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ENANTIOSELECTIVE SYNTHESIS OF (-)-VELBANAMINE AND (+)-ISOVELBANAMINE USING L-GLUTAMIC ACID AS CHIRAL TEMPLATE

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Abstract: Enantioselective synthesis of (-)-velbanamine(1) and (+)-isovelbanamine (2) has been accomplished using L-glutamic acid as chiral template.

Synthesis of velbanamine[1](1) has attracted considerable interest not only because of its potential utility for the synthesis of the practical oncolytic agents, vinblastine[2,3] and vincristine[2,3], but also its potential utility for the synthesis of the *pandaca* alkaloids[4]. Although there have been reported some interesitng syntheses[5,6], there are still rooms for improvement in these approache especially, in introducing the chirality. We now report here the first enantioselective synthesis of (-)-velbanamine(1) and (+)-isovelbanamine(2) in an efficier manner using L-glutamic acid as chiral template. (-)-Velbanamine(1) produced by the present synthesis consisted with the antipode of that from vinblastine and vincristine, however the chiralities of the products (1) and (2) correspond to those of the *pandaca* alkaloids, pandoline[4] and isopandoline[4].

Tritylation of the γ-lactone 3(trityl chloride in pyridine, room temperature, 45 h), prepared from L-glutamic acid by using the method of Yamada and co-workers[7] furnished the ether[8] 4, mp 153∿154 °C, $[\alpha]_D$+21.5°(CH_2Cl_2), in 64 % yield. Treatmen of 4 with 2-ethylallyl bromide[9] in the presence of lithium diisopropylamide(THF, -78∿-30 °C, 16 h) allowed stereoselective alkylation from the less hindered side of the molecule to give the (2R)-allyllactone 5, mp 117∿118 °C, $[\alpha]_D$ +27.25°

(CH_2Cl_2), δ 1.07(t, 3H, $-CH_2\underline{CH_3}$), 4.47∿4.90(m, 3H, $\underline{H}\!\!>\!\!=$, $\underline{H}\text{-}\underline{C}\text{-}O$), in 51 % yield. Reduction of 5 with lithium aluminum hydride(THF, room temperature, 2.5 h) gave the diol 6, wax, which was converted into the triol 7, oil, in 79.7 % yield by stirring with methanol containing trace of concd hydrochloric acid(150:1) at room temperature for 3 h. Oxidation of 7 with sodium metaperiodate(aq.MeOH, 0 °C, 1 h furnished the hemiacetal 9, oil, in 88 % yield spontaneously through the aldehyde 8. Treatment of 9 with methyl orthoformate in the presence of p-toluenesulfonic acid(MeOH, reflux, 2 h) afforded the acetal 10, oil, which on oxidation with m-chloroperbenzoic acid(CH_2Cl_2, room temperature, 2.5 h) produced the epoxide 11, oil, as an unseparable mixture of epimers in 86.4 % overall yield from 9. The epoxide 11, without separation, was heated at 160 °C in methanol using a sealed tube(15 h) to yield the amino-acetal 12 as a mixture of epimers. The amino-acetal 12, without separation, upon refluxing with aqueous acetic acid(70 %), produced the tricyclic amino-alcohols[10] 13, mp ∿265 °C(decomp), $[\alpha]_D$ -63.04°(MeOH) δ 0.91(t, 3H, $-CH_2\underline{CH_3}$), and 14, mp 226∿229 °C, $[\alpha]_D$ -55.24°(MeOH), δ 0.98(t, 3H, $-CH_2\underline{CH_3}$), in 22 % and 21 % yield[11] after purification by a silica gel chromatography. Treatment of 13 with methanesulfonyl chloride(pyridine, 0 °C∿room temperature, 2 h) allowed selective mesylation at the primary alcohol affording the mesylate 15 which spontaneously formed the pentacyclic quaternary salt 17. Cleavage of 17 under the dissolving metal reduction conditions[12] furnished (-)-velbanamine(1), mp 125∿130 °C(lit. 139∿141 °C), $[\alpha]_D$ -49.3°($CHCl_3$)(lit.[1] $[\alpha]_D$ +56.2°($CHCl_3$)) in 63.3 % yield from 13. On similar treatments, 14 produced (+)-isovelbanamine(2), mp 175∿178 °C(lit.[6] 190∿194 °C), $[\alpha]_D$ +34.9°($CHCl_3$), in 70.3 % overall yield from 14 through 16 and 18.

The studies outlined above demonstrate effective chiral route to potential intermediates of the *pandaca* alkaloids in the natural configuration and the preser methodology would lead to a chiral synthesis of a potential intermediate of the medicinally important dimeric indole alkaloids in the natural optically active fo

ACKNOWLEDGMENT

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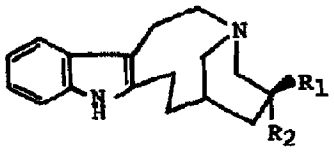
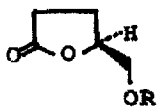


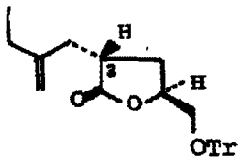
1, R_1=Et, R_2=OH

2, R_1=OH, R_2=Et



3, R=H

4, R=Trityl



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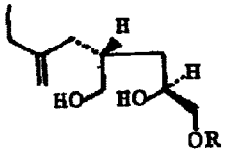
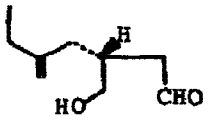


6, R=Trityl

7, R=H



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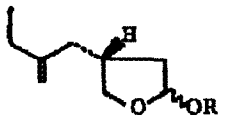
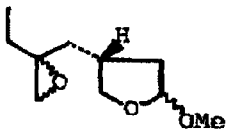


9, R=H

10, R=Me



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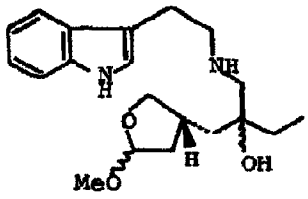

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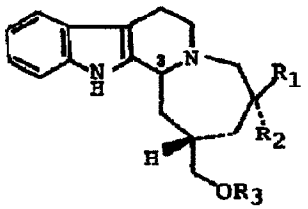
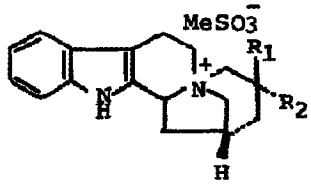


13, R_1=Et, R_2=OH, R_3=H

14, R_1=OH, R_2=Et, R_3=H

15, R_1=Et, R_2=OH, R_3=SO_2Me

16, R_1=OH, R_2=Et, R_3=SO_2Me



17, R_1=Et, R_2=OH

18, R_1=OH, R_2=Et

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8. All new compounds reported in this work gave satisfactory spectral and analytical data(±0.3 %) or correct high resolution mass spectral value except 9, 10, and 11.
9. S. Takano, M. Hirama, T. Araki, and K. Ogasawara, J. Amer. Chem. Soc., 98, 7084 (1976).
10. Stereochemistry of the C-3 center of each compound could not be determined.
11. Two other stereomers of 13 and 14 were also obtained in minor amount.
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