Asymmetric Syntheses of β-Phenylalanine, α-Methyl-β-phenylalanines and Derivatives

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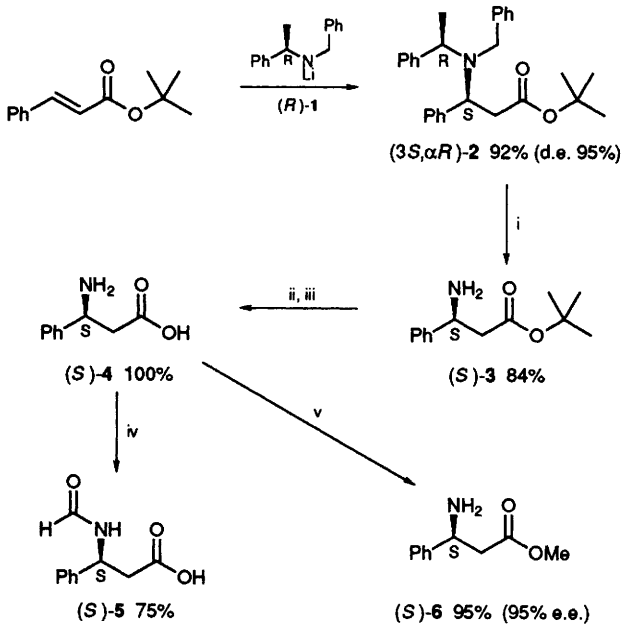
A strategy of highly stereoselective conjugate additions of lithium (*R*)-(α-methylbenzyl)benzylamide to *tert*-butyl cinnamate and its 2-methyl derivative combined with appropriate tandem or sequential electrophilic quenches allows the asymmetric syntheses of β-phenylalanine (95% enantiomeric excess) and homochiral (2*R*,3*S*)- and (2*S*,3*S*)-α-methyl-β-phenylalanine and the corresponding β-lactams (3*R*,4*S*)- and (3*S*,4*S*)-3-methyl-4-phenylazetidinones.

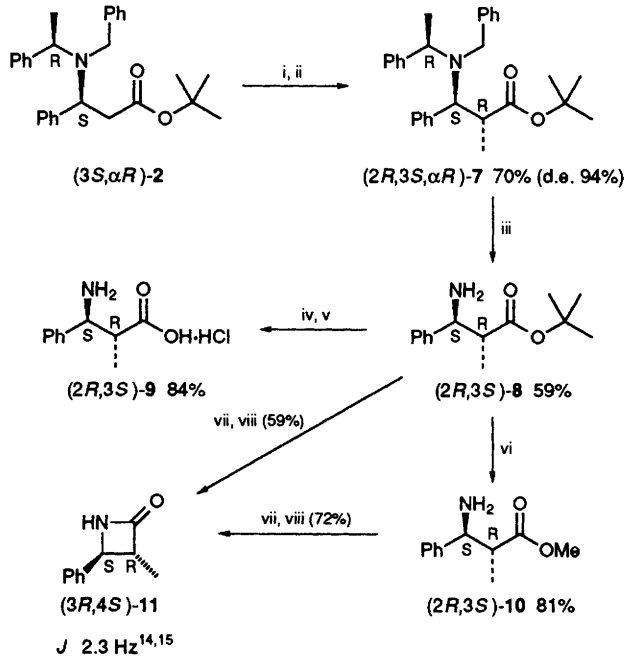
Many classes of natural products contain β-amino acid derivatives as fragments. For example, β-phenylalanine derivatives are constituents of many of the taxane alkaloids[1] and of naturally occurring pseudopeptides such as andrimid.[2] We have previously reported that Michael additions of homochiral lithium (α-methylbenzyl)benzylamide to α,β-unsaturated esters provide convenient asymmetric syntheses of homochiral β-amino butanoic acid and β-tyrosine.[3] We describe here the extension of this methodology to β-phenylalanine, and α-methyl-β-phenylalanine and derivatives. Homochiral α-substituted-β-amino acids are known in nature[4,5] and are also interesting as conformationally restricted fragments in pseudopeptides, however, only a few approaches to their asymmetric synthesis, for example *via* enantioselective additions to imines and alkylations of 5,6-dialkylperhydropyrimidin-4-ones, have been reported.[4,6]

Our synthesis of β-phenylalanine is shown in Scheme 1. Addition of the lithium amide (*R*)-**1**, derived from treatment of (*R*)-(α-methylbenzyl)benzylamine with butyllithium, to *tert*-butyl cinnamate at −78 °C gave, after protic work up, the corresponding β-phenylalanine derivative (3*S*,α*R*)-**2** with a diastereoisomeric excess (d.e.) of 95%. Hydrogenolysis in acetic acid of (3*S*,α*R*)-**2** cleanly removed the *N*-benzyl and *N*-(α-methylbenzyl) groups to release the *tert*-butyl ester of (*S*)-β-phenylalanine (*S*)-**3**[7] {$[\alpha]_D^{20}$ −21.0 (*c* 1.0, $CHCl_3$)}. Hydrolysis of (*S*)-**3** followed by ion exchange chromatography furnished (*S*)-β-phenylalanine (*S*)-**4** {$[\alpha]_D^{20}$ −7.0 (*c* 1.0, H_2O) lit.[8] $[\alpha]_D^{25}$ −7.5 ± 1 (*c* 1.0, H_2O)}. The enantiomeric excess (e.e.) of (*S*)-**4** could not be assessed directly, but conversion to the *N*-formyl derivative (*S*)-**5** {$[\alpha]_D^{20}$ −112.5 (*c* 1.9, EtOH) lit.[9] $[\alpha]_D^{25}$ −114.5 (*c* 2.0, EtOH)}, and ^1H NMR chiral shift experiments with (*S*)-*O*-acetyl mandelic acid[10] on the derived methyl ester (*S*)-**6**[11] confirmed an e.e. of 95%. Given the known[9,12] absolute configuration of (*S*)-β-phenylalanine, conversion of (3*S*,α*R*)-**2** to (*S*)-**4** unambiguously establishes the configuration of C-3 in **2** as *S*.

Trapping the intermediate enolate in the formation of (3*S*,α*R*)-**2** with iodomethane gave the corresponding C-2 methyl derivative but with low stereoselectivity (d.e. 30%). A sequential Michael addition–alkylation strategy was, therefore, explored (Scheme 2). Thus, deprotonation of (3*S*,α*R*)-**2** with lithium diisopropylamide (LDA) followed by methylation of the thus formed enolate generated (2*R*,3*S*,α*R*)-**7** with good C-2 stereoselectivity (97%). Chromatography gave (2*R*,3*S*,α*R*)-**7** {$[\alpha]_D^{25}$ −36.8 (*c* 0.6, $CHCl_3$)} in 70% yield (d.e. 94%). The difference between the tandem and sequen-

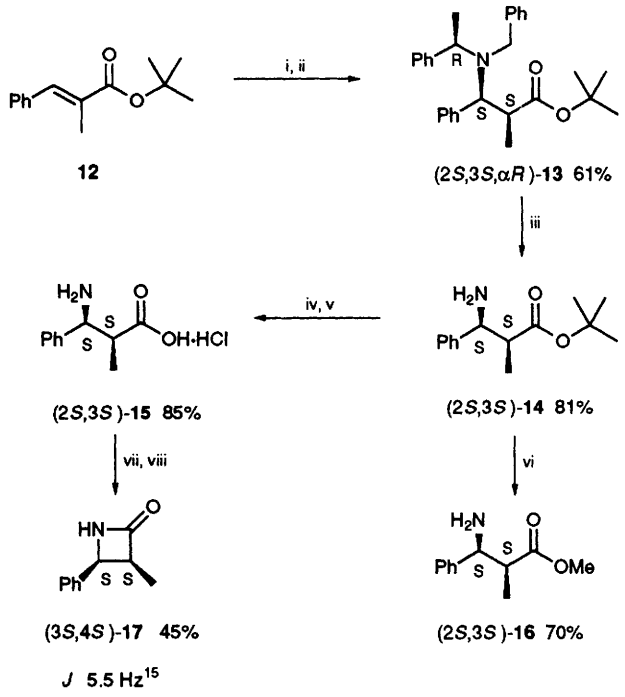


Scheme 1 *Reagents and conditions*: i, H_2 (7 atm), Pd/C, AcOH; ii, trifluoroacetic acid (TFA); iii, Dowex 50X8-200; iv, HCO_2COMe; v, MeOH, $SOCl_2$, reflux



Scheme 2 *Reagents and conditions*: i, LDA; ii, MeI; iii, H_2 (4 atm), Pd/C, AcOH, 50 °C; iv, TFA; v, HCl; vi, MeOH–HCl; vii, LDA; viii, pH 7 buffer

tial selectivities for the ester series may be governed by enolate geometry. Trimethylsilylchloride capture of the intermediate enolates prepared by the two different procedures afforded highly selectively two isomeric silyl ketene acetals. This type of complementary enolate formation and attendant diastereofacial selectivity differences in electrophilic quenching is consistent with the observations of Yamamoto *et al.*[13] Debenzylation of the amine group in (2*R*,3*S*,α*R*)-**7** gave the ester (2*R*,3*S*)-**8** in 79% yield (d.e. 94%). Chromatography gave pure (2*R*,3*S*)-**8** {$[\alpha]_D^{25}$ −37.7 (*c* 1.06, $CHCl_3$)} in 59% yield. The ester **8** could be converted either with trifluoroacetic acid to the corresponding acid, which was isolated as the hydrochloride salt (2*R*,3*S*)-**9** {$[\alpha]_D^{25}$ +10.2 (*c* 1.94,



Scheme 3 *Reagents and conditions*: i, (*R*)-**1**, toluene; ii, 2,6-di-*tert*-butylphenol, tetrahydrofuran; iii, H_2 (4 atm), Pd/C, AcOH; iv, TFA; v, HCl; vi, MeOH–HCl; vii, Dowex 50X8-200, viii; PPh_3–$(PyS)_2$–MeCN, reflux

MeOH), or transesterified to the methyl ester (2*R*,3*S*)-**10** {$[\alpha]_D^{25}$ −29.2 (*c* 1.00, $CHCl_3$)}. Treatment of either of the esters **8** or **10** with LDA furnished the *trans*-β-lactam (3*R*,4*S*)-3-methyl-4-phenylazetidinone (3*R*,4*S*)-**11** {$[\alpha]_D^{25}$ −39.0 (*c* 1.00, $CHCl_3$)} whose relative stereochemistry was established by comparison of its NMR data with literature values of the racemic material.[14,15]

Addition of the lithium amide (*R*)-**1** to (*E*)-*tert*-butyl 2-methylcinnamate **12** followed by protonation of the intermediate enolate with the hindered acid 2,6-di-*tert*-butylphenol[16] generated the C-2 epimer of (2*R*,3*S*,α*R*)-**7**, (2*S*,3*S*,α*R*)-**13** with very high C-2 stereoselectivity >99% (Scheme 3). The formation of (2*S*,3*S*,α*R*)-**13** is consistent with *anti* addition of nucleophile and electrophile to the α,β-unsaturated ester. Chromatography gave pure (2*S*,3*S*,α*R*)-**13** {$[\alpha]_D^{25}$ −68.1 (*c* 1.00, $CHCl_3$)} in 61% yield. Debenzylation of (2*S*,3*S*,α*R*)-**13** gave the amino ester (2*S*,3*S*)-**14** {$[\alpha]_D^{25}$ + 19.3 (*c* 2.37, $CHCl_3$)} which was converted to the free acid, isolated as the hydrochloride salt (2*S*,3*S*)-**15** {$[\alpha]_D^{25}$ +1.7 (*c* 1.1, H_2O)}, and transesterified to the methyl ester (2*S*,3*S*)-**16** {$[\alpha]_D^{25}$ +15.8 (*c* 1.00, $CHCl_3$)}. In contrast to esters **8** and **10** which closed smoothly to the *trans*-β-lactam **11** on LDA treatment, the corresponding C-2 epimeric esters **14** and **16** seemed inert to ring closure and C-2 epimerisation under the same conditions. This is consistent with the ring closure for formation of a *cis*-β-lactam being disfavoured relative to that for *trans*-β-lactam formation with the implication that **11** is formed directly from **8** and **10** and not *via* the *cis*-β-lactam followed by epimerisation under the basic conditions. Finally, liberation of the free amino acid from the salt **15** followed by ring closure under standard conditions[17] furnished the *cis*-β-lactam (3*S*,4*S*)-**17** {$[\alpha]_D^{25}$ −206.7 (*c* 1.04, $CHCl_3$)}, whose relative stereochemistry was established by comparison of its NMR data with literature values of the racemic material[15] and with those of (3*R*,4*S*)-**11**.

In summary, the conjugate addition reaction of lithium (*R*)-(α-methylbenzyl)benzylamide with cinnamic acid derivatives has been used to prepare β-phenylalanine (95% e.e.) and both diastereoisomers of α-methyl-β-phenylalanine in a highly stereoselective fashion. The relative stereochemistries of the

latter two compounds were assigned by converting each to the corresponding homochiral *cis*- and *trans*-3-methyl-4-phenyl-azetidinones which have only been prepared previously in racemic form. The absolute configurations of all these products were assigned unambiguously from the known specific rotation of β-phenylalanine, and all compounds were fully characterised.

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