CHIRAL ROUTE TO SOME ALKALOIDS THROUGH ASYMMETRIC IODOLACTONIZATION

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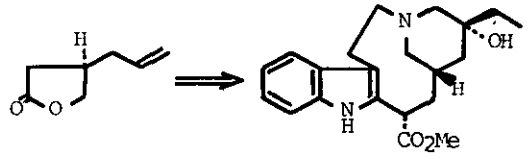
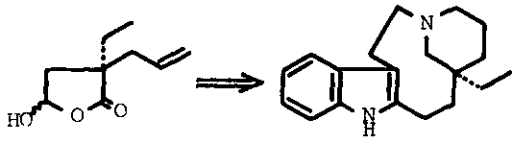
Abstract: Three chiral γ-lactone derivatives(1), (2), and (3), leading to chiral synthesis of three alkaloids, (-)-secopandoline(4), (-)-quebrachamine(5), and (+)-mesembrine(6), have been synthesized through the asymmetric iodolactonization of the amides(8) from the symmetric carboxylic acids(7) and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

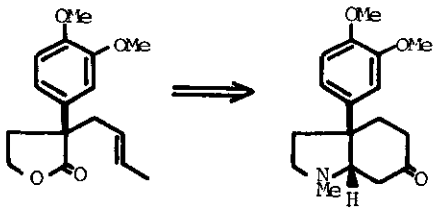
The lactones have been used in the synthesis of a number of alkaloids[1]. For example, the γ-lactone derivatives(1), (2), and (3), have been used as the key synthons in the synthesis of the following alkaloids, secopandoline(4)[2], quebrachamine(5)[3], and mesembrine(6)[4], respectively (Scheme 1).



(1) secopandoline(4)



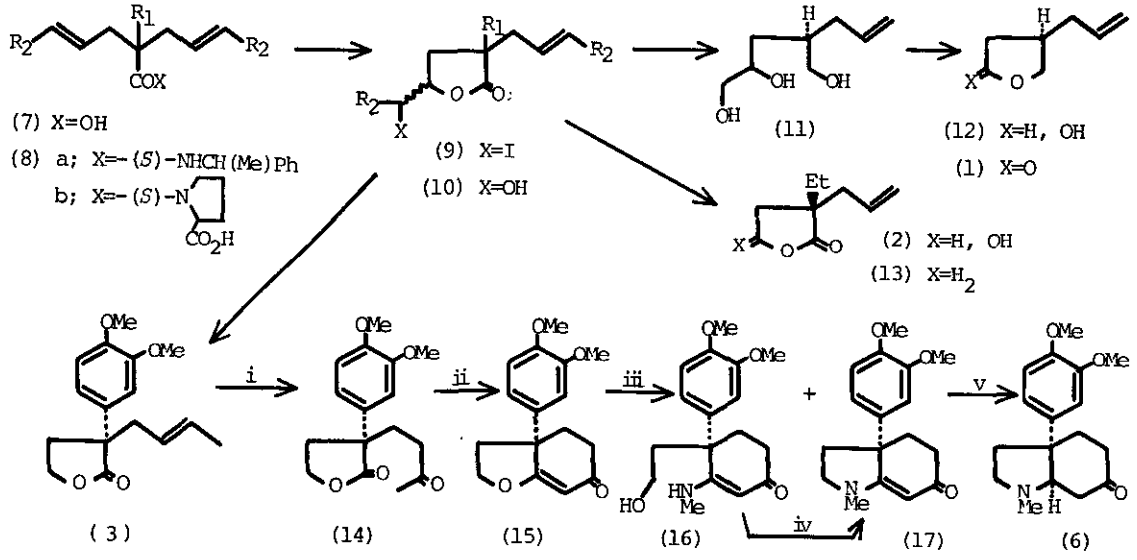
(2) quebrachamine(5)



(3) mesembrine(6)

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 equimol) 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.



i) $PdCl_2$-CuCl, wet DMF, O_2 ii) t-BuOK, THF, then acid work up
iii) 40% $MeNH_2$ soln. iv) Ph_3P, $(=N-COOEt)_2$
v) Li, liq NH_3

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 hydroxymethyllactones(10)[10](Scheme 2 and Table).

The hydroxymethyllactone(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°(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° (C 2.65, $CHCl_3$), prepared separately from (S)-glutamic acid[11] via the trityllactone(9: R_1=R_2=H, X=OTr)[3] and the triol(11).

Next, the hydroxymethyllactone(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°(C 2.6, MeOH), which was correlated to the authentic material(13), $[\alpha]_D$ +12.77°(C 3.1, MeOH), prepared from L-glutamic acid[3].

On similar sequential treatments(10% KOH and $NaIO_4$), followed by reduction with sodium borohydride, the hydroxyehtyllactone(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 us[4]. Optical rotation observed, $[\alpha]_D$ +8.8°(C 0.96, MeOH), revealed that mesembrine(6) synthesized was antipodal to the natural one(6), $[\alpha]_D$ -55.4°(MeOH).

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

REFERENCES AND NOTES

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5. Satisfactory analytical(combustion and /or high-resolution MS) and spectral (IR, ^{1}H-NMR, MS) data have been obtained for all new compounds.
6. Prepared via the reaction of the corresponding acid chlorides with (*l*)-(-)-1-phenethylamine or (S)-(+)-proline.
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10. Obtained as a mixture of epimers.
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