A New Class of Non-Racemic Chiral Macrocycles: A Conformational and Synthetic Study

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Abstract: Amino alcohols have been used to introduce non-racemic chirality into macrocycles using a modular approach that relies on a Heck macrocyclisation reaction. A wide variety of macrocycles have been synthesised, and their structures studied using X-ray crystallography and molecular modelling. A fragmentation reaction encountered during the use of (*S*)-1,1-dimethylvalinol revealed that carboxylic acids generate acylals under reaction conditions often used for Heck reactions.

Keywords: acylals · chirality · Heck reaction · macrocycles · molecular modeling

Introduction

The architecture of macrocyclic compounds naturally provides them with cavities suitable for a range of functions such as the formation of inclusion complexes, leading to applications in host–guest chemistry,[1] asymmetric catalysis,[2] mimicry of natural enzymes,[3] and chiral molecular recognition.[4] The pharmaceutical activity of certain classes of macrocycles has also given them a role in drug development.[5] Their stereochemistry is fascinating, and control of the interplay between planar and tetrahedral chirality within macrocyclic species is still in its infancy.[6]

Our interest in using the intramolecular Heck reaction to synthesise medium-sized rings[7] recently led us to the serendipitous discovery of a head-to-tail coupling reaction that gave a range of macrocycles containing dehydrophenylalanine units.[8] Analysis of our approach revealed that the macrocycles were generated from two units, variation of which might be expected to affect the architecture of the resulting macrocycle, that is, a disubstituted benzene and an ω-hydroxyalkene, and a further unit whose contribution to macrocylic architecture might be expected to be relatively constant, that is, an ester of serine (Figure 1a). In order to exemplify the flexibility in the synthesis and to explore the effect of varying the disubstituted benzene and the ω-hydroxyalkene, macrocycles were generated using 1,4-diiodo-

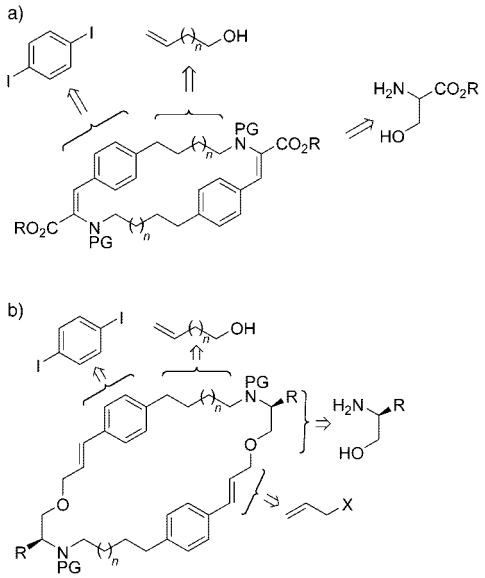

Figure 1. Analysis of macrocycle synthesis based on a) an ester of serine, and b) amino alcohols derived from amino acids.

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benzene and 1,3-diiodobenzene, and a range of ω-hydroxyalkenes. Examination of the macrocycles produced by X-ray crystallography and molecular modelling revealed two distinct classes of structure, one of which resembled a "barrel" and the other of which was elongated and "staggered" with respect to the arene rings.[8b]

In view of the interest and potential of non-racemic chiral macrocycles in for example catalysis and molecular recognition, we decided to modify the approach summarised in Figure 1a to allow us to introduce non-racemic chiral centres. Not only did we wish to retain the flexibility associated with the aromatic ring and the distance between the aromatic ring and the amino acid derived functionalities, but we also wished to develop an approach that was versatile with respect to the chiral centres that were to be introduced. An analysis of our new approach is presented in Figure 1b, and its realisation is presented herein. Some of the macrocycles described below were included in a preliminary communication of this topic,[9] but the unexpected generation of an acylal during the course of a routine Heck reaction, and the single crystal X-ray and molecular modelling analyses are presented for the first time in this full account of our work.

Results and Discussion

We initially decided to test the viability of the proposed macrocyclic synthesis outlined in Figure 1b by using 1,4-diiodobenzene, 4-hydroxy-1-butene, valinol, and three different alkenes as potential Heck partners. 1,4-Diiodobenzene and 4-hydroxy-1-butene react under palladium catalysis to give 4-(4-iodophenyl)butanal (**4**);[8b] alternatively aldehyde **4** may be prepared in three straightforward steps from 4-phenylbutanoic acid (Scheme 1).[8b] In principle, a large number of analogues of **4** containing different carbon chain lengths and *para*, *meta* or *ortho* disubstituted arenes are accessible via the palladium catalysed zipper reaction between an appropriate di-iodoarene and an ω-hydroxyalkene.[8b,10] Aldehyde **4** was subjected to reductive amination with (*S*)-valinol to give the secondary amine **4v**, which was protected as its benzyl derivative **4v(Bn)**. Alcohol **4v(Bn)** was then primed with three alkenes that could potentially act as Heck partners in the proposed macrocyclisation step. It was thus treated with appropriate electrophiles to give its 2-**c**arboxyprop-2-enyl, **a**llyl and **p**rop-2-enoyl derivatives, **4v(Bn)c**, **4v(Bn)a** and **4v(Bn)p**. Subjecting these three compounds to Heck reaction conditions gave different outcomes: the carboxyprop-2-enyl primed system **4v(Bn)c** cyclised to give a product that arises from two head-to-tail Heck coupling reactions, **m^2-4v(Bn)c**, the allyl primed system proved to be insufficiently activated for a reaction to occur, and the prop-2-enoyl primed system reacted to give two products, one arising from two head-to-tail Heck coupling reactions, **m^2-4v(Bn)p**, and the other arising from three head-to-tail Heck coupling reactions, **m^3-4v(Bn)p**. In each successful cyclisation, isolated macrocyclisation products accounted for 40% of the substrate.

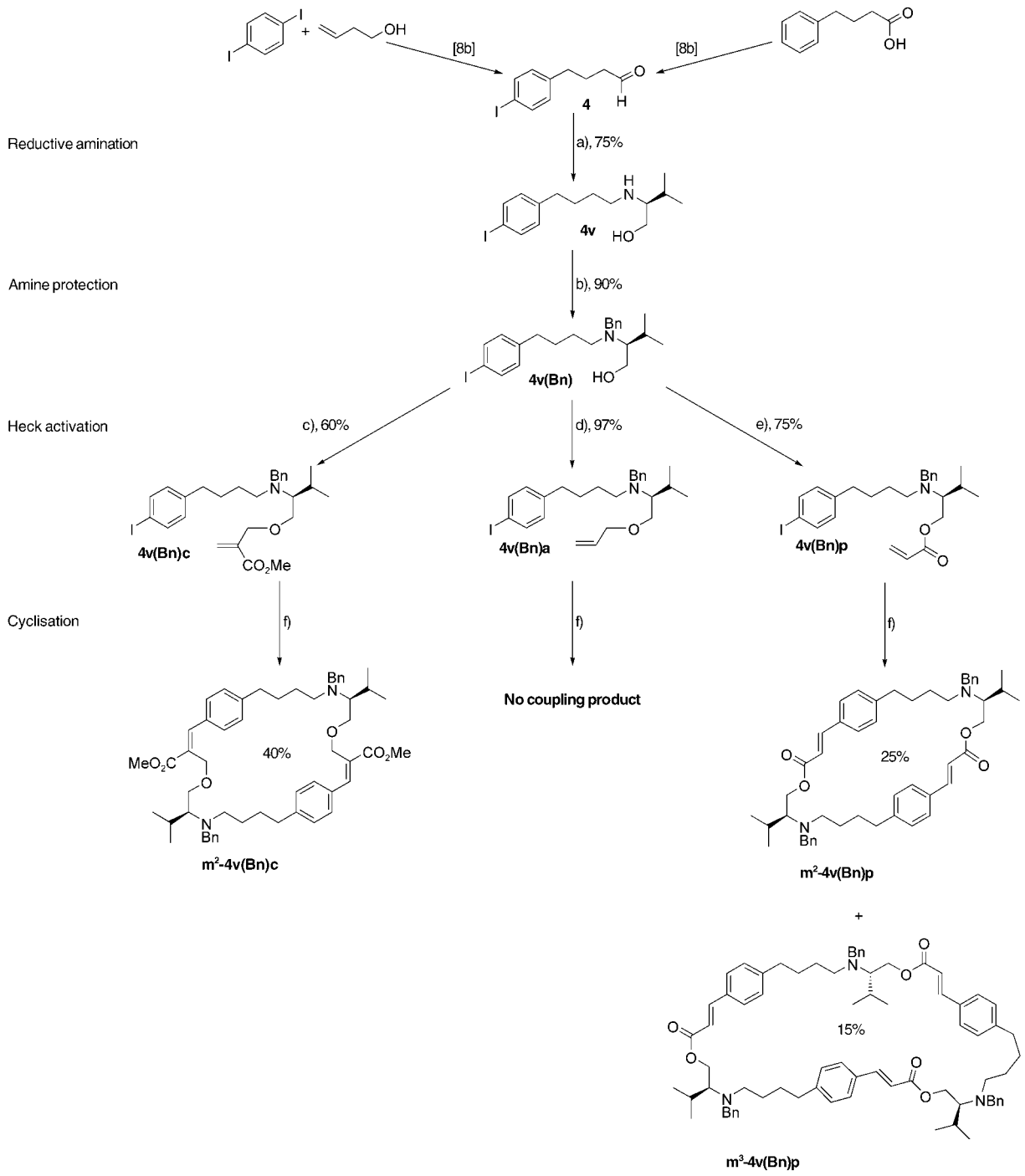
Attempts to increase this yield using different catalysts and reaction conditions did not deliver any significant improvement. The 60% of substrate that was unaccounted for was tentatively assumed to have been converted into intractable polymeric material.

The three macrocycles were characterised by elemental analysis, IR and NMR spectroscopy (^{1}H and ^{13}C), and mass spectrometry. In addition, **m^2-4v(Bn)p** was characterised by X-ray crystallography which showed the 30-membered macrocycle to adopt an elongated ellipse-like conformation (Figure 2) with a nitrogen···nitrogen separation of about 14.4 Å. The structure is disordered in the vicinity of ring B, there being two partial occupancy conformations for ring B and its adjacent -CH_2-CH_2- unit (see Supporting Information, especially Figures S1–S3); the major (ca. 58%) occupancy orientation is shown in Figure 2. The centroid···centroid separation between the two aromatic rings A and B is about 5.39 Å [4.91 Å for the minor occupancy conformation]. Although the molecule could have adopted C_2 symmetry about an axis perpendicular to the plane of the 30-membered macrocycle, it has not done so. The most obvious departure from this possible symmetry lies in the inclinations of the aromatic rings A and B with respect to the plane of the macrocycle (as defined by the mean plane of the centroids of rings A and B, and the other 22 atoms that form the macrocycle) with ring A being near parallel to the macrocycle (ca. 23°) whilst ring B is near orthogonal (ca. 77°). Though the A···B and A···B′ centroid···centroid separations of about 5.39 and 4.91 Å suggest a degree of *trans*-macrocycle π–π edge-to-face interaction, the mutual inclination of the two rings (ca. 54 and 52′ for A/B and A/B′, respectively) combined with the presence of the disorder itself, make this interaction unlikely to be a determining factor in the overall conformation.

Having established that our new approach to macrocycles was viable, we chose to examine the effect on the macrocyclisation step of varying a) the length of the carbon chain between the aromatic residue and the amino alcohol residue, and b) the amino alcohol.

The effect of varying the length of the carbon chain between the aromatic residue and the amino alcohol residue was probed by using 4-iodobenzaldehyde **1** (Scheme 2). This was synthesised from 4-iodobenzoic acid, **2**, by reduction to alcohol **3** and oxidation to the required aldehyde **1**.

Aldehyde **1** was reductively aminated with (*S*)-valinol to give secondary amine **1v**, which was protected as its benzyl derivative **1v(Bn)**. Alcohol **1v(Bn)** was then primed for the Heck reaction with 1-bromo-2-carbomethoxy-2-propene and 2-propenoyl chloride, and the substrates formed, **1v(Bn)c** and **1v(Bn)p**, were subsequently subjected to Heck reaction conditions. The products isolated from these reactions, **m^2-1v(Bn)c**, **m^2-1v(Bn)p** and **m^3-1v(Bn)p**, revealed that macrocyclisation had indeed occurred with the shorter one carbon tether between the aryl group and the amine, albeit in significantly lower isolated yield than observed for the systems with a four-carbon tether between the aryl group and the amine.



Scheme 1. a) (S)-valinol (1.5 equiv), $MgSO_4$, CH_2Cl_2, rt, 24 h; then $NaBH_4$ (2.0 equiv), MeOH, rt, 24 h; b) K_2CO_3 (1.5 equiv), [18]crown-6 (0.1 equiv), BnBr (1.5 equiv), acetone, rt, 20 h; c) NaH (1.1 equiv), THF, reflux, 5 h; then Bu_4NI (0.02 equiv), methyl 2-(bromomethyl)acrylate (1.2 equiv), 0 °C to rt, 3 h; d) NaH (1.1 equiv), THF, reflux, 5 h; then Bu_4NI (0.02 equiv), allylBr (1.5 equiv), rt, 14 h; e) Et_3N (1.1 equiv), hydroquinone (0.01 equiv), acryloyl-Cl (1.1 equiv), 0 °C, 2 h; f) $Pd(OAc)_2$ (0.1 equiv), Bu_4NCl (1.0 equiv), $NaHCO_3$ (2.5 equiv), DMF (0.05 M), 110 °C, 16 h.

It was noted that the 2-carboxy-2-propenyl system again gave just a two unit cyclisation product, whilst the prop-2-enoyl system again gave both two unit and three unit cyclisation products.

It is interesting to compare the generation of the two unit and three unit cyclisation products in this Heck cyclisation, with two recently reported and related transition metal catalysed macrocyclisations. Subjecting a range of dienes represented by structure **5** (Figure 3) to ring-closing metathesis conditions, led to quite different and as yet unexplained outcomes. When $n=1$, only the "dimer" was isolated, when $n=2$, the "dimer" and "trimer" were isolated, when $n=3$ only

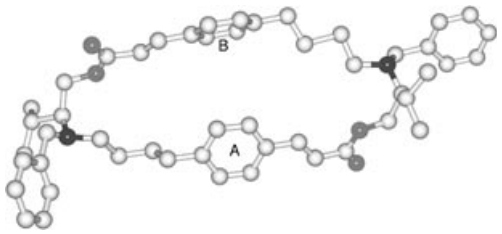


Figure 2. ORTEP view of the 30-membered macrocyle **m²-4v(Bn)p**.

the dimer was isolated and when $n=9$ the dimer and monomer were isolated.[11] In each case the total product yield fell in the range 74–81%.

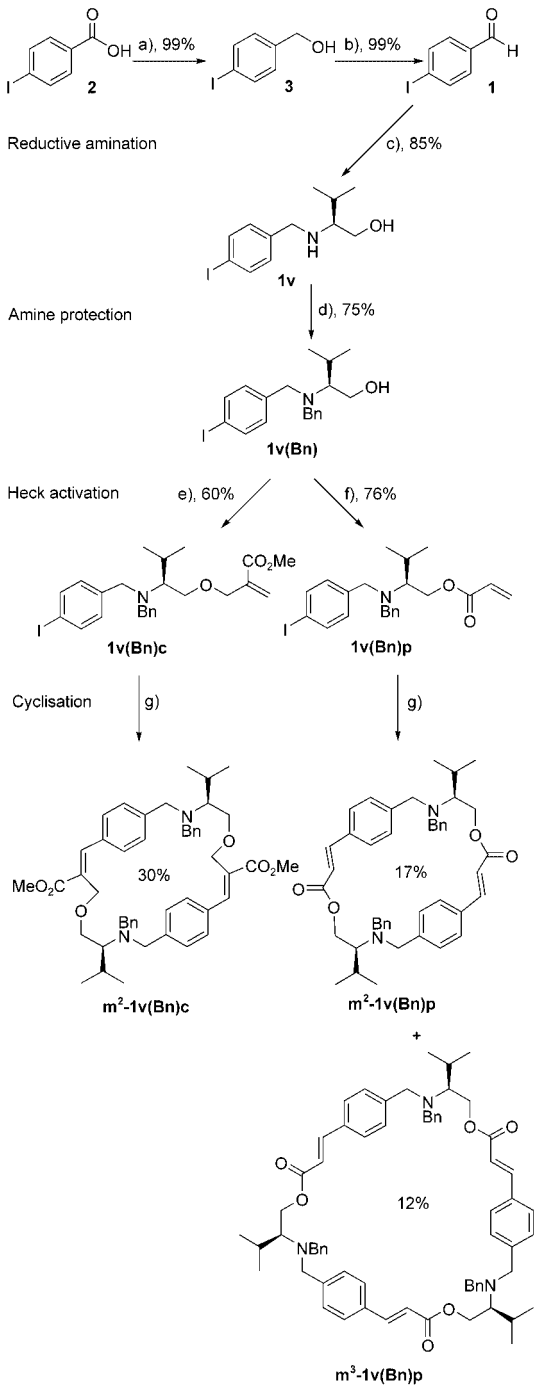
In a separate study, aimed initially at the synthesis of the paracyclophane natural product, pondaplin, but subsequently at the structural properties of the interesting macrocycles produced, aryl iodide **6** was subjected to Heck reaction conditions. The head-to-tail coupling product of two units, referred to as a pondaplin dimer, was isolated under a range of reaction conditions in yields of up to 38%, whilst under very concentrated reaction conditions, it proved possible to isolate the "dimer" and a pondaplin trimer, albeit in quite low yield (7% of each).[12]

Returning to our study, the effect on cyclisation of varying the amino alcohol component was examined next using two amino alcohols containing conformational constraints that it was anticipated might favour intramolecular reactions that is, cyclisations, over intermolecular reactions that is, polymerisation.

The first such amino alcohol to be examined was (*S*)-prolinol. Aldehyde **1** was thus reductively aminated with (*S*)-prolinol to give tertiary amine **1p** (Scheme 3). The primary alcohol of **1p** was then primed, as before, with 1-bromo-2-carbomethoxy-2-propene and 2-propenoyl chloride to give Heck substrates **1pc** and **1pp**.

Although **1pc** and **1pp** did undergo Heck macrocyclisation, the yields of the macrocycles isolated, **m²-1pc**, **m²-1pp** and **m³-1pp**, revealed that the conformational constraints introduced by the prolinol residue had no significant effect on the course of the Heck macrocyclisation.

Attention then turned to a second conformationally limited amino alcohol, (*S*)-1,1-dimethylvalinol (**7**), which was derived from the methyl ester of (*S*)-valine using a modification of a literature procedure.[13] Protection of the amine of the valine ester gave the Boc-derivative **8**, which was treated with four equivalents of methylmagnesium iodide to give the tertiary alcohol **9** (Scheme 4). Deprotection gave the required amino alcohol **7**. Reductive amination of aldehyde **1** with (*S*)-1,1-dimethylvalinol **7** proceeded smoothly to give the secondary amine $\mathbf{1v_{Me_2}}$, which was protected to give its benzyl derivative $\mathbf{1v_{Me_2}(Bn)}$. Reaction of the tertiary alcohol of $\mathbf{1v_{Me_2}(Bn)}$ with 2-propenoyl chloride gave the potential Heck macrocyclisation substrate $\mathbf{1v_{Me_2}(Bn)p}$. Subjecting $\mathbf{1v_{Me_2}(Bn)p}$ to Heck conditions identical to those used in all the previous macrocyclisations (0.1 equiv $Pd(OAc)_2$, 1 equiv Bu_4NCl, 2.5 equiv $NaHCO_3$, 0.05 M DMF, 110 °C, 16 h), however, gave none of the expected macrocycles.



Scheme 2. a) BH_3·THF (2 equiv), THF, rt, 16 h; b) MnO_2 (26 equiv), $CHCl_3$, reflux, 72 h; c) (S)-valinol (1.5 equiv), $MgSO_4$, CH_2Cl_2, rt, 24 h; then $NaBH_4$ (2.0 equiv), MeOH, rt, 24 h; d) K_2CO_3 (1.5 equiv), [18]crown-6 (0.1 equiv), BnBr (1.5 equiv), acetone, rt, 20 h; e) NaH (1.1 equiv), THF, reflux, 5 h; then Bu_4NI (0.02 equiv), methyl 2-(bromomethyl)acrylate (1.2 equiv), 0 °C, 3 h; f) Et_3N (1.1 equiv), hydroquinone (0.01 equiv), acryloylCl (1.1 equiv), 0 °C, 2 h; g) $Pd(OAc)_2$ (0.1 equiv), Bu_4NCl (1.0 equiv), $NaHCO_3$ (2.5 equiv), DMF (0.05 M), 110 °C, 16 h.

Instead a product that was tentatively identified as the acylal **10**, on the basis of its analytical data, was isolated in 46% yield.

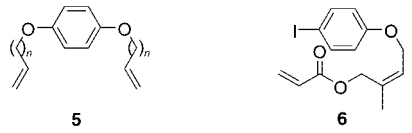
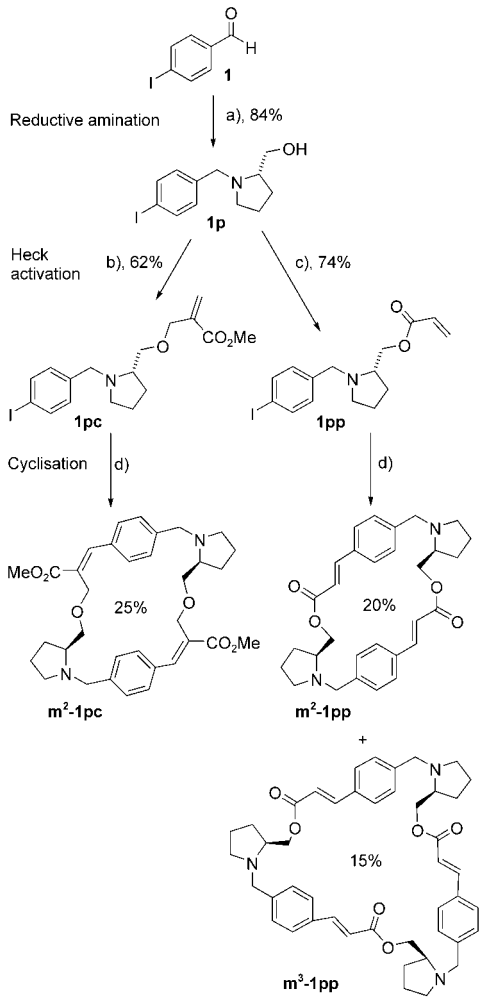
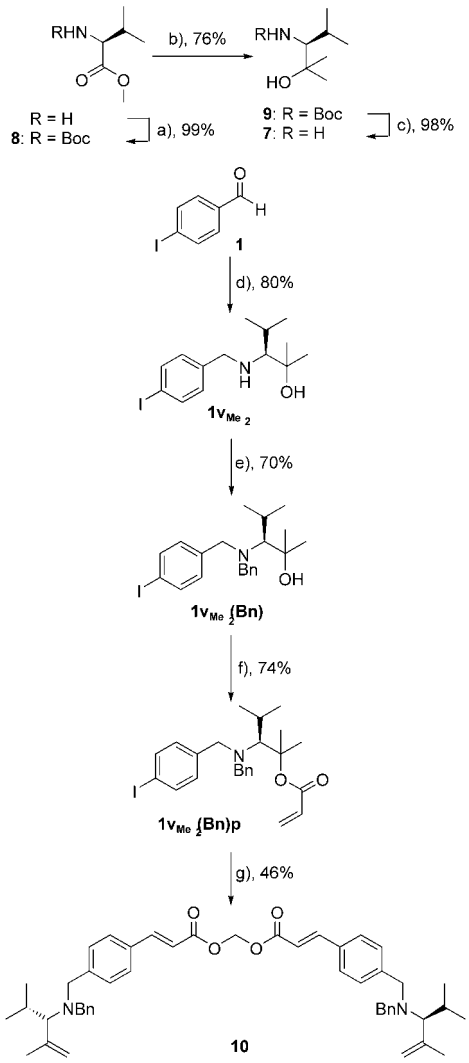


Figure 3. Related macrocylisation: diene **5** has been subjected to ring closing metathesis conditions,[11] aryl iodide **6** has been subjected to Heck reaction conditions.[12]



Scheme 3. a) (*S*)-Prolinol (1.5 equiv), $MgSO_4$, CH_2Cl_2, rt, 24 h; then $NaBH_4$ (2.0 equiv), MeOH, rt, 24 h; b) NaH (1.1 equiv), THF, reflux, 5 h; then Bu_4NI (0.02 equiv), methyl 2-(bromomethyl)acrylate (1.2 equiv), 0 °C to rt, 3 h; c) Et_3N (1.1 equiv), hydroquinone (0.01 equiv), acryloyl-Cl (1.1 equiv), 0 °C, 2 h; d) $Pd(OAc)_2$ (0.1 equiv), Bu_4NCl (1.0 equiv), $NaHCO_3$ (2.5 equiv), DMF (0.05 M), 110 °C, 16 h.

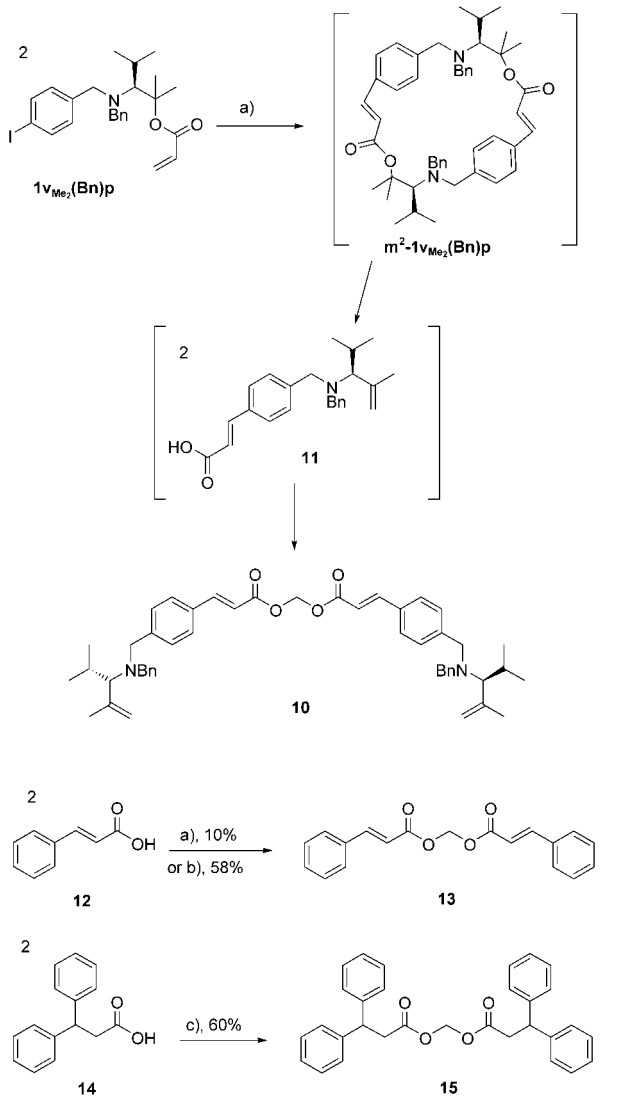


Scheme 4. a) Boc_2O (1.5 equiv), THF/MeOH (4:1), rt, 16 h; b) MeMgI (4 equiv), THF, rt, 16 h; c) HCl (3 N)/EtOAc, rt, 16 h; then $NaHCO_3$, rt; d) **7** (1.5 equiv), $MgSO_4$, CH_2Cl_2, rt, 24 h; then $NaBH_4$ (2.0 equiv), MeOH, rt, 24 h; e) NaH (1.2 equiv), DMF, rt, 6 h; then BnBr (1.5 equiv), rt, 16 h; f) Et_3N (1.1 equiv), hydroquinone (0.01 equiv), acryloyl-Cl (1.1 equiv), 0 °C, 2 h; g) $Pd(OAc)_2$ (0.1 equiv), Bu_4NCl (1.0 equiv), $NaHCO_3$ (2.5 equiv), DMF (0.05 M), 110 °C, 16 h.

Examination of the structure of compound **10** led to the postulation that its formation was a result of the instability of the expected products under the reaction conditions. Thus, it was proposed that the expected products of the reaction, for example, **m²-1v$_{Me_2}$(Bn)p**, underwent elimination to give compound **11** containing a 1,1-disubstituted alkene and a carboxylic acid derived from the elimination process (Scheme 5). It was proposed that carboxylic acid **11** was subsequently converted into the observed acylal **10** under the reaction conditions.

In order to test the feasibility of the proposed carboxylic acid to acylal conversion under the reaction conditions, model compound cinnamic acid **12** was subjected to identical reaction conditions to those used for the formation of **10** (Scheme 5). Under these conditions it proved possible to isolate a small amount (10%) of the cinnamic acylal **13**, thus providing support for the proposed pathway for the conversion of **1v$_{Me_2}$(Bn)p** to acylal **10**.

Acylals, also known as geminal dicarboxylates and diesters of 1,1-diols have been synthesised by several approaches. The most common involves reacting aldehydes with carboxylic anhydrides in the presence of a catalyst.[14]



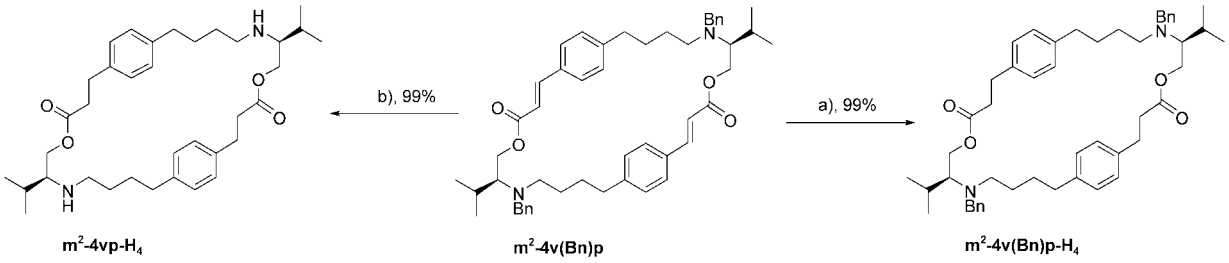
Scheme 5. a) $Pd(OAc)_2$ (0.1 equiv), Bu_4NCl (1.0 equiv), $NaHCO_3$ (2.5 equiv), DMF (0.05 M), 110 °C, 16 h; b) Bu_4NCl (1.5 equiv), $NaHCO_3$ (1.5 equiv), DMF (0.05 M), 110 °C, 40 h; c) Bu_4NCl (1.2 equiv), $NaHCO_3$ (1.2 equiv), DMF (0.05 M), 110 °C, 72 h.

Symmetric acylals are also readily formed by reacting 1,1-dihaloalkanes with carboxylates. For example, tetrabutylammonium carboxylates react with dichloromethane to give the corresponding methanal acylals in excellent yield.[15]

The reaction conditions used to form **10** and convert **12** into **13** are significantly different to any of the methods currently used for synthesising acylals.[14] We thus thought it would be of interest to study the conversion of carboxylic acid **12** into acylal **13** with a view to gaining more insight into the process. After some experimentation, it became clear that the palladium acetate was unnecessary for the success of the reaction. Optimisation of the reaction conditions (1.5 equiv Bu_4NCl, 1.5 equiv $NaHCO_3$, 0.05 M DMF, 40 h, 110 °C) gave a significantly increased yield of acylal **13** (58 %) (Scheme 5). Under similar conditions, 3,3-diphenylpropanoic acid **14** was converted into its methanal acylal **15** in 60 % yield, indicating that α,β-unsaturation in the acid component is unnecessary for the success of this reaction. With respect to the mechanism of this reaction it is proposed that the carboxylic acid reacts *via* its tetrabutylammonium salt. This is consistent with the known participation of such salts in the formation of acylals from dichloromethane (see above). The source of methanal or a methanal surrogate is assumed to be DMF[16] which degrades *via* hydrolysis and reduction processes under the harsh reaction conditions.

Returning to the macrocycles, with a view to their future applications, we wished to develop conditions to reduce the alkenes and perhaps produce some more flexible ligands, and to remove the nitrogen protecting groups so that we could access ligands containing two secondary amine binding sites. After some experimentation, it proved possible to identify hydrogenation conditions that led to the clean reduction of the two alkenes to give **m^2-4v(Bn)p-H$_4$** (Scheme 6), and conditions that led to both alkene reduction and amine deprotection to give **m^2-4vp-H$_4$**.

Finally a modelling study was undertaken in order to probe the architectures of the macrocycles produced. The structures of eight molecules were examined. All structures were minimised and then subjected to molecular dynamics and a conformation hunt that collected all the resulting conformations occurring within a 15 kcal range. The conformations that lay within 3 kcal of the global minimum that is, 99 % of the conformations that occur at physiological temperature, were then examined. The lowest energy conformations are depicted in Figure 4. Modelling of the valinol derivative **m^2-4v(Bn)p** gave three conformations within 3 kcal of the global minimum, all of which had a broadly similar structure to that observed when the solid state was probed by X-ray crystallography (see Figure 2 for comparison).



Scheme 6. a) H_2 (50 psi), Pd/C (10 % *w*/*w*), EtOAc, 24 h, rt; b) H_2 (100 psi), Pd/C (10 % *w*/*w*), EtOAc, 48 h, rt.

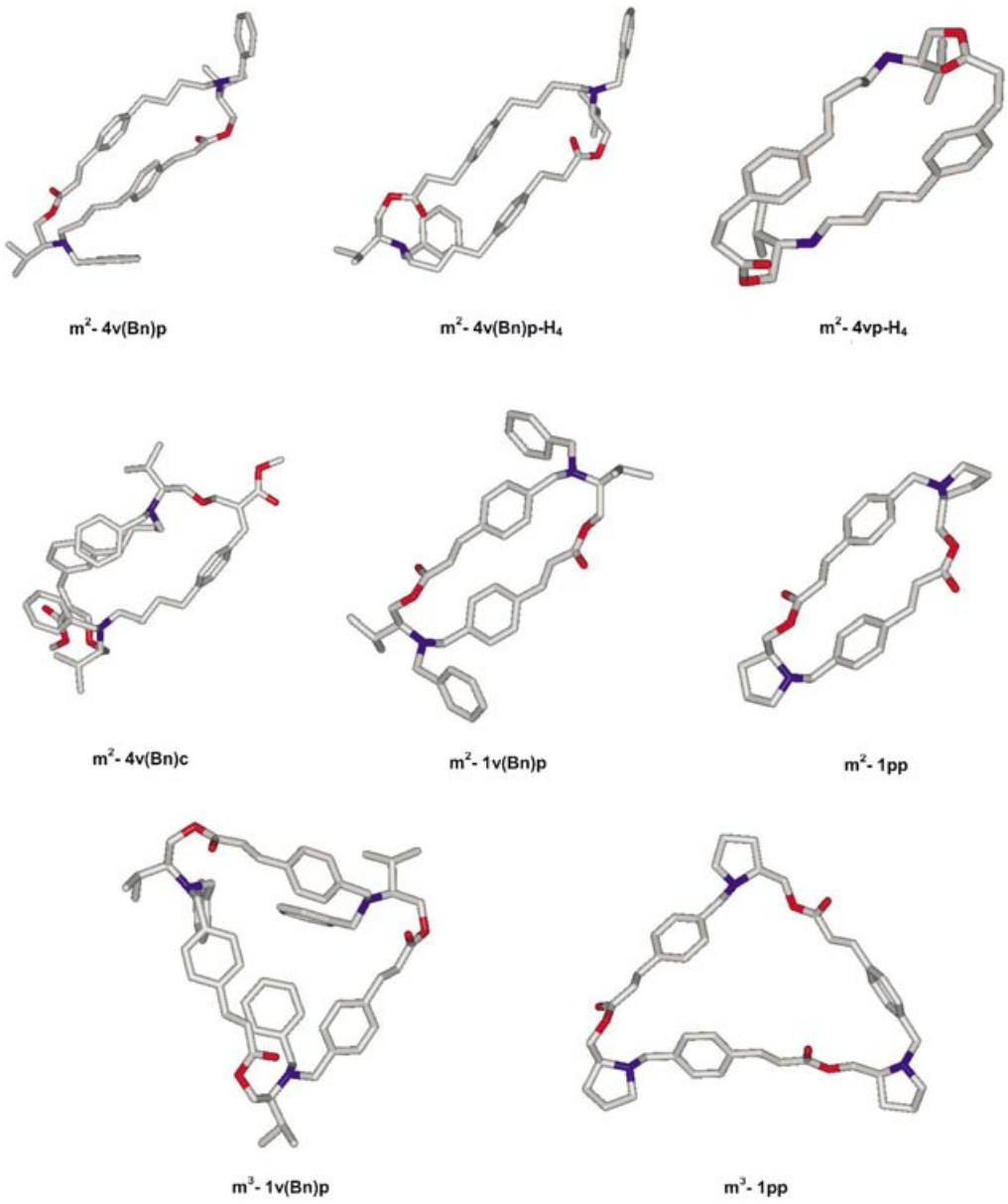


Figure 4.

Modelling of the alkene hydrogenation product, **m²-4v(Bn)p-H$_4$**, and the alkene hydrogenation/debenzylated product, **m²-4vp-H$_4$**, produced four and five conformations, respectively, within 3 kcal of the global minimum, a result consistent with the increased flexibility expected in these systems. Modelling **m²-4v(Bn)c** and comparing it with **m²-4v(Bn)p** suggests that the change in Heck acceptor leads to a more extended turn element and hence a less elongated cavity. Examination of **m²-1v(Bn)p** alongside **m²-4v(Bn)p** revealed quite similar turn elements. The differing carbon chain lengths, however, altered the relationship between the aromatic rings significantly. Comparison of **m²-1v(Bn)p** with the "trimer" **m³-1v(Bn)p**, which is a bucket-like structure containing six aromatic units, revealed that the turn motifs in these systems were slightly different. In contrast the prolinol unit in **m²-1pp** and **m³-1pp** gave a well-defined and consistent turn motif. In fact modelling of the prolinol system, **m²-1pp**, produced only one conformation within 3 kcal of the global minimum, suggesting that this macrocycle has a relatively well defined structure.

Conclusion

We have developed a short and versatile route to non-racemic chiral macrocycles based on amino alcohols derived from amino acids. A range of macrocycles have been readily synthesised in good quantities, and their structures have been examined by X-ray crystallography and molecular modelling. Fragmentation of macrocycles based on (*S*)-1,1-

dimethylvalinol generated an acylal product, which revealed that carboxylic acids are unstable to Heck reaction conditions involving DMF, Bu_4NCl and $NaHCO_3$ and prolonged heating. We are now in a position to start to investigate the catalytic and host-guest properties of the macrocycles.

Experimental Section

All reactions were carried out under an inert atmosphere of dry nitrogen using standard vacuum line and Schlenk tube techniques[17] unless otherwise noted. THF was distilled from sodium/benzophenone. $CHCl_3$ and CH_2Cl_2 were distilled from calcium hydride (CaH_2). Methanol (MeOH) was distilled from calcium hydride and stored over 3 Å molecular sieves. Acetone was distilled and stored over activated potassium carbonate (K_2CO_3). Triethylamine (Et_3N) was distilled and stored over potassium hydroxide (KOH). The hydrogen used in the hydrogenation experiments was BOC grade 0. All remaining chemicals were used as received from commercial sources. Thin layer chromatography was performed on Merck silica gel glass plates (60 F_{254}) using UV light (254 nm) as visualizing agent and/or vanillin or potassium permanganate and heat as developing agents. Flash column chromatography was performed using Merck silica gel (60, particle size 0.040–0.063 mm). Melting points were recorded in open capillaries on a Büchi 510 melting point apparatus, and are uncorrected. Optical rotations were performed on a Perkin–Elmer 241 Polarimeter using a 1 dm path length and concentrations are given as g mL^{-1}. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer. NMR spectra were recorded on Bruker AC300F, AM360, DRX400, AM500 or DRX500 instruments in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in ppm relative to residual undeuterated solvent as an internal reference. The following abbreviations are used to define the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. The carbons have been assigned with the aid of DEPT and $^1H/^{13}C$ correlation experiments wherever necessary. For the sake of clarity in the assignment of the NMR spectra, the carbons of the arene ring of the aldehydes through to the macrocyclic products are numbered as shown in Figure 5.

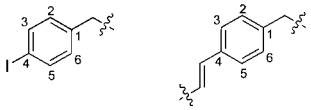


Figure 5.

Mass spectra were recorded on JEOL AX 505W and Kratos MS890MS spectrometers at King's College London and Micromass Quattro II and Waters Micromass ZQ4000 spectrometers at the EPSRC mass spectral facility, Swansea. Elemental analyses were performed by the London Metropolitan University microanalytical service and the University of Cambridge microanalytical service. BH_3·THF = borane/tetrahydrofuran complex in THF. Boc_2O = di-*tert*-butyl dicarbonate.

Where similar procedures have been used, a general method is given together with data for one representative product. Data for the remaining products are provided in the Supporting Information.

General procedure for reductive amination: The appropriate amino alcohol L-valinol, L-prolinol or **7** (90.0 mmol) and anhydrous magnesium sulfate (6.0 g) were added to a solution of aldehyde **4** or **1** (60.0 mmol) in dry dichloromethane (110 mL). The mixture was stirred under a slight over pressure of nitrogen, at room temperature for 24 h. The reaction mixture was then transferred via filter cannula to another flask. The solution was concentrated in vacuo and the resulting residue was redissolved in dry methanol (110 mL), cooled to 0 °C and sodium borohydride (4.5 g, 120 mmol) was added cautiously. After the addition was complete, the ice bath was removed and the solution was stirred at room temperature for 24 h. The reaction mixture was quenched with distilled water (100 mL) and extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo.

Compound 4v: Purification of the crude product by flash column chromatography (silica gel; hexane/ethyl acetate/triethylamine 4:1:0.01 → 1:1:0.1) afforded **4v** as a pale yellow oil (16.3 g, 75%). R_f = 0.2 (silica gel; hexane/ethyl acetate/triethylamine 1:1:0.01); $[\alpha]_D^{20} = +2.9$ (c = 0.01 in CH_2Cl_2); IR: $\tilde{\nu}_{max}$ = 3200–3600 cm^{-1} (NH and OH); ^1H NMR (360 MHz, $CDCl_3$): δ = 0.87 (d, J = 7.0 Hz, 3H; CHCH_3), 0.92 (d, J = 7.0 Hz, 3H; CHCH_3), 1.39–1.45 (m, 2H; NHCH$_2$CH_2), 1.55 (quintet, J = 8 Hz, 2H; ArCH$_2$CH_2), 1.67–1.73 (m, 1H; CH$_3$CHCH$_3$), 2.26–2.28 (m, 1H; NHCH), 2.45–2.51 (m, 2H; ArCH_2), 2.57–2.62 (m, 2H; NHCH_2), 3.19 (dd, J = 7.5, 10.5 Hz, 1H; CHHOH), 3.50 (dd, J = 2.0, 10.5 Hz, 1H; CHHOH), 6.83–6.87 (m, 2H; Ar$H_{2,6}$), 7.48–7.53 ppm (m, 2H; Ar$H_{3,5}$); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 18.7 (CH_3), 20.0 (CH_3), 29.2 (CH$_3$CHCH$_3$), 29.3 (ArCH$_2$CH_2), 30.4 (NHCH$_2$CH_2), 35.7 (ArCH_2), 47.2 (NHCH_2), 60.7 (CH_2OH), 64.8 (NHCH), 91.1 (C_{Ar}I), 130.9 ($C_{Ar2,6}$H), 137.7 ($C_{Ar3,5}$H), 142.3 ppm (C_{Ar}CH$_2$); MS (CI): m/z (%): 362 (100) [M^++H], 275 (10) [M^+−(CH$_3$)$_2$CHCH$_2$OH], 257 (9) [M^+−(CH$_3$)$_2$CHCH$_2$OHNH$_4$], 190 (11) [M^+−(CH$_3$)$_2$CH−I]; elemental analysis calcd (%) for $C_{15}H_{24}INO$ (361.26): C 49.87, H 6.7, N 3.88; found: C 50.04, H 6.65, N 3.91.

General procedure for benzylation of 4v and 1v: The aminoalcohol **4v** or **1v** (40.0 mmol) in dry acetone (160 mL) was placed in a 500 mL flask under an inert atmosphere of nitrogen. Activated potassium carbonate (60.0 mmol) and [18]crown-6 (4.0 mmol) were added while stirring the reaction mixture at room temperature. Benzyl bromide (60.0 mmol) was then added to the mixture and the reaction vessel was left stirring at room temperature for 20 h. The reaction was then quenched with water (50 mL) and the organics extracted with diethyl ether (100 mL × 3). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo.

Compound 4v(Bn): Purification of the crude product by flash column chromatography (silica gel; hexane/ethyl acetate 9:1 → 3:1) afforded **4v(Bn)** as a pale yellow oil (16.2 g, 90%). R_f = 0.5 (silica gel; hexane/ethyl acetate 4:1); $[\alpha]_D^{20} = +13.4$ (c = 0.0097 in CH_2Cl_2); IR: $\tilde{\nu}_{max}$ = 3453 cm^{-1} (OH); ^1H NMR (360 MHz, $CDCl_3$): δ = 0.83 (d, J = 7.0 Hz, 3H; CHCH_3), 1.07 (d, J = 7.0 Hz, 3H; CHCH_3), 1.27–1.29 (m, 1H; NCH$_2$CHH), 1.38–1.45 (m, 3H; ArCH$_2$CH_2 and NCH$_2$CHH), 1.89–1.95 (m, 1H; CH$_3$CHCH$_3$), 2.38–2.42 (t, J = 7.0 Hz, 2H; NCH_2CH$_2$), 2.50–2.53 (m, 1H; NCH), 2.62–2.69 (m, 2H; ArCH_2), 3.26 (t, J = 10.5 Hz, 1H; CHCHHOH), 3.41 (brs, 1H; OH), 3.58 (dd, J = 5, 10.5 Hz, 1H; CHCHHOH), 3.61 (d, J = 13.5 Hz, 1H; NCHHAr), 3.85 (d, J = 13.5, 1H; NCHHAr), 6.79–6.83 (m, 2H; Ar$H_{2,6}$), 7.25–7.34 (m, 5H; NCH$_2$$Ar$), 7.52–7.57 ppm (m, 2H; Ar$H_{3,5}$); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 20.1 (CH_3), 22.6 (CH_3), 28.3 (CH$_3$CHCH$_3$), 28.6 and 29.1 (NHCH$_2$CH_2 and ArCH$_2$CH_2), 35.0 (ArCH_2), 50.8 (NCH_2Ar), 55.3 (NCH_2), 59.7 (CH_2OH), 67.6 (NCH), 90.6 (C_{Ar}I), 127.1 (NCH$_2$$C_{Ar}$H), 128.5 (NCH$_2$$C_{Ar}$H), 128.9 (NCH$_2$$C_{Ar}$H), 130.5 ($C_{Ar2,6}$H), 137.2 ($C_{Ar3,5}$H), 140.3 and 141.9 ppm (NCH$_2$$C_{Ar}CH_2$ and C_{Ar}CH$_2$); MS (EI): m/z (%): 451 (2) [M^+], 420 (100) [M^+−CH$_2$OH], 408 (38) [M^+−(CH$_3$)$_2$CH]; elemental analysis calcd (%) for $C_{22}H_{30}INO$ (451.38): C 58.54, H 6.70, N 3.10; found: C 58.63, H 6.70, N 3.08.

General procedure for the formation of carboxypropenyl alkenes 4v(Bn)c, 1v(Bn)c and 1pc: Compound **4v(Bn)**, **1v(Bn)** or **1p** (1.0 mmol) in tetrahydrofuran (1 mL) was added at 0 °C to a solution of sodium hydride (60% dispersion in mineral oil) (1.1 mmol), previously washed with hexane, in tetrahydrofuran (3.0 mL). The reaction mixture was heated to reflux under nitrogen for 5 h. The flask was then allowed to cool to 0 °C in an ice bath and tetrabutylammonium iodide (0.02 mmol) and methyl 2-(bromomethyl)acrylate (1.2 mmol) were added in succession. The reaction mixture was stirred for 3 h allowing the ice to melt. The reaction was then quenched with water (1 mL) and extracted with dichloromethane (2 × 10 mL). The combined extracts were washed with brine (10 mL), dried over magnesium sulphate and then concentrated in vacuo to afford the crude product. All reactions were performed on a 5–20 mmol scale.

Compound 4v(Bn)c: Purification of the crude product by flash column chromatography (silica gel; hexane/ethyl acetate 100:0 → 95:5) afforded **4v(Bn)c** as a colourless oil (4.90 g, 60%). R_f=0.4 (silica gel; hexane/ethyl acetate 95:5); $[\alpha]_D^{20}$=+4.9 (c = 0.003 in CH_2Cl_2); IR: $\tilde{\nu}_{max}$=1732 (C=O), 1637 cm^{-1}(C=C); ^1H NMR (360 MHz, $CDCl_3$): δ=0.88 (d, J= 7 Hz, 3H; CHCH_3), 1.0 (d, J=7 Hz, 3H; CHCH_3), 1.36–1.58 (m, 4H; NCH$_2$CH_2 and ArCH$_2$CH_2), 1.83–1.88 (m, 1H; CH$_3$CHCH$_3$), 2.33–2.42 (m, 2H; NCH_2), 2.47–2.56 (m, 2H; ArCH_2), 3.38 (d, J=13.5 Hz, 1H; NCHHAr), 3.55–3.56 (m, 2H; NCHCH_2OCH$_2$), 3.66 (s, 3H; COOCH_3), 3.79 (d, J=13.5 Hz, 1H; NCHHAr), 4.05–4.07 (m, 2H; OCH_2C=CH$_2$), 5.87 (dd, J=1.5, 3.3 Hz, 1H; CHH=C, *trans*-C(=O)O-R), 6.28 (dd, J= 1.5, 2.8 Hz, 1H; CHH=C, *cis*-C(=O)O-R), 6.79–6.82 (m, 2H; Ar$H_{2,6}$), 7.16–7.32 (m, 5H; NCH$_2$*Ar*), 7.51–7.54 ppm (m, 2H; Ar$H_{3,5}$); ^{13}C NMR (90 MHz, $CDCl_3$): δ=20.9 (*C*H$_3$CHCH$_3$), 21.8 (CH$_3$CH*C*H$_3$), 28.6 (ArCH$_2$*C*H$_2$), 28.9 (CH$_3$*C*HCH$_3$), 29.2 (NHCH$_2$*C*H$_2$), 35.6 (Ar*C*H$_2$), 51.0 (N*C*H$_2$), 52.2 (COO*C*H$_3$), 56.0 (N*C*H$_2$Ar), 65.2 (N*C*HCH), 69.6 and 69.7 (CH*C*H$_2$OCH$_2$ and CHCH$_2$O*C*H$_2$), 90.9 (C_{Ar}I), 125.0 (*C*H$_2$=C), 127.10 (NCH$_2$$C_{Ar}$H), 128.5 (NCH$_2$$C_{Ar}$H), 128.9 (NCH$_2$$C_{Ar}$H), 130.9 ($C_{Ar2,6}$H), 137.6 ($C_{Ar3,5}$H), 137.9 (CH$_2$=*C*), 141.9 and 142.7 ($C_{Ar}CH_2$ and C_{Ar}CH$_2$N), 166.7 ppm (*C*OOCH$_3$); MS (EI): m/z (%): 549 (3) [M^+], 506 (100) [M^+ −(CH$_3$)$_2$CH], 421 (97) [M^+−(CH$_3$)$_2$CH−CH$_2$=CCOOCH$_3$], 294 (10) [M^+−(CH$_3$)$_2$CH−CH$_2$=CCOOCH$_3$−I]; elemental analysis calcd (%) for $C_{27}H_{36}INO_3$ (549.48): C 59.02, H 6.60, N 2.55; found: C 59.09, H 6.76, N 2.79.

Compound 4v(Bn)a: Compound **4v(Bn)** (0.90 g, 2.0 mmol) in tetrahydrofuran (4 mL) was added at 0°C to a solution of sodium hydride (60% dispersion in mineral oil) (0.096 g, 2.2 mmol), previously washed with hexane, in tetrahydrofuran (6 mL). The reaction mixture was heated to reflux under nitrogen for 5 h. The flask was then allowed to cool to 0°C in an ice bath. Tetrabutylammonium iodide (0.015 g, 0.039 mmol) and allyl bromide (0.26 mL, 3.0 mmol) were added in succession and the reaction mixture was left stirring for 14 h allowing the ice to melt. The reaction was then quenched with water (5 mL) and extracted with dichloromethane (2×20 mL). The combined extracts were washed with brine (2× 10 mL) dried over magnesium sulphate and then concentrated in vacuo to afford the crude product as pale oil. Purification of the crude product by flash column chromatography (silica gel; hexane/diethyl ether 10:0 → 4:1) afforded **4v(Bn)a** as a colourless oil (0.95 g, 97%). R_f=0.5 (silica gel; hexane/diethyl ether 4:1); $[\alpha]_D^{20}$=−48.8 (c=0.06 in CH_2Cl_2); IR: $\tilde{\nu}_{max}$=1646 cm^{-1} (C=C); ^1H NMR (360 MHz, $CDCl_3$): δ=0.81 (d, J= 7.0 Hz, 3H; CHCH_3), 0.92 (d, J=7.0 Hz, 3H; CHCH_3), 1.29–1.38 (m, 4H; NCH$_2$CH_2 and ArCH$_2$CH_2), 1.73–1.76 (m, 1H; CH$_3$CHCH$_3$), 2.26–2.47 (m, 5H; NCH_2, ArCH_2 and NCHCH), 3.41 (d, J=14 Hz, 1H; NCHHAr), 3.49 (d, J=4.5 Hz, 2H; OCH_2CH=CH$_2$), 3.79 (d, J=14 Hz, 1H; NCHHAr), 3.84–3.87 (m, 2H; NCHCH_2OCH$_2$), 5.08 (ddd, J=1.5, 4.5, 12.0 Hz, 1H; CH=CHH, *cis*), 5.84 (dd, J=1.5, 17.0 Hz, 1H; CH= CHH, *trans*), 5.80–5.87 (m, 1H; CH=CH$_2$), 6.73–6.75 (m, 2H; Ar$H_{2,6}$), 7.11–7.25 (m, 5H; NCH$_2$*Ar*), 7.44–7.46 ppm (m, 2H; Ar$H_{3,5}$); ^{13}C NMR (90 MHz, $CDCl_3$): δ=19.4 (*C*H$_3$CHCH$_3$), 20.3 (CH$_3$CH*C*H$_3$), 27.1 (ArCH$_2$*C*H$_2$), 27.6 (CH$_3$*C*HCH$_3$), 27.8 (NHCH$_2$*C*H$_2$), 34.2 (Ar*C*H$_2$), 49.7 (N*C*H$_2$), 54.5 (N*C*H$_2$Ar), 63.8 (N*C*HCH), 67.6 (NCH*C*H$_2$O), 70.9 (CH*C*H$_2$O), 89.4 (C_{Ar}I), 115.3 (CH=*C*H$_2$), 125.3 (NCH$_2$$C_{Ar}$H), 127.0 (NCH$_2$$C_{Ar}$H), 127.8 (NCH$_2$$C_{Ar}$H), 129.4 ($C_{Ar2,6}$H), 134.1 (CH$_2$=*C*H), 136.1 ($C_{Ar3,5}$H), 140.6 ($C_{Ar}CH_2$N), 141.3 ppm ($C_{Ar}CH_2$); MS (CI): m/z (%): 492 (100) [M^++H], 448 (7) [M^+−(CH$_3$)$_2$CH]; elemental analysis calcd (%) for $C_{25}H_{34}INO$ (491.45): C 61.10, H 6.97, N 2.85; found: C 61.25, H 6.96, N 2.84.

General procedure for the formation of propenoyl alkenes 4v(Bn)p, 1v(Bn)p, 1pp and 1v$_{Me_2}$(Bn)p: Aminoalcohol **4v(Bn)**, **1v(Bn)**, **1p** or **1v$_{Me_2}$(Bn)** (1.0 mmol) was dissolved in dry dichloromethane (4 mL) and cooled to 0°C under an inert atmosphere of nitrogen. Triethylamine (1.1 mmol) was slowly added followed by hydroquinone (0.01 mmol). Keeping the reaction mixture at 0°C, acryloyl chloride (1.1 mmol) was added drop-wise over 15 minutes. The reaction was left stirring at the same temperature for 2 h and was then poured into a separating funnel containing 1.50 mL of cold water. The aqueous phase was extracted with dichloromethane (2×8 mL) and the combined extracts, to which more hydroquinone (0.01 mmol) was added, were dried over magnesium sulphate and then concentrated in vacuo to afford the crude product. All reactions were performed on 1.8–20 mmol scale.

Compound 4v(Bn)p: Purification of the crude product by flash column chromatography (silica gel; hexane/thyl acetate 9:1 → 7:1) afforded **4v(Bn)p** as a colourless oil (5.71 g, 75%). R_f=0.5 (silica gel; hexane/ethyl acetate 7:1); $[\alpha]_D^{20}$=−45.3 (c=0.01 in CH_2Cl_2); IR: $\tilde{\nu}_{max}$=1739 (C= O), 1642 cm^{-1} (C=C); ^1H NMR (360 MHz, $CDCl_3$): δ=0.84 (d, J= 7.0 Hz, 3H; CHCH_3), 0.95 (d, J=7.0 Hz, 3H; CHCH_3), 1.30–1.48 (m, 4H; NCH$_2$CH_2 and ArCH$_2$CH_2), 1.80–1.82 (m, 1H; CH$_3$CHCH$_3$), 2.33–2.52 (m, 5H; NCH_2 and ArCH_2 and NCHCH), 3.43 (d, J=14 Hz, 1H; NCHHAr), 3.80 (d, J = 14 Hz, 1H; NCHHAr), 4.22–4.33 (m, 2H; NCHCH_2O), 5.76 (dd, J = 1.5, 10.5 Hz, 1H; CH=CHH, *cis*), 6.05 (dd, J = 10.5, 17.5 Hz, 1H; CH=CH$_2$), 6.31 (dd, J = 1.5, 17.5 Hz, 1H; CHH= CH, *trans*), 6.75–6.77 (m, 2H; Ar$H_{2,6}$), 7.12–7.26 (m, 5H; NCH$_2$*Ar*), 7.46–7.49 ppm (m, 2H; Ar$H_{3,5}$); ^{13}C NMR (90 MHz, $CDCl_3$): δ=20.7 (*C*H$_3$CHCH$_3$), 21.7 (CH$_3$CH*C*H$_3$), 28.7 (ArCH$_2$*C*H$_2$), 28.9 (CH$_3$*C*HCH$_3$), 29.1 (NCH$_2$*C*H$_2$), 35.5 (Ar*C*H$_2$), 50.7 (NBnCH$_2$), 55.7 (N*C*H$_2$Ar), 63.0 (CH*C*H$_2$O), 64.1 (NBn*C*HCH), 90.9 (C_{Ar}I), 127.0 (*C*H=CH$_2$), 128.6 (NCH$_2$$C_{Ar}$H), 128.7 (NCH$_2$$C_{Ar}$H), 128.9 (NCH$_2$$C_{Ar}$H), 130.9 ($C_{Ar2,6}$H), 131.1 (*C*H$_2$=C), 137.6 ($C_{Ar3,5}$H), 141.2 ($C_{Ar}CH_2$N), 142.6 ($C_{Ar}CH_2$), 166.6 ppm (O*C*=OCH); MS (CI): m/z (%): 506 (83) [M^++H], 464 (50) [M^+−(CH$_3$)$_2$CH+2H], 355 (100) [M^+−I−CH$_2$=CH+4H]; elemental analysis calcd (%) for $C_{25}H_{32}INO_2$ (505.43): C 59.41, H 6.38, N 2.77; found: C 59.56, H 6.25, N 2.83.

Typical procedure for the Heck coupling reactions: A flask containing a stirrer bar and fitted with a condenser was placed under an inert atmosphere of nitrogen and charged with the appropriate Heck acceptor alkene **4v(Bn)c**, **4v(Bn)a**, **4v(Bn)p**, **1v(Bn)c**, **1v(Bn)p**, **1pc**, **1pp** or **1v$_{Me_2}$(Bn)p** (1.0 mmol), palladium(II) acetate (0.1 mmol), sodium hydrogencarbonate (2.5 mmol) and tetra-*n*-butyl ammonium chloride (1.0 mmol). Dry DMF (0.05 M) was then added and the mixture was saturated with nitrogen. The flask was lowered into a preheated oil bath held at 110°C and stirred for 16 h. After cooling, the product mixture was diluted with diethyl ether (40 mL) and the precipitate filtered. The filtrate was concentrated in vacuo to afford the crude products. Reactions were performed on 0.7–12.0 mmol scale.

Compound m^2-4v(Bn)c: Purification of the crude product by careful flash column chromatography (silica gel; hexane/diethyl ether 10:0→4:1) afforded **m^2-4v(Bn)c** as a white feathery solid (0.464 g, 40%). R_f=0.32 (silica gel; hexane/diethyl ether 1:1); m.p. 96–98°C; $[\alpha]_D^{20}$=−21.7 (c= 0.011 in CH_2Cl_2); IR: $\tilde{\nu}_{max}$=1708 (C=O), 1644 cm^{-1} (C=C); ^1H NMR (360 MHz, $CDCl_3$): δ=0.79 (d, J=6.5 Hz, 3H; CHCH_3), 0.92 (d, J= 6.5 Hz, 3H; CHCH_3), 1.30–1.43 (m, 4H; NCH$_2$CH_2 and ArCH$_2$CH_2), 1.77–1.80 (m, 1H; CH$_3$CHCH$_3$), 2.29–2.45 (m, 4H; NCH_2CH_2 and ArCH_2CH$_2$), 2.56–2.60 (m, 1H; NCHCH), 3.39–3.52 (m, 2H; CHCH$_2$OCH_2), 3.44 (d, J=14.0 Hz, 1H; NCHHAr), 3.60 (s, 3H; OCH_3), 3.78 (d, J=14.0 Hz, 1H; NCHHAr), 4.02 (dd, J=6.5, 10.5 Hz, 1H; CHCHHOCH$_2$), 4.19 (dd, J=2.0, 10.5 Hz, 1H; CHCHHOCH$_2$), 6.83–6.85 (m, 2H; Ar$H_{2,6}$), 7.04–7.06 (m, 2H; Ar$H_{3,5}$), 7.11–7.27 (m, 5H; NCH$_2$*Ar*), 7.39 ppm (s, 1H; ArCH=C); ^{13}C NMR (90 MHz, $CDCl_3$): δ= 20.7 (CH$_3$CHCH$_3$), 21.7 (*C*H$_3$CHCH$_3$), 28.4 (CH$_3$*C*HCH$_3$), 29.74, 29.78 and 29.95 (NCH$_2$CH$_2$, ArCH$_2$CH$_2$ and CHCH$_2$OCH$_2$), 35.9 (ArCH$_2$CH$_2$), 51.5 (NCH$_2$CH$_2$), 51.6 (COO*C*H$_3$), 55.6 (N*C*H$_2$Ar), 64.7 (N*C*H), 73.4 (NCH*C*H$_2$), 110.6 (C=CH*C*$_{Ar}$), 127.1, 128.4, 128.5, 128.7, 129.0 (CH$_2$CH$_2$*C*$_{Ar3,5,}$ CH$_2$CH$_2$*C*$_{Ar2,6}$H and NCH$_2$*Ar*), 138.0 (ArCH$_2$=*C*), 140.5 and 141.1 (NCH$_2$*C*$_{Ar}$ and *C*$_{Ar}$CH$_2$CH$_2$), 158.7 (ArCH=C), 169.1 ppm (*C*= O); MS (FAB, positive): m/z (%): 844 (100) [M^++H], 800 (32) [M^+ −(CH$_3$)$_2$CH]; elemental analysis calcd (%) for $C_{54}H_{70}N_2O_6$ (843.14): C 76.92, H 8.37, N 3.32; found: C 76.93, H 8.40, N 3.40.

Compounds m^2-4v(Bn)p and m^3-4v(Bn)p: Purification of the crude products by careful flash column chromatography (silica gel; hexane/diethyl ether 10:1 → 3:1) afforded **m^2-4v(Bn)p** as a fluffy white solid (0.475 g, 25%) and **m^3-4v(Bn)p** as a bright yellow fluffy solid (0.284 g, 15%). Data for **m^2-4v(Bn)p**: R_f=0.45 (silica gel; hexane/diethyl ether 3:1); m.p. 88–90°C; $[\alpha]_D^{20}$=−43.5 (c=0.08 in CH_2Cl_2); IR: $\tilde{\nu}_{max}$=1709 (C=O), 1635 cm^{-1} (C=C); ^1H NMR (360 MHz, $CDCl_3$): δ=0.87 (d, J=6.5 Hz, 3H; CHCH_3), 0.97 (d, J=6.5 Hz, 3H; CHCH_3), 1.28–1.38 (m, 1H; NCH$_2$CHH), 1.39–1.52 (m, 3H; ArCH$_2$CH_2 and NCH$_2$CHH), 1.89–1.95

(m, 1H; CH_3CHCH_3), 2.38–2.45 (m, 2H; NCH_2CH_2), 2.49–2.59 (m, 2H; $ArCH_2CH_2$), 2.60–2.75 (m, 1H; NCHCH), 3.58 (d, $J=14$ Hz, 1H; NCHHAr), 3.73 (d, $J=14$ Hz, 1H; NCHHAr), 4.19 (dd, $J=7$, 12 Hz, 1H; CHHOC=O), 4.40 (dd, $J=2$, 12 Hz, 1H; $CHHOCH_2$), 6.25 (d, $J=16$ Hz, 1H; CH=CHC=O), 6.90–6.93 (m, 2H; $ArH_{2,6}$), 7.08–7.21 (m, 5H; NCH_2Ar), 7.25–7.27 (m, 2H; $ArH_{3,5}$), 7.50 ppm (d, $J=16$, 1H; ArCH=CH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=20.9$ (CH_3), 22.2 (CH_3), 27.9 (CH_3CHCH_3), 28.8 (NCH_2CH_2), 29.8 ($ArCH_2CH_2$), 36.1 ($ArCH_2$), 51.3 (NCH_2CH_2), 55.6 (NCH_2Ar), 62.4 ($CHCH_2O$), 64.1 (NCH), 117.7 (CH=CHC=O), 127.1 ($CH_2CH_2C_{Ar3,5}H$), 128.53, 128.55, 129.0, 129.2 ($CH_2CH_2C_{Ar2,6}H$ and NCH_2Ar), 132.1 (CH=CHC$_{Ar}$), 141.3 (NCH_2C_{Ar}), 145.1 (ArCH=CH), 146.2 ($CH_2CH_2C_{Ar}$), 167.4 ppm (C=O); MS (ESI): m/z (%): 755 (98) [M^+], 452 (50) [$M^+-(CH_2)_4(NBn)CH(CH_3)_2CHCH_2OC{=}OCH{=}CH-2H$], 410 (35) [$M^+-(CH_2)_4(NBn)CH(CH_3)_2CHCH_2OC{=}OCH{=}CH-(CH_3)_2CH-H$], 242 (69) [$CH_2CH(CH_3)_2CHN(CH_2)_4ArCH{=}CH^+$], 119 (100) [$CH_2NBn^+$]; elemental analysis calcd (%) for $C_{50}H_{62}N_2O_4$ (755.04): C 79.54, H 8.28, N 3.71; found: C 79.49, H 8.08, N 3.67.

Data for m^3-4v(Bn)p: $R_f=0.35$ (silica gel; hexane/diethyl ether 3:1); m.p. 78–80 °C; $[\alpha]_D^{20}=-59.4$ ($c=0.05$ in CH_2Cl_2); IR: $\tilde{\nu}_{max}=1711$ (C=O), 1634 cm^{-1} (C=C); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=0.84$ (d, $J=6.5$ Hz, 3H; $CHCH_3$), 0.95 (d, $J=6.5$ Hz, 3H; $CHCH_3$), 1.32–1.50 (m, 4H; $ArCH_2CH_2$ and NCH_2CH_2), 1.78–1.80 (m, 1H; CH_3CHCH_3), 2.43–2.59 (m, 5H; NCH_2CH_2, $ArCH_2CH_2$ and NCHCH), 3.50 (d, $J=14$ Hz, 1H; NCHHAr), 3.77 (d, $J=14$ Hz, 1H; NCHHAr), 4.22 (dd, $J=7$, 12 Hz, 1H; CHHOC=O), 4.34 (dd, $J=2$, 12 Hz, 1H; $CHHOCH_2$), 6.25 (d, $J=16$ Hz, 1H; CH=CHC=O), 6.94–6.96 (m, 2H; $ArH_{2,6}$), 7.08–7.21 (m, 5H; NCH_2Ar), 7.30–7.33 (m, 2H; $ArH_{3,5}$), 7.57 ppm (d, $J=16.0$, 1H; ArCH=CH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=19.3$ (CH_3), 20.4 (CH_3), 27.3 (NCH_2CH_2), 27.6 (CH_3CHCH_3), 27.7 ($ArCH_2CH_2$), 34.6 ($ArCH_2$), 49.9 (NCH_2), 54.2 (NCH_2Ar), 62.1 ($CHCH_2O$), 62.8 (NCH), 116.1 (CH=CHC=O), 125.6 ($CH_2CH_2C_{Ar3,5}H$), 127.1, 127.6, 127.7, 128.2, ($CH_2CH_2C_{Ar2,6}H$ and NCH_2Ar), 130.8 (CH=CHC$_{Ar}$), 139.9 (NCH_2C_{Ar}), 143.8 (ArCH=CH), 144.5 ($CH_2CH_2C_{Ar}$), 166.1 ppm (C=O); MS (ESI): m/z (%): 1132 (13) [M^+], 510 (27) [$Ar(CH_2)_4(NBn)CH(CH_3)_2CHCH_2OC{=}OCH{=}CHAr(CH_2)_4+H^+$], 326 (25) [$CH_2OC{=}OCH{=}CHAr(CH_2)_4NCHCH_2OC{=}OCH{=}CH^+-H$], 119 (100) [$CH_2NBn^+$]; elemental analysis calcd (%) for $C_{75}H_{93}N_3O_6$ (1132.56): C 79.54, H 8.28, N 3.71; found: C 79.35, H 8.19, N 3.59.

Compound 10: Purification of the crude products by careful flash column chromatography (silica gel; hexane/diethyl ether 10:0 → 4:1) afforded **10** as a white waxy solid (0.11 g, 46%). $R_f=0.70$ (silica gel; hexane/diethyl ether 1:1); m.p. 65–67 °C; $[\alpha]_D^{20}=+88.7$ ($c=0.0023$ in CH_2Cl_2); IR: $\tilde{\nu}_{max}=$ 1734 (C=O), 1633 (C=C), 1607 cm^{-1} (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.65$ (d, $J=6.5$ Hz, 6H; $CHCH_3$), 1.05 (d, $J=6.5$ Hz, 6H; $CHCH_3$), 1.67 (s, 6H; $CH_2{=}CCH_3$), 1.89–1.99 (m, 2H; CH_3CHCH_3), 2.49 (d, $J=11.0$ Hz, 2H; NCHC), 3.27 (d, $J=14.5$ Hz, 2H; NCHHAr), 3.30 (d, $J=14.5$ Hz, 2H; NCHHAr), 3.79 (d, $J=16.5$ Hz, 2H; NCHHAr), 3.81 (d, $J=16.5$ Hz, 2H; NCHHAr), 4.43 (s, 2H; CHH=CCH$_3$ *cis*), 4.97 (s, 2H; CHH=CCH$_3$ *trans*), 5.93 (s, 2H; C=OOCH_2OC=O), 6.35 (d, $J=16$ Hz, 2H; C=OCH=CH), 7.06–7.39 (m, 18H; $ArH_{2,6}$, NCH_2Ar and $ArH_{3,5}$), 7.68 ppm (d, $J=16$ Hz, 2H; C=OCH=CHAr); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=20.9$ (CH_3CHCH_3), 21.1 (CH_3CHCH_3), 21.8 ($CH_2{=}CCH_3$), 27.4 (CH_3CHCH_3), 54.3 and 54.6 ($NCH_2Ar\times2$), 70.7 ($NCHCH_2$), 79.7 (C=OOCH$_2$OC=O), 116.3 (CH=CHC$_{Ar}$), 116.9 ($CH_2{=}CCH_3$), 127.1, 128.67, 128.69, 128.9, 129.4 ($CH_2CH_2C_{Ar3,5}H$ $CH_2CH_2C_{Ar2,6}H$ and NCH_2Ar), 132.9 ($C_{Ar}CH{=}CH$), 140.8 and 141.6 ($NCH_2C_{Ar}\times2$), 144.6 ($CH_2{=}CCH_3$), 147.2 (ArCH=CH), 166.2 ppm (C=O); MS (ESI, Na^+): m/z (%): 762 (100) [M^++Na], 739 (52) [M^+], 609 (20) [$M^+-Bn-CH_2{=}CCH_3+2H$], 346 (12) [$ArCH{=}CHC{=}OOCH_2OC{=}OCH{=}CHArCH_2NCH^+-H$]; elemental analysis calcd (%) for $C_{49}H_{58}N_2O_4$ (739.00): C 79.64, H 7.91, N 3.79; found: C 79.65, H 7.90, N 3.84.

Alcohol 3:[18] A 1.0 M solution of BH_3·THF complex (200 mL) was added via a cannula over 20 minutes under an inert atmosphere of nitrogen to a solution of 4-iodobenzoic acid **2** (25.0 g, 100 mmol) in dry tetrahydrofuran (200 mL). The reaction mixture was left stirring at rt for 16 h and was then quenched with a 2 N HCl solution (500 mL). The organic product was extracted with dichloromethane (2×700 mL), washed with saturated sodium hydrogencarbonate (2×400 mL), brine (2×400 mL) dried over magnesium sulphate and concentrated in vacuo to afford **3** as a white solid (23.2 g, 99%). M.p. 65–67 °C; IR (nujol): $\tilde{\nu}_{max}=3280$ cm^{-1} (OH); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=4.64$ (d, $J=6$ Hz, 2H; $ArCH_2OH$), 7.10–7.13 (m, 2H; $ArH_{2,6}$), 7.68–7.70 ppm (m, 2H; $ArH_{3,5}$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=69.5$ ($ArCH_2OH$), 95.6 ($C_{Ar}I$), 129.0 ($C_{Ar2,6}H$), 137.1 ($C_{Ar3,5}H$), 140.5 ppm ($C_{Ar}CH_2OH$); MS (CI, NH_3): m/z (%): 252 (100) [M^++NH_4], 234 (9) [M^+]; HMRS (EI, Na): calcd for C_7H_7IO: 256.9420, found 256.9421 [M^++Na].

Aldehyde 1:[18] MnO_2 (224.0 g, 2570 mmol) was added to a solution of alcohol **3** (23.2 g, 99.2 mmol) in dry chloroform (900 mL). The reaction mixture was refluxed for 3 d and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to yield **1** as a white solid (22.7 g, 99%). M.p. 72–74 °C; IR (nujol): $\tilde{\nu}_{max}=1705$ cm^{-1} (C=O); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=7.58$–7.60 (m, 2H; $ArH_{2,6}$), 7.90–7.92 (m, 2H; $ArH_{3,5}$), 9.96 ppm (s, 1H; CHO); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=103.2$ ($C_{Ar}I$), 131.1 ($C_{Ar2,6}H$), 135.9 ($C_{Ar}CHO$), 138.8 ($C_{Ar3,5}H$), 191.9 ppm (CHO); MS (CI, NH_3): m/z (%): 250 (100) [M^++NH_4], 232 (91) [M^+]; HMRS (EI): calcd for C_7H_5IO: 232.0185, found 232.0187 [M^+].

Ester 8:[19] Solid sodium hydrogencarbonate (14.4 g, 170 mmol) was added in one portion to a stirred solution of L-valine methyl ester hydrochloride (9.5 g, 56.7 mmol) in dry tetrahydrofuran/methanol (4:1) (150 mL) at 0 °C, immediately followed by addition of solid Boc_2O (18.5 g, 84.9 mmol). The reaction was allowed to warm to room temperature, stirred for 20 h and then quenched with water (100 mL). The organic product was extracted with diethyl ether (2×300 mL), washed with saturated sodium hydrogencarbonate (2×100 mL), brine (2×100 mL), dried over magnesium sulphate and concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel; hexane/ethyl acetate 9:1 → 6:1) afforded **8** as a colourless oil (13.0 g, 99%). $R_f=$ 0.3 (silica gel; hexane/ethyl acetate 6:1); $[\alpha]_D^{20}=+13.2$ ($c=0.025$ in CH_2Cl_2); IR: $\tilde{\nu}_{max}=1741$, 1694 cm^{-1} (C=O×2); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=0.88$ (d, $J=7.0$ Hz, 3H; $CHCH_3$), 0.94 (d, $J=7.0$ Hz, 3H; $CHCH_3$), 1.43 (s, 9H; $C(CH_3)_3$), 2.09–2.14 (m, 1H; $(CH_3)_2CH$), 3.78 (s, 3H; OCH_3), 4.21 (dd, $J=4.8$, 9.1 Hz, 1H; NHCH), 5.03 ppm (br d, $J=9.0$ Hz, 1H; NH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=17.9$ ($CHCH_3$), 20.0 ($CHCH_3$), 28.6 $C(CH_3)_3$, 31.6 (CH_3CHCH_3), 52.4 (OCH_3), 58.9 (NHCH), 80.1 ($C(CH_3)_3$), 156.0 ($COOC(CH_3)_3$), 173.3 ppm ($COOCH_3$); MS (EI): m/z (%): 231 (20) [M^+], 130 (100) [$M^+-COOtBu$]; HRMS (EI): calcd for $C_{11}H_{21}NO_4$: 231.1471, found 231.1477 [M^+].

Alcohol 9:[13] Ester **8** (13.0 g, 56.2 mmol) was dissolved in freshly distilled THF (250 mL) and cooled to 0 °C. Methylmagnesium iodide (3.0 M solution in diethyl ether) (74.9 mL, 224.8 mmol) was added dropwise under nitrogen over 30 min and the reaction was warmed to room temperature and left stirring for 20 h. The reaction mixture was then cooled to 0 °C, and cautiously quenched with a saturated aqueous solution of NH_4Cl (250 mL). The organics were extracted with diethyl ether (3×300 mL), washed with brine (2×200 mL), dried over magnesium sulphate and concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel; hexane/ethyl acetate 9:1 → 4:1) afforded **9** as a white solid (9.9 g, 76%). $R_f=0.4$ (silica gel; hexane/ethyl acetate 4:1); m.p. 46–48 °C; $[\alpha]_D^{20}=+9.1$ ($c=0.01$ in CH_2Cl_2); IR (nujol): $\tilde{\nu}_{max}=3444$ (OH), 1696 cm^{-1} (C=O); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=0.90$ (d, $J=7.0$ Hz, 3H; $CHCH_3$), 0.94 (d, $J=7.0$ Hz, 3H; $CHCH_3$), 1.22 (s, 3H; $C(CH_3)OH$), 1.25 (s, 3H; $C(CH_3)OH$), 1.44 (s, 9H; $C(CH_3)_3$), 2.06–2.09 (m, 1H; CH_3CHCH_3), 3.48 (dd, $J=2.5$, 10.0 Hz, 1H; NHCH), 4.87 ppm (br d, $J=10$ Hz, 1H; NH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=16.8$ ($CHCH_3$), 17.2 ($CHCH_3$), 22.7 (CCH_3), 23.02 (CCH_3), 28.7 $CH(CH_3)_3$, 29.4 (CH_3CHCH_3), 62.1 (NHCH), 74.1 ($C(CH)_3OH$), 79.4 ($C(CH_3)_3$), 157.3 ppm ($COOC(CH_3)_3$); MS (EI): m/z (%): 231 (5) [M^+], 130 (100) [$M^+-COOtBu$]; HMRS (EI): calcd for $C_{12}H_{25}NO_3$: 231.1834, found 231.1838 [M^+].

Amino alcohol 7:[20] A 3 M HCl/EtOAc (150 mL) solution (1:1) was added to **9** (9.0 g, 39.0 mmol) and the mixture was left stirring for 16 h at room temperature. The reaction was then stopped and the volatiles were removed in vacuo. The residue was dissolved in EtOAc (300 mL) and cautiously washed with saturated $NaHCO_3$ (4×300 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give **7** (5.02 g, 98%) as

a white solid. M.p. 40–42 °C; $[\alpha]_D^{20} = -13.9$ ($c = 0.033$ in CH_2Cl_2); IR (nujol): $\tilde{\nu}_{max} = 3339$ and 3400 cm^{-1} (OH and NH_2); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 7.0$ Hz, 3H; $CHCH_3$), 0.96 (d, $J = 7.0$ Hz, 3H; $CHCH_3$), 1.10 (s, 3H; $C(CH_3)OH$), 1.18 (s, 3H; $C(CH_3)OH$), 1.87–1.98 (m, 1H; CH_3CHCH_3), 2.02 (br s, 2H; NH_2), 2.40 ppm (d, $J = 2.8$ Hz, 1H, NH_2CH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 17.2$ (CH_3), 23.2 (CH_3), 24.5 (CH_3), 28.3 $CH(CH_3)_2$, 28.9 (CH_3), 65.1 (NH_2CH), 72.1 ppm ($C(CH_3)_2OH$); MS (CI): *m/z* (%): 149 (100) $[M^+ + NH_4]$, 132 (45) $[M^+ + H]$; HMRS (EI): calcd for $C_7H_{17}NO$: 131.1310, found 131.1311 $[M^+]$.

Compound $1v_{Me_2}$(Bn): $1v_{Me_2}$ (0.900 g, 2.60 mmol) in DMF (5 mL) was added at 0 °C to a solution of sodium hydride (60 % dispersion in mineral oil) (0.125 g, 3.12 mmol), previously washed with hexane, in DMF (10 mL). The reaction mixture was allowed to reach room temperature and stirred under nitrogen for 6 h. The flask was then cooled to 0 °C in an ice bath and benzyl bromide (0.460 mL, 3.89 mmol) was added. The reaction mixture was warmed to room temperature and stirred under nitrogen for 16 h. The reaction was then quenched with water (5 mL) and the organics extracted with dichloromethane (2 × 10 mL). The combined extracts were washed with brine (15 mL), dried over magnesium sulphate and then concentrated in vacuo to afford the crude product. Purification of the crude product by flash column chromatography (silica gel; hexane/ethyl acetate 10:0 → 6:1) afforded **$1v_{Me_2}$(Bn)** as a pale yellow oil (0.795 g, 70 %). $R_f = 0.45$ (silica gel; hexane/ethyl acetate 8:1); $[\alpha]_D^{20} = -8.57$ ($c = 0.006$ in CH_2Cl_2); IR: $\tilde{\nu}_{max} = 3450$ cm^{-1} (OH); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 0.97$ (d, $J = 7.0$ Hz, 3H; $CHCH_3$), 1.01 (s, 3H; CH_3CCH_3), 1.13 (d, $J = 7.0$ Hz, 3H; $CHCH_3$), 1.16 (s, 3H; CH_3CCH_3), 2.02–2.16 (m, 1H; CH_3CHCH_3), 2.30 (d, $J = 8$ Hz, 1H; NCH), 3.56 (d, $J = 18$ Hz, 2H; NCHHAr), 3.58 (d, $J = 18$ Hz, 2H; NCHHAr), 3.84 (d, $J = 20.5$ Hz, 2H; NCHHAr), 3.86 (d, $J = 20.5$ Hz, 2H; NCHHAr), 4.75 (s, 1H; OH), 6.84–6.86 (m, 2H; $ArH_{2,6}$), 7.13–7.24 (m, 5H; NCH_2Ar), 7.46–7.49 ppm (m, 2H; $ArH_{3,5}$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 23.4$ (CH_3), 24.6 (CH_3), 26.8 (CH_3), 29.1 (CH_3CHCH_3), 31.8 (CH_3), 56.8 and 57.2 ($NCH_2Ar \times 2$), 71.2 (CH_3CCH_3), 72.9 (NCH), 93.2 ($C_{Ar}I$), 127.4 ($NCH_2C_{Ar}H$), 128.9 ($NCH_2C_{Ar}H$), 129.8 ($NCH_2C_{Ar}H$), 131.7 ($C_{Ar2,6}H$), 137.9 ($C_{Ar3,5}H$), 139.61 and 139.65 ppm ($C_{Ar}CH_2 \times 2$); MS (CI): *m/z* (%): 438 (100) $[M^+ + H]$, 421 (40) $[M^+ - OH + H]$; elemental analysis calcd (%) for $C_{21}H_{28}INO$ (437.36): C 57.67, H 6.45, N 3.20; found: C 57.71, H 6.47, N 3.20.

Compound 13:[14] A flask containing a stirrer bar and fitted with a condenser was placed under an inert atmosphere of nitrogen and charged with **12** (1.00 g, 6.75 mmol), sodium hydrogencarbonate (0.855 g, 10.1 mmol) and tetra-*n*-butyl ammonium chloride (2.81 g, 10.1 mmol). Dry DMF (135 mL, 0.05 M) was added and the mixture was saturated with nitrogen. The flask was lowered into a preheated oil bath held at 110 °C and stirred for 40 h. The reaction was stopped, quenched with water (50 mL) and the organics extracted with diethyl ether (100 mL × 2). The organic layer was then washed with water (100 mL × 2), brine (100 mL), dried over magnesium sulphate and the volatiles were removed in vacuo. Purification of the crude product by flash column chromatography (silica gel; hexane/ethyl acetate 10:0 → 4:1) afforded **13** as a white solid (0.612 g, 58 %). $R_f = 0.40$ (silica gel; hexane/ethyl acetate 4:1); m.p. 86–88 °C; IR: $\tilde{\nu}_{max} = 1734$ (C=O), 1630 cm^{-1} (C=C); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 5.90$ (s, 2H; OCH_2O), 6.31 (d, $J = 16.0$ Hz, 2H; C=OCH=CH), 7.22–7.23 (m, 6H; *Ar*), 7.34–7.37 (m, 4H; *Ar*), 7.65 ppm (d, $J = 16$ Hz, 2H; C=OCH=CH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 79.8$ (OCH_2O), 117.2 (CH=CHAr), 128.7, 129.4, 131.1 (*Ar*), 137.7 ($C_{Ar}CH$=CH), 147.2 (CH=CHAr), 165.9 ppm (C=O); MS (EI, Na): *m/z* (%): 331 (100) $[M^+ + Na]$, 308 (40) $[M^+]$; HMRS (EI): calcd for $C_{19}H_{16}O_4$: 331.0946, found 331.0949 $[M^+ + Na]$.

Compound 15: A flask containing a stirrer bar and fitted with a condenser was placed under an inert atmosphere of nitrogen and charged with **14** (0.300 g, 1.32 mmol), sodium hydrogencarbonate (0.134 g, 1.58 mmol) and tetra-*n*-butyl ammonium chloride (0.439 g, 1.58 mmol). Dry DMF (25 mL, 0.05 M) was added and the mixture was saturated with nitrogen. The flask was lowered into a preheated oil bath held at 110 °C and stirred for 72 h. The reaction was stopped, quenched with water (10 mL) and the organics extracted with diethyl ether (30 mL × 2). The organic layer was then washed with water (30 mL × 2), brine (30 mL), dried over magnesium sulphate and the volatiles removed in vacuo. Purification of the crude product by flash column chromatography (silica gel; hexane/ethyl acetate 10:0 → 4:1) afforded **15** as a white solid (0.184 g, 60 %). $R_f = 0.45$ (silica gel; hexane/ethyl acetate 4:1); m.p. 89–91 °C; IR: $\tilde{\nu}_{max} = 1759$ cm^{-1} (C=O); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 2.90$ (d, $J = 8.0$ Hz, 4H; Ar_2CHCH_2), 4.41 (t, $J = 8.0$ Hz, 2H; Ar_2CHCH_2), 5.46 (s, 2H; OCH_2O), 7.04–7.19 ppm (m, 20H; *Ar*); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 40.7$ (Ar_2CHCH_2), 47.1 (Ar_2CHCH_2), 79.2 (OCH_2O), 127.1, 128.0 and 129.0 (*Ar*), 143.4 ($C_{Ar}CH$), 170.8 ppm (C=O); MS (EI, Na): *m/z* (%): 487 (100) $[M^+ + Na]$, 239 (10) $[Ar_2CHCH_2C{=}OOCH_2^+]$; elemental analysis calcd (%) for $C_{31}H_{28}O_4$ (464.55): C 80.15, H 6.08; found: C 80.10, H 6.10.

Compound m^2-4v(Bn)p-H_4: A pressure vessel was charged with **m^2-4v(Bn)p** (0.0501 g, 0.0663 mmol) and 10 % palladium on charcoal (0.0050 g, 10 % *w/w*) in degassed EtOAc (4 mL). The reaction vessel was then evacuated and filled with hydrogen (10 ×). The reaction was stirred for 24 h under a hydrogen pressure of 50 psi, followed by filtration through Kieselguhr and evaporation in vacuo to afford **m^2-4v(Bn)p-H_4** as a white fluffy solid (0.0502 g, 99 %). M.p. 80–82 °C; $[\alpha]_D^{20} = -41.1$ ($c = 0.0058$ in CH_2Cl_2); IR: $\tilde{\nu}_{max} = 1733$ cm^{-1} (C=O); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 0.74$ (d, $J = 6.5$ Hz, 3H; $CHCH_3$), 0.89 (d, $J = 6.5$ Hz, 3H; $CHCH_3$), 1.20–1.46 (m, 4H; NCH_2CH_2 and $ArCH_2CH_2$), 1.61–1.73 (m, 1H; CH_3CHCH_3), 2.30–2.54 (m, 7H; NCH_2CH_2, $ArCH_2CH_2$, NCHCH and $ArCH_2CH_2C$=O), 2.83 (t, $J = 7.5$ Hz, 2H; $ArCH_2CH_2C$=O), 3.35 (d, $J = 14.0$ Hz, 1H; NCHHAr), 3.70 (d, $J = 14.0$ Hz, 1H; NCHHAr), 4.10 (dd, $J = 6$, 12 Hz, 1H; CHHOC=O), 4.17 (dd, $J = 3.5$, 12 Hz, 1H; CHHOC=O), 6.92–7.00 (m, 2H; $ArH_{2,6}$ and $ArH_{3,5}$), 7.10–7.28 ppm (m, 5H; NCH_2Ar); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 19.3$ (CH_3), 20.3 (CH_3), 27.3 (CH_3CHCH_3), 27.4 ($ArCH_2CH_2C$=O), 27.9 (NCH_2CH_2), 29.5 ($ArCH_2CH_2$), 34.3 and 35.1 ($ArCH_2$ and $ArCH_2CH_2C$=O), 49.45 (NCH_2CH_2), 54.1 (NCH_2Ar), 61.6 ($CHCH_2O$), 62.3 (NCH), 125.6, 127.0, 127.2, 127.4 and 127.9 ($C_{Ar3,5}$, $C_{Ar2,6}$ and NCH_2Ar), 136.5 (NCH_2C_{Ar}), 139.5 and 139.8 ($CH_2CH_2C_{Ar}$ and $C_{Ar}CH_2CH_2C$=O), 171.9 (C=O); MS (ESI): *m/z* (%): 759 (60) $[M^+]$, 675 (40) $[M^+ - 2 \times (CH_3)_2CH + 2H]$, 362 (100) $[C{=}O(CH_2)_2Ar(CH_2)_4(NBn)CH(CH_3)_2CHCH_2^+ - H]$; elemental analysis calcd (%) for $C_{50}H_{66}N_2O_4$ (759.07): C 79.11, H 8.76, N 3.69; found: C 79.15, H 8.82, N 3.71.

Compound m^2-4vp-H_4: A pressure vessel was charged with **m^2-4v(Bn)p** (0.750 g, 0.993 mmol) and 10 % palladium on charcoal (0.075 g, 10 % *w/w*) in degassed EtOAc (4 mL). The reaction vessel was then evacuated and filled with hydrogen (x 10). The reaction was stirred for 48 h under a hydrogen pressure of 100 psi, followed by filtration through Kieselguhr and evaporation in vacuo to afford **m^2-4vp-H_4** as a white fluffy solid (0.574 g, 99 %). M.p. 70–72 °C; $[\alpha]_D^{20} = +12.0$ ($c = 0.0042$ in CH_2Cl_2); IR: $\tilde{\nu}_{max} = 1737$ (C=O), 3359 cm^{-1} (NH); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J = 6.5$ Hz, 3H; $CHCH_3$), 0.95 (d, $J = 6.5$ Hz, 3H; $CHCH_3$), 1.48–1.61 (m, 4H; NCH_2CH_2 and $ArCH_2CH_2$), 1.61–1.73 (m, 1H; CH_3CHCH_3), 2.26–2.30 (m, 1H; NHCH), 2.48–2.67 (m, 6H; NCH_2CH_2, $ArCH_2CH_2$, $ArCH_2CH_2C$=O), 2.92 (t, $J = 7.5$ Hz, 2H, $ArCH_2CH_2C$=O), 4.10 (dd, $J = 7$, 12 Hz, 1H; CHHOC=O), 4.17 (dd, $J = 4.5$, 12 Hz, 1H; CHHOC=O), 7.10 ppm (s, 4H; $ArH_{2,6}$ and $ArH_{3,5}$); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 18.3$ (CH_3), 19.8 (CH_3), 29.5 (CH_3CHCH_3), 29.6 ($ArCH_2CH_2C$=O), 30.0 (NCH_2CH_2), 31.0 ($ArCH_2CH_2$), 35.7 and 36.6 ($ArCH_2$ and $ArCH_2CH_2C$=O), 47.4 (NCH_2CH_2), 61.8 (NHCH), 65.2 ($CHCH_2O$), 128.6 and 128.8 ($C_{Ar3,5}$,$C_{Ar2,6}$), 137.9 and 140.8 ($CH_2CH_2C_{Ar}$ and $C_{Ar}CH_2CH_2C$=O), 173.3 (C=O); MS (ESI): *m/z* (%): 578 (5) $[M^+]$, 534 (20) $[M^+ - (CH_3)_2CH - H]$, 290 (100) $[(CH_3)_2CHCHCH_2OC{=}O(CH_2)_2Ar(CH_2)_4NH_2^+]$; elemental analysis calcd (%) for $C_{36}H_{54}N_2O_4$ (578.83): C 74.70, H 9.40, N 4.84; found: C 74.75, H 9.46, N 4.85.

X-ray crystallography of m^2-4v(Bn)p: Crystal data for **m^2-4v(Bn)p**: $C_{50}H_{62}N_2O_4$, $M = 755.02$, monoclinic, $P2_1$ (no. 4), $a = 14.873(3)$, $b = 6.3127(17)$, $c = 24.225(5)$ Å, $\beta = 97.973(13)°$, $V = 2252.5(9)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.113$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 0.541$ mm^{-1}, $T = 293$ K, colourless platy needles; 4215 independent measured reflections, F^2 refinement, $R_1 = 0.060$, $wR_2 = 0.172$, 2905 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 130°$], 515 parameters. The absolute structure of **m^2-4v(Bn)p** could not be determined by crystallographic methods [*R* factor tests: $R_1^+ = 0.0599$, $R_1^- = 0.0599$; Flack parameter: $x^+ =$

+1.1(15), $x^- = +0.00(15)$] and so was assigned by internal reference on the α-valine carbon atoms.

CCDC-233091 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB 1EZ, UK; fax: (+44) 1223–336–033; or e-mail: deposit@ccdc.cam.ac.uk).

Molecular modelling: Molecular modelling was carried out using a Silicon Graphics O2 workstation running under IRIX. The software used was a proprietary package, which incorporated a modified version of COSMIC equipped with XED (eXtended Electronic Distribution) charges[21] rather than the original atom-centred charges.

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