

which must be considerable since the iron system will even abstract dinitrogen (although more slowly and less cleanly) from $[W-(N_2)_2(\text{depe})_2]$ (depe = 1,2-bis(diethylphosphino)ethane), to which it is particularly strongly bound.^{10,11}

The reaction rate exhibits first-order dependence on the concentration of both iron and molybdenum complexes, but currently we cannot speculate about the mechanism of the H_2/N_2 exchange.¹²

These observations suggest an alternative interpretation of the functions of iron, molybdenum, and vanadium in the nitrogenases. Iron is believed to be involved in electron transfer, ultimately to the active site, but it may also mediate the reduction of dinitrogen under mild conditions analogous to those we have used here.¹³ Molybdenum and vanadium (neither of which has been observed to change oxidation state when the appropriate proteins are reduced)¹⁴ could have the function of trapping N_2 and passing it to iron. Indeed, the third (iron?) nitrogenase could be the ancestral nitrogenase, the vanadium and molybdenum nitrogenases being more efficient, younger variants. Structural¹⁵ and abundance data¹⁶ are at least consistent with this interpretation.

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Total Synthesis of Allosamidin: An Application of the Sulfonamidoglycosylation of Glycols

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Chitin¹ (1) is a major structural constituent of the exoskeleton of arthropods² and fungal cell walls.³ Molecules that are able to inhibit chitin synthases and chitinases might function as insecticides⁴ or fungicides⁵ since a proper balance is necessary to control the morphology of insects⁶ and fungi.⁷ Interestingly, chitinases appear to operate defensively against fungal pathogens in plants⁸ and may aid digestion in some vertebrates.⁹ Thus,

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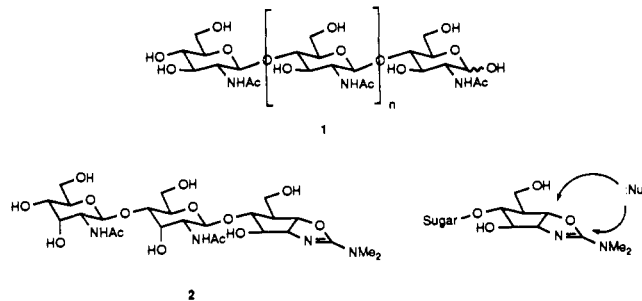
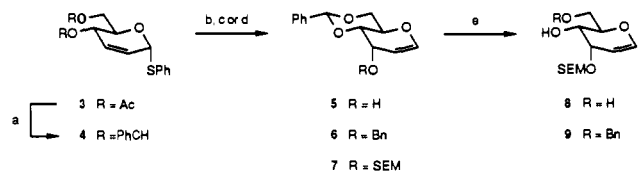


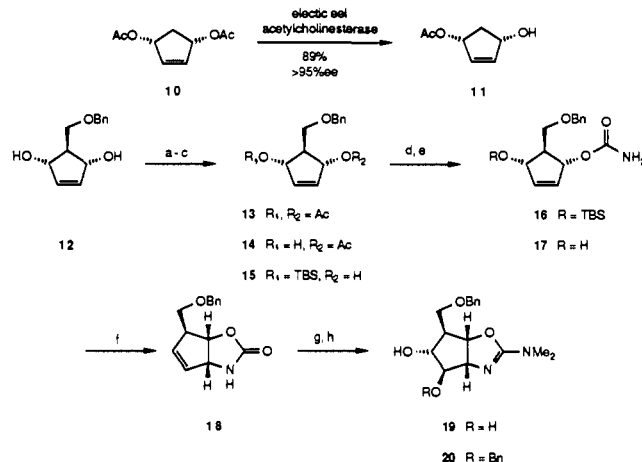
Figure 1.

Scheme I^a



^a (a) NaOMe, MeOH; PhCH(OMe)₂, TsOH, DMF, 71%; (b) 2,2-dimethyldioxirane, CH₂Cl₂, -78 °C; Et₂NH, THF, 96%; (c) NaH, THF; BnBr, Bu₄Ni, 96%; (d) SEMCl, *i*-Pr₂NEt, CH₂Cl₂, 100%; (e) Na, NH₃; Bn₂SnO, MeOH, reflux; CsF, BnBr, DMF, 69% (21% of recovered 8).

Scheme II^a



^a (a) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 89%; (b) electric eel acetylcholinesterase, NaN₃, pH 6.9 phosphate buffer, 95%, >95% ee; (c) TBSCl, imidazole, CH₂Cl₂; NH₃, MeOH, 100%; (d) ClCO₂Ph, pyridine, CH₂Cl₂, 0 °C; NH₃, MeOH, 82%; (e) aqueous HF, CH₃CN, 94%; (f) Et₃N, TFAA, THF, -78 °C → room temperature, 63%; (g) MeOTf, CH₂Cl₂; Me₂NH, 87%; CF₃CO₂H, TFA; TFA, H₂O, 44%; (h) Bu₂SnO, MeOH, reflux; BnBr, CsF, DMF, 46%.

compounds that selectively inhibit the ability of specific organisms to degrade chitin could well be advantageous.

Allosamidin (2), isolated from mycelial extracts of *Streptomyces* sp. 1713, is an encouraging first success in screening for selective chitinase inhibitors.¹⁰ The original structural formulation¹¹ of allosamidin was revised^{12,13} to a chitin "look alike" consisting of 3,3'-*epi*-chitobiose β-linked to a novel aglycon sector termed "allosamidoline", which was recently synthesized in racemic form by Trost.¹⁴ While allosamidin may be a transition-state analogue

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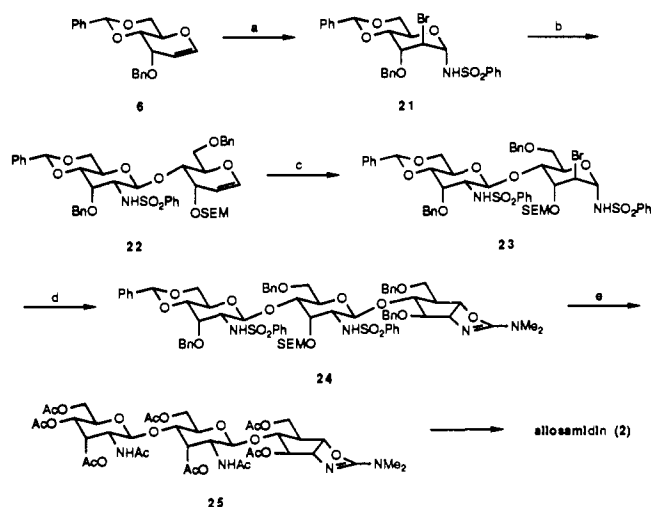
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Scheme III^a

^a(a) Br₂NSO₂Ph, CH₂Cl₂, 0 °C; NH₄I, EtOH, 63%; (b) 9, KHMDS, DMF, -40 °C → room temperature, 81% (95% based on recovered 9); (c) Br₂NSO₂Ph, CH₂Cl₂, 0 °C; NH₄I, EtOH, 57%; (d) 20, KHMDS, -40 °C → room temperature, 30% (79% based on recovered 20); (e) 5% aqueous HCl-MeOH; Na, NH₃; Ac₂O, pyridine, 23%; (f) NH₃, MeOH, 74%.

for the hydrolysis of chitin,¹⁵ we note that in principle the oxazoline linkage in the aglycon may be viewed as a potential electrophilic locus¹⁶ for covalent attachment to the chitin-degrading enzyme (Figure 1).

As a consequence of its novel structure and in response to the difficulties that have been encountered in attempts to obtain adequate amounts of allosamidin for biological investigation, we embarked on a program directed toward its total synthesis. The key features of our effort are (i) expeditious syntheses of axial glycal derivatives 6 and 9 via our recently disclosed [2,3] sigmatropic rearrangement of anomeric phenylsulfinyl pseudoglycals,¹⁷ (ii) use of an enzyme-mediated hydrolysis of prochiral diacetate 13 to provide an enantiospecific route to the properly protected aglycon (20), and (iii) the application of our sulfonamidoglycosylation¹⁸ methodology for the construction of 22 and 24.

Ferrier-type rearrangement¹⁹ of tri-*O*-acetyl-*D*-glucal with thiophenol afforded glycal 3 (Scheme I).^{17,20} The 4,6-diol obtained from the methanolysis of 3 was converted to benzylidene derivative 4 (mp 122.5–123.5 °C). The latter upon oxidation with 2,2-dimethyldioxirane²¹ followed by exposure to diethylamine provided a 96% yield of 4,6-*O*-benzylidene-*D*-allal (5), which was identical with authentic material.²² Benzoylation under standard conditions gave glycal 6 (mp 103–103.5 °C). Alternatively, the axial alcohol of allal derivative 5 was protected as its SEM derivative.²³ Reaction of the latter (7) with sodium in ammonia liberated diol 8, which was directly protected at C₆ via its stannylene derivative²⁴ to give glycal 9.

The action of electric eel acetylcholinesterase on meso diacetate 13, prepared by acetylation of diol 12,²⁵ provided alcohol 14 in >95% enantiomeric excess²⁶ (Scheme II). We note that the

enantiotopic sense of the hydrolysis is formally opposite²⁷ to that which has been observed with the parent diacetate 10, wherein 11 is produced in >95% enantiomeric excess.²⁹ Protection of alcohol 14 as the TBS ether followed by deacetylation with methanolic ammonia afforded 15. Following installation of the carbamate in the usual way, the TBS group of 16 was readily cleaved to provide 17 (mp 114–114.5 °C). Treatment with trifluoroacetic anhydride-triethylamine gave oxazolidinone 18 (mp 87.5–88 °C), an intermediate in the previous synthesis. Following Trost's published route from 12 to 19 via 18,¹⁴ the oxazolidinone was converted to the (dimethylamino)oxazoline, followed by epoxidation of the olefin and subsequent hydration. Diol 19 (mp 139–143 °C), thus obtained, was selectively benzylated via stannylene methodology to provide 20 (mp 119–120 °C).

With building blocks 6, 9, and 20 in hand, we were well positioned to converge on our target (Scheme III). Treatment of 6 with *N,N*-dibromobenzenesulfonamide afforded 21 as previously described.¹⁸ Potassium hexamethyldisilazide (KHMDS) promoted coupling of 21 and 9 gave an 81% yield of 22. At this stage we would attempt to extend the sulfonamidoglycosylation method to an extensively functionalized glycosyl acceptor bearing a particularly hindered secondary alcohol. Bromosulfonamide 23, prepared from 22 (cf. 6 → 21), was coupled with 20 in the presence of KHMDS to produce allosamidin derivative 24 (30%). The SEM³⁰ and benzylidene groups were cleaved by treatment with 5% HCl in methanol, sodium in ammonia reductively deprotected the sulfonamides and benzyl ethers, and the fully deprotected product was peracetylated to provide readily characterizable 24. Finally, cleavage of all the acetyl esters with methanolic ammonia afforded allosamidin (2), identical in all respects with authentic material [¹H NMR, ¹³C NMR, IR, HRMS (FAB), [α]_D -24.0 (*c* = 0.42, 0.1 M AcOH), mp > 224 dec].³¹

The total synthesis described above potentially provides greater access to compounds for evaluation of the relationship between structure and chitinase inhibition than would be available from natural product isolation. From a synthetic standpoint this synthesis demonstrates the value of using glycals, not only as glycosyl donors but also as glycosyl acceptors. This theme is proving to be useful in a variety of glycoside syntheses.^{18,32} Other instances will be disclosed in due course.

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