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Chemical dynamic resolution of unprotected β_2- and β_3-amino acids with a novel Me-proline-derived chiral ligand

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β-Amino acids (β-AAs) and their analogs are becoming an increasingly common structural feature among newly developed pharmaceuticals and biomaterials in healthcare industries. In this regard, availability of structurally varied β-AAs came to be a critically important rate-determining factor in exploring rich biochemistry and applications of β-AAs. However, previously developed chemical or chemo-enzymatic methods do not work on free β-AAs requiring the chemical protection steps. Herein, we have developed the first purely chemical method for the dynamic resolution of both unprotected racemic α-substituted-β-amino acids (β_2-AAs) and β-substituted-β-amino acids (β_3-AAs) using specially designed, Me-proline-derived, non-racemizable chiral ligand. The chelation of the novel chiral ligand (R)-1 with racemic β-AAs 2 or 3 formed two nickel complex diastereoisomers, major product (1R,2S)-4 or 5 and minor product (1S,2R)-4 or 5 in high yield and diastereoselectivity (Figure 1). Due to the less thermodynamic stability, the minor diastereoisomer could be interconverted to the major one under base conditions via gradual epimerization to achieve the dynamic resolution process. After simple hydrolysis of the major nickel complexes, C,N-unprotected enantiomerically pure (>99% ee) β-AAs could be obtained in nearly quantitative yield (>90% yield), and fully recyclable source of chirality of ligand 1 could be achieved on account of its excellent thermodynamic stability, thus allowing its reuse. The method showed a broad synthetic generality for various alkyl and aryl substituted β-AAs. Besides, the presented method involved operationally simple and convenient reaction conditions, thus allowing its scalability. The method also has been successfully applied in the scalable synthesis of anti-HIV drug maraviroc in 49% overall yield within six steps, possibly making it be of great interest to industry.

Figure: Chemical resolution of unprotected racemic β_2-AAs and β_{tr}-AAs with Me-proline-derived ligand 1.

Recent Publications

1. Del Borgo M P, Kulkarni K and Aguilar M I (2017) Using beta-amino acids and beta-peptide templates to create bioactive ligands and biomaterials. Current Pharmaceutical Design 23:3772-3785.
2. Nian Y, Wang J, Zhou S B, Wang S N, Moriwaki H, et al. (2015) Recyclable ligands for the non-enzymatic dynamic kinetic resolution of challenging α-amino acids. Angewandte Chemie-International Edition 54:12918-12922.
3. Takeda R, Kawamura A, Kawashima A, Sato T, Moriwaki H, et al. (2014) Chemical dynamic kinetic resolution and S/R interconversion of unprotected alpha-amino acids. Angewandte Chemie-International Edition 53:12214-12217.
4. Kudo F, Miyanaga A and Eguchi T (2014) Biosynthesis of natural products containing beta-amino acids. Natural Product Reports 31:1056-1073.
5. Weiner B, Szymanski W, Janssen D B, Minnaard A J and Feringa B L (2010) Recent advances in the catalytic asymmetric synthesis of beta-amino acids. Chemical Society Reviews 39:1656-1691.

Biography

Shuni Wang received her Bachelor's in Pharmaceutical Sciences at Sun Yat-sen University, China. In 2013, she began her PhD under the supervision of Professor Hong Liu at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, China. Her research interests are focused on the discovery and synthesis of pharmacologically active molecules acting on targets related to epigenetics for the treatment of cancer, such as LSD1 and NSD2. In the aspect of synthetic methodology, she has participated in the design of novel chiral ligands for the applications to dynamic resolution of unprotected amino acids.

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