Asymmetric synthesis of *N*-acetylneuraminic acid

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Received (in Cambridge, UK) 29th November 1999, Accepted 6th January 2000

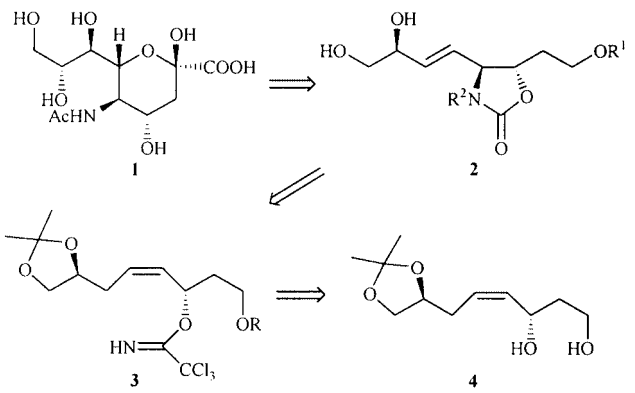
A highly diastereoselective synthesis of *N*-acetylneuraminic acid 1 has been completed by stereoselective functionalization of *cis*-olefin 6 and *trans*-olefin 10 *via* intramolecular phenylselenoamidation and osmylation, respectively.

Sialic or neuraminic acids are a family of amino sugars comprising nine or more skeletal carbon atoms, and usually occur at the nonreducing terminal positions of oligosaccharides, glycoproteins and glycolipids.[1] They are involved in the modulation of a variety of important biological phenomena[2] such as cellular aggregation,[3] recognition,[4] lifetime[5] and viscosity of biofluids.[6] The family provides a potential therapeutic lead in developing inhibitors of sialidase[7] and sialyltransferase.[8] The most common member is the nine-carbon derivative 5-(acetylamino)-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid **1** (*N*-acetylneuraminic acid, Neu5Ac),[9] which is an essential constituent of sialoglycosphingolipids (ganglioside) and other glycoconjugates which mediate cellular interactions, differentiations and growth.[10]

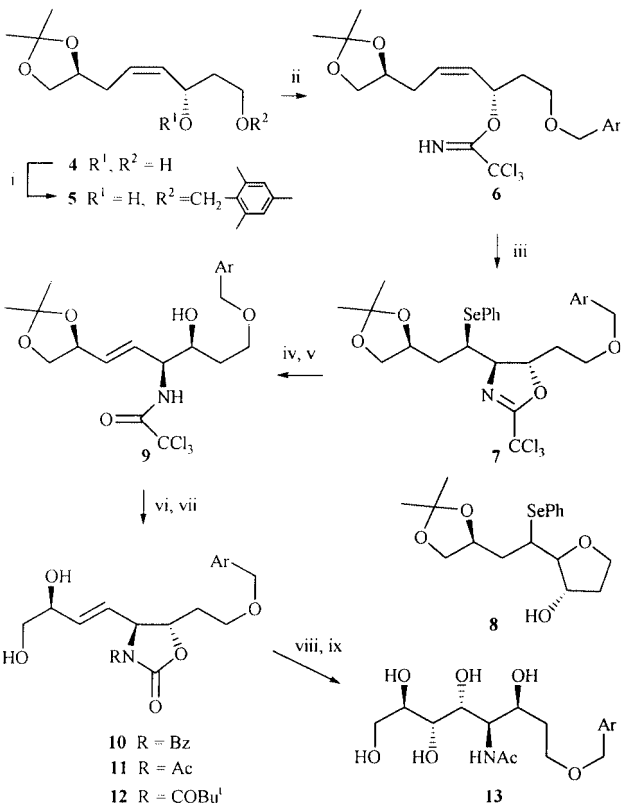
While most of the known syntheses of Neu5Ac have been attained from carbohydrate sources,[11] only two syntheses have been established from noncarbohydrate precursors *via* hetero-Diels–Alder cycloaddition[12] and azido hydroxylation of *cis*-1,2-dihydrocatechol,[13] respectively. Its intriguing molecular structure and biological significance also led us to the enantioselective synthesis of *N*-acetylneuraminic acid **1** from diol **4**, which had been readily prepared from (*S*)-butane-1,2,4-triol.[14] The key steps of our synthetic route to **1** include the intramolecular phenylselenoamidation of *cis*-olefinic allylic trichloroacetimidate **3** and the stereoselective dihydroxylation of *trans*-olefin **2**, followed by introduction of the indispensable α-keto carboxylic acid functional group (Scheme 1).

Diol **4** was regioselectively protected by reacting with dibutyltin oxide in toluene using a Dean–Stark trap and subsequently with 2,4,6-trimethylbenzyl chloride in the presence of TBAB[15] to give a 7:1 mixture of the desired ether **5**, $[\alpha]_D^{20}$ + 19.9 (*c* 1.2, $CHCl_3$), and the isomeric secondary alkyl benzyl ether in 96% combined yield (Scheme 2). For the disposition of the required amino group and (*E*)-olefinic double bond, the allylic alcohol **5** was sequentially subjected to Cl_3CCN in the presence of DBU in MeCN and benzeneselenyl bromide in the presence of methyl trichloroacetimidate in a 4:1 mixture of MeCN and propylene oxide to provide *trans*-oxazoline **7**, $[\alpha]_D^{21}$ −18.4 (*c* 1.1, $CHCl_3$), in 67% yield. While the stereoisomeric *cis*-oxazoline could not be identified in the phenylselenocyclization, 9% of the enantiomerically pure tetrahydrofuran **8** was isolated as the major side product after hydrolysis. It is noted that methyl trichloroacetimidate and propylene oxide were expected to function as dehydrating agent and acid scavenger. The oxazoline ring of **7** was partially hydrolyzed in the presence of PPTS in aqueous acetone and the residual phenylselenyl group was oxidatively eliminated to afford *trans*-olefin **9**, $[\alpha]_D^{24}$ + 19.0 (*c* 1.2, $CHCl_3$), in 75% overall yield along with 5–6% of the corresponding *cis*-isomer.

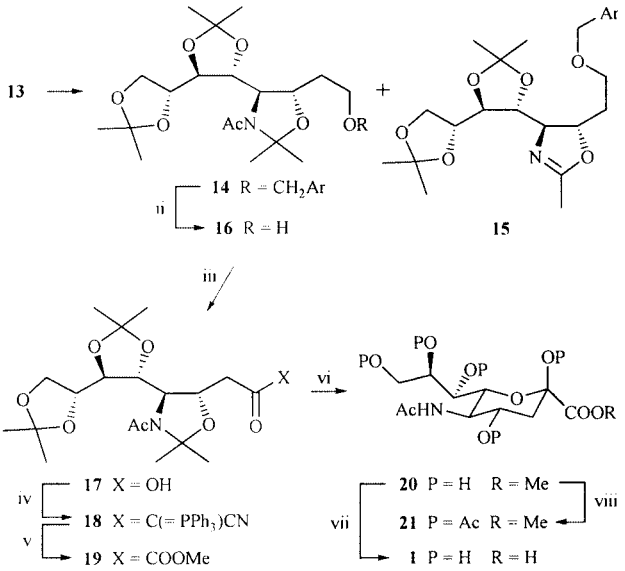
The pendent amino and hydroxy groups of **9** were variously functionalized in order to induce the best stereoselectivity in the subsequent dihydroxylation of the olefinic double bond. In consequence, **9** was converted into dihydroxy oxazolidinone **10**, mp 110.3–111.0 °C, $[\alpha]_D^{25}$ + 23.9 (*c* 1.05, $CHCl_3$), in 91%



Scheme 1



Scheme 2 *Reagents and conditions*: i, Bu_2SnO, PhMe, Dean–Stark trap, then 2,4,6-trimethylbenzyl chloride, Bu_4NBr, 80 °C; ii, Cl_3CCN, DBU, MeCN, −30 to −20 °C; iii, PhSeBr (3 equiv.), $MeOC(=NH)CCl_3$ (3 equiv.), propylene oxide–MeCN (1:4), −30 to 0 °C; iv, PPTS, H_2O–acetone (1:4), 20 °C; v, 30% H_2O_2, THF, 20 °C; vi, DBU, CH_2Cl_2, 20 °C, then BzCl, DMAP, Et_3N, 0 °C; vii, H_2O–AcOH (1:4), 20 °C; viii, OsO_4, NMO, H_2O–acetone (1:7), 0 °C; ix, $Ba(OH)_2$, H_2O–EtOH (1:2), 70 °C, then Ac_2O, 0 to 20 °C.



Scheme 3 *Reagents and conditions*: i, $C(OMe)_2Me_2$, PPTS, $CHCl_3$, 70 to 80 °C; ii, H_2, 20% $Pd(OH)_2/C$, $NaHCO_3$, EtOH, 20 °C; iii, $RuCl_3$ hydrate, $NaIO_4$, MeCN–CCl_4–H_2O (2:2:3), 20 °C; iv, $CH(=PPh_3)CN$, EDCl, DMAP, CH_2Cl_2, 20 °C; v, O_3, MeOH, −78 °C; vi, AcCl, MeOH, 20 °C; vii, K_2CO_3, H_2O, MeOH, 20 °C, then Dowex 50WX8-100 ion-exchange resin; viii, Ac_2O, DMAP, pyridine, 20 °C.

overall yield by a sequence of cyclization with DBU, *in situ* benzoylation with BzCl and deprotection in aqueous AcOH. The following dihydroxylation of **10** produced a mixture of several compounds, which seemed to be generated from migration of *N*-benzoyl group in the dihydroxylated products. The mixture was completely hydrolyzed with $Ba(OH)_2$ and the demasked amino group was acetylated in one pot to furnish an 18:1 mixture of the desired pentaol **13**, mp 190.4–191.0 °C, $[\alpha]_D^{22}$ −23.0 (*c* 0.3, MeOH) and the diastereomeric pentaol in 81% combined overall yield. Interestingly, dihydroxylation of acetyl carbamate **11** and pivaloyl carbamate **12** resulted in much lower stereoselectivities of 9:1 and 7:1, respectively.

Since **13** comprises all the requisite chiral functional groups of *N*-acetylneuraminic acid **1**, the remaining synthetic operation is to transform the benzyloxy group into an α-keto carboxylic acid functionality. Accordingly, **13** was protected as a triacetonide using 2,2-dimethoxypropane in the presence of PPTS in $CHCl_3$ to give the desired triacetonide **14** $[\alpha]_D^{22}$ −14.3 (*c* 1.2, $CHCl_3$), in 74% yield along with 12% of diacetonide oxazoline **15**, which was more significantly formed under a variety of other attempted reaction conditions (Scheme 3). After debenzylation of **14** in 94% yield by hydrogenolysis, Wasserman's protocol[16] was employed for the installation of α-keto carboxylate moiety to primary alcohol **16**, $[\alpha]_D^{24}$ −16.0 (*c* 0.9, $CHCl_3$). Alcohol **16** was oxidized with $NaIO_4$ in the presence of $RuCl_3$, followed by coupling with $CH(=PPh_3)CN$ in the presence of EDCI and DMAP. The resulting phosphorane **18** was exposed to O_3 in MeOH to provide α-keto ester **19**, $[\alpha]_D^{16}$ −11.9 (*c* 1.46, $CHCl_3$), in 71% overall yield from **16**. Triacetonide **19** was consecutively deprotected and cyclized with methanolic HCl, and then the generated methyl ester **20**[17,18] was hydrolyzed to *N*-acetylneuraminic acid **1**, $[\alpha]_D^{17}$ −32.0 (*c* 1.19, H_2O),[11b] in 84% overall yield. For further identification, **20** was peracetylated with Ac_2O to produce a 6:1 mixture of pentaacetate **21**, $[\alpha]_D^{18}$ −32.0 (*c* 0.54, $CHCl_3$),[11f,17c,18] and the corresponding anomeric acetate.[19]

This work was supported by Creative Research Initiatives of the Korean Ministry of Science and Technology.

Notes and references

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18 The spectroscopic data of the synthetic **20** and **21** are identical to those of **20** and **21** prepared from the commercially available Neu5Ac **1** (Aldrich).
19 All new compounds showed satisfactory spectral data.

Communication a909400h