Double asymmetric iodoamination; synthesis of C_2 symmetric and *meso*-amino alcohols

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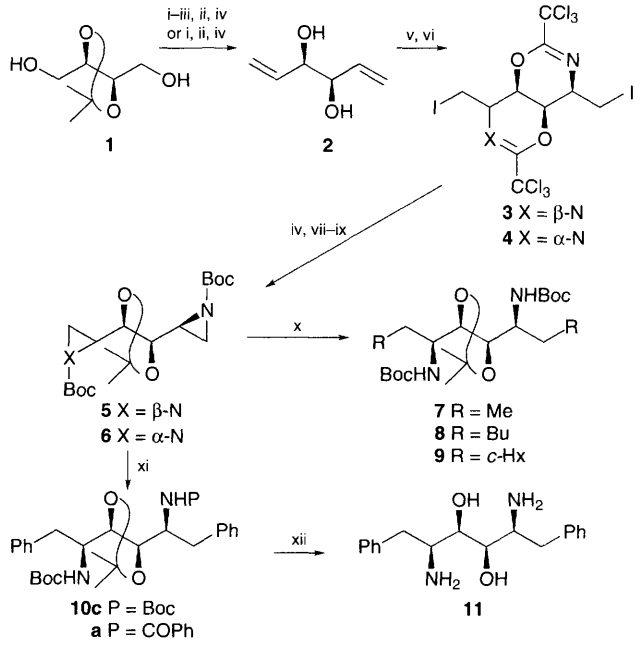
Alkenic diols 2 and 14 are iodocyclized providing dihydro-1,3-oxazine 3 and dihydrooxazole 15 in 90 and 93% de, respectively, which are precursors of various C_2 symmetric and *meso*-amino alcohols.

Intense effort has been made to develop an effective therapeutic agent for the treatment of acquired immunodeficiency syndrome (AIDS). For the replication of mature and infectious virions, it is essential to cleave the *gag* p55 precursor into four structural proteins of the viral core (p17, p24, p7 and p6) and the *gag-pol* p160 polyprotein into three enzymes (protease, reverse transcriptase and integrase) as well as the structural proteins.[1] Since HIV protease encoded by the retrovirus is responsible for proteolytic processing, its various inhibitors have been designed as anti-HIV agents.[2] One of the most prominent classes among them is the C_2 symmetric inhibitors, which may form stronger transition state complexes with retroviral protease and exhibit higher specificity.[3] These logical conclusions are based on the facts that the active HIV protease is a homodimeric aspartic protease composed of two identical 99 amino acid peptides and its substrate binding sites are more symmetric than the related mammalian aspartic protease. The prospective findings led us to explore methods to secure C_2 symmetric and *meso*-amino alcohols stereoselectively. Here we describe an enantioselective and versatile synthetic route to them.

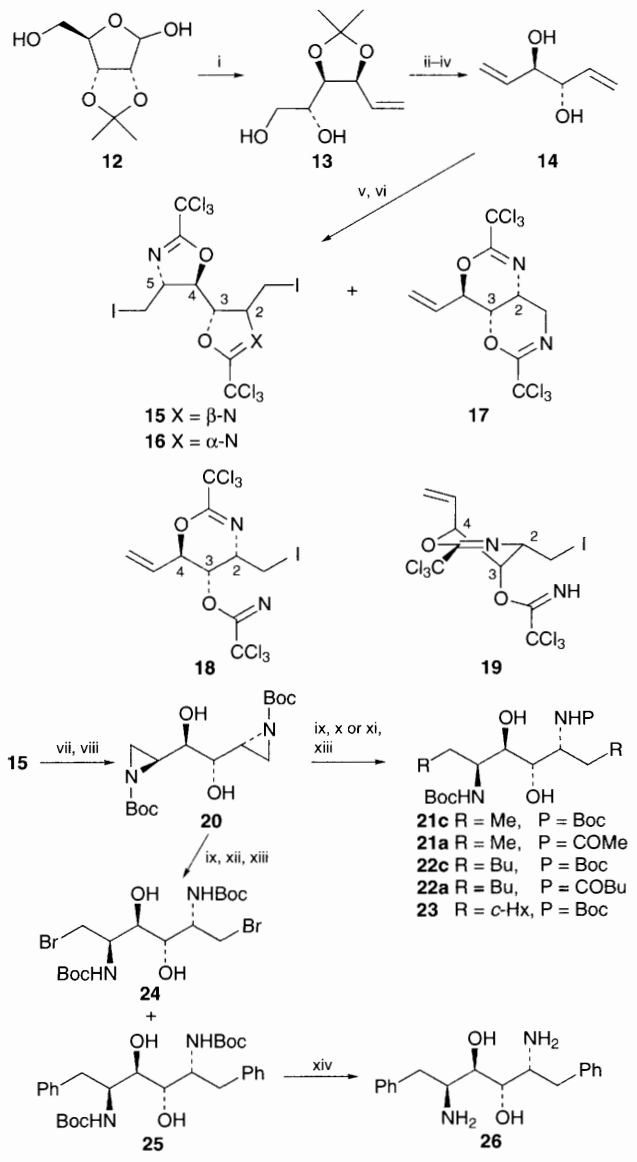
Our pivotal synthetic strategy is double iodoamination of bis(trichloroacetimidate)s derived from 3,4-dihydroxyhexa-1,5-dienes in a regio- and stereo-controlled manner. The starting diol **2** was prepared from D-tartaric acid instead of D-mannitol[4] because its enantiomer could be obtained by the same reaction sequence using L-tartaric acid. Acetonide **1** from D-tartaric acid[5] was oxidized using Dess–Martin periodinane (Scheme 1).[6] The resulting unstable mixture of mono- and di-aldehyde was then methylenated to yield 35% of monoolefinic alcohol along with dialkene, of which acidic deprotection gave diol **2** in 21% overall yield. The monoalkenic alcohol was also transformed into **2** in 71% overall yield by Swern oxidation,[7] olefination and acidic deprotection. Bis(trichloroacetimidate), generated from **2** with trichloroacetonitrile and DBU, reacted with iodine in the presence of sodium hydrogen carbonate in acetonitrile at 0 °C to afford a 15 : 1 inseparable mixture of dihydro-1,3-oxazines **3** and **4** in 71% overall yield accompanied by 10% of 5-membered oxazolines. Alternatively, when it was cyclized with iodobromide in the presence of potassium carbonate in propionitrile at −90 °C, a 20 : 1 mixture of only the 6-membered compounds **3** and **4** was furnished in 90% overall yield. Their 6-membered ring structures were deduced by C=N stretching bands[8] at 1680 cm^{-1} and their stereochemistries established by converting **3** into the known C_2 symmetric amino alcohol **11** (*vide infra*).[3,9] After complete deprotection of the mixture of **3** and **4** under acidic conditions, the produced amino and dihydroxy groups were protected as *tert*-butyl carbamates and acetonides, respectively. The subsequent treatment of the protected diiodides with sodium hydride provided a 20 : 1 separable mixture of diaziridines **5**, $[\alpha]_D^{21}$ −74.1 ($CHCl_3$, *c* 0.82) and **6** in 85% overall yield. Diaziridine **5** was exposed to methyl-, butyl- and cyclohexyl-magnesium halide in the presence of dilithium tetrachlorocuprate in THF to yield carbamates **7** (92%), **8** (91%) and **9** (81%) efficiently. In contrast, the phenyl substituent was difficult to introduce. Some experimentation revealed that switching the reaction solvents from ethers to toluene was vital to achieve successful substitution. Consequently **4** was treated with phenylmagnesium bromide in the presence of a cuprous bromide–dimethyl sulfide complex in toluene at −20 °C to give an 8 : 1 mixture of carbamate **10c** and amide **10a** in 92% yield. Acidic deprotection of the mixture generated the known C_2 symmetric amino alcohol **11**, $[\alpha]_D^{19}$ +27.8 (MeOH, *c* 0.49) in 69% overall yield from **5**. It is noted that carbamates **7–9** and **10c** existed as symmetric and unsymmetric rotamers, of which the ratios were 1.1–1.6 to 1 in favour of symmetric. In addition their ^1H NMR spectra at 50 °C merged into symmetric ones.

Another starting *meso*-diol **14** was derived from D-ribose acetonide **12** (Scheme 2). After Wittig olefination in 55% yield, the resulting diol **13** was sequentially subjected to mesylation, reductive elimination and acidic hydrolysis to afford **14** in 72% overall yield. Bis(trichloroacetimidate) from **14** was cyclized with iodine in the presence of sodium hydrogen carbonate at 0 °C to furnish a 31 : 1 separable mixture of dihydrooxazoles **15** and **16** in 87% yield along with a few % of dihydro-1,3-oxazine **17**, which was conceived to be formed *via* the monocyclized imidate **18**. Their ring structures and stereochemistries were determined by C=N stretching bands and the proton–proton coupling constants as follows: for **15**: 1666 cm^{-1} and $J_{H2,H3}$ = 4.2 Hz. For **16**: 1662 cm^{-1}, $J_{H2,H3}$ = 9.4 and $J_{H4,H5}$ = 5.4 Hz.



Scheme 1 *Reagents and conditions*: i, Dess–Martin periodinane, CH_2Cl_2, 20 °C; ii, Ph_3P^+ MeI^-, BuLi, THF, HMPA, 0 °C; iii, Swern ox.; iv, 6 mol dm^{-3} HCl, MeOH, 20 °C; v, CCl_3CN, DBU, MeCN, −30 °C; vi, IBr, K_2CO_3, EtCN −90 ~ −78 °C; vii, Boc_2O, $NaHCO_3$, MeOH, −15 °C; viii, $Me_2C(OMe)_2$, acetone, *p*-TsOH, 0 °C; ix, NaH, THF, 0 °C; x, MeMgBr, BuMgBr or *c*-HxMgCl, Li_2CuCl_4, THF, −25 ~ −20 °C; xi, PhMgBr in THF, CuBr·SMe_2, PhMe, −20 ~ −15 °C; xii, 6 mol dm^{-3} HCl, reflux

For **17**: 1683 cm^{-1} and $J_{H2,H3}$ = 2.5 Hz. On the other hand, when iodoamination of the above *meso*-bis(imidate) was conducted with iodobromide in the presence of potassium carbonate at −90 to −20 °C, the monocyclized iodide **18** (25%), dihydrooxazole **15** (10%) and several unidentifiable compounds were produced. Iodide **18** is believed to exist as conformer **19** judging from $J_{H3,H4}$ = 1.7 Hz and C-2 methine hydrogen signal enhancement upon irradiation of the vinyl hydrogen. The probable conformer **19** explains why the monocyclized intermediate **18** was resistant to the second iodocyclization.



Scheme 2 *Reagents and conditons* i, $Ph_3P^+MeI^-$, BuLi, THF, reflux; ii, MsCl, DMAP, pyridine, CH_2Cl_2 20 °C; iii, Zn, NaI, DMF, 150 °C; iv, 6 mol dm^{-3} HCl, MeOH, 20 °C; v, CCl_3CN, DBU, MeCN, −30 °C; vi, I_2, $NaHCO_3$, MeCN, 0 °C; vii, 6 mol dm^{-3} HCl, MeOH, 20 °C; viii, $NaHCO_3$, MeOH, 20 °C then Boc_2O; ix, TMSCl, Et_3N, THF, 20 °C; x, MeMgBr or BuMgBr, Li_2CuCl_4, THF, −25 ~ 0 °C; xi, *c*-HxMgCl in Et_2O, Li_2CuCl_4, $PhCH_3$, −25 ~ 0 °C; xii, PhMgBr in THF, $CuBr{\cdot}SMe_2$, PhMe, −25 ~ 0 °C; xiii, acidic (pH = 3) work-up; xiv, 6 mol dm^{-3} HCl, reflux

Hydrolysis of **15** followed by cyclisation and protection generated diaziridine **20** in 76% yield. Since cuprate reactions of **20** did not proceed cleanly, its two hydroxy groups were protected as a trimethylsilyl (TMS) ether. The protected diaziridine was smoothly opened with methyl-, butyl-, cyclohexyl- and phenyl-substituents under the similar conditions to those described for **5**. While methyl- and butyl-magnesium bromide provided the mixtures of carbamate and amide in 74 (**21c**:**21a** = 7:2) and 79% yield (**22c**:**22a** = 2:3), respectively, only carbamate **23** could be isolated with cyclohexylmagnesium chloride in 32% yield. The substitution reaction using phenylmagnesium bromide yielded 65% of the desired carbamate **25** along with 7% of the dibromide **24**. Finally acidic deprotection of **25** produced *meso*-amino alcohol **26** in 90% yield.

A stereoselective double iodoamination of 3,4-dihydroxyhexa-1,5-dienes has been achieved to give dihydro-1,3-oxazine or dihydrooxazole, which could be transformed into C_2 symmetric or *meso*-amino alcohols efficiently.

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