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Intramolecular Cyclization of C_2 Symmetric and *meso*-Iodo Amino Alcohols : A Synthetic Approach to Azasugars

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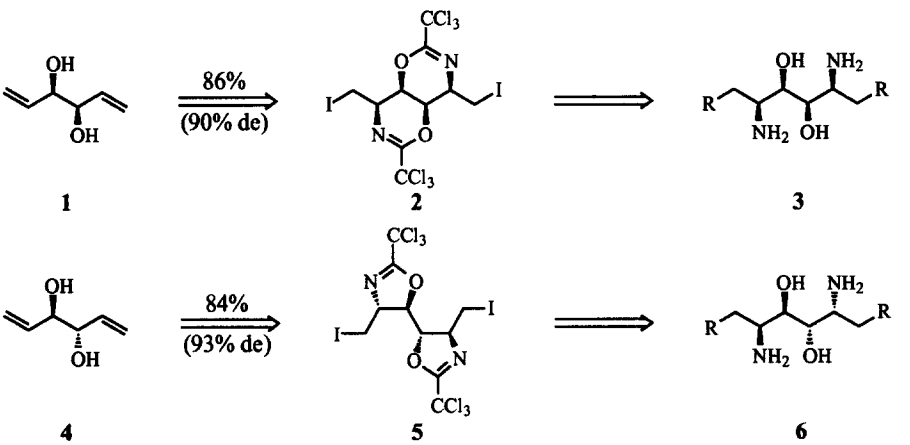
Abstract: C_2 Symmetric and *meso*-iodo hydroxy ammonium chlorides generated from **2** and **5** have been cyclized under basic conditions to produce various heterocycles chemoselectively, which comprise tetrahydrofurans **7** and **19**, piperidines **13**, **15** and **21**, and pyrrolidines **17** and **18**.

Polyhydroxylated piperidines and pyrrolidines (azasugars), in which the ring oxygen is replaced by an imino group, show strong inhibitory activities against glycosidases and glycosyltransferases involved in carbohydrate processing.[1] They proved to have potential therapeutic utility in the treatment of metabolic disorders such as diabetes mellitus[2] and in the suppression of tumorial metastasis.[3] They also serve as a source of a promising lead for the development of antiviral agents, in particular anti-AIDS agents[4] by interfering glycoprotein processing in viral envelopes to prevent HIV from binding CD 4 receptor. In addition five-membered acetamido azasugars have recently been manifested to be competitive inhibitors of β-N-acetylglucosaminase.[5]

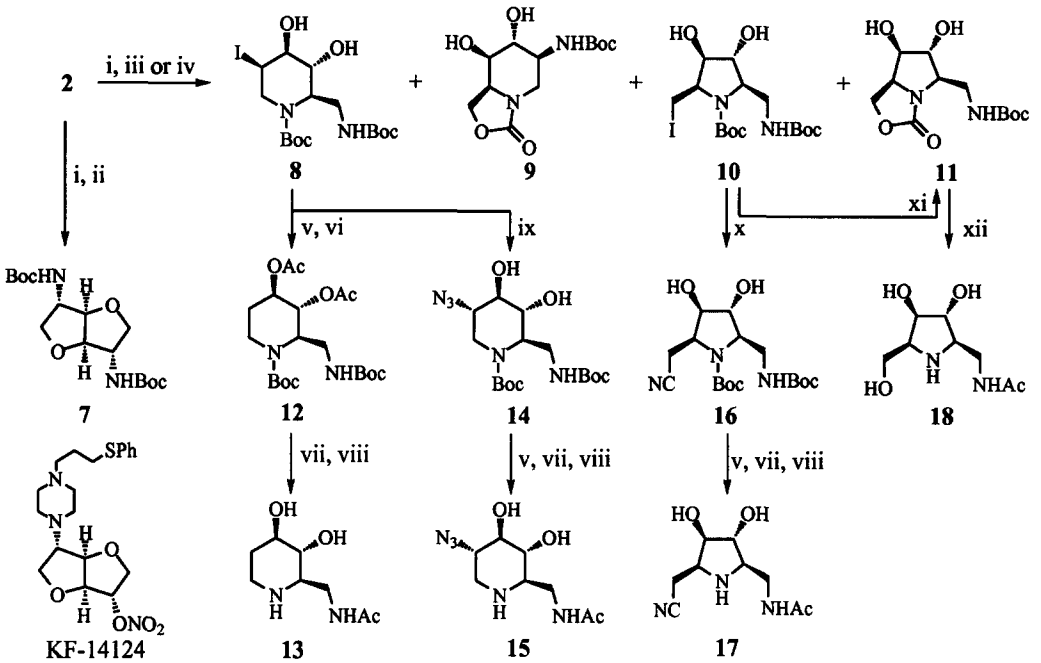
We reported double iodoamination of bis(trichloroacetimidate)s derived from 3,4-dihydroxyhexa-1,5-dienes **1** and **4** followed by hydrolysis to produce C_2 symmetric and *meso*-amino alcohols **3** and **6** in a regio- and stereocontrolled manner.[6] While the former was generated via bis(dihydro-1,3-oxazine) **2**, the latter



was delivered via bisoxazoline **5**. Since **2** and **5** are equivalent to amino hydroxy iodides, the intramolecular cyclization of the unmasked **2** and **5** was conceived to control the formation of piperidine, pyrrolidine and tetrahydrofuran derivatives by the appropriate choice of the cyclization conditions. In this context we have investigated the intramolecular cyclization of **2** and **5** for the chemoselective synthesis of the described heterocycles.

After the complete hydrolysis of **2** with methanolic hydrochloric acid, the resulting C_2 symmetric iodo hydroxy ammonium chloride was cyclized with potassium carbonate in the methanol at 25℃ and then

Scheme 1



Reagents : i) 6N HCl, MeOH, 25℃. ii) K_2CO_3, MeOH, 25℃ ; Boc_2O, 25℃. iii) $NaHCO_3$, MeOH, 50℃ ; Boc_2O, 0℃. iv) Propylene oxide, Boc_2O, MeOH, 50℃. v) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 25℃. vi) *n*-Bu_3SnH, AIBN, PhMe, 110℃. vii) CF_3COOH, 25℃. viii) aq. NaOH (pH ≈ 11). ix) NaN_3, DMF, 70℃. x) NaCN, DMSO, 45℃. xi) AgOAc, AcOH, DMF, 70℃. xii) $Ba(OH)_2$, H_2O, reflux ; *p*-$O_2NC_6H_4OAc$, aq. NaOH (pH ≈ 11), 0℃.

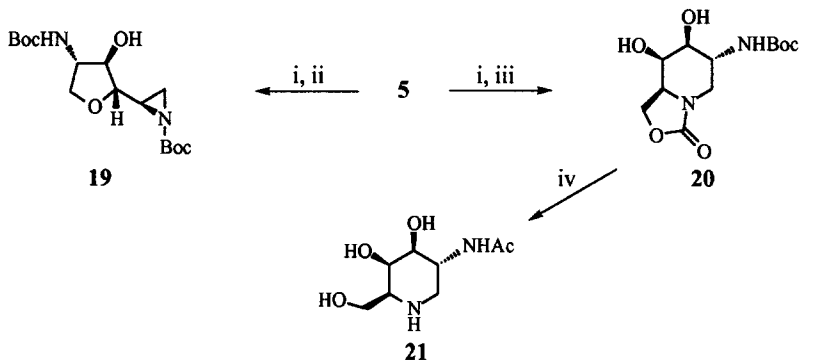
reacted with di-*t*-butyl dicarbonate to give the fused tetrahydrofuran **7**, $[\alpha]_D^{22}$ -2.2 (*c* 1.0, $CHCl_3$) in 92% overall yield, of which the skeleton is structurally related to KF-14124 clinically useful in the treatment of angina pectoris and heart failure[7] (Scheme 1). On the other hand, the use of sodium bicarbonate at 50°C instead of potassium carbonate produced a 4:2:1:2 mixture of piperidines **8** and **9**, and pyrrolidines **10** and **11** in 90% combined overall yield. It is speculated that aziridinium cation was involved in the formation of **8** and **10**.[8] When the crude C_2 symmetric ammonium chloride was subjected to propylene oxide[9] in the presence of di-*t*-butyl dicarbonate in methanol at 50℃, pyrrolidine **10**, $[\alpha]_D^{21}$ +1.7 (*c* 1.0, $CHCl_3$) was generated in 69% overall yield along with 25% of piperidine **9**.

Acetylation of **8** followed by reductive deiodination with tributyltin hydride yielded diacetate **12**. The two *t*-butoxycarbonyl groups of **12** were removed chemoselectively in trifluoroacetic acid, and the ensuing treatment of the resulting diacetate ammonium salt with aqueous sodium hydroxide effected the transfer of an acetyl group from oxygen to nitrogen and hydrolysis of the remaining acetate to afford piperidine **13**, $[\alpha]_D^{26}$ +13.2 (*c* 0.25, H_2O) in 93% overall yield from **8**. Substitution of the six-membered iodide **8** by sodium azide in DMF at 70°C provided azide **14** in 80% yield, which was converted into piperidine **15**, $[\alpha]_D^{27}$ +18.7 (*c* 0.30, H_2O) in 89% overall yield by the sequential treatment with acetic anhydride in triethylamine, trifluoroacetic acid and aqueous sodium hydroxide. The five-membered iodide **10** was substituted by sodium cyanide in DMSO at 45℃ to furnish cyanide **16** in 72% yield.[10] Subjection of **16** to the same reaction conditions as in the transformation of **14** into **15** gave pyrrolidine **17**, $[\alpha]_D^{27}$ +48.8 (*c* 0.25,

H_2O) in 70% overall yield. When **10** was heated at 70℃ with silver acetate in a 2:1 mixture of DMF and acetic acid,[11] oxazolidinone **11**, $[\alpha]_D^{20}$ +27.3 (*c* 0.40, $CHCl_3$) was prepared in 98% yield. The two carbamate groups in **11** were hydrolyzed by heating in aqueous barium hydroxide at reflux,[12] and subsequently the unmasked primary amino group was chemoselectively acetylated *in situ* at 0°C using *p*-nitrophenyl acetate[13] to produce pyrrolidine **18**, $[\alpha]_D^{26}$ +27.2 (*c* 0.23, H_2O) in 85% yield.

Hydrolysis of **5** with methanolic hydrochloric acid yielded *meso*-iodo hydroxy ammonium chloride, which was sequentially exposed to potassium carbonate in methanol and di-*t*-butyl dicarbonate to afford the racemic tetrahydrofuran **19** in 84% overall yield (Scheme 2). On the other hand, while cyclization of the *meso*-ammonium chloride did not proceed cleanly in the presence of propylene oxide,[9] its successive treatment with sodium bicarbonate in methanol and di-*t*-butyl dicarbonate furnished the racemic oxazolidinone **20** in 90% overall yield from **5**. After hydrolysis of the carbamate groups in **20** in aqueous barium hydroxide, the resulting reaction mixture was treated with *p*-nitrophenyl acetate at 45℃ to provide the racemic piperidine **21** in 87% yield.[14]

Scheme 2



Reagents : i) 6N HCl, MeOH, 25℃. ii) K_2CO_3, MeOH, 25℃ ; Boc_2O, 25℃. iii) $NaHCO_3$, MeOH, 25℃ ; Boc_2O, 0°C. iv) $Ba(OH)_2$, H_2O, reflux ; *p*-$O_2NC_6H_4OAc$, aq. NaOH (pH ≈ 11), 45°C.

In conclusion, we have prepared potentially valuable tetrahydrofurans **7** and **19**, piperidines **13**, **15** and **21**, and pyrrolidines **17** and **18** from C_2 symmetric bis(dihydro-1,3-oxazine) **2** and *meso*-bisoxazoline **5** with good to moderate chemoselectivity. While azapyranose **13**, **15** and **21** have 2-deoxy-D-gluco, D-gluco and DL-galacto configuration, respectively, **17** and **18** correspond to azafuranoses of D-gluco configuration.

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14. All new compounds showed satisfactory spectral data. *Selected NMR data* : **7** : ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (18H, s), 3.73 (2H, dd, *J* 2.1, 9.6 Hz), 3.92 (2H, dd, *J* 4.7, 9.6 Hz), 4.06-4.18 (2H, m), 4.52 (2H, s) and 4.86 (2H, br d, *J* 6.1 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 28.3, 57.4, 72.5, 80.0, 86.4 and 155.0. **13** : ^{1}H NMR (300 MHz, D_2O) δ 1.35-1.50 (1H, m), 1.92-2.01 (1H, m), 2.00 (3H, S), 2.51-2.61 (3H, m), 2.95 (1H, ddd, *J* 2.3, 4.4, 12.9 Hz), 3.06 (1H, t, *J* 9.4 Hz), 3.28 (1H, dd, *J* 7.4, 14.3 Hz), 3.47-3.53 (1H, m) and 3.53 (1H, dd, *J* 3.7, 14.3 Hz). ^{13}C NMR (50.3 MHz, D_2O) δ 22.8, 33.1, 41.4, 43.6, 60.3, 73.5, 75.0 and 175.6. **15** : ^{1}H NMR (300MHz, Py-d_5) δ 2.03 (3H, s), 2.57 (1H, dd, *J* 11.2, 12.1 Hz), 2.89 (1H, ddd, *J* 3.1, 6.7, 9.5 Hz), 3.23 (1H, dd, *J* 5.1, 12.1 Hz), 3.63-3.73 (2H, m), 3.82-3.96 (2H, m) and 4.03 (1H, ddd, *J* 3.1, 5.4, 13.4 Hz). ^{13}C NMR (75.5MHz, D_2O) δ 22.8, 41.3, 47.5, 59.6, 63.4, 73.8, 77.6 and 175.5. **17** : ^{1}H NMR (300 MHz, D_2O) δ 2.07 (3H, s), 2.60 (1H, dd, *J* 7.4, 16.2 Hz), 2.69 (1H, dd, *J* 6.4, 16.2 Hz), 3.43-3.51 (1H, m), 3.54 (1H, dd, *J* 7.1, 13.8 Hz), 3.64 (1H, dd, *J* 5.3, 13.8 Hz), 3.83-3.90 (1H, m), 4.05 (1H, dd, *J* 2.2, 3.5 Hz) and 4.21 (1H, dd, *J* 2.2, 4.2 Hz). ^{13}C NMR (75.5 MHz, D_2O) δ 22.6, 35.1, 41.0, 59.9, 65.0, 77.3, 79.0, 176.0 and 179.3. **18** : ^{1}H NMR (300 MHz, D_2O) δ 2.01 (3H, s), 3.14-3.21 (1H, m), 3.35-3.52 (3H, m), 3.72 (1H, dd, *J* 6.7, 11.5Hz), 3.83 (1H, dd, *J* 5.8, 11.5 Hz), 3.88 (1H, dd, *J* 2.7, 4.7 Hz) and 4.15 (1H, dd, *J* 2.7,4.8 Hz). ^{13}C NMR (75.5 MHz, D_2O) δ 22.7, 42.1, 60.2, 62.0, 64.2, 77.5, 80.2, and 175.6. **19** : ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.44 (9H, s), 2.30 (1H, d, *J* 6.3Hz), 2.32 (1H, d, *J* 2.8 Hz), 2.63 (1H, ddd, *J* 2.8, 3.6, 6.3 Hz), 3.63-3.72 (1H, m), 3.90 (1H, t, *J* 2.9Hz), 3.97-4.04 (2H, m), 4.29 (1H, br s) and 5.62 (1H, br d, *J* 6.2 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 27.9, 28.4, 28.6, 38.7, 59.1, 72.5, 79.8, 80.8, 81.6, 82.0, 156.0 and 162.1. **21** : ^{1}H NMR (300 MHz, D_2O) δ 2.01 (3H, s), 2.38 (1H, t, *J* 12.2 Hz), 2.77 (1H, t, *J* 6.6 Hz), 3.09 (1H, dd, *J* 5.0, 13.1 Hz), 3.57-3.66 (3H, m), 3.97 (1H, dt, *J* 5.0, 11.0 Hz) and 4.02 (1H, br s). ^{13}C NMR (75.5 MHz, D_2O) δ 22.9, 48.0, 49.3, 59.6, 62.1, 69.2, 73.4 and 175.4.

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