which must be considerable since the iron system will even abstract dinitrogen (although more slowly and less cleanly) from [W-$(N_2)_2$(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. Structural[15] and abundance data[16] are at least consistent with this interpretation.

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

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Chitin[1] (**1**) is a major structural constituent of the exoskeleton of arthropods[2] and fungal cell walls.[3] Molecules that are able to inhibit chitin synthases and chitinases might function as insecticides[4] or fungicides[5] since a proper balance is necessary to control the morphology of insects[6] and fungi.[7] Interestingly, chitinases appear to operate defensively against fungal pathogens in plants[8] and may aid digestion in some vertebrates.[9] Thus, 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 formulation[11] 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 "allosamizoline", which was recently synthesized in racemic form by Trost.[14] While allosamidin may be a transition-state analogue

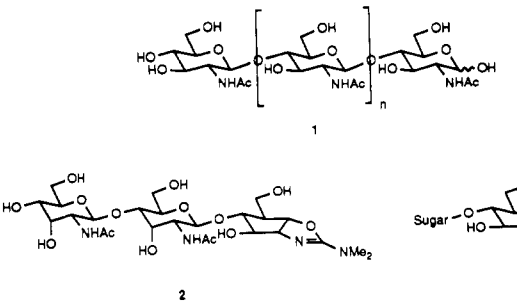
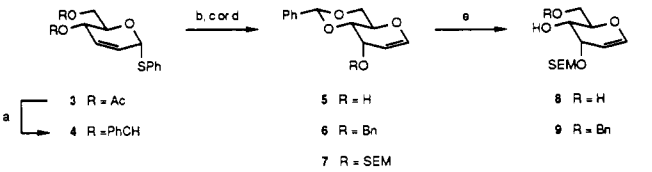


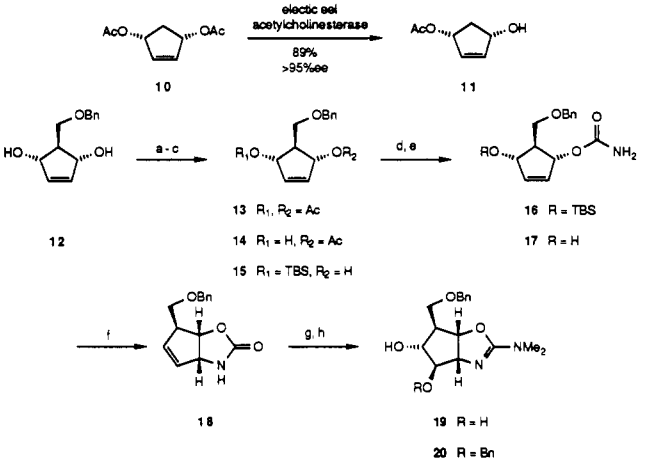
Figure 1

Scheme I[a]



[a] (a) NaOMe, MeOH; $PhCH(OMe)_2$, TsOH, DMF, 71%; (b) 2,2-dimethyldioxirane, CH_2Cl_2, −78 °C; Et_2NH, THF, 96%; (c) NaH, THF; BnBr, Bu_4NI, 96%; (d) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, 100%; (e) Na, NH_3; Bn_2SnO, MeOH, reflux; CsF, BnBr, DMF, 69% (21% of recovered **8**).

Scheme II[a]



[a] (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 89%; (b) electric eel acetylcholinesterase, NaN_3, pH 6.9 phosphate buffer, 95%, >95% ee; (c) TBSCl, imidazole, CH_2Cl_2; NH_3, MeOH, 100%; (d) $ClCO_2Ph$, pyridine, CH_2Cl_2, 0 °C; NH_3, MeOH, 82%; (e) aqueous HF, CH_3CN, 94%; (f) Et_3N, TFAA, THF, −78 °C → room temperature, 63%; (g) MeOTf, CH_2Cl_2; Me_2NH, 87%; CF_3CO_3H, TFA; TFA, H_2O, 44%; (h) Bu_2SnO, MeOH, reflux; BnBr, CsF, DMF, 46%.

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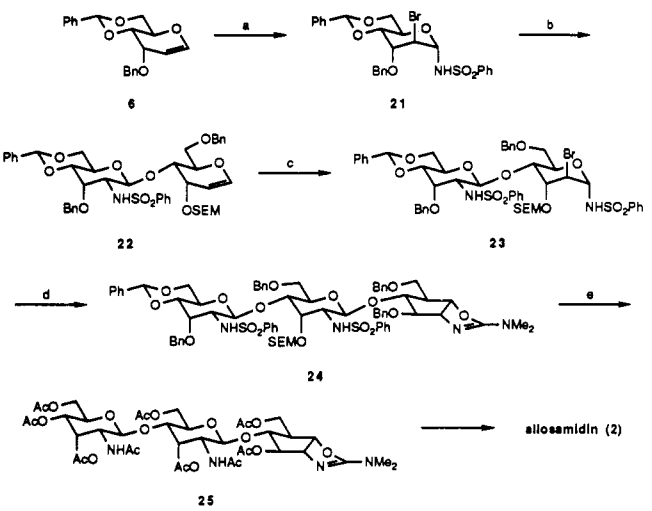
Scheme III[a]



[a] (a) Br_2NSO_2Ph, CH_2Cl_2, 0 °C; NH_4I, EtOH, 63%; (b) **9**, KHMDS, DMF, −40 °C → room temperature, 81% (95% based on recovered **9**); (c) Br_2NSO_2Ph, CH_2Cl_2, 0 °C; NH_4I, EtOH, 57%; (d) **20**, KHMDS, −40 °C → room temperature, 30% (79% based on recovered **20**); (e) 5% aqueous HCl–MeOH; Na, NH_3; Ac_2O, pyridine, 23%; (f) NH_3, 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 locus[16] 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 sulfonamidoglycosylation[18] methodology for the construction of **22** and **24**.

Ferrier-type rearrangement[19] of tri-*O*-aceyl-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-dimethyldioxirane[21] followed by exposure to diethylamine provided a 96% yield of 4,6-*O*-benzylidene-D-allal (**5**), which was identical with authentic material.[22] Benzylation 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 C_6 via its stannylene derivative[24] 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 excess[26] (Scheme II). We note that the enantiotopic sense of the hydrolysis is formally opposite[27] 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 SEM[30] and benzylidine 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 [^{1}H NMR, ^{13}C NMR, IR, HRMS (FAB), $[\alpha]_D$ −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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