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LETTERS

An alkylidene carbene C–H insertion strategy for the enantioselective synthesis of α,α-dialkyl-α-amino acids

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Abstract

A synthesis of the α,α-dialkyl-α-amino acid (1*S*,3*R*)-2,5-methano-leucine has been achieved using an alkylidene carbene 1,5-C–H insertion reaction as a key step. Treatment of the ketone **11** with 1.2 equivalents of lithio(trimethylsilyl)diazomethane in THF resulted in the formation of the cyclopentene **13** in 62% yield. The enantiomeric excess of the product **18** was determined to be >95% by chiral HPLC (Chiracel OD column).

Keywords: alkylidene carbene; enantioselective; α,α-dialkyl-α-amino acid; C–H insertion.

The α,α-dialkyl-α-amino acid moiety is a key structural feature present in a number of biologically interesting molecules, such as the anti-tumour agent altemicidin **1**[1] and the excitatory amino acid (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) **2** (Fig. 1).[2] Although a number of excellent procedures have been developed for the enantioselective syntheses of a wide range of α,α-dialkyl-α-amino acids,[3] none of these methods seemed particularly suitable for the preparation of the cyclopentane-containing targets **1** and **2**. In this letter, we wish to describe our preliminary studies in this area, which have resulted in the synthesis of the novel conformationally restricted leucine analogue, (1*S*,3*R*)-2,5-methano-leucine **3**.

At the outset of our work, we wondered whether it would be possible to construct quaternary amino acid centres in a rather direct manner by utilising a stereoselective alkylidene carbene mediated C–H insertion reaction into nitrogen bearing tertiary stereogenic centres. In theory this should negate the need for the presence of any external directing functionality. Retrosynthetic analysis of **3** identified the cyclopentene **4** as a key late stage precursor (Scheme 1). Further disconnection of **4**, via the alkylidene carbene **5**, revealed the ketone **6** as a potential starting material. We felt that an intramolecular alkylidene carbene insertion reaction would be particularly suitable for this application for a number of reasons. Firstly, the key reactive intermediate (e.g. **5**) should be readily available from the corresponding ketone (e.g. **6**) in high yield by treatment with lithio-(trimethylsilyl)diazomethane (LTDM).[4] Secondly, the

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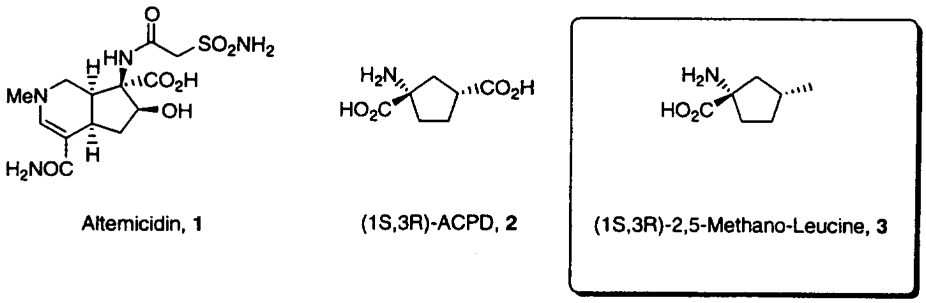
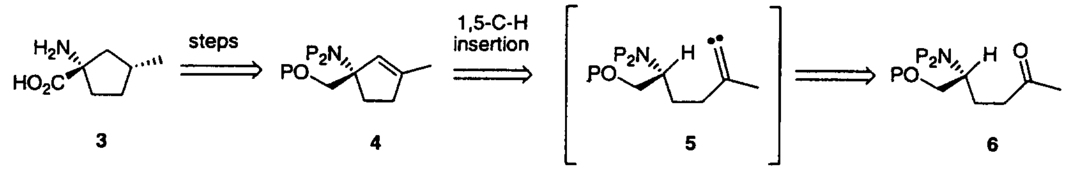
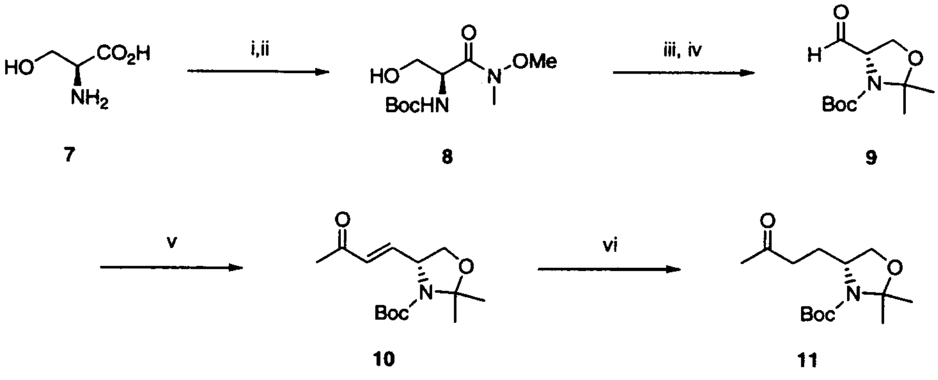


Figure 1.

C–H insertion reactions of alkylidene carbenes have been shown to proceed with a high degree of stereoselectivity via their singlet ground state.[5] Upon inspection of the literature, we were surprised to find that this type of C–H insertion reaction had not been reported previously.[6] We found this quite unusual, as the corresponding insertion reactions into oxygen-bearing stereogenic centres have been used to great effect in synthesis.[7] From a theoretical point of view, we could see no reason why insertion into nitrogen-bearing stereogenic centres should prove problematic. In order to test the validity of our strategy, we needed to first develop an expedient synthesis of the desired alkylidene carbene precursor (e.g. **6**). To our pleasure, we were able to synthesise the desired ketone **11** in good overall yield from (L)-serine **7** in only six steps (Scheme 2).



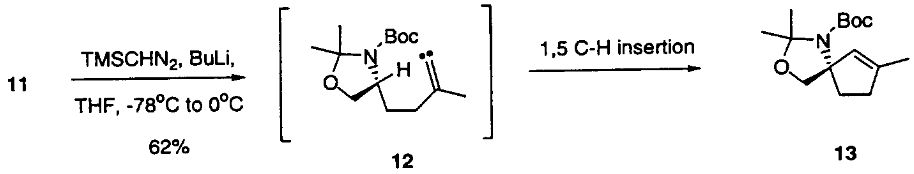
Scheme 1.



Scheme 2. *Reagents*: (i) Boc_2O, NaOH, 100%; (ii) $MeN(OMe)H_2Cl$, Et_3N, EDCl, 90%; (iii) $BF_3{\cdot}OEt_2$, acetone, 2,2-dimethoxypropane, 93%; (iv) $LiAlH_4$, THF, 94%; (v) $Ph_3PCHC(O)CH_3$, CH_2Cl_2, 79%; (vi) H_2, Pd(C), EtOAc, 80%

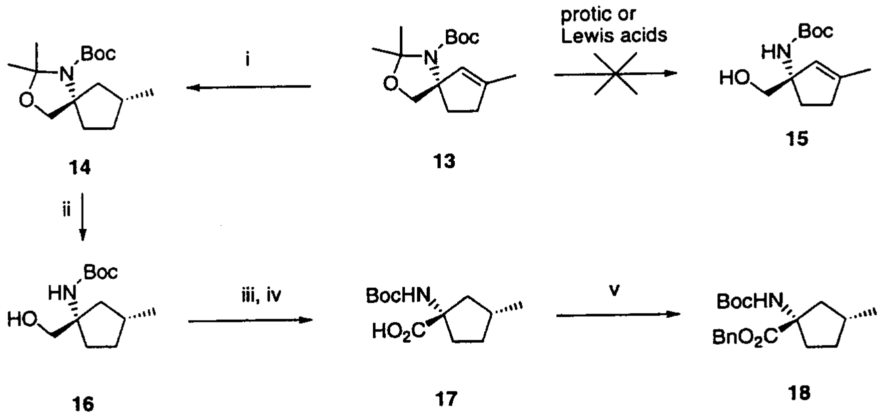
Firstly, the Garner aldehyde **9** was prepared according to the modified procedure of Taylor et al.[8] Wittig olefination of **9** with 1-triphenylphosphoranylidene-2-propanone next provided the unsaturated ketone **10** in good yield. Hydrogenation (Pd/C, H_2, EtOAc) of **10** then provided the key alkylidene carbene precursor **11**. With multi-gram quantities of **11** in hand, we were now in a position to examine the key C–H insertion reaction. Treatment of **11** with 1.2 equivalents of LTDM (generated in situ from

TMS–diazomethane and *n*-BuLi) at −78°C, followed by warming to 0°C resulted in the evolution of nitrogen to afford the alkylidene carbene **12**. To our delight, the desired 1,5-C–H insertion reaction proceeded smoothly and the cyclopentene product **13**, $[\alpha]_D$ −77, (*c* 1.16, $CHCl_3$), was isolated in a pleasing 62% yield (Scheme 3). The synthesis of **13** was also repeated in racemic form to provide reference samples for an enantiomeric excess determination.



Scheme 3.

Unfortunately, however, it was not possible to determine the enantiomeric excess of **13** at this stage. ^1H NMR/chiral shift reagent techniques were hampered by the presence of rotameric mixtures caused by the Boc-protecting group and its low polarity (and hence retention times) meant that chiral HPLC was not practical. In order to overcome the rotamer problem and also make the material more polar, a number of attempts to deprotect **13**, to provide the alcohol **15**, were made. It was hoped that even if the enantiomeric excess of **15** could not be determined directly, the hydroxyl group would provide an excellent handle for further derivatisation. Unfortunately, no conditions could be found to effect the desired deprotection reaction, with only complete decomposition of **13** being observed under a wide range of acidic conditions. Although we were frustrated at this finding, we were confident that an enantiomeric excess could be determined at a later stage in the synthesis (vide infra).



Scheme 4. *Reagents*: (i) H_2, Pd/C, EtOAc, 79%; (ii) $BF_3\cdot 2AcOH$, MeOH, 60–70%; (iii) Dess–Martin Periodinane, CH_2Cl_2, 67–100%; (iv) $NaClO_2$, NaH_2PO_4, *tert*-butanol, H_2O, 72%; (v) BnBr, Et_3N, acetone, 90%

Catalytic hydrogenation of **13** using palladium on carbon, yielded the desired product **14** as a single diastereoisomer, with the hydrogen being delivered opposite to the bulky Boc-protecting group (Scheme 4).[9] Having removed the olefin, deprotection of **14** proceeded smoothly by treatment with $BF_3\cdot 2AcOH$ in methanol[10] to produce the alcohol **16** in good yield. Finally, oxidation of **16** to the desired acid **17** was readily accomplished in two steps by oxidation with Dess–Martin periodinane,[11] followed by further oxidation with sodium chlorite under standard conditions. Having completed the synthesis of the desired α,α-dialkyl-α-amino acid **3** as its *N*-Boc derivative **17**, we were now in a position to determine the enantiomeric excess of this material. Derivatisation of the acid **17** as its benzyl ester **18** proceeded in high yield. Fortunately, this material proved suitable for chiral HPLC (Chiracel OD, 10% isopropanol in hexane) and **18** was found to have an enantiomeric excess of >95%.

In summary, we have completed a synthesis of the *N*-Boc-α,α-dialkyl-α-amino acid **17** in excellent enantiomeric excess using an alkylidene carbene C–H insertion reaction as a key step. To our knowledge, this is the first reported example of a stereoselective alkylidene carbene insertion into a nitrogen-bearing stereocentre. We are currently examining the syntheses of other α,α-dialkyl-α-amino acid containing targets using this methodology, and these results will be reported in due course.

Acknowledgements

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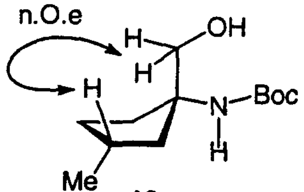

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