Synthesis of Enantiomerically Pure, All *Syn*, Tetra and Pentasubstituted Cyclopentanes by the Desymmetrisation of *Endo*-Norborn-5-ene-2,3-Dicarboxylic Anhydrides

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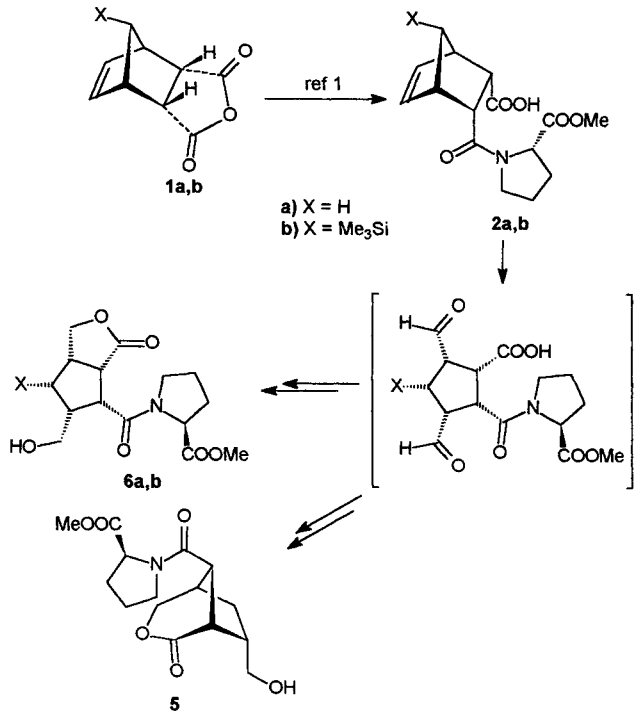
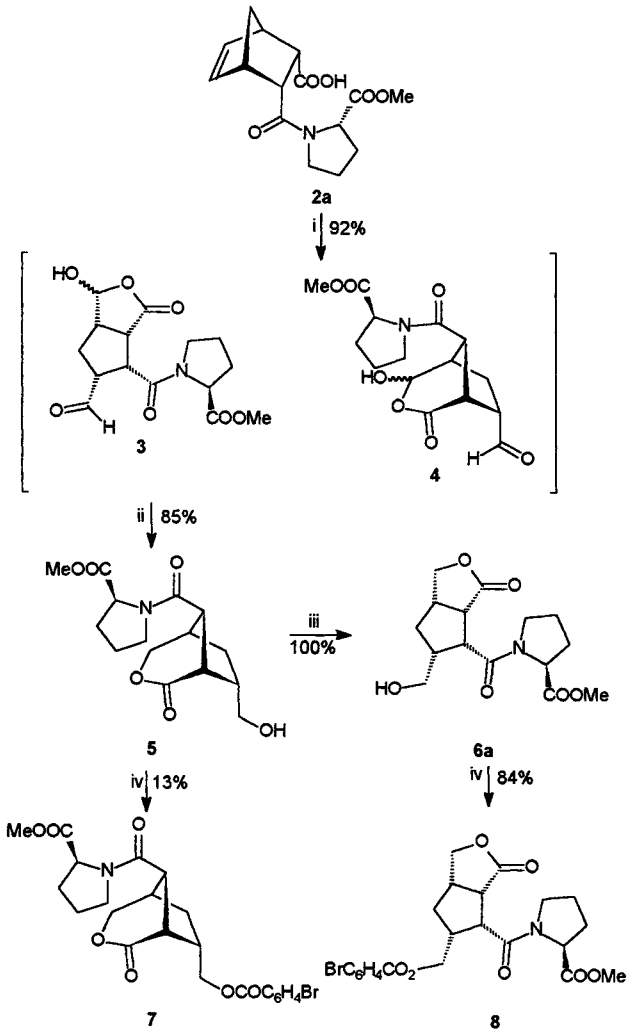
Abstract: Ozonolysis of diastereomerically pure norbornene derivatives incorporating methyl (*S*)-prolinate provides a route for the synthesis of enantiomerically pure cyclopentanes bearing four or five substituents all orientated *syn* to one another.

In recent publications we have reported the facile desymmetrisation of *meso*-anhydrides by esters of (*S*)-proline, and have shown that the adducts can be used in the synthesis of conformationally constrained peptides and *pseudo*-peptides.[1] In this communication we show how this methodology can be used to prepare highly substituted, enantiomerically pure cyclopentane derivatives by ozonolysis of the alkene in desymmetrised norbornene amido-acids as outlined in Scheme 1. The cyclopentane derivatives will be useful in a variety of applications including the synthesis of nucleoside analogues, and the construction of template assembled synthetic proteins.



Scheme 1

Ozonolysis of amido-acid **2a** in dichloromethane or methanol followed by reductive work-up using dimethyl sulphide[2] (Scheme 2) gave two inseparable products, each of which was shown by NMR and IR analysis to contain a single aldehyde group and an alcoholic rather than acid OH group. The products appeared to be either compound **3** or compound **4**, each of which could exist as a mixture of epimers at the newly created stereocentre, though the possibility that isomerisation had occurred at one or more of the other stereocentres could not be ruled out at this stage. To simplify the analysis of this mixture, the product was reduced with sodium borohydride followed by lactonisation on silica to give lactone **5** or **6a**. In the event, it proved possible to isolate either lactone from the reduction, since the [3,2,1]-lactone **5** was found to be



Scheme 2. *Reagents*; i) O_3 then Me_2S; ii) $NaBH_4$ / MeOH then SiO_2; iii) $CDCl_3$ or *p*-$TolSO_3H$; iv) BrC_6H_4COCl / Et_3N

the kinetic product of the reaction[3] but to isomerise to the thermodynamically more stable [3,3,0] lactone **6a** on standing in $CDCl_3$ or $CHCl_3$, or more rapidly on treatment with *p*-toluenesulphonic acid.[4]

The structures of lactones **5** and **6a** were unambiguously determined by X-ray crystallography.[5] The [3,3,0]-lactone **6a** formed crystals suitable for direct X-ray analysis, an ORTEP diagram being shown in Figure 1. The [3,2,1]-lactone **5** however had to be converted into the corresponding 4-bromobenzoyl derivative **7** prior to structure determination by X-ray crystallography (Figure 2). Lactone **6a** was also converted into its 4-bromobenzoyl derivative **8** to prove that no isomerisation of **5** to **6a** had occurred during the esterification reaction. The X-ray structures also showed that no epimerisation had occurred at any of the stereocentres during the synthesis of compounds **5** / **6a**. Both lactones (**5** and **6a**) contain a cyclopentane ring with four differentiated carbon based functionalised substituents attached all *syn* to one another.

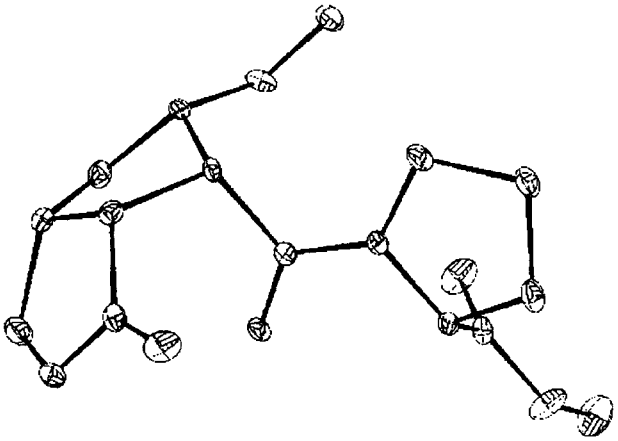
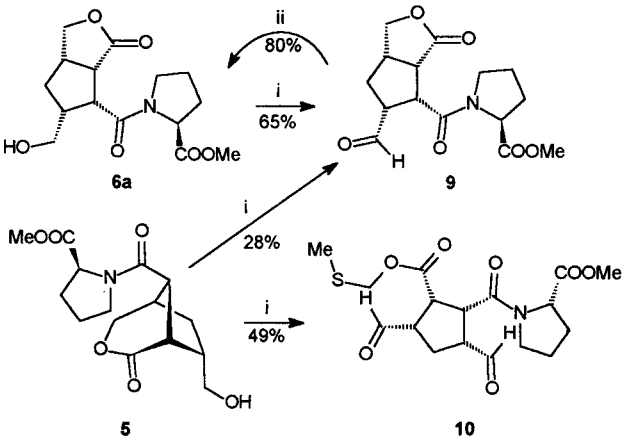


Figure 1. ORTEP Diagram of Lactone **6a**



Scheme 3. *Reagents;* i) Me_2SO / Et_3N / ClCOCOCl; ii) $NaBH_4$

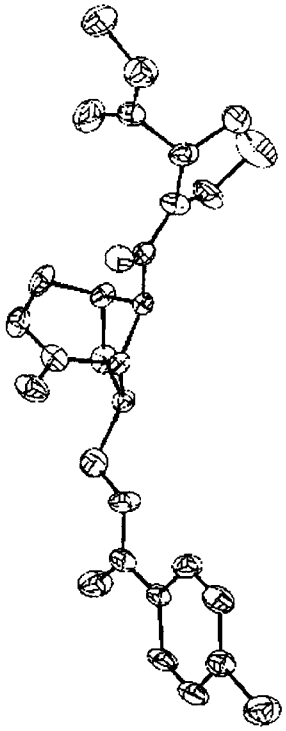
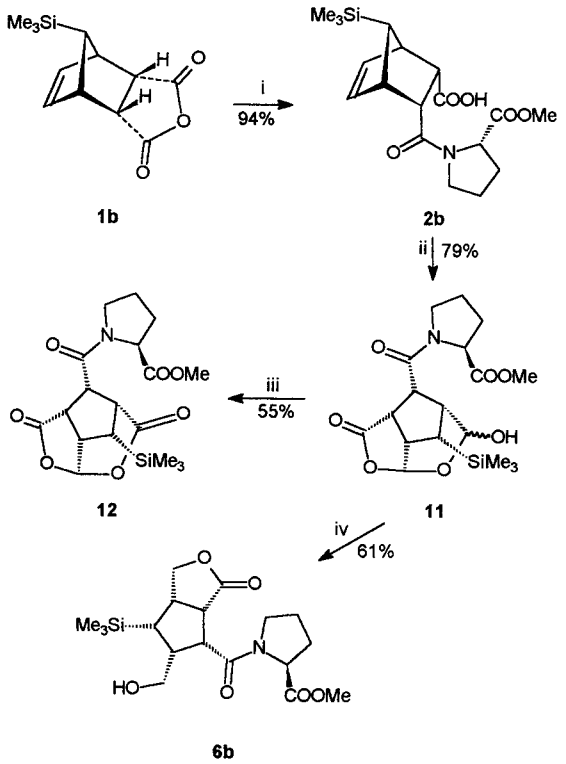


Figure 2. ORTEP Diagram of Lactone 7

To allow further manipulation of the lactones, the Swern oxidation[6] of the primary alcohol of lactones **5** / **6a** was investigated. With the thermodynamic lactone **6a**, the oxidation proceeded without difficulty, giving aldehyde **9**. However, attempts to oxidise the alcohol of the kinetic lactone **5** always resulted in concomitant ring opening of the lactone ring, giving dialdehyde **10** as shown in Scheme 3. This reaction probably occurs by attack of a Pummerer rearranged DMSO derivative on the lactone carbonyl followed by ring opening of the lactone by a second molecule of DMSO.[7] It was not possible to prevent this ring opening, use of stoichiometric amounts of DMSO and oxalyl chloride in the Swern oxidation gave a mixture of dialdehyde **10** and aldehyde **9**, the latter of which could be rereduced to lactone **6a** using sodium borohydride. This unusual side reaction during a Swern oxidation is presumably due to the strain present in the [3,2,1] ring system.

The above chemistry was then extended to the synthesis of cyclopentane derivatives bearing five substituents all *syn* to one another. Trimethylsilyl was chosen as the fifth substituent since methodology exists for the conversion of silyl groups into other functionalities,[8] the required precursor was readily available, and the steric bulk of the trimethylsilyl group was expected to challenge the limits of the methodology. A solution of 5-(trimethylsilyl)cyclopentadiene[9] was reacted with maleic anhydride at room temperature to give norbornene derivative **1b**, as the diastereomerically pure *endo*-7-anti diastereomer. Desymmetrisation of anhydride **1b** using methyl (*S*)-prolinate gave a 3:1 ratio of diastereomers of amido-acid **2b**, in which the major diastereomer is assumed to be as drawn in structure **2b** by analogy with all other *endo*-norbornene derivatives.[1] Ozonolysis of compound **2b** gave a mixture of species which ^1H and ^{13}C NMR showed not to contain an aldehyde, and which were thus assigned as the epimers of



Scheme 4. *Reagents;* i) (*S*)-Pro-OMe / Et_3N; ii) O_3 / MeOH; iii) Me_2SO / Et_3N / ClCOCOCl; iv) $NaBH_4$ then H^+

hemiacetal **11** (Scheme 4).[10] Swern oxidation of compound **11** gave bis-lactone **12** as a single stereoisomer after chromatographic purification. Sodium borohydride reduction of hemiacetal **11** followed by lactonisation gave lactone **6b** as a single stereoisomer after flash chromatography. The structure of this lactone is based on the similarity of the spectral data for **6a** and **6b**.

In summary, we have demonstrated that the desymmetrisation of anhydrides **1a,b** using methyl (*S*)-prolinate provides a versatile approach to the synthesis of enantiomerically and diastereomerically pure cyclopentane derivatives bearing four or five substituents all *syn* to one another. Our work in this area is continuing, and further results will be reported in due course.

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3) Preparation of lactone **5**: A solution of amido-acid **2a** (1.0g, 3.44mmol) in CH_2Cl_2 was cooled to -78°C and treated with ozone until a permanent blue colour was observed. Dimethyl sulphide (1.26ml, 17.2mmol) was then added, and the reaction allowed to stir at room temperature for 16 hours. The solvents were evaporated *in vacuo* and the residue subjected to flash chromatography (EtOAc) to give compounds **3** / **4** (1.0g, 92%) as a white powder. This product was dissolved in methanol (15ml), cooled (0°C), and sodium borohydride (0.6g, 15.9mmol) added. The solution was stirred at room temperature for 5 hours, then the solvent was evaporated *in vacuo* and the residue subjected to flash chromatography (9:1 EtOAc / MeOH) to give lactone **5** (0.8g, 85%) as a white powder. m.p. 47-50°C; δ_H ($CDCl_3$) 1.8-2.3 (6H, m), 2.4-2.6 (1H, m), 2.65-2.8 (1H, m), 3.2-3.3 (1H, m), 3.41 (1H, t *J* = 7.4Hz), 3.5-4.0 (5H, m), 3.72 (3H, s), 4.05 (1H, dd *J* = 10.9, 3.7Hz), 4.63 (1H, dd *J* = 8.7, 2.9Hz), 4.3-5.0 (1H, br); m / z (FAB) 334 ($M+Na^+$, 40), 312 (MH^+, 100); Found 312.1430 ($C_{15}H_{22}NO_6$ requires 312.1447).

4) Preparation of lactone **6a**: Lactone **5** (0.5g, 1.6mmol) was dissolved in $CHCl_3$ (20ml) and allowed to stand at room temperature for 2 days. The solvent was then evaporated *in vacuo* to give lactone **6a** (0.5g, 100%) as a crystalline solid. m.p. 91-93°C; $[\alpha]_D^{22}$ = -48.4 (c = 1, $CHCl_3$); δ_H ($CDCl_3$) 1.3-2.3 (6H, m), 2.6-2.85 (1H, m), 3.0-3.25 (1H, m), 3.3-3.5 (2H, m), 3.6-3.8 (3H, m), 3.77 (3H, s), 3.9-4.0 (1H, m), 4.31 (1H, dd *J* = 8.9, 5.0Hz), 4.52 (1H, t *J* = 8.9Hz), 4.67 (1H, dd *J* = 8.8, 3.4Hz); m / z (CI) 312 (MH^+, 76); Found 312.1447 ($C_{15}H_{22}NO_6$ requires 312.1447).

5) Full details of the X-ray structures will be published elsewhere.

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