STEREOSELECTIVE SYNTHESIS OF DIAMINO DIOL DERIVATIVES WITH C_2-AXIS OF SYMMETRY§

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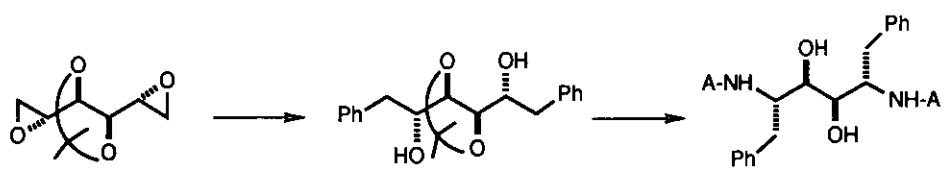
Abstract–An efficient and stereocontrolled synthesis of C_2-symmetric diamino diol derivatives (**7**) was achieved through selective opening of *N*-Boc bis-aziridine (**6**), prepared from D-mannitol *via* cyclic sulfate(**4**).

2-Amino alcohol moiety frequently serves as isosteric functional group for asparatic protease inhibitors and functions as transition-states mimetics of hydrolysis of dipeptide.[1] Recently diamino diol derivatives such as **1** with C_2-axis of symmetry were designed based on symmetrical nature of human immunodeficency virus (HIV) protease and proved to be a potent and selective inhibitor of the protease.[2] Pinacol coupling reaction of *N*-Boc phenylalaninal was applied to non-stereoselective synthesis of amino alcohol moiety of **1**.[2b] In order to obtain a range of symmetrical inhibitors which have non-natural amino acid side chains, flexible and stereoselective methods not starting with amino acids are highly required. More recently, a stereocontrolled synthesis of **1** using stereoselective cleavage of di-epoxide derived from D-mannitol was reported (Scheme 1).[3] However introduction of amino functionality to C-2 and C-5 positions has been problematic due to competing E_2-reaction.[3]

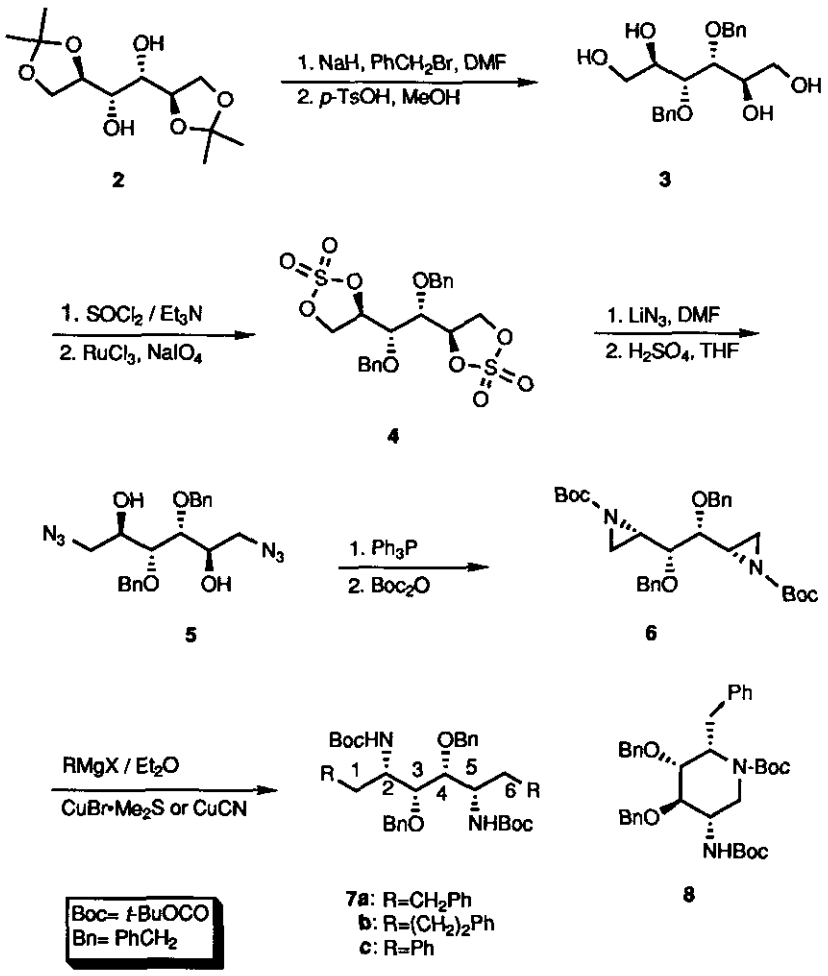
Scheme 1



1 A=Cbz-Val

In this paper we report an efficient stereoselective synthesis of diamino diols (**7**) through selective opening of bis *N*-Boc aziridine (**6**) prepared from D-mannitol *via* cyclic sulfate (**4**) in a stereocontrolled manner. This synthesis allow us to prepare a various diamino diols (**7**) with high stereoselectivity and convergency (Scheme 2).

Scheme 2



2 **3** **4** **5** **6** **8**

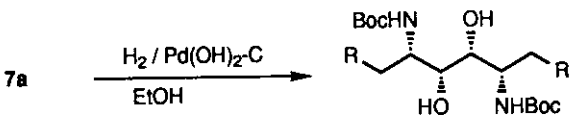
In an attempt to obtain a versatile intermediate for transformation of D-mannitol, bis cyclic sulfate (**4**) was selected as a synthon for selective functionalization to the C-1 and C-6 positions. Dibenzylation [NaH, $PhCH_2Br$, DMF] of di-*O*-isopropylidene-D-mannitol (**2**),[4] followed by acid hydrolysis [*p*-TsOH, MeOH] gave tetraol (**3**),[5] mp 76-78 °C, $[\alpha]_D^{25}$+10.3° (c 1.0, $CHCl_3$), in 79% yield. Treatment of **3** with $SOCl_2$ in CH_2Cl_2 in the presence of Et_3N and subsequent oxidation

[$RuCl_3$•n-H_2O, $NaIO_4$] according to the method of Sharpless[6] yielded the desired bis cyclic sulfate (**4**),[7] mp 111-112 °C, $[\alpha]_D^{25}$+15.9° (c 0.54, MeCN), in 78% yield.

Stereoselective introduction of nitrogen functionality to C-2 and C-5 positions of **4** was easily achieved through regioselective azide formation at terminal positions, followed by its migration to 2- and 5-positions by reductive ring closure with inversion of the configuration. Upon treatment of **4** with LiN_3 (2.5 equiv.) in DMF at 25 °C for 2 h and subsequent hydrolysis [*c*.H_2SO_4, H_2O, THF], bis azide alcohol (**5**),[6] mp 44-44.5 °C, $[\alpha]_D^{25}$+81.3° (c 1.0, $CHCl_3$), was obtained selectively in 80% yield. The reaction of **5** with Ph_3P (2.5 equiv.) in toluene at 25 to 80 °C for 2 h and successively *t*-butoxycarbonylation [Boc_2O, Et_3N, DMAP, THF] of the resulting bis NH-aziridine gave bis *N*-Boc aziridine (**6**),[7] $[\alpha]_D^{25}$–121.5° (c 1.0, $CHCl_3$), as an oil in 56% yield.[8]

Regioselective ring-opening of **6** was achieved by copper(I)-catalyzed addition of Grignard reagents. Treatment of **6** with benzylmagnesium chloride (10 equiv.) in the presence of CuBr•Me_2S(1.0 equiv.) in ether-toluene at –20 °C for 1 h gave the desired di-benzylation product (**7a**),[9] mp 88-91 °C, $[\alpha]_D^{25}$+9.44° (c 1.0, $CHCl_3$), in 61% yield. Under similar conditions [$Ph(CH_2)_2MgCl$ (10 equiv.), 1.0 equiv. of CuBr•Me_2S], **7b** was obtained as an oil in 59 % yield. Phenylation of **6** with phenylmagnesium bromide (20 equiv.) was performed in the presence of CuCN (2.0 equv.) in ether at 0 °C. Although trace amounts of **7c** were isolated from the reaction mixture, most of the products were found to be a mono-phenylation product such as **8**.[10]

Hydrogenolysis of **7a** over $Pd(OH)_2$-C(20%) in EtOH gave the corresponding *N*-Boc diamino diol (**9**),[3] mp 173-175 °C (lit.,[3] mp174-176 °C) in 65% yield. Thus the methods described in this paper are useful for the synthesis of analogous key components of symmetrical protease inhibitors such as **1** in a convergent manner.



9: R=CH_2Ph

REFERENCES AND NOTES

§ Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

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5. All new compounds gave satisfactory analytical and spectroscopic data.
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7. **4**: ^{1}H-Nmr ($CDCl_3$, 300 MHz) δ 7.58-7.35(5H, m), 7.35-7.21(5H, m), 4.90(2H, d, *J*=11.0 Hz), 4.88-4.75(4H, m), 4.55-4.42(2H, m), 4.51(2H, d, *J*=11.0 Hz), 4.18(2H,s); **5**: ^{1}H-Nmr ($CDCl_3$, 300 MHz) δ 7.45-7.25(10H, m), 4.61(4H, d, *J*=11.3 Hz), 4.56(4H, d, *J*=11.3 Hz), 4.12-4.03(2H, m), 3.77(2H, d with small spilitting, *J*=7.8 Hz), 3.57(2H, dd, *J*=3.0, 12.9 Hz), 3.36(2H, dd, J=4.71, 12.9 Hz); **6**: ^{1}H-Nmr ($CDCl_3$, 300 MHz) δ 7.38-7.25(10H, m), 4.92(2H, d, *J*=12 Hz), 4.76(2H, d, *J*=12 Hz), 3.15(2H, d with small spilitting, *J*=6.35 Hz), 2.93-2.83(2H, m), 2.18(2H, d, *J*=6.65 Hz), 1.84(2H, d, *J*=3.76 Hz), 1.48(18H, s).
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9. **7a**: Ms *m/z* 708 (M^+), ^{1}H-Nmr ($CDCl_3$, 300 MHz) δ 7.35-7.20 (14H, m), 7.20-7.09 (6H, m), 4.95 (1H,d, *J*=10 Hz), 4.90(2H, d, *J*=11 Hz), 4.53 (2H, d, *J*=11 Hz), 4.05-3.95 (2H, m), 3.59 (2H, broad s), 2.75-2.51(4H, m), 1.90-1.69(4H, m), 1.45(18H, s).
10. Similar reaction was reported by Duréault *et al.*; A. Duréault, I. Tranchepain, C. Greck, and J-C, Depezay, *Tetrahedron Lett.*, **1987**, *28*, 3341.

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