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An enantioselective approach to trehazolin: a concise and efficient synthesis of the aminocyclopentitol core

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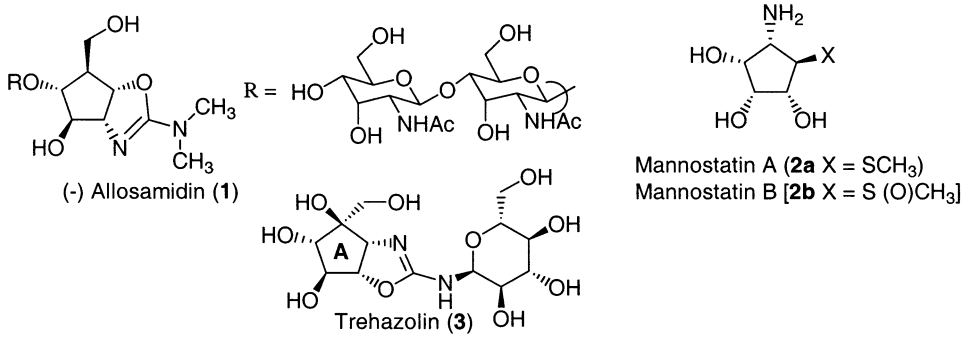
Abstract—A concise and efficient synthesis of the aminocyclopentitol core of trehazolin is presented.

Several aminocyclopentitol containing natural products have been discovered and found to display potent and selective inhibitory effects on a variety of important glycosidases.[1,2] Examples include allosamidin **1**, representing a new family of pseudotrisaccharide chitinase inhibitors, mannostatins A **2a** and B **2b**, which are selective mannosidase inhibitors and trehazolin **3** which inhibits the trehalase-catalyzed breakdown of trehalose into two molecules of glucose.

Different research groups have examined the chemical and biological properties of these natural products and interesting synthetic analogs as well as structure–activity relationships have been obtained.[2] There have been several strategies adopted towards the synthesis of the aminocyclopentitol core present in these compounds. These strategies[2] include 1,3-dipolar cycloaddition, radical carbocyclizations of carbohydrate precursors, desymmetrization of substituted cyclopentene-4-meso-diols, heterocycloadditions of cyclopentadienes, and more recently the very efficient ketyl radical cyclizations promoted by samarium diiodide.[3]

Recently ring closing metathesis (RCM) has emerged as a powerful tool for the cyclizations of dienes.[4] In connection, we were the first to report the RCM on substituted internal dienes, to give complex polyhydroxylated cyclopentenes.[5] Thus, an alternative strategy to aminocyclopentitol core can be devised using an intermediate polyhydroxylated cyclopentene. We have recently reported a short and very efficient synthesis of carba-arabinose precursor **4** in five steps (47% yield) using RCM.[6] This precursor **4** bears a striking structural similarity to ring A of **3**. Logical retrosynthetic analysis suggests that the target aminocyclopentitol



Keywords: cyclopentenes; amino sugars; cyclitols; carbohydrate mimetics.

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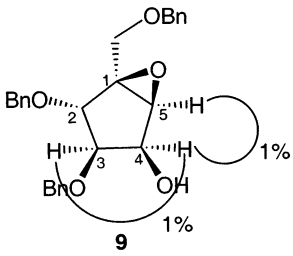
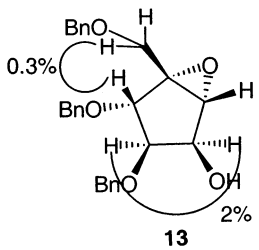
moiety **5** could be readily assembled by elaboration of precursor **4** (Scheme 1).

Having our key cyclopentenes in hand, the *p*-methoxybenzyl (PMB) group of the β isomer (62%) **4β** was deprotected to give the allylic alcohol **8**. Of note, the corresponding α isomer (38%) **4α** was deprotected and inverted under standard Mitsunobu conditions to the β allylic alcohol **8**.[7] The combined material was then treated with *m*CPBA to afford an epoxide **9**. Here a single diastereomer was observed consistent with the influence of the stereodirecting effect of the β hydroxy group.[8] Ring opening using NaN_3 gave the diol **10**. The azide was then treated under Staudinger reduction conditions[9] to give the key aminocyclopentitol unit **11** in 69% overall yield from **4** (Scheme 2).

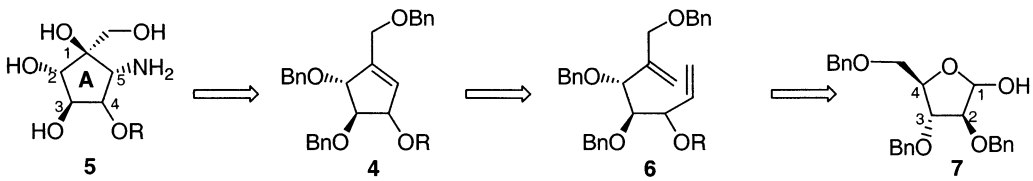
Confirmation of the stereochemistry around C-1 and C-5 came from a comparison of the two diastereomeric epoxides **9** and **13** (Scheme 3).[10] The epoxide **13** was prepared by treatment of **4β** with *m*CPBA followed by deprotective removal of the *p*-methoxybenzyl group. As before, only one diastereomer was observed and this is thought to arise from the steric crowding of the β-face by the PMB group, thus making the α face more accessible to epoxy approach.

The NOE analysis of the epoxides **9** and **13** are shown below. For epoxide **9**, a 1% NOE was observed between H_3 and H_4 and also for H_4 and H_5. This result confirms a *syn* arrangement of the epoxide with the C_4-OH group. For epoxide **13**, a 2% NOE was observed between H_3 and H_4, a 0.3% NOE between H_2 and CH_2OBn and no NOE between H_4 and H_5. This data confirms an *anti* arrangement of epoxide with respect to C_4-OH.

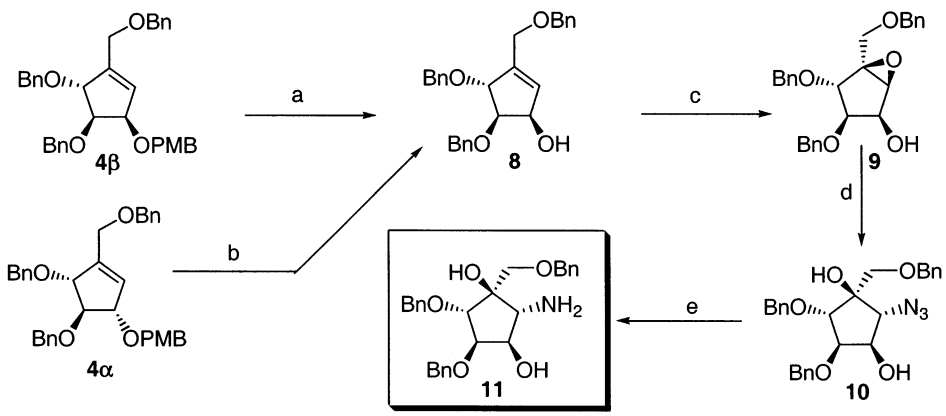




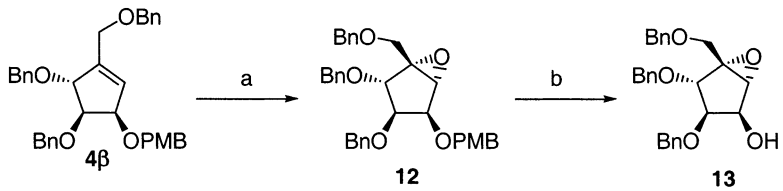
The key aminocyclopentitol **11** can be converted in four steps to trehazolin **3**, via a procedure developed by Storch de Gracia and co-workers.[3] In their procedure the pseudo anomeric centre C-4 was inverted using triflic anhydride in the presence of pyridine at low temperature to give the corresponding aminooxazoline,



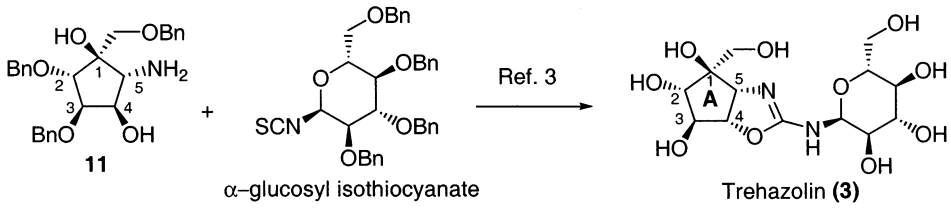
Scheme 1.



Scheme 2. (a) DDQ, CH_2Cl_2, H_2O, 84%; (b) (i) DDQ, CH_2Cl_2, H_2O, 84%, (ii) PPh_3, DEAD, C_6H_5COOH, NaOMe, 95%; (c) *m*CPBA, CH_2Cl_2, 89%; (d) NaN_3, DMF, 97%; (e) PPh_3, THF, 98%.



Scheme 3. (a) *m*CPBA, CH_2Cl_2, 73%; (b) DDQ, CH_2Cl_2, 79%.



Scheme 4.

which was then subjected to hydrogenolysis to afford trehazolin **3** (Scheme 4).

Of note, the α-allylic alcohol **4α** is the right candidate for the direct synthesis of trehazolamine, however, all attempts at diastereoselective epoxidation failed, and an inseparable mixture of epoxides were obtained.

Overall this is the first use of the RCM in the construction of trehazoline intermediates. This method represents a simple and direct preparation of the aminocyclopentitol core. The synthesis involved nine steps with an overall yield of 32%. The strategy allows for the stereocontrolled preparation of a series of diverse analogs of trehazaloamine.

Acknowledgements

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10. Selected spectroscopic data for compounds are as follows. Epoxide **9**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.86 (d, $J=10.8$ Hz, O-H), 3.43 (d, $J=11.6$ Hz, CH_2-OBn), 3.54 (s, H_5), 3.74 (d, $J=7.3$ Hz, H_3), 4.04 (s, H_2), 4.20 (d, $J=11.6$ Hz, CH_2-OBn), 4.28 (ABq, $J=11.4$ Hz, $\Delta\delta=0.07$ ppm, 2H), 4.44 (dd, $J=7.3$, 10.8 Hz, H_4), 4.47 (d, $J=13.5$ Hz, 2H), 4.48 (ABq, $J=12.0$ Hz, $\Delta\delta=0.17$ ppm, 2H), 7.28 (m, 15H). ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 62.3, 64.8, 66.7, 71.7, 72.6, 73.2, 73.3, 79.1, 81.0, 127.8–128.7 (several signals), 137.3, 137.5, 138.0. MS (ES) m/z (M+ Na^+), 455, (M+NH_4^+), 450 (base peak). Epoxide **13**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.56 (bs, O-H), 3.58 (d, $J=11.2$ Hz, CH_2-OBn), 3.59 (s, H_5), 3.84 (dd, $J=5.2$, 6.0 Hz, H_3), 3.94 (d, $J=11.2$ Hz, CH_2-OBn), 4.20 (d, $J=5.2$ Hz, H_4), 4.28 (d, $J=6.0$ Hz, H_2), 4.55 (ABq, $J=11.8$ Hz, $\Delta\delta=0.08$ ppm, 2H), 4.56 (s, 2H), 4.7 (ABq, $J=11.8$ Hz, $\Delta\delta=0.03$ ppm, 2H). ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 60.2, 64.3, 66.8, 70.0, 72.6, 73.1, 73.2, 81.8, 82.5, 127.8–128.7 (several signals), 137.2, 137.7, 138.2. MS (ES) m/z (M+Na^+), 455, (M+NH_4^+), 450 (base peak). Aminocyclopentitol **11**: ^{1}H NMR (C_6D_6, 270 MHz) δ 3.17 (d, $J=6.0$ Hz, H_5), 3.65 (ABq, $J=9.4$ Hz, $\Delta\delta=0.2$ ppm, 2H, CH_2-OBn), 3.93 (dd, $J=6.0$, 7.0 Hz, H_4), 4.07 (dd, $J=$ 6.0, 7.0 Hz, H_3), 4.15 (d, $J=6.0$ Hz, H_2), 4.21 (s, 2H), 4.45 (ABq, $J=11.6$ Hz, $\Delta\delta=0.06$ ppm, 2H), 4.70 (ABq, $J=11.9$ Hz, $\Delta\delta=0.14$ ppm, 2H), 7.31 (m, 15H). ^{13}C NMR ($CDCl_3$, 67.5 MHz). δ 66.0, 69.2, 72.9 (two signals), 73.9, 75.3, 79.8, 81.4, 89.0, 127.8–128.6 (several signals), 137.6, 137.8, 138.3. MS (ES) m/z (M+H^+), 450 (base peak), 391, 279.