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Synthesis of the Glucoallosamidin Pseudo-disaccharide: Use of an Efficient Hg(II) Mediated Cyclization

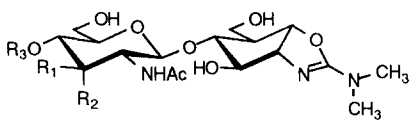
William D. Shrader and Barbara Imperiali*

Division of Chemistry and Chemical Engineering
California Institute of Technology, Pasadena, CA 91125

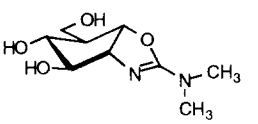
Abstract: The title compound **1a** was prepared from cyclopentadienylthallium in 11 steps. The key component of the pseudo-disaccharide **1a**, (-)-allosamizoline **2**, was synthesized in 2 steps starting from the known cyclopentene **4** by formation of the aminoimidate **5** followed by a mercury(II)trifluoroacetate mediated cyclization and radical oxygenation. Regioselective and stereospecific coupling of 6-*O*-benzyl-(-)-allosamizoline **8** with the oxazoline glycosyl donor **11** and subsequent deprotection afforded the β-1,4-pseudo-disaccharide **1a**.

The allosamidins are a potent class of pseudo-tri- and disaccharide chitinase inhibitors isolated and characterized originally from the fermentation broths of *Streptomyces sp.* by Sakuda *et al.*[1] The allosamidin class of natural products (**1a-d**) consists of an aglycon section, allosamizoline **2**, which is linked to a carbohydrate via a β-1,4 glycosidic bond to either a mono or β-1,4-disaccharide of *N*-acetylallosamine or *N*-acetylglucosamine.[2] (Scheme I)

Scheme I **Allosamidin Structures**



1a: R_1=OH, R_2=H, R_3=H
1b: R_1=H, R_2=OH, R_3=H
1c: R_1=OH, R_2=H, R_3=β-1,4-*N*-acetylglucosamine
1d: R_1=H, R_2=OH, R_3=β-1,4-*N*-acetylallosamine

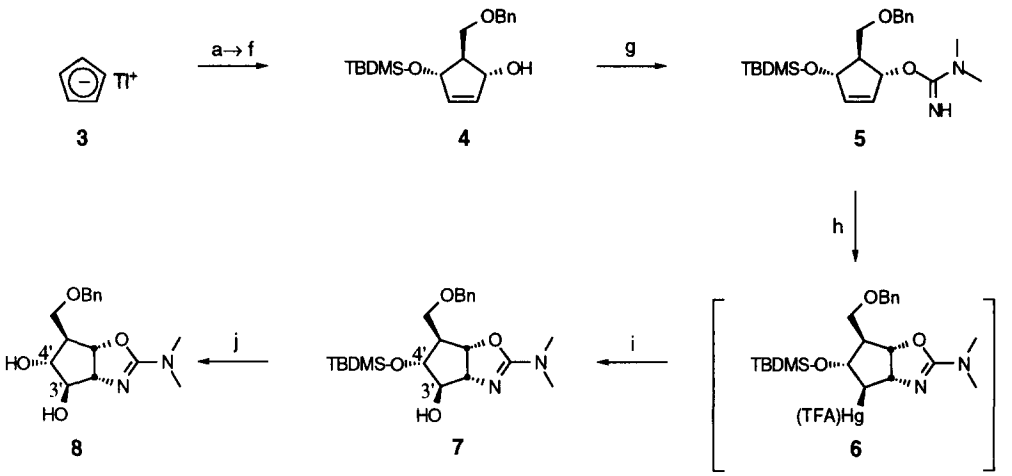


2: Allosamizoline

The potent biological activity and structural complexity of the allosamidins has generated significant synthetic interest.[3-16] Since the first published synthesis of (+/-)-allosamizoline **2** in 1990,[3] eight synthetic routes have been reported.[4-14] To date all synthetic approaches towards allosamizoline **2** have started with either D-glucosamine[8-12, 14] or the *meso*-diol, 4-benzyloxymethyl-3,5-dihydroxy-cyclopentene.[3-7, 13]

Presented herein is a short asymmetric synthesis of 6-*O*-benzyl-(-)-allosamizoline **8** (Scheme II) and its subsequent regioselective and stereospecific coupling with an *N*-acetylglucosamine glycosyl donor **11** (Scheme III). In our synthesis of **1a**, we chose to synthesize the allosamizoline portion of this target starting from *meso*-diol, 4-benzyloxymethyl-3,5-dihydroxy-cyclopentene which had been employed by Trost, Danishefsky and Ganem.[3-7, 13] The synthesis presented begins with the optically active alcohol **4**, which was prepared in 5 steps from cyclopentadienylthallium **3** by the method of Danishefsky and coworkers.[7]

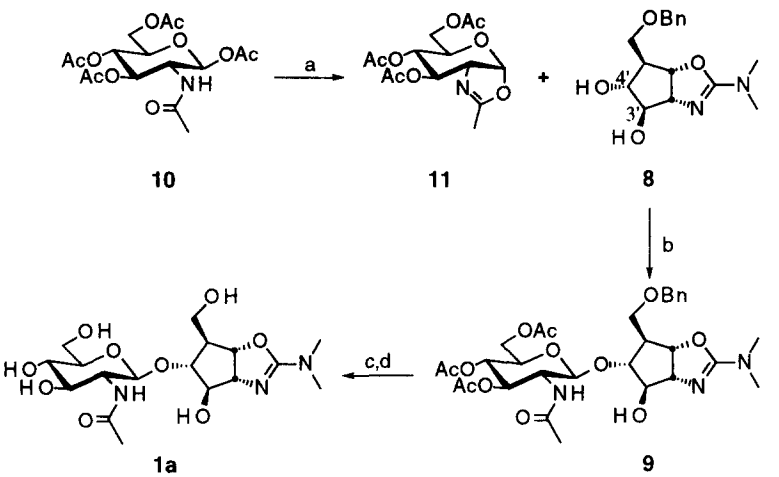
Scheme II **Synthesis of 6-*O*-Benzyl-(-)-allosamizoline**



a. benzylchloromethylether 1.05 equiv, Et_2O -20° C 3.5 h; b. O_2, hv, methylene blue, thiourea, CH_3OH 0° C 1h, followed by stirring at 0° C 18h (60% a→b); c. Ac_2O 2 equiv, DMAP 0.1 equiv, CH_2Cl_2 0° C 1h (95%); d. electric eel acetylcholinesterase, 0.2 M KH_2PO_4/5% MeOH, pH 7.0 rt 4 days (90%); e. TBDMSCl/imidazole, CH_2Cl_2 30 min rt (95%); f. anhydrous NH_3/CH_3OH -10°→rt 18 h (95%); g. neat dimethylcyanamide, NaH 1.1 equiv, -78°→rt 5 h (93%); h. mercury(II) trifluoroacetate 1.5 equiv, THF rt 36h; i. vigorous O_2 flush, 1M $NaBH_4$ in 2M NaOH, 1,4-dioxane rt 2h (69% 2-steps); j. 1N HF in CH_3CN, rt 18h (90%).

The oxazoline ring system was formed stereoselectively in two steps. Generation of the sodium alkoxide of **4**, followed by treatment with dimethylcyanamide provided aminoimidate **5**.[17, 18] This transformation was achieved by freezing the allylic alcohol **4** in neat dimethylcyanamide at -80° C, to which NaH was added and the resulting mixture slowly warmed to room temperature over 5 h; following purification, the product aminoimidate **5** was isolated in 95% yield as a clear oil.[19] Aminoimidate **5** was subsequently cyclized via a highly stereoselective Hg(II) mediated ring closure to provide oxazoline **6** as a single diastereomer.[20, 21] In a single step, this cyclization correctly transfers the stereochemical information from the C-1' position to the cyclic C-2' position, and additionally functionalizes the C-3' center. The resultant alkyl mercurium species **6**, under radical oxygenation conditions, undergoes demercuration and reaction with molecular oxygen from the desired, convex face of the ring system to provide the protected allosamizoline derivative **7** in 69% yield from aminoimidate **5**. The product corresponding to addition of molecular oxygen to the undesired face of the ring system was not observed. The mercurial species **6** is stable to chromatography, but in practice the unpurified product from the cyclization is directly oxygenated. 6-*O*-benzyl-(-)-allosamizoline **8** is obtained directly by desilylation of TBDMS-ether **7** with 1N HF in CH_3CN. This synthesis provides enantiomerically pure 6-*O*-benzyl-(-)-allosamizoline **8** in 3 steps and 58% yield from the known optically active alcohol **4**. Additionally, the corresponding C-3' deoxy 6-*O*-benzyl-(-)-allosamizoline derivative was obtained from aminoimidate **5** in 75% yield by conducting the $NaBH_4$ radical demercuration step (Scheme II, step i) in a rigorously oxygen free environment.

Scheme III Coupling of 6-*O*-Benzyl-(-)-allosamizoline with glycosyl donor 11



a. BF_3•Et_2O 3 equiv, CH_2Cl_2 5h rt (90%); b. TfOH 1 equiv, CH_3NO_2/$PhCH_3$ 2 h 60°C (50%); c. $Pd(OH)_2/H_2$ in MeOH, 18 h rt (95%); d. anhydrous NH_3 in MeOH, 36 h rt (95%).

The synthesis of target **1a** requires formation of a β-glycosidic bond between the anomeric carbon of *N*-acetyl-D-glucosamine with the C-4' hydroxyl of allosamizoline derivative **8**. (Scheme III) To assure β-selectivity in the formation of the glycosidic bond, the oxazoline 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-d]-Δ^2-oxazoline **11** was used as the glycosyl donor.[22-24] Oxazoline **11** was formed in a single step by treatment of commercially available 2-acetamido-2-deoxy-β-D-glycopyranose-1,3,4,6-tetraacetate **10** in CH_2Cl_2 with 3 equiv of BF_3•Et_2O. Diol **8** was coupled to oxazoline **11** at the correct 4'-hydroxyl with 6:1 selectivity (4':3' hydroxyl)[6] using catalytic triflic acid in a 1:1 nitromethane/toluene mixture to give the β-anomer exclusively. The desired protected pseudo-disaccharide **9** in was isolated in 50% yield. Deprotection via hydrogenolysis followed by treatment with anhydrous methanolic ammonia afforded the target molecule, **1a**. Pseudo-disaccharide **1a** and other related structures are currently being evaluated as eukaryotic glycosyl transferase inhibitors.

Acknowledgments

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19. [1*R*-(1α,4α,5β)]-5-[(Benzyloxy)methyl]-4-[(*tert*-butyldimethylsilyl)oxy]-1-*O*-(dimethylamidino)-2-cyclopentene (5): $[\alpha]_D^{20}$ +15.0° (*c* = 1.18, MeOH); IR (neat) υ_{max} 2952, 2928, 2885, 2856, 1623, 1392, 1361, 1250, 1097, 1049, 862, 836, 776 cm^{-1}; ^1H NMR (500 MHz in $CDCl_3$): δ 0.04 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 2.30 (m, 1 H, H-5), 2.87 (s, 6 H, $N(CH_3)_2$), 3.64 (dd, *J* = 9.3, 5.3, 1 H, CH*H*OBn), 3.70 (dd, *J* = 9.4, 4.4, 1 H, CH*H*OBn), 4.56 (AB_q, *J* = 11.9 Hz, υ = 25.2 Hz, 2 H, OCH_2Ph), 4.59 (m, 1 H, H-1), 5.40 (d, *J* = 4.8, 1 H, H-4), 5.90 (dt, *J* = 5.8, 1.5, 1 H, H-2), 5.99 (d, *J* = 5.7, 1 H, H-3), 7.25-7.31 (m, 5 H, Ar*H*), 7.33 (d, *J* = 4.5, 1 H, imino-N*H*); ^{13}C NMR (125 MHz in $CDCl_3$): δ -4.71, -4.58, 18.02, 25.79, 37.24, 55.64, 68.15, 73.23, 76.41, 80.68, 127.50, 127.75, 128.27, 131.59, 137.66, 138.22, 160.76; MS (DCI, NH_3^+), parent ion 405 $(M+H)^+$; HRMS: Calcd for $C_{22}H_{37}N_2O_3Si$: *m/z* = 405.257347; Found: 405.257100. 6-*O*-Benzyl-4-*O*-(*tert*-butyldimethylsilyl)-(-)-allosamizoline (6): $[\alpha]_D^{20}$ + 7.7° (*c* = 0.96, MeOH); IR (neat) υ_{max} 2927, 2895, 2856, 1652, 1645, 1471, 1455, 1411, 1359, 1247, 1193, 1144, 1099, 1045, 978, 899, 837, 778 cm^{-1}; ^1H NMR (500 MHz in $CDCl_3$): δ 0.03 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 2.22 (m, 1 H, H-5), 2.87 (s, 6 H, $N(CH_3)_2$), 3.57 (dd, *J* = 9.4, 5.4, 1 H, CH*H*OBn), 3.66 (dd, *J* = 9.5, 3.7, 1 H, CH*H*OBn), 3.83-3.87 (m, 2 H, H-2, H-3) 4.11 (dd, *J* = 8.7, 3.4, 1 H, H-1) 4.53 (AB_q, *J* = 11.9 Hz, υ = 3.0 Hz, 2 H, OCH_2Ph), 4.84 (dd, *J* = 8.7, 5.1, 1 H, H-1), 7.26-7.36 (m, 5 H, Ar*H*); ^{13}C NMR (125 MHz in $CDCl_3$): δ -5.06, -4.29, 17.90, 25.72, 37.67, 52.75, 68.29, 73.26, 75.25, 77.53, 83.47, 85.03, 127.64, 127.66, 128.39, 138.12, 161.76; MS (FAB^+), parent ion 421 $(M+H)^+$; HRMS: Calcd for $C_{22}H_{37}N_2O_4Si$: *m/z* = 421.252261; Found: 421.249542
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