Synthesis of Allosamidin

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Allosamidin, a novel chitinase inhibitor has been synthesized by a convergent approach using a regioselective glycosidation of a racemic allosamizoline derivative, with a disaccharide trichloroacetamidate.

Allosamidin, isolated from the mycelia of *Streptomyces sp.* No. 1713 by Sakuda *et al.*[1] and from fermentation broths of culture A82516 (*Streptomyces sp.*) by Somers *et al.*,[2] is a strong inhibitor of chitinases both of insect and fungal origin.[1–5] Allosamidin is a pseudotrisaccharide possessing the novel structure **1** (Fig. 1).[6–8] We report its synthesis.

Solvolysis[9] of the mesylate **2**,† obtained from allyl 2-acetamido-4,6-*O*-benzylidine-2-deoxy-α-D-glucopyranoside[10] gave the *N*-acetylallosamine derivative **3** {$[\alpha]_D^{25}$ +84.5° (*c* 1.2, $CHCl_3$), m.p. 197–198 °C} (Scheme 1). The acetamide **3** was hydrolysed to the amine **4**‡ (m.p. 115–117 °C) which was treated with phthalic anhydride to yield the phthalamide **5** {$[\alpha]_D^{25}$ +82.3° (*c* 1, MeOH), m.p. 158–160 °C}. Benzylation of **5** afforded two main products, the phthalimide **7** {$[\alpha]_D^{25}$ +53.3° (*c* 1.3, $CHCl_3$), IR: 1715 cm^{-1}} and the ester **6** {$[\alpha]_D^{25}$ +20.4° (*c* 1.2, $CHCl_3$), m.p. 81–84 °C}, which was converted into **7** by hydrolysis and treatment with Ac_2O and pyridine. This sequence yielded **7** in an overall yield of 71% from **5**. In contrast to this, benzylation of **8**, which was obtained in less than 50% yield from **5**, proved very difficult. Deallylation[11] of **7** afforded the β-D-hemiacetal **10** {$[\alpha]_D^{25}$ −144° (*c* 1.1, $CHCl_3$), m.p. 149–150 °C, ^1H NMR ($CDCl_3$): $J_{1,2}$ 8.6 Hz} which upon

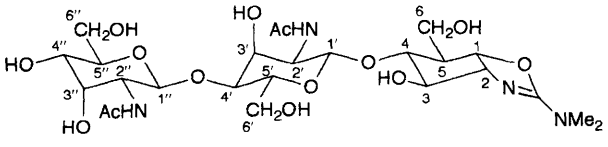
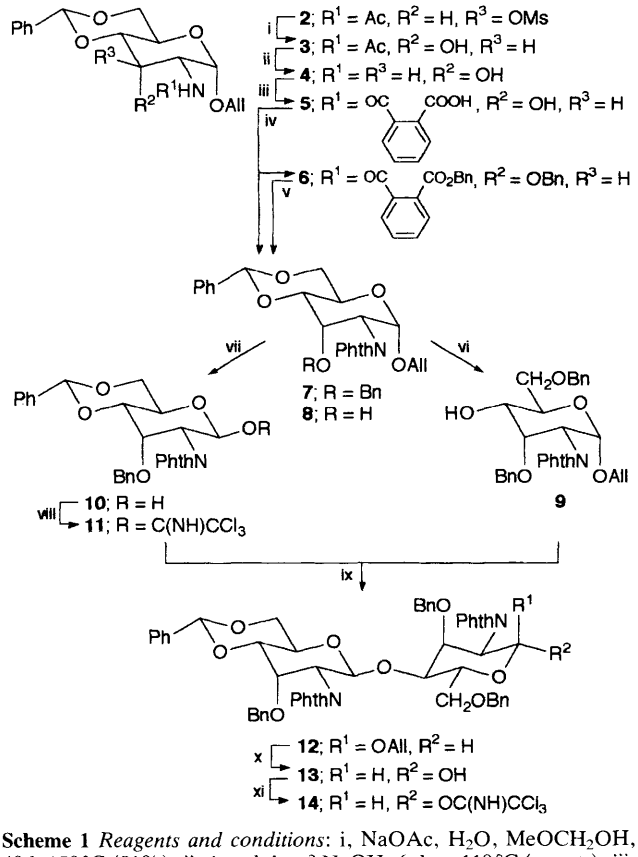


Fig. 1 Structure of allosamidin (**1**)

† The structures of compounds **2–14**, have been confirmed by elemental analysis and spectroscopy (^1H, ^{13}C NMR, IR, MS, $[\alpha]_D$). The structures of compounds **15–22**, have been confirmed by (^1H, ^{13}C NMR, IR, MS, $[\alpha]_D$).

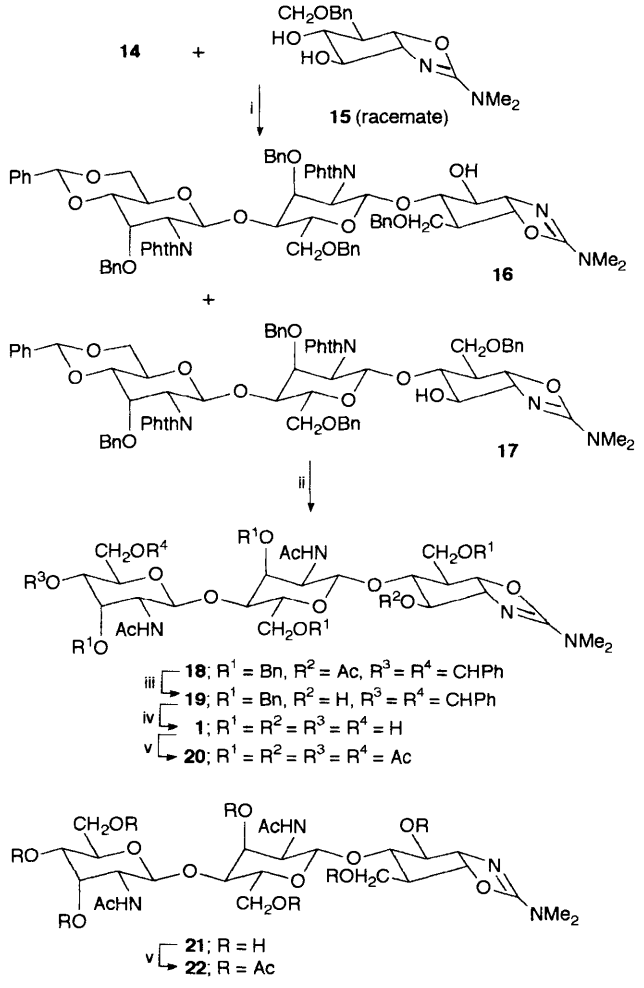
‡ We thank Dr B. Bernet for detailed procedures for the preparation of **2–4** and for a generous supply of **3**.



Scheme 1 *Reagents and conditions*: i, NaOAc, H_2O, $MeOCH_2OH$, 40 h 150 °C (81%); ii, 1 mol dm^{-3} NaOH, 6 days 110 °C (quant.); iii, phthalic anhydride, NEt_3, MeOH, 30 min. r.t. (95%); iv, BnBr, NaH, DMF, 48 h r.t. [**7** (49%) and **6** (30%)]; v, *a*, dioxane/1 mol dm^{-3} NaOH, 5 h r.t.; *b*, pyridine, Ac_2O, 48 h r.t. (75% from **6**); vi, Me_3NBH_3, $AlCl_3$, THF, molecular sieves 4 Å, 14 h r.t. (84%); vii, *a*, 1,5-cyclooctadiene-bis(methyldiphenylphosphine)iridium hexafluorophosphate, H_2, THF, 4 h r.t.; *b*, acetone/H_2O: 9/1, 30 min. r.t. (75% from **7**); viii, CCl_3CN, K_2CO_3, CH_2Cl_2, 8 h r.t. (81%); ix, TMSOTf (1.2 eq.), CH_2Cl_2, molecular sieves 4 Å, 10 min. 0 °C (80%); x, same as vii (73%); xi, CCl_3CN, K_2CO_3, CH_2Cl_2, 12 h r.t. (86%)

treatment with Cl_3CCN and K_2CO_3[12] gave the glycosyl donor **11** {$[\alpha]_D^{25}$ −106° (*c* 1, $CHCl_3$), m.p. 164–166 °C, IR: 3340 and 1680 cm^{-1}}. The glycosyl acceptor **9** {$[\alpha]_D^{25}$ +71.5° (*c* 0.9, $CHCl_3$), ^1H NMR ($CDCl_3$): change of ddd of H-C(4) to dd after addition of D_2O} was obtained by reductive opening of the benzylidene group of **7** with Me_3NBH_3 and $AlCl_3$.[13] Glycosidation of **9** with the imidate **11** in the presence of TMSOTf afforded the disaccharide **12**§ {$[\alpha]_D^{25}$ −55.7° (*c* 0.5, $CHCl_3$}. The disaccharide **12** was deallylated and transformed into the β-D-imidate **14** [IR: 3340 and 1680 cm^{-1}, ^1H NMR ($CDCl_3$): $J_{1,2}$ 9.1 Hz] essentially as described for the analogous transformation of **7** into **11**.

Glycosidation of the racemic partially protected allosamizoline **15**[14] with the imidate **14** promoted by TMSOTf gave a mixture of pseudotrisaccharides in an overall yield of 61% (Scheme 2). The regioselectivity of this glycosidation was as expected, favouring glycosidation of the hydroxy group further removed from the electron-withdrawing dihydro-oxazole moiety. Thus, the diastereoisomeric pseudotrisaccharides **16**§ {$[\alpha]_D^{25}$ −73.8° (*c* 0.8, $CHCl_3$)} and **17**§ {$[\alpha]_D^{25}$ = −92° (*c* 0.6, $CHCl_3$)} were isolated in 24 and 27%, respectively. In addition, 5% of both regioisomeric pseudotrisaccharides and only traces of the pseudopentasaccharides were obtained. The pseudotrisaccharide **17** was dephthaloylated under mild conditions ($MeNH_2$, EtOH, r.t.)[15] to avoid concomitant opening of the dihydro-oxazole ring. The reaction product was acetylated to the pseudotrisaccharide **18** {$[\alpha]_D^{25}$ −51° (*c* 1, $CHCl_3$)}. The low field shift of H-C(3) (δ 5.3) confirmed the regioselectivity of the glycosidation. De-*O*-acetylation of **18** led to the alcohol **19** {$[\alpha]_D^{25}$ = −35° (*c* 0.9, $CHCl_3$)}. Hydrogenolysis of **19** under acidic conditions and chromatography (Sephadex G 10) yielded **1**, which could not be distinguished {^1H and ^{13}C NMR (D_2O with 0.3% CD_3CO_2D), $[\alpha]_D^{22}$ = −22.9° (*c* 0.3, 1 mol dm^{-3} AcOH), $[\alpha]_D^{25}$ = −21.4° (*c* 0.3, H_2O)} from an authentic sample of allosamidin.¶



Scheme 2 *Reagents and conditions*: i, TMSOTf (1.2 eq.), CH_2Cl_2, molecular sieves 4 Å, 20 min. 0 °C [**17** (27%) and **16** (24%)]; ii, *a*, $MeNH_2$, EtOH, 48 h r.t.; *b*, Ac_2O, pyridine, 12 h r.t. (70%); iii, MeONa, MeOH, 14 h r.t. (96%); iv, H_2 7 bars, Pd/C 10%, MeOH/AcOH: 9/1 (95%); v, Ac_2O, pyridine, DMAP, 12 h r.t. (97%)

The diastereoisomer **16** was similarly deprotected to the pseudotrisaccharide **21** {$[\alpha]_D^{25}$ −12.3° (*c* 0.26, H_2O)} in an overall yield of 65%. The spectroscopic data and the specific rotation of **21** were clearly different from those of **1**. In addition, samples of authentic and of synthetic **1** were peracetylated (Ac_2O, pyridine and DMAP) to yield two identical samples of **20**§ {$[\alpha]_D^{25}$ −40° (*c* 0.2, $CHCl_3$)} while similar peracetylation of **21** gave **22**§ {$[\alpha]_D^{25}$ −55° (*c* 0.1, $CHCl_3$)} clearly different from **20**.

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§ *Selected spectroscopic data* [400 M Hz, ($CDCl_3$)]: **12**: δ 6.27 [d, *J* 8.5 Hz, H-C[(1′)]; 5.47 [d, *J* 3.7 Hz, H-C(1)]; 4.94 [t, *J* 2.7 Hz, H-C(3)]; 4.47 [m, H-C(6′)]; 4.39 [ddd, *J* 10.2, 5.5, 2 Hz, H-C(5)]; 4.28–4.23 [m, H-C(5′), H-C(2)]; 4.21–4.18 [m, H-C(3′) and 1 all. H]; 4.14 [dd, *J* 2.9, 8.5 Hz, H-C(2′)]; 4.09 [dd, *J* 2.9, 8.5 Hz, H-C(4)]; 3.84 [m, H-C(4′), H-C(6)]; 3.64 [dd, *J* 5.5, 10.7 Hz, H-C(6)]; 3.52 [dd, *J* 2, 10.7 Hz, H-C(6)].

16: δ 6.25 [d, *J* 8.5 Hz, H-C(1″)]; 5.99 [d, *J* 8.7 Hz, H-C(1′)]; 4.66 [dd, *J* 6, 9.2 Hz, H-C(1)]; 4.50–4.43 [m, 3 CH_2Ph, H-C(6″)]; 4.34 (m, 2 CH_2Ph); 4.28 [dt, *J* 5.6, 10.3 Hz, H-C(5″)]; 4.26 [t, *J* 2.6 Hz, H-C(3′)]; 4.18 [t, *J* 2.6 Hz, H-C(3″)]; 4.12 [dd, *J* 2.7, 8.5 Hz, H-C(2″)]; 4.06 [dd, *J* 2.5, 10 Hz, H-C(4′)]; 4.01 [dd, *J* 5.8, 9.2 Hz, H-C(2)]; 4–3.97 [m, H-C(5′)]; 3.94 [dd, *J* 2.7, 8.7 Hz, H-C(2′)]; 3.88 [dd, *J* 7.6, 10.1 Hz, H-C(4)]; 3.84 [m, H-C(4″)]; 3.80 [t, *J* 10.3 Hz, H-C(6″)]; 3.69 [dd, *J* 5.8, 7.5 Hz, H-C(3)]; 3.63 [dd, *J* 3.2, 9.8 Hz, H-C(6)]; 3.53 [dd, *J* 5, 10.6 Hz, H-C(6′)]; 3.48 [dd, *J* 5.6, 9.8 Hz, H-C(6)]; 3.45 [dd, *J* 2, 10.6 Hz, H-C(6′)]; 2.8 {[s, 6H, $N(CH_3)_2$]; 2.13 [m, H-C(5)]}.

17: δ 6.24 [d, *J* 8.6 Hz, H-C(1″)]; 5.95 [d, *J* 8.7 Hz, H-C(1′)]; 4.64 [dd, *J* 6.5, 9.1 Hz, H-C(1)]; 4.29–4.21 [m, H-C(5′), CH_2Ph]; 4.05 [dd, *J* 5.8, 9.1 Hz, H-C(2)]; 3.98 [dd, *J* 2.7, 8.7 Hz, H-C(2′)]; 3.87 [m, with D_2O: dd, *J* 7.4, 5.8 Hz, H-C(3)]; 3.83–3.77 [m, H-C(4′), H-C(4″), H-C(6′)]; 3.69 [dd, *J* 7.4, 10.7, H-C(4)]; 3.41 [t, *J* 9.6 Hz, H-C(6′)]; 3.35 [dd, *J* 3.5, 11.6, H-C(6)]; 3.33 [dd, *J* 2.4, 9.7 Hz, H-C(6′)]; 3.19 [dd, *J* 5.6, 11.6 Hz, H-C(6)]; 2.84 [s, 6H, $N(CH_3)_2$]; 2.08 [m, H-C(5)].

20: δ 6.39 (d, *J* 8.4 Hz, N*H*′Ac); 6.31 (d, *J* 8.2 Hz, N*H*″Ac); 5.64 [t, *J* 2.7 Hz, H-C(3′)]; 5.52 [t, *J* 2.9 Hz, H-C(3″)]; 5.27 [dd, *J* 3.8, 6.6 Hz, H-C(3)]; 4.85 [dd, *J* 2.9, 10.4 Hz, H-C(4″)]; 4.79 [dd, *J* 8.8, 6 Hz, H-C(1)]; 4.74 [d, *J* 7.5 Hz, H-C(1′)]; 4.60 [dd, *J* 3.9, 11.8 Hz, H-C(6′)]; 4.54 [d, *J* 8.6 Hz, H-C(1″)]; 4.4 [dd, *J* 5.4, 11.6 Hz, H-C(6)]; 4.31 [dd, *J* 3.7, 8.8 Hz, H-C(2)]; 4.23–4.18 [m, H-C(6), H-C(2″)]; 4.15–4.11 [m, 2 H-C(6″)]; 4.10–4.02 [m, H-C(2′), H-C(6′)]; 3.97–3.86 [m, H-C(5′), H-C(5″)]; 3.82 [dd, *J* 6.6, 9.4 Hz, H-C(4)]; 3.61 [dd, *J* 2.8, 8.4 Hz, H-C(4′)]; 2.94 [s, 6H, $N(CH_3)_2$]; 2.51 [m, H-C(5)]; 2.18 (s, Ac); 2.16 (s, Ac); 2.12 (s, Ac); 2.11 (s, Ac); 2.10 (s, Ac); 2.08 (s, Ac); 2.07 (s, Ac); 1.97 (s, Ac); 1.94 (s, Ac).

22: 6.45 (d, *J* 7 Hz, N*H*′Ac): 6.29 (d, *J* 8.6 Hz, N*H*″Ac); 5.09 [dd, *J* 4.1, 6 Hz, H-C(3)]; 4.74 [dd, *J* 8.9, 6.4 Hz, H-C(1)]; 4.55 [d, *J* 8.4 Hz, H-C(1″)]; 4.53 [d, *J* 7.5 Hz, H-C(1′)]; 4.31 [dd, *J* 3.8, 8.9 Hz, H-C(2)]; 4.29 [dd, *J* 4, 11.4 Hz, H-C(6)]; 4.21 [dd, *J* 5.6, 11.4 Hz, H-C(6)]; 3.54 [dd, *J* 2.8, 9.6 Hz, H-C(4′)]; 2.90 [s, 6H, $N(CH_3)_2$]; 2.44 [m, H-C(5)]; 2.17 (s, Ac); 2.16 (s, Ac); 2.13 (s, Ac); 2.11 (s, Ac); 2.09 (s, Ac); 2.05 (s, Ac); 1.96 (s, 2 Ac); 1.95 (s, Ac).

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