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An efficient synthesis of protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid, a constituent of callipeltins A and D☆

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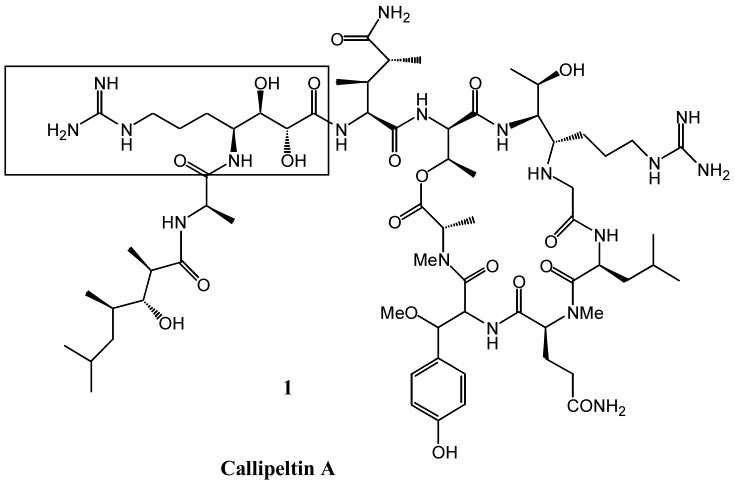
Abstract—An efficient and stereoselective synthesis of protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid, a constituent of the depsipeptides, callipeltins A and D, from D-ribose is described.

Cyclic depsipeptides have emerged as very important classes of bioactive compounds in marine natural products.[1] Among these cyclic depsipeptides, callipeltin A shows anti-HIV, antifungal and cytotoxic activities against selected human carcinoma cell lines.[2] The isolation of callipeltins **1** and **2** was reported by Minale et al. in 1996 from a shallow water sponge of the *Callipelta* species[3] and later by D'Auria and co-workers from *Latruncula* sp.[4] They show marked activity in cytotoxic assays against KB and P388 cells and recently it was found that callipeltin A is a selective and powerful inhibitor of Na/Ca cardiac exchange and a positive inotropic agent in guinea pig left atria.[5] Callipeltin A contains a number of novel amino acid residues: methoxy-tyrosine, (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE) and (3*S*,4*R*)-3,4-dimethyl-L-glutamine.

Recent reports have revealed that the side-chain attached to the macrocycle in callipeltin A is essential for anti-HIV activity and it is also present in callipeltin D.[4] The key residue in the side-chain is the novel amino acid (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE) **3**. Two syntheses have been reported for this fragment to date and one of these was from our laboratory starting from D-glucose.[6] Recently



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Callipeltin A

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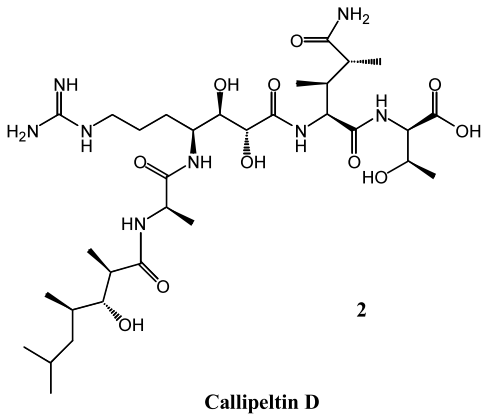
Lipton et al. reported this fragment from protected L-ornithine.[7] In this paper we report an efficient synthesis of the AGDHE fragment **3** starting from readily available D-ribose.

D-Ribose was converted into compound **4** via a reported procedure in one step.[8] Compound **4** underwent Swern oxidation and Wittig olefination to afford **5**, whose NMR spectral data were in agreement with the literature.[8] Reduction of **5** using LAH gave compound **6**, which was subsequently converted to azide **7**. Under acidic conditions compound **7** underwent isopropylidene cleavage to give diol **8**, which was protected as the dibenzyl ether **9**. Hydrolysis of the *O*-glycosidic bond of **9** afforded the corresponding lactol **10**. Compound **10** was treated with LAH, resulting in opening of the lactol and reduction of the azide to the corresponding amine. The reaction was quenched with 15% NaOH solution and immediately $(Boc)_2O$ was added to convert the amine into the *N*-Boc derivative. Interestingly, it was found that the primary hydroxy was also protected as its Boc ester **11**, selectively, in good yield. Compound **11** was converted into azide **12** in 90% yield by S_N2 displacement of the intermediate mesylate. In comparison to our earlier synthesis[6] conversion of the secondary hydroxyl to azide is efficient in the presence of *O*-Boc. Compound **12** was *N*-benzylated using NaH/BnBr in DMF. Under these conditions concomitant cleavage of the *O*-Boc ester occurred to give **13**. Azido alcohol **13** was reduced to the corresponding amine using TPP/benzene–H_2O and was immediately protected as the Boc derivative **14**, $[\alpha]_D^{25} = -14.2$ (*c* 0.8, $CHCl_3$), [lit.[6] $[\alpha]_D^{25} = -14.8$ (*c* 0.7, $CHCl_3$)], whose NMR spectral data were in agreement with the literature.[6] Compound **14** is known to give methyl ester **15** in one step.[6]

In conclusion we have developed a short strategy for the synthesis of **15**, which is useful in making reasonable quantities for the total synthesis of callipeltins and



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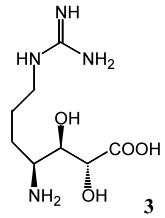
Callipeltin D



3 AGDHE

will also help in making different analogues. The selective protection of the primary hydroxyl as the *O*-Boc derivative during the LAH reduction of **10** and its removal during benzylation of **12**, minimized the number of transformations required in reaching the target (Scheme 1).

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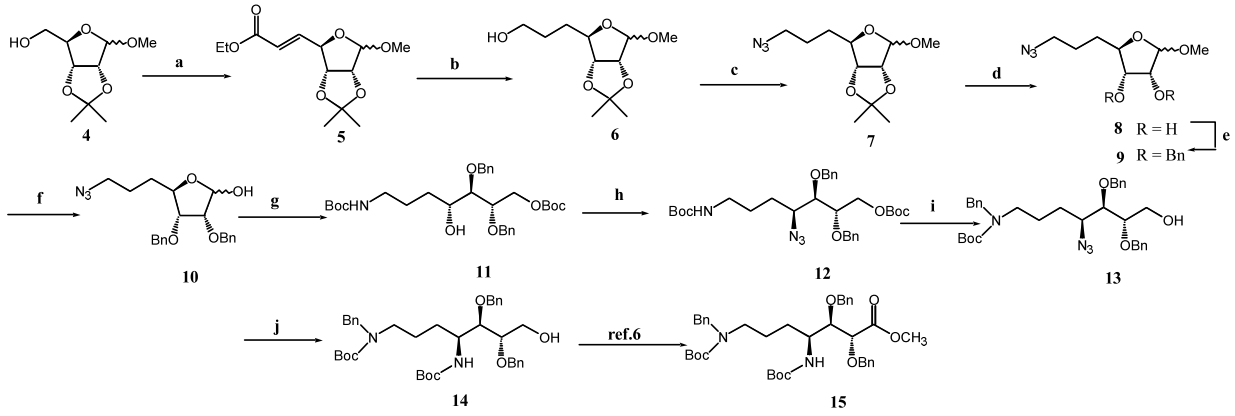

Scheme 1. *Reagents and conditions*: (a) (i) $(COCl)_2$, DMSO, −78°C, 30 min, then **4**, Et_3N, −78°C to rt, 1 h; (ii) Ph_3P=CHCOOEt, DCM, rt, 1 h, 79%; (b) LAH, THF, 0°C to rt, 6 h, 87%; (c) (i) TsCl, DCM, Et_3N, 0°C to rt, 6 h; (ii) NaN_3, DMF, 90°C, 8 h, 74%; (d) MeOH, conc. HCl (cat.), 60°C, 4 h, 86%; (e) BnBr, NaH, DMF, 0°C to rt, 2 h, 92%; (f) 60% AcOH–H_2O, HCl (cat.), 60°C, 2 h, 76%; (g) LAH, THF, 0°C, 30 min, 15% NaOH, H_2O, $(Boc)_2O$, 12 h, 93%; (h) (i) MsCl, Et_3N, DCM, 0°C to rt, 6 h; (ii) NaN_3, DMF, 90°C, 12 h, 93%; (i) NaH, BnBr, DMF, 0°C to rt, 6 h, 79%; (j) (i) PPH_3, H_2O, benzene, 11 h; (ii) Et_3N, $(Boc)O_2$, 12 h, 81%.

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