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A Stereospecific Synthesis of Both Enantiomers of 2-(1′-Amino-2′-Methylpropyl) Imidazole, a Key Synthon in the Synthesis of SB 203386; a Potent Protease Inhibitor

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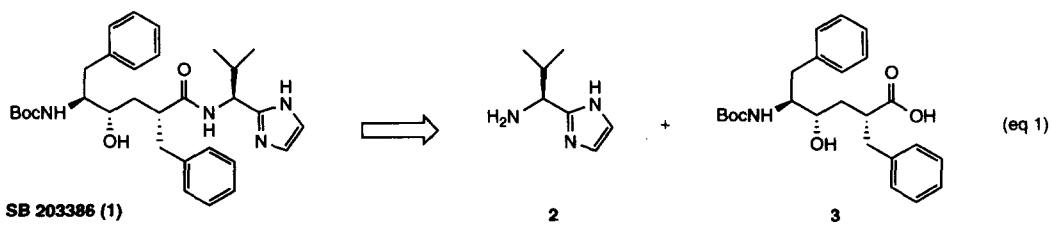
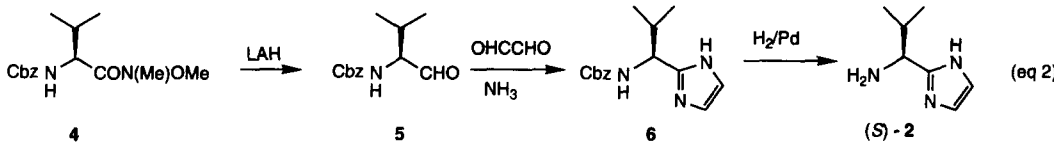
Abstract: Two methods for the asymmetric synthesis of both enantiomers of 2-(1′-amino-2′-methylpropyl)imidazole (**2**) have been developed by adding nucleophilic organometallics to nonracemic 2-oxazolidinones employing 2-phenylglycinol as the source of chirality. Excellent stereochemical yields were obtained.

A world wide effort to comprehend and control the spread of human immunodeficiency virus type 1 (HIV-1), led to the discovery that inhibition of the homodimeric aspartyl protease enzyme prevents the maturation and replication of the virus in cell culture.[1] Because the HIV protease displays an unusual preference for Tyr-Pro or Phe-Pro primary cleavage sites, attention has been focused on their replacement by a hydrolyzable peptide bond with a non-hydrolyzable isostere. Thus, much synthetic effort has been placed on developing hydroxyethylene dipeptide isotere inhibitors of HIV-1 protease. Our entry into this area led to the discovery of SB 203386 **1**, an orally bioavailable HIV-1 protease inhibitor containing an imidazole derived peptide bond replacement.[2,3] Since structure activity relationships have shown that the 4*S*-hydroxyl stereochemistry is generally optimal for aspartyl protease inhibitors, a stereochemically defined synthesis of **1** is essential for biological activity. The stereoselective synthesis of the carboxylic acid portion **3**, containing three stereocenters, has been previously reported by other researchers in this department.[4] A novel procedure to stereoselectively synthesize 2-(1′-amino-2′-methylpropyl)imidazole (**2**) is the subject of this communication.



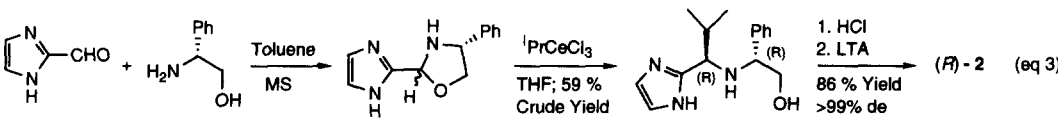
(eq 1)

The original three step synthesis of the imidazole **2** utilized the Weinreb Cbz-protected amide (eq 2), where the chirality was imparted from the naturally occurring valine precursors.[4]



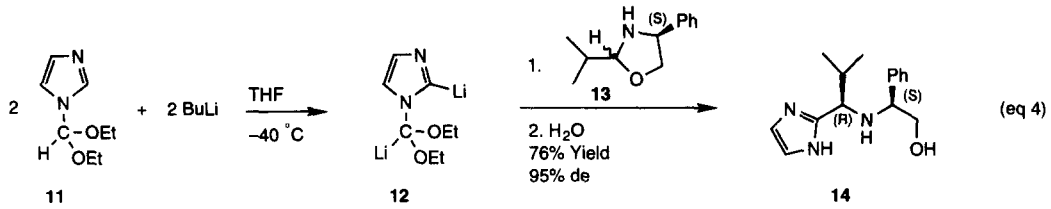
4 **5** **6** **(*S*) - 2**

Recently, a method for the efficient synthesis of nonracemic amines has been reported from this laboratory wherein organometallic nucleophiles were added to nonracemic oxazolidines which in turn were prepared by condensation of the appropriate aldehyde with either enantiomer of phenylglycinol.[5] Oxidative removal of the chiral auxiliary yielded nonracemic primary amines.[6] This approach has since found wide applicability for the synthesis of many varied nonracemic primary amines.[7] This protocol was successfully employed to synthesize **10** as a single diastereoisomer in >99% de and in 59% crude yield as shown in equation 3. Compound **10** was converted to *(R)*– **2** in 86% flashed yield and >99 % ee on treatment with lead tetraacetate.[6] This material was compared to an authentic sample prepared via eq 2 and revealed that indeed the *R* enantiomer, and not *S*, had been formed.



7 **8** **9** **10**

Although concise, this method was still not sufficiently cost efficient to overcome the expense of the starting material, 2-imidazolecarboxaldehyde (**7**). An attractive alternative is to reverse the roles of the imidazole and isopropyl groups in eq 3 by employing the imidazole as a nucleophilic agent and an isopropyloxazolidine as the electrophilic substrate. Direct lithiation of the 2-position of protected imidazoles is well documented.[8] Imidazole orthoamides [9] are especially attractive because of the ease of their preparation and the facility with which the protecting group may be removed. When the dilithio anion of the ortho ester protected imidazole **12** was reacted with nonracemic 2-isopropyloxazolidine **13**, the desired addition product was obtained 76% yield and 95% de. As expected, ^{1}H NMR analysis revealed that this diastereomer (**14**) was different than **10** and subsequently was proven to be the (1*R*), (1′*S*) diastereomer (eq 4). Diastereomer **14** maybe converted to (*R*)-**2** by treatment with lead tetraacetate as described above for **10**.[6] The enantiomer of **14** was prepared in 84% yield using the (*R*)-2-phenyl glycinol as auxiliary which would furnish (*S*)-**2**.



11 12 14

In summary, we have demonstrated two different diastereospecific approaches to prepare nonracemic 2-(1-amino-2-methylpropyl)imidazole (**2**). One has the option of employing the chemistry as demonstrated in eq 3 where the nucleophilic isopropyl organocerium is added to **9** to yield (*1R, 1'R*) -**10** , or alternatively, the chemistry demonstrated in eq 4 may be chosen where the role of the nucleophilic / electrophilic pair is reversed and the dilithio anion of the ortho ester protected imidazole **12** is added to the 2-oxazolidine **13** to yield (*1R, 1'S*)–**14**. Each synthesis proceeds in moderate to good yield with high diastereoselectivity.[10]

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10. The starting oxazolidine **9** was prepared from **7** and **8** in refluxing toluene under a Dean–Stark trap for 25 h while oxazolidine **13** was prepared[11] from propionyl aldehyde and (*S*)-2-phenyl glycinol in methylene chloride in the presence of $MgSO_4$ at room temperature for 4 h. All compounds gave satisfactory spectral and/or combustion analyses. Two representative experimental conditions for the organometallic additions are described:

(*1R,1'R*)-*N*-2'-Hydroxy-1'-(phenylethyl)-2-Methyl-1-(2-imidazoyl)propylamine (10). Cerium chloride was suspended in 270 mL of dry THF and stirred 1 h at ambient temperature. Isopropyl Grignard reagent (0.105 mol) was added at –73 °C and the suspension was stirred for 30 min at –73 °C. To this gray suspension at –73 °C was added a suspension of (*4R*)-2-(2-imidazoyl)-4-phenyl-1,3-oxazolidine (**9**) (5.0 g, 0.023 mol) in THF (20 mL). The reaction mixture was stirred at –73 °C for 4 h then allowed to stir at 23 °C for 18 h. The reaction mixture was quenched by pouring into NH_4Cl (satd), then extracted with diethyl ether. The ether extract was dried ($MgSO_4$) and concentrated in vacuo to yield the product **10** (3.5 g, 59 %) as a white solid: mp 114–117 °C; $[\alpha]_D^{25}$ –18.15° (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.10 (m, 6H), 6.74 (s, 2H), 3.85–3.69 (m, 3H), 3.65–3.53 (m, 1H), 2.17–1.98 (m, 1H), 0.94 (d, 3H, *J* = 6.7 Hz), 0.84 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 141.1, 128.3(3), 127.2(4), 65.7, 63.5, 61.2, 33.1, 19.2, 18.6; MS (CI/NH_3) *m/e* 260 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{12}N_3O$: C, 69.47; H, 8.16; N, 16.20. Found: C, 69.20; H, 8.25; N, 16.32.

(*1R,1'S*)-*N*-2'-Hydroxy-1'-(phenylethyl)-2-Methyl-1-(2-imidazoyl)propylamine (14). 1-Diethoxymethylimidazole (0.5 g, 2.93 mmol) was dissolved in dry THF (10 mL). The mixture was cooled to –40 °C then butyllithium (2.5 M in hexane, 1.2 mL, 3.0 mmol) was added over a 5 min period. After 30 min, the oxazolidine **13** (0.281 g, 1.47 mmol) was added all at once and the mixture was allowed to warm to 23 °C and stirred for 3 h. The reaction mixture was quenched with satd. NH_4Cl (1.0 mL) and the solvent removed under vacuum. The residue was dissolved in 50/1 (v/v) CH_2Cl_2/MeOH (50 mL) and was extracted with water (2 x 40 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired product **14** (0.28 g, 76%) as a thick oil: IR (neat) 3400 (br), 2940, 2860, 1600, 1550, 1490, 1450, 1380, 1360, 1110, 1090, 1060, 1020, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.15 (m, 6H), 6.81 (s, 2H), 3.70–3.42 (m, 4H), 2.10–1.85 (m, 1H), 0.85 (d, 3H, *J* = 7.0 Hz). 0.75 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 140.9, 128.5, 127.5, 127.4 121.2, 67.3, 62.7, 60.3, 34.0, 19.4, 18.5; MS *m/e* = 260 $(m+H)^+$.

Compound **10** was treated with 2 equiv of HCl then converted to (*R*)-**2** via our previously published lead tetraacetate procedure[6] and compared to an authentic sample of (*S*)-**2**.

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