New procedures for the Juliá–Colonna asymmetric epoxidation: synthesis of (+)-clausenamide

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The oxidation of chalcone 1 to optically active epoxide 2 [a precursor of (+)-clausenamide (+)-3] may be effected using a 15-mer or 20-mer of L-leucine bound to a PEG based support; poly-L-leucines of this type may be used as immobilised catalysts in a fixed-bed reactor.

The polyamino acid catalysed asymmetric epoxidation of α,β-unsaturated ketones was discovered by Juliá and Colonna.[1] The reaction entailed taking a polyamino acid, such as poly-L-leucine, and allowing it to swell to form a gel in the presence of an organic solvent, 4 M aq. NaOH and H_2O_2. After several hours, the substrate was added to the three-phase system (insoluble polyamino acid, organic solvent–substrate, and water–H_2O_2–NaOH). This system was used by Lantos[2] and Ferreira[3] in the synthesis of selected target molecules.

Recently, it has been shown that the original three-phase system used by Juliá and Colonna can be replaced by a non-aqueous two-phase system[4] and this modified procedure has been used to prepare diltiazem, Taxol™ side-chain[5] and other interesting structures.[6]

These recent advances in the utilisation of the Juliá–Colonna oxidation focused our attention on three issues: (i) understanding the mechanism of the reaction; (ii) finding a suitable methodology for conducting the reaction on a large scale; and (iii) broadening the range of target molecules that can be made by using the Juliá–Colonna technique as the key step. Some progress has been made in each of these areas, as detailed below.

Understanding the mechanism of the Juliá–Colonna oxidation is the key to the application of the methodology to a broader range of substrates. Typically the polyamino acid catalyst is prepared by synthesis of the appropriate amino acid N-carboxy anhydride (NCA) and then initiating polymerisation using a nucleophile (water, an alcohol or an amine). Using L-leucine and 1,3-diaminopropane this procedure gives a polymer with a molecular weight range of 1500–3000;[7] it was of interest to determine whether the heterogeneous nature of the polymer and/or the method of preparation[8] were important with regard to the intriguing catalytic properties of the system.

Thus, L-leucine NCA was polymerised using a polyethylene glycol polystyrene based[9] amino nucleophile as the initiator to give CAT 1. At the same time a PEG-polystyrene supported 15-mer of L-leucine (CAT 2) and a PEG-polystyrene supported 20-mer of L-leucine (CAT 3) were prepared using a peptide synthesiser. The effectiveness of these catalysts for the conversion of chalcone 1 into the corresponding epoxide 2 (Scheme 1) is detailed in Table 1.

It is clear that the homogeneous polymers of leucine behave in a very similar manner to the material prepared in the usual way from the N-carboxy anhydride. This is the first time that a simple polyamino acid, prepared using a peptide synthesiser, has been shown to catalyse the Juliá–Colonna asymmetric epoxidation reaction. Variation in the amino acid content of the homogeneous peptide chain (i.e. 'point mutation' of the
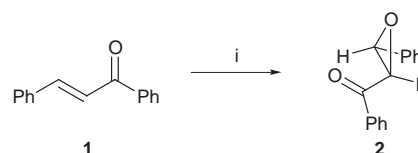
Scheme 1 Reagents and conditions: i, biphasic conditions: base, oxidant, e.g. urea–H_2O_2, solvent, e.g. THF, room temp.

'synthetic enzyme'[10]) is currently under way to help to elucidate the mechanism of this fascinating reaction.

Under the biphasic reaction conditions the polypeptide does not swell to any appreciable extent. This suggested that the substrate in a suitable solvent might be passed through a column of the catalyst mixed with the oxidant to furnish a fixed-bed reactor convenient for a large scale continuous flow synthesis of optically active epoxides. A miniature system was studied.

Poly-L-leucine, immobilised on cross-linked aminomethyl-polystyrene[11] (CLAMPS), was slurry packed into a Pasteur pipette together with oxidant. A solution of chalcone 1 dissolved in a solvent containing DBU (0.5% v/v) was passed through the column. Gratifyingly, good conversions of 1 to epoxide 2 of good to excellent optical purity was observed. A comparison of two oxidants and five solvents (Table 2) suggested that DABCO–H_2O_2[12] and tert-butyl methyl ether are the components of choice for further study.

The epoxide 2 was utilised to prepare (+)-clausenamide 3, an antiamnaesic agent with potent hepatoprotective activity[13] (Scheme 2). Oxidation of ketone 2 under the conditions recommended by Flisak[14] afforded the ester 4, which was converted into the amide 5 using (±)-2-methylamino-1-phenyl-ethanol. Oxidation of the hydroxy amide 5 and subsequent base-catalysed cyclisation under prescribed conditions[15] furnished a 1:1 mixture of diastereomeric lactams (+)-7 and (−)-8 [epimerisation of (−)-8 to provide further quantities of (+)-7 may be effected by base[16]]. Diastereoselective reduction of (+)-7 with $NaBH_4$ generated (+)-clausenamide (+)-3 in 89% yield; the synthetic material had physical properties in accord with those documented previously.[17] This naturally occurring compound is now available from chalcone 1 in six steps and 40% overall yield.

**Table 1** Oxidation of chalcone 1 using polyleucine catalysts[a]

Catalyst	t/h	Conversion (%)	Ee[b] (%)
CAT 1	1.5	78	83
CAT 2	1.5	89	87
CAT 3	1.5	66	89

[a] Typical reaction conditions: chalcone (25 mg) in THF (0.75 cm³) with catalyst (50 mg), DBU (6 equiv.) and urea–H_2O_2 (4.8 equiv.). [b] Ees determined by chiral HPLC.

Table 2 Oxidation of chalcone **1** using a fixed-bed of poly-L-leucine[a]

Oxidant	Solvent	Residence time/min	Conversion (%)	Ee[b](%)
Urea–H$_2$O$_2$	THF	15	63	94
Urea–H$_2$O$_2$	EtOAc	20	87	96
Urea–H$_2$O$_2$	Bu^{t}OMe	20	93	96
DABCO–H$_2$O$_2$	THF	15	80	98
DABCO–H$_2$O$_2$	CH$_2$Cl$_2$	15	74	84
DABCO–H$_2$O$_2$	EtOAc	15	57	92
DABCO–H$_2$O$_2$	Bu^{t}OMe	20	>97	>98
DABCO–H$_2$O$_2$	MeCN	25	87	86

[a] *Reagents and conditions*: immobilised poly-L-leucine (300 mg) was packed in a column with oxidant (30 mg). Chalcone **1** (50 mg) in solvent (0.5 cm³) was added and the column was eluted with the same solvent. [b] Ees determined by chiral HPLC.
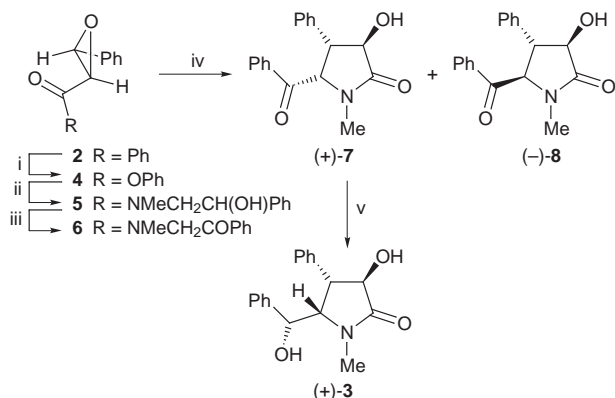
Scheme 2 *Reagents and conditions*: i, MCPBA, CH$_2$Cl$_2$, reflux, 78%; ii, (±)-2-methylamino-1-phenylethanol, CH$_2$Cl$_2$, 0 °C to room temp., 93%; iii, KMnO$_4$–CuSO$_4$, CH$_2$Cl$_2$, room temp., 76%; iv, aq. LiOH, Et$_2$O–THF, room temp., 93%; v, NaBH$_4$, MeOH, 0 °C to room temp., 83%

Notes and References

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