Tetrahedron Letters, Vol. 33, No. 12, pp. 1581-1584, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

A Practical Synthesis of the Dihydroxyethylene Dipeptide Isostere, (2S, 3R, 4S) 2-[(*tert*-Butyloxycarbonyl)amino]-1-cyclohexyl-3,4-dihydroxy-6-methylheptane, from D-Isoascorbic Acid

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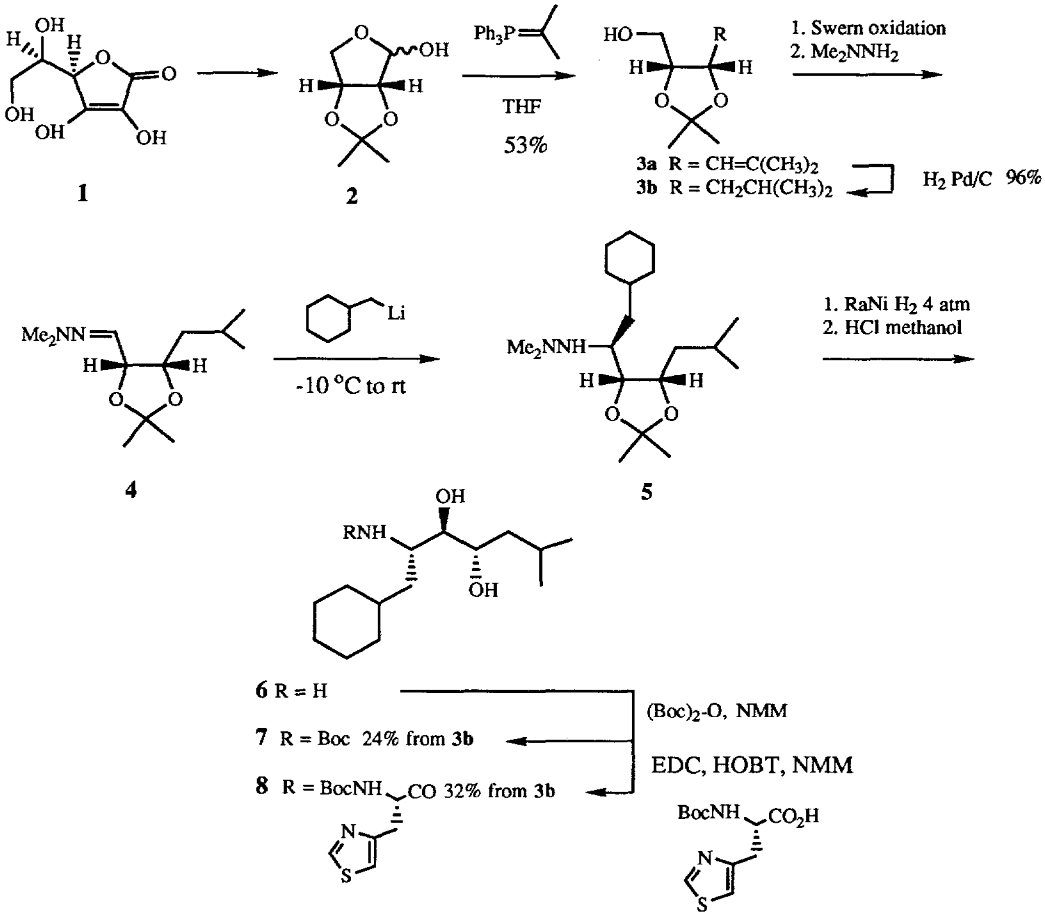
Key Words: D-isoascorbic acid; dihydroxyethylene dipeptide isostere; stereoselective organometalic addition reaction

Abstract: *The N-Boc dihydroxyethylene dipeptide isostere 7 and its N-Boc 3-(thiazol-4-yl)alanyl derivative 8 were synthesized, without purification of intermediates, from (4S,5R)-2,2-dimethyl-4-(2-methylpropyl)-5-hydroxymethyl-1,3-dioxolane (3b), in 24 and 32% overall yield, respectively. Alcohol 3b was readily prepared from inexpensive and commerically available D-isoascorbic acid in four steps. The synthesis featured a stereoselective addition of cyclohexylmethyllithium to the dimethyl hydrazone of (4S,5S)-2,2-dimethyl-4-(2-methylpropyl)-5-formyl-1,3-dioxolane (4).*

As part of program directed toward the development of dipeptide renin inhibitors for use has antihypertensive agents, we required a practical and cost effective synthesis of the dihydroxyethylene isostere **6**.[1] Although three syntheses of isostere **6** have been reported,[2] we believed that a more practical synthesis of **6** could be devised, one suitable for large scale production. The synthesis would employ inexpensive starting materials, require minimal purification of intermediates, and allow for the purification of the final products by direct crystallization from the crude reaction mixtures. We have developed an efficient and practical synthesis of isostere **6** from D-isoascorbic acid and our approach is outlined in the Scheme.

2,3-O-Isopropylidene-D-erythrose (**2**) was synthesized from D-isoascorbic acid (**1**) by literature procedures[3] and reacted with 2-isopropylidene triphenylphosphorane[4] in THF at -40 °C to rt over 18 h to give the unsaturated alcohol **3a**[5] in 53% yield. Catalytic reduction of **3a** produced alcohol **3b**[6] in 96% yield. Swern oxidation of alcohol **3b** followed by addition of 4 equivalents of dimethylhydrazine and anhydrous magnesium sulfate (rt, 1h) gave hydrazone **4** as a yellow oil in 62% isolated yield. Alternatively, hydrazone **4** was used in the next step without further purification. Using the procedure of Claremon et al.,[7] crude hydrazone **4** was reacted with 1.5 equivalents of cyclohexylmethyllithium, prepared by halogen-metal exchange of cyclohexylmethyl iodide[8] with *t*-butyllithium in diethyl ether (-10 °C to rt , 1.5 h), to give hydrazine **5** and its diastereomer in a ratio of 98 : 2 as judged by capillary GC-mass spectoscopy.[9] The stereochemistry of the major addition product was established by completion of the synthesis and comparison to authentic N-Boc amino diol **7**.[10] Thus, reduction of the crude hydrazine **5** (RaNi, H_2, 4 atm, 48 h), deprotection of the acetonide (6N HCl, methanol, rt, 4 h), and acylation of the amino diol hydrochloride with di-*tert*-butyl dicarbonate and N-methylmorpholine in THF gave, after crystallization of the reaction mixture from hexanes, the N-Boc amino diol **7** as white needles in 24% overall yield from **3b**.[11] In addition, the crude amino diol hydrochloride was coupled to N-Boc 4-thiazoylalanine[12] using standard peptide coupling procedures (EDC, HOBT, N-methylmorpholine, -23 °C to rt, DMF) to give, after crystallization of the crude reaction mixture from ethyl acetate/hexane, derivative **8** (32% overall yield from **3b**).[13]

Scheme



In conclusion, we have developed a practical and stereoselective synthesis of the N-Boc dihydroxyethylene isostere **7** and the amino acid derivative **8**. Three key goals were achieved. First, the target compounds **7** and **8** were obtained from inexpensive and readily available D-isoascorbic acid, five steps from **3b** in 24 and 32% yield, respectively. Second, intermediates **4**, **5**, and **6** were utilized without purification. Third, isolation of the final products **7** and **8** was accomplished by direct crystallization of the crude reaction mixtures.

Acknowledgement The authors wish to thank Dr. Howard Morton for assistance in obtaining GC-MS data.

References and notes

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5. Compound **3a**: bp 81 °C (0.6 mmHg). $[\alpha]^{25}_D$ +43.1° (c 1.65, CHCl$_3$); IR (CDCl$_3$) 3680-3320 (OH) cm^{-1}; ^{1}H NMR (DMSO-D6, 300 MHz) δ 5.14 (d, J = 9 Hz, 1H, HC=C), 4.81 (dd, J = 9, 11 Hz, 1H, O-CH-C=), 4.57 (t, J = 6 Hz, 1H, OH), 4.06 (dd, J = 6, 12 Hz, 1H, O-CH), 3.33 (t , J = 6 Hz, 2H, O-CH$_2$), 1.69 (s, 3H, C=CCH$_3$), 1.63 (s, 3H, C=CCH$_3$), 1.36 (s, 3H , CH$_3$), 1.27 (s, 3H, CH$_3$); mass spectrum (DCI) 204 (M+NH$_4$).
6. Compound **3b:** bp 63-65 °C (0.6 mm Hg): $[\alpha]^{25}_D$ +26.3° (c 2.2, CHCl$_3$); IR (CDCl$_3$) 3680-3320 (OH) cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 4.26 (7 line m, 1H, O-CH), 4.12 (dd, J = 6 Hz, 1H, O-CH), 3.60 (m, 2H, O-CH$_2$), 1.85 (dd, J = 4, 6 Hz, 1H, OH), 1.82-1.69 (14 line m, 1H, CH), 1.59-1.48 (8 line m, 1H, CH$_2$), 1.47 (s, 3H, dioxolane CH$_3$), 1.37 (s, 3H, dioxolane CH$_3$), 1.28-1.18 (8 line m, 1H, CH$_2$); 0.96 (d, J = 9Hz, 3H, CH$_3$), 0.93 (d, J = 9Hz, 3H, CH$_3$); mass spectrum (DCI) 189 (M+H), 206 (M+NH$_4$).
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9. GC-mass spectra were obtained on a HP 5890 gas chromatograph with a HP 5970 series MS detector using a HP-1 cross linked methylsilicone gum (0.33μm film thickness) capilary column; 25 m x 0.2 mm, with a helium flow rate of 100 mL/min. Initial oven temperature was 110 °C and then raised 20 °C/min to a final temperature of 250 °C. Retension times for compound **5** and its diastereomer were 19.936 and 19.594 min, respectively.
10. Physical properties for (2S,3R,4S) N-Boc-2-amino-3,4-dihydroxy-6-methylheptane (**7**) are: mp 124-26 °C;[1] $[\alpha]^{25}_D$ -64.9 ° (c 2.20, CHCl$_3$).[2b]
11. **Experimental procedure**: Swern oxidation of **3b** (10.0 g, 53.1 mmol) using oxalyl chloride (5.1 mL, 58 mmol), DMSO (9.1 mL, 117 mmol), triethylamine (37 mL, 266 mmol) in 140 mL of CH$_2$Cl$_2$ from -40 °Cto rt and addition of dimethylhydrazine (16.1 mL, 212 mmol) and MgSO$_4$ (12.7 g) and stirring at rt for 1 h gave the crude hydrazone **4**.

    To a solution of cyclohexylmethyllithium (prepared from 17.9 g (80 mmol) of cyclohexylmethyl iodide and 91 mL, 1.7 M (154 mmol) of t-butyllithium) in diethyl ether at -10 °C was added the crude hydrazone **4**. The reaction was stirred to rt over 1 h, recooled in an ice-water bath and quenched with water. The organic layer was separated, dried ($MgSO_4$) and concentrated to give 11.55 g of the crude hydrazine **5** a yellow oil.

The crude hydrazine **5** was dissolved in 250 mL methanol, and reduced at 4 atm, rt with 27 g of 2800 Raney nickel, at 4 atm for 48 h. The catalyst was filtered, and 27.5 mL of 6N HCl was added to the filtrate. The solution stirred for 4 h and concentrated to dryness. The resultant brown foamy solid was dissolved in 100 mL THF, 7.2 mL N-methylmorpholine, and 10.7 g (mmol) of di-*tert*-butyl dicarbonate. After 2 h at rt the THF was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with aq. $NaHCO_3$, dried ($MgSO_4$). Concentration of the solvents gave a brown oil which was redissolved in hexanes. The diol **7** crystallized from the hexanes as white needles affording 3.9 g (24% from **3b**): mp 124-27 °C; $[\alpha]^{25}_D$ -63.6 ° (c 2.2, $CHCl_3$) ; ^1H, ^{13}C NMR, and TLC were identical to a sample of **7** previously prepared.[1, 2b]

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13. Renin inhibitors employing the amino acid derivative **8** have been reported, see: Rosenberg, S. H.; Spina, K. P.; Kleinert, H. D. Martin, D. L.; Verburg, K. M.; Stein, H. H.; Cohen, J.; Egan, D. A.; Barlow, J. L.; Klinghofer, V.; Hoffman, D. J.; Garren, K. W.; Baker, W. R. Abstract 64, 201st National Meeting of the American Chemical Society, Division of Medicinal Chemistry, Atlanta, April 1991. Physical properties of **8** are: mp 156-57 °C, $[\alpha]^{25}_D$ -37.5° (c 1, CH_2Cl_2).

(Received in USA 15 October 1991; accepted 27 December 1991)