SYNTHESES OF OPTICALLY ACTIVE, UNUSUAL, AND BIOLOGICALLY IMPORTANT HYDROXY-AMINO ACIDS FROM D-GLUCOSAMINE

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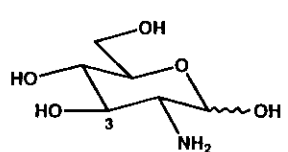
Abstract: Manipulation of D-glucosamine as a chiral pool including stereoinversion of the C3-hydroxyl group, degradation of the C6-carbon, and/or one carbon homologation at the C1-position realized chiral syntheses of (2*S*,3*S*)-dihydroxy-(4*S*)-amino acid moieties, important structural components of a gastroprotective substance AI-77-B and a group of antitumor substances calyculins.

Naturally occurring unusual amino acids in the sense of the position and the configuration of functional groups including the amino group have attracted much attention from the view point of biological role in physiological and pharmacological activities of a variety of natural products.[1] Thus, efficient synthesis of those unusual amino acids has been desired for obtaining enough amount of those inaccessible natural products in order to investigate biological activities.[2] Although D-glucosamine (**1**) is the sole aminosugar which is available inexpensively, it has not been so frequent that the compound is utilized as a chiral building block for synthesis of biologically active amino-alcohols, amino-acids, and related nitrogen containing compounds.[3] We have focused attention on D-glucosamine as a chiral poly-hydroxylated amine source and recently applied the compound to chiral synthesis of (3*S*,4*S*)-statine, the key component of inhibitory peptide of aspartic proteases pepsin and renin.[4]

We wish to report herein chiral syntheses of (2*S*,3*S*)-dihydroxy-(4*S*)-amino acid moieties (**2**) and (**3**), which are the biologically important structural components of a gastroprotective substance AI-77-B[5] and a



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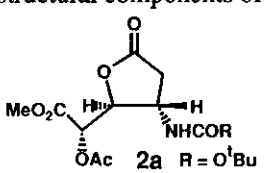
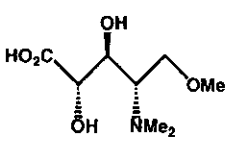


2a R = O^{t}Bu
b R = CF_3



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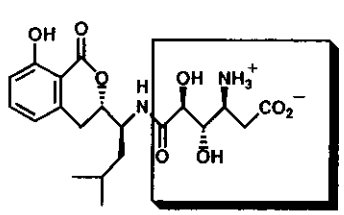
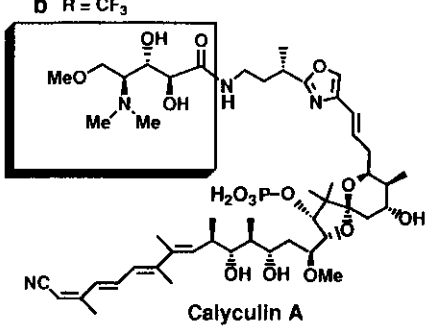


AI-77-B

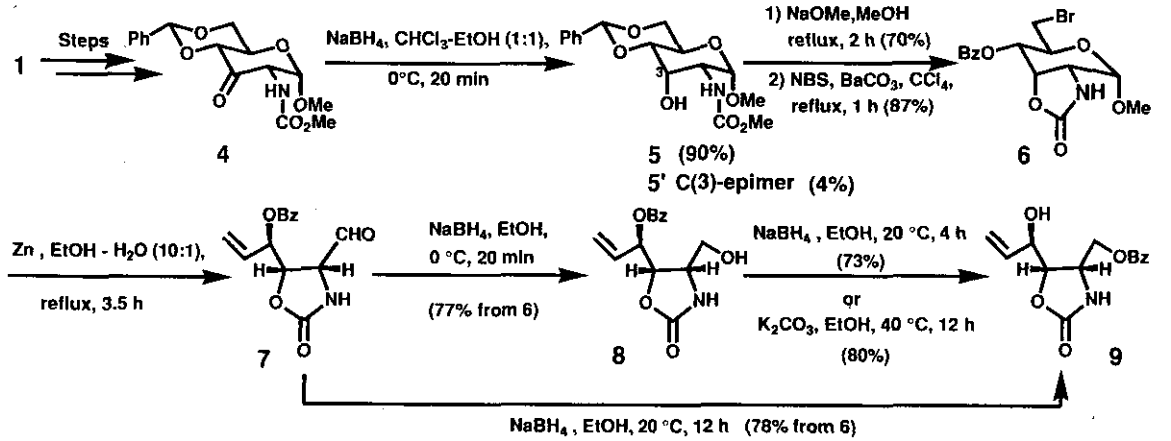


Calyculin A

group of antitumor substances calyculins,[6] respectively, starting from **1** as a chiral pool. Present synthesis features facile derivatization of **1** to the common chiron *cis*-4,5-disubstituted oxazolidin-2-one (**7**) *via* highly stereoselective inversion of the C3-hydroxyl group through oxidation-reduction sequence of reactions followed by formation of a oxazolidinone ring and reductive elimination reaction of the C6-brominated intermediate (**6**) (Scheme 1).

Among the known methods [7] for inversion of the C3-hydroxyl group of **1**, we selected a procedure including oxidation to the corresponding ketone followed by the hydride-reduction as the most reliable process.[7a] Thus, methyl 4,6-*O*-benzylidene-2-methoxycarbonylamino-2-deoxy-α-*D*-ribo-hexopyranosid-3-ulose (**4**) prepared *via* four steps from **1** according to the literature [8] was reduced with $NaBH_4$ to give a D-allopyranoside (**5**)[9] in a high yield along with a trace amount of the C3-epimer (**5'**), which could be removed by recrystallization. Crystalline 6-bromopyranoside (**6**) was obtained in 61% overall yield from **5** *via* oxidative bromination of the benzylidene acetal functionality.[10] Structure of **6** including the stereochemistry at the C3-carbon atom was established by the X-ray crystallography.[11] Debrominative ring fission of the pyranoside (**6**) was realized by heating with Zn[12] to lead to the key intermediate aldehyde (**7**), which without purifications was treated with $NaBH_4$ in EtOH at 0 °C for 20 min to give a secondary benzoate (**8**) as an oil and, on the other hand, at room temperature for 12 h to give the isomeric primary benzoate (**9**) as a crystal (mp 150-152°C), respectively.

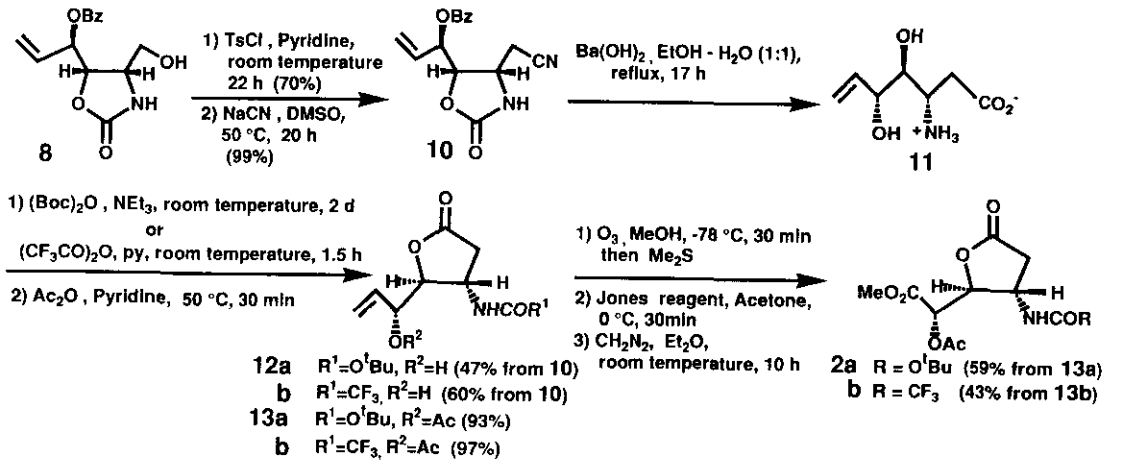
Scheme 1



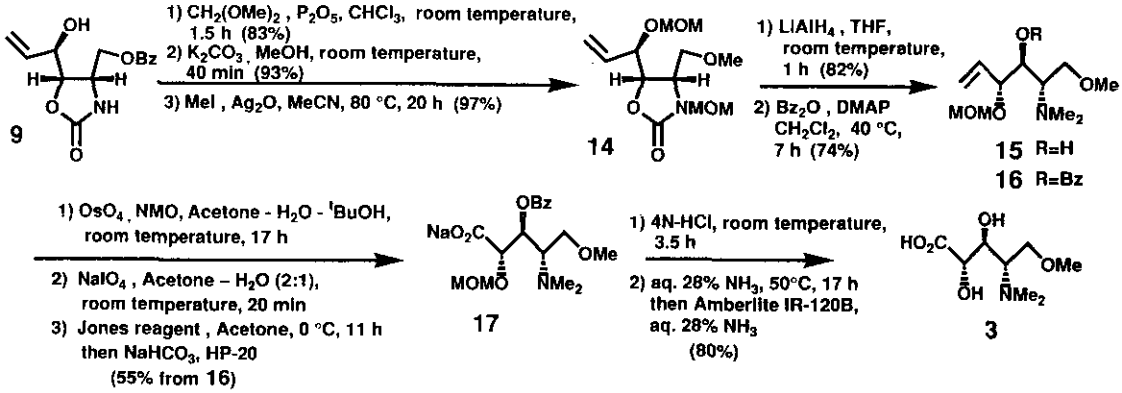
The protected amino acid moiety (**2**) [13] for AI-77-B was derived from **8** *via* one carbon homologation on the C4-side chain followed by one carbon degradation on the C5-side chain of the oxazolidinone skeleton (Scheme 2). Tosylation of **8** followed by cyanation gave a nitrile (**10**) in 69% overall yield from **8**. Alkaline hydrolysis of both of the cyanide and oxazoline functionalities of the nitrile (**10**) gave a linear amino acid (**11**) which was converted without purifications into the corresponding *N*-protected lactones, *N*-Boc derivative (**12a**) and *N*-$COCF_3$ derivative (**12b**), respectively in 47% and 60% overall yields from **11**. The corresponding crystalline acetates (**13a**) and (**13b**) derived almost quantitatively from the alcohols (**12a**) and (**12b**) were degraded one-carbon by successive treatment with ozone, Jones reagent, and CH_2N_2 to lead to crystalline γ-lactone methyl esters (**2a**) (mp 136-138°C) and (**2b**) (mp 165-168 °C), which are protected hydroxy-amino acid portions for AI-77-B.

Transformation of the primary benzoate (**9**) to the hydroxy-amino acid moiety (**3**)[14] for calyculins was

Scheme 2



Scheme 3



attained *via* *N,N*-dimethylation by reduction of *N*-protecting groups and one carbon degradation of the terminal olefin portion (Scheme 3). The primary benzoate (**9**) was converted into *N,O*-MOM-methyl ether (**14**) in 75% overall yield by a three-step sequence including *N,O*-dimethoxymethylation, alkaline debenzoylation, and methylation with MeI and Ag_2O. Treatment of **14** with $LiAlH_4$ successfully produced the *N,N*-dimethylamino derivative (**15**), which was converted to the benzoate (**16**). One carbon degradation of **16** was carried out in 55% overall yield by a three-step sequence including catalytic OsO_4-oxidation of **16**, periodate oxidation of the resulted glycol, and Jones oxidation of an intermediate aldehyde to lead to a crude amino acid, which afforded the corresponding crystalline sodium salt (**17**) by treatment with a resin HP-20. Final deprotection of the glycol function of **17** afforded in 80% yield a crystalline hydroxyamino acid (**3**) (mp 96-99 °C; $[\alpha]_D$-39.0° (EtOH-H_2O/1:1)), structure of which was verified by ^{1}H-nmr spectral comparison with the corresponding authentic (+)-**3** isomer.[14b]

In conclusion, the present work stands for the first chiral syntheses of the unusual amino acid moieties of AI-77-B and calyculins starting from the readily available aminosugar D-glucosamine.

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