oxy functionalization at the styrene moiety with thallium trinitrate in methanol to form the isoquinolinium compound (**13**) with dimethoxyethyl functionality. Successive exposure of this plausible intermediate to $NaBH_4$, 15% hydrochloric acid, and sodium cyanoborohydride effected reduction of the iminium moiety, cyclization, and reduction of the resulting iminium salt to yield (±)-ambinine (**1**) in 53% overall yield from **12**, along with (±)-11-

Dedicated to the memory of Professor Zen-ichi Horii.



epiambinine (**14**: 16%). The synthetic ambinine was identical with the natural one as shown by spectral comparison and thin layer chromatography. Therefore, we could unambiguously confirm the structure of **1**[4] by its synthesis. The structure of **14** was established by conversion into the corresponding 11-keto derivative (**15**), which was identified with the authentic sample derived from ambinine (**1**).

Thus, we could succeed not only in a first synthesis of (±)-ambinine , but also in demonstrating the generality of our biomimetic procedure for cis-10b-methylhexahydrobenzo[c]phenanthridine alkaloids.

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