Synthesis of an α-Mannosidase Inhibitor, (±)-Mannostatin A and its Isomer

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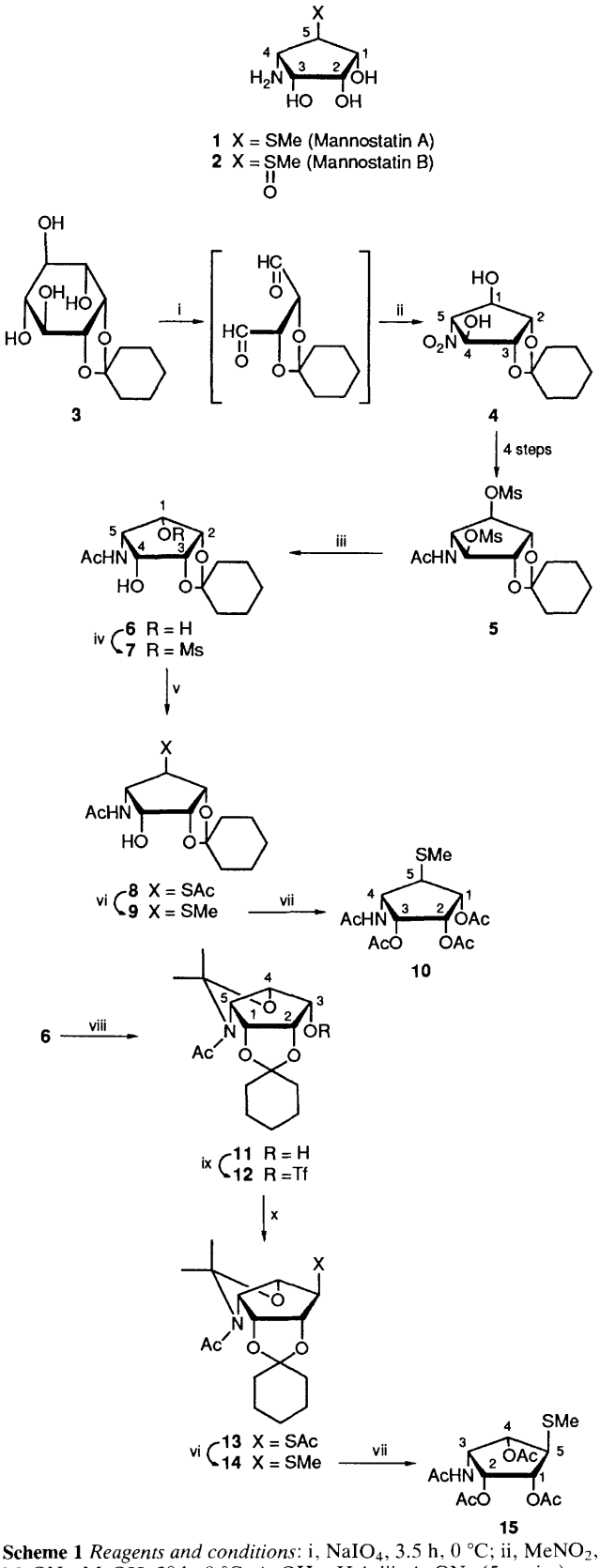
(±)-Mannostatin A **1**, a potent α-mannosidase inhibitor, and its isomer are synthesised for the first time as the tetra-*N,O*-acetyl derivatives **10** and **15**, starting from *myo*-inositol.

In 1989, mannostatins A **1** and B **2** were isolated by Aoyagi *et al.*[1] from a fermentation broth of *Streptoverticillium quintum* as a colourless syrup. The structure of **2** has been determined[2] to be (1,2,3,4/5)-4-amino-5-methylsulphinyl-1,2,3-cyclopentanetriol[3] on the basis of the ^{1}H NMR spectrum, the (1,*S*)-configuration being clearly established by X-ray diffraction analysis of mannostatin B tetra-*N,O*-acetate. Chemical and spectroscopic properties suggested that mannostatin B is the sulphoxide derivative of **1** as depicted in Scheme 1.

In connection with our synthetic studies[4] on inhibitors of sugar hydrolases, we describe here a synthesis of (±)-mannostatin A starting from *myo*-inositol.

Base-catalysed nitromethane cyclisation of the dialdehyde generated by periodate oxidation of (±)-1,2-*O*-cyclohexylidene-*myo*-inositol[5] **3** afforded[6,7] mainly the nitrodiol **4** (~60%) with 1,4/2,3,5-configuration. A nucleophilic displacement reaction of the protected dimesylate **5** of 5-acetamido-1,2,3,4-cyclopentanetetrol,[7] derived in four steps (35% overall yield) from **4**, with sodium acetate in aqueous 80% 2-methoxyethanol at reflux temperature, involved inversion of the configurations at C-1 and C-4 *via* neighbouring-group participation of the 5-acetamido group, affording the stereoisomer **6** with 1,2,3,4,5,/0-configuration. The structure was confirmed by the ^{1}H NMR spectrum, as well as, by converting it into the known penta-*N,O*-acetate.[7] Reaction of **6** with 1.4 equiv. of methanesulphonyl chloride in pyridine produced (after quenching at the point of about half of **6** being consumed) (50 min, 0 °C) the monomesylate **7** (62%) together with a trace of the dimesylate. The mesylate **7** was displaced *via* S_N2 fashion with potassium thioacetate in *N,N*-dimethylformamide (DMF) for 50 min at 120 °C to give the thioacetate



Scheme 1 *Reagents and conditions*: i, $NaIO_4$, 3.5 h, 0 °C; ii, $MeNO_2$, MeONa–MeOH, 20 h, 0 °C; AcOH, pH 4; iii, AcONa (5 equiv.), aq 80% 2-methoxyethanol, 3 h, reflux; iv, $MeSO_2Cl$ (1.4 equiv.), pyridine, 50 min, 0 °C; v, KSAc (10 equiv.), *N,N*-dimethylformamide (DMF), 50 min, 120 °C; vi, MeONa–MeOH, 0 °C; MeI, MeOH; vii, aq 80% AcOH, 15 h, 100 °C; Ac_2O, pyridine; viii, $Me_2C(OMe)_2$, *p*-TsOH·H_2O, DMF, 18 h, 60 °C; ix, $(CF_3CO)_2O$, $ClCH_2CH_2Cl$–pyridine (1 : 5), 15 min, 0 °C; x, KSAc (5 equiv.), DMF, 5 min, room temp. For convenience, the structural formulae of the compounds (**7–15**) synthesised in this paper depict only one of the respective enantiomers.

8, which, without purification, was *S*-deacetylated with methanolic sodium methoxide followed by treatment with methyl iodide to give the methylthio derivative **9**. Acid hydrolysis of **9** with aqueous 80% acetic acid followed by acetylation afforded the tetra-*N,O*-acetate **10** (13.4% overall yield from **7**) of (±)-mannostatin A, the ^1H NMR spectrum† of which was superimposable on that of an authentic sample.[2]‡

Next, an attempt was made to protect one of the two hydroxys of **6** adjacent to the *N,O*-isopropylidene group in order to give ready access to the 1(4)-monosulphonate. Treatment of **6** with 2,2-dimethoxypropane in DMF in the presence of toluene-*p*-sulphonic acid gave§ a single *O*-cyclohexylidene-*N,O*-isopropylidene derivative **11**, which, without purification, was treated with trifluoromethanesulphonic anhydride¶ in pyridine to give the sole triflate **12**. By a similar reaction sequence, compound **6** was transformed into **15**, the isomer of **10**, in 15% overall yield *via* **12**. The structure of **15** was assigned DL-(1,2,3,4/5)-3-acetamido-5-methylthio-1,2,4-cyclopentanetriol as shown in Scheme 1, on the basis of the proposed reaction mechansim, and, more convincingly, by the ^1H NMR spectrum.‖ In the isopropylidenation of **6**, acid-catalysed migration of the 2,3-*O*-cyclohexylidene group to C-3,4 (1,2) seemed to occur, being accompanied by the formation of the *N,O*-isopropylidene group at C-1,5 (4,5). And the isomer **10** was formed by direct displacement of the resulting 3-triflate **12** with thioacetate anion.

Biological assays of the free bases readily obtained from **10** and **15** are now underway.

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† **10**, *^1H NMR spectral data*: δ_H (270 MHz, $CDCl_3$) (*inter alia*) 2.05, 2.06, 2.08, 2.12 and 2.17 (each 3 H, 5 s, NAc, 3 OAc, and SMe), 3.10 (1 H, dd, $J_{1,5}$ 6.4, $J_{4,5}$ 8.6 Hz, 5-H), 4.39 (1 H, ddd, $J_{3,4}$ 5.3, $J_{4,5}$ 8.6, $J_{4,NH}$ 8.9 Hz, 4-H), 5.17 (1 H, dd, $J_{1,2}$ 6.2 Hz, 1-H), 5.34 (1 H, dd, $J_{2,3}$ 4.5 Hz, H-3), 5.40 (1 H, dd, H-2), 5.81 (1 H, d, NH).

‡ We thank Dr T. Aoyagi (Institute of Microbial Chemistry, Shinagawa, Tokyo) for carrying out the identification of the synthetic (±)-mannostatin A tetra-*N,O*-acetate by comparing its ^1H NMR spectrum with that of an authentic sample.

§ In addition to **11**, formation of the 1,2(3,4)-*O*-cyclohexylidene-3,4(1,2)-*O*-isopropylidene derivative was observed.

¶ Compound **11** could not be converted into the corresponding mesylate under conventional conditions.

‖ **15**, *^1H NMR spectral data*: δ_H (270 MHz, $CDCl_3$) (*inter alia*) 2.00, 2.05, 2.13, 2.14 and 2.18 (each 3 H, 5 s, NAc, 3 OAc and SMe), 3.18 (1 H, dd, $J_{1,5}$ 7.7, $J_{4,5}$ 4.3 Hz, 5-H), 4.82 (1 H, ddd, $J_{2,3}$ 4.8, $J_{3,4}$ 6.8, $J_{3,NH}$ 9.2 Hz, 3-H), 5.08 (1 H, dd, $J_{1,2}$ 4.5 Hz, 1-H), 5.20 (1 H, dd, H-4), 5.37 (1 H, dd, H-2), 5.67 (1 H, d, NH).