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Asymmetric Synthesis of the Abbott Amino Dihydroxyethylene Dipeptide Isostere Subunit

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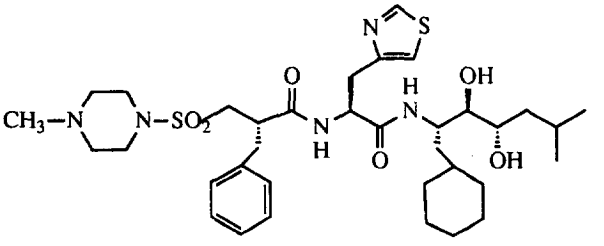
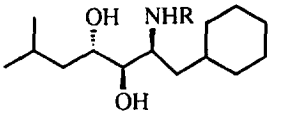
Abstract: The aminodiol **1b**, a N-benzyl protected form of the Abbott dipeptide isostere **1a** is prepared, starting from an appropriate α,β-unsaturated ester, involving an asymmetric dihydroxylation and a rearrangement of an intermediate *anti* α,β-aminoepoxide.

Some years ago, Luly and coll. reported that the aminodiol, (2*S*, 3*R*, 4*S*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol **1a** (also known as the Abbott Aminodiol), when incorporated into a specific protected dipeptide, was a potent inhibitor of the renin-angiotensin system[1]. For example, this dihydroxyethylene dipeptide isostere subunit is found into the renin inhibitor A-72517, a therapeutic agent for the treatment of hypertension and congestive heart failure[2]. Due to its promising activity, a number of publications related to the preparation of **1a** have been reported[3].



A-72517

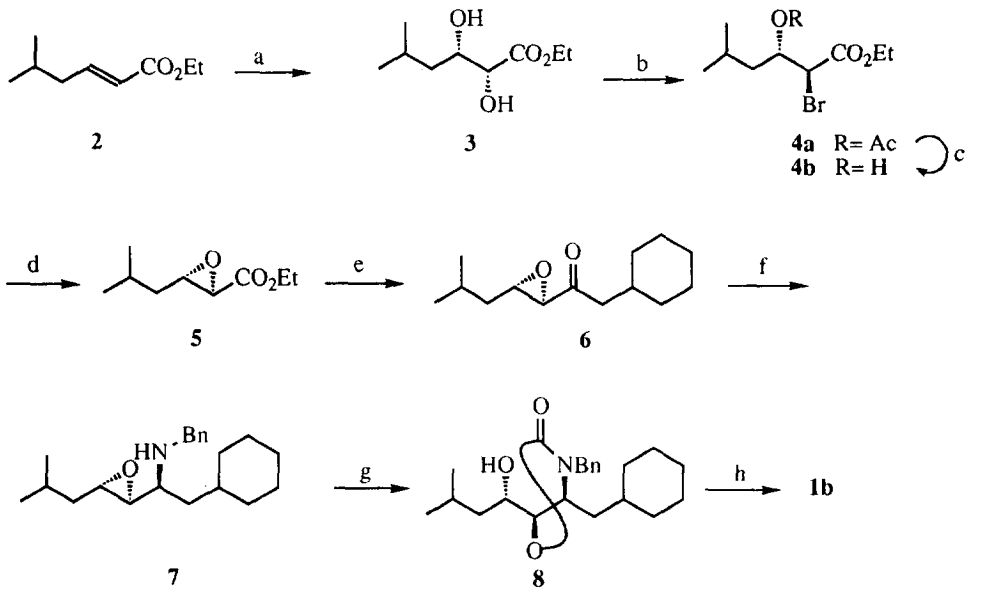


1a R=H
1b R=Bn

Herein, we describe the synthesis of the N-benzyl protected aminodiol **1b**, starting from the easily accessible α,β-unsaturated ester **2**, as shown below (**Scheme 1**).

The Sharpless asymmetric dihydroxylation (ADH)[4] of alkene **2** with AD-mix-α in the presence of methanesulfonamide proceeded smoothly to give diol **3** in 82 % yield. An enantiomeric excess of 80 % was measured according to the method described by König and coll.[5]. Thus, a sample of **3** was converted into its corresponding cyclic carbonate ($COCl_2$/pyridine), and submitted to gas chromatography using the XE-60-L-valine-(S)-α-phenylethylamide phase. In the next step, compound **3** was treated with trimethyl orthoacetate in the presence of catalytic boron trifluoride

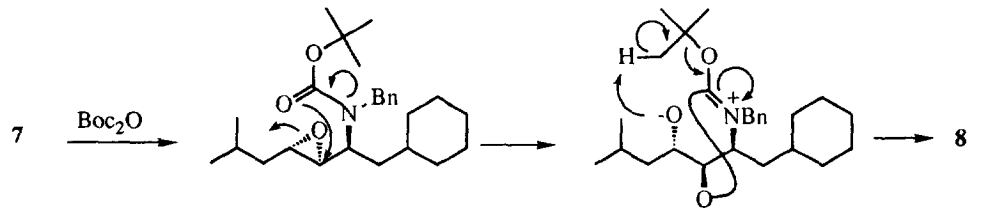
etherate, followed by acetyl bromide and triethylamine[6] to give the bromohydrin **4a** in 85 % yield. Attempt to effect directly deprotection of the remaining hydroxyl and cyclisation to obtain the epoxide **5** failed; only the formation of vinyl bromide was observed, resulting from elimination of HOAc. However, **5** could be isolated by firstly removing the acetate group in acidic medium (30 % HBr/ HOAc) and treating the free alcohol **4b** by K_2CO_3 in ethanol (76 % for the two steps)[7]. Condensation of **5** with cyclohexylmethylmagnesium bromide at -85 °C[8] afforded the α,β-epoxy ketone **6** in 50 % yield[3h]. Reductive amination of **6** with tetramethyl ammonium triacetoxyborohydride (TBAH) and benzylamine using the conditions developed in the laboratory[9] furnished the *anti* α,β-epoxy amine **7** in 64 % yield as a single diastereomer (only a trace of the *syn* diastereomer was detected by ^1H NMR). The key step of the synthesis was the transformation of **7** into oxazolidinone **8** (75 % yield)[10] by gently warming **7** in di-tert-butyl dicarbonate as solvent. Such a participation of the tert-butoxycarbonyl had already been observed in intramolecular epoxide opening under Lewis acid conditions[11], but to our knowledge this is the first case where it occurred in a neutral medium.



Scheme 1

Reagents and conditions: a) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH-H_2O (1:1), 0°C to rt, 72 h. b) $MeC(OCH_3)_3$, $BF_3.OEt_2$; CH_3COBr, NEt_3. c) 30 % HBr/HOAc, 45 °C, 48 h. d) K_2CO_3, EtOH, 3 h , rt. e) $C_6H_{11}CH_2MgBr$, THF, -85 °C. f) $PhCH_2NH_2$, AcOH, $Me_4NBH(OAc)_3$, CH_2Cl_2, 4 Å molecular sieves, 8 h. g) Boc_2O, 60 °C, 48 h. h) NaOH 6N, EtOH, reflux, 12 h.

The likely mecanism is a participation of the neighbouring alkoxide generated by epoxide opening as shown in **scheme 2**.



Scheme 2

Finally, the target compound **1b** was obtained in 76 % yield by the usual basic hydrolysis of the oxazolidinone (NaOH/ EtOH) [12].

In conclusion, we have developed a new practical preparation of the N-protected Abbott aminodiol with a fairly satisfactory overall yield, starting from easily accessible, nonchiral material.

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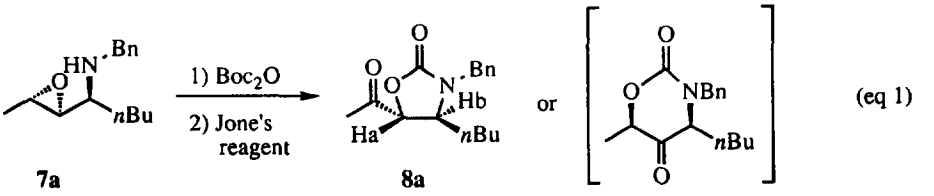
10. In order to establish the structure of **8**, we prepared the model epoxy amine **7a**, which was submitted to the same rearrangement followed by oxidation to afford the ketone **8a** (eq 1).



7a **8a** (eq 1)

^{1}H NMR of the latter showing the presence of a single signal at 2.24 ppm allowed us to deduce unambiguously the structure of **8a**. Furthermore, the vicinal ^{1}H coupling constant ($J_{a,b}$=4.8 Hz), as well as the chemical shift of H_a (4.40 ppm) are in full agreement with a trans stereochemistry[13]. It must be pointed out that this result is in opposition to those reported by Urabe and coll.[11a] who obtained the other regioisomer with similar compounds (epoxide opening under Ti(O-*i*-Pr)$_4$ catalysis).

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12. Experimental procedure for **1b**: Compound **8** (0.1 g, 0.27 mmol) in a solution of EtOH (10 ml) and 6N NaOH (1 ml) was refluxed overnight. After cooling, the solution was neutralized with 3N HCl and extracted with AcOEt three times. The combined organic layer was dried over $MgSO_4$. Crude **1b** was subjected to flash chromatography (CH_2Cl_2/ MeOH, 90/ 10) to yield 71 mg of pure **1b** (76 %).
spectral data for **1b:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.79 (6H, d, J = 6.6 Hz), 0.81-1.95 (16H, m), 3.11 (1H, m), 3.44 (1H, m), 4.03 (2H, AB system, J = 13.2 Hz), 4.08 (1H, m), 6.22 (3H, br), 7.37 (5H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.8, 23.5, 24.5, 26.0, 26.1, 26.4, 32.4, 34.1, 35.6, 42.0, 49.3, 54.1, 70.8, 73.0, 128.6, 128.9, 129.7, 134.4; MS (CI,NH_3) m/z 334 (M+1, 15%), 216 (100%); $[\alpha]_D^{22}$ +24.1 (c 1.16, CH_2Cl_2).

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