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Desymmetrisation of Bicyclic, *Meso*-Anhydrides by Proline Esters

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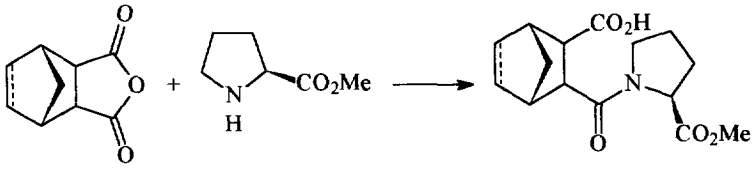
Abstract: The desymmetrisation of cyclopropane and cyclopentane derived, bicyclic meso-anhydrides using proline esters provides a versatile approach to the synthesis of enantiomerically pure amido acids which can subsequently be converted into β-amino acid containing peptide analogues.

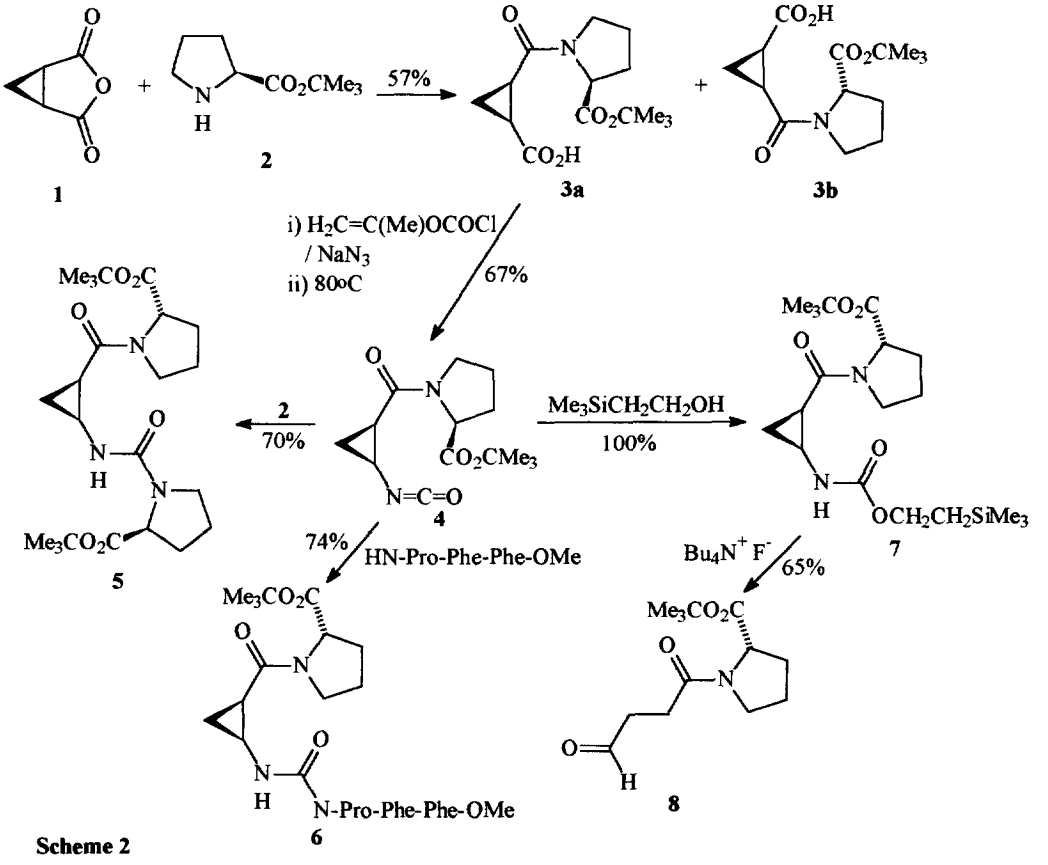
In recent publications,[1] we have reported the facile desymmetrisation of tricyclic, *meso*-anhydrides derived from norbornane using methyl (*S*)-prolinate as shown in **Scheme 1**. This chemistry has allowed us to access enantiomerically pure amido acids which are versatile building blocks for the synthesis of conformationally constrained peptide analogues[2] and also have other potential applications. The asymmetric induction observed during this process seems to depend upon the steric difference between the two faces of the tricyclic anhydride.[1] Attempts to extend this chemistry to bicyclic anhydrides derived from cyclohexane-1,2-dicarboxylic acid resulted in no asymmetric induction, and cyclopropane dicarboxylic anhydride gave only an inseparable mixture of diastereomers in 3:1 ratio.[1] In the present paper, we report the successful desymmetrisation of bicyclic anhydrides derived from cyclopropane and cyclopentane anhydrides using proline esters.



Scheme 1

In an attempt to improve the diastereoselectivity of the desymmetrisation of cyclopropane anhydride **1**, the use of *tert*-butyl (*S*)-prolinate **2** was investigated (**Scheme 2**). We reasoned that the larger ester substituent on the proline would be better able to discriminate between the two faces of anhydride **1**, and so give a better

asymmetric induction. Surprisingly however, the desired amido acid **3a,b** was obtained in 57% yield as a 3:1 ratio of diastereomers, the same ratio that had been obtained using methyl (*S*)-prolinate.[1] In this case however, the two diastereomers of acid **3** were readily separable, as trituration with diethyl ether removed the minor isomer, leaving acid **3a** as a white crystalline solid in 40% isolated yield.[3] The absolute configuration of the major diastereomer **3a** was determined to be as shown in **Figure 1** by X-ray crystallography.[4]



Scheme 2

Amido acid **3a** proved to be a useful starting material for the synthesis of *pseudo*-peptides incorporating a *cis*-2-amino-cyclopropane carboxylate unit. Thus Curtius rearrangement[5] of acid **3a** gave isocyanate **4** in 67% yield. Reaction of isocyanate **4** with *tert*-butyl (*S*)-prolinate **2** or HN-(*S*)-Pro-(*S*)-Phe-(*S*)-Phe-OMe gave β-amino cyclopropane carboxylate containing *pseudo*-peptides **5** and **6** in 70 and 74% yields respectively as shown in **Scheme 2**. However, all attempts to convert isocyanate **4** into the corresponding amine were unsuccessful, resulting only in decomposition. Reaction of the isocyanate with β-(trimethylsilyl)ethanol did produce urethane **7** in quantitive yield, however attempted removal of the β-(trimethylsilyl)ethoxycarbonyl protecting group with tetrabutylammonium fluoride resulted in concomitant ring opening of the cyclopropane to give aldehyde **8** in 65% yield.[6]

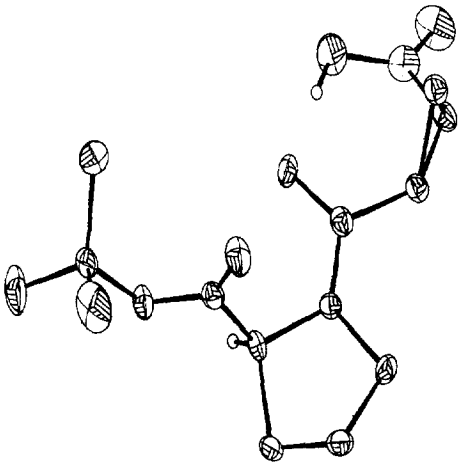
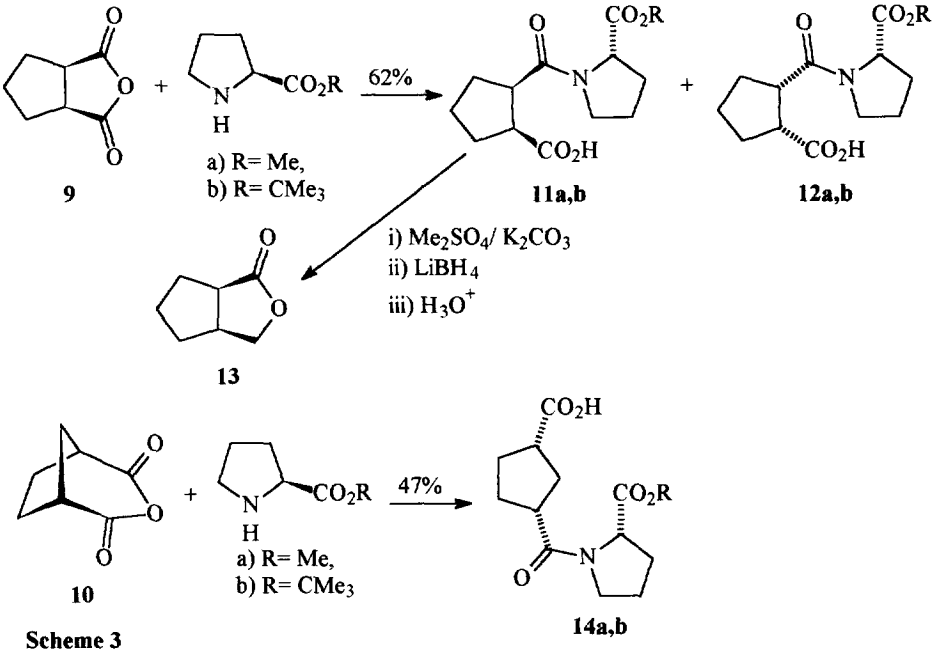


Figure 1: ORTEP Diagram of Acid **3a**



9 **11a,b** **12a,b** **13** **10** **14a,b**

Scheme 3

The desymmetrisation of *cis*-1,2- and *cis*-1,3-cyclopentane dicarboxylic anhydrides[7] (**9** and **10** respectively was also investigated as shown in **Scheme 3**. Anhydride **9** gave a 3:1 ratio of diastereomers **11a, 12a** when desymmetrised using methyl (*S*)-prolinate, and a 4:1 ratio of diastereomers **11b**, **12b** when treated with *tert*-butyl (*S*)-prolinate. These results are very similar to those obtained with cyclopropane anhydride **1**. The major isomer in these reactions was identified as **11a,b**, by conversion of the amido acids into lactone **13** by esterification using dimethyl sulphate, followed by chemoselective reduction with lithium borohydride and

acidic cyclisation of the resulting amido alcohols.[1] Lactone **13** was found to possess a negative specific rotation and so to be the enantiomer of a known lactone,[8] and hence to have the stereochemistry shown in structure **13**.

In the case of the 1,3-anhydride **10**, a single diastereomer of amido acid **14a,b** was obtained using either methyl or *tert*-butyl (*S*)-prolinate. The much better asymmetric induction obtained with anhydride **10** is probably due to the similarity between the structure of this anhydride and that of the tricyclic norbornane derivatives investigated previously.[1] Unfortunately, all attempts to convert amido acids **14a,b** into the corresponding lactone were unsuccessful. However, the stereochemistry of the amido acid is assumed to be as shown in structure **14a,b**, based upon analogy with the desymmetrisation of structurally related norbornene anhydrides.

In conclusion, the desymmetrisation of bicyclic, *meso*-anhydrides using chiral, proline esters can proceed with useful to excellent asymmetric induction, and the adducts can be transformed into β-amino acid containing peptides. Our work on the scope and applications of this chemistry is continuing, and further results will be published in due course.

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