# Synthesis of a Carbocyclic Analogue of *N*-Acetylneuraminic Acid (Pseudo-*N*-acetylneuraminic Acid)

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A carbocyclic analogue of *N*-acetylneuraminic acid was synthesized from the Diels–Alder *endo*-adduct of furan and acrylic acid, and its ammonium salt was subjected to biological assay.

Extensive synthetic studies of many kinds of analogues[1,2] and derivatives[3] of *N*-acetylneuraminic acid (NANA) **1** both as potential inhibitors of sialidases and as probes for the elucidation of involvement in enzymic sialic acid metabolism have been carried out. Since the analogues,[4] which contain a nitrogen atom instead of the pyranoid oxygen atom showed some activity, we were interested in a synthesis of the carbocyclic analogue **2**, *N*-acetyl-6a-carbaneuraminic acid, of **1**. Starting from the *endo*-adduct **3** of furan and acrylic acid, per-*O*-acetyl derivative **28** of the methyl ester of **2** was successfully obtained in 21 steps reaction, and the ammonium salt of **2** was assayed for neuraminidases.

Iodolactonization of the optically resolved *endo*-adduct (+)-**3**[5] gave **4**† (86%), $[\alpha]^{25}_{D}$ −113 (*c* 1.04 in $CHCl_3$), which was reduced with lithium aluminium hydride in tetrahydrofuran (THF) to afford, after acetylation, **5** (61%). Cleavage of the epoxide ring of **5** with titanium tetrachloride in $CH_2Cl_2$ containing acetic acid afforded the triacetate **7** (37%), along with the chloride **6** (19%). The hydroxy group of **7** was first protected with methoxymethyl (MOM) group (→**8**, 93%) and **8** was then deacylated, isopropylidenated, and benzylated to give **9** (90% overall yield). Removal of the isopropylidene group of **9** followed by selective benzoylation of the primary hydroxy gave **10** (96% overall yield), which was blocked with triethylsilyl (TES) group (→**11**, 97%) and then *O*-debenzoylated to give **12** (87%). Oxidation of **12** with pyridinium chlorochromate (PCC) gave the aldehyde, successive Horner–Emmons alkenylation of which with trimethylacetylphosphonate in THF in the presence of potassium hexamethyldisilazane gave the propenates *E*-**13** (18%) and *Z*-**13** (68%). The stereochemistry of the isomers were deduced on the basis of the $^1$H NMR spectral signals due to the alkenic protons, which resonated at δ 5.80 (2-H) and 7.00 (3-H) in *E*-**13**, and at δ 5.78 (2-H) and 6.29 (3-H) in *Z*-**13**.

Reduction of the major *Z*-**13** with diisobutylaluminium hydride (→**14**),‡ followed by protection of the primary hydroxy with *tert*-butyldimethylsilyl (tBDMSi) group, gave **15** (97%). Osmium oxidation of **15** in the presence of *N*-methylmorphorine *N*-oxide (NMO) gave nonselectively two *cis*-diols **16a** (44%) and **16b** (48%), which were converted into the respective trimethoxymethyl ethers **17a** and **b**, quantitatively.

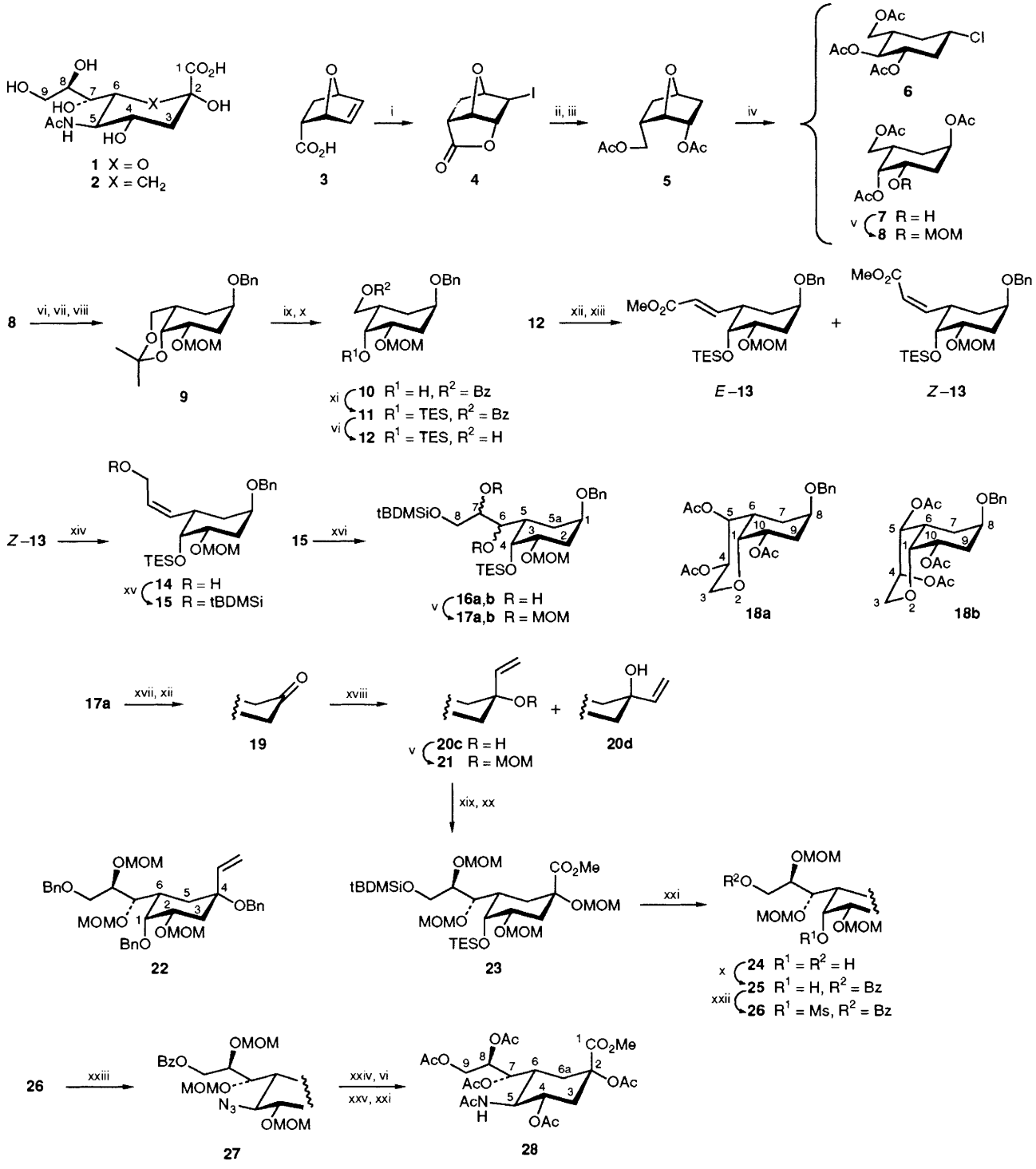
In order to elucidate the configurations of **16a** and **b**, the following transformations were carried out. After removal of

† All new compounds were characterized by 90 or 270 MHz $^1$H NMR, IR and elemental analyses. Selected $^1$H NMR data (270 MHz, $CDCl_3$) (*inter alia*), for **18a**: δ 2.26 (1 H, br d, 6-H), 3.64 [1 H, t (apparent), *J* 11 Hz, 3ax-H], 3.90 (1 H, br t, 8-H), 3.93 (1 H, dd, *J* 11 5.9 Hz, 3eq-H) and 4.08 (1 H, br s, 1-H). For **18b**: δ 2.40 (1 H, m, 6-H), 3.68 (1 H, dd, *J* 13.2, 1.5 Hz, 3ax-H), 3.79 (1 H, br s, 1-H), 3.91 (1 H, br t, 8-H), 4.12 (1 H, dd, *J* 13.2, 1.5 Hz, 3eq-H) and 5.06 (1 H, dd, *J* 5.1, 4 Hz, 5-H). For **22**: δ 1.69 (1 H, m, 6-H), 1.85 (1 H, dd, 5ax-H), 2.15 and 2.15 (each 1 H, 2 dd, *J* 12.1, 3.3 Hz, 3eq-H, 5eq-H), 2.24 [1 H, t (apparent), *J* 12.1, 3ax-H], 3.54 (1 H, ddd, *J* 12.1, 3.3, ~1 Hz, 2-H), 3.80 (1 H, br s, 1-H), 5.35 (1 H, dd, *J* 17.6, 1.1 Hz, CH=C*H*$_2$ *trans*), 5.40 (1 H, dd, *J* 11, 1.1 Hz, CH=C*H*$_2$ *cis*) and 5.72 (1 H, dd, *J* 17.6, 11 Hz, C*H*=CH$_2$). For **28**: δ 1.71 [1 H, t (apparent), *J* 13.2 Hz, 6a.ax-H], 1.79 [1 H, t (apparent), *J* 12.5 Hz, 3ax-H], 1.91, 2.01, 2.04, 2.06, 2.10 and 2.11 (each 3 H, 6 s, 6 Ac), 2.11 (1 H, m, 6-H), 2.54 (1 H, ddd, *J* 13.2, 2.6 Hz, 6a.eq-H), 2.77 (1 H, ddd, *J* 12.5, 2.6, 2.2 H, 3eq-H), 3.74 (3 H, s, $CO_2Me$), 3.95 [1 H, q (apparent), *J* 10.3 Hz, 5-H], 3.98 (1 H, dd, *J* 12.5, 6.2 Hz, 9-H), 4.23 (1 H, dd, *J* 12.5, 2.9 H, 9′-H), 5.20 (3 H, m, 4-H, 8-H, NH) and 5.24 (1 H, dd, *J* 8.4, 2.6 Hz, 7-H).

‡ The structure of *Z*-**13** was also verified by the following transformation: deprotection of the silyl group of **14** gave the allyl alcohol (81%), which was oxidized with manganese dioxide to give rise to the α,β-unsaturated δ-lactone (80%); IR $\nu_{max}$ cm$^{-1}$ 1720 (C=O).

the tBDMSi group of **17a** with tetra-n-butylammonium fluoride, the resulting alcohol was converted into the toluene-*p*-sulfonate, cyclization of which with methanolic sodium methoxide at 50 °C afforded the bicyclic compound that was characterized by converting into the pentaacetate **18a** (53% overall yield) by acid hydrolysis with HCl (2 mol $dm^{-3}$ 60 °C) and acetylation. Comparison of the $^1H$ NMR data of **18a** and the other isomer **18b** derived similarly from **17b** allowed their structures to be established as depicted in Scheme 1. The configurations of C-6,7 of **16a** were, therefore, shown to correspond to those of C-7,8 of **1**.

Hydrogenolysis of **17a** with Pd/C in ethanol effected the removal of the *O*-benzyl group, affording the alcohol which was successively oxidized with PCC to give the ketone **19**. Grignard reaction of **19** with vinylmagnesium bromide in THF yielded **20c** and **d** in 54 and 9% yields based on **17a**,




**Scheme 1** MOM = $MeOCH_2$, Bn = $CH_2Ph$, TES = $Et_3Si$, Ts = *p*-$MeC_6H_4SO_2$, tBDMSi = $Bu^tMe_2Si$, TMS = $Me_3Si$, Ms = $MeSO_2$, Bz = COPh. *Reagents and conditions*: i, $NaHCO_3$, $I_2$, THF–$H_2O$ (1:5); ii, $LiAlH_4$, THF, reflux; iii, $Ac_2O$, pyridine; iv, $TiCl_4$, AcOH, $CH_2Cl_2$, room temp.; v, *N*,*N*-$Pr^i_2EtN$, MOMCl, $CH_2Cl_2$, reflux; vi, MeONa, MeOH, room temp.; vii, $Me_2C(OMe)_2$, DMF; viii, NaH, BnBr, DMF, room temp.; ix, AcOH-$H_2O$ (4:1), room temp.; x, BzCl, pyridine; xi, TESCl, pyridine, 60 °C; xii, PCC, $CH_2Cl_2$; xiii, $(MeO)_2P(O)CH_2CO_2Me$, 18-crown-6, $(TMS)_2NK$, THF, −78 °C; xiv, $Bu^i_2AlH$, $CH_2Cl_2$, −78 °C; xv, 4-*N*,*N*-dimethylamino pyridine, $Et_3N$, tBDMSiCl, $CH_2Cl_2$, room temp.; xvi, NMO, $OsO_4$ (0.1 equiv.), acetone–$H_2O$ (3:2), room temp.; xvii, $H_2$, 10% Pd–C, EtOH; xviii, $CH_2$=CHMgBr, THF, room temp.; xix, $O_3$, MeOH, −78 °C; $Na_2HPO_4$, $NaClO_2$, $NH_2SO_2OH$, −78 °C; xx, $CH_2N_2$, $Et_2O$, 0 °C; xxi, $Bu^nNF$, THF, 0 °C; xxii, MsCl, pyridine, room temp.; xxiii, $NaN_3$, DMF, 90 °C; xxiv, $H_2$, Raney Ni, $Ac_2O$, EtOH; xxv, HCl aq., 60 °C.

respectively. The $^1$H NMR spectrum of the tribenzyl ether **22**, derived from the major **20c** by desilylation and subsequent benzylation, was easily amenable to observation of the NOE (nuclear Overhauser effect) between the signals for 3-H and 5-H, and that for the alkenyl methine proton, supporting the proposed structure of **20c**.

Compound **20c** was then converted into the methoxymethyl ether **21** (93%), which was subjected to ozonolysis in methanol at −78 °C to give, after the usual processing and subsequent esterification with diazomethane, the methyl ester **23** (90%). Deblocking of the triethylsilyl group (→**24**, 79%), followed by selective benzoylation of the primary hydroxy (→**25**, 89%) and successive mesylation, gave **26** (88%). Treatment of **26** with sodium azide in *N*,*N*-dimethylformamide (DMF) (90 °C) caused a preferential $S_N2$ reaction to give the azide **27** (78%), hydrogenation of which with Raney nickel T-4 in methanol, followed by acid hydrolysis with hydrochloric acid (2 mol dm$^{-3}$, 60 °C) afforded the pseudo-neuraminic acid hydrochloride, which, on conventional acetylation and esterification, was converted into the methyl hexa-*N*,*O*-acetyl derivative **28** (80% overall yield), $[\alpha]^{27}_D$ + 10 (*c* 0.34 in $CHCl_3$). The $^1$H NMR spectrum of **28** fully supported the assigned structure.

The ammonium salt of **2** was obtained by hydrolysis of **28** with sodium hydroxide (0.5 mol dm$^{-3}$) in THF–$H_2O$ (1 : 1) at room temp. for 2 h, neutralisation with Amberlite IR-120B ($H^+$) resin, and successive treatment with aqueous ammonia. About 5 mg of compound **2** was obtained from the adduct **3** (*ca.* 0.6 g, less than 0.7% overall yield, calculated) and subjected to inhibition assay. It showed *ca.* 30% inhibition against sialidase from *Streptococcus* sp. at the final concentration of 0.1 mmol dm$^{-1}$, and almost no inhibitory activity against that from *Arthrobacter ureafaciens*.

We thank Mr H. Arita and Mr H. Hata for their elemental analyses, and Dr M. Ito (MECT Corporation, Tokyo, Japan) for carrying out bioassays.

*Received, 30th October 1991; Com. 1/05524K*

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