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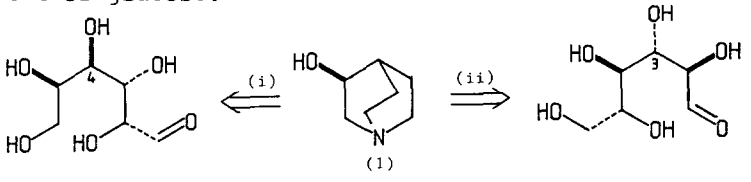
AN ENANTIOSPECIFIC SYNTHESIS OF S-QUINUCLIDINOL FROM D-GLUCOSE

George W. J. Fleet,[a] Keith James,[b] Robert J. Lunn[a] and Christopher J. Mathews[a]

[a]Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY
[b]Pfizer Central Research, Sandwich, Kent CT13 9NJ

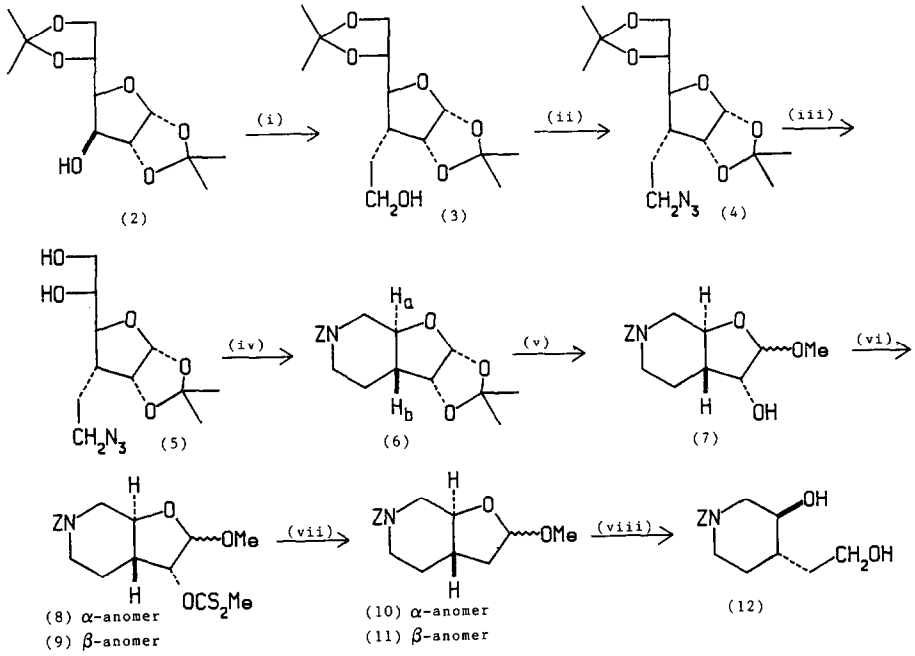
An enantiospecific synthesis of S-quinuclidinol is reported in which the quinuclidine bridge is derived by introduction of a two carbon chain at C-3 of D-glucose.

The accompanying paper discusses two strategies for the synthesis of chiral quinuclidines from hexoses and describes the synthesis of S-quinuclidinol (1) by a two carbon chain extension at C-4 of glucose (i) [Scheme 1], with the chirality of the quinuclidinol being derived from C-5 OH group.[1] This paper reports the enantiospecific synthesis of S-quinuclidinol by the second strategy involving the introduction of a two carbon chain destined to become the bridge of the quinuclidine at C-3 of D-glucose (ii); the chirality of S-quinuclidinol (1) is derived from C-4 of glucose.



SCHEME 1

Oxidation of diacetone glucose (2) with pyridinium chlorochromate, followed by treatment with the stabilised ylid, carbomethoxymethylene triphenylphosphorane, hydrogenation in the presence of a palladium catalyst and subsequent reduction with lithium aluminum hydride,according to literature procedures,[2] gave the primary alcohol (3), $[\alpha]_D^{20}$ +57.1° (c, 2.0 in EtOH) {lit.[2] $[\alpha]_D^{20}$ +61° (c, 2.0 in EtOH)} in an overall yield of 79 %. Esterification of (3) with methanesulphonyl chloride in pyridine, followed by nucleophilic displacement of mesylate with azide, gave 3-(2-azidoethyl)-3-deoxy-1,2:5,6-di-O-isopropylideneallofuranose (4),$[\alpha]_D^{20}$ +72.9° (c, 1.4 in $CHCl_3$) in 87% yield.[3] Mild acid hydrolysis of (4) with acetic acid in aqueous methanol caused removal of the 5,6-isopropylidene group to give the diol (5),$[\alpha]_D^{20}$ +96.7 ° (c, 0.68 in $CHCl_3$) [90% yield]; periodate oxidation of (5), followed by hydrogenation of the resulting azidoaldehyde in the presence of palladium black and protection of the amino function as the benzylcarbamate formed (6), m.p.79-81°, $[\alpha]_D^{20}$ -26.5° (c, 0.57 in $CHCl_3$) in 66% yield from (5) [48% yield from (3)], as an intermediate in which the first of the required rings has been formed between C-5 of glucose and the two carbon chain extension introduced at C-3.[4]



(i) pyridinium chlorochromate, CH_2Cl_2, 20°; Ph_3PCHCO_2Me, C_6H_6, reflux; H_2, Pd, MeOH; $LiAlH_4$ in THF (ii) MsCl, pyridine, 0°; NaN_3, DMF, 40° (iii) AcOH/MeOH/H_2O, 40° (iv) $NaIO_4$, MeOH/H_2O; H_2, Pd black, AcOH; $PhCH_2OCOCl$, Et_2O/H_2O-$NaHCO_3$, 20° (v) Dowex (H+) resin, MeOH (vi) NaH, CS_2, MeI, THF, 20° (vii) Bu_3SnH, xylene, AIBN, 110° (viii) CF_3CO_2H, 20°; $NaBH_4$, EtOH/H_2O.

SCHEME 2

Methanolysis of (6) in the presence of acid ion exchange resin gave a mixture of the methyl furanosides (7) (α:β ratio 1:2) [52% yield]. Removal of the free hydroxyl group in (7) was accomplished by the Barton deoxygenation[5]; thus the anomeric mixture (7) was converted to the readily separable mixture of the α- (8) {$[\alpha]_D^{20}$ +18.2° (c, 0.7 in $CHCl_3$)} and β- (9) {$[\alpha]_D^{20}$ -38.0° (c, 1.5 in $CHCl_3$)} xanthates[6] in a combined yield of 67%. Treatment of (8) and (9) with tributyl tin hydride gave the corresponding deoxygenated α- (10) {$[\alpha]_D^{20}$ +75.8° (c, 0.6 in $CHCl_3$)} and β- (11) {$[\alpha]_D^{20}$ -59.1° (c, 0.8 in $CHCl_3$)} methyl furanosides (87% yield). Hydrolysis of (10) and (11) by aqueous trifluoracetic acid acid, followed by reduction of the resulting lactols with sodium borohydride, gave the diol (12) [50% yield], identical in all respects to an authentic sample.[1] Since (12) has been converted into S-quinuclidinol, this constitutes an enantiospecific synthesis of S-quinuclidinol.[1,7]

This work demonstrates the viability of this strategy for the synthesis of the chiral quinuclidine skeleton and provides intermediates for elaboration into complex quinuclidines suitable for conversion into the cinchona and other alkaloids.

References
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2. A.Rosenthal and L.B.Nguyen, J. Org. Chem., 1969, 34, 1029.
3. All new compounds reported in this paper have satisfactory analytical and/or spectroscopic data.
4. J (Ha,Hb) of 10.5Hz indicates a trans ring junction in (6).
5. S. Iacono and J.R.Rasmussen, Org. Synth., 1985, 64, 57; D.H.R.Barton and W.B.Motherwell, Pure Appl. Chem., 1981, 53, 15.
6. The deoxygenation and hydrolysis steps were carried out on both anomers separately and on a mixture of the anomers.
7. A CASE award to RJL with Pfizer Central Research is gratefully acknowledged.

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