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INTRAMOLECULAR OXIMERCURATION-DEMERCURATION REACTION : A NEW STEREOCONTROLLED APPROACH TO SIALIC ACID CONTAINING DISACCHARIDES

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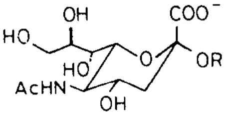
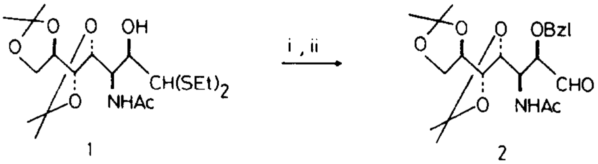
Summary :Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside has been converted into Neu5Ac α(2-6)Glu and Neu5Ac β (2-6)Glu derivatives, using an intramolecular oximercuration-demercuration reaction.

N-Acetylneuraminic acid[1] (Neu5Ac)- a head member of the sialic acid family- is a component of glycoconjugates and oligosaccharides, present as glycosides in cellular organelles, body fluids and microorganisms[2,3] where it controls many biological functions. Most frequently, sialic acids occupy terminal, non-reducing positions in oligosaccharide chains and their glycosidic linkages possess the α-configuration as illustrated in the following scheme:



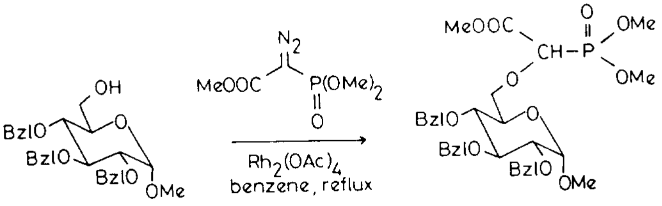
The controlled synthesis of Neu5Ac containing oligosaccharides- one of the most obvious current challenge in glycosylation reactions- has only been approached so far by conventional procedures[4] and presents serious difficulties, as reflected by the moderate yields which have often been obtained.We reported[5] in 1980 a stereocontrolled synthesis of a sialic acid ketoside by intramolecular oximercuration-demercuration of an acyclic precursor.We have in the meantime explored the possibility to extend this reaction to the synthesis of model Neu5Ac containing disaccharides and would like to disclose our strategy in this letter. A related approach has been applied in 1982 by the group of Mukaiyama to a synthesis of 2-deoxyglycosides[6].

The aldehyde 2- a general precursor of the Neu5Ac unit- was first prepared in two steps from the known[7] diethyldithioacetal 1: benzylation (i, $PhCH_2Br$, DMF, NaH,BaO,$Ba(OH)_2.8H_2O$, 2h, room temperature) gave a crystalline derivative[8] (83%),m.p.57-58°C(from hexane),$[\alpha]_D$ -13°,which was converted[9] (ii,red HgO,$BF_3.Et_2O$,aq.T.H.F.,30 min, room temperature) into 2 (96%); ^{1}H-N.M.R.($CDCl_3$ 90MHz): δ9.58 (s,1H, -CHO).



1   2

The model primary alcohol methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside[10] (3) has been selected to demonstrate the feasibility of this novel synthetic route. The insertion of diazotrimethylphosphonoacetate[11] (3 equiv) into 3 was smoothly catalyzed by rhodium acetate[12] (C_6H_6, reflux, 2h) to give the phosphonate 4 (80%), as a diastereoisomeric mixture.



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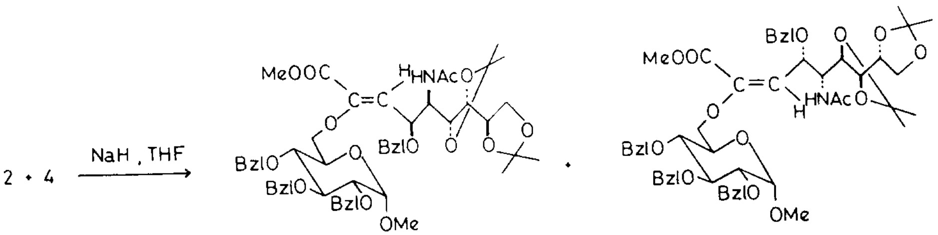
4

Horner-Wittig type[13] reaction of the aldehyde 2 with the phosphonate 4 (THF, NaH, 0°C, 1h) afforded the enol ethers 5 (60%), $[\alpha]_D$ +11°; ^{1}H-N.M.R. ($CDCl_3$, 90MHz): δ 6.04 (d, 1 H, J 9Hz, vinylic H, Z isomer[14]) and 6 (30%), $[\alpha]_D$ 0° (E isomer), easily separated by silica gel chromatography (hexane-ethyl acetate, 1:2, v/v, containing 0.1% of triethylamine).



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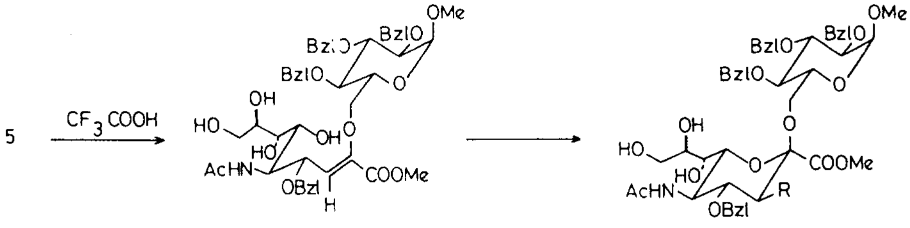
6

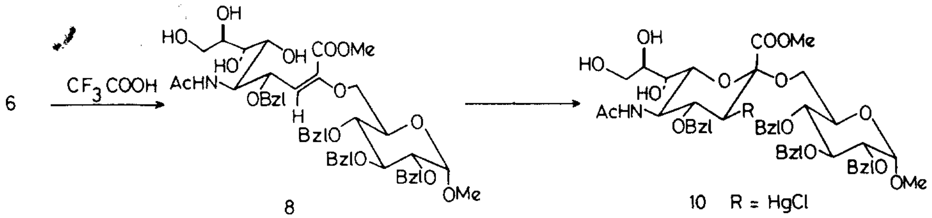
Acid hydrolysis of 5 and 6 (CF_3COOH-H_2O, 9:1, v/v, 0°C, 30 min) gave respectively the two geometrical isomers in pure form : 7 (80%), $[\alpha]_D$ +34°; ^{1}H-N.M.R. ($CDCl_3$, 90MHz): δ 6.08 (d, 1H, J 8.5 Hz, vinylic H, Z isomer[14]) and 8 (80%), $[\alpha]_D$ -3° (E isomer).



7

9 R = HgCl

11 R = H

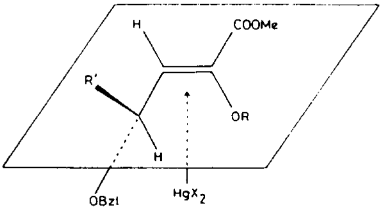


8

10 R = HgCl

12 R = H

When the Z isomer 7 was submitted to Hg (II) induced cyclisation [i, Hg $(OCOCF_3)_2$, THF, 0°C, 2h; ii, aq.KCl, 0°C, 12h], the chloromercuri derivative 9,$[\alpha]_D$ -21.5°,was obtained as the only detectable isomer in about 80% yield. The remarkable stereospecificity of the cyclization reaction may be rationalized in assuming (i) a chair product-like $^{2}C_{5}$ (D) conformation for the transition state and (ii) a conformational preference[15] of 7 as A. Mercuration would take place from the sterically less hindered α face to yield 9[16].



A

The trans-diequatorial relationship between the chloromercuri group and the adjacent O-benzyl group was deduced from ^{1}H-N.M.R. data ($CDCl_3$, 90MHz): δ 2.60 (1H,d, $J_{2,3}$ 11 Hz[17], H-3). Demercuration of 9 was best performed with Ph_3SnH in the presence of anhydrous sodium acetate[18] (toluene, room temperature, 12h, 90%) to give exclusively the β anomer 11[19], $[\alpha]_D$ +12°.Cyclisation of the E isomer 8 likewise provided exclusively the chloromercuri derivative 10 in 80% yield, $[\alpha]_D$ -13°,which was converted into the α anomer 12, $[\alpha]_D$ +9.5.

The oximercuration-demercuration approach delineated in this letter provides a novel solution to the problem of the stereocontrolled synthesis of Neu5Ac α -and β -glycosides. Its main originality is that the steric outcome is dictated by that of a Wittig type condensation . On the other hand, a compound like 12 should be a good precursor for the preparation of more complex oligosaccharides, where Neu5Ac is substituted or glycosylated either on positions 7, 8 or 9.Application of this strategy to the synthesis of various Neu5Ac containing oligosaccharides is underway[21].

References and Notes

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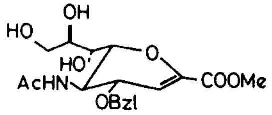
14.The Z isomery is clearly deduced from the chemical shift of the vinylic proton of both 5 and 7, see R.E. Ireland, R.H. Mueller and A.K.Willard, J.Am.Chem.Soc., 98, 2868(1976).

15.See E.L. Eliel, N.L. Allinger, S.I. Angyal and G.A. Morrison, Conformational analysis, Interscience Publishers, New York, 1965, p. 19. See also G. Schmid, T. Fukuyama, K. Akasaka and Y. Kishi, J.Am.Chem.Soc., 101; 259 (1979) and references cited herein.

16.The adjacent and suitably located O-benzyl group may also exert a strong directing effect, see H.B. Henbest and B. Nicholls, J.Chem.Soc., 227 (1959).

17.A value of 11.6 Hz has been reported for $J_{2,3}$ in the case of methyl 2-acetoxymercuri-2-deoxy-3,4,6-tri-O-acetyl- β -D-glucopyranoside, see K. Takiura and S. Honda, Carbohydr.Res., 21, 379 (1972).

18.In the absence of sodium acetate, trans-diequatorial elimination occured to provide the following insaturated derivative , m.p. 193-194°C (from ethanol); ^{1}H-N.M.R. data (CD_3OD, 90MHz): δ 1.92 (3H,s,Ac), 3.72 (3H,s,COOMe), 4.26 (1H,dd,$J_{3,4}$2.4, $J_{4,5}$8Hz, H-4), 4.6 (2H,AB system,CH_2Ph), 6.05 (1H,d,$J_{3,4}$2.7 Hz, H-3), 7,28 (5H,s,Ph).



19. The presence of a β-glycosidic linkage in 11 was evidenced by 250MHz ^{1}H-N.M.R. spectroscopy in deuterium oxide, after removal of the benzyl groups by palladium-catalyzed hydrogenolysis, showing the Neu5Ac proton, H-3 eq at δ 2.50. In the case of 12, debenzylation provided a disaccharide showing H-3 eq at δ 2.74.These chemical shifts data for reporter H-3eq in D_2O at pD 7 are descriminative[20] of α - and β-glycosidically linked sialic acids- including the esterified form.

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21.This strategy has also been applied to the stereocontrolled synthesis of KDO containing disaccharides, F. Paquet and P. Sinaÿ, to be published.

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