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CHIRALITY CONTROL BY KINETIC PROTONATION: ENANTIOSELECTIVE SYNTHESES OF (+)-VELBANAMINE, (-)-ISOVELBANAMINE, AND (+)-CLEAVAMINE

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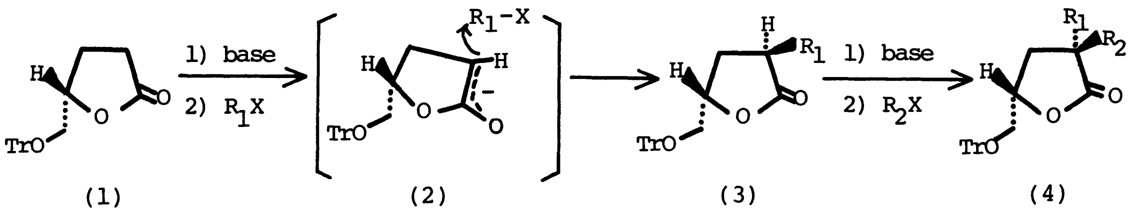
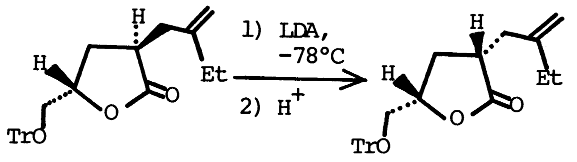
Optimal conditions for inversion of the chirality at 2-position of the 2-alkyllactone(5) have been established. By utitizing the inversion method developed, three indole alkaloids, (+)-velbanamine(16), (-)-isovelbanamine(17), and (+)-cleavamine(18), have been synthesized from the chiral lactone(1) which has been previously used for the syntheses of the enantiomers of these alkaloids.

The chiral lactone(1), easily accessible from L-glutamic acid[1] or D-mannitol,[2] has been used for the enantioselective syntheses of a variety of natural products, such as sugars,[1] lignans,[3] terpenes,[4] alkaloids,[5] and β-lactams[6] as a chiral building block. Utility of this versatile synthon, however, is restricted to one enantiomer since the alternate requires less accessible D-glutamic acid or L-mannitol as a progenitor. We report now a simple method which makes the single chiral lactone precursor(1) play dual role[7] in the enantioselective syntheses of certain natural products occurring in nature in both enantiomeric forms like the iboga type indole alkaloids.[8] Our principle of the stereochemical control lies in kinetically controlled reaction between the enolate(2) from the lactone(1) and an electrophile leading to preferential anti introduction of the nucleophile to the substituent at 4-position(Scheme 1).



Scheme 1

As efficiency of the principle has been well established in alkylation,[4-6] we examined here protonation of the enolate generated from the alkyllactone(5),[5c] with expecting to invert the chiral center at 2-position of the original lactone(5) to yield the epimeric lactone(6) (Scheme 2). The expected inversion did occur without difficulty and as shown in Table the best result was obtained by using saturated aqueous sodium sulfate as a proton donor(entry 6). The observed inversion ratio seemed to be roughly proportional to increase of the bulkiness and decrease of the acidity of the proton donors besides aqueous sodium sulfate. The conditions using aqueous sodium sulfate also exhibited its efficiency in the inversion of the related alkyllactone(5:Et=H)[5c] to its epimer(6:Et=H) in ratio of 1:9.



(5) (6)

Scheme 2

Table

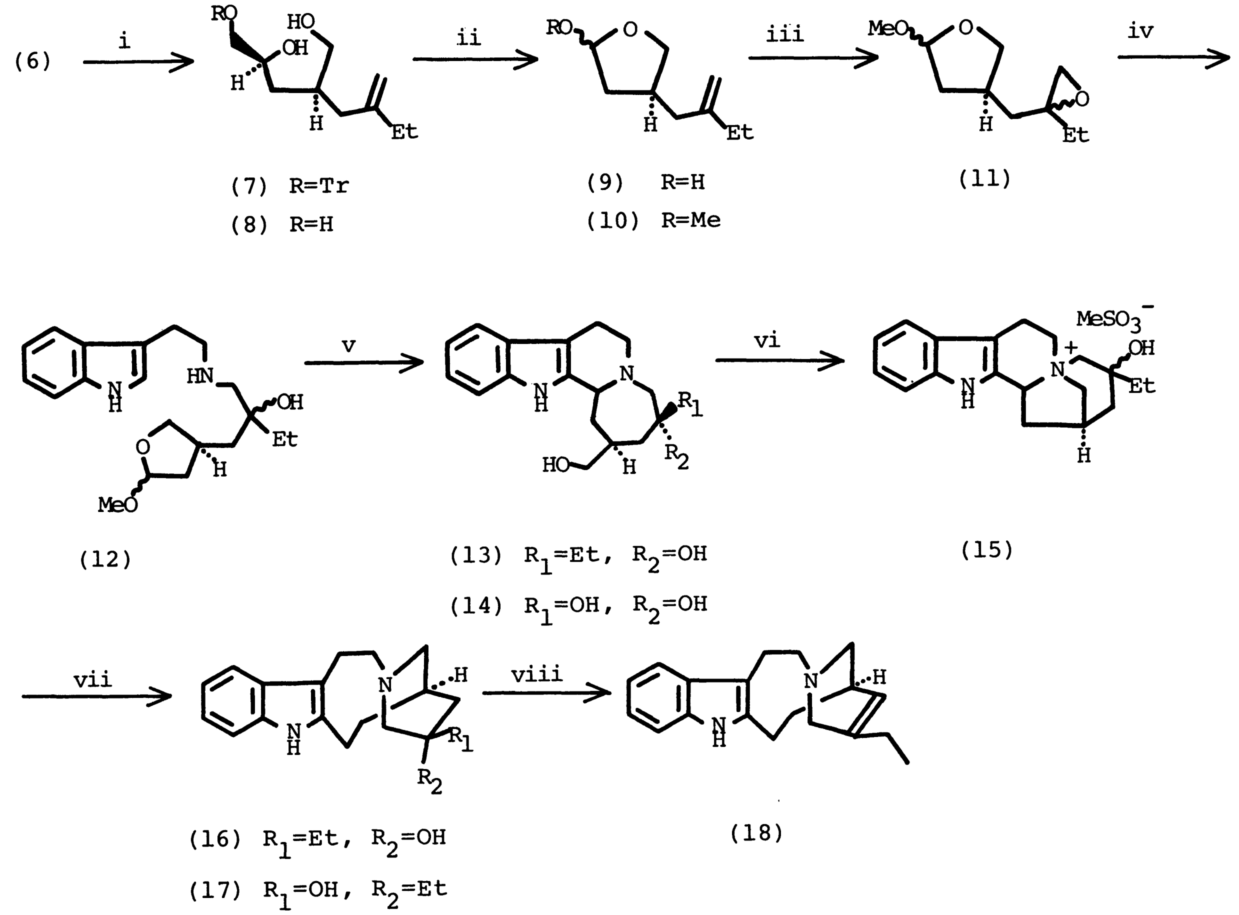
entry	proton donor	ratio[c] (5:6)
1	D-camphoric acid[a]	1 : 4.7
2	acetic acid[a]	1 : 4.9
3	pivalic acid[a]	1 : 6.5
4	t-butyl alcohol[a]	1 : 7.3
5	2,6-di-t-butylphenol[a]	1 : 7.6
6	sat.Na_2SO_4 aq.[b]	1 : 9.0

a. To a cooled solution of an excess proton donor(THF, -78°C) was added a cooled solution of the enolate(THF, -78°C) using a cannula.

b. Proton donor solution was added in a portion to a cooled solution of the enolate(THF, -78°C).

c. Determined by HPLC(collumn LS-320K: solvent Et_2O: hexane(1:6)).

Having established optimal conditions for the inversion of the chirality at 2-position of the alkyllactone(5), we carried out the enantioselective syntheses of (+)-velbanamine(16),[9] (-)-isovelbanamine(17),[10] and (+)-cleavamine(18),[9,11] intermediates for the syntheses[10,12] of potent antitumor alkaloids, vinblastine[13] and vincristine,[13] to demonstrate the efficiency of the present methodology by employing the procedure developed for the syntheses of the enantiomers of these alkaloids.[5c,14] The lactone(6),[15] $[\alpha]_D$ +39.2°(CH_2Cl_2), obtained from (5)[5c] by the kinetic protonation, was reduced, detritylated, and oxidatively cleft to give the hemiacetal(9). Acetalization and the following epoxidation transformed (9) into (11) as an inseparable mixture of diastereomers. Condensation of (11) with tryptamine gave the amino-alcohol(12) which on treatment with hot aqueous acetic acid yielded a separable 1:1 mixture of epimeric amino-alcohols, (13), mp 285°(decomp), $[\alpha]_D$ +65.6°(MeOH), and (14), mp 234-236°C, 234-236°C, $[\alpha]_D$ +97.2°(MeOH), in 29.2% overall yield from (6). Upon methanesulfonation, followed by Birch reduction, (13) furnished (+)-velbanamine(16), mp 143-145°C, $[\alpha]_D$ +50.3°($CHCl_3$) (lit.[9] mp 139-141°C, $[\alpha]_D$ +56.2°($CHCl_3$)), in 89% yield, while (14) furnished (-)-isovelbanamine(17), mp 195-199°C, $[\alpha]_D$ -20.1° (lit.[10] mp 190-194°C) in 97% yield. Each upon treatment with cold sulfuric acid gave (+)-cleavamine(18), mp 100-103°C, $[\alpha]_D$ +60.4°($CHCl_3$) from (16) and $[\alpha]_D$ +58.0°($CHCl_3$) from (17) (lit.[11] mp 102-113°C, $[\alpha]_D$ +68.0°($CHCl_3$)).



i) $LiAlH_4$, THF, reflux, then conc.HCl(cat.)-MeOH, room temp. ii) $NaIO_4$, aq.MeOH, then p-TsOH(cat.)-MeOH. iii) m-CPBA, $NaHCO_3$, CH_2Cl_2. iv) tryptamine, MeOH, sealed tube, 160°C. v) 70% AcOH, reflux, then aq.NaOH. vi) $MeSO_2Cl$, pyridine, then NH_4OH. vii) Na, liq.NH_3-EtOH. viii) conc.H_2SO_4, 0°C.

Scheme 3

Since we have already established the syntheses of the enantiomers of these three alkaloids,[5c,14] potential synthetic intermediates for the pandaca type alkaloids,[16] starting from the same alkyllactone(5), a dual utility of the single chiral synthon(1) in the enantioselective synthesis has been now demonstrated.

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