Tetrahedron Letters, Vol.22, No.45, pp 4479 - 4482, 1981
Printed in Great Britain

0040-4039/81/454479-04$02.00/0

ENANTIOSELECTIVE SYNTHESIS OF NATURAL MESEMBRINE USING (D)-MANNITOL AS A CHIRAL TEMPLATE, A MODEL STUDY FOR THE ENANTIOSELECTIVE SYNTHESIS OF THE AMARYLLIDACEAE ALKALOIDS

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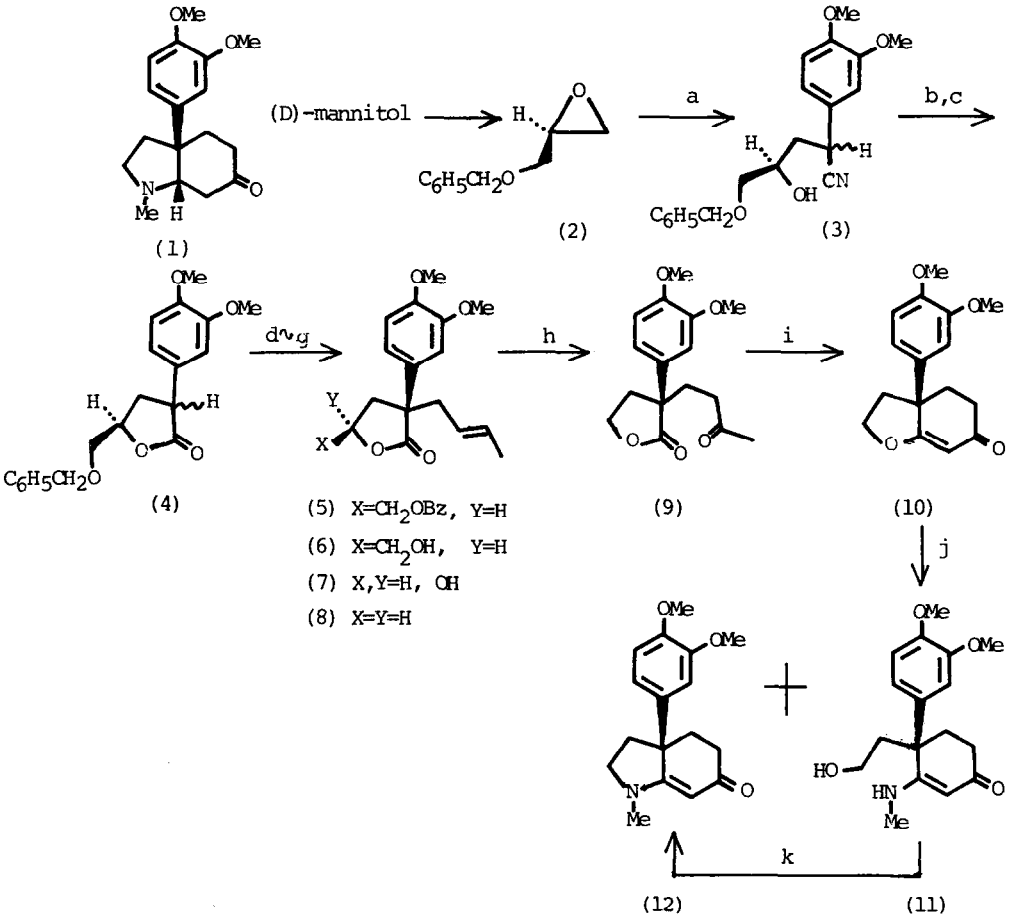
Summary: Enantioselective synthesis of (-)-mesembrine(1) has been achieved using (D)-mannitol with the intention of developing the enantioselective synthesis of the Amaryllidaceae alkaloids.

Although the Sceletium alkaloid, mesembrine(1), has been synthesized in a number of ways as its being convenient testing target for new synthetic methodologies[1,2], no enantioselective synthesis leading to its natural configuration has not been reported so far[3]. Enantioselective synthesis of natural (-)-mesembrine(1) itself may not be particularly significant because of uselessness of mesembrine(1) and its congeners, however it would be important provided the approach employed could be applicable to the enantioselective synthesis of the less accessible Amaryllidaceae alkaloids[4]. We report here the first enantioselective synthesis of mesembrine(1) in natural form starting from D-mannitol which could be regarded as the model study for the enantioselective synthesis of the Amaryllidaceae alkaloids.

Condensation of (S)-(-)-benzyl 2,3-epoxypropyl ether(2), prepared from (D)-mannitol[5], with 3,4-dimethoxybenzyl cyanide afforded the epimeric cyano alcohols(3)

which on alkaline hydrolysis gave the epimeric γ-lactones(4), mp 92 °C, in 64 % overall yield. Treatment of (4) with crotyl bromide in the presence of lithium diisopropylamide allowed a preferential alkylation from less hindered side of the molecule to give the α,α-disubstituted lactone(5), $[\alpha]_D$ -26.1°(c=2.74, MeOH), in 75 % yield[7]. Acid catalyzed debenzylation of (5) afforded the primary alcohol(6), $[\alpha]_D$ -28.2°(c=2.90, MeOH), which on sequential saponification, periodate cleavage and reduction gave the lactone(8), $[\alpha]_D$ -44.6°(c=1.62, MeOH), in 75 % overall yield via the epimeric γ-hydroxy-γ-lactones(7). Palladium catalyzed oxidation[8] of (8) led to a regioselective carbonylation to give the desired methyl ketone(9), mp 78 °C, $[\alpha]_D$ -42.6°(c=2.26, MeOH), in 73 % yield[9]. Base induced intramolecular cyclization of the keto ester(9) yielded the enantiomerically pure bicyclic enone (10), $[\alpha]_D$ -163.1°(c=1.38, MeOH), in 66 % yield after separation of a minor amount of the cryatalline racemate(10)(mp 128 °C) by fractional crystallization. Treatment of the enantiomerically pure enone(10) with aqueous methylamine gave the monocyclic vinylogous amide(11), $[\alpha]_D$ -12.2°(c=4.78, MeOH), in 41 % yield accompanied by 7 % yield of the desired bicyclic compound(12), $[\alpha]_D$ -121.2° (c=1.45, MeOH). Conversion of the former into the latter was very difficult and was eventually accomplished in 85 % yield by the unprecedented carbon-nitrogen bonding reaction using an equimolar amount of diethyl azodicarboxylate and triphenyl phosphine[10]. Reduction of (12) by two equivalents of lithium metal in liquid ammonia[11] furnished (-)-mesembrine(1), $[\alpha]_D$ -62.8°(c=1.40, MeOH)(lit[12]. $[\alpha]_D$ -55.4° (MeOH)[12a]: -59°(MeOH)[12b])((1)·HCl, mp 204.5∿206 °C(decomp)(lit[12a]. mp 205∿206 °C), $[\alpha]_D$ -8.8°(c=0.632, MeOH)(lit.[12a] $[\alpha]_D$ -8.4±0.5°(MeOH)), in 77 % yield, whose ^{1}H-NMR and IR spectra were identical with those reported[13].

Since the present methodology is particularly suited for the functionalization of the pyrrolidine moiety, it would be applicable to the enantioselective synthesis of the medicinally important less accessible Amaryllidaceae alkaloids, such as pretazettine[14]. Further synthetic study based on the present model study is under way.



a) 3,4-dimethoxybenzyl cyanide(1 eq), LDA(1.2 eq), THF, -78 °C ⟶ r.t.

b) 10 % KOH-EtOH, reflux over night c) 10 % HCl-EtOH, r.t.

d) LDA(2 eq), crotyl bromide(2 eq), THF, -78 °C ⟶ r.t.

e) c.HCl-EtOH=1:1, reflux, 3 hr f) 20 % KOH-MeOH; CO_2 gas; then $NaIO_4$

g) $NaBH_4$ then acid work-up. h) $PdCl_2$-CuCl, wet DMF, O_2, 1 week

i) KO^tBu, THF, reflux, over night, then acid work-up

j) 40 % aq.$MeNH_2$, sealed tube, 180 °C, 1 hr

k) $(NCO_2Et)_2$, Ph_3P, THF, 10 min

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6. All new compounds reported in this work gave satisfactory spectral(IR, ^{1}H-NMR, MS) and analytical(combustion and/or high resolution MS) data.

7. This product contained about 15 % of inseparable diastereomer.

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9. The isomeric ethyl ketone was also generated in less than 5 % yield and was easily separated by a silica-gel column chromatography.

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(Received in Japan 25 July 1981)