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β-Peptides as catalysts: poly-β-leucine as a catalyst for the Juliá–Colonna asymmetric epoxidation of enones

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Poly-β-leucines have been evaluated as catalysts for the Juliá–Colonna asymmetric epoxidation of enones; the β³-isomer was found to be an effective catalyst for the epoxidation of chalcone (70% ee) and some analogues.

Peptides, generated from α-amino acids, can adopt a number of stable conformations such as the α-helix and β-sheet. In combination these secondary structural units allow a protein to adopt a defined tertiary structure, which can lead to catalytic behaviour. Recent work by Seebach,[1] Gellman[2] and others,[3] as well as earlier studies,[4] has shown that peptides generated from β-amino acids (so called β-peptides) show similar secondary structural characteristics to their natural counterparts. This suggests that, in principle, the β-analogues of proteins may exhibit related catalytic behaviour. It is notable that short β-peptides show promise as therapeutic agents as they can exhibit similar biological profiles to α-peptides with increased stability to peptidases, leading to improved bioavailability.[5] Careful tuning of β-amino acid structure has allowed a wide range of structural units to be reliably prepared using the β-peptide backbone.

Work initiated by Juliá and Colonna[6a] has shown that polyamino acids, typically containing 30 or more identical residues of α-leucine or α-alanine, are capable of catalysing the Weitz–Scheffer epoxidation of enones with remarkable levels of asymmetric control.[6] More recently, modifications have been made to the original reaction conditions[6b] and as a result the method is now applicable to a wide range of *trans*-enones.[6c] As part of an ongoing program investigating and developing this transformation, β-analogues of the Juliá–Colonna poly-α-leucine catalysts have been prepared, in order to evaluate their potential as asymmetric catalysts.

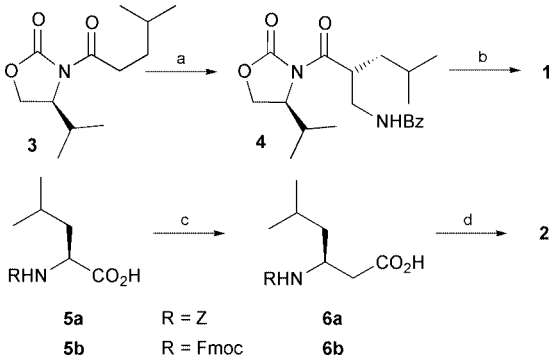
The addition of a methylene unit to an α-amino acid generates two possible structurally-isomeric β-amino acids. Seebach has termed these β² and β³ depending on which carbon bears the side chain.[1] In order to prepare the two isomeric β-leucine polymers, the monomer amino acids β²-(**1**) and β³-leucine (**2**) were required in enantiomerically enriched form (Fig. 1).

Following the method of Seebach, β²-leucine **1** was prepared by amidomethylation of **3** with *N*-(chloromethyl)benzamide using the Evans auxiliary to control the formation of the stereocentre (Scheme 1).†[7] The β³ isomers are generally synthesised using an Arndt–Eistert homologation of the corresponding α-amino acids.[8] Thus, we were able to prepare protected β³-leucines **6a** and **6b** from the corresponding α-amino acids **5a** and **5b**. Compound **6a** was then deprotected to afford **2** {$[\alpha]_D^{22}$ +35 (*c* 1.0, H_2O) lit.[9] +34.7 (*c* 1.0, H_2O}} (Scheme 1).

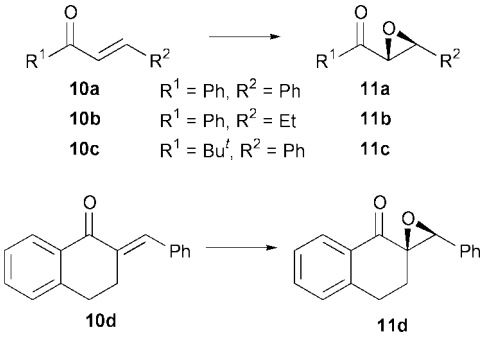
Poly-α-amino acids are typically prepared from the corresponding monomers by activation as the *N*-carboxyanhydride, followed by polymerisation using a nucleophilic initiator.[10] This approach is less effective in the case of β-amino acids[10] and even employing recent synthetic improvements[11] a pure sample of the β³-leucine *N*-carboxyanhydride could not be prepared.

We have shown that a 20-mer of poly-L-α-leucine, prepared using solid phase synthesis, exhibits similar catalytic activity to material generated by polymerisation of L-leucine NCA.[12] Moreover, Seebach has shown that solid phase techniques can be used to prepare β-peptides.[8] Thus, solid phase automated peptide synthesis was carried out using the two isomeric Fmoc protected β-leucines† to afford two 20-mer peptides β²-Leu_{19}-α-Leu-R **7** and β³-Leu_{19}-α-Leu-R **8**.‡[13]

The polymers **7** and **8** were tested under two sets of reaction conditions; first, a triphasic protocol, consisting of aqueous NaOH and H_2O_2 and a solution of the substrate in toluene,[6a] and



Scheme 1 Synthesis of isomeric β-leucines. *Reagents and conditions*: (a) $TiCl_4$, TEA, $ClCH_2NHBz$, DCM, –10 °C, 53%; (b) i. H_2O_2, LiOH, THF, H_2O, 0 °C, 82%; ii. aq. HCl, AcOH, 110 °C, 86%; (c) i. isobutylchloroformate, TEA, THF, Et_2O, 0 °C; ii. CH_2N_2, Et_2O; iii. Na_2CO_3, $Na_2S_2O_3$, AgO_2CCF_3, dioxane, H_2O, 53% over three steps where R = Fmoc; (d) HBr, AcOH, 110 °C, 90% where R = Z.



Scheme 2 Epoxidations.

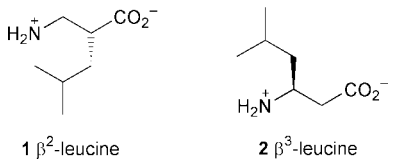


Fig. 1 Isomeric β-leucine monomers.

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Table 1 Epoxidation of enones using poly-β-amino acid catalysts

Entry	Substrate	Catalyst	Activation	Conditions	Major product	Time/h	Conversion (%)[a]	Ee (%)[b]
1	**10a**	α-Leu-R	None	Biphasic[c]	**11a**	1.5	66	89
2	**10a**	β^2-Leu_{19}-α-Leu-R **7**	None	Biphasic[c]	**11a**	4	21	3
3	**10a**	β^3-Leu_{19}-α-Leu-R **8**	None	Biphasic[c]	**11a**	1.5	20	23
4	**10a**	β^3-Leu_{19}-α-Leu-R **8**	None	Triphasic[d]	**11a**	4	15	25
5	**10a**	β^3-Leu_{19}-α-Leu-R **8**	Aq. NaOH–PhMe[e]	Triphasic[d]	**11a**	24	92	70
6	**10a**	β^3-Leu_{20}-R **9**	DBU–PhMe[f]	Biphasic[c]	**11a**	24	96	39
7	**10a**	β^3-Leu_{20}-R **9**	Aq. NaOH–PhMe[e]	Biphasic[c]	**11a**	24	77	20
8	**10b**	β^3-Leu_{20}-R **9**	DBU–PhMe[f]	Triphasic[d]	**11b**	24	98	15
9	**10b**	$\beta^3$$Leu_{20}$-R **9**	DBU–PhMe[f]	Biphasic[c]	**11b**	24	98	28
10	**10c**	β^3-Leu_{20}-R **9**	DBU–PhMe[f]	Biphasic[c]	**11c**	24	10	85
11	**10d**	β^3-Leu_{20}-R **9**	DBU–PhMe[f]	Triphasic[d]	**11d**	24	25	22
12	**10d**	β^3-Leu_{20}-R **9**	DBU–PhMe[f]	Biphasic[c]	**11d**	24	35	9

[a] Determined by HPLC. [b] Determined by chiral HPLC, major enantiomer **11**. [c] Substrate (0.24 mmol), urea–H_2O_2 (28 mg), DBU (56 μl), catalyst (100 mg) in THF (1 ml). [d] Substrate (0.24 mmol), catalyst (100 mg), 30% aq. H_2O_2 (0.7 ml), 4 M aq. NaOH (0.5 ml) and PhMe (1 ml). [e] Catalyst (100 mg) stirred with 4 M aq. NaOH (0.5 ml) and toluene (1 ml) for 70 hours, then filtered and dried. [f] Catalyst (100 mg) stirred with DBU (56 μl) in THF (1 ml) for 16 hours then reagents for reaction added directly.

secondly, biphasic conditions, employing urea–H_2O_2 and DBU in THF.[6b] Like their α-analogues, the poly-β-leucines proved to be insoluble in both organic and aqueous solvents.§

In the first instance, the poly-β-amino acids were tested as catalysts for the epoxidation of chalcone (**10a**) (Scheme 2). Under the biphasic conditions, with catalysis by α-Leu_{20}-R, the (2*R*,3*S*)-epoxide **11a** was obtained (66% conversion, 89% ee) after 1.5 hours (Table 1, entry 1). Catalysis using β^2-Leu_{19}-α-Leu-R **7** afforded essentially racemic epoxide under the same conditions; moreover, the rate of reaction was considerably diminished (entry 2). On the other hand, the β^3-Leu_{19}-α-Leu-R catalyst **8** gave a significant ee of (2*R*,3*S*)-**11a** under both biphasic (23% ee) and triphasic (25% ee) reaction conditions, albeit still with a decreased rate (entries 3 and 4 respectively).

Previous studies have shown that the activity of poly-α-amino acid catalysts can be improved by various washing procedures.[14] Two such activations were investigated with the catalyst **8** and a third 20-mer: β^3-Leu_{20}-R **9**. In the first procedure the catalyst was stirred for 70 hours in a mixture of 4 M aq. NaOH and toluene, before filtering, washing and drying;[14] in the second it was stirred with DBU in toluene for 16 hours before adding the reagents for epoxidation directly. Both activation procedures significantly increased the enantioselectivity of the catalysed epoxidation reaction. For example, NaOH–PhMe-activated **8** catalysed the epoxidation of **10a** with 92% conversion and 70% ee under the triphasic conditions (entry 5).¶

The catalyst **9** was tested against a range of other substrates **10b–d**. Using DBU–PhMe-activated **9** the ees for the epoxidation of the β-ethyl enone **10b** were somewhat lower than for chalcone (entries 6, 8 and 9); under the biphasic conditions the ethyl epoxide **11b** had an ee of 28% (entry 9). On the other hand, under similar conditions the *tert*-butyl ketone **10c** was epoxidised in a high ee (entry 10), however the reaction rate was significantly retarded, with only 10% conversion to the epoxide **11c** being obtained after 24 hours. The final substrate investigated was 2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (**10d**). In this case the triphasic reaction conditions gave an ee of 22%; however the reaction was again slow (entry 11).

In conclusion, peptides generated from β-amino acids exhibit catalytic behaviour analogous to that shown by poly-α-amino acids. Specifically, poly-β^3-leucine catalyses the epoxidation of (*E*)-α,β-enones with significant enantioselectivity. Although this methodology is not competitive with the poly-α-amino acid analogues it is possible that variation of the β-amino acid monomer may lead to altered catalytic behaviour. Results of such studies and approaches to preparing poly-β-amino acids *via* polymerisation reactions will be reported in due course.

Notes and references

† Fmoc β^2-leucine was prepared from **1** using FmocCl under standard conditions {$[\alpha]_D^{22}$ = +12 (*c* 1.0, $CHCl_3$) lit.[8] +10.8 (*c* 0.6, $CHCl_3$)}.

‡ The oligoleucines were linked *via* a hydroxymethylphenoxyacetic acid linker to PEG and thence to polystyrene resin (loading 0.18 mmol g^{-1}). These oligomers are represented as Leu_n-R where R = linker–PEG–resin.

§ The poly-β-amino acids remained attached to the support; the solubility of the non-immobilised material was not investigated.

¶ Ees using activated β^2-Leu_{19}-α-Leu-R **7** remained below 10%.

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