Ring Closing Metathesis for the Asymmetric Synthesis of (*S*)-Homopipecolic Acid, (*S*)-Homoproline and (*S*)-Coniine

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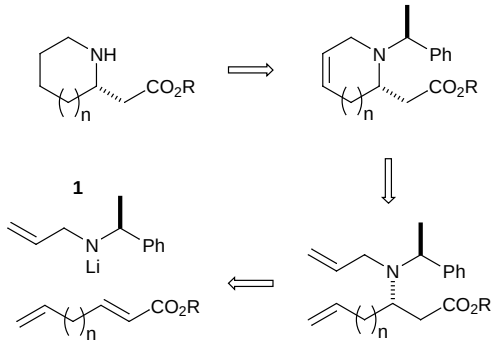
Abstract: Diastereoselective conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide to α,β-unsaturated esters or Weinreb amides, followed by ring closing metathesis is used to afford the cyclic β-amino acids (*S*)-homopipecolic acid and (*S*)-homoproline and the amine (*S*)-coniine in high ee.

Key words: lithium amide, conjugate addition, ring closing metathesis, asymmetric synthesis, cyclic β-amino acids

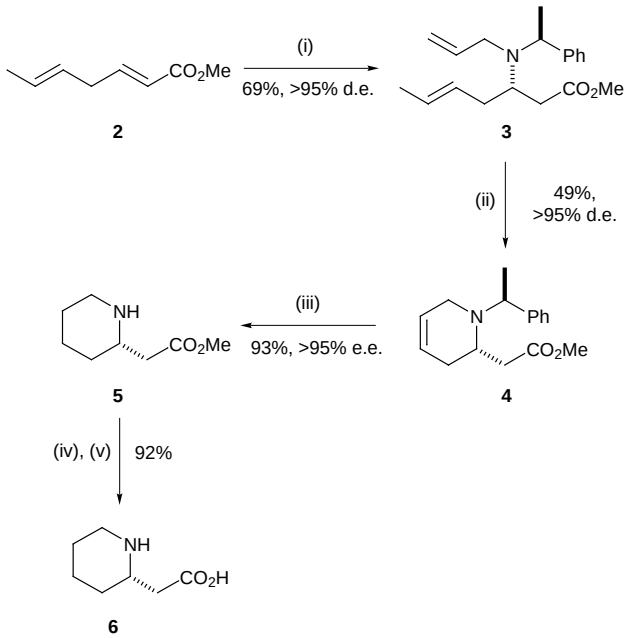
The synthesis of conformationally constrained amino acid derivatives has received much recent attention due to their ability to act as conformational probes when incorporated into peptides and peptidomimetics.[1] Asymmetric approaches toward these targets have largely focused upon the production of novel α-amino acid derivatives,[2] with the preparation of homochiral cyclic β-amino acids relatively less studied, although these attractive synthetic targets have previously been constructed by homologation of α-amino acids,[3] intramolecular ring closure[4] and stereoselective hydrogenation.[5] Previous investigations from our laboratory have shown that the highly diastereoselective conjugate addition of homochiral lithium *N*-alkyl-*N*-α-methylbenzylamides to a range of α,β-unsaturated esters and subsequent *N*-deprotection offers an efficient route to the asymmetric synthesis of β-amino acid derivatives.[6] In order to extend the utility of this methodology, a protocol involving functionalisation, rather than deprotection, of the *N*-alkyl groups of the chiral lithium amide used in the conjugate addition reaction was desired. The *N*-allyl functionality contained within (*S*)-*N*-allyl-*N*-α-methylbenzylamide **1** was selected for this purpose and we describe herein the use of ring closing olefin metathesis[7] for the synthesis of cyclic β-amino acids and amines (Figure).[8]

The initial target for this methodology was the synthesis of (*S*)-homopipecolic acid **6**.[9] Thus, conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide **1** to (*E*,*E*)-methyl heptan-2,5-dieneoate **2** gave (3*S*,α*S*)-methyl 3-(*N*-allyl-*N*-α-methylbenzylamino)hept-5-enoate **3** in 69% yield and >95% de.[10] Treatment of β-amino ester **3** with Grubbs' ruthenium alkylidene catalyst[11] furnished cyclic *N*-protected β-amino ester **4** in 49% yield and in >95% de, indicating that no epimerisation had taken place during the ring closing metathesis protocol. *N*-deprotection via



Figure

catalytic hydrogenation afforded β-amino ester **5** in 93% yield and >95% ee,[12] with subsequent ester hydrolysis giving (*S*)-homopipecolic acid **6** {$[\alpha]_D^{26}$ +24.0 (c 0.87, H_2O); lit.[13] $[\alpha]_D$ +22.1 (c 0.6, H_2O)} in 92% yield after ion exchange chromatography (Scheme 1).



Scheme 1 Reagents and conditions: (i) (*S*)-**1**, THF, –78 °C; (ii) 4 mol% $RuCl_2(=CHPh)(PCy_3)_2$, DCM, Δ, 12 hours; (iii) 10% Pd-C, H_2; (iv) 2 M HCl; (v) Dowex 50WX8-200.

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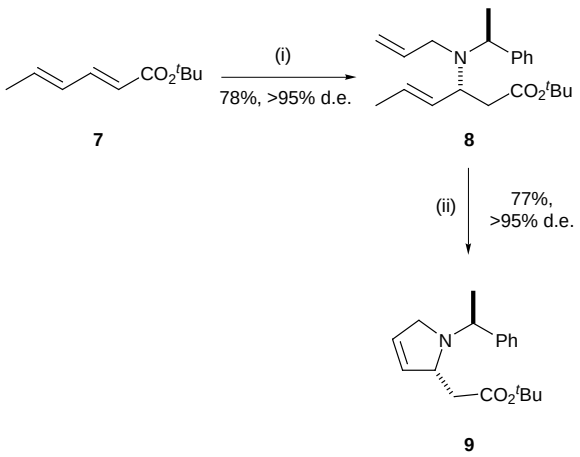
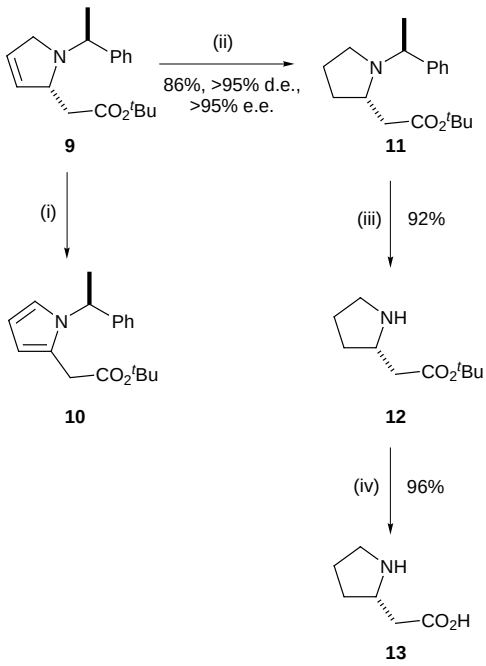
Further application of this procedure to the synthesis of (*S*)-homoproline **13**[14] was investigated. Thus, addition of (*S*)-**1** to (*E,E*)-*tert*-butyl hexa-2,4-dieneoate **7** gave (3*R*,α*S*)-*tert*-butyl 3-(*N*-allyl-*N*-α-methylbenzylamino)hex-4-enoate **8** in 78% yield and >95% de.[10] Treatment of β-amino ester **8** with Grubbs' ruthenium alkylidene catalyst gave the desired *N*-α-methylbenzyl-protected cyclic β-amino acid **9**[15] in 77% yield as a single diastereoisomer (Scheme 2).



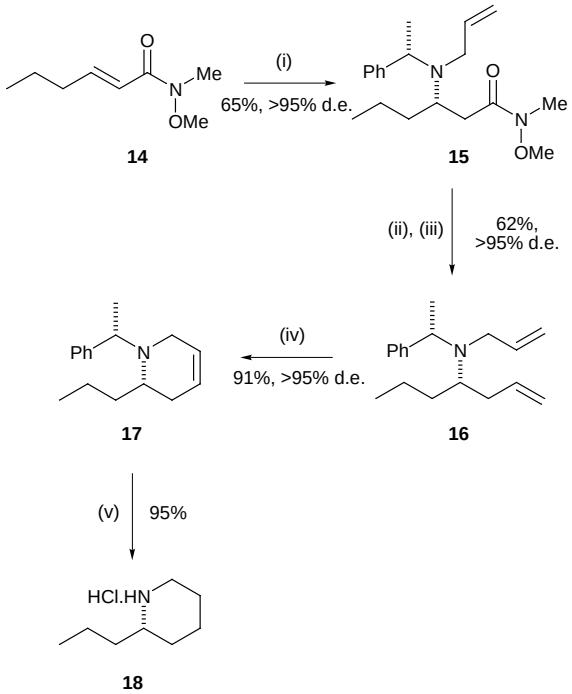
Scheme 2 Reagents and conditions: (i) (*S*)-**1**, THF, –78 °C; (ii) 4 mol% $RuCl_2(=CHPh)(PCy_3)_2$, DCM, Δ, 12 hours.

Attempted Pd-mediated hydrogenation of cyclic β-amino ester **9** proved problematic, resulting in the predominant formation of pyrrole **10**. An alternative deprotection protocol was therefore followed, involving initial hydrogenation of the alkene with Wilkinson's catalyst to furnish *N*-α-methylbenzyl β-amino ester **11** in 86% yield as a single diastereoisomer in >95% ee.[16] Subsequent *N*-benzyl deprotection via catalytic hydrogenation, a protocol known to proceed without racemisation,[6] furnished β-amino ester **12** in 92% yield with ester hydrolysis affording (*S*)-homoproline **13** {$[\alpha]_D^{23}$ +3.4 (c 1.0, H_2O); lit.[17] $[\alpha]_D^{25}$ +4.0 (c 1.0, H_2O)} in excellent yield after purification by ion exchange chromatography (Scheme 3).

Having shown the utility of this approach for the synthesis of cyclic β-amino acids, a related protocol for the synthesis of (*S*)-coniine, a simple cyclic alkaloid known to have potent neurotoxic effects[18] was developed.[19] Thus, conjugate addition of lithium (*S*)-**1** to (*E*)-*N*-methoxy-*N*-methyl hex-2-enamide **14** gave (3*S*,α*S*)-*N*-methoxy-*N*-methyl 3-(*N*-allyl-*N*-α-methylbenzylamino)hexanamide **15** in 65% yield and >95% de.[10] Reduction with DIBAL and subsequent Wittig reaction furnished diene **16** in 62% yield over two steps in >95% de. Ring closing metathesis produced the *N*-protected cyclic amine **17** in 91% yield, which, after hydrogenation and treatment with HCl, furnished (*S*)-coniine hydrochloride **18** in 95% yield, with specific rotation {$[\alpha]_D^{21}$ +8.3 (c 0.7, EtOH); lit, $[\alpha]_D^{25}$ +9.4 (c 0.32, EtOH)[20]; $[\alpha]_D^{25}$ +8.1 (c 0.6, EtOH)[21]} and spectroscopic properties consistent with those of the literature (Scheme 4).



Scheme 3 Reagents and conditions: (i) $Pd(OH)_2$ on C, H_2 (5 atm); (ii) $Rh(PPh_3)_3Cl$, H_2 (2 atm), MeCN, r.t.; (iii) $Pd(OH)_2$ on C, H_2 (1 atm), MeOH–H_2O–AcOH (40:4:1), r.t.; (iv) HCl (aq) then Dowex 50WX8-200.



Scheme 4 Reagents and Conditions: (i) (*S*)-**1**, THF, –78 °C; (ii) DIBAL, THF, –78 °C; (iii) $NaNH_2$, PPh_3CH_3Br, DCM, –40 °C to r.t.; (iv) 4 mol% $RuCl_2(=CHPh)(PCy_3)_2$, DCM, Δ, 12 hours; (v) 10% Pd-C, H_2 (5 atm), MeOH, r.t.; then HCl.

In conclusion, we have demonstrated that conjugate addition of (*S*)-*N*-allyl-*N*-α-methylbenzylamide to an α,β-unsaturated acceptor, followed by functionalisation of the

N-allyl group by ring closing metathesis offers an efficient route to the cyclic β-amino acids (*S*)-homopipecolic acid and (*S*)-homoproline and the amine (*S*)-coniine in high ee. The application of this methodology to the synthesis of other constrained amino derivatives is currently under investigation within our laboratory.

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(15) Ring closing metathesis procedure for the synthesis of **9**: $RuCl_2(=CHPh)(PCy_3)_2$ (0.2 g, 0.25 mmol) was added to a stirred solution of **8** (2.1 g, 6.3 mmol) in DCM (200 mL) under Ar and refluxed for 18 hours. After concentration in vacuo, the residue was purified by column chromatography on silica gel (40-60 petrol–Et_2O, 18:1) to furnish **9** as a clear yellow oil (1.4 g, 77%); $[\alpha]_D^{24}$ –132.0 (c 0.99, $CHCl_3$); IR(film)/ cm^{-1}: 1728 (C=O); δ_H (500 MHz, $CDCl_3$), 1.46 [3 H, d, *J* = 6.7 Hz, C(α)*Me*], 1.49 [9 H, s, OC(*Me*)$_3$], 2.37 (1 H, dd, *J* = 14.5 Hz, *J* = 8.9 Hz, C*H*CO$_2$^{t}Bu), 2.63 (1 H, dd, *J* = 14.5 Hz, *J* = 4.0 Hz, C*H*CO$_2$^{t}Bu), 3.38–3.43 and 3.60–3.64 (2 × 1 H, m, NC*H*$_2$), 3.88 [1 H, q, *J* = 6.7 Hz, C(α)*H*], 4.16–4.21 (1 H, m, NC*H*CH$_2$), 5.70–5.78 (2 H, m, C*H*=C*H*), 7.22–7.36 (5 H, m, *Ph*); δ_c (125 MHz, $CDCl_3$) 22.8, 28.0, 43.0, 58.3, 62.0, 64.7, 80.0, 126.6, 126.8, 127.3, 128.2, 130.6, 144.7, 171.3; *m/z* (APCI$^+$) 288 (MH$^+$, 80%), 219 (MH$^+$-C_4H_8); HRMS (CI$^+$) $C_{18}H_{26}NO_2$ requires 288.1964; found 288.1967.

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