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Asymmetric synthesis of novel α-amino acids with β-branched side chains

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Abstract—An asymmetric synthesis of α-amino acids with novel β-branched side chains has been implemented. The syntheses feature a *p*-toluenesulfinylimine induced chiral Strecker approach and were found to be applicable to the introduction of both aliphatic and aromatic β-branched sidechains for preparation of previously unknown α-amino acids.

In an effort to discover metabolically more stable and biologically interesting pharmacophore components for our current medicinal chemistry programs, we have implemented an asymmetric synthesis of α-amino acids with novel β-branched side chains.[1] The syntheses feature a *p*-toluenesulfinylimine induced chiral Strecker approach and were found to be applicable to the introduction of both aliphatic and aromatic β-branched sidechains for the preparation of previously unknown α-amino acids.[2] Herein, we wish to report three examples of such α-amino acid syntheses shown in Figure 1.

Bis-(trifluoromethyl)-valine **1** is believed to be metabolically more stable due to its fluorine cap. It, therefore, is a much desired building block for drug design; however, its synthesis had proved much more difficult than initially thought. The presence of polyfluoro groups has a major impact on the reactivity and stability of the synthetic intermediates, therefore, reaction conditions applicable to normal nucleophilic or electrophilic reactions cannot be applied directly to these cases. Shown in Schemes 1 and 2 are synthetic routes that helped resolve these issues and led to the successful preparation of this fluorine-capped α-amino acid.

Pivotal to the success for the synthesis of **1** was the preparation of the key Horner–Emmons precursor **6**. While conversion of trifluoropropyl iodide **4** to its phosphonium salt **5** is easily accomplished, preparation of **6** via nucleophilic addition of **5** to ethyl chloroformate using two equivalents of potassium hexamethyldisilazide was problematic, affording only 30–40% yield of **6** under the optimum carefully controlled conditions. A simple change of the base from potassium to lithium hexamethyldisilazide improves the yield dramatically. As illustrated in Scheme 1, the proposed side reaction is largely due to the nucleophilicity of the potassium base toward ethyl chloroformate and leads to undesired car-

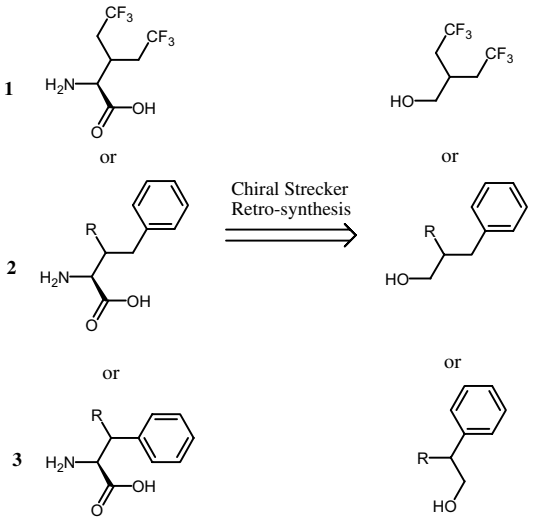

Figure 1. Retrosynthesis of β-branched α-amino acids **1**, **2**, and **3**.

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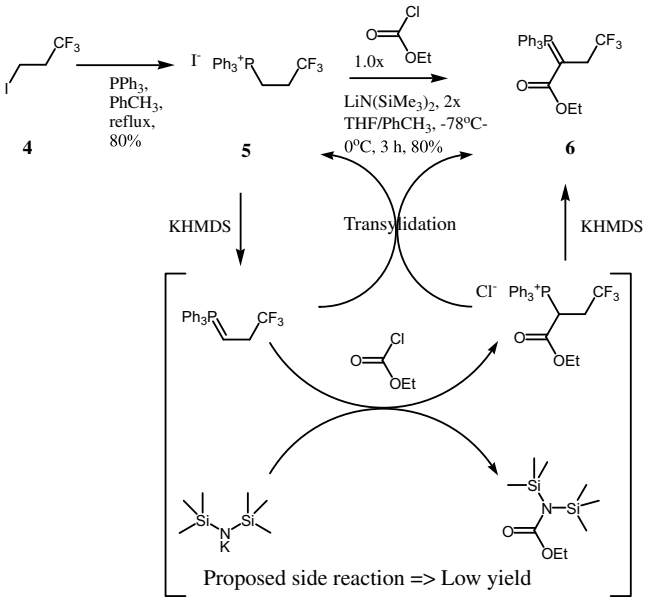
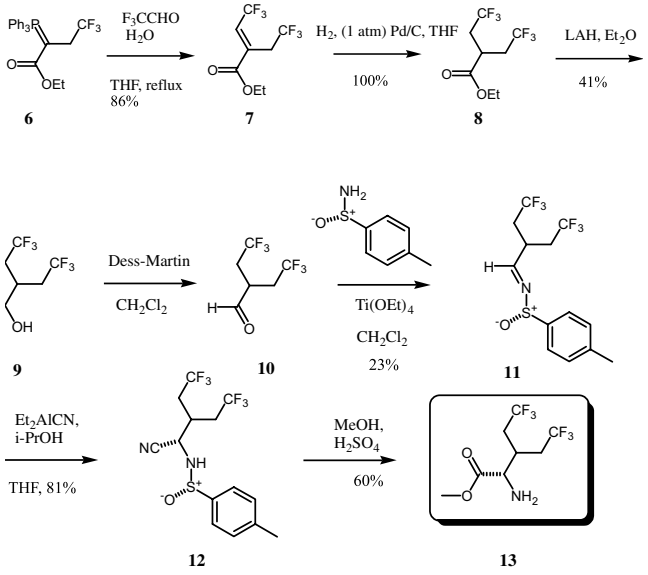


Scheme 1. Conditions and side reactions for the preparation of **6**.



Scheme 2. Conditions for the preparation of **13** from **6**.

bamate by-product. The lithium counter ion is probably modulating the nucleophilicity of the base and suppressing the side product formation.

Scheme 2 illustrates the synthetic route from intermediate **6** to the desired methyl ester of bis-(trifluoromethyl)-valine **13**. The key precursor to the asymmetric Strecker reaction is the aldehyde **10**. The precursor **6** is converted to **8** via the proposed Horner–Emmons reaction of **6** with excess trifluoroacetaldehyde at reflux conditions in THF followed by hydrogenation of the olefin **7**. LAH reduction of the ester **8** and oxidation of the resulting alcohol **9** with Dess–Martin periodinane at 0–25 °C in CH_2Cl_2 provided the aldehyde **10**. The asymmetric induction of the desired amino ester **13** was accomplished by using *p*-toluenesulfinylimine as a chiral auxilliary originally introduced by

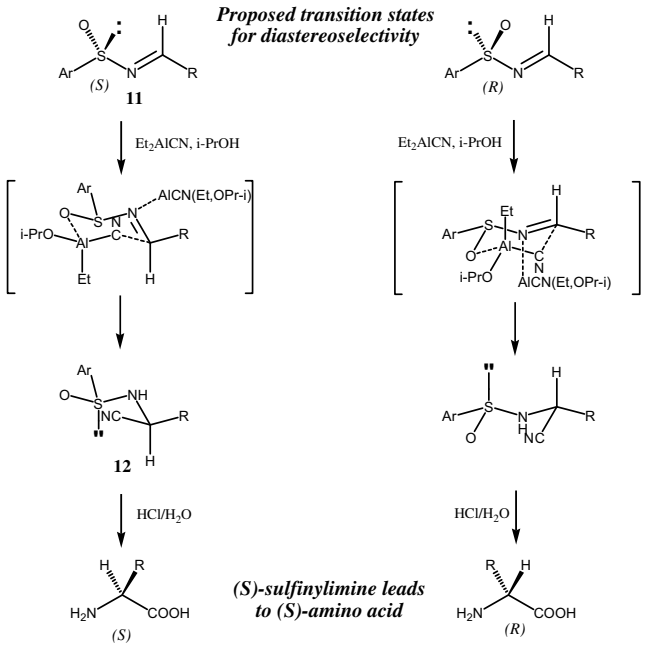
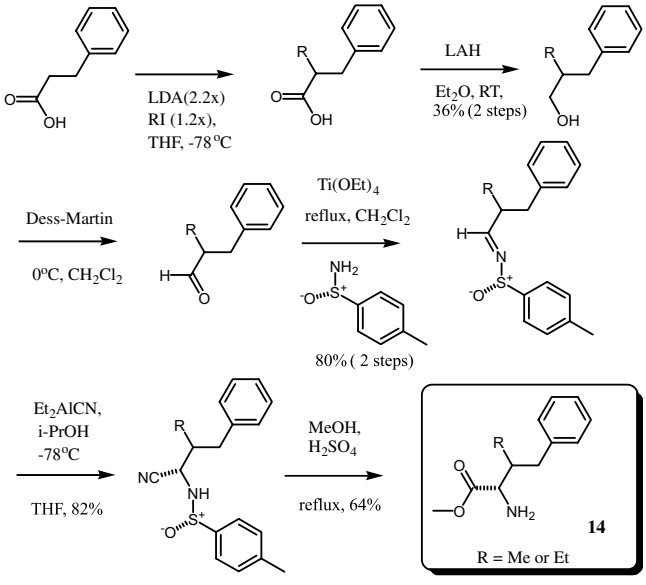


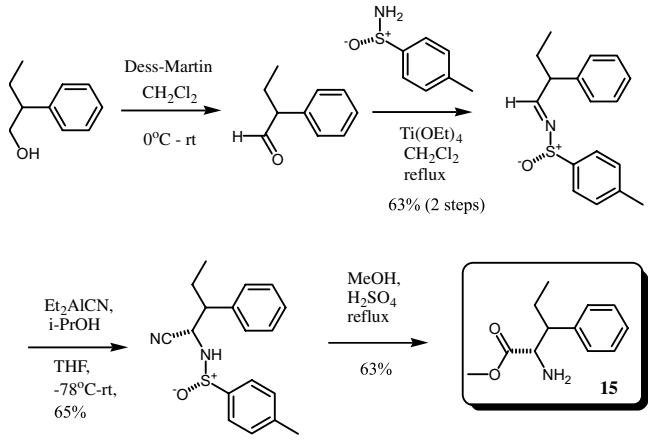
Figure 2. Proposed transition states for the asymmetric induction.

Franklin Davis and coworkers.[2] As illustrated in Figure 2, the sulfinylimine **11** is believed to form an aluminum complex with the cyanide source and isopropanol in a least crowded chair-like transition state to deliver diastereoselectivity. Consequently, use of (*S*)-*p*-toluenesulfinamide leads to (*S*)-**12**.

Due to the volatility of the aldehyde, crude **10** was used in the preparation of **11**, resulting in an overall yield of 23% for the two steps (un-optimized). The diastereoselectivity from **11** to **12** is over 90% on repeated trials and can be further enriched in subsequent purifications by re-crystallization. The sulfinylimine **12** is converted to the desired methyl ester of bis-(trifluoromethyl)-va-



Scheme 3. Preparation of β-methyl or β-ethyl homophenyl-alanine.



Scheme 4. Preparation of the methyl ester of β-ethyl phenylalanine.

line **13** by refluxing in methanol in presence of catalytic sulfuric acid, or to **1** in presence of sulfuric acid and water.[3,4]

The asymmetric Strecker synthesis of novel α-amino acids demonstrated above were also applied to the syntheses of the previously unknown α-amino acids **14** and **15** as shown in Schemes 3 and 4[3–6]

A typical procedure for the asymmetric synthesis of a β-branched α-amino acid from a β-branched primary alcohol outlined above is given in the references and notes section.[3]

Applications of these novel α-amino acids as new building blocks and key pharmacophore components for drug design in our medicinal chemistry programs will be reported in future publications.

References and notes

1. (a) Kreft, A.F.; Resnick, L.; Mayer, S.C.; Diamantidis, G.; Cole, D.C.; Harrison, B.L.; Zhang, M.; Hoke, M.; Ting, W.; Galante, R.C.U.S. Patent 20040198778, 2004; (b). *Chem. Abstr.* **2004**, *141*, 314147.
2. Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y. *J. Org. Chem.* **1996**, *61*, 440.
3. To a solution of the primary alcohol (5.8 mmol) in methylene chloride (17 mL) at 0 °C was added Dess–Martin periodinane (2.5. g, 5.9 mmol) slowly. The reaction mixture was left to stir and warm to room temperature overnight. The solution was diluted with diethylether (15 mL) and a solution of $Na_2S_2O_4$ (3.2 g) in a saturated aqueous solution of $NaHCO_3$ (30 mL). The liquid layers were extracted with ethyl acetate. The organic layer was separated and concentrated to afford the crude aldehyde. The crude aldehyde in methylene chloride was then treated with titanium (iv) ethoxide (4 mL, 20 mmol) followed by (*S*)-toluenesulfinimide (0.85 g, 5.5 mmol). The solution was refluxed for approximately 5 h. Water (18 mL) was added dropwise to precipitate titanium salts. The suspension was filtered though Celite and the filter cake was washed with CH_2Cl_2. The layers of filtrate were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. Column chromatography affords the purified sulfinylimine. To diethylaluminum cyanide (5 mL, 1.0 M in toluene, 5.2 mmol) in THF (12 mL) at 0 °C was added *i*-PrOH (267 μL, 3.5 mmol). After 15 min, this solution was added to a −78 °C solution of the sulfinylimine (3.5 mmol) in THF (19 mL). After 1 h, an additional solution of diethylaluminum cyanide and *i*-PrOH (in the same amounts) was added to the reaction. After another 2 h, the reaction mixture was quenched into saturated aqueous solution of ammonium chloride and extracted 2× with ethyl acetate. Column chromatography with ethyl acetate–hexane (0–50% gradient) affords the chiral Strecker product. A solution of this product (3.5 mmol) in MeOH (8 mL) was treated with H_2SO_4 (2 mL) dropwise and refluxed for 5 h and then left to stir at room temperature overnight. Extraction with 1 N NaOH and EtOAc affords the methyl ester of the desired α-amino acids.[4–6]
4. For **13**: mass spectrum (+ESI): 268.1 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ: 2.3 (4H, m, $2CH_2$), 2.7 (1H,m, CH), 2.9 (2H, d, NH_2), 3.6 (1H, 2t, CHN).
5. For **14**: mass spectrum (+ESI): 222.7 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ:1.0 (3H, m, CH_3), 1.2 (2H, m, CH_2CH_3), 1.3 (1H, m, CH_2CH), 2.0 (1H, m, CHN), 2.2 (2H, m, NH_2), 2.7 (2H, m, $ArCH_2$), 3.7 (3H, s, OCH_3), 7.0–7.4 (5H, m, ArH).
6. For **15**: mass spectrum (+ESI): 208.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ: 0.5 (3H, m, CH_3), 1.7 (2H, m, CH_2), 1.9 (2H, m, NH_2), 2.8 (1H, m, CH), 3.5 (3H, s, OCH_3), 3.6 (1H, 2t, CHN), 7.0–7.4 (5H, m, ArH).