Towards peptide isostere libraries: aqueous aldol reactions on hydrophilic solid supports

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Polar polyoxyethylene-polyoxypropylene (POEPOP) resin was derivatised with a 4-hydroxymethyl phenoxy linker and used as a solid support for lanthanide triflate catalysed Mukaiyama type solid phase aldol reactions. The conditions were optimised using resin bound 4-alkoxybenzaldehyde and it was shown that use of an aqueous solvent was crucial. Also, the reactions were performed with an N-terminal peptide aldehyde substrate in very high yields. POEPOP resins prepared with different monomer chain lengths and commercially available PEG-grafted NovaSyn TG resin were compared in the reactions.

Introduction

In recent years, solid phase synthesis has emerged as a powerful tool for creating large numbers of highly diverse compounds for utilisation in various screening protocols, and libraries of organic molecules and peptides have proven to be highly efficient for the discovery process of new therapeutic lead compounds.[1] Linear peptides are generally not suited for use as drugs because of their poor oral availability and fast metabolism in the body, however, it is possible to improve resistance towards proteases through several types of modifications. Biologically active dipeptide mimetics as well as linear peptides in which an amide bond has been replaced by a non-hydrolysable bond or by a functionality which mimics the transition state of hydrolysis, have been described as protease inhibitors.[2–7] Currently, work is progressing in this laboratory to expand the concept of preparing combinatorial libraries of peptides to include the synthesis of peptide libraries containing amide bond isosteres formed in a variety of organic reactions on the solid phase, for on-bead screening for endoprotease inhibitors.

The aldol reaction is one of the most powerful organic reactions for the formation of carbon–carbon bonds,[8–10] and several examples of solid phase aldol reactions have appeared in the literature.[11–18] Among the myriad of variants of the aldol reaction, the Mukaiyama-directed cross aldol reaction[19–22] has been extensively utilized. In this transformation, silyl enol ethers derived from ketones, aldehydes, esters, thioesters or amides are reacted with aldehydes in the presence of a catalyst in either stoichiometric or sub-stoichiometric amounts. By far, most of the common catalysts for this reaction are Lewis acids, and chiral induction has been successfully demonstrated in the aldol reaction by use of chiral Lewis acids.[23–26] However, as most Lewis acids are very sensitive to water, the reactions normally require strictly anhydrous conditions as even small amounts of water significantly lower the yields due to decomposition of the catalyst and hydrolysis of the silyl enol ethers. Thus, the discovery of lanthanide trifluoromethanesulfonates (triflates) as water tolerant Lewis acids[27–29] has greatly expanded the scope of the reaction, especially from an industrial point of view. Also, the use of scandium triflate as an efficient catalyst in solid phase aldol reactions has been reported, albeit in non-aqueous media.[14]

Several novel solid supports compatible with conditions used in enzymatic reactions and allowing enzymes to penetrate to the interior of the resins, were previously developed in this laboratory.[30–35] Thus, polyoxyethylene–polyoxypropylene (POEPOP) resin, containing only ether and hydroxy functionalities, was designed as a chemically inert hydrophilic resin compatible with the aqueous conditions used in enzymatic reactions and screening and also with various conditions generally used in organic synthesis. In the context of performing organic reactions on peptide derived substrates attached to a solid support, the use of polar, hydrophilic resins and water tolerant catalysts is a very attractive approach, which greatly facilitates the ease and robustness of the operation since time-consuming steps to dry the hygroscopic solid supports are eliminated.

This paper describes model studies for performing lanthanide triflate catalysed aldol reactions on hydrophilic solid supports in aqueous media, including the first examples of solid phase aldol reactions of an N-terminal peptide aldehyde. Also, a comparison of POEPOP resin with commercially available hydrophilic PEG-grafted NovaSyn TG resin is made.

Results and discussion

Derivatisation of resins

Preparation of POEPOP–HMP resins. To enable a comparison of the synthetic utility of POEPOP resin in the work presented here, one of the most widely used commercially available hydrophilic resins, NovaSyn TG–HMP, was selected as a reference system. In order to make a direct comparison it was necessary to derivatise POEPOP, made with different PEG-monomer lengths, with the 4-hydroxymethylphenoxy (HMP) linker moiety. Initially, POEPOP was per-mesylated and reacted in an S_N2 reaction with several equivalents of HMP overnight in DMF at temperatures ranging from 50–90 °C in the presence of Cs_2CO_3. Since this strategy did not satisfactorily incorporate HMP into the resin, probably due to the presence of secondary alcohol functionalities in POEPOP, attention was turned towards Mitsunobu chemistry.[36] Several examples of successful solid phase Mitsunobu ether formations have been published.[37–43] As HMP is a bifunctional compound with respect to Mitsunobu couplings, the benzylic alcohol was protected with the dimethoxytrityl (DMT) group to avoid polymerisation. DMT was selected as it allows simple and direct monitoring and for incorporation to be quantified by cleavage of a known amount of resin by treatment with mild

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Table 1 Mitsunobu reactions on POEPOP and NovaSyn TG-OH

Entry	Resin	Conditions	Yield(%)[a]
1	$POEPOP_{400}$	DEAD[b]–PPh_3–**1** (1 : 1 : 1) (5 eq.) 0.12 M in THF	14
2	$POEPOP_{400}$	DEAD–PPh_3–**1** (1 : 1 : 1) (5 eq.) 0.12 M in NEM	<10
3	$POEPOP_{400}$	DEAD–PPh_3–**1** (1 : 1 : 1) (5 eq.) 0.12 M in THF–DCM (1 : 1)	68
4	$POEPOP_{400}$	DEAD–PPh_3–**1** (1 : 1 : 1) (5 eq.) 0.25 M in THF–DCM (1 : 1)	>95
5	$POEPOP_{400}$	DEAD–PPh_3–**1** (1 : 1 : 0.6) (5 eq.) 0.25 M in THF–DCM (1 : 1)	17
6	$POEPOP_{1500}$	DEAD–PPh_3–**1** (1 : 1 : 1) (5 eq.) 0.05 M in THF–DCM (1 : 1)	<10
7	$POEPOP_{1500}$	DEAD–PPh_3–**1** (1 : 1 : 1) (5 eq.) 0.1 M in THF–DCM (1 : 1)	47
8	$POEPOP_{1500}$	DEAD–PPh_3–**1** (1 : 1 : 1) (10 eq.) 0.2 M in THF–DCM (1 : 1)	49
9	$POEPOP_{1500}$	DEAD–PPh_3–**1** (1 : 1 : 1) (10 eq.) 0.2 M in THF–DCM (1 : 1) × 2	45
10	$POEPOP_{1500}$	**2** : **1** (1 : 1) (5 eq.) 0.08 M in DCM	51
11	$POEPOP_{900}$	DEAD–PPh_3–**1** (1 : 1 : 1) (5 eq.) 0.1 M in THF–DCM (1 : 1)	53
12	NovaSyn TG-OH	DEAD–PPh_3–**1** (1 : 1 : 1) (5eq.) 0.25 M in THF–DCM (1 : 1)	21

[a] Determined spectrophotometrically at 498 nm. [b] DEAD: diethyl azodicarboxylate.

acid followed by spectrophotometric quantitation of the released DMT cations. The results are summarised in Table 1.

Initially, literature procedures[38,41,42] were tested (entries 1–3). One of the most widely used solvents in Mitsunobu chemistry is THF. However, using this solvent gave unsatisfactory results in the coupling between **1** and $POEPOP_{400}$ resin (entry 1). The swelling of POEPOP is very low in THF, possibly preventing good solvation and accessibility of resin bound reactants. In contrast, when 50% THF in DCM was used, the swelling of POEPOP was improved, and good yields were obtained (entry 3). The yield could be further improved by increasing the concentration of reagents (entry 4). It was not possible to obtain the reaction using *N*-ethyl morpholine as the solvent (entry 2). The importance of using equimolar amounts of reagents is demonstrated in entry 5. Changing to $POEPOP_{1500}$ led to a significant drop in coupling efficiency (entry 6); this may be explained by the fact that $POEPOP_{1500}$ has a much higher swelling and also a lower loading compared with $POEPOP_{400}$, leading to lowered concentrations of both reagents and resin bound reactant. To counteract this dilution, care was taken to diminish the amount of solvent used to increase the concentration of reagents, leading to a somewhat improved yield (entry 7). However, increasing the concentration of reagents further to the level optimal for $POEPOP_{400}$ had no effect on the yield (entry 8). Surprisingly, double coupling did not increase the level of incorporation (entry 9). A Mitsunobu-like process has been reported by Castro *et al.*[44] using the triphenylphosphine-cyclic sulfamide betaine **2**, and the reaction has been successfully applied on solid phase.[45–47] However, no improvement was obtained using **2** in the coupling between $POEPOP_{1500}$ and **1** (entry 10). Similar results were obtained with $POEPOP_{900}$ (entry 11). For comparison, **1** was also reacted with NovaSyn TG-OH resin under the same conditions, leading to an incorporation of only 21% (entry 12).

To eliminate any interference from any residual free hydroxy groups remaining on $POEPOP_{900}$ and $POEPOP_{1500}$ after derivatisation, the resins were capped using acetic anhydride in pyridine prior to deprotection of the linker.

Preparation of polymer supported 4-alkoxybenzaldehyde. POEPOP–HMP resins or NovaSyn TG–HMP, obtained from a commercial source, were mesylated and added to a DMF solution of sodium 4-phenoxybenzaldehyde to provide polymer supported 4-alkoxybenzaldehydes **4a**–**d** (Scheme 1). The yields were quantified by NMR of the crude product by cleaving a known amount of resin against an added internal standard (EtOAc). The reactions worked equally well for all resins, as the loadings of 4-alkoxybenzaldehyde were always above 80% compared with initial loading of linker. Products **4a**–**d** exhibited a typical carbonyl IR absorbance at 1698 cm^{-1}.

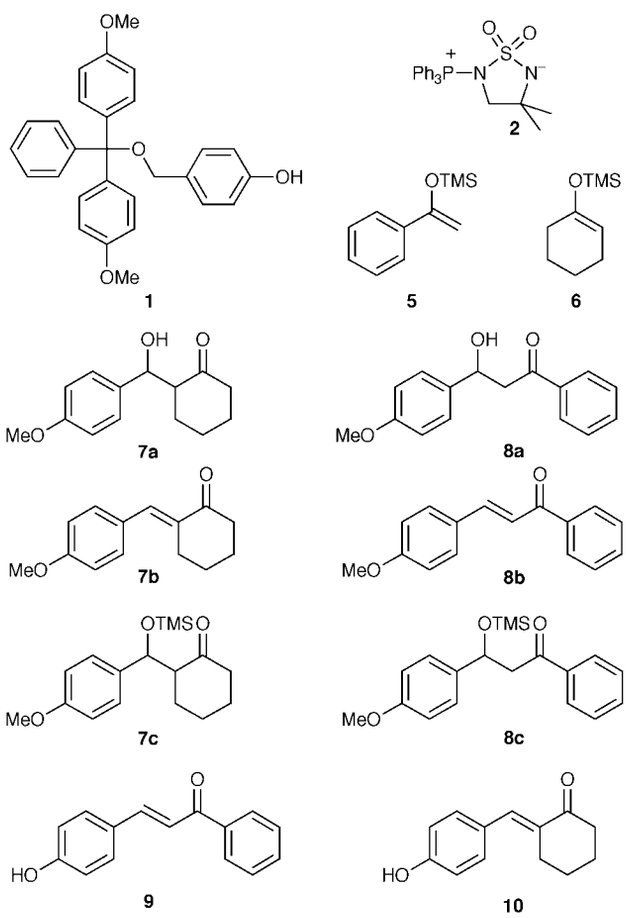
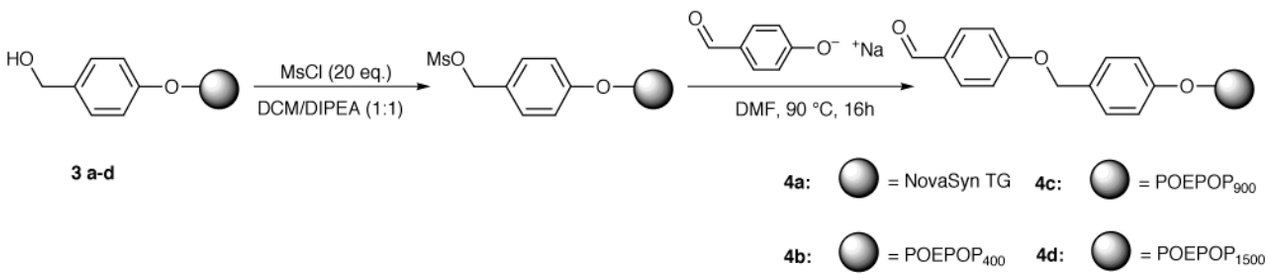


Table 2 Solution phase aldol reactions of 4-hydroxybenzaldehyde using 10 mol% of lanthanide triflates as catalysts at rt

Entry	Catalyst	Silyl enol ether	Solvent (ratio)	Product [a]	Yield (%) [b]
1	$Yb(OTf)_3$	**5**	THF–H_2O (4:1)	**8a**	20
2	$Y(OTf)_3$	**5**	THF–H_2O (4:1)	**8a**	25
3	$Yb(OTf)_3$	**5**	THF–DCM (2:3)	**8b**	40
4	$Y(OTf)_3$	**5**	THF–DCM (2:3) [c]	**8a**	65
				8c	35
5	$Yb(OTf)_3$	**6**	THF–H_2O (4:1)	**7a** [d]	75
6	$Y(OTf)_3$	**6**	THF–DCM (2:3) [c]	**7c** [e]	30

[a] Products identified by NMR of crude mixture after aqueous work-up. [b] Yield determined by NMR of crude mixture by comparing signals of products and anisaldehyde. [c] Performed at 0 °C. [d] *syn*:*anti*: 75:25. [e] 50:50.

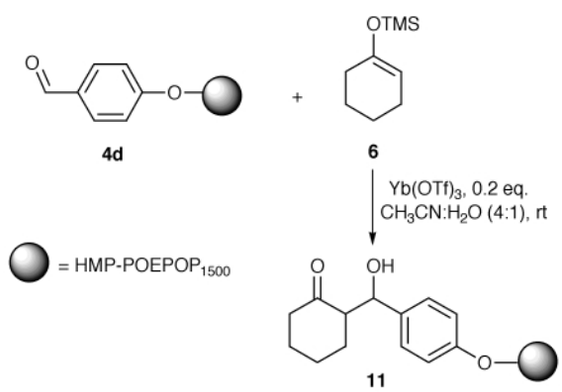


Scheme 1 Derivatisation of resins **3a**–**d** with 4-hydroxybenzaldehyde.

Aldol reactions

Lanthanide triflate catalysed aldol reactions in aqueous media were initially reported by Kobayashi and Hachiya,[27,28] enabling the facile use of aqueous formaldehyde solutions in the reaction as well as several other aldehydes. In the work presented here, initial solution experiments were conducted with model substrates to optimise the conditions. 4-Methoxybenzaldehyde was selected as the aldehyde component along with silyl enol ethers **5** and **6** representative of silyl enol ethers reacting from primary or secondary positions, respectively. The results are summarized in Table 2. The conditions established by Kobayashi *et al*. for the ytterbium triflate ($Yb(OTf)_3$) catalysed reaction of 4-methoxybenzaldehyde with **6**, as given in entry 5, lead to the aldol product **7a** in 75% yield. However, reaction of silyl ether **5** only gave 20% of product **8a** under these conditions, due to rapid hydrolysis of **5** (entry 1). Consequently, the catalyst was substituted with the weaker Lewis acid yttrium triflate ($Y(OTf)_3$). This did not lead to any significant improvement (entry 2). However, when the aqueous solvent was substituted with an organic mixture of THF–DCM, the yields were increased. Using $Yb(OTf)_3$ under these conditions led to the formation of the dehydrated product **8b** (entry 3), whereas using $Y(OTf)_3$ as the catalyst gave a mixture of the aldol product **8a** and the silylated aldol product **8c** in quantitative yield after aqueous work-up (entry 4). Reaction of **6** under the latter conditions led to only a 30% yield of silylated aldol product **7c** (entry 6).

Next, the reactions were attempted on a solid phase. The aldol reactions were studied using a stoichiometric amount of catalyst in different solvents. The products were cleaved from the resins by treating with TFA:H_2O (95:5) for 2 h at ambient temperature and analysed by NMR. Under the cleavage conditions, the aldol products eliminated water to form the α,β-unsaturated compounds **9** and **10**. This was also shown in control experiments in which **7a** and **8a** were submitted to the cleavage conditions in solution and were shown to be converted into **7b** and **8b**, respectively. No retro-aldol reaction was observed. In the case of the reaction of **4d** with **6**, it was demonstrated that the primary product formed on the solid phase, as in solution, was the aldol product **11** (Scheme 2). On-bead 1D-^{1}H- and 2D-^{1}H-NMR spectroscopy (COSY, TOCSY) were aquired with a resin sample from the reaction



Scheme 2 Solid phase aldol reaction of **4d** and **6**.

using nanoprobe MAS-NMR spectroscopy. From these spectra, the structure of the expected aldol product (**11**) was assigned. Also, the on-bead 1D-spectrum showed the *syn*:*anti* ratio of 79:21 obtained on the solid phase to be close to that obtained in solution (75:25) (Fig. 1). By analogy with this experiment and the solution phase studies, it is most likely that the primary products formed on the solid phase are the aldol products. The results of the solid phase aldol reactions are summarised in Table 3.

Initially, the optimal solution conditions determined for the reaction of 4-methoxybenzaldehyde with **5** were tested with resin **4a**, but in contrast to the solution reaction no product was obtained. It has been shown that when running $Yb(OTf)_3$ catalysed aldol reactions in THF in solution, the use of an additive increased the yields, water being the most efficient.[27] Thus, when 50 equivalents of water relative to the catalyst were added, the highest yields were obtained in the reactions. Consequently, these experimental conditions were attempted on the solid phase by adding 50 equivalents of water to the organic solvent mixture; however, this only led to a yield of less than 10% (entry 2). It was suspected that the catalyst was not sufficiently dissolved to enter the interior of the resin, hence, the $Yb(OTf)_3$ catalysed aldol reaction using **6** was performed in an organic solvent mixture of CH_3CN–DCM in which $Yb(OTf)_3$ is completely soluble (entry 3), yet no reaction was observed. These findings are in contrast to reported solid phase aldol

Table 3 Solid phase aldol reactions of resin bound 4-hydroxybenzaldehyde using stoichiometric amounts of lanthanide triflates as catalysts at rt

Entry	Resin	Catalyst	Silyl enol ether	Solvent (ratio)	Product[a]	Yield (%)[b]
1	**4a**	$Y(OTf)_3$	**5**	THF–DCM (2:3)[c]		—
2	**4a**	$Y(OTf)_3$	**5**	THF–DCM (2:3)[d]	**9**	<10
3	**4a**	$Yb(OTf)_3$	**6**	CH_3CN–DCM (3:2)		—
4	**4a**	$Y(OTf)_3$	**5**	THF–H_2O (4:1)	**9**	27
5	**4a**	$Yb(OTf)_3$	**5**	THF–H_2O (4:1)	**9**	35
6	**4a**	$Yb(OTf)_3$	**6**	THF–H_2O (4:1)	**10**	75
7	**4a**	$Yb(OTf)_3$	**6**	CH_3CN–H_2O (4:1)	**10**	81
8	**4a**	$Yb(OTf)_3$	**6**	CH_3CN–H_2O (4:1)	**10**	91[e]
9	**4b**[f]	$Yb(OTf)_3$	**6**	CH_3CN–H_2O (4:1)	**10**	10
10	**4c**[f]	$Yb(OTf)_3$	**5**	CH_3CN–H_2O (4:1)	**9**	28
11	**4c**[f]	$Yb(OTf)_3$	**6**	CH_3CN–H_2O (4:1)	**10**	80
12	**4d**[f]	$Yb(OTf)_3$[g]	**5**	CH_3CN–H_2O (4:1)	**9**	32
13	**4d**[f]	$Yb(OTf)_3$[g]	**6**	CH_3CN–H_2O (4:1)	**10**	83

[a] Products obtained after cleavage from solid supports as identified by NMR. [b] Yield is determined by NMR of the crude cleavage mixture by comparing signals from starting materials and products. All recoveries, as determined by integrating signals from starting materials and product against an added internal standard (EtOAc), are above 60% compared with initial loading. [c] Performed at 0 °C. [d] 50 Equivalents of water relative to the catalyst were added. [e] The resin was reacted twice in the aldol reaction. [f] Resin was re-capped prior to use. [g] Performed with 0.2 equivalents of catalyst relative to aldehyde.

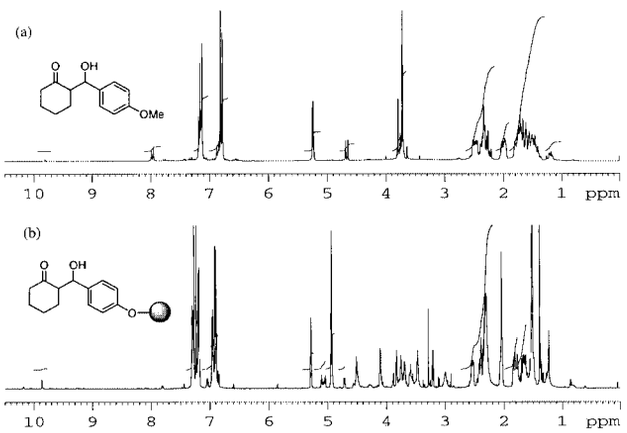


Fig. 1 (a) ^{1}H-NMR spectrum of the diastereomeric mixture of aldol products obtained from the reaction of anisaldehyde and **6**. The signals at δ 4.68 and 5.25 correspond to the protons α to the hydroxy groups (*syn* and *anti* isomers, respectively). (b) Nanoprobe MAS ^{1}H-NMR spectrum of the diastereomeric mixture of aldol products obtained from the reaction of **4d** and **6**. The signals at δ 4.72 and 5.28 correspond to the protons α to the hydroxy groups (*syn* and *anti* isomers, respectively), proving that the primary products obtained on the solid phase are the aldol products, and that elimination takes place during cleavage from the resin. The signals at δ 4.95, 6.91 and 7.19 belong to the HMP-linker. Also, the spectrum displays two $CDCl_3$ signals, one from solvent inside and outside the bead, respectively. The signals from δ 2.91 to 4.55 are residual resin peaks.

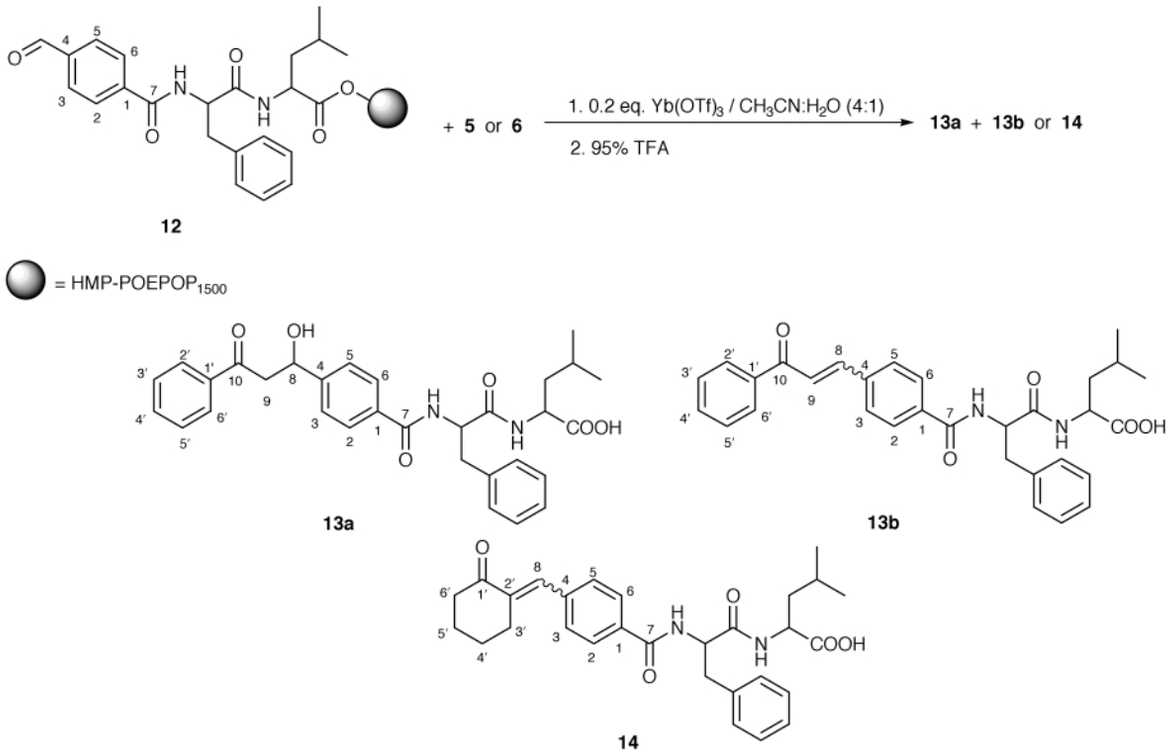
reactions in which insoluble $Sc(OTf)_3$ was used as a catalyst in DCM for reactions run on a polystyrene support.[14] These combined results suggest that the nature of the resins used play an important role in all these reactions, and that addition of water is crucial when performing the reactions on polar, hydrophilic supports, possibly due to low mobility of the catalyst caused by chelation of resin polyethyleneglycol in the absence of water. In contrast, running the $Y(OTf)_3$ catalysed aldol reaction of **5** with an aqueous solvent increased the yield to 27% (entry 4), paralleling the yield obtained using these conditions in solution; this was further increased to 35% upon changing the catalyst to $Yb(OTf)_3$, thus exceeding the yield obtained in solution under similar conditions. The optimal conditions found for the reaction of **6** in solution gave equally good results on the solid phase with **4a**. As the POEPOP polymers may not be well solvated in THF, an alternative solvent mixture in which THF was exchanged for acetonitrile was tested in the reaction of **4a** with **6** leading to an improved yield of 81%, which could be further improved to 91% upon double coupling. Surprisingly, when $POEPOP_{400}$ was used as the solid support, a dramatic decrease in the yield of the reaction was observed, whereas $POEPOP_{900}$ and $POEPOP_{1500}$ led to identical results to those obtained using NovaSyn TG as solid support as shown in entries 10–13 (Table 3). However, it was found that with POEPOP resin, it was important to re-cap any free hydroxy groups that may have been released on the resin backbone under the hydrolytic conditions during the washing of the resins after alkylation, as the yields were otherwise lowered. It has been previously reported that salicylaldehyde is a substrate for the lanthanide triflate catalysed aldol reaction,[27] our results, however, indicate that this tolerance to a free hydroxy group in the reaction is probably the exception rather than the rule. As shown for $POEPOP_{1500}$ in entries 12 and 13 (Table 3), the reactions performed equally well when only a catalytic amount (20 mol% relative to aldehyde) of $Yb(OTf)_3$ was used.

To explore the utility of the reaction in the context of preparing peptide isostere libraries for solid phase screening, the reaction conditions were tested on a peptide like substrate. Peptide **12** (Scheme 3) was selected as an N-terminal aldehyde model substrate. The regularly spaced amide and ester carbonyls could potentially act as bidentate ligands to the catalyst due to the oxyphilic nature of lanthanides, and thereby influence the results of the reactions. As polyethyleneglycol (PEG) resins based on PEG_{1500} are biocompatible with enzyme reactions and the resins of choice for preparing libraries for solid phase screening, it was appropriate to prepare **12** on $POEPOP_{1500}$ only. Using the optimised conditions determined for the reactions of **4a**–**d**, peptide **12** was shown to undergo nearly quantitative reactions with **5** as well as **6** in the presence of 0.2 equivalents of catalyst relative to the aldehyde as shown in Table 4. These results indicate that even in the presence of several amide and ester carbonyls, $Yb(OTf)_3$ shows a strong preference for coordinating to the aldehyde moiety, facilitating sufficiently rapid aldol reactions to efficiently compete with hydrolysis of the silyl enol ethers, resulting in very high yields of aldol product using only catalytic amounts of catalyst.

The results are promising for expanding the concept of performing aldol reactions on N-terminal peptide aldehydes to form combinatorially generated libraries of protease inhibitors, and currently work is being carried out towards this aim.

Conclusion

In the work presented here, the first examples of solid phase aldol reactions in aqueous media, including aldol reactions of an N-terminal peptide aldehyde substrate, using a polar, hydrophilic resin and catalytic amounts of $Yb(OTf)_3$ are reported.



Scheme 3 Solid phase aldol reactions of a model peptide substrate. Numberings refer to numbering used in interpretation of NMR data (see Experimental section).

Table 4 Solid phase aldol reactions of peptide **12** using 0.2 equivalents of $Yb(OTf)_3$ in CH_3CN–H_2O (4 : 1) at rt

Entry	Silyl enol ether	Product [a]	Yield (%) [b]
1	**5**	**13a**, **13b** [c]	>95
2	**6**	**14**	>95 [d]

[a] Products obtained after cleavage from solid support as identified by NMR of crude cleavage mixture. [b] Yield is determined by NMR of the crude cleavage mixture by comparing signals from starting material and product. [c] Ratio between **13a** and **13b** (*E* and *Z* isomers): 2 : 1 : 1. [d] *E* : *Z*: initially 94 : 6, equilibrating to 50 : 50 over one week.

The reactions proceed in high yields, which is important for the methodology to be successfully adapted to synthesis in a combinatorial one-bead-one-compound format. In the course of optimising the conditions for the reactions, it was discovered that the use of an aqueous solvent is essential for the success of the reaction on polar solid supports. This is the first observation of this phenomenon. Hydrophilic POEPOP resins, compatible with performing on-bead enzymatic reactions and screenings and prepared using different monomer lengths, were derivatised with the HMP linker using Mitsunobu chemistry. Also, the POEPOP resins were compared with commercially available NovaSyn TG-OH or NovaSyn TG–HMP in all reactions reported. In the aldol reaction, identical results were obtained using NovaSyn TG, $POEPOP_{900}$ or $POEPOP_{1500}$, whereas only minor yields were obtained using $POEPOP_{400}$. In the S_N2-reactions between mesylated **3a**–**d** and 4-hydroxybenzaldehyde, all resins performed equally well and high yields were obtained in all cases. However, in the Mitsunobu reaction significantly higher yields were obtained using the POEPOP resins, particularly $POEPOP_{400}$. The results obtained, comparing POEPOP to NovaSyn TG, thus suggest that the synthetic utilities of $POEPOP_{900}$ and $POEPOP_{1500}$ resin are similar to that of NovaSyn TG, whereas $POEPOP_{400}$ differs significantly from both NovaSyn TG and POEPOP resins made from PEG-monomer of longer chain lengths.

Experimental

Novasyn TG–HMP resin, Novasyn TG–OH resin, 1-(mesitylene-2-sulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) were purchased from Novabiochem (Läufelfingen, Switzerland). *N*-(Fluoren-9-ylmethoxycarbonyl) (Fmoc)-leucine and Fmoc-phenylalanine pentafluorophenyl (Pfp) ester were obtained from Bachem (Bubendorf, Switzerland). 1-Methylimidazole, PPh_3, DEAD, 4-hydroxymethylphenol, methylsulfonyl(mesyl)chloride, caesium carbonate, 4-hydroxybenzaldehyde, $Y(OTf)_3$, $Yb(OTf)_3$, 1-phenyl-1-trimethylsilyloxyethylene and 1-(trimethylsilyloxy)-cyclohexene were purchased from Fluka (Buchs, Switzerland). *p*,*p*′-Dimethoxytrityl chloride and 4-carboxybenzaldehyde were obtained from Aldrich (Steinheim, Germany). Trichloroacetic acid was purchased from Merck (Darmstadt, Germany) and trifluoroacetic acid from Merck-Schuchardt (Hohenbrun, Germany). Piperidine was purchased from Riedel-de-Häen (Seelze, Germany). All solvents were HPLC grade and were purchased from LabScan (Dublin, Ireland). All reagents and solvents were used as received without further purification. POEPOP resins [32] and compound **2** [44] were prepared according to literature procedures. Nanoprobe MAS NMR-spectra were recorded on a Varian Unity Inova 500 MHz spectrometer equipped with a 4 mm Nano NMR probe at 25 °C using a spin rate of approximately 2000 Hz. Solution phase NMR spectra were recorded on a Varian Unity Inova 500 MHz spectrometer or a Bruker AMX 250 MHz spectrometer. All *J* values are given in Hz.

4-(*p*,*p*′-Dimethoxytrityl)oxymethylphenol (DMT–HMP, 1)

A solution of *p*,*p*′-dimethoxytrityl chloride (8.5 g, 25 mmol) in pyridine (40 cm^3) was added dropwise over 2 h to a stirred solution of 4-hydroxybenzyl alcohol (3.1 g, 25 mmol) in pyridine (60 cm^3) at 0 °C and stirring was continued for 18 h at ambient temperature. The reaction was quenched by addition of methanol (20 cm^3) and the solvents were removed under

reduced pressure. The residue was dissolved in DCM (50 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (3×50 cm^3) and brine (50 cm^3). The organic fraction was dried and evaporated under reduced pressure to leave a brown oil, which was purified by flash column chromatography on silica using ethyl acetate–*n*-heptane (15:85 to 40:60) containing 1% triethylamine as eluent to give **1** (10.2 g, 95%) as a light yellow foam. δ_H (250 MHz; $CDCl_3$) 3.67 (6H, s, OMe), 3.96 (2H, s, O–CH_2–Ar), 6.68–7.49 (17H, Ar); δ_C (67.8 MHz; $CDCl_3$) 55.21 (OMe), 65.23 (O–*C*H_2–Ar), 99.58 (O–*C*–Ar_3), 113.09 (–*C*H–C–OMe), 115.14 (–*C*H–C–OH), 126.69 (Ph), 127.79 (Ph), 128.23 (Ph), 128.65 (–*C*H–CH–C–OH), 130.09 (–*C*H–CH–C–OMe), 131.36 (–*C*–$(CH)_2$–C–OH), 136.44 (–*C*–$(CH)_2$–C–OMe), 145.13 (Ph), 154.84 (*C*–OH), 158.40 (*C*–OMe).

Solid phase Mitsunobu reaction

A solution of PPh_3 (590 mg, 2.25 mmol) in THF–DCM (1:1) (0.5 cm^3) was added dropwise to a stirred solution of DEAD (350 mm^3, 2.25 mmol) in THF–DCM (1:1) (0.5 cm^3) in an argon atmosphere at 0 °C. The bright red mixture was transferred to the $POEPOP_{1500}$ resin (1 g, loading: 0.45 mmol g^{-1}) which was swollen in THF–DCM (1:1) (16 cm^3) in an argon atmosphere at 0 °C and mixed well. DMT–HMP (**1**) (960 mg, 2.25 mmol) was dissolved in THF–DCM (1:1) (2 cm^3) and added to the resin mixture. The reaction was allowed to run overnight at ambient temperature. The solution was removed by filtration and the resin was washed sequentially with THF–DCM (1:1) (3×), DCM (5×), acetonitrile (5×) and DCM (3×) and dried *in vacuo*. The substitution level determined spectrophotometrically at 498 nm by cleavage of the DMT protecting group from a known amount of resin using a 2% w/w solution of trichloroacetic acid in DCM followed by calibration against a standard curve was 0.21 mmol g^{-1} (47%). The remaining free hydroxy groups on the resin were acetylated using acetic anhydride in pyridine solution (1:1) (10 cm^3) for 18 h. Deprotection of resin: the resin was washed with a 2% w/w solution of trichloroacetic acid in DCM until the solution remains colourless. The resin was washed sequentially with DCM (5×), tetrahydrofuran (3×), acetonitrile (5×), water (5×), 10% aqueous sodium hydrogen carbonate (3×), water (5×), acetone (5×) and DCM (3×).

Mitsunobu-like reactions using triphenylphosphine–cyclic sulfamide betaine 2

$POEPOP_{1500}$ (1 g, loading: 0.45 mmol g^{-1}) was swollen in a solution of DMT–HMP (**1**) (958 mg, 2.25 mmol) in DCM (30 cm^3) in an argon atmosphere. Triphenylphosphine–cyclic sulfamide betaine **2** (1.04 g, 2.25 mmol) was added portionwise over 15 min with careful mixing. After 48 h at ambient temperature the resin was drained and washed with DCM (5×), acetonitrile (5×) and DCM (3×). The level of incorporation of the linker was determined as described in the typical procedure for solid phase Mitsunobu reactions to be 0.23 mmol g^{-1} (51%). The residual hydroxy functionalities on the resin were acetylated and the linker was deprotected as described in the procedure for solid phase Mitsunobu reactions.

Attachment of 4-hydroxybenzaldehyde to POEPOP–HMP or NovaSyn TG–HMP was accomplished by the following general method described for the preparation of resin **4a**.

Preparation of resin 4a

4-Hydroxybenzaldehyde (175 mg, 1.43 mmol) and sodium hydroxide (52 mg, 1.3 mmol) were stirred in DMF (5 cm^3) at 90 °C until all was dissolved. Mesyl chloride (405 mm^3, 5.2 mmol) was added dropwise to a suspension of NovaSyn TG–HMP (1 g, loading: 0.26 mmol g^{-1}) in DCM : *N*,*N*-diisopropylethylamine (1:1) (10 cm^3) at 0 °C and was stirred at 0 °C for 1 h and at ambient temperature for 1 h. The resin was drained and washed with DCM (5×) and DMF (3×) and was added to the preformed DMF solution of sodium 4-carboxyphenolate. The reaction was stirred overnight at 90 °C. The resin was drained and washed with DMF (5×), DMF : water (1:1) (5×), water (5×), acetonitrile (5×) and DCM (5×) and dried *in vacuo*. The incorporation level was determined after cleavage of 50 mg of resin with 95% trifluoroacetic acid–H_2O (95:5) (2 cm^3) for 2 h at ambient temperature. The cleavage mixture was drained from the resin and the resin was rinsed with acetonitrile (5×2 cm^3). The cleavage mixture and the washings were combined and evaporated under reduced pressure and the residue was quantified by ^{1}H-NMR spectroscopy by integrating signals from 4-hydroxybenzaldehyde against a known amount of EtOAc as an added internal standard. The incorporation was 0.22 mmol g^{-1} resin (85%).

Aqueous solution phase aldol reactions

These were performed as described in ref. 27.

2-[Hydroxy(4-methoxyphenyl)methyl]cyclohexanone 7a. The yield determined through ^{1}H-NMR of the crude mixture by integrating signals from product and starting material, was 75%, *syn* : *anti* = 75:25. The NMR-spectrum of the product was in accordance with published data.[27]

3-Hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one 8a. The yield determined through ^{1}H-NMR of the crude mixture by integrating signals from product and starting material, was 20% using $Yb(OTf)_3$ as the catalyst and 25% using $Y(OTf)_3$ as the catalyst. The NMR-spectrum of the product was in accordance with published data.[48]

Non-aqueous solution phase aldol reactions

2-[Trimethylsilyloxy(4-methoxyphenyl)methyl]cyclohexanone 7c. 4-Hydroxybenzaldehyde (121 mm^3, 1 mmol) and 1-(trimethylsilyloxy)cyclohexene (211 mm^3, 1.1 mmol) were dissolved in THF (1 cm^3) and added to a stirred suspension of $Y(OTf)_3$ in DCM (1.5 cm^3) at 0 °C. After 1 h the reaction mixture was allowed to come to ambient temperature and stirred for another 1.5 h. At this point TLC showed no remaining silyl enol ether. DCM (2 cm^3) was added and the reaction mixture was washed with water (3×5 cm^3), dried and evaporated. The crude mixture was analysed by ^{1}H-NMR and the product was identified in agreement with literature data.[49] The yield, determined through ^{1}H-NMR of the crude mixture by integrating signals from product and starting material, was 30%, *syn* : *anti* = 50:50.

The following examples were synthesised following the above procedure.

3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one 8b. The yield of **8b**, determined through ^{1}H-NMR of the crude mixture by integrating signals from the product and starting material, was 40% using $Yb(OTf)_3$ as the catalyst. The product was identified by NMR and the spectrum was in accordance with literature.[50,51]

3-Trimethylsilyloxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one 8c and 3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one 8a. The yields, determined through ^{1}H-NMR of the crude mixture by integrating signals from products (no detectable starting material in crude product), were 65% **8a** and 35% **8c** using $Y(OTf)_3$ as the catalyst. The products were identified by NMR and the spectra were in accordance with literature.[48,49]

Typical procedure for solid phase aldol reactions

2-(4-Hydroxybenzylidene)cyclohexanone 10. Resin **4d** (50 mg, loading = 0.23 mmol g^{-1}) was swollen in a solution of $Yb(OTf)_3$ (1.4 mg, 0.0023 mmol) in acetonitrile–water (2:1) (375

mm^3) and allowed to stand for 1 h at ambient temperature. 1-(Trimethylsilyloxy)cyclohexene (22 mm^3, 0.115 mmol) was dissolved in acetonitrile (250 mm^3) and added to the resin suspension. The reaction was allowed to run overnight. The resin was drained and washed with acetonitrile–water (4:1) (5×), acetonitrile (5×) and DCM (5×). The product was cleaved from the resin with 95% trifluoroacetic acid in water (3 cm^3) for 2 h at ambient temperature. The cleavage solution was drained from the resin and the resin was washed with acetonitrile (5 × 3 cm^3). The cleavage solution and washings were combined and evaporated under reduced pressure. The residue was dissolved in $CDCl_3$ with a few drops of d^6-DMSO added and analysed by ^{1}H-NMR. The yield of **10** determined by integrating signals from product and starting material was 83%. The product was identified by NMR: δ_H (250 MHz; $CDCl_3$) 1.71 (2H, m), 1.83 (2H, m), 2.44 (2H, m), 2.77 (2H, m), 6.80 (2H, d, *J* 8.8, Ar), 7.25 (2H, d, *J* 8.8, Ar), 7.41 (1H, br s, vinyl-H); δ_C (62.5 MHz; $CDCl_3$) 23.7, 24.3, 29.5, 40.8, 116.2 (Ar), 127.4 (Ar), 133.1 (Ar), 137.1 (vinyl-C), 158.8 (Ar).

3-(4-Hydroxyphenyl)-1-phenylprop-2-en-1-one 9. The reaction between **4d** and **5** was performed following the above procedure. The yield, determined by integrating signals from the product and starting material, was 32%. The product was identified in accordance with published data.[50]

Preparation of peptide aldehyde 12

N-Fmoc-leucine (39 mg, 0.11 mmol), MSNT (33 mg, 0.11 mmol) and *N*-methylimidazole (8 mm^3, 0.11 mmol) were combined in DCM (3 cm^3) and the mixture was added to POEPOP–HMP resin (100 mg, loading = 0.22 mmol g^{-1}). The reaction was run at ambient temperature for 45 minutes and was then repeated. The resin was washed with DCM (5×), DMF (5×) and DCM (3×) and dried in a high vacuum. The loading, measured by cleavage of a known amount of resin in 20% piperidine in DMF solution and spectrophotometric analysis of the released fluoren-9-ylpiperidine adduct against a standard curve at 290 nm, was 0.22 mmol g^{-1}. The resin bound *N*-Fmoc-leucine was deprotected in 20% piperidine in DMF solution and washed with DMF (6×). *N*-Fmoc-phenylalanine-Pfp ester (61 mg, 0.11 mmol) was dissolved in DMF (2 cm^3) and added to the resin. The reaction was followed using the Kaiser test [52] and was washed with DMF (6×) when the reaction was complete. The resin was deprotected as described above and washed with DMF (6×). 4-Carboxybenzaldehyde (10 mg, 0.07 mmol) was dissolved in DMF (2 cm^3) and *N*-ethylmorpholine (14 mm^3, 0.11 mmol) was added, followed by TBTU (20 mg, 0.06 mmol). The mixture was left standing for 5 minutes before addition to the resin and the coupling reaction was followed using the Kaiser test. After coupling the resin was capped using acetic anhydride in pyridine (1:1) for two hours at ambient temperature and was washed with DCM (5×), acetone (5×), water (5×), 10% aqueous sodium hydrogen carbonate (3×), water (5×), acetonitrile (5×), DCM (5×) and dried in a high vacuum. A resin sample was cleaved as described for the preparation of **4a** and peptide aldehyde **12** was analysed by NMR: δ_H (500 MHz; $CDCl_3$) 0.79 (3H, d, *J* 6.6, Me (Leu)), 0.81 (3H, d, *J* 6.6, Me (Leu)), 1.48 (1H, m, β-H (Leu)), 1.57 (1H, m, γ-H (Leu)), 1.59 (1H, m, β-H (Leu)), 3.07 (1H, dd, *J* 7.2 and 14, β-H (Phe)), 3.18 (1H, dd, *J* 6.3 and 14, β-H (Phe)), 4.42 (1H, m, α-H (Leu)), 4.83 (1H, m, α-H (Phe)), 7.09 (1H, d, *J* 8.2, N–H (Leu)), 7.09 (1H, t, *J* 7.3, Ph (Phe)), 7.15 (2H, dd, *J* 7.3 and 8.3, Ph (Phe)), 7.19 (2H, d, *J* 8.3, Ph (Phe)), 7.60 (1H, d, *J* 7.7, N–H (Phe)), 7.78 (2H, d, *J* 9.2, 2-H and 6-H), 7.81 (2H, d, *J* 9.2, 3-H and 5-H), 9.9 (1H, s, CHO); δ_C (125 MHz; $CDCl_3$) 22.43 (Me (Leu)), 23.43 (Me (Leu)), 25.28 (C-γ (Leu)), 38.34 (C-β (Phe)), 41.77 (C-β (Leu)), 51.48 (C-α (Leu)), 55.27 (C-α (Phe)), 127.24 (Ph (Phe)), 128.45 (C-2 and C-6), 128.86 (Ph (Phe)), 129.98 (Ph (Phe)), 130.13 (C-3 and C-5), 137.45 (Ph (Phe)), 138.68 (C-4), 139.95 (C-1), 166.59 (C-7), 171.25 (CO (Phe)), 174.72 (COOH (Leu)), 192.16 (CHO); *m/z* (ESI) 411.3 [(M + H)$^+$, 821.5 [(2M + H)$^+$), 19], 843 [(2M + Na$^+$), 8].

Solid phase aldol reactions of peptide aldehyde **12** were performed following the typical procedure described above using 0.2 equivalents of $Yb(OTf)_3$ as the catalyst.

13a + 13b. The yield of the combined products, determined through ^{1}H-NMR of the crude mixture by integrating signals from products and starting material, was >95%. The product was obtained as a mixture of **13a** and the (*E*) and (*Z*) isomers of **13b** in a ratio of 2:1:1. Only a single diastereomer of **13a** was identified.

13a. δ_H (500 MHz; $CDCl_3$) 0.61 (3H, d, *J* 6.1, Me (Leu)), 0.63 (3H, d, *J* 6.4, Me (Leu)), 1.32 (2H, m, β-H (Leu)), 1.39 (1H, m, γ-H (Leu)), 2.85 (1H, dd, *J* 8.3 and 14.3, β-H (Phe)), 2.95 (1H, dd, *J* 8.4 and 16.5, 9-H), 3.0 (1H, dd, *J* 5.1 and 14.3, β-H (Phe)), 3.19 (1H, dd, *J* 4.1 and 16.5, 9-H), 4.20 (1H, m, α-H (Leu)), 4.63 (1H, ddd, *J* 5.1, 8.0 and 8.3, α-H (Phe)), 5.07 (1H, dd, *J* 4.1 and 8.4, 8-H), 6.9 (1H, t, *J* 7.3, Ph (Phe)), 6.96 (2H, dd, *J* 7.3 and 7.9, Ph (Phe)), 7.0 (2H, d, *J* 7.9, Ph (Phe)), 7.19 (2H, dd, *J* 7.5 and 7.9, 3′-H and 5′-H), 7.21 (2H, d, *J* 8.3, 2-H and 6-H), 7.30 (1H, t, *J* 7.5, 4′-H), 7.33 (1H, d, *J* 8.6, N–H (Leu)), 7.44 (2H, d, *J* 8.3, 3-H and 5-H), 7.46 (1H, d, *J* 8.0, N–H (Phe)), 7.67 (2H, d, *J* 7.9, 2′-H and 6′-H); δ_C (125 MHz, $CDCl_3$) 21.94 (Me (Leu)), 23.06 (Me (Leu)), 24.83 (C-γ (Leu)), 37.78 (C-β (Phe)), 41.18 (C-β (Leu)), 47.91 (C-9), 50.92 (C-α (Leu)), 54.66 (C-α (Phe)), 69.46 (C-8), 125.95 (C-2 and C-6), 126.61 (Ph (Phe)), 127.48 (C-3 and C-5), 128.24 (C-2′ and C-6′), 128.34 (Ph (Phe)), 128.72 (C-3′ and C-5′), 129.56 (Ph (Phe)), 133.41 (C-1), 133.44 (C-4′), 137.02 (C-1′), 137.47 (Ph (Phe)), 148.25 (C-4), 167.09 (C-7), 171.24 (CO (Phe)), 174.38 (COOH), 198.67 (C-10); *m/z* (ESI) 531.2 [(M + H)$^+$, 74%], 553.2 [(M + Na)$^+$, 100].

13b. (*E*)-isomer: δ_H (500 MHz; $CDCl_3$) 0.61 (3H, d, *J* 6.1, Me (Leu)), 0.63 (3H, d, *J* 6.4, Me (Leu)), 1.32 (2H, m, β-H (Leu)), 1.39 (1H, m, γ-H (Leu)), 2.81 (1H, dd, *J* 8.3 and 14, β-H (Phe)), 2.97 (1H, dd, *J* 5.4 and 14, β-H (Phe)), 4.20 (1H, m, α-H (Leu)), 4.58 (1H, ddd, *J* 5.4, 8.1 and 8.3, α-H (Phe)), 6.9 (1H, t, *J* 7.3, Ph (Phe)), 6.96 (2H, dd, *J* 7.3 and 7.9, Ph (Phe)), 7.0 (2H, d, *J* 7.9, Ph (Phe)), 7.23 (2H, d, *J* 8.3, 2-H and 6-H), 7.25 (2H, 3′-H and 5′-H), 7.30 (1H, d, *J* 8.3, N–H (Leu)), 7.34 (1H, 4′-H), 7.35 (1H, d, *J* 15.87, 9-H), 7.49 (1H, d, *J* 15.87, 8-H), 7.51 (2H, d, *J* 8.3, 3-H and 5-H), 7.53 (1H, d, *J* 8.1, N–H (Phe)), 7.76 (2H, 2′-H and 6′-H); δ_C (125 MHz, $CDCl_3$) 21.94 (Me (Leu)), 23.06 (Me (Leu)), 24.83 (C-γ (Leu)), 37.72 (C-β (Phe)), 41.18 (C-β (Leu)), 50.92 (C-α (Leu)), 54.72 (C-α (Phe)), 123.63 (C-9), 126.61 (Ph (Phe)), 126.78 (C-2 and C-6), 127.42 (C-8), 128.14 (C-3 and C-5), 128.34 (Ph (Phe)), 128.58 (C-2′ and C-6′), 128.84 (C-3′ and C-5′), 129.56 (Ph (Phe)), 133.18 (C-4′), 135.30 (C-1), 137.47 (Ph (Phe)), 137.93 (C-1′), 140.72 (C-4), 166.79 (C-7), 171.18 (CO (Phe)), 174.38 (COOH), 190.13 (C-10).

(*Z*)-isomer: δ_H (500 MHz; $CDCl_3$) 0.61 (3H, d, *J* 6.1, Me (Leu)), 0.63 (3H, d, *J* 6.4, Me (Leu)), 1.32 (2H, m, β-H (Leu)), 1.39 (1H, m, γ-H (Leu)), 2.81 (1H, dd, *J* 8.3 and 14, β-H (Phe)), 2.97 (1H, dd, *J* 5.4 and 14, β-H (Phe)), 4.20 (1H, m, α-H (Leu)), 4.58 (1H, ddd, *J* 5.4, 8.1 and 8.3, α-H (Phe)), 6.46 (1H, d, *J* 12.9, 9-H), 6.74 (1H, d, *J* 12.9, 8-H), 6.9 (1H, t, *J* 7.3, Ph (Phe)), 6.96 (2H, dd, *J* 7.3 and 7.9, Ph (Phe)), 7.0 (2H, d, *J* 7.9, Ph (Phe)), 7.21 (2H, 3′-H and 5′-H), 7.23 (2H, d, *J* 8.3, 2-H and 6-H), 7.30 (1H, d, *J* 8.3, N–H (Leu)), 7.34 (1H, 4′-H), 7.51 (2H, d, *J* 8.3, 3-H and 5-H), 7.53 (1H, d, *J* 8.1, N–H (Phe)), 7.67 (2H, 2′-H and 6′-H); δ_C (125 MHz, $CDCl_3$) 21.94 (Me (Leu)), 23.06 (Me (Leu)), 24.83 (C-γ (Leu)), 37.72 (C-β (Phe)), 41.18 (C-β (Leu)), 50.92 (C-α (Leu)), 54.72 (C-α (Phe)), 126.61 (Ph (Phe)), 126.78 (C-2 and C-6), 128.14 (C-3 and C-5), 128.94 (C-2′ and C-6′), 128.34 (Ph (Phe)), 128.37 (C-9), 128.90 (C-3′ and C-5′), 129.56 (Ph (Phe)), 133.99 (C-4′), 135.30 (C-1), 136.03 (C-1′), 137.47

(Ph (Phe)), 138.14 (C-8), 140.72 (C-4), 166.79 (C-7), 171.18 (CO (Phe)), 174.38 (COOH), 194.21 (C-10).

m/z (ESI) 513.2 [$(M + H)^+$, 37%], 535.2]$(M + Na)^+$, 69].

14. The yield of **14**, determined through ^{1}H-NMR of the crude mixture by integrating signals from product and starting material, was >95%. The product was obtained as the (*E*) isomer, which rearranged to an *E*:*Z* 50:50 mixture of over one week.

(*E*)-isomer: δ_H (500 MHz; $CDCl_3$) 0.72 (3H, s, Me (Leu)), 0.74 (3H, s, Me (Leu)), 1.40 (1H, m, β-H (Leu)), 1.49 (2H, m, β-H (Leu) and γ-H (Leu), 1.61 (2H, m, 4′-H), 1.79 (2H, m, 5′-H), 2.36 (2H, m, 6′-H), 2.65 (2H, m, 3′-H), 2.99 (1H, m, β-H (Phe)), 3.10 (1H, m, β-H (Phe)), 4.33 (1H, m, α-H (Leu)), 4.74 (1H, m, α-H (Phe)), 7.02–7.11 (5H, m, Ph (Phe)), 7.10 (1H, d, N–H (Leu)), 7.23 (2H, d, 3-H and 5-H), 7.26 (1H, s, 8-H), 7.39 (1H, d, N–H (Phe)), 7.58 (2H, d, 2-H and 6-H); δ_C (125 MHz; $CDCl_3$) 22.27 (Me (Leu)), 23.27 (Me (Leu)), 23.70 (C-5′), 24.20 (C-4′), 25.22 (C-γ (Leu)), 29.41 (C-3′), 38.22 (C-β (Phe)), 40.73 (C-6′), 41.69 (C-β (Leu)), 51.36 (C-α (Leu)), 54.95 (C-α (Phe)), 127.04 (Ph (Phe)), 127.67 (C-2 and C-6), 128.76 (Ph (Phe)), 129.85 (Ph (Phe)), 130.50 (C-2 and C-6), 134.34 (C-1), 134.48 (C-8), 137.43 (Ph (Phe)), 138.56 (C-2′), 139.03 (C-4), 167.04 (C-7), 171.31 (CO (Phe)), 174.69 (COOH (Leu)), 201.78 (C-1′).

(*Z*)-isomer: δ_H (500 MHz; $CDCl_3$) 0.72 (3H, s, Me (Leu)), 0.74 (3H, s, Me (Leu)), 1.40 (1H, m, β-H (Leu)), 1.49 (2H, m, β-H (Leu) and γ-H (Leu)), 1.75 (2H, m, 4′-H), 1.82 (2H, m, 5′-H), 2.38 (2H, m, 6′-H), 2.47 (2H, m, 3′-H), 2.99 (1H, m, β-H (Phe)), 3.10 (1H, m, β-H (Phe)), 4.33 (1H, m, α-H (Leu)), 4.74 (1H, m, α-H (Phe)), 6.22 (1H, s, 8-H), 7.02–7.11 (5H, m, Ph (Phe)), 7.10 (1H, d, N–H (Leu)), 7.15 (2H, d, 3-H and 5-H), 7.33 (1H, d, N–H (Phe)), 7.46 (2H, d, 2-H and 6-H); δ_C (125 MHz; $CDCl_3$) 22.27 (Me (Leu)), 23.27 (Me (Leu)), 25.22 (C-γ (Leu)), 26.87 (C-4′), 26.96 (C-5′), 38.22 (C-β (Phe)), 38.85 (C-3′), 41.69 (C-β (Leu)), 44.78 (C-6′), 51.36 (C-α (Leu)), 54.95 (C-α (Phe)), 127.04 (Ph (Phe)), 127.46 (C-2 and C-6), 128.76 (Ph (Phe)), 129.05 (C-3 and C-5), 129.85 (Ph (Phe)), 129.87 (C-8), 133.52 (C-1), 137.43 (Ph (Phe)), 139.32 (C-4), 142.84 (C-2′), 167.36 (C-7), 171.31 (CO (Phe)), 174.69 (COOH (Leu)), 209.16 (C-1′).

m/z (ESI) 491.6 [$(M + H)^+$, 81%], 981 [$(2M + H)^+$, 16], 1003.1 [$(2M + Na)^+$, 5].

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