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TOTAL SYNTHESIS OF (+)-MESEMBRINE BY ASYMMETRIC SYNTHESIS WITH AMINO ACID

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An earlier paper[1)] dealing with asymmetric synthesis of 4,4-disubstituted 2-cyclohexenones (IV) by alkylation of aldehyde enamines (III) obtained from disubstituted acetaldehyde (I) and an L-proline derivative (II), with methyl vinyl ketone, showed that all cyclohexenones obtained were optically active and that their absolute configurations could be determined.

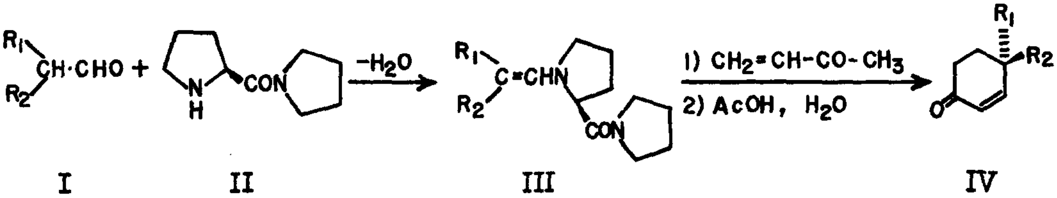

Chart I

In this paper, we report an application of this method to the total synthesis of (+)-mesembrine. Total synthesis of (±)-mesembrine has been reported by several authors.[2)] Our scheme for asymmetric synthesis of (+)-mesembrine is shown in Chart 2.

Key intermediate IX for this asymmetric synthesis was prepared as follows. 1,2-Dimethoxybenzene and β-phthaloylaminopropionic acid were condensed to

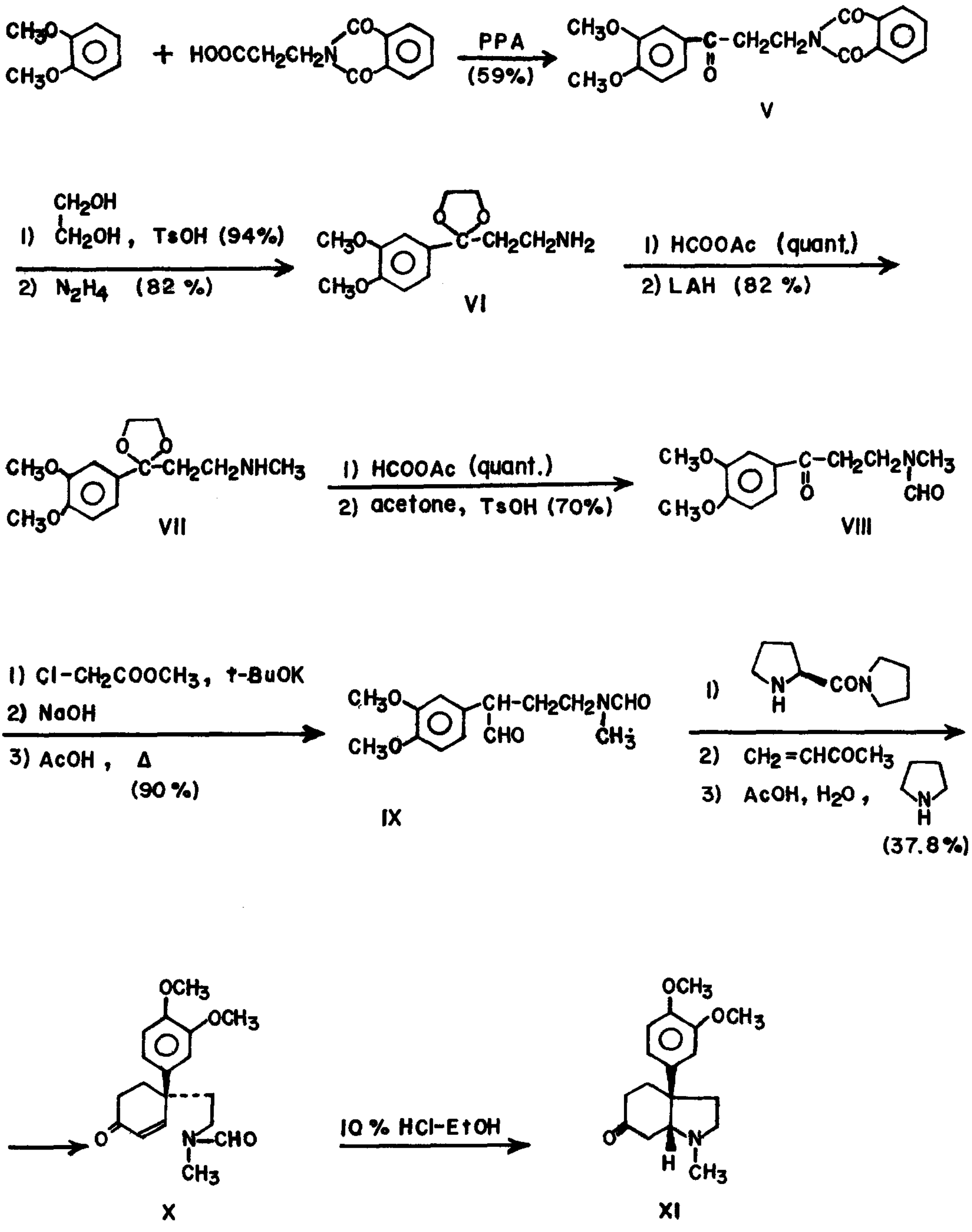
PPA
(59%)
V
1) CH2OH CH2OH, TsOH (94%)
2) N2H4 (82 %)
VI
1) HCOOAc (quant.)
2) LAH (82 %)
VII
1) HCOOAc (quant.)
2) acetone, TsOH (70%)
VIII
1) Cl-CH2COOCH3, t-BuOK
2) NaOH
3) AcOH, Δ
(90 %)
IX
1) CON
2) CH2=CHCOCH3
3) AcOH, H2O,
(37.8%)
X
10 % HCl-EtOH
XI

Chart 2

phthaloylamino ketone V, m.p. 162-164°C. Ketalization of V with ethylene glycol followed by treatment with hydrazine hydrate gave an amine VI, b.p. 178-180°C (3 mmHg). After formylation of VI, reduction of formamide with $LiAlH_4$ gave a secondary amine VII, b.p. 160°C (3 mmHg). Further formylation of VII followed by hydrolysis gave ketone VIII, m.p. 112-114°C. Coversion of ketone VIII to the required aldehyde IX was accomplished with modified Darzens method. The amide aldehyde IX obtained was used successively for asymmetric synthesis without purification since it was unstable. Its structure and purity were confirmed by IR and NMR spectra, by TLC and by elemental analysis of semicarbazone, m.p. 136-139°C.

Asymmetric synthesis of optically active cyclohexenone X from IX was performed using a previously reported method.$^{1)}$ A solution of the amide aldehyde IX and L-proline pyrrolidide in benzene was heated. The water produced was removed by distillation until the distillate became clear, then the benzene was evaporated. Methyl vinyl ketone was added to a solution of the residual oil in methanol. The reaction mixture was allowed to stand 44 hrs at room temperature (10-20°C). After treatment with aqueous acetic acid and 10% hydrochloric acid, neutral fractions were extracted with $CHCl_3$, and the $CHCl_3$ layer was dried and evaporated. The residue was dissolved in methanol containing acetic acid, water and pyrrolidine. This solution was refluxed for 2 hrs. The crude product was chromatographed on silica gel, and the cyclohexenone derivative X, $[\alpha]_D^{20}$ +12.7° (c=1.48, MeOH), was obtained in 38% yield. Since X exhibited a positive Cotton effect, $[\phi]_{364}^{max}$ +770° (CH_3OH) and $[\theta]_{351}^{max}$ +43 (CH_3OH), its absolute configuration was expressed by the structure X following the earlier report.$^{1)}$

Transformation of (+)-X to mesembrine (XI) in a 70% yield was easily carried out with ethanolic hydrochloric acid by reference to the synthesis of (±)-mesembrine by M. Shamma and H.R. Rodriguez,$^{3)}$ and (+)-mesembrine (XI), an antipode of naturally occurring (-)-mesembrine, was obtained from (+)-X. This partially optically active (+)-XI, $[\alpha]_D^{20}$ +16.1° (MeOH), was identical with natural (-)-mesembrine based on IR ($CHCl_3$) and NMR spectra ($CDCl_3$) and TLC. Partially optically active (+)-XI hydrochloride was repeatedly recrystallized from i-propanol and was separated to two crystal forms, needles and prisms, whose IR spectra (KBr) differed. IR spectrum (KBr) of the needles was identical with that (KBr) of natural (-)-mesembrine hydrochloride. The needles were almost optically pure, $[\alpha]_D^{20}$ +7.3±0.5° (CH_3OH), and the prisms were racemic. Furthermore, synthetic optically active (+)-mesembrine exhibited a positive Cotton effect which shows a pattern antipodal to natural (-)-mesembrine.

It is clear that (+)-mesembrine derived from (+)-cyclohexenone X, possesses the absolute configuration represented by the structure XI. Thus an absolute configuration of natural (-)-mesembrine, that is antipodal to XI, as proposed by P.W. Jeffs et al$^{4)}$ rather than that proposed by M. Shamma and his co-workers$^{5)}$ has been assigned. This result is consistent with the most resent report on the X-ray analysis of 6-epimesembranol methiodide.$^{6)}$

To our knowledge, this is the first paper which reports successful synthesis of an optically active, and complicated alkaloid by asymmetric synthesis. This method provides convenient preparation of various optically active carbonyl compounds by utilizing readily available asymmetric synthesis.

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