A New Homolytic Method for the Stereospecific Synthesis of (2*S*,9*S*)-2-Amino-8-oxo-9,10-epoxydecanoic Acid in Protected Form

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(2*S*,9*S*)-2-Amino-8-oxo-9,10-epoxydecanoic acid **1**, (AOE), has been synthesized in protected form by homolytic homologation from protected (*S*)-2-amino-5-iodopentanoic acid.

AOE **1** is the active component[1] of the physiologically active family of cyclic tetrapeptides which includes chlamydocin[2] **2a**. Structure–activity studies have demonstrated the epoxy ketone functionality to be crucial for *in vitro* cytostatic and antimitogenic activity. From a synthetic standpoint the epoxy ketone represents a problem because of its high susceptibility to nucleophilic attack. Consequently, only Schmidt's syntheses of chlamydocin **2a**[3] and WF-3161 **2b**[4] are of value whereby the epoxy ketone functionality was unmasked after assembly of the incipient AOE residue in a cyclic tetrapeptide

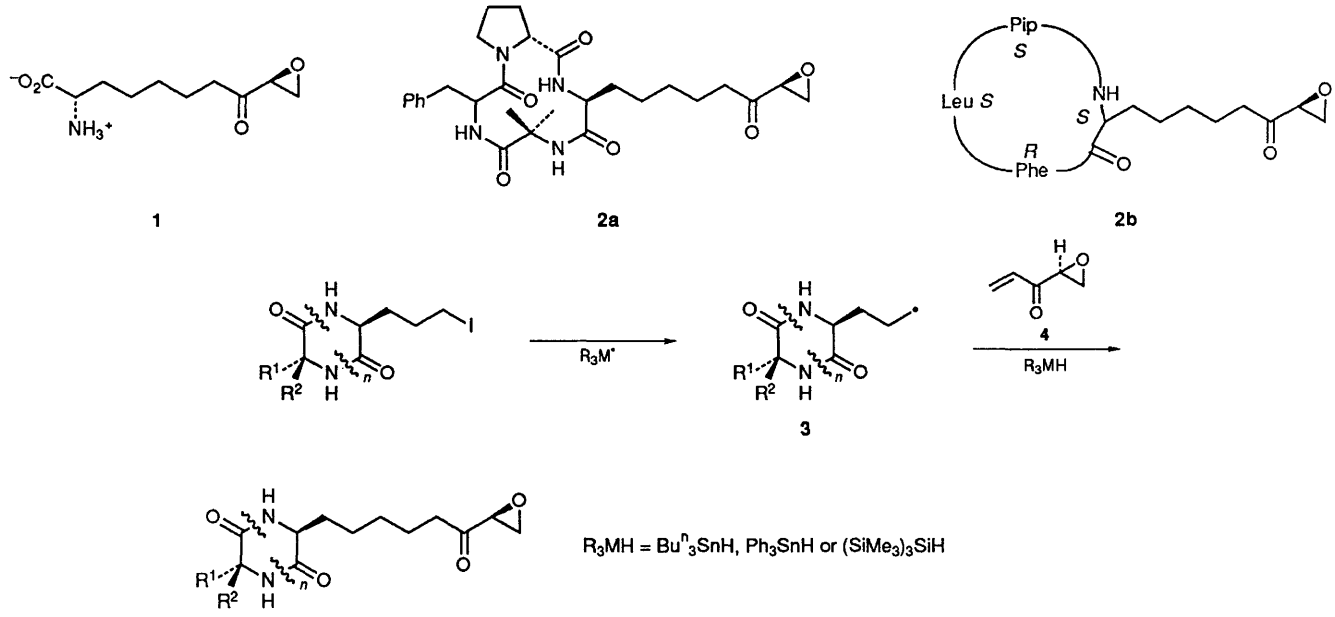
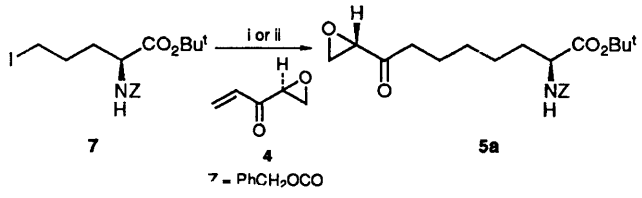
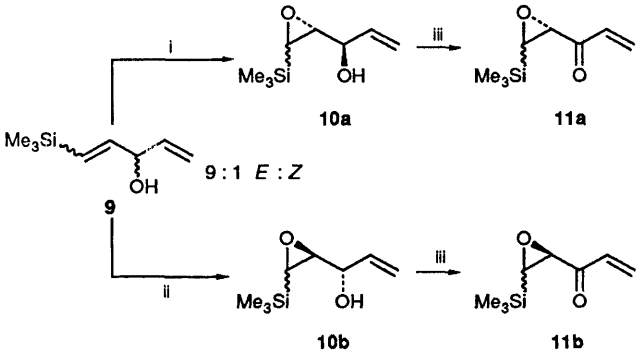


Fig. 1



Scheme 1 *Reagents and conditions*: i, Ph_3SnH or Bu^n_3SnH (1 equiv.) (slow addition over 4 h), cat. AIBN, benzene, reflux; ii $(SiMe_3)_3SiH$ (1.1 equiv.), cat. AIBN, benzene, reflux; AIBN = azoisobutyronitrile



Scheme 2 *Reagents and conditions*: i, 5 mol% (−)-DIPT, 6 mol% $Ti(OPr^i)_4$, Bu^tO_2H (0.5 equiv.), dried mol. sieves, CH_2Cl_2, −16 °C, 4 h; ii, 5 mol% (+)-DIPT, 6 mol% $Ti(OPr^i)_4$, Bu^tO_2H (0.5 equiv.), dried mol. sieves, CH_2Cl_2, −16 °C, 4 h; iii, TFAA (1.5 equiv.), DMSO (2 equiv.), NEt_3 (3 equiv.), CH_2Cl_2, −65 °C then warm to 20 °C; DIPT = diisopropyl tartrate; TFAA = trifluoroacetic anhydride; DMSO = dimethyl sulphoxide

framework. Unfortunately, such a method required multistep sequences (*e.g.* 14 steps from diethyl tartrate to give a precursor to AOE in the synthesis of WF-3161 **2b**[4]) and lacked flexibility. Other reported syntheses of protected AOE[5,6] are not only long but also suffer from not being applicable to the syntheses of the biologically significant tetrapeptide forms.† We proposed that a superior approach would be *via* addition of a free-radical **3** derived from a suitably functionalised cyclopeptide, to a chiral epoxyenone **4**, as a late step in the synthesis (Fig. 1). As such, flexibility with respect to the pendant chain length and absolute configuration of the epoxy ketone could readily be accommodated.

Table 1

Compound	Addition yield (%)	Compound	Desilylation yield (%)
12a	62	**5a**	64
12b	65	**5b**	58
13a	61	**6a**	61
13b	67	**6b**	64

In order to test this proposal we firstly attempted a synthesis of (2*S*,9*S*) AOE **5a** in protected form. Initially, protected (2*S*)-2-amino-5-iodo-pentanoic acids **7** and **8**, and (4*S*)-4,5-epoxypent-1-en-3-one **4** were synthesized.‡

Two different methods of radical homologation were then attempted. Slow addition of either tributyltin hydride or triphenyltin hydride (1 equiv.) to a refluxing solution of the iodoamino ester **7** (1 equiv.) and epoxyenone **4** (4 equiv.) in benzene gave (2*S*,9*S*) *tert*-butyl-*N*-benzyloxycarbonyl-2-amino-9,10-epoxy-8-oxo-decanoate, **5a**, in 35% yield. Using tris(trimethylsilyl)silyl hydride[7] (1.1 equiv.) as the reducing agent gave similar results (Scheme 1). A significant problem encountered in these protocols was decomposition of the enone under the reaction conditions.

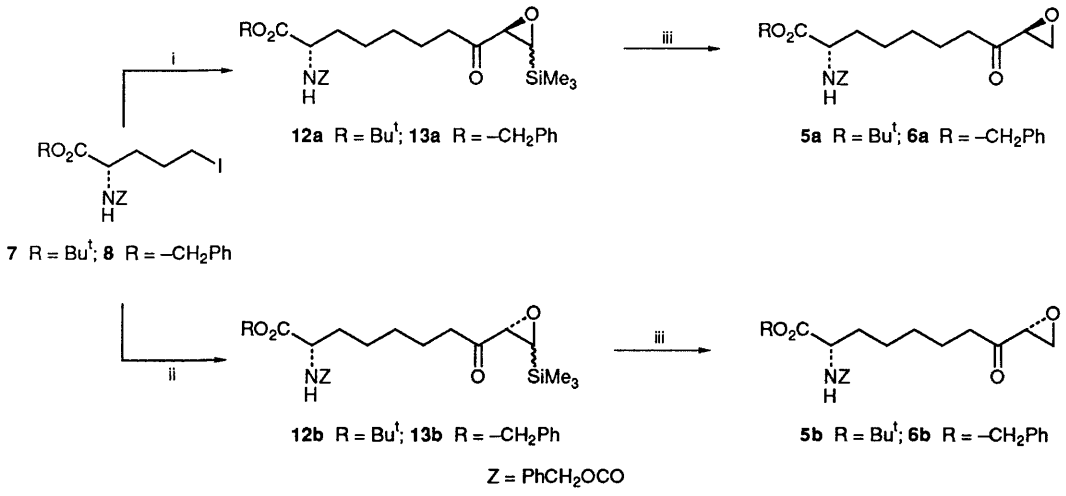
Further improvement in the coupling reaction was then demonstrated by the use of (4*S*)- and (4*R*)-5-trimethylsilyl-4,5-epoxypent-1-en-3-ones,§ **11a** and **11b**, (Scheme 2) as the radicalophile in the coupling reaction.

Addition of tributyltin hydride (1 equiv.) over 4 h to a refluxing solution of degassed benzene containing protected iodoamino acid (either **7** or **8**) with the trimethylsilyl epoxyenones in fourfold excess gave the terminally silylated AOEs in about 65% yield (Scheme 3) (Table 1). Use of tris(trimethylsilyl)silyl hydride as the reducing agent gave variable results ranging from 5 to 60%. The silyl group was then removed by TBAF treatment in DMSO to give both (9*R*)- and (9*S*)-AOEs, **5** and **6**, in protected form (Table 1).

† For example, attempted unmasking of any *N*-protection in order to join onto a tripeptide fragment would result in competing reaction with the sensitive epoxyketone functionality.

‡ Details will appear elsewhere.

§ The desilylated Mosher's esters[8] of the corresponding alcohols, **10a** or **10b**, were shown to be essentially homochiral by ^{19}F NMR analysis.



Scheme 3 *Reagents and conditions*: i, reagent **11a**, Bu^n_3SnH (slow addition over 4 h), cat. AIBN, benzene, reflux; ii, reagent **11b**, $Bu_3{}^nSnH$ (slow addition over 4 h), cat. AIBN, benzene, reflux; iii, TBAF (1.1 equiv.), DMSO, 10 min, 20 °C; TBAF = tetrabutylammonium fluoride

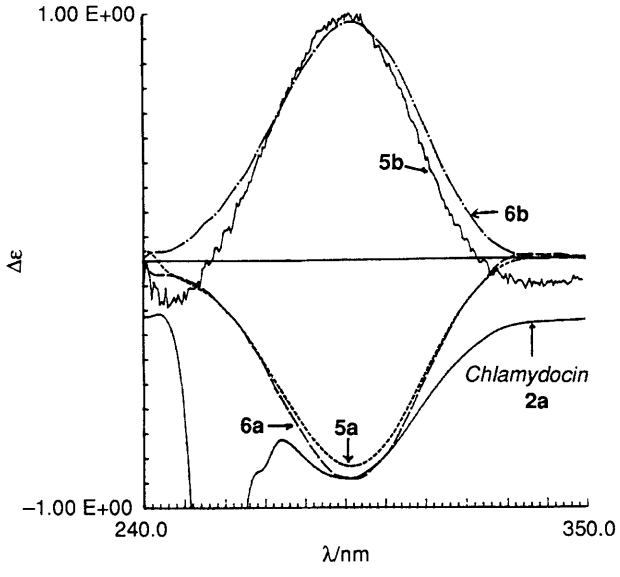


Fig. 2 CD spectra of **5a, 6a, 5b, 6b** and chlamydocin (**2a**)

Circular dichroism (CD) spectra of (2*S*, 9*S*) AOEs **5a** and **6a** showed Cotton effects of the same sign and magnitude as natural chlamydocin **2a**[9] whereas (2*S*, 9*R*) AOEs **5b** and **6b** showed opposite Cotton effects (Fig. 2).

In summary we have developed two related homolytic approaches for the facile assembly of both (2*S*, 9*S*) and (2*S*, 9*R*)-2-amino-8-oxo-9,10-epoxydecanoic acids in protected form. The methodologies are, in principle, suitable for the total synthesis of chlamydocin **2a** and related homologues. Such approaches are current objectives.

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