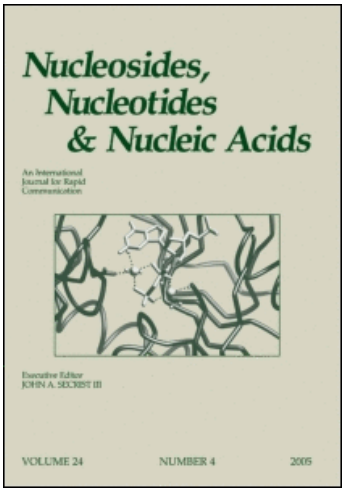

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Stereoselective Synthesis of 6-Amln0-5,6dideoxy-D-ribo-heptafuranouronates with the Aid of Glycine. Chiral Templates

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STEREOSELECTIVE SYNTHESIS OF 6-AMINO-5,6-DIDEOXY-D-*RIBO*-HEPTAFURANOURONATES WITH THE AID OF GLYCINE CHIRAL TEMPLATES.

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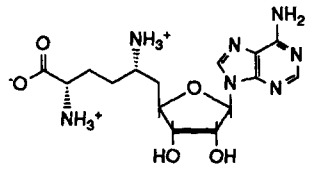
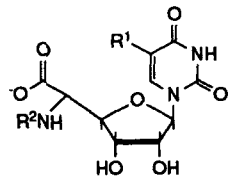
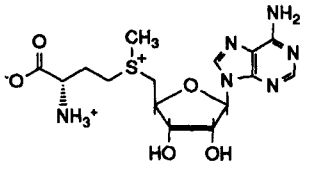
Our current interest in developing peptido-nucleosides, e.g. sinefungin derivatives as potential inhibitors of *Leishmania* parasite growth, [1] and homologues of polyoxins and neopolyoxins as prototypes of "low charge" nucleotide analogues, has prompted us to investigate synthetic methods for the enantioselective preparation of 6-amino-5,6-dideoxy-D-*ribo*-heptafuranouronates as key intermediates. Sinefungin, a nucleoside antibiotic, is a potent inhibitor of S-adenosylmethionine (SAM)-dependent methylases, and is very similar structurally to SAM .[1] Polyoxins, uracil nucleosides containing a peptide moiety, mimic anionic N-acetylglucosyl-uridine 5'-diphosphate and are powerful competitive inhibitors of chitin UDP-N-acetylglucosoamine-transferase.[2]



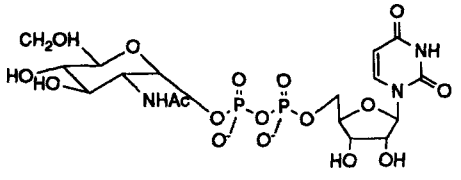
Sinefungin



Polyoxin

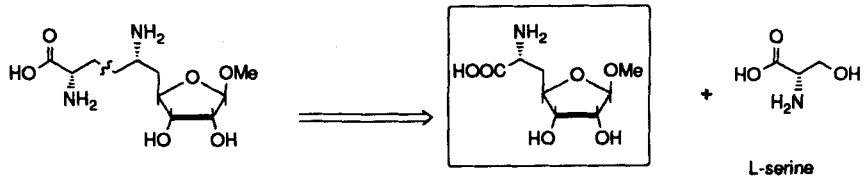


S-Adenosyl-L-methionine (SAM)



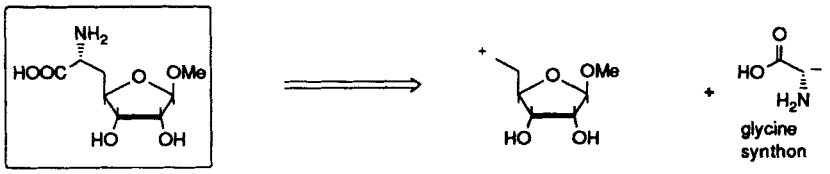
N-acetyl-glucosaminyl-UDP

Synthesis of the unusual carbohydrate moiety of sinefungin requires construction of a four carbon chain at the C-5 position of the ribofuranose, placement of the amino group at the C-6 in the S configuration, and the incorporation of an L-α-amino acid at the end of the side chain.[3] Our strategy for the stereoselective synthesis is based upon the use of two enantiomerically correct fragments obtained by a dissection of the sinefungin sugar component: 6-amino-5,6-dideoxy-D-*ribo*-heptafuranouronate containing the 6-amino group in the R configuration, and L-serine.

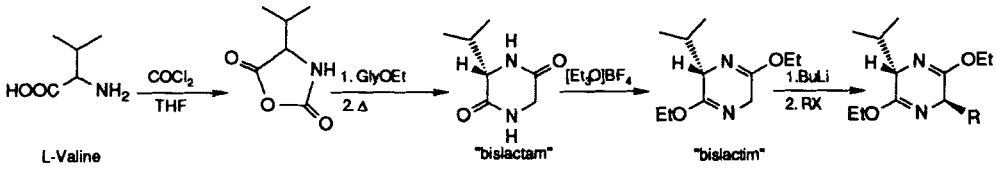


L-serine

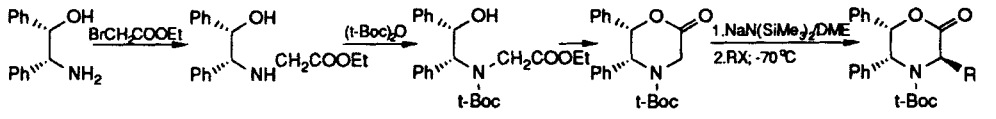
This communication presents our investigations to construct the stereochemically correct sugar intermediate from appropriate ribofuranosyl and glycine synthons.



Diastereoselective alkylation of chiral glycine templates, widely employed in asymmetric syntheses of amino acids, with methyl 5-substituted 5-deoxy-2,3-O-isopropylidene-β-D-ribofuranose appeared to be a promissing approach. Schollkopf and collaborators have outlined a versatile method of a highly stereoselective synthesis of amino acids based on the lithiation and alkylation of the bislactim ether of cyclo-(L-Val-Gly).[4] The lithium compound reacts with various electrophiles with better than 95% ee. The electrophile enters *trans* to the large isopropyl group on C-6 which leads to the R configuration at C-3. Acidic hydrolysis yields the (R)-amino acid methyl ester. The only serious limitation of this method for synthesis of our target sugar intermediates is the acidic removal of the chiral auxiliary.



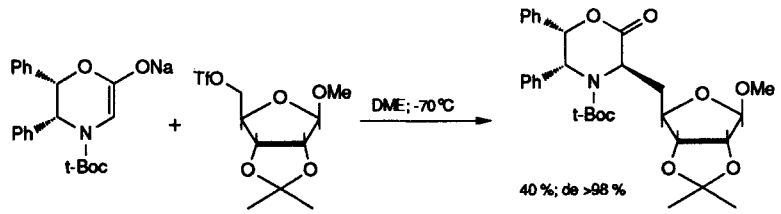
Williams and Im have shown that optically active 4-(*tert*-butoxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-ones can be similarly adapted to synthesis of optically active amino acids.[5] The required enolate anions, derived from these oxazinones by treatment with the lithium or sodium salts of hexamethyldisilazane, can be alkylated with a high degree of diastereoselectivity (>99% de) yielding crystalline *anti*-lactones in good yields. The adducts then can be directly converted into corresponding N-t-Boc protected amino acids by lithium in liquid ammonia.[6]



Results

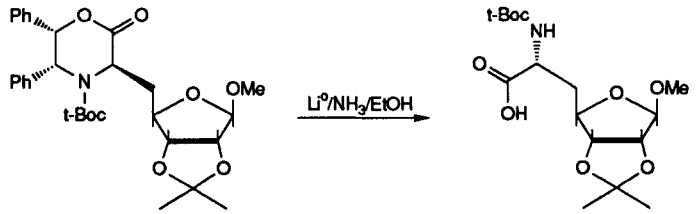
The latter methodology was employed in our laboratory to synthesize 6-amino-5,6-dideoxy-D-*ribo*-heptafuranouronates mainly to achieve of the non-acidic release of the corresponding amino acid moiety from the chiral auxiliary. Our attempt to use methyl 5-iodo-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranose as the alkylating agent has failed. The iodo derivative is completely inert in the reaction conditions (-70°C; DME). The methyl 5-methanesulfonyl-2,3-O-isopropylidene-β-D-ribofuranose is also not reactive enough to form any adduct with the sodium enolate. After a prolonged time (8 h) only a small amount of a new sugar product was formed from latter reagent, presumably due to the elimination of methanesulfonic acid (not isolated) from methyl 5-methanesulfonyl-2,3-O-isopropylidene-β-D-ribofuranose.

In order to increase reactivity of the sugar reagent, we considered substitution of the 5-hydroxyl by trifluoromethanesulfonate (triflate). Triflyl group is at least 10^4 times better living group than iodo or mesyl groups.[7] Methyl 5-triflyl-2,3-O-isopropylidene-β-D-ribofuranose was prepared, accordingly to Binkley *et al.*,[8] in a closed system at -70°C to avoid methoxy group migration to 5-OH, [9] and to reduce sugar deprotection by traces of triflic acid. The product was purified by filtration of the reaction mixture through silica gel, and after solvent removal, was used in the reaction with the glycine chiral templates, (5S,6R)- and (5R,6S)-4-(t-Boc)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (only the latter appears in the schemes presented here). The desired adducts were obtained in a moderate yield of 40 %, but with diastereoselectivity better than 98% de. The products were isolated by means of flash chromatography on silica gel and crystallization from ethanol-hexane.



The structure determination of the adduct was based on the analysis of proton NMR spectra. The Δδ of its benzylic methine protons (H-5 and H-6) is 1.03 ppm. According to Williams *et al.* ,[6] the Δδ of H5 and H6 of *anti* and *syn* lactone isomers is characteristic: ~0.94 to ~1.1 ppm for *anti* and ~0.6 to ~0.7 ppm for *syn* . Therefore, the found Δδ value is clearly an indication of *anti* stereochemistry of the adducts. The sites of coupling between the chiral template and the sugar reagent are unequivocally C-3 of the template and C-5 of the ribose. The remaining, single H-3 methine proton signal forms a quartet due to coupling with exocyclic 5'-methylene protons, and the 5' and 5'' proton signals are shifted upfield to form a multiplet centered at ~2.4 ppm, indicating the absence of methoxy group migration in these reaction conditions.

Both, 1-O-methyl (6R)- and (6S)-[(tert-butoxycarbonyl)amino]-5,6-dideoxy-2,3-O-isopropylidene-β-D-*ribo*-heptafuranouronates were released from the chiral auxiliaries by dissolving metal reduction (Li^o/NH_3/EtOH), according to Williams *et al.*.[6] These products were isolated from the aqueous phase by extraction of the dibenzyl by-product with ethyl acetate, ion-exchange and reverse-phase chromatography in moderate yield of ~40%. An improved procedure for product recovery is currently under development.



Experimental Section

Synthesis of methyl 2,3-O-isopropylidene-5-triflyl-β-D-ribofuranose. A 100 mL round-bottom flask stoppered with a rubber septum was charged with dry methylene chloride (20 mL) and pyridine (0.43 mL; 5.5 mmol), and cooled to -70° in an chloroform/dry ice bath. A solution of triflic anhydride (0.86 mL; 5.1 mmol) in methylene chloride (10 mL) was added dropwise through a syringe to the pyridine solution with vigorous stirring. The resulting suspension was stirred for 0.5 h. Methyl 2,3-O-isopropylidene-β-D-ribofuranose (1 g; ~5 mmol) in methylene chloride (10 mL) was added dropwise and stirring continued for 2 h. The reaction mixture was transferred through a double-tipped needle onto a closed silica gel column (2x10 cm) and filtered into a septum-stoppered evaporation flask. TLC (silica gel; 5% EtOAc in toluene) of the filtrate showed the presence of ~90% of the less polar triflate (R_F 0.8) and ~10% of a more polar component (R_F 0.1). The solvent was evaporated under vacuum at room temperature. The oil obtained was kept under vacuum (.03 mmHg) at 0° C for 1h. The product was dissolved rapidly in 1,2-dimethoxyethane (DME) (10 mL) and used in the enolate alkylation.

Procedure for enolate alkylation. Sodium hexamethyldisilazane (3.5 mmol; 3.5 mL of 1 M solution in hexane) was added dropwise to a stirred solution of (5S,6R)- or (5R,6S)-4-(t-Boc)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (1.5 g; 3.5 mmol) in DME (25 mL) at -70°C (external temperature). The mixture was stirred for 0.5h at -70°C and the solution of the sugar reagent was added dropwise. The solution was stirred at the same temperature for 1h and allowed to reach RT overnight. TLC (silica; 10% EtOAc in toluene) showed, besides the sugar decomposition products, a new UV absorbing spot, giving a positive reaction (a dark orange color) with anisaldehyde spray (2% anisaldehyde, 2% H_2SO_4 in ethanol). The reaction mixture was poured into water (100 mL). The product was isolated by extraction of the aqueous phase with EtOAc (2x100 mL), flash-chromatography on silica gel (5% EtOAc in toluene) and crystallization from hexane-ethanol in ~40% yield.

(3R,5R,6S)-4-(t-Butoxycarbonyl)-5,6-diphenyl-3-(1-methyl-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranosyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one. ^1H NMR (200 MHz) (DMSO-d_6, 398°K): δ 1.21 (9H, s), 1.33 (3H, s), 1.45 (3H,s), 2.32 and 2.42 (2H, m, J = 7.6,

7.0, 8.0, 6.2 and -14.7 Hz), 3.33 (3H, s), 4.41 (1H, m, J = 7.6 , 7.0 and 1.2 Hz), 4.64 (1H, d, J = 5.9 Hz), 4.81 (1H, m, J = 5.9 and 1.2 Hz), 4.94 (1H, s), 4.98 (1H, m, J = 8.0 and 6.2 Hz), 5.19 (1H, d, J = 3.2 Hz), 6.23 (1H, d, J = 3.2 Hz), 6.58 (2H, m) and 7.01 - 7.26 (8H, m). mp. 131-3°C.

(3S,5S,6R)-4-(t-Butoxycarbonyl)-5,6-diphenyl-3-(1-methyl-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranosyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one. ^{1}H NMR (200 MHz) (DMSO-d_6, 398°K): δ 1.18 (9H, s), 1.31 (3H, s), 1.45 (3H,s), 2.36 and 2.48 (2H, m, J = 9.2, 4.4, 9.0, 4.7 and -14.2 Hz), 3.37 (3H, s), 4.40 (1H, m, J = 9.2 , 4.4 and 1.3 Hz), 4.68 (1H, d, J = 6.0 Hz), 4.62 (1H, m, J = 6.0 and 1.3 Hz), 4.95 (1H, s), 4. (1H, m, J = 9.0 and 4.7 Hz), 5.20 (1H, d, J = 3.2 Hz), 6.23 (1H, d, J = 3.2 Hz), 6.58 (2H, m) and 7.01 - 7.26 (8H, m). mp. 168-9°C.

The chiral auxiliaries were removed according to the method reported by Williams *et al.*.[6]

1-O-Metyl 6(R or S)-[(t-butoxycarbonyl)amino]-5,6-dideoxy-2,3-O-isopropylidene-β-D-*ribo*-heptafuranuronate. (300 MHz) (DMSO-d_6, 293°K): δ 1.25 (3H, s), 1.36 (3H, s), 1.38 (9H, s), 1.76 and 1.91 (2H, m, J = 5.4, 6.6, 6.6, 5.6 and -14.2 Hz), 3.97 (1H, broad m, J = 5.4, 6.6 and 8.1 Hz), 4.17 (1H, t, J = 6.6 and 5.6 Hz), 4.58 and 4.62 (2H, m, J = 6.0 Hz), 4.87 (1H, s) and 7.15 (1H, d, J = 8.1 Hz).

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