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A novel and efficient synthesis of chiral C_2-symmetric 1,4-diamines

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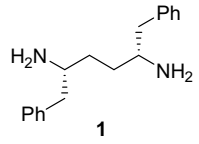
ABSTRACT

A novel and efficient method for synthesis of (*R*,*R*)- and (*S*,*S*)-C_2-symmetric 1,4-diamines was established. The key steps are a combination of Pinacol Coupling and Corey–Winter olefination.

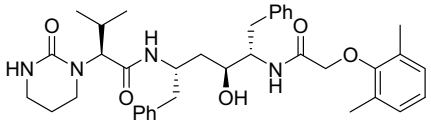
Diastereo- and enantiomerically pure 1,*n*-diamines ($n = 2–5$) are recognized as important structural elements of many biologically active compounds. In addition, 1,2-diamines are widely used as chiral auxiliaries and ligands in asymmetric synthesis. Therefore, it is not surprising that a number of synthetic methods exist for the diastereo- and enantioselective synthesis of vicinal diamines.[1] However, there are limited methods available for synthesis of other diamines. In one of our medicinal chemistry programs, we needed to synthesize chiral C_2-symmetrical 1,4-diamine **1** (Figure 1). Herein, we report our investigations that led to the sequential use of Pinacol Coupling and Corey–Winter olefination as methods of choice for the synthesis of 1,4-diamines.



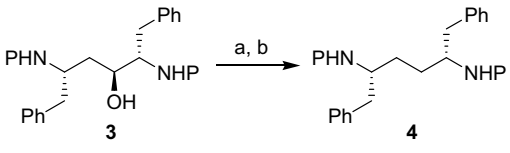
1

Figure 1.

One direct approach to 1,4-diamine **1** was to utilize the key intermediate **3** from the published synthesis of lopinavir (**2**).[2] As shown in Scheme 1, the removal of the hydroxyl group was achieved through free radical-mediated deoxygenation to provide diamine **4**.[3] However, the deoxygenation step required high dilution and use of tin-containing reagents, and therefore was judged unsuitable for synthesis on gram-scale which was needed for preparing analogs to establish SARs.



2 lopinavir



3 **4**

(P is protecting groups)

Scheme 1. Reagents: (a) TCDI; (b) AIBN/Bu_3SnH.

After we carefully analysed the few methods available for the diastereoisomeric synthesis of 1,4-diamines in the literature,[4] we decided to use the procedures optimized by Gurjar to generate the diamine **1** (Scheme 2). Both aldehyde **6b** and sulfone **7** were prepared from L-phenylalaninol **5**. Under Julia olefination conditions, the coupling reaction between aldehyde **6b** and sulfone **7** afforded alkene **9**. Debenzylation of **9**, followed by hydrogenation and deprotection of the Boc-group, gave diamine **1** from **6b** in 33% overall yield. Diamine **1** prepared through this method served our initial purpose of establishing limited SAR. However, the fact that the Julia olefination required the use of *n*-butyllithium at low temperature (−78 °C), and a large amount of mercury (for Na/Hg amalgam) limited its application to large-scale production. In addition, the necessity of benzyl protection of the amino function of the aldehyde **6b** to facilitate smooth Julia olefination resulted in the use of sodium/ammonia in the debenzylation step, which presented further challenges in a multi-gram synthesis for preclinical evalua-

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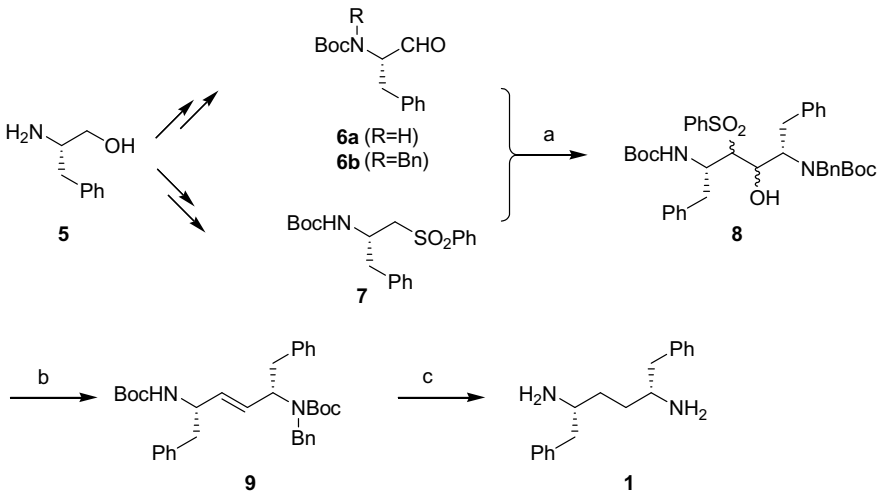
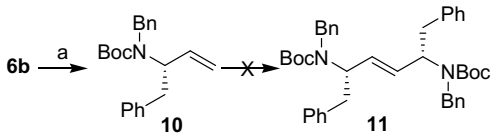
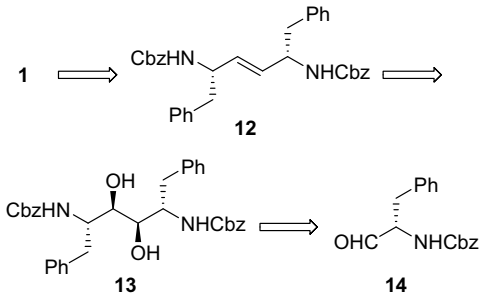


Scheme 2. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; (b) (i) Ac_2O, Py, CH_2Cl_2, rt; (ii) 6%Na–Hg, Na_2HPO_4, MeOH, rt; (c) (i) Na/liq NH_3, THF, −33 °C; (ii) H_2, 10% Pd/C, rt; (iii) HCl/dioxane.



Scheme 3. Reagents: (a) KHMDS, $BrP^+Ph_3CH_3$.



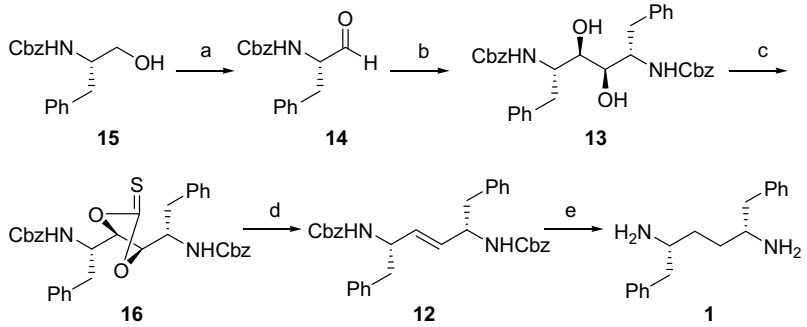
Scheme 4.

tion. The efforts to use aldehyde **6a**, where benzyl protection was absent, for Julia olefination met with failure. Furthermore, preparation of both aldehyde **6b** and sulfone **7** involved many steps. The synthesis of diamine **1** from commercial phenylalaninol took 12 total steps, or 9 steps in the longest linear sequence. Modified Julia olefination, such as Julia–Kocienski olefination, was considered but it only partially removed those limitations discussed above. We felt that, in order to provide a large quantity of 1,4-diamine **1**, it was necessary to develop a new and efficient synthesis.

A potential route to prepare compound **11**, which could be converted to diamine **1** using a similar procedure as in the transformation of compound **9** to **1**, is through metathesis of olefin **10**. Olefin **10** was synthesized according to the literature procedure from **6b**.[5] Unfortunately, no desired olefin **11** was observed after treating olefin **10** with different metathesis conditions[6] (Scheme 3).

A second method we envisioned, as outlined in Scheme 4, was one in which diol **13** could be converted into alkene **12** through Corey–Winter olefination,[7] which after hydrogenation should afford desired 1,4-diamine **1**. Diol **13** could be easily accessed from aldehyde **14** through a Pinacol Coupling reaction. Aldehyde **14** would be obtained from commercially available amino alcohol or amino acid. The combination of Pinacol Coupling and Corey–Winter olefination could provide a new procedure for the synthesis of chiral C_2-symmetrical 1,4-diamines.

The method is summarized in Scheme 5. Cbz-L-phenylalaninol **15**, prepared easily from L-phenylalaninol **5**[8] or obtained from commercial sources directly, was oxidized with SO_3-pyridine in DMSO to afford the aldehyde **14**. Aldehyde **14** can also be prepared from either the free acid of or an ester of Cbz-L-phenylalanine.[9] The aldehyde **14** was transformed into the diol **13** through an intermolecular vanadium-assisted Pinacol Coupling reaction according to the literature procedure.[10] As reported in the literature, high diastereomeric purity of diol **13** was achieved after recrystallization in tetra-



Scheme 5. Reagents and conditions: (a) SO_3-pyridine/Et_3N/DMSO; (b) VCl_3–$(THF)_3$/Zn/THF; (c) TCDI/THF/70 °C; (d) $P(OEt)_3$/160 °C; (e) H_2/10%Pd/C/MeOH; over all yield 70–80% from **13**.

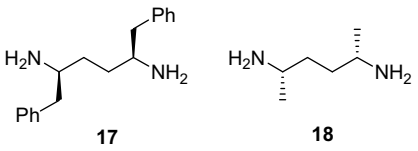


Figure 2.

hydrofuran (THF)/hexanes. Reaction of diol **13** with 1,1′-thiocarbonyldiimidazole in refluxed THF yielded cyclic thiocarbonate **16**. Treatment of thiocarbonate **16** with triethylphosphite at 160 °C generated alkene **12**. We found that the purity of the thiocarbonate **16** was very important for a successful elimination. The desired purity of thiocarbonate **16** could be achieved by a quick flash chromatography or by washing the reaction mixture with dilute hydrochloric acid. The symmetric alkene **12** was a highly crystalline compound, and it could be recrystallized easily in ethyl acetate/hexanes. Finally, hydrogenation of alkene **12** under one atmosphere of hydrogen catalyzed by 10%Pd/C afforded diamine **1**. In this sequence, diamine **1** was prepared from diol **13** in excellent yields (70–80%).[11] Using this method, the diamine **1** can be prepared in total five steps from Cbz-protected phenylalaninol. The reactions were carried out on hundred-gram scales, and purifications for the whole sequence were achieved through recrystallizations.

Similarly, the (*S*,*S*)-enantiomer **17** (Fig. 2) was synthesized on a hundred-gram scale following the same sequence starting from Cbz-D-phenylalaninol. Other alkyl-substituted C_2-symmetric 1,4-diamines, such as diamine **18**, were also prepared in a similar manner and in comparable yields when starting from the corresponding amino alcohols or amino acids (Fig. 2).

In conclusion, we have developed a novel and practical method for diastereoselective synthesis of chiral C_2-symmetric 1,4-diamines from easily accessible amino alcohols or amino acids.

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11. *Typical experimental procedure*: Diol **13** (50.0 g, 88 mmol) was dissolved in THF (1500 ml) with heating, and the solution was cooled to 25 °C. 1,1′-Thiocarbonyldiimidazole (31.3 g, 176 mmol) was added, and the mixture was refluxed for 60 h. The reaction mixture was cooled to 25 °C and filtered. Then, the mixture was concentrated to give a brown solid. The solid was dissolved in ethyl acetate (1000 ml), and the resulted solution was washed with 2.5% HCl solution (400 ml/200 ml/200 ml), followed by water (200 ml), saturated sodium bicarbonate solution (200 ml), and brine. The solution was dried over sodium sulfate and concentrated to give compound **16** as a yellow solid (56.0 g). To above solid was added triethylphosphite (200 ml), and the mixture was heated at 165 °C for 24 h. Excess triethylphosphite was removed under reduced pressure to give compound **12**. Recrystallization of the crude material from ethyl acetate and hexanes gave pure olefin **12** as a white solid (36.5 g) in 77% yield. *m*/*z*: 535.1 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 7.4–7.0 (20H, m), 5.47 (2H, m), 5.07 (4H, s), 4.62 (2H, m), 4.45 (2H, m), 2.78 (4H, d, J = 6.1 Hz).