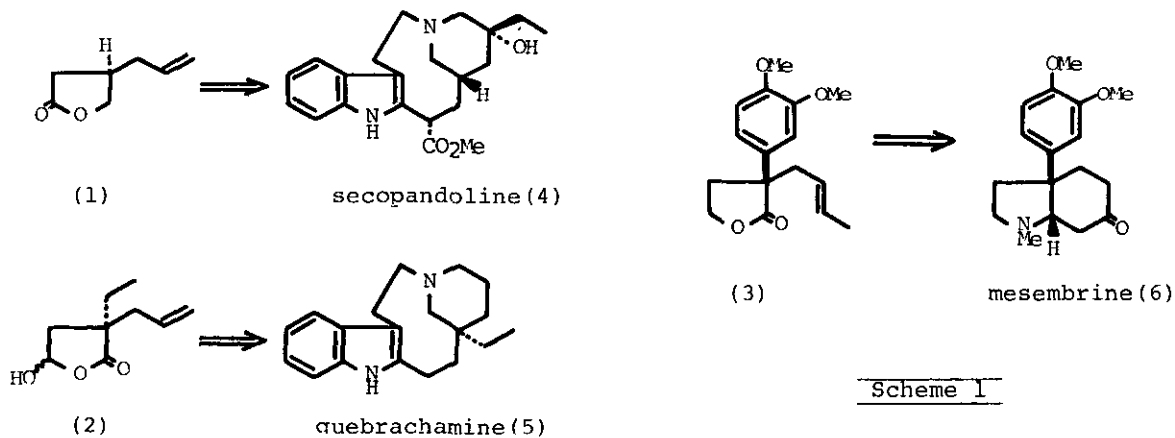


CHIRAL ROUTE TO SOME ALKALOIDS THROUGH ASYMMETRIC IODOLACTONIZATION

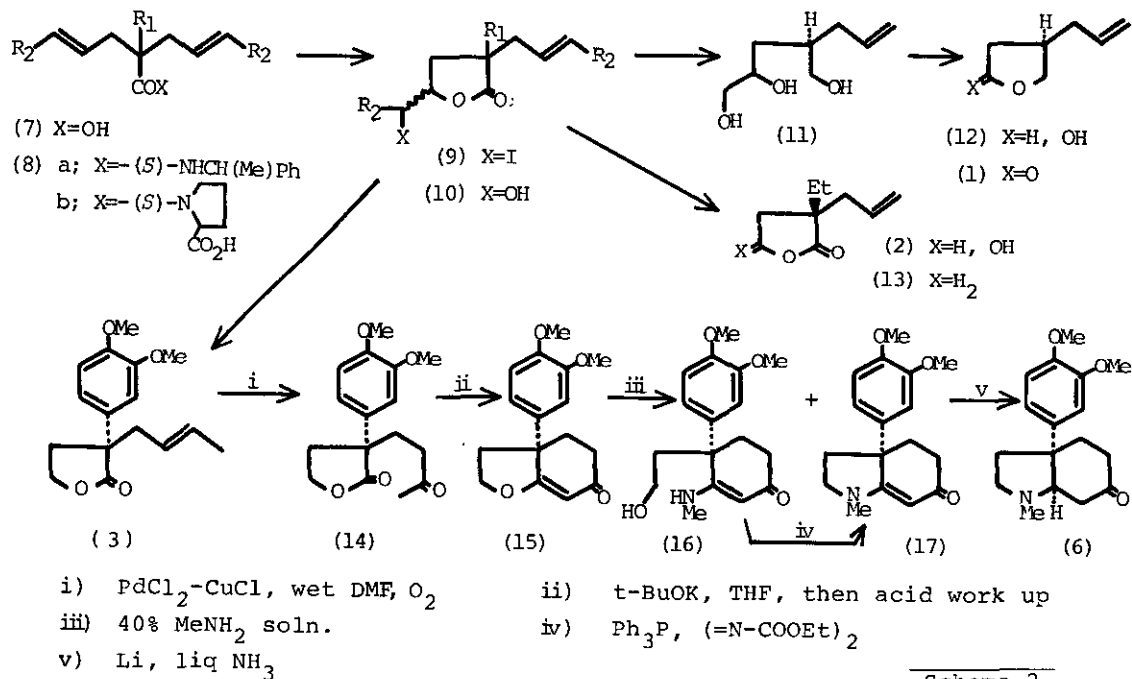
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Abstract: Three chiral γ -lactone derivatives(1), (2), and (3), leading to chiral synthesis of three alkaloids, (-)-secopandoline(4), (-)-quebrachamine(5), and (+)-mesembrine(6), have been synthesized through the asymmetric iodolactonization of the amides(8) from the symmetric carboxylic acids(7) and the chiral amines.

The lactones have been used in the synthesis of a number of alkaloids¹. For example, the γ -lactone derivatives(1), (2), and (3), have been used as the key synthons in the synthesis of the following alkaloids, secopandoline(4)², quebrachamine(5)³, and mesembrine(6)⁴, respectively (Scheme 1).



We described here a simple methodology leading to an enantioselective formation of these synthons through asymmetric iodolactonization reaction on the amides (8)^{5,8} obtained from the symmetric bis- γ,δ -unsaturated carboxylic acids (7) and the chiral amines. Thus, upon treatment with iodine (3 equivol) in aqueous sodium bicarbonate solution (method A) or in aqueous tetrahydrofuran (method B), the amides (8) yielded the corresponding iodolactones (9) with spontaneous loss of the amine.



Scheme 2

amide (8)	method	chemical yield (10)	optical purity	
R ₁ =R ₂ =H	(a)	(A)	no reaction	
		(B)	77 %	16 % (1)
	(b)	(A)	70.5 %	16.5% (1)
		(B)	75.3 %	16.5% (1)
R ₁ =Et, R ₂ =H	(a)	(A)	no reaction	
		(B)	96 %	24.3% (13)
	(b)	(A)	38 %	15 % (13)
		(B)	73.4 %	11 % (13)
R ₁ =3,4-dimethoxyphenyl R ₂ =Me	(b)	(B)	38 %	15.9% (6)

Table

The iodolactones(9) obtained were sequentially treated with aqueous potassium hydroxide(10 %) and diluted hydrochloric acid(10 %) to give the hydroxymethyl-lactones(10)¹⁰ (Scheme 2 and Table).

The hydroxymethylactone(10: $R_1=R_2=H$) obtained from the acid(7: $R_1=R_2=H$)⁹ on reduction with lithium aluminum hydride, followed by oxidation with sodium metaperiodate gave the hemiacetal(12) in 89 % overall yield through the triol(11). The hemiacetal(12) was converted into the synthon(1), $[\alpha]_D +2.47^\circ$ (C 13.8, $CHCl_3$) by Jones oxidation. Absolute configuration and optical purity(16.5 %) of the product(1) was deduced by correlating to the authentic compound(1), $[\alpha]_D +15.0^\circ$ (C 2.65, $CHCl_3$), prepared separately from (S)-glutamic acid¹¹ via the trityl-lactone(9: $R_1=R_2=H$, $X=OTr$)³ and the triol(11).

Next, the hydroxymethylactone(10: $R_1=Et$, $R_2=H$)¹² was converted into the synthon(2) in 97 % overall yield by sequential treatments with aqueous potassium hydroxide and sodium metaperiodate. To deduce absolute configuration and optical purity(24.3 %) the compound(2) was reduced with sodium borohydride to give the lactone(13), $[\alpha]_D -3.1^\circ$ (C 2.6, MeOH), which was correlated to the authentic material(13), $[\alpha]_D +12.77^\circ$ (C 3.1, MeOH), prepared from L-glutamic acid³.

On similar sequential treatments(10% KOH and $NaIO_4$), followed by reduction with sodium borohydride, the hydroxyethylactone(10: $R_1=3,4$ -dimethoxyphenyl, $R_2=Me$) afforded the synthon(3) in 85.5 % overall yield. In order to determine its absolute configuration and optical purity(15.9 %), this lactone was transformed into mesembrine(6) along the route recently developed by us⁴. Optical rotation observed, $[\alpha]_D +8.8^\circ$ (C 0.96, MeOH), revealed that mesembrine(6) synthesized was antipodal to the natural one(6), $[\alpha]_D -55.4^\circ$ (MeOH).

Futher studies for improving enantioselectivity in the iodolactonization stage are now under investigation.

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