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Intramolecular Cycloaddition of 3-O-Cyclohexenyl Carbohydrate Nitrones : Diastereoselective Synthesis of Optically Pure Tetrahydropyrano[2,3]cyclohexane Derivatives

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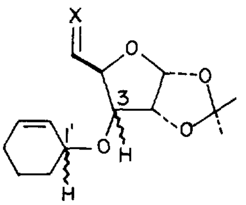
Abstract : The intramolecular cycloaddition of nitrones derived from 3-O-cyclohexenylfuranoside-5-aldehydes led to diastereoselective formation of tetrahydropyrano[2,3]cyclohexane ring systems with six chiral centres. Copyright © 1996 Elsevier Science Ltd

The recent application of O-allylcarbohydrate nitrone cycloaddition has led to the synthesis of various chiral cyclic ether ring systems.[1,2] The current interest[3] in similar cycloadditions involving cyclohexenyl moiety as the dipolarophile has prompted us to disclose herein the expedient synthesis of optically pure tetrahydropyrano[2,3]cyclohexane derivatives containing six chiral centres by the intramolecular cycloaddition of 3-O-cyclohexenylcarbohydrate nitrones.

The treatment of 3-O-cyclohexenyl furanoside-5-aldehyde **1a**[4] (as a 1:1 mixture of 1'-epimers) with N-benzylhydroxylamine led to the formation of the isoxazolidines **3** (50%), **4**(18%) and **5** (32%) incorporating the tetrahydropyrano[2,3]cyclohexane skeleton via the diastreomeric nitrones **2a**. The structures[5] of the cycloadducts **3** and **4** were established on the basis of NMR spectroscopic analysis including ROESY. The elucidation of the structure of **5** was troublesome due to considerable broadening of the relevant regions of its ^1H and ^{13}C NMR spectra and the limited amount of information available indicated the assigned structure. Similarly, the cycloaddition of the diastereomeric mixture of the nitrones **2b** obtained from the corresponding mixture of aldehydes **1b**[4] led to the formation of only **6** and **7**. It is noteworthy that from the four nitrones represented by **2a** and **2b**, three products viz. **3**, **6** and **7** were formed with 100% diastereoselectivity. As observed[3] usually, the faciality of approach of the nitrone dipole is determined by the orientation of the oxygen substituent in the cyclohexenyl moiety.

The readiness with which the isoxazolidines can be converted to chiral tetrasubstituted pyranocyclohexane derivatives is demonstrated by



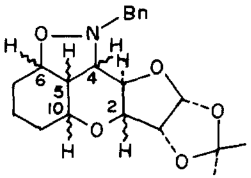
mixture of 1'-epimers(1:1)

1a : 3-H_{α}; X = O

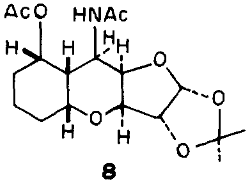
1b : 3-H_{β}; X = O

2a : 3-H_{α}; $X = \overset{+}{\underset{Bn}{N}}-\bar{O}$

2b : 3-H_{β}; $X = \overset{+}{\underset{Bn}{N}}-\bar{O}$



3-7



8

m.p. 88°-89°C; $[\alpha]_D$-3.0

	2-H	4-H	5-H	6-H	10-H	m.p.°C	$[\alpha]_D$
3	α	α	β	β	β	172-173	-133.8
4	α	α	α	α	α	151-152	-53.0
5	α	β	α	α	α	141-142	+31.2
6	β	β	β	β	β	141-142	-24.0
7	β	β	α	α	α	210-211	-112.0

the cleavage of the N-O bond in **3** by transfer hydrogenation (cyclohexene, 10% Pd-C) followed by acetylation leading to **8**.

The application of the above methodology to the combinatorial generation of tetrahydropyranocyclohexane ring systems is under investigation.

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2. Mukhopadhyay, R.; Kundu, A.P.; Bhattacharjya, A. Tetrahedron Lett. **1995**, 36, 7729.
3. Aurich, H.G.; Geiger, M.; Gentes, C., Koster, H. Tetrahedron Lett. **1996**, 37, 841 and references cited therein.
4. The aldehyde **1a** and **1b** were prepared[1] by the sequential reactions; (i) alkylation of 1,2:5,6-diisopropylidine glucose/allose with (±)3-bromocyclohexene in presence of NaH in THF (ii) partial deprotection with 75% aq. AcOH (iii) oxidation with $NaIO_4$.
5. Satisfactory MS and microanalytical data were obtained for **3-8**.

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