Pergamon

Tetrahedron Letters 39 (1998) 3749–3752

TETRAHEDRON LETTERS

Asymmetric Synthesis of α,α-Disubstituted α-Amino Acid Derivatives Using MABR Promoted Rearrangement

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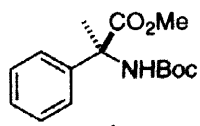
Received 4 February 1998; revised 9 March 1998; accepted 13 March 1998

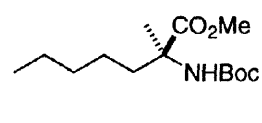
Abstract: An efficient route for the asymmetric synthesis of α,α-disubstituted α-amino acids derivatives (**1**, **2**, and **3**) starting from readily available epoxy silyl ethers (**6**) has been developed. High enantiomeric purity can be realized by the present method using a combination of MABR rearrangement of a chiral epoxide and Curtius rearrangement.

Synthesis of α,α-disubstituted α-amino acids, an important class of nonproteinogenic amino acids, are of current interest because these irregular amino acids frequently play an important role in the inhibition of enzyme activities and modification of the conformation of bioactive peptides. Although a wide variety of synthetic approaches to the α,α-disubstituted α-amino acids has been developed,[1-4] most of them are based on the stereoselective alkylation of cyclic compounds, i.e., Schöllkopf's bislactim ether,[2a] Seebach's oxazolidine,[2b] and William's oxazinone.[1b] Various modifications have been attempted to overcome the limitations of these cyclic approaches.[1b,5]

In this communication, we would like to report the synthesis of (*S*)-α-methylphenylglycine, (*S*)-α-pentylalanine, and (*R*)-α-methylserine derivatives[4a,6] (**1**, **2**, and **3**) by a completely different approach which allows us to introduce various types of substituents to the α-position of amino acids in a stereocontrolled manner.



1



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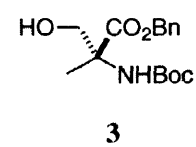
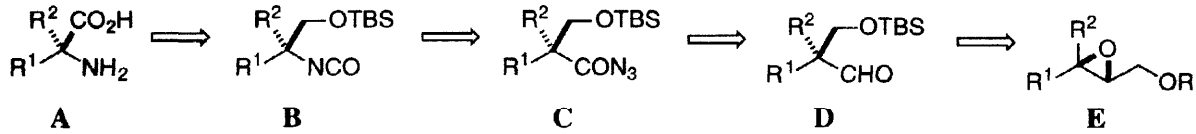


3

Our synthetic strategy is based on two rearrangements as outlined in Scheme 1.[3] The amino group of disubstituted amino acid **A** is introduced through **B** by Curtius rearrangement of an acylazide **C**. Aldehyde **D**, the precursor of **C**, is constructed by the rearrangement of an epoxy silyl ether **E**, which is accessible by the asymmetric epoxidation[7] or asymmetric dihydroxylation[8] of an allylic alcohol in high enantiomeric purity.[4] By this approach, any desired substituent could be attached to the α-position of **A**, if an appropriate allylic alcohol

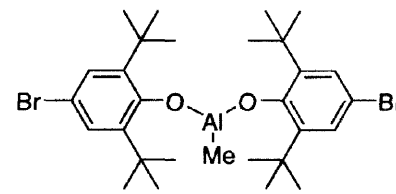
0040-4039/98/$19.00
PII: S0040-4039(98)00576-0

is chosen as the starting material. Another advantage of this approach is that it is possible to synthesize both enantiomers of a disubstituted amino acid if desired, since the preparative method for both enantiomers of the epoxide **E** has been established. Methylaluminum bis(4-bromo-2,6-di-*tert*-butyl-phenoxide) (MABR), an



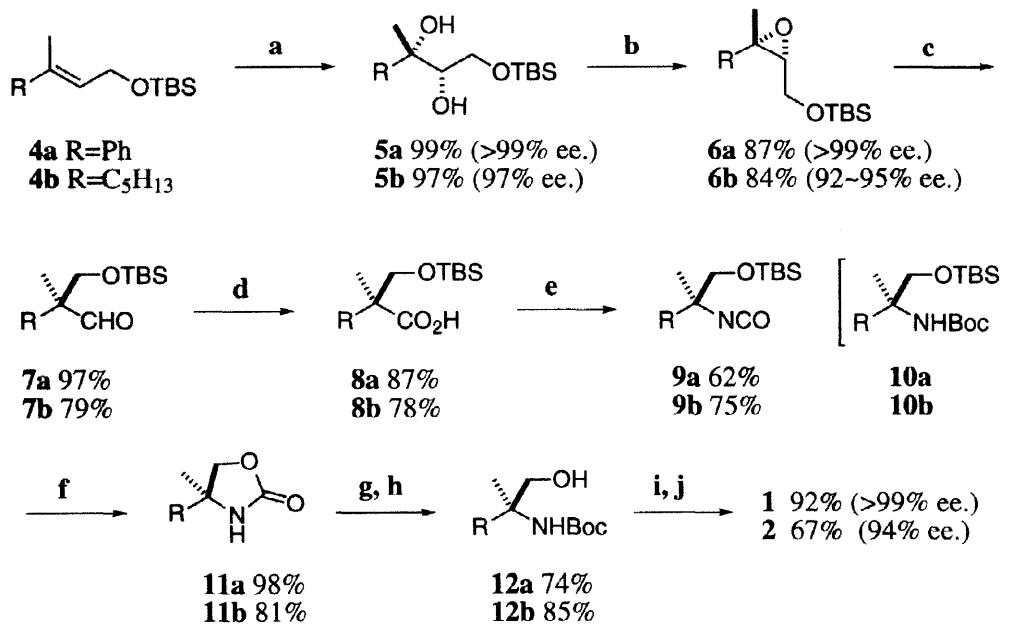
Scheme 1

exceptionally bulky Lewis acid reported by Maruoka and Yamamoto,[9] seems to be most effective for the rearrangement of epoxy silyl ether **E** to **D** because this type of rearrangement has been shown to take place stereoselectively. Based on this strategy, we attempted to synthesize three α,α-disubstituted α-amino acid derivatives (**1**, **2**, **3**) having different types of substituents.



MABR

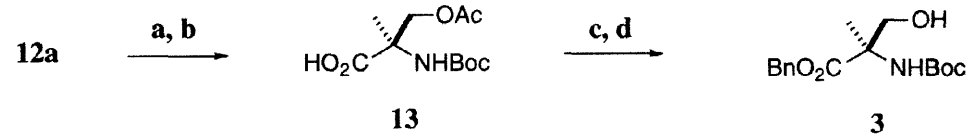
Asymmetric dihydroxylation[8] of allylic ethers **4a** and **4b** gave diols **5a** and **5b** in high enantiomeric purity, which were converted into epoxides **6a** and **6b** through mesylates.[10] The rearrangement of **6** took place smoothly by treatment with MABR at -78 °C for 0.5 h to afford β-siloxy aldehyde **7a** and **7b**. The optical



Scheme 2 **a**: AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 0 °C; **b**: i) MsCl or Ms_2O, 4-DMAP, Et_3N, CH_2Cl_2, -78 °C, ii) K_2CO_3, MeOH; **c**: MABR, CH_2Cl_2, -78 °C; **d**: RuO_4, $NaIO_4$, CCl_4, CH_3CN, H_2O; **e**: DPPA, Et_3N, toluene, reflux; **f**: BF_3·OEt_2, THF; **g**: Boc_2O, Et_3N, 4-DMAP, THF; **h**: Cs_2CO_3 or K_2CO_3, MeOH; **i**: i) Dess-Martin reagent, CH_2Cl_2; ii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, H_2O; **j**: CH_2N_2, ether.

purity of the products was determined after converting them into the final products **1** and **2**.[11] The aldehydes **7** were oxidized to carboxylic acids **8a** and **8b**, which were subjected to Curtius rearrangement using DPPA[12] to yield isocyanates **9a** and **9b**. In this reaction, addition of *tert*-butyl alcohol gave **9** again, instead of carbamates **10** obtained usually. $BF_3 Et_2O$-mediated cyclization of **9** afforded the oxazolidinones **11a** and **11b**,[13] which were protected with the *tert*-butoxycarbonyl (Boc) group and hydrolyzed to give the alcohols **12a** and **12b**. Successive treatment of **12** with Dess-Martin reagent,[14] $NaClO_2$, and then diazomethane yielded (*S*)-α-methylphenylglycine and (*S*)-α-pentylalanine derivatives (**1** and **2**).[15] Optical purity of **1** (>99% ee) and **2** (94% ee)[16] proved that no racemization occurred during the two rearrangements.

(*R*)-α-methylserine derivative **3** also could be synthesized from the amino alcohol **12a** as follows. Acetylation of **12a** followed by oxidative cleavage of the phenyl group[17] afforded carboxylic acid **13**, which was saponified and then benzylated to give rise to **3**. Spectroscopic data and optical rotation of the synthetic substance were identical with those of the reported compounds.[15]



Scheme 3 **a**: Ac_2O, 4-DMAP, Et_3N, CH_2Cl_2; **b**: RuO_4, $NaIO_4$, CCl_4, CH_3CN, H_2O; **c**: K_2CO_3, MeOH; **d**: BnBr, K_2CO_3, DMF. 27% for 4 steps.

In conclusion, we have developed a new, widely applicable method for the synthesis of the α,α-disubstituted α-amino acid derivatives. Application of the present methodology to the synthesis of natural products is in progress in our laboratories.

Acknowledgements: The authors wish to thank Professors S. Hatakeyama and H. Irie, Nagasaki University, for providing a copy of NMR spectra of authentic **3**.

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10. The optical purity of the epoxides **8** was determined by ^{1}H NMR (600 MHz) after deprotection of the silyl ethers and converting into the MTPA esters. Katsuki-Sharpless epoxidation of the corresponding allyl alcohols gave optically active products up to 90% ee.
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15. Optical rotation, ^{1}H NMR (200 MHz), and ^{13}C NMR (50 MHz) data as follows. **1**: $[\alpha]_D^{21}$ +44.2° (*c* 1.44, $CHCl_3$); δ 7.47-7.27 (5H, m), 5.82 (1H, br.s), 3.69 (3H, s), 1.99 (3H, s), 1.37 (9H, s); 173.67 (s), 154.22 (s), 141.01 (s), 128.53 (d), 127.81 (d), 125.72 (d), 79.80 (s), 61.91 (s), 52.97 (q), 28.25 (q), 23.22 (q). **2**: $[\alpha]_D^{22}$ +6.6° (*c* 0.72, $CHCl_3$); δ 5.22 (1H, br.s), 3.75 (3H, s), 1.80-1.60 (2H, m), 1.52 (3H, s), 1.43 (9H, s), 1.40-1.05 (6H, m), 0.87 (3H, t, *J* = 6.7 Hz); δ 175.1 (s), 154.3 (s), 79.4 (s), 59.6 (s), 52.4 (q), 37.3 (t), 31.6 (t), 23.3 (q), 23.5 (t), 23.3 (q), 22.4 (t), 13.9 (q). **3**: $[\alpha]_D^{24}$ -8.3° (*c* 0.4, $CHCl_3$), [Lit. (*S*)-isomer:+7.3° (*c* 1.2 $CHCl_3$) (4a), (*R*)-isomer: -8.2° (*c* 1.2 $CHCl_3$) (6); δ 7.34-7.37 (5H, m), 5.27 (1H, s), 5.23 (1H, d, *J* = 12.2 Hz), 5.18 (1H, d, *J* = 12.2 Hz), 3.95-4.08 (1H, m), 3.87-3.70 (1H, m), 3.20 (1H, br.s), 1.48 (3H, s), 1.42 (9H, s); δ 173.3 (s), 155.4 (s), 135.4 (s), 128.6 (d), 128.3 (d), 128.1 (d), 80.3 (s), 67.4 (t), 67.0 (t), 61.0 (s), 28.3 (q), 20.8 (q).
16. Optical purity of **1** and **2** was determined as follows; saponification of the methyl ester with potassium trimethylsilanolate and deprotection of the Boc group with TFA yielded free amino acids, which were directly analyzed by HPLC using ligand exchange chiral column. (condition: SUMICHIRAL OA-5000 (4.6 mm x 15 cm, Sumika Chemical Analysis Service Ltd.); mobile phase: 2 mM copper (II) sulfate in [water/isopropanol (85/15)]; flow rate: 1.0 ml/min; detector: UV 254 nm; room temperature).
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