Asymmetric synthesis of moiramide B

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The first asymmetric synthesis of Moiramide B 1 is achieved using lithium amide 4 and pyrrolidinone auxiliary 5; pyrrolidinone auxiliary 5 is used to create the novel (*S*)-2-methyl-*N*-benzyloxysuccinimide 15 which is subsequently acylated with the highly reactive *tert*-butoxycarbonyl-protected *N*-carboxanhydride of L-valine (Boc-Val-NCA) under strongly basic conditions, without racemization, while lithium amide 4 is used to synthesize homochiral D-β-phenylalanine *tert*-butyl ester 8.

Moiramide B **1**, a recently discovered pseudopeptide antibiotic isolated from the marine bacterium *Pseudomonas fluorescens*, exhibits potent *in vitro* antibacterial activity against methicillin resistant *Staphylococcus aureus* and a range of other antibiotic-resistant human pathogens.[1] Moiramide B **1** belongs to a novel class of antibiotics which contain, as part of their structural make up, a D-β-phenylalanine unit and an acyl succinimide unit bearing a (4*S*)-methyl substituent, which is essential for the observed antimicrobial activity.[2] These interesting structural motifs, combined with the potential to exploit the chiral auxiliaries and methodologies developed previously within our laboratory, made moiramide B an attractive synthetic target.

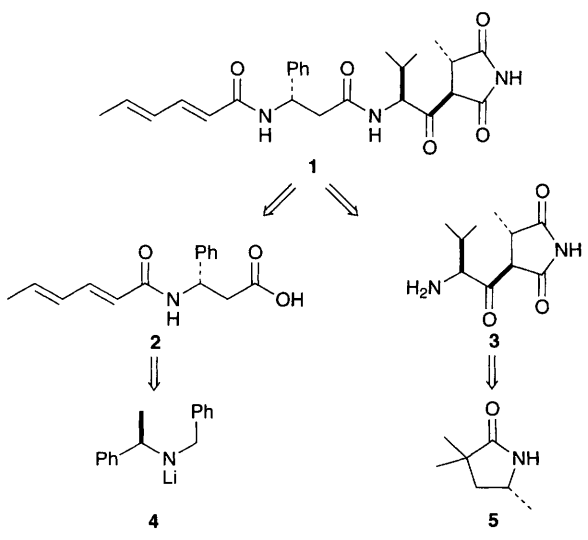
Herein, we wish to report the first highly diastereoselective total synthesis of moiramide B. The synthesis was accomplished from hexa-2,4-dienoyl D-β-phenylalanine **2** and the acyl succinimide fragment **3**, which were synthesised, each with high diastereoselectivities, using respectively lithium(*R*)-*N*-benzyl-α-methylbenzylamide **4**[3] and the (5*R*)-3,3,5-trimethylpyrrolidin-2-one **5** 'Quat' chiral auxiliary.[4]

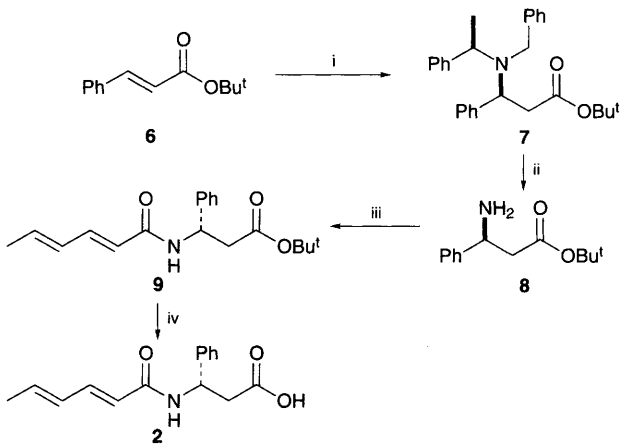
The highly diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-α-methylbenzylamide **4** to α,β-unsaturated esters has been described.[3] Using this protocol, D-β-phenylalanine *tert*-butyl ester **8** was readily obtained in good overall yield by the conjugate addition (>95% de) of this lithium amide (*R*)-**4** to *tert*-butyl cinnamate **6** and subsequent hydrogenolysis of the conjugate adduct **7**. The synthesis of the hexa-2,4-dienoyl D-β-phenylalanine unit **2** was then completed by treating the D-β-phenylalanine *tert*-butyl ester **8** with commercially available hexa-2,4-dienoic acid under standard peptide coupling conditions and subsequent hydrolysis of the ester **9** (Scheme 1).†

The pyrrolidinone auxiliary **5** has been shown to induce high diastereoselectivities in enolate alkylations of attached acyl side chains.[4] This, combined with the mild, non-racemizing conditions required to cleave the chiral side chain from the auxiliary made **5** ideally suited for the synthesis of the acyl succinimide unit **3**. It was anticipated therefore that this auxiliary could be used to generate the stereogenic centre bearing the methyl group on a suitably *N*-protected succinimide ring, which in turn could be acylated with an appropriate cationic valine source under anionic conditions.[5]

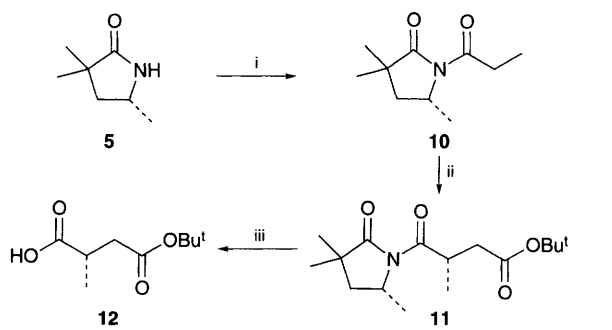
Acylation of the pyrrolidinone auxiliary **5** with propionyl chloride and BuLi gave the *N*-propionyl pyrrolidinone **10** in excellent yield. Subsequent treatment with LDA at −78 °C followed by *tert*-butyl bromoacetate afforded the succinate derivative **11** in good yield and high diastereoselectivity (>95% de). Hydrolysis of **11** with LiOH led to the synthesis of homochiral *tert*-butyl hydrogen (*S*)-methylsuccinate **12** (Scheme 2).†

Treatment of *tert*-butyl hydrogen (*S*)-methylsuccinate **12** with neat trifluoroacetic acid gave a quantitative yield of (*S*)-





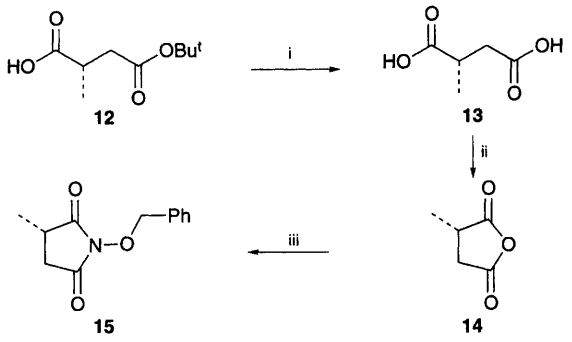
Scheme 1 *Reagents and conditions*: i, **4**, THF, −78 °C then H^+ (96%); ii, H_2 (7 atm), $Pd(OH)_2$ (75%); iii, hexa-2,4-dienoic acid, DCC, 1-hydroxybenzotriazole, THF (80%); iv, TFA (99%)



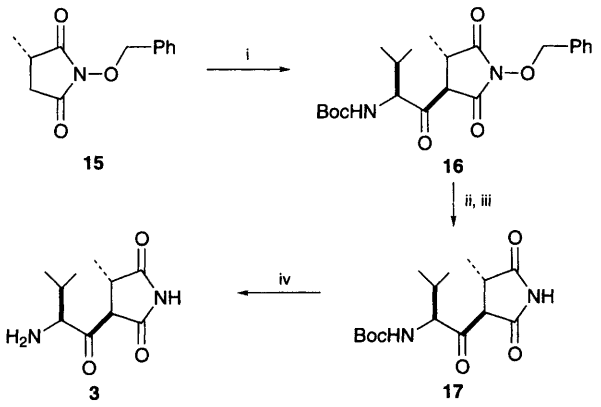
Scheme 2 *Reagents and conditions*: i, BuLi, propionyl chloride (95%); ii, LDA, *tert*-butyl bromoacetate (92%); iii, LiOH (89%)

methylsuccinic acid **13**. This was cyclised to the (*S*)-methylsuccinic anhydride **14** with acetyl chloride at reflux, in excellent yield. Finally, treatment of **14** with *O*-benzyl hydroxylamine followed by 1,1′-carbonyldiimidazole (CDI) afforded homochiral (*S*)-2-methyl-*N*-benzyloxysuccinimide **15** again in excellent yield (Scheme 3).†

Our investigations led us to the discovery that the novel (*S*)-2-methyl-*N*-benzyloxysuccinimide **15** was crucial in the synthesis of the acyl succinimide fragment **3** owing to its ready synthesis, utility in enolate chemistry and most importantly, its mild and efficient *N*-deprotection. Treatment of **15** with an equimolar amount of the highly reactive *tert*-butoxycarbonyl-protected *N*-carboxanhydride of L-valine (Boc-Val-NCA)[6]



Scheme 3 *Reagents and conditions*: i, TFA (100%); ii, acetylchloride (99%); iii, *O*-benzyl hydroxylamine, CDI (95%)



Scheme 4 *Reagents and conditions*: i, Boc-Val-NCA, LHMDS (53%); ii, H_2, Pd/C; iii, 2′-bromoacetophenone, Et_3N, (69%); iv, TFA (100%)

followed by excess lithium hexamethyldisilazide (LHMDS) in THF at −78 °C afforded the fully protected acyl succinimide **16** in 53% isolated yield and high diastereoselectivity (>95% de). The modest yield in this acylation step was probably due to a competitive base-induced dimerization reaction of the Boc-Val-NCA.[7] Removal of the succinimide protecting group was possible *via* a modification of a two step literature procedure.[8] Hydrogenolysis of the benzyl group under standard conditions followed by treatment of the resultant *N*-hydroxy acylsuccinimide with 2′-bromoacetophenone and triethylamine gave the acyl succinimide **17** in good yield. Finally, quantitative removal of the *tert*-butoxycarbonyl group with trifluoroacetic acid in dichloromethane afforded the desired acyl succinimide **3** as the trifluoroacetate salt (Scheme 4).†

The synthesis of moiramide B **1** was completed by coupling equimolar amounts of fragment **2** and **3** using the BOP reagent (1.0 equiv.) and DMAP (3.0 equiv.) in DMF at 0 °C for 30 min in 65% yield. The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, CD) of the synthetic moiramide B **1** were in accordance with the reported values.[1] The specific rotation of moiramide B **1** was $[\alpha]_D^{25}$ −96.6 (*c* 0.28, MeOH).

We thank Oxford Asymmetry Ltd and the EPSRC for a CASE award (to D. J. D.).

Footnote

† All new compounds were fully characterised and gave satisfactory elemental analyses.

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Received, 7th May 1996; Com. 6/03138B