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An Enantiospecific Total Synthesis of Allosamizoline

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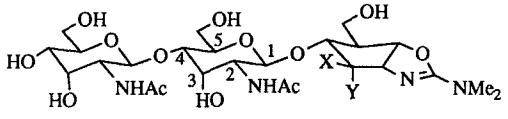
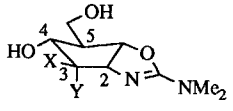
Abstract: An enantiospecific total synthesis of allosamizoline has been accomplished in a short stereoselective sequence starting from glucosamine.

The importance of chitin as a structural component in both fungal cell walls and insect exoskeleton means that chemical agents able to interfere with either its biosynthesis or degradation might be valuable as fungicides or insecticides. In 1986 Sakuda and co-workers reported the isolation of a novel compound from mycelial extracts of *Streptomyces* sp. 1713, named allosamidin, and originally formulated as (**1**), which shows potent chitinase inhibitory activity.[1] The paucity of the supply of allosamidin from natural sources, along with the novel structure of the compound, which incorporates a synthetically challenging aminocyclitol (**2**), encouraged us to devise a synthesis of this target.



(1) X = H, Y = OH
(3) X = OH, Y = H



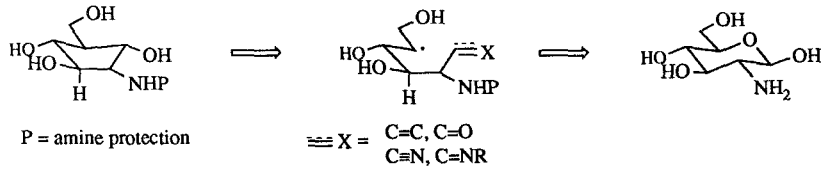
(2) X = H, Y = OH
(4) X = OH, Y = H

During the course of our studies the structure of allosamidin was revised to (**3**) (and hence (**2**) to (**4**)) but, as will be seen below, our synthetic design is flexible enough to allow the synthesis of either diastereoisomer.[2] Herein we describe our synthetic efforts in this area which have resulted in a concise enantiospecific route to the aminocyclitol (**4**), called allosamizoline.[3]

The originally proposed structure (**1**) consists of a disaccharide, made up of two allosamine units, β-linked to the aminocyclitol (**2**). Our synthetic analysis began with the observation that the configurations at the four contiguous chiral centres, C-2 to C-5, in allosamine bear an obvious relationship to those at the corresponding centres in the aminocyclitol. Thus a method which allowed the linking of the anomeric carbon of allosamine to C-5, with retention of configuration at the latter centre, would enable the conversion of the sugar into a cyclitol ideal for conversion through to (**2**). With the recognition that the configuration at C-3 of the aminocyclitol[4] is actually β as in (**4**), this analysis looks even more appealing since the starting sugar required is simply glucosamine.

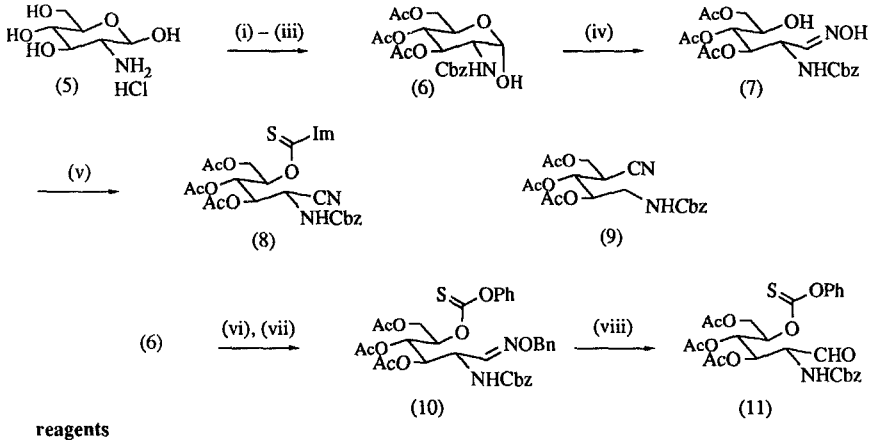
Our choice of a radical approach to the problem of the carbohydrate to carbocycle conversion was made bearing in mind the unique suitability of carbon-centred radicals for carbon–carbon bond formation in situations where carbanion chemistry fails due to β-elimination.[5] Significant contributions have recently been made in this area, most notably by Rajanbabu, further convincing us of the viability of this approach.[6] We were also very attracted to the possibility of using an aldehyde as the radical acceptor in the key cyclisation, as

described by Fraser-Reid,[7] since this appeared to offer the most attractive way of establishing the desired secondary alcohol at C-1, Scheme 1.



Scheme 1

Our synthesis starts with glucosamine hydrochloride (**5**), which was converted by standard procedures to the *N*-Cbz tri-*O*-acetyl sugar (**6**) in 69% overall yield.[8] With this material available in quantity the first real problem was to trap the sugar in an open-chain form suitable for the establishment of the radical generating group at C-5 and some type of acceptor at C-1. Treatment of (**6**) with $NH_2OH{\cdot}HCl$ gave an open- chain oxime (**7**) which, when treated with thiocarbonyldiimidazole (TCDI), gave the nitrile (**8**). Efforts to cyclise this compound under standard radical conditions were unrewarding, spectroscopic evidence pointing to the formation of transposed nitrile (**9**) by a process described previously by Beckwith, Scheme 2.[9]



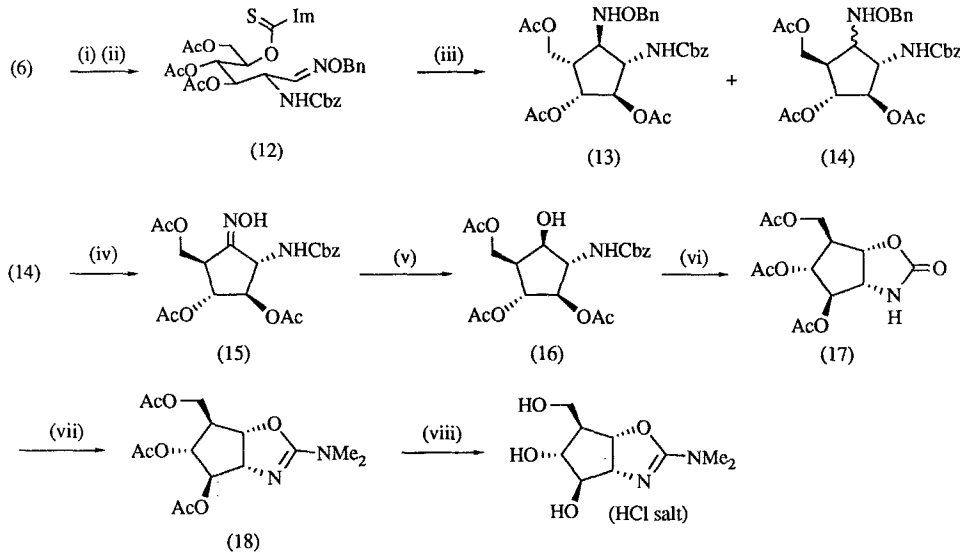
reagents

(i) CbzCl, $NaHCO_3$, H_2O (96%)
(ii) Ac_2O, Et_3N, DMAP, THF (82%)
(iii) $(NH_4)_2CO_3$, MeOH, THF (88%)
(iv) $NH_2OH{\cdot}$ HCl, py, MeOH (74%)
(v) TCDI, CH_2Cl_2 (58%)
(vi) $NH_2OBn{\cdot}$ HCl, py, CH_2Cl_2 (88%)
(vii) PhO(Cl)C=S, py, CH_2Cl_2 (78%)
(viii) HCHO, H_2O, THF, CSA (74%)

Scheme 2

Alternatively, reaction of (**6**) with the *O*-benzyl ether of hydroxylamine, followed by derivatisation of the liberated secondary alcohol with PhO(Cl)C=S gave (**10**).[10] Treatment of this compound with dilute acid in the presence of aqueous formaldehyde then gave aldehyde (**11**). It was hoped that this compound could be cyclised to give the desired cyclopentanol as described by Fraser-Reid; however, again we found that under a variety of conditions we were unable to effect this conversion. The failure of the two attempted cyclisations described above presumably reflects the ability of the intermediate cyclised oxygen- or nitrogen-centred radicals to undergo cleavage to give a radical α to the stabilising NCbz group.

We next focused our attention on a report by Bartlett and co-workers describing successful cyclisations of radicals onto oxime ethers.[11] We were delighted to find that treatment of thiocarbonylimidazolide (**12**) with Bu_3SnH and AIBN under reflux in benzene resulted in clean conversion to a mixture of diastereomeric products (**13**) and (**14**) Scheme 3.



reagents

(i) $NH_2OBn \cdot HCl$, py, CH_2Cl_2 (88%)
(ii) $Im_2C{=}S$, benzene (82%)
(iii) Bu_3SnH, AIBN, benzene (**13**) (12%) and (**14**) (54%)
(iv) MCPBA, Na_2CO_3, EtOAc (79%)
(v) O_3, CH_2Cl_2, -40°C; MeOH, $NaBH_4$, -40°C to RT
(vi) $SOCl_2$ (82%)
(vii) Et_3OBF_4, CH_2Cl_2; Me_2NH, CH_2Cl_2 (80%)
(viii) NaOMe, MeOH; HCl (98%)

Scheme 3

The configuration shown for the minor isomer (**13**) is based on the previous results of Bartlett. The configuration of the major product (**14**), obtained as a mixture of epimers at C-1, was expected to be as shown, and was proven by subsequent conversion of the mixture of to allosamizoline.

The conversion of the benzyloxyamino group in (**14**) to the desired secondary alcohol proved to be a major stumbling block, and we were surprised to find so few methods available for this transformation in the literature. The best method tried involves firstly, oxidation of the mixture of benzyloxyamines with MCPBA to give oxime (**15**) in 79% yield,[12] followed by reaction with ozone and direct reductive workup.[13] The overall yield for the conversion of (**15**) to the alcohol (**16**) is only in the range 20–40%, but the shortness of the sequence, combined with the good to excellent yields obtained in all the other steps allowed us to continue the synthesis on a reasonable scale. The configuration at C-1 in (**16**) was assigned on the basis of subsequent conversions. Thus reaction with thionyl chloride gave oxazolidinone (**17**) (a reaction which should proceed with inversion at C-1), which, on treatment with Et_3OBF_4 in CH_2Cl_2 followed by Me_2NH, gave the desired allosamizoline triacetate (**18**) in 80% overall. Subsequent saponification of this compound with NaOMe then gave allosamizoline hydrochloride $[\alpha]_D^{23}$ -21.7 (c 0.9 in H_2O) (lit.[1] $[\alpha]_D$ -22.2 (c 0.5 in H_2O), having spectral data in accord with that reported previously.[14]

The synthesis described above further underlines the usefulness of radical cyclisations in natural product synthesis. The route described here should be useful for accessing allosamizoline as well as a range of related compounds simply by choice of the appropriate starting sugar. Studies aimed at improving or bypassing the poor yielding step highlighted above, as well as coupling of allosamizoline with sugar partners, are underway.

Acknowledgements

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14) Selected data for compounds in our synthetic sequence: (**12**) $[\alpha]_D^{22}$ +38.3 (c 0.23 in $CHCl_3$), δ_C (22.5 MHz; $CDCl_3$) 20.9 (q, 3 x $OCOCH_3$), 50.9 (d), 60.9 (t), 67.0 (t), 68.2 (d), 69.6 (d), 76.2 (t), 78.1 (d), 117.8 (d), 127.9 (d), 128.0 (d), 128.2 (d), 130.9 (d), 136.0 (s), 136.9 (s), 145.4 (d), 155.5 (s), 169.3 (s), 169.4 (s), 170.0 (s) and 182.8 (s), *m/z*(FAB) 655 (M^++H, 5%); (**14**) mixture of epimers at C-1, ν_{max} (film) 3351 and 1740 cm^{-1}, *m/z* 529 (M^++H, 11%); (**15**) $[\alpha]_D^{30}$ -3.5 (c 0.2 in EtOH). Found: C, 55.2; H, 5.5; N, 6.2. $C_{20}H_{24}N_2O_9$ requires C, 55.0; H, 5.5; N, 6.4%); (**16**) $[\alpha]_D^{22}$ +31 (c 0.1 in $CHCl_3$), ν_{max} (KBr) 3429, 3340, 1728, 1694, 1252 and 1038cm^{-1}, δ_C (22.5 MHz; $CDCl_3$) 20.8 (q), 44.6 (d), 61.2 (t), 63.4 (d), 67.4 (t), 74.0 (d), 75.9 (d), 78.9 (d), 128.2 (d), 128.3 (d), 128.6 (d), 135.9 (s), 157.4 (s), 170.1 (s), 171.1 (s) and 171.5 (s); (**17**) $[\alpha]_D^{26}$ -24.1 (c 0.46 in $CHCl_3$) (lit.[3] -25), δ_H (250 MHz; $CDCl_3$) 2.11 (3H, s), 2.12 (3H, s), 2.13 (3H, s), 2.63 (1H, m, H-5), 3.95 (1H, dd, *J* 9.3 and 4.3 Hz, H-2), 4.21 (2H, d, *J* 5.2 Hz, CH_2OAc), 4.76 (1H, dd, *J* 7.5 and 9.6 Hz, H-3), 4.87 (1H, dd, *J* 9.3 and 6.3 Hz, H 1), 5.25 (1H, dd, *J* 9.6 and 7.5 Hz, H-4), and 5.82 (1H, s, NH), Found: M^++H, 316.1041. $C_{13}H_{18}NO_8$ requires M, 316.1033; (**18**) $[\alpha]_D^{26}$+28.8 (c 0.2 in $CHCl_3$), Found: M^+-AcOH, 282.1209. $C_{13}H_{18}N_2O_5$ requires M, 282.1216. Allosamizoline hydrochloride δ_H (250MHz; D_2O, 298K) 2.42 (1H, m), 3.08 (3H, s), 3.10 (3H, s), 3.73 (1H, dd, *J* 11.6 and 7.2 Hz), 3.83 (1H, m), 3.90 (1H, dd, *J* 11.6 and 4.5Hz), 4.08 (1H, dd, *J* 6.9 and 4.9 Hz), 4.33 (1H, dd, *J* 9.1 and 4.9 Hz) and 5.36 (1H, dd, *J* 9.1 and 5.3 Hz).

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