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ENANTIOSPECIFIC SYNTHESIS OF S-QUINUCLIDINOL FROM D-GLUCOSE: A STRATEGY FOR THE SYNTHESIS OF CHIRAL QUINUCLIDINES.

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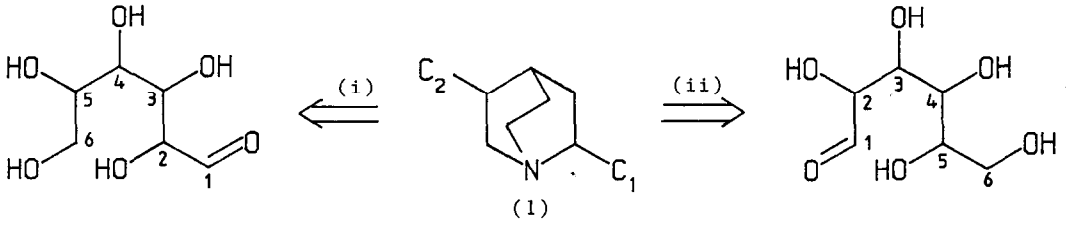
Two alternative strategies for the synthesis of quinuclidines from hexoses are outlined. One of these is employed in an enantiospecific synthesis of S-quinuclidinol whereby a two carbon fragment is introduced at C-4 of D-glucose.

There are a large number of alkaloids containing the quinuclidine nucleus including the sarpagine, ajmaline[1] and cinchona[2] families. Frequently, the quinuclidine fragment in these compounds is extensively substituted, and hexoses may be good starting materials for the synthesis of such structures. A common feature of many of these alkaloids, exemplified by structure (1), is the presence of a one carbon chain on one of the ring bridges and a two carbon chain on another of the bridges. Such a system could be constructed by either of the two strategies outlined in Scheme 1.

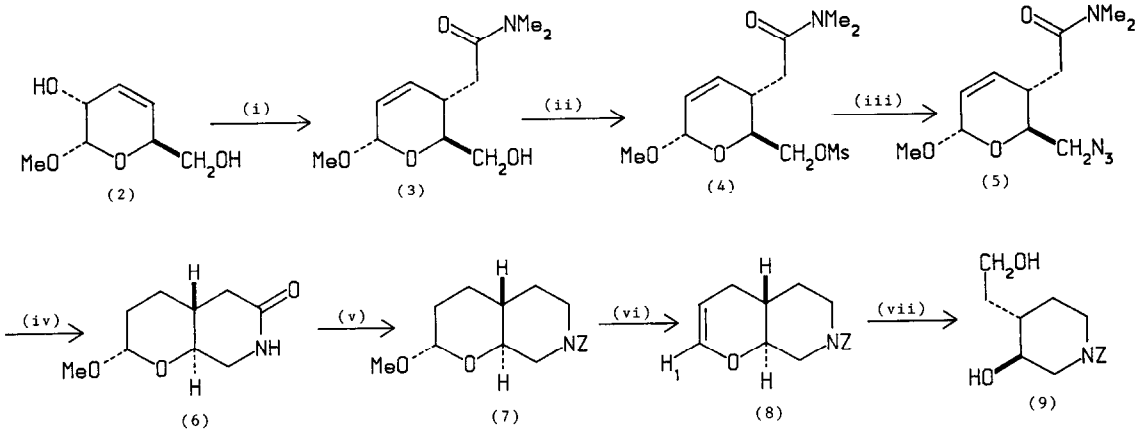


(1)

SCHEME 1

The first approach (i) involves the introduction of the two carbon chain destined to become the bridge of the quinuclidine at C-4 of the hexose; the two carbon substituent is therefore introduced at C-5. The second approach (ii) involves the introduction of the bridge of the quinuclidine at C-3 of the hexose, and therefore the two carbon substituent at C-2.

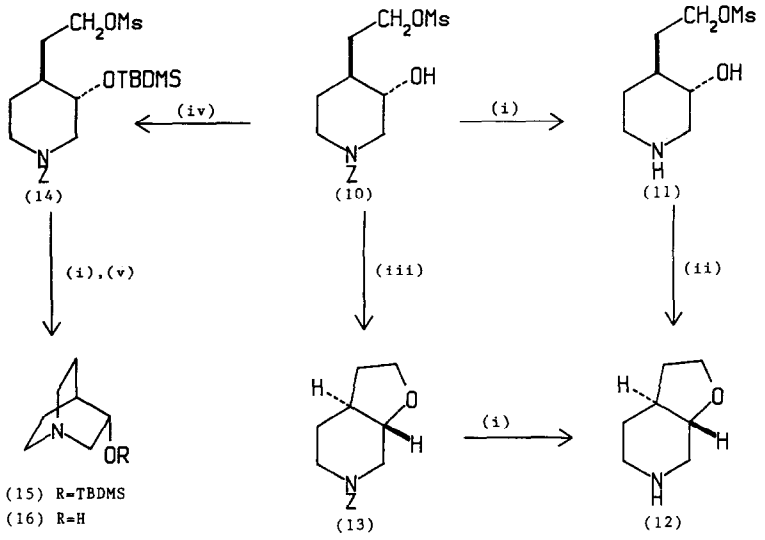
This paper describes the enantiospecific synthesis of S-quinuclidinol (16) from D-glucose, in which the quinuclidine ring is constructed by the first of these alternative strategies; initially, a two carbon chain introduced at C-4 of glucose is joined by nitrogen to C-6 to form a key intermediate lactam (6) which is then elaborated to the mesylate (10) for closure to the quinuclidine framework.



(i) $MeC(OMe)_2NMe_2$, diglyme, 160°; then K_2CO_3, MeOH, 1h (ii) $MeSO_2Cl$, pyridine, 0°, 2h (iii) NaN_3, DMF, 65°, 8h (iv) H_2, palladium black, EtOH; then 1.1 equiv. LDA, -40°, THF (v) $LiAlH_4$ in THF; then $PhCH_2OCOCl$, aq. $NaHCO_3$, ether (vi) $TiCl_4$ in $CDCl_3$, -20°, 10min; then add DBU (vii) O_3 in MeOH / CH_2Cl_2, -65°, 20 min; then $NaBH_4$.

SCHEME 2

Methyl α-D-glucopyranoside was converted to the diol (2),m.p.59-60°,(lit.[3] oil) in three steps by literature procedures in an overall yield of 38%. Treatment of (2) with N,N-dimethylacetamide dimethylacetal according to Corey's procedure[4] produced the amide (3),m.p.49-52° (lit.[4] oil) in 75% yield on a 30 g scale (Scheme 2). Esterification of the primary hydroxyl group with mesyl chloride in pyridine gave the mesylate (4)[5], m.p.100-102°, $[\alpha]_D^{20}$ + 104° (c, 0.4 in $CHCl_3$)(86% yield) which on treatment with sodium azide in dimethylformamide formed the azidoamide (5), m.p. 85.5-86.5°, $[\alpha]_D^{20}$ + 24° (c, 0.91 in $CHCl_3$) (89% yield). Hydrogenation of (5) in the presence of palladium black in ethanol simultaneously reduced the double bond and the azide to an amine which was cyclised by lithium diisopropylamide to the lactam (6), m.p. 170.5-171.5°, $[\alpha]_D^{20}$ + 88° (c, 0.2 in $CHCl_3$) [68% from (5); 51% from (3)]. Reduction of the lactam (6) with lithium aluminum hydride, followed by protection of the secondary amine with benzylchloroformate, gave the carbamate (7) (75% yield). Reaction of (7) with titanium tetrachloride[6] in deuteriochloroform[7] at -20° for 10 min, followed by addition of DBU to the reaction mixture, led to the formation of the vinyl ether (8), m.p. 50-51°, $[\alpha]_D^{20}$ +26.4° (c, 0.47 in $CHCl_3$) (44% yield); (8) has a characteristic low field signal at δ6.35 due to proton attached to C-1 so that these two consecutive reactions could readily be followed by NMR. Ozonolysis of (8) at -65° in methanol/dichloromethane, followed by borohydride[8] reduction, formed the diol (9) $[\alpha]_D^{20}$ -4° (c, 0.80 in $CHCl_3$) in 87% yield which was selectively esterified with mesyl chloride in pyridine at -10° to give the primary mesylate (10) (84% yield).



(i) H_2, palladium black, EtOH, 2h, 20° (ii) EtOH, 36h, 20° (iii) NaH, THF, 20° (iv) $CF_3SO_3SiMe_2Bu^t$, lutidine, CH_2Cl_2, -20° (v) EtOH, 6h, 50°.

SCHEME 3

Hydrogenation of (10) in ethanol in the presence of palladium black gave the deprotected primary mesylate (11) which underwent spontaneous ring closure with the formation of the tetrahydrofuran (12), in which intramolecular attack by oxygen competed successfully with the anticipated attack by nitrogen; (12) could also be formed by treatment of (10) with base to give (13) followed by hydrogenolytic removal of the protecting group [Scheme 3]. However , protection of the secondary hydroxyl group in (10) as the silyl ether (14), m.p. 63.5-64.5° $[\alpha]_D^{20}$ -8.9° (c, 1.0 in $CHCl_3$), (84% yield) followed by hydrogenolytic removal of the Z protecting group, led to the formation of the quinuclidine (15), $[\alpha]_D^{20}$ +5.1° (c, 1.1 in $CHCl_3$) in 67% yield. The silyl ether (15) was hydrolysed with aqueous trifluoroacetic acid to give S-quinuclidinol (16), $[\alpha]_D^{20}$ +35.2° (c, 0.23 in 1 N HCl), [lit.[9] $[\alpha]_D^{20}$ +43.8° (c, 3.0 in 1 N HCl)].The ^{13}C and ^{1}H NMR,and the mass spectra, of both (16) and (15) were identical to authentic samples of racemic quinuclidinol[10] and its silyl ether, respectively. The synthetic, optically active quinuclidinol (16) was converted to its hydrochloride, m.p.>300° (lit.[11] >300°). Racemic quinuclidinol was converted into the corresponding Mosher's esters, with ^{19}F NMR signals at δ -72.9 and -73.2; formation of the Mosher's ester[12] from the synthetic quinuclidinol (16) demonstrated that the synthesis reported here was enantiospecific and that the signal at δ -73.2 corresponds to the S-quinuclidinol ester with (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.

So far, relatively little work on the synthesis , and very little indeed on the enantiospecific synthesis, of quinuclidine alkaloids has been reported.[13] It is clear that intermediates very similar to those used in this approach to S-quinuclidinol could be used in making complex quinuclidines with easy control of the introduction of both carbon chains and other functional groups; we are currently employing this strategy towards the synthesis of a number of such targets.The accompanying paper describes the use of the second strategy outlined in Scheme 1 for the enantiospecific synthesis of quinuclidinol.[14]

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References

1. A. Koskinen and M.Lounasmaa, Prog.Chem. Natural Prod., 1983, 43, 267.
2. R.B.Woodward, N.L.Wendler and F.J.Brutschy, J. Am. Chem. Soc.,1945, 67, 860.
3. N.L.Holder and B. Fraser-Reid, Can. J. Chem.,1973, 51, 3357.
4. E.J.Corey, M.Shibasaki and J. Knolle, Tetrahedron Lett.,1977, 1625.
5. All new compounds reported in this paper have satisfactory analytical and/or spectroscopic data.
6. L.J.Haynes and F.H.Newth, Adv.Carbohydr. Chem.,1955, 10, 207; A. J. Rhind-Tutt, J. Chem. Soc., 1960, 4637.
7. The use of $CDCl_3$ allows the conversion of (7) to (8) to be easily monitored.
8. J.A.Sousa and A.L.Bluhm, J. Org. Chem., 1960, 25, 108.
9. R.W.Baker and P.J.Pauling, J. Chem. Soc., Perkin Trans. 2, 1972, 2340; G. Lambrecht, Arch. Pharm., 1976, 309, 235.
10. An authentic sample of racemic quinuclidinol was obtained from Aldrich Chemical Co.
11. J.I.G.Cadogan, R.A.Raphael and C.W.Rees, Heilbron's Dictionary of Organic Compounds, 5th edn., Chapman and Hall, 1982, vol. 5, p.4894.
12. J.A.Dale, D.L.Dull and H.S.Mosher, J. Org. Chem., 1969, 34, 2543; G.R.Sullivan, J.A.Dale and H.S.Mosher, J. Org. Chem., 1973, 38, 2143.
13. P.L. Stotter, M.D.Friedman, and D.E.Minter, J. Org. Chem., 1985, 50, 29; D.L.Coffen and T.E.McEntee, J.Chem. Soc., Chem. Commun., 1971, 539; G. Grethe, H.L.Lee, T.Mitt and M.R.Uskokovic, J. Am. Chem. Soc., 1978, 100, 589 and references cited in these papers.
14. G.W.J.Fleet, K. James, R.J. Lunn and C.J. Mathews, Tetrahedron Lett., 1986, following paper.

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