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STEREOSELECTIVE CYCLOADDITION OF *N*-GLYCOPYRANOSYL 1,2-DIHYDROPYRIDINES WITH METHYL ACRYLATE.

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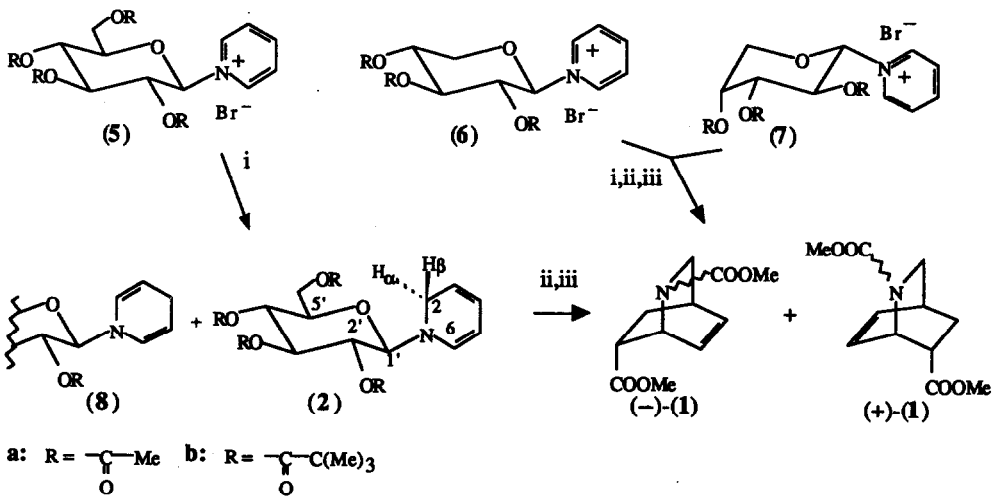
Summary: Stereoselective cycloaddition of *N*-glycopyranosyl 1,2-dihydropyridines (2)-(4) with methyl acrylate allowed asymmetric synthesis of isoquinuclidines (–)-(1) (84% e.e.) or (+)-(1) (72% e.e.).

The isoquinuclidine (azabicyclo-[2.2.2]-octane system) derivatives, such as (1) (Scheme 1) and related compounds, are valuable intermediates in alkaloid synthesis,[1] especially iboga type indole alkaloids.[2] These bicyclic products are accessible by way of cycloaddition between electron-rich 1,2-dihydropyridines (DHPs) as dienes and electrophilic dienophiles. We recently reported[3] the first examples of *asymmetric* cycloaddition involving 1,2-DHPs synthesized from chiral amines. While isoquinuclidine derivatives of good enantiomeric purity could be obtained in a few steps, only modest diastereoselectivity (20-30% d.e.) was observed.

We now report much improved selectivities in this cycloaddition procedure resulting in an enantioselective synthesis of (–)-(1) (84% e.e.) or (+)-(1) (72% e.e.), using peracylated *N*-glycopyranosyl 1,2-DHPs (2)–(4) (Table 1) as dienes.



Scheme 1. i. $NaBH_4$, H_2O-Et_2O, 0°, 15 min; ii. methyl acrylate, 80°, overnight; iii. methyl chloroformate, reflux, 2h.

Large scale preparation of the pyridinium salts (**5a**), (**6a**) and (**7a**) was first ensured by reacting pyridine with tetra-*O*-acetyl-α-D-glucopyranosyl, tri-*O*-acetyl-α-D-xylopyranosyl and tri-*O*-acetyl-β-D-arabinosyl bromides, respectively, according to literature procedures.[4] The β-anomers (**5a**), (**6a**) and the α-anomer (**7a**) were purified by crystallization.[4a] We also prepared in the same way the per-*O*-trimethylacetyl-glycopyranosyl pyridinium salts (**5b**), (**6b**) and (**7b**) from the corresponding bromides[5] (70-80% yield). These latter salts were amorphous but, fortunately, the procedure[4a] adopted for their preparation gave practically pure β-anomers (**5b**) and (**6b**) and α-anomer (**7b**), as established by ^{1}H n.m.r. spectroscopy.

Reduction of the salt (**5a**) with sodium borohydride and sodium dithionite was reported earlier[6a,b] and, more recently, was claimed[6c] to give exclusively the 1,2-DHP (**2a**) and the 1,4-DHP (**8a**), respectively. However, 400-MHz ^{1}H n.m.r spectroscopy revealed that the product which precipitated from the reduction of the salt (**5a**) with sodium borohydride in water was in fact a mixture of 1,2-DHP (**2a**) and 1,4-DHP (**8a**) in a 2:1 ratio. Similar reduction of the salts (**6a**) and (**7a**) gave 1,2-DHPs (**3a**) and (**4a**), also mixed with the corresponding 1,4-DHPs in the same ratio. In each case, the two isomers were inseparable by chromatography or crystallization. By contrast, 1-2-DHPs (**2b**), (**3b**) and (**4b**), each of which was also obtained as a 2:1 mixture with the corresponding 1,4-isomer (80-90% total yield), could be isolated in pure form by crystallization from methanol. These compounds were stable as crystals, but in $CDCl_3$ or C_6D_6 solutions a slow isomerisation of 1,2-DHP (**2b**) to the 1,4- derivative (**8b**) was observed by ^{1}H n.m.r. spectroscopy. Reduction of *O*-trimethylacetylglycopyranosyl pyridinium salts were performed in a two-phase system (H_2O-Et_2O), at 0°C, to prevent any hydrolysis of the trimethylacetyl esters.Some features of *N*-glycopyranosyl 1,2-DHPs (**2**)–(**4**) are of interest. These are unusually stable compounds when compared to simple *N*-alkyl-1,2-DHPs which are very prone to polymerization and oxidation. Noteworthy is the fact that the borohydride reduction in water stopped at the dihydro- stage, whereas under similar conditions *N*-alkyl pyridinium salts are transformed to tetrahydropyridines. Also, the rotation around the C-1'-N bond seemed to be restricted in solution, strong n.O.e's being observed between H-6 and anomeric H-1' and between H-2β and H-2' for (**2a**) and (**2b**) (400-MHz ^{1}H n.m.r spectroscopy in $CDCl_3$ revealed the H-2α and H-2β of the 1,2-DHPs rings as well separated multiplets). These observations suggested a preferred conformation in which the plane of the 1,2-DHP ring is practically perpendicular to the plane of the pyranose ring, and that all 1,2-DHPs (**2**)–(**4**), whose ^{1}H.n.m.r. spectra displayed the same features, should be as depicted in Table 1.

With 1,2-DHPs (**2**)–(**4**) in hand, conditions for their cycloaddition with methyl acrylate were investigated. In practice, we used the mixture of 1,2- and 1,4-DHPs directly obtained from sodium borohydride reduction without separation, since the 1,4- derivative was supposed to be unreactive toward methyl acrylate. The reaction took place only at the temperature of refluxing methyl acrylate (80°C). Crude *N*-glycopyranosyl substituted isoquinuclidines, obtained after 15-20 hours at reflux, were characterized by mass spectroscopy. Attempts to purify these adducts by column chromatography failed since they decomposed on silica gel or alumina. However, after removal of the excess methyl acrylate under reduced pressure, the residue was treated with methyl chloroformate at reflux during 2 hours. The isoquinuclidine carbamate (**1**), so obtained, was isolated as a colourless oil by precipitation of the major part of sugar residue in ether, filtration over alumina, and finally bulb to bulb distillation. Its *endo* structure was established by comparison with an authentic sample.[3] The corresponding *exo* isomer was not detected. The yields of (**1**) from the starting DHP mixtures fell regularly in the range 30-35% based on the 1,2-DHP present in the mixture.

We checked the degree of optical purity of isoquinuclidine (–)-(1) or (+)-(1) obtained from 1,2-DHPs (2), (3) and (4). The results are summarized on Table 1.

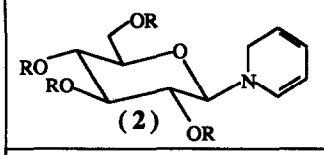
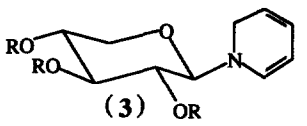
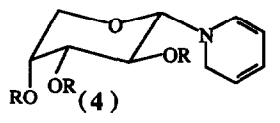
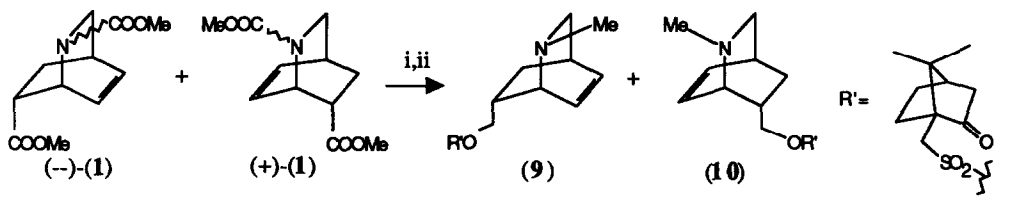
1,2-DHP		(9) : (10)[a]	$[\alpha]_D$ in $CHCl_3$[b]	e.e.%[c]
 (2)	(2a)	6.7 : 1	– 89° (c 2)	74
	(2b)	11.5 : 1	– 102° (c 2)	84
 (3)	(3a)	1.5 : 1	– 23° (c 2)	20
	(3b)	4 : 1	– 64° (c 2)	60
 (4)	(4a)	1 : 4	+ 58° (c 1.9)	60
	(4b)	1 : 6.1	+ 94° (c 3.5)	72

Table 1. a. ratio obtained from 400-MHz ^1H n.m.r. spectroscopy on (9) and (10) mixtures (scheme 2); b. found on (1) after bulb to bulb distillation (30-35% yield from the corresponding 1,2-DHP); c. deduced from the ratio (9): (10).

Since we have previously established[3] the absolute configuration of optically pure (–)-(1) and (+)-(1), we could evaluate, from the sign as well as the magnitude of the optical rotation data, the absolute configuration and the e.e. of the major enantiomer formed. The e.e. was measured with more accuracy by 400-MHz ^1H n.m.r spectroscopy of the diastereoisomeric derivatives (9) and (10), obtained after reduction of (1) with lithium aluminium hydride and subsequent coupling with (+)-camphor sulfonyl chloride (Scheme2).



Scheme 2. i.$LiAlH_4$, THF, reflux, 2h; ii. (+)-camphor sulfonyl chloride, NEt_3, DMAP, CH_2Cl_2, r.t. overnight.

Some important aspects of the cycloaddition process emerged from the results depicted in Table 1. In addition to a practically exclusive *endo* selectivity, the observed e.e. for (+)- or (–)-(1) reflected a significant diastereoselection, especially if one considers the elevated temperature of the reaction and compares these results with other examples of Diels-Alder reactions implying oxygenated dienes grafted at the anomeric position of sugars.[7]

Structural modification of the sugar auxiliary has significant effects on the stereochemistry of the reaction. 1,2-DHPs (2) and (3) obtained from D-(+)-glucose or D(+)-xylose led predominantly to (–)-(1), while 1,2-DHPs (4), obtained from D-(-)-arabinose and which could be considered, with respect to C-1' and C-2' configurations, as mirror images of (2) and (3), led to (+)-(1) as major enantiomer. Incidentally, arabino- derivatives are interesting auxiliaries since both D-(+)- and L-(-)-arabinoses are commercially available

inexpensive carbohydrates which have also been recently exploited as chiral templates for the synthesis of amino acids.[8] Substitution at the 5'-position of the glycopyranosyl seemed to be important, particularly in view of more efficient stereoselections observed with glucopyranose derivatives (**2**) compared to xylopyranose series (**3**); on the other hand, arabinopyranose (**4**) series gave better selectivities than xylopyranose ones. The reasons for these interesting variations are unclear at present . A comparison of the results obtained from acetylated (**2a-4a**) and trimethylacetylated (**2b-4b**) *N*-glycosyl 1,2-DHPs showed that bulky trimethylacetyl groups favoured the selectivity of the cycloaddition process. This pointed out the importance of the steric effect of the 2'-substituent of sugar auxiliary and also suggested an attack of methyl acrylate from the opposite side of C-2', that is to say from the side of the pyranose ring oxygen. The absolute configuration of the resulting isoquinuclidine (**1**) implied a preferred reaction on the more stable conformation (*vide supra*) of 1,2-DHPs (**2**)–(**4**).

In summary, 1,2-DHPs grafted to the anomeric position of per-trimethylacylated sugars, particularly (**2b**) and (**4b**), which are readily accessible from inexpensive sugars, revealed as promising templates for asymmetric cycloaddition with methyl acrylate as a dienophile. Considering the reaction conditions used, 80°C and the absence of any catalyst, the observed diastereoselection was indeed significant. However, the low reactivity of methyl acrylate, known as a poor dienophile, is very probably a limiting factor both for the overall yield and the selectivity, and reactions at lower temperatures with more activated dienophiles should now be investigated.

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