

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

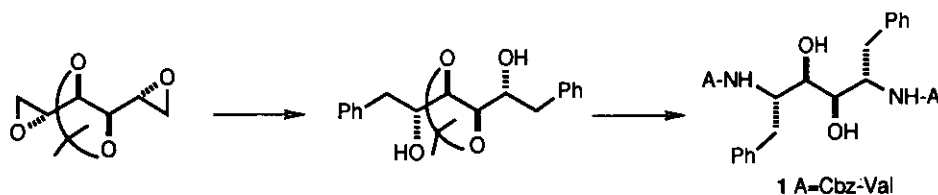
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Abstract—An efficient and stereocontrolled synthesis of C_2 -symmetric diamino diol derivatives (**7**) was achieved through selective opening of *N*-Boc bis-aziridine (**6**), prepared from D-mannitol via cyclic sulfate(**4**).

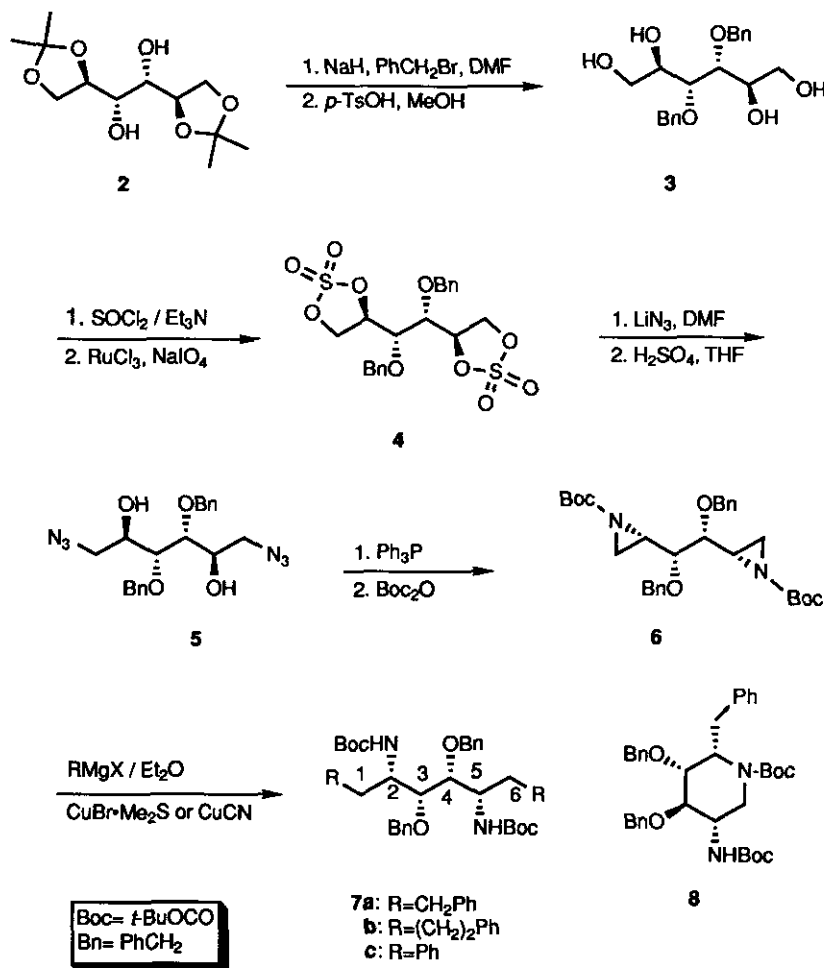
2-Amino alcohol moiety frequently serves as isosteric functional group for aspartic protease inhibitors and functions as transition-states mimetics of hydrolysis of dipeptide.¹ Recently diamino diol derivatives such as **1** with C_2 -axis of symmetry were designed based on symmetrical nature of human immunodeficiency 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



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



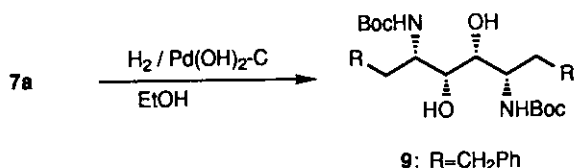
In an attempt to obtain a versatile intermediate for transformation of D-mannitol, bis cyclic sulfate (**4**) was selected as a synthon for selective functionalization to the C-1 and C-6 positions. Dibenzylation [NaH, PhCH₂Br, DMF] of di-O-isopropylidene-D-mannitol (**2**),⁴ followed by acid hydrolysis [*p*-TsOH, MeOH] gave tetraol (**3**),⁵ mp 76-78 °C, [α]_D²⁵+10.3° (c 1.0, CHCl₃), in 79% yield. Treatment of **3** with SOCl₂ in CH₂Cl₂ in the presence of Et₃N and subsequent oxidation

[RuCl₃·n-H₂O, NaIO₄] according to the method of Sharpless⁶ yielded the desired bis cyclic sulfate (**4**),⁷ mp 111-112 °C, [α]_D²⁵+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 LiN₃ (2.5 equiv.) in DMF at 25 °C for 2 h and subsequent hydrolysis [c.H₂SO₄, H₂O, THF], bis azide alcohol (**5**),⁶ mp 44-44.5 °C, [α]_D²⁵+81.3° (c 1.0, CHCl₃), was obtained selectively in 80% yield. The reaction of **5** with Ph₃P (2.5 equiv.) in toluene at 25 to 80 °C for 2 h and successively *t*-butoxycarbonylation [Boc₂O, Et₃N, DMAP, THF] of the resulting bis NH-aziridine gave bis *N*-Boc aziridine (**6**),⁷ [α]_D²⁵-121.5° (c 1.0, CHCl₃), 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·Me₂S (1.0 equiv.) in ether-toluene at -20 °C for 1 h gave the desired di-benzylation product (**7a**),⁹ mp 88-91 °C, [α]_D²⁵+9.44° (c 1.0, CHCl₃), in 61% yield. Under similar conditions [Ph(CH₂)₂MgCl (10 equiv.), 1.0 equiv. of CuBr·Me₂S], **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 equiv.) 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 mp 174-176 °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.



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: $^1\text{H-Nmr}$ (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: $^1\text{H-Nmr}$ (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 splitting, $J=7.8$ Hz), 3.57(2H, dd, $J=3.0, 12.9$ Hz), 3.36(2H, dd, $J=4.71, 12.9$ Hz); 6: $^1\text{H-Nmr}$ (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 splitting, $J=6.35$ 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).
8. F. Carreaux, A. Duréault, and J. C. Depezay, *Synlett*, **1992**, 527 and references cited therein.
9. 7a: $\text{Ms } m/z$ 708 (M^+), $^1\text{H-Nmr}$ (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.

Received, 27th November, 1992