Pergamon

Tetrahedron 56 (2000) 1505–1516

TETRAHEDRON

Epoxidation of Peptidyl Olefin Isosteres. Stereochemical Induction Effect of Chiral Centers at Four Adjacent C_α Positions

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Received 11 October 1999; revised 15 December 1999; accepted 6 January 2000

Abstract—Four tripeptidyl olefin isosteres were prepared, each of which contains a single chiral center derived from the bulky amino acid phenylalanine at positions corresponding to the P_2–P'_2 positions of a protease substrate. The effect of these chiral centers on the stereochemical outcome of mCPBA epoxidation of the olefin functionality was studied. A chiral center at P_2 or P'_2 position has no significant effect, and the P'_1 position exerts a small stereoselectivity. A chiral center at the P_1 position, on the other hand, has a profound chiral induction effect on the epoxidation reaction.

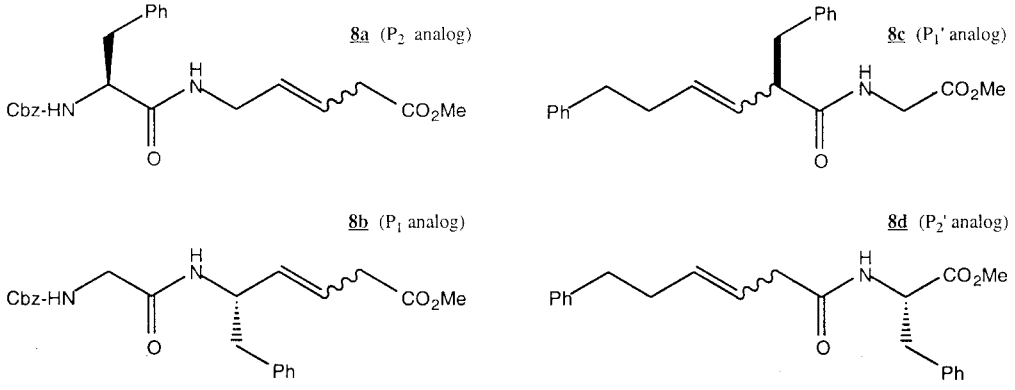
Introduction

Peptidyl epoxides bearing the epoxide moiety at their C-terminal (*exo* peptidyl epoxides) have been used as protease inhibitors[1] or as starting building blocks for peptide isosteres[2,3] and other compounds.[4] Stereoselective procedures for the preparation of both the *erythro* and the *threo* isomers of such peptidyl epoxides and N-protected α-amino epoxides were introduced.[2c,5] *Endo* peptidyl epoxides, where the epoxide is an isosteric replacement of a peptide bond of a di- or a polypeptide, were also studied as potential protease inhibitors,[6] but much less work was carried out on their stereoselective synthesis. The stereoselectivity of the epoxidation of the dipeptide olefinic analogs Phe-Gly, Phe-Phe and Phe-d-Phe was studied.[6a,7] Oxidative epoxidation of β-hydroxyselenides was also introduced as a route to sterically well defined *endo* peptidyl epoxides.[8] In the present study we explored the effect of the P_2–P'_2[9] four individual chiral centers adjacent to the olefinic peptide isostere of tripeptides on the stereochemical outcome of the mCPBA epoxidation reaction. Such information may be useful in the design of epoxy- and other peptide isosteres. The origin of the observed stereoselectivity, whether being due to simple steric interference or due to specific hydrogen bonding between substrate and oxidant, was also addressed.

Results

Synthesis of peptidyl olefins

A set of four tripeptidyl olefins, **8a**–**d** (Scheme 1), was synthesized, each of which contains a single chiral center



Scheme 1. The peptidyl olefins bearing a single stereogenic center at four positions adjacent to the olefin.

Keywords: peptide analogs/mimetics; stereocontrol; epoxidation; enzyme inhibitors.

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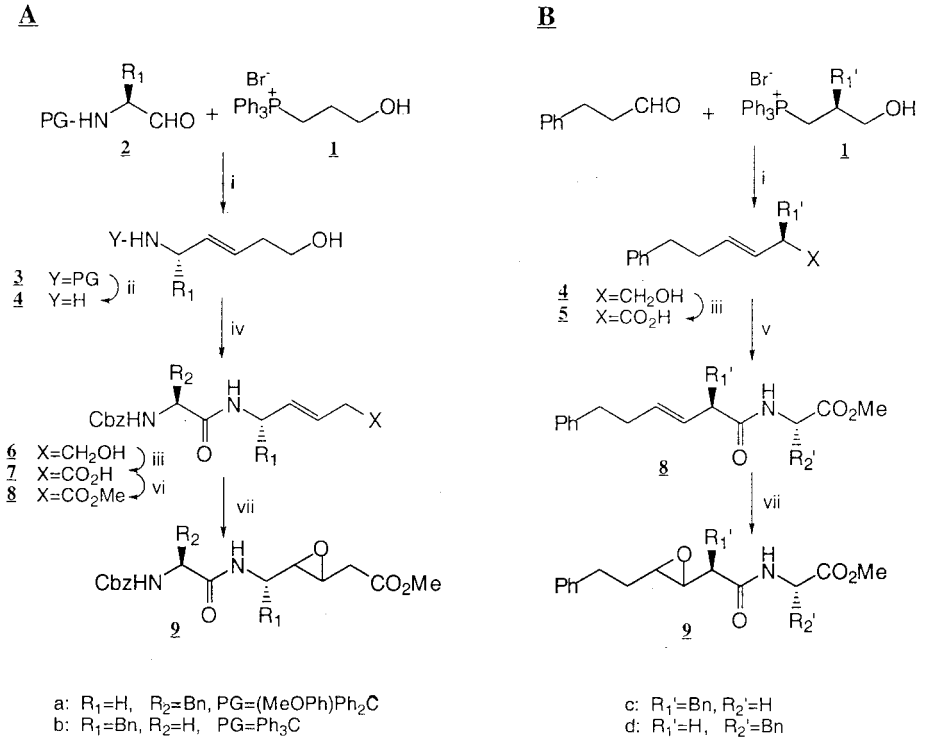
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00036-3

derived from the bulky substituted phenylalanine. The other two amino acids in each peptide olefin are either the unsubstituted glycine or an unsubstituted alkane (Scheme 1). Therefore, the effect of each individual chiral center in the four possible positions, P_2–P'_2, on the stereoselectivity of the epoxidation reaction could be studied.

The olefin dipeptide unit was prepared by the Wittig reaction between N-protected α-amino aldehydes (for the P_2 and P_1 chiral center analogs) or a simple non-chiral aldehyde (for the P'_1 and P'_2 analogs) and phosphonium salts corresponding to the C-terminal amino acid of the olefin dipeptide isostere (Scheme 2). These were either glycine or phenylalanine derivatives. The former (**1a**) was prepared, in quantitative yield (after crystallization), from bromopropanol and triphenyl phosphine. The latter (**1c**) was prepared in four steps from diethyl benzylmalonate (via the corresponding diol, mono tosylate and bromo alcohol), in moderate yield. For peptide olefins bearing P'_1 and P'_2 substituents, the appropriate phosphonium ylide was condensed with 3-phenylpropanal, thus mimicking the amino acid phenylalanine but excluding its amino group and chirality.

The key aldehyde for the synthesis of the P_2 peptide olefin isostere **8a**, N-protected glycinal (**2a**), was prepared in two ways: glycine methyl ester was protected, in 90% yield, by either trityl chloride or *p*-anisylchlorodiphenylmethane. These protecting groups enabled the following Wittig reaction to proceed in good yield.[5d] The ester functionality was then reduced by DIBALH directly to the desired aldehyde (60% yield). Alternatively, aminoethanol was similarly N-protected (81% yield), followed by Swern oxidation ($(COCl)_2$, DMSO, 60% yield). The aldehyde was reacted with the phosphonium ylide of 3-hydroxypropyl triphenylphosphonium bromide (**1a**), to give a 1.6:1 *trans*/*cis* mixture of olefin **3a** in 47% yield. Standard deprotection (giving **4a**), N-terminal coupling to N-Cbz-phenylalanine (giving **6a**), Jones' oxidation to the C-terminal carboxylic acid **7a** (57% yield) and esterification (52% yield) provided the P_2 peptide olefin analog Cbz-Phe-GlyΨ[CH=CH]-GlyOMe (**8a**, Scheme 2A). For the P_1 peptide olefin **8b** (Cbz-Gly-PheΨ[CH=CH]GlyOMe), N-trityl-phenylalaninal (**2b**) was prepared from phenylalanine methyl ester via protection–reduction–oxidation sequence, as previously described.[5d] It was reacted with the same ylide, derived from 3-hydroxypropyl triphenylphosphonium bromide, yielding a 1.6:1 *cis*/*trans* mixture of the olefin **3b** in 60% yield. Deprotection of the amino group (giving **4b**, 78% yield), coupling with N-Cbz-glycine (giving **6b**, 60% yiled), Jones' oxidation to **7b** (27% yield) and esterification (76% yield) completed the synthesis of the tripeptide P_1 olefin analog **8b** (Scheme 2A). The P'_1 peptide olefin **8c** ($PhCH_2CH_2$-Ψ[CH=CH]Phe-GlyOMe) was prepared in a few steps, starting with 3-phenylpropanal and the ylide of the phenylalanine phosphonium salt analog **1c**. The Wittig reaction afforded hydroxy olefin **4c** in low (24%) yield. The reason for the difficulty of this reaction is unclear and no optimization experiments were carried out. It was followed by Jones' oxidation (yielding **5c**, 50% yield) and coupling (in 43% yield)—with glycine methyl ester (Scheme 2B). The P'_2 peptide olefin **8d** ($PhCH_2CH_2$-Ψ[CH=CH]Gly-PheOMe) was prepared by the Wittig reaction between the same aldehyde (3-phenylpropanal) and the phosphonium ylide of 3-hydroxypropyl triphenylphosphonium bromide **1a** (78% yield of **4d**, 1.2:1 *trans*/*cis* ratio), followed by Jones' oxidation (yielding **5d**, 87% yield) and coupling with phenylalanine methyl ester (58% yield, Scheme 2B).



Scheme 2. Synthesis of peptidyl epoxides. Reagents: (i) BuLi, THF; (ii) HCl, acetone; (iii) CrO_3, H_2SO_4; (iv) Cbz-(R_2)amino acid, DCC, THF; (v) (R'_2) amino acid methyl ester, DCC or CDI, THF; (vi) CH_2N_2, ether; (vii) mCPBA, CH_2Cl_2.

Table 1. The induced chirality exerted by the P_2–P'_2 chiral centers on the epoxidation reaction

Position	Peptidyl epoxide	Isomeric ratio[a]	
		trans Epoxide (major/minor)	*cis* Epoxide (major/minor)
P_2	Cbz-Phe-Gly-epoxy-GlyOMe	1.09	1.22
P_1	Cbz-Gly-Phe-epoxy-GlyOMe	>30[b]	>30[b]
P'_1	$PhCH_2CH_2$-epoxy-Phe-GlyOMe	1.9	4.5
P'_2	$PhCH_2CH_2$-epoxy-Gly-PheOMe	1.10	1.08

[a] Calculated from 600 MHz ^{1}H NMR or 150 MHz ^{13}C NMR spectra of the crude reaction products.
[b] Only one isomer was detected by NMR.

The epoxidation reaction

The four olefins, **8a**–**d**, were treated with mCPBA, yielding the corresponding epoxides **9a**–**d** in moderate to good yield (typically 50–90%). In most cases, the mixture of *trans* and *cis* olefins was not separated prior to the epoxidation reaction, and the mixture of the crude epoxides (containing up to four isomers) was analyzed by 600 MHz ^{1}H NMR or (150 MHz) ^{13}C NMR spectroscopy (Table 1).

Discussion

Synthesis

A variety of synthetic approaches were applied for the synthesis of olefin dipeptide isosteres.[6a,10] In the present study we utilized the Wittig reaction with N-protected α-amino aldehydes. Racemization at C_α of α-amino aldehydes during Wittig reactions is of concern. Nevertheless, our previous experience shows that this can be avoided under careful experimental conditions.[5d] Furthermore, the present study concentrates on the epoxidation reaction of peptidyl olefins that bear a single chiral center. Therefore, racemization at this center will not affect the analysis of the stereochemical outcome of the epoxidation reaction in terms of relative stereochemistry. The Wittig reaction yields both *trans* and *cis* olefins. Therefore, we were able to determine the stereochemistry of the epoxidation reaction of both isomers. The dipeptide olefin can then be coupled on both amino and carboxy termini to the appropriately protected amino acids or peptides to form the desired peptide olefin.

The Wittig reaction yields a mixture of *trans* and *cis* isomers. This ratio could be controlled, to a limited degree, by the reaction conditions (molar amount of the base, its cation nature, side-chain substitution on the phosphonium salt).[11] In all the Wittig reactions disscussed in this work, the phosphonium ylide (**1**) contained an unprotected γ-hydroxy substituent and two molar equivalents of BuLi were used as a base. Therefore, a '*trans* selective' reaction was expected. Indeed, three of the four reactions yielded an excess of the *trans* isomer (1.2–2.4:1 *trans*/*cis* ratio) and only one reaction yielded a moderate (1.6:1) excess of the *cis* isomer. To demonstrate the '*cis* selective' Wittig protocol, an O-silyl phosphonium salt **1e** was prepared from the corresponding bromopropyl silyl ether. It was reacted with 3-phenyl propanal, using only one molar equivalent of BuLi. As expected, this reaction afforded the corresponding olefin **4e** in a 8.5:1 *cis*/*trans* ratio. Efficient deprotection afforded the dipeptide olefin **4d** in high *cis*/*trans* ratio.

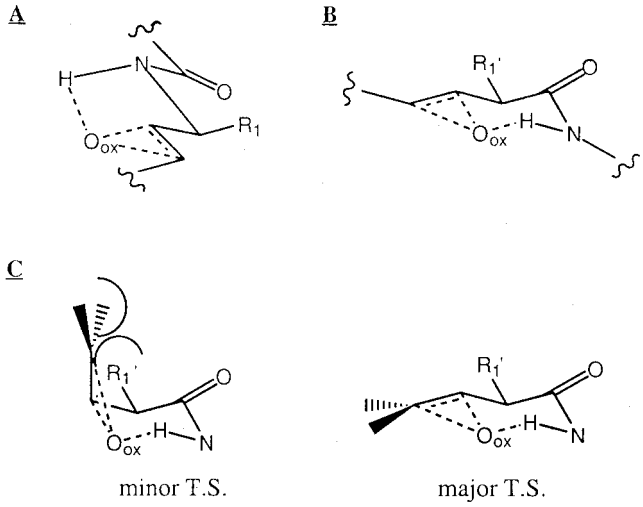
Stereoselectivity

The data clearly demonstrates that a chiral center four bonds away from the olefin (the P_2 and P'_2 analogs **8a** and **8d**) has a negligible chiral induction on the epoxidation reaction. The P'_1 olefin analog, $PhCH_2CH_2$-Ψ[CH=CH]Phe-GlyOMe (**8c**) exhibited only a poor (31% de in the *trans* isomer) to moderate (64% de in the *cis* isomer) stereoselectivity of the epoxidation reaction (see below). It is only the P_1 analog, Cbz-Gly-PheΨ[CH=CH]GlyOMe (**8b**), that undergoes a highly stereoselective epoxidation (only one diastereomer was detected), as was previously observed for similar terminal olefin[2,5d] and *endo* olefin[7] systems. This selectivity is exhibited both for the *trans* and the *cis* olefins. We tentatively assigned a *threo* relative configuration for their product epoxides **9b** ([3*R*,4*R*]-3,4-*trans* epoxy and [3*S*,4*R*]-3,4-*cis* epoxy). This assignment is based on the known stereoselectivity of this epoxidation reaction on terminal olefins[5d,k] and a similar *endo* olefin,[7] and on comparison with published data for a similar epoxide.[7]

Furthermore, we assigned the major isomer of all other epoxides as also bearing a relative *threo* configuration. (Note that the absolute configuration of the epoxidic carbons of the P_1 and P_2 epoxides, **9b** and **9a**, is the opposite of the corresponding carbons of the corresponding isomers of the P'_1 and P'_2 epoxides, **9c** and **9d**.) This assignment is supported by the ^{1}H NMR spectra of the different isomers. In all cases, the same epoxidic proton (H_3 in the P_1 and P_2 peptidyl epoxides and H_6 in the P'_1 and P'_2 epoxides) of the major isomer resonates at lower field than the corresponding proton of the minor isomer. The same trend was observed previously both by us[1a,5e] and by others.[7]

The results presented here emphasize that only the chiral center of the P_1 amino acid exerts a significant chiral induction on the epoxidation of peptidyl olefin isosteres. The P'_1 analog has a minor effect, and the effect diminishes completely as the chiral center is removed further away from the double bond to be epoxidized. These results are in good agreement with the trend observed by Jenmalm et al.[7] However, it should be emphasized that in the present work we analyzed the isolated effect of a chiral center at the P'_1 position, while Jenmalm and co-workers measured a cooperative effect of two adjacent chiral centers.

The present set of epoxidation experiments also clearly demonstrate that the stereoselectivity observed in the epoxidation reaction is not due to a simple steric effect, but rather stems from selective complexation (H-bonding) of the amide functionality with the incoming peracid.[5d,12] This is



Scheme 3. Proposed transition states for the epoxidation of P_1 (A) and P'_1 (B) peptidyl olefins. The different degree of stereoselectivity for the *trans* and *cis* isomers of the P'_1 peptidyl olefin can also be explained in terms of T.S. stability (C).

evident from the fact that although in both the P_1 and the P'_1 analogs the chiral center is one C–C bond away from the olefin, the selectivity it induces is markedly different. This difference may be explained in terms of the stability of the transition state of the 'complexed' epoxidation reaction; whereas the epoxidation of the P_1 peptidyl olefin (**8b**) features a five-membered ring transition state (Scheme 3A),[5d,12] the P'_1 peptidyl olefin (**8c**) should undergo complexed epoxidation via a six-membered ring transition state (Scheme 3B). While the former has two partially sp^2 hybridized atoms (the amide nitrogen and the olefin carbon), the latter has as many as three partially sp^2 hybridized atoms (the amide nitrogen and carbon and the olefin carbon). Therefore, it is expected that the five-membered ring transition state of the former reaction is more stable than the six-membered ring transition state of the latter, and therefore contributes more to the stereoselectivity of the overall epoxidation reaction.

The different stereoselectivity exhibited by the *trans* and *cis* P'_1 olefins is also interesting. While epoxidation of the former proceeds with only 31% de, the latter yields the two epoxides in 64% de. This difference may be explained in terms of the relative stability of the two epoxidation transition states of each of the isomers. The energetic difference between the *threo* (major) and *erythro* (minor) transition states of the *cis* isomer is larger than that of the *trans* isomer due to steric repulsion between the R'_1 side chain and the olefinic substituent (Scheme 3C).

Experimental

General

^1H and ^{13}C NMR spectra were recorded at 600 or 300 MHz and 150 or 75 MHz, respectively, in $CDCl_3$, unless otherwise specified. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or relative to solvent resonance in other solvents. ^1H NMR assignments were supported by homonuclear decoupling or homonuclear COSY experiments, while ^{13}C NMR assignments were supported by off-resonance heteronuclear decoupling, DEPT or 2-D hetero COSY experiments. Mass spectra were recorded in DCI mode with methane as the reagent gas, unless otherwise indicated. TLC was performed on E. Merck 0.2 mm precoated silica gel F-254 plates, and viewed by phosphomolybdic acid or Cl_2/KI-tolidine.[13] Chromatography refers to flash column chromatography,[14] carried out on silica gel 60 (230–400 mesh ASTM, E. Merck). Anhydrous solvents were dried and freshly distilled (THF and toluene from sodium/benzophenone, and CH_2Cl_2 from $CaCl_2$).

Phosphonium salts

$(Ph)_3P^+(CH_2)_3OH\ Br^-$ (1a). $(Ph)_3P$ (9.8 g, 37.4 mmol) was heated to 120°C under argon atmosphere. Then 3-bromo-1-propanol (5.2 g, 37.4 mmol) was added. After 5 min, a white precipitate was formed. After heating for additional 10 min, the solid was dissolved in EtOH (30 ml) and ether was added for crystallization. The crystals were filtered and washed with ether, affording 15.1 g of the phosphonium salt (96% yield). Mp 229–230°C. ^1H NMR: 1.84 (m, 2H, $CH_2CH_2CH_2$); 3.82 (m, 4H, PCH_2, CH_2O); 7.75 (m, 15H, Ph_3). ^{13}C NMR: 20.36 (d, J=52.0 Hz, PCH_2); 25, 96 (d, J=4.2 Hz, $CH_2CH_2CH_2$); 60.31 (d, J=16.9 Hz, CH_2O); 118.54 (d, J=85 Hz), 131.54 (d, J=12 Hz), 133.56 (d, J=9.5 Hz), 135.05 (d, J=2.5 Hz) (Ph). MS 262: (Ph_3P^+, 100), 243 (M−HBr−Ph, 57), 223 (44), 183 (58), 178 (45), 168 (63), 141 (64), 115 (48). HRMS for $C_{15}H_{16}OP$ (M−HBr−Ph): calcd 243.0939, found 243.0950.

$PhCH_2CH(CH_2OH)_2$. Diethyl benzyl malonate (50 ml, 215 mmol) was added dropwise (within 1–2 h) to a refluxing suspension of $LiAlH_4$ (5.63 g, 150 mmol) in dry THF (250 ml). After further 20 h in reflux, the reaction mixture was cooled to rt and carefully treated with 0.5 M HCl (70 ml). Extraction with ether (5×200 ml) and evaporation of the organic phase afforded the diol as white, thick oil, which solidified on standing (19.4 g, 117 mmol). Further

continuous extraction (in a commercial liquid/liquid continuous extractor) overnight afforded additional 3.2 g (19 mmol) of the product (total 22.6 g, 63% yield). A sample was crystallized from ether/hexane, mp 58–60°C. ^{1}H NMR: 2.00 (m, 1H, CH); 2.61 (d, J=7.5 Hz, 2H, $PhCH_2$); 3.64 (dd, J=10.5, 6.9 Hz, 2H, CH_2OH); 3.77 (dd, J=10.6, 3.7 Hz, 2H, CH_2OH); 3.91 (bs, 2H, OH); 7.15–7.30 (m, 5H, Ph). ^{13}C NMR: 34.05 ($PhCH_2$); 43.81 (CH); 63.97 (CH_2OH); 125.90, 128.23, 128.83, 139.75 (Ph). MS: 167 (MH^+), 166 (M^+), 148 (54), 130 (24), 118 (26), 117 (88), 104 (25), 92 (44), 91 (100). HRMS for $C_{10}H_{15}O_2$: calcd 167.1072, found 167.1062.

$TsOCH_2CH(CH_2Ph)CH_2OH$. Pyridine (4.78 ml, 59 mmol) was added to a solution of 2-benzyl-1,3-propanediol (9.83 g, 59 mmol) and TsCl (11.66 g, 61 mmol) in chloroform (75 ml). After 5 days of stirring at rt, HCl (conc., 20 ml) was added and the phases separated. The organic phase was washed with $NaHCO_3$ (sat. aq. solution) and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The mono tosyl ester product was purified by chromatography (EtOAc/hexane 1:1), affording 12.28 g (65% yield). ^{1}H NMR: 2.07 (m, 1H, CH); 2.40 (s, 3H, CH_3); 2.55 (dd, J=13.8, 7.5 Hz, 1H, $PhCH_2$); 2.62 (dd, J=14.1, 7.5 Hz, 1H, $PhCH_2$); 3.51 (dd, J=11.1, 6.6 Hz, 1H, C*H*$_2$OH); 3.58 (dd, J=11.1, 5.1 Hz, 1H, C*H*$_2$OH); 3.97 (dd, J=9.9, 5.4 Hz, 1H, CH_2OTs); 4.06 (dd, J=9.8, 4.7 Hz, 1H, CH_2OTs); 7.02–7.24 (m, 5H, Ph); 7.29 (d, J=8.1 Hz, 2H, Ts); 7.74 (d, J=8.4 Hz, 2H, Ts). ^{13}C NMR: 21.34 (CH_3); 33.23 ($PhCH_2$); 42.23 (CH); 60.94 (CH_2O); 69.49 (CH_2OTs); 126.00, 127.60, 128.20, 128.74, 129.69, 132.31, 138.53, 144.72 (Ph). MS: 321 (MH^+, 91), 191 (25), 148 (58), 131 (100), 117 (38). HRMS for $C_{17}H_{21}O_4S$: calcd 321.1161, found 321.1164.

$BrCH_2CH(CH_2Ph)CH_2OH$. To a solution of the tosylate (10.7 g, 33.4 mmol) in toluene (50 ml) were added NaBr (14.8 g, 144 mmol in 50 ml of water) and tetrabutyl ammonium bromide (1.8 g, 5.6 mmol). After 6 days of reflux, the phases were separated, the aqueous phase extracted with toluene (50 ml) and the combined organic phase was washed successively with saturated $NaHCO_3$ aq. solution (100 ml) and brine (2×100 ml) and dried over $MgSO_4$. Filtration and evaporation afforded 5.0 g (21.8 mmol) of the bromo alcohol (65% yield). ^{1}H NMR: 2.24 (m, 1H, CH); 2.79 (d, J=6.4 Hz, 2H, CH_2Ph); 3.49 (dd, J=10.2, 5.0 Hz, 1H, CH_2Br); 3.65 (dd, J=10.3, 4.2 Hz, 1H, CH_2Br); 3.75 (dd, J=10.9, 7.2 Hz, 1H, C*H*$_2$OH); 3.81 (dd, J=10.9, 5.2 Hz, 1H, C*H*$_2$OH); 7.20–7.45 (m, 5H, Ph). ^{13}C NMR: 35.25 (CH_2); 35.41 (CH_2Br); 43.84 (CH); 63.01 (CH_2O); 126.20, 128.37, 128.94, 138.86 (Ph). MS: 228, 230 (M^+), 210, 212 (6), 131 (100), 117 (32), 105 (51), 91 (85). HRMS for $C_{10}H_{13}{}^{79}BrO$: calcd 228.0150, found 228.0169.

$Ph_3P^+CH_2CH(CH_2Ph)CH_2OH\ Br^-$ (1c). Prepared as described above for **1a** in 50% yield. It was obtained as white crystalline material. ^{1}H NMR: 2.12–2.21 (m, 1H, CH); 2.33 (dd, J=13.7, 6.3 Hz, 1H, CH_2Ph); 2.63 (ddd, J=13.7, 8.4, 1.5 Hz, 1H, CH_2Ph); 2.84 (ddd, J=16.2, 12.9, 6.0 Hz, 1H, PCH_2); 3.50 (ddd, J=11.6, 3.4, 2.3 Hz, 1H, CH_2O); 3.55 (dd, J=11.7, 6.2 Hz, 1H, CH_2O); 4.70 (ddd, J=16.1, 14.0, 4.8 Hz, 1H, PCH_2); 6.87 (dd, J=7.8, 1.9 Hz, 2H, *o*-*Ph*CH_2); 7.20 (m, 3H, m, *p*-*Ph*CH_2); 7.66–7.80 (m, 15H, Ph_3P). ^{13}C NMR: 23.67 (d, J=54.8 Hz, PCH_2); 38.23 (d, J=4.0 Hz, CH); 38.73 (d, J=6.0 Hz, $PhCH_2$); 62.68 (d, J=7.1 Hz, CH_2O); 118.70 (d, J=85.2 Hz, *i*-Ph_3P); 126.48 (*p*-*Ph*CH_2); 128.56 (*m*-*Ph*CH_2); 129.12 (*o*-*Ph*CH_2); 130.38 (d, J=6.5 Hz, *m*-Ph_3P); 133.67 (d, J=9.9 Hz, *o*-Ph_3P); 134.90 (d, J=2 Hz, *p*-Ph_3P); 138.49 (*i*-*Ph*CH_2). MS: 333 (M−HBr−Ph, 100), 262 (Ph_3P^+, 100), 201 (18), 183 (23), 91 (16). HRMS for $C_{22}H_{22}OP$ (M−HBr−Ph): calcd 333.1408, found 333.1394.

$(Ph)_3P^+(CH_2)_3OSi(Me)_2{}^tBu\ Br^-$ (1e). $Br(CH_2)_3OSi(Me)_2{}^tBu$ (9.5 g, 37.5 mmol) and $(Ph)_3P$ (9.8 g, 37.4 mmol) were refluxed in cyclohexane overnight. The white precipitate was filtered and washed with hexane, affording the phosphonium salt (7.3 g, 38% yield). ^{1}H NMR: 0.04 (s, 6H, $SiCH_3$); 0.867 (s, 9H, CCH_3); 1.91 (m, 2H, $CH_2CH_2CH_2$); 3.74 (m, 2H, PCH_2); 3.82 (bt, J=14.8 Hz, 2H, CH_2O); 7.32, 7.69–7.87 (m, 15H, Ph_3). ^{13}C NMR: −4.44 ($SiCH_3$); 19.03 (C); 21.04 (d, J=57 Hz, PCH_2); 26.53 (CCH_3); 26.81 ($CH_2CH_2CH_2$); 61.39 (d, J=15 Hz, CH_2O); 119.39 (d, J=84 Hz), 130.91, 134.14 (d, J=9 Hz), 135.66 (Ph).

N-protection

Protection of glycine methyl ester or amino ethanol with *p*-anisylchlorodiphenylmethane was carried out by the method applied for simple tritylation, according to published procedure.[15]

$(MeOPh)(Ph)_2CNHCH_2COOMe$. 89% yield. ^{1}H NMR: 3.13 (s, 2H, CH_2); 3.55 (s, 3H, CO_2Me); 3.72 (s, 3H, PhOMe); 6.77–7.48 (m, 14H, Ph). ^{13}C NMR: 45.69 (CH_2); 51.57 (COO*Me*); 55.01 (PhO*Me*); 70.17 (C); 113.12, 126.32, 127.81, 128.40, 129.72, 137.34, 145.53, 157.93 (Ph); 172.62 (CO_2). MS: 362 (MH^+, 4), 284 (57), 273 (100). HRMS for $C_{23}H_{24}NO_3$: calcd 362.1756, found 362.1755.

$(MeOPh)(Ph)_2CNHCH_2CH_2OH$. 81% yield. ^{1}H NMR: 2.36 (t, J=6.1 Hz, 2H, N*CH*$_2$); 3.68 (t, J=6.1 Hz, 2H, CH_2O); 3.79 (s, 3H, Me); 6.8–7.5 (m, 14H, Ph). ^{13}C NMR: 45.88 (NCH_2); 54.96 (Me); 62.24 (CH_2O); 69.96 (C); 112.99, 126.07, 127.64, 128.40, 129.66, 137.97, 146.08, 157.74 (Ph). MS: 333 (M^+), 273 (100), 256 (36), 165 (71), 152 (39). HRMS for $C_{22}H_{23}NO_2$: calcd 333.1729, found 333.1724.

N-protected α-amino aldehyde could be obtained either by standard DIBAH reduction[5d] of the methyl ester (60% yield) or by Swern oxidation[16] of the corresponding alcohol in 60% yield. It was transferred to the next reaction without further purification.

$(MeOPh)(Ph)_2CNHCH_2CHO$ (2a). ^{1}H NMR: 2.33 (s, 2H, CH_2); 3.74 (s, 3H, Me); 6.75–7.43 (m, 14H, Ph); 9.5 (s, 1H, CHO). ^{13}C NMR: 21.39 (CH_2); 55.11 (Me); 70.14 (C); 113.24, 126.49, 127.86, 128.43, 129.76, 137.41, 145.61, 158.07 (Ph); 199.27 (CHO).

$Ph_3CNHCH(CH_2Ph)CHO$ (2b). Prepared as previously described.[5d]

Wittig reaction

To a suspension of the phosphonium salt (7.2 mmol) in THF (50 ml) at 0°C under argon atmosphere, was added BuLi (1.6 M in hexane, 14 mmol). The solution was stirred for 30 min, followed by addition of the aldehyde (3.5 mmol, except for phenyl propionaldehyde where 8 mmol were taken) in THF (5 ml). Stirring was continued at rt overnight. Excess phosphonium salt was precipitated with hexane (~30 ml) and filtered off. CH_2Cl_2 (80 ml) was added and extracted with water (3×80 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness.

(MeOPh)(Ph)$_2$CNHCH$_2$CH=CHCH$_2$CH$_2$OH (3a). 1.6:1 *trans*/*cis* mixture, which was separated by chromatography (1:4 ether/hexane), 47% yield.

cis Isomer: ^{1}H NMR: 2.07 (dt, *J*=7.5, 6.3 Hz, 2H, C*H*$_2$CH$_2$O); 2.81 (d, *J*=6.4 Hz, 2H, NCH$_2$); 3.49 (t, *J*=6.3 Hz, 2H, CH$_2$O); 3.74 (s, 3H, MeO); 5.45 (dt, *J*=10.8, 7.5 Hz, 1H, =CH); 5.71 (dt, *J*=10.7, 6.9 Hz, 1H, CH=); 7.12–7.47 (m, 14H, Ph). ^{13}C NMR: 30.74 (*C*H$_2$CH$_2$O); 40.36 (NCH$_2$); 55.08 (MeO); 61.65 (CH$_2$O); 70.53 ((Ph)$_3$*C*); 113.05, 126.18, 127.74, 127.87, 128.49, 128.74, 129.75, 137.94, 146.04, 157.79 (C=C, Ph). MS: 374 (MH$^+$, 8), 296 (7), 273 (100), 197 (11), 167 (10.2). HRMS for $C_{25}H_{28}NO_2$: calcd 374.2120, found 374.2100.

trans Isomer: ^{1}H NMR: 2.25 (q, *J*=6.2 Hz, 2H, C*H*$_2$CH$_2$O); 2.73 (d, *J*=5.4 Hz, 2H, NCH$_2$); 3.58 (t, *J*=6.3 Hz, 2H, CH$_2$O); 3.72 (s, 3H, MeO); 5.53 (dt, *J*=15.3, 6.6 Hz, 1H, =CH); 5.68 (dt, *J*=15.3, 5.5 Hz, 1H, CH=); 7.3–7.45 (m, 14H, Ph). ^{13}C NMR: 35.69 (*C*H$_2$CH$_2$O); 45.80 (NCH$_2$); 55.03 (MeO); 61.75 (CH$_2$O); 70.25 ((Ph)$_3$*C*); 113.00, 126.10, 126.16, 127.09, 127.69, 128.40, 128.45, 129.72, 129.65, 131.86, 138.09, 146.19, 157.71 (C=C, Ph). MS: 374 (MH$^+$, 10), 296 (9), 273 (100), 197 (20), 167 (13). HRMS for $C_{25}H_{28}NO_2$: calcd 374.2120, found 374.2160.

(Ph)$_3$CNHCH(CH$_2$Ph)CH=CHCH$_2$CH$_2$OH (3b). 1.6:1 *cis*/*trans* mixture (after chromatography, 1:4 ether/hexane), 60% yield. ^{1}H NMR: 1.39 (dddt, *J*=14.7, 7.3, 6.6, 1.5 Hz, 1H, C*H*$_2$CH$_2$O (*cis*)); 1.67 (dddt, *J*=14.7, 7.3, 6.6, 1.7 Hz, 1H, C*H*$_2$CH$_2$O (*cis*)); 1.94 (dt, *J*=7.4, 5.9 Hz, 2H, C*H*$_2$CH$_2$O (*trans*)); 2.19 (dd, *J*=12.5, 8.6 Hz, 1H, CH$_2$Ph (*cis*)); 2.23 (dd, *J*=12.7, 4.7 Hz, 1H, CH$_2$Ph (*cis*)); 2.30 (dd, *J*=13.0, 8.4 Hz, 1H, CH$_2$Ph (*trans*)); 2.48 (dd, *J*=13.0, 5.4 Hz, 1H, CH$_2$Ph (*trans*)); 3.00 (dt, *J*=10.4, 6.6 Hz, 1H, CH$_2$O (*cis*)); 3.11 (dt, *J*=10.4, 6.5 Hz, 1H, CH$_2$O (*cis*)); 3.17 (ddd, *J*=8.5, 8.0, 5.4 Hz, 1H, NCH (*trans*)); 3.27 (dt, *J*=10.8, 5.9 Hz, 1H, CH$_2$O (*trans*)); 3.34 (dt, *J*=10.7, 5.8 Hz, 1H, CH$_2$O (*trans*)); 3.47 (td, *J*=9.0, 4.7 Hz, 1H, NCH (*cis*)); 4.78 (dt, *J*=15.2, 7.4 Hz, 1H, =CH (*trans*)); 5.01 (dt, *J*=10.9, 7.3 Hz, 1H, =CH (*cis*)); 5.20 (ddt, *J*=15.4, 8.0, 1.0 Hz, 1H, CH= (*trans*)); 5.34 (ddt, *J*=11.0, 9.4, 1.6 Hz, 1H, CH= (*cis*)); 6.8–7.6 (m, 10H, Ph (*cis*+*trans*)). ^{13}C NMR: 31.19 (*C*H$_2$CH$_2$O (*cis*)); 35.70 (*C*H$_2$CH$_2$O (*trans*)); 43.85 (CH$_2$Ph (*cis*)); 44.14 (CH$_2$Ph (*trans*)); 52.95 (NCH (*cis*)); 57.37 (NCH (*trans*)); 61.67 (CH$_2$O (*trans*)); 61.97 (CH$_2$O (*cis*)); 71.57 (Ph$_3$*C*) (*trans*)); 71.75 (Ph$_3$*C*) (*cis*)); 124.00 (CH= (*cis*)); 125.59 (CH= (*trans*)); 125.94, 126.04, 126.31, 126.55, 127.64, 127.72, 128.02, 129.01, 129.61, 129.89 (Ph); 136.18 (CH= (*cis*)); 136.87 (CH= (*trans*)); 138.75, 138.92, 146.77, 146.89 (Ph). MS (EI): 433 (M$^+$), 342 (6), 243 (100), 165 (20), 91 (7). HRMS for $C_{31}H_{31}NO$: calcd 433.2406, found 433.2494.

PhCH$_2$CH$_2$CH=CHCH(CH$_2$Ph)CH$_2$OH (4c). 2.4:1 *trans*/*cis* mixture (after chromatography, 3:7 ether/hexane), 24% yield. ^{1}H NMR: 2.12 (ddd, *J*=7.1, 4.1, 1.7 Hz, 1H, PhC*H*$_2$CH$_2$ (*trans*)); 2.17 (ddd, *J*=7.1, 2.5, 1.6 Hz, 1H, PhC*H*$_2$CH$_2$ (*trans*)); 2.26 (m, 2H, PhCH$_2$C*H*$_2$ (*trans*)); 2.41 (m, 1H, CH (*trans*)); 2.60 (m, 2H, CHC*H*$_2$Ph); 2.75 (m, 1H, CH (*cis*)); 3.30 (dd, *J*=10.7, 7.4 Hz, 1H, CH$_2$O (*trans*)); 3.31 (dd, *J*=10.5, 7.2 Hz, 1H, CH$_2$O (*cis*)); 3.45 (dd, *J*=10.5, 5.1 Hz, 1H, CH$_2$O (*trans*)); 3.45 (dd, *J*=10.5, 5.5 Hz, 1H, CH$_2$O (*cis*)); 5.14 (ddt, *J*=11.0, 9.8, 1.2 Hz, 1H, =CH (*cis*)); 5.18 (ddt, *J*=15.5, 8.3, 1.3 Hz, 1H, =CH (*trans*)); 5.41 (dtd, *J*=15.3, 6.7, 0.7 Hz, 1H, CH= (*trans*)); 5.49 (dtd, *J*=11.1, 7.2, 0.6 Hz, 1H, CH= (*cis*)); 7.23–7.40 (m, 10H, Ph). ^{13}C NMR: 29.35 (PhCH$_2$*C*H$_2$ (*cis*)); 34.20 (PhCH$_2$*C*H$_2$ (*trans*)); 35.48 (PhCH$_2$ (*cis*)); 35.57 (PhCH$_2$ (*trans*)); 37.57 (PhCH$_2$ (*trans*)); 37.84 (PhCH$_2$ (*cis*)); 42.26 (CH (*cis*)); 46.85 (CH (*trans*)); 64.91 (CH$_2$O (*trans*)); 65.56 (CH$_2$O (*cis*)); 125.66, 125.73, 128.00, 128.07, 128.12, 128.31, 128.77, 129.00 (Ph); 130.44 (CH= (*cis*)); 131.20 (CH= (*trans*)); 131.98 (CH= (*cis*)); 132.33 (CH= (*trans*)); 139.72 (Ph (*trans*)); 139.80 (Ph (*cis*)); 141.50 (Ph (*trans*)); 141.58 (Ph (*cis*)). MS: 267 (MH$^+$, 3.5), 249 (100), 171 (58), 145 (58), 131 (36). HRMS for $C_{31}H_{31}NO$: calcd 267.1749, found 267.1764.

PhCH$_2$CH$_2$CH=CHCH$_2$CH$_2$OH (4d). 1.2:1 *trans*/*cis* mixture (after chromatography, 1:1 CH_2Cl_2/hexane), 78% yield. ^{1}H NMR: 2.23 (q, *J*=6.9 Hz, 2H, C*H*$_2$CH$_2$O (*trans*)); 2.24 (q, *J*=6.8 Hz, 2H, C*H*$_2$CH$_2$O (*cis*)); 2.35 (q, *J*=7.5 Hz, 2H PhCH$_2$C*H*$_2$ (*trans*)); 2.39 (q, *J*=7.5 Hz, 2H, PhCH$_2$C*H*$_2$ (*cis*)); 2.67 (t, *J*=7.8 Hz, 2H, PhCH$_2$ (*trans*)); 2.69 (t, *J*=7.5 Hz, 2H, PhCH$_2$ (*cis*)); 3.53 (t, *J*=6.6 Hz, 2H, CH$_2$O (*trans*)); 3.56 (t, *J*=6.3 Hz, 2H, CH$_2$O (*cis*)); 5.35 (dtt, *J*=15.3, 6.9, 1.2 Hz, 1H, =CH (*trans*)): 5.38 (dtt, *J*=10.8, 7.5, 1.3 Hz, 1H, =CH (*cis*)); 5.56 (dtt, *J*=15.0, 6.6, 1.3 Hz, 1H, CH= (*trans*)); 5.58 (dtt, *J*=10.8, 7.2, 1.5 Hz, 1H, CH= (*cis*)); 7.14–7.31 (m, 5H, Ph). ^{13}C NMR: 29.20 (PhCH$_2$*C*H$_2$ (*cis*)); 30.68 (*C*H$_2$CH$_2$O (*cis*)); 34.37 ((PhCH$_2$*C*H$_2$ (*trans*)); 35.72 (PhCH$_2$ (*trans*)); 35.76 (PhCH$_2$ (*cis*)); 35.86 (*C*H$_2$CH$_2$O (*trans*)); 61.82 (CH$_2$O (*trans*)); 62.08 (CH$_2$O (*cis*)); 125.78 (=CH (*cis*)); 126.73 (=CH (*trans*)); 125.97, 128.23, 128.41, 128.45 (Ph); 131.93 (CH= (*cis*)); 133.03 (CH= (*trans*)); 141.73 (Ph). MS (DCI-*i*-butane): 177 (MH$^+$), 159 (MH$^+$−H$_2$O), 131 (M$^+$−C$_2$H$_4$OH), 91 ($C_7H_7^+$).

Alternatively, the same hydroxy olefin could be obtained by Wittig reaction (as described above) with O-protected phosphonium salt **1e**, followed by deprotection.

PhCH$_2$CH$_2$CH=CHCH$_2$CH$_2$OSi(Me)$_2$^{t}Bu (4e). 8.5:1 *cis*/*trans* mixture (after chromatography, 1:20 CH_2Cl_2/hexane), 41% yield. ^{1}H NMR: 0.033 (s, 6H, SiCH$_3$ (*cis*)); 0.034 (s, 6H, SiCH$_3$ (*trans*)); 1.00 (s, 9H, CCH$_3$ (*cis*)); 1.01 (s, 9H, CCH$_3$ (*trans*)); 2.18 (q, *J*=6.9 Hz, 2H, C*H*$_2$CH$_2$O (*cis*)); 2.32 (q, *J*=7.7 Hz, 2H, PhCH$_2$C*H*$_2$ (*cis*)); 2.62 (t, *J*=7.7 Hz, 2H, PhCH$_2$ (*cis*)); 3.49 (t, *J*=7.0 Hz, 2H, CH$_2$O (*cis*)); 3.55 (t, *J*=6.9 Hz, 2H, CH$_2$O (*trans*)); 5.35 (dt,

J=10.8, 7.0 Hz, 1H, =CH (*cis*)); 5.45 (dt, J=10.8, 7.0 Hz, 1H, CH= (*cis*)); 7.11–7.25 (m, 5H, Ph). ^{13}C NMR: −5.24 ($SiCH_3$ (*cis*)); −4.68 ($SiCH_3$ (*trans*)); 18.37 (C); 25.97 (CCH_3); 29.26 (CH_2CH (*cis*)); 31.13 (CH_2CH (*cis*)); 34.52 (CH_2CH (*trans*)); 35.98 ($PhCH_2$); 36.28 (CH_2CH (*trans*); 62.90 (CH_2O (*cis*)); 63.29 (CH_2O (*trans*)); 125.77 (Ph); 126.49 (CH (*cis*)); 127.21 (CH (*trans*)); 128.25, 128.45 (Ph); 130.56 (CH (*cis*)); 131.54 (CH (*trans*)); 142.00 (Ph). MS: 291 (MH^+, 8), 275 (25), 233 (100), 159 (30), 117 (40), 91 (60), 75 (62).

$PhCH_2CH_2CH$=$CHCH_2CH_2OH$ (4d). $PhCH_2CH_2CH$=$CHCH_2CH_2OSi(Me)_2{}^tBu$ (240 mg, 0.83 mmol) was stirred with Bu_4NF (2.5 mmol) in THF (10 ml) for 1 h. Water (20 ml) was added and the solution extracted with CH_2Cl_2 (3×20 ml). The organic layer was extracted successively with water pH 2.5 and neutral water (20 ml each), dried over $MgSO_4$ and evaporated to dryness. Chromatography (1:1 CH_2Cl_2/hexane) afforded 124 mg of the free alcohol as a 8.3:1 *cis*/*trans* mixture (85% yield).

Removal of the N-protecting group

H_2NCH_2CH=$CHCH_2CH_2OH$·HCl (4a). The N-protected alcohol **3a** (370 mg, 1 mmol) was stirred with conc. HCl (3.1 mmol) in acetone (20 ml) at rt overnight. Then the acetone was evaporated and water (4 ml) and ether (4 ml) were added. After separation, the aqueous phase was extracted with ethyl acetate (2×10 ml). The product, in the aqueous phase, was transferred to the next reaction without further purification.

cis Isomer: ^{1}H NMR (D_2O): 2.47 (q, J=6.3 Hz, 2H, CH_2CH_2O); 3.73 (t, J=6.3 Hz, 2H, CH_2O); 3.81 (d, J=7 Hz, 2H, NCH_2); 5.76 (dt, J=11, 7.3 Hz, 1H, CH); 5.97 (dt, J=11, 7.5 Hz, 1H, CH). ^{13}C NMR: 34.86 (CH_2CH_2O); 41.53 (NCH_2); 61.05 (CH_2O); 123.40, 135.69 (C=C).

trans Isomer: ^{1}H NMR (D_2O): 2.60 (q, J=6.5 Hz, 2H, CH_2CH_2O); 3.85 (d, J=7 Hz, 2H, NCH_2); 3.92 (t, J=6.5 Hz, 2H, CH_2O); 5.93 (dt, J=15.5, 7.0 Hz, 1H, CH); 6.18 (dt, J=15.6, 7.4 Hz, 1H, CH). ^{13}C NMR: 29.81 (CH_2CH_2O); 36.19 (NCH_2); 60.54 (CH_2O); 122.23, 134.22 (C=C). MS: 102 (MH^+, 100), 85 (8), 84 (9), 70 (5). HRMS for $C_5H_{12}NO$: calcd 102.0919, found 102.0910.

$H_2NCH(CH_2Ph)CH$=$CHCH_2CH_2OH$ (4b). The N-protected alcohol **3b** (340 mg, 0.78 mmol) was refluxed with conc. HCl (1.7 mmol) in acetone (25 ml) for 4.5 h. Then CH_2Cl_2 (30 ml) was added and extracted with HCl 1 M (3×30 ml) and the layers were separated. The aqueous phase was adjusted to pH 9.5 (with solid Na_2CO_3) and extracted with ethyl acetate (3×50 ml). Drying ($MgSO_4$) and evaporation afforded the free amine as a 1.1:1 *trans*/*cis* mixture in 78% yield. ^{1}H NMR: 2.09 (dq, J=13.8, 5.1 Hz, 1H, CH_2CH_2O (*cis*)); 2.24 (q, J=6.2 Hz, 2H, CH_2CH_2O (*trans*)); 2.35 (obscured, 1H, CH_2CH_2O (*cis*)); 2.61 (dd, J=13.4, 8.0 Hz, 1H, CH_2Ph (*trans*)); 2.66 (dd, J=13.1, 7.7 Hz, 1H, CH_2Ph (*cis*)); 2.76 (dd, J=13.8, 8.4 Hz, 1H, CH_2Ph (*cis*)); 2.78 (dd, J=13.4, 8.0 Hz, 1H, CH_2Ph (*trans*)); 3.45 (ddd, J=10.5, 8.4, 5.0 Hz, 1H, CH_2O (*cis*)); 3.53 (dt, J=10.5, 5.5 Hz, 1H, CH_2O (*cis*)); 3.54 (td, J=5.7, 4.8 Hz, 1H, NCH (*trans*)); 3.56 (t, J=6.3 Hz, 2H, CH_2O (*trans*)); 3.84 (dt, J=13.7, 7.4 Hz, 1H, NCH (*cis*)); 5.46 (ddd, J=10.8, 6.0, 4.9 Hz, 1H, =CH (*cis*)); 5.50 (dd, J=10.8, 5.1 Hz, 1H, CH= (*cis*)); 5.51 (dt, J=15.3, 4.8 Hz, 1H, =CH (*trans*)); 5.55 (dd, J=15.3, 5.4 Hz, 1H, CH=(*trans*)); 7.16–7.29 (m, 5H, Ph). ^{13}C NMR: 30.95 (CH_2CH_2O (*trans*)); 35.62 (CH_2CH_2O (*cis*)); 44.38 (CH_2Ph (*cis*)); 44.59 (CH_2Ph (*trans*)); 49.52 (NCH (*trans*)); 54.79 (NCH (*cis*)); 60.92 (CH_2O (*trans*)); 61.35 (CH_2O (*cis*)); 126.28, 128.3, 129.26 (Ph); 126.89, 128.13 (CH=); 135.22 (CH= (*cis*)); 136.15 (CH= (*trans*)); 138.33 (Ph (*cis*)); 138.55 (Ph (*trans*)).

Coupling with Cbz-amino acid

N-Cbz-amino acid (0.87 mmol), DCC (0.89 mmol) and the amino alcohol or amino ester (0.77 mmol) (when the amino alcohol was presented as the hydrochloride salt in water, Na_2CO_3 was added to pH 9.5) were stirred in THF (5 ml) at rt overnight. The reaction mixture was filtered to remove the precipitation, CH_2Cl_2 (20 ml) was added and extracted successively with 1 M HCl, saturated Na_2CO_2 and water (20 ml each), dried on $MgSO_4$ and evaporated to dryness.

$PhCH_2OCONHCH(CH_2Ph)CONHCH_2CH$=$CHCH_2CH_2OH$ (6a). 20% Overall yield for the deprotection–coupling steps. Purification (and isomer separation) was carried out by chromatography (ethyl acetate/hexane 1:1).

cis Isomer: ^{1}H NMR: 2.26 (m, 2H, CH_2CH_2O); 3.01 (dd, J=13.4, 7.5 Hz, 1H, $CHCH_2Ph$); 3.08 (dd, J=13.5, 5.9 Hz, 1H, $CHCH_2Ph$); 3.57 (dd, J=10.5, 5.1 Hz, 1H, CH_2OH); 3.60 (dd, J=9.9, 3.7 Hz, 1H, CH_2OH); 3.74 (dd, J=14.4, 6.5 Hz, 1H, NCH_2); 3.79 (dd, J=14.2, 6.2 Hz, 1H, NCH_2); 4.32 (q, J=7.4 Hz, 1H, NCH); 5.07 (s, 2H, $PhCH_2O$); 5.41 (s, 1H, N*H*CH); 5.45 (dtt, J=10.7, 7.2, 1.3 Hz, 1H, CH=); 5.54 (dt, J=10.7, 7.9 Hz, 1H, =CH); 6.22 (s, 1H, N*H*CH_2); 7.19–7.36 (m, 10H, Ph). ^{13}C NMR: 30.54 (CH_2CH_2O); 36.18 (NCH_2); 38.76 ($CHCH_2Ph$); 56.40 (NCH); 61.26 (CH_2OH); 67.02 ($PhCH_2O$); 126.96, 127.26, 128.03, 128.22, 128.54, 128.65, 129.35, 130.71, 132.05, 132.11 (C=C, Ph); 156 (OCON); 170.65 (CON). MS: 383 (MH^+, 32), 339 (100), 275 (41), 257 (14), 191 (16). HRMS for $C_{22}H_{27}N_2O_4$: calcd 383.1971, found 383.1950.

trans Isomer: ^{1}H NMR: 2.20 (qd, J=6.4, 1 Hz, 2H, CH_2CH_2O); 3.03 (d, J=6.9 Hz, 2H, $CHCH_2Ph$); 3.58 (t, J=6.2 Hz, 2H, CH_2OH); 3.71 (t, J=5.4 Hz, 2H, NCH_2); 4.41 (q, J=8 Hz, 1H, NCH); 5.00 (d, J=12.3 Hz, 1H, $PhCH_2O$); 5.05 (d, J=12.3 Hz, 1H, $PhCH_2O$); 5.72 (d, J=7.6 Hz, 1H, N*H*CH); 5.35 (dtt, J=15.4, 5.8, 2 Hz, 1H, CH=); 5.44 (dt, J=15.4, 7 Hz, 1H, =CH); 6.42 (s, 1H, N*H*CH_2); 7.16–7.33 (m, 10H, Ph). ^{13}C NMR: 35.40 (CH_2CH_2O); 38.72 ($CHCH_2Ph$); 41.18 (NCH_2); 56.33 (NCH); 61.46 (CH_2OH); 66.92 ($PhCH_2O$); 126.87, 127.82, 127.87, 128.11, 128.44, 129.152, 129.27, 129.48, 129.85, 136.45 (C=C, Ph); 156.03 (OCON); 170.86 (CON). MS: 383 (MH^+, 31), 365 (9), 339 (100), 275 (40), 191 (8). HRMS for $C_{22}H_{27}N_2O_4$: calcd 383.1971, found 383.1960.

$PhCH_2OCONHCH_2CONHCH(CH_2Ph)CH$=$CHCH_2CH_2OH$ (6b). 1:1 *cis*/*trans* mixture (after chromatography, ethyl

acetate/hexane 1:1), 60% yield. ^{1}H NMR: 1.95 (dqd, *J*=14.5, 4.9, 1.5 Hz, 1H, C*H*$_2$CH$_2$O (*cis*)); 2.15 (q, *J*=6.0 Hz, 2H, C*H*$_2$CH$_2$O (*trans*)); 2.31 (dtdd, *J*=14.5, 9.0, 5.0, 1.0 Hz, 1H, C*H*$_2$CH$_2$O (*cis*)); 2.68 (dd, *J*=13.5, 7.8 Hz, 1H, CHC*H*$_2$Ph (*cis*)); 2.75 (dd, *J*=13.5, 7.0 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 2.81 (dd, *J*=13.5, 6.75 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 2.86 (dd, *J*=13.5, 6.0 Hz, 1H, CHC*H*$_2$Ph (*cis*)); 2.93 (bs, 1H, OH (*trans*)); 3.34 (bs, 1H, OH (*cis*)); 3.40 (m, 1H, C*H*$_2$OH (*cis*)); 3.49 (bs, 2H, C*H*$_2$OH (*trans*)); 3.50 (m, 1H, C*H*$_2$OH (*cis*)); 3.68 (dd, *J*=16.0, 5.5 Hz, 1H, NCH$_2$ (*cis*)); 3.69 (dd, *J*=16.0, 5.0 Hz, 1H, NCH$_2$ (*trans*)); 3.74 (dd, *J*=15.5, 5.5 Hz, 1H, NCH$_2$ (*cis*)); 3.77 (dd, *J*=15.5, 5.5 Hz, 1H, NCH$_2$ (*trans*)); 4.63 (dt, *J*=13.0, 7.0 Hz, 1H, NCH (*trans*)); 4.82 (quintet, *J*=8.0 Hz, 1H, NCH (*cis*)); 5.06 (s, 2H, PhCH$_2$O); 5.31 (t, *J*=10 Hz, 1H, CH= (*cis*)); 5.42 (td, *J*=10.0, 5.0 Hz, 1H, =CH (*cis*)); 5.43 (m, 2H, C=C (*trans*)); 5.99 (t, *J*=5.5 Hz, 1H, N*H*CH$_2$ (*trans*)); 6.02 (t, *J*=5.8 Hz, 1H, N*H*CH$_2$ (*cis*)); 6.82 (d, *J*=8.3 Hz, 1H, N*H*CH (*trans*)); 6.93 (d, *J*=6.8 Hz, 1H, N*H*CH (*cis*)); 7.09–7.31 (m, 10H, Ph). ^{13}C NMR: 30.84 (*C*H$_2$CH$_2$O (*cis*)); 35.35 (*C*H$_2$CH$_2$O (*trans*)); 40.88 (CH*C*H$_2$Ph) (*cis*)); 41.00 (CH*C*H$_2$Ph) (*trans*)); 44.33 (NCH$_2$); 48.31 (NCH) (*cis*)); 52.01 (NCH) (*trans*)); 61.17 (CH$_2$OH (*cis*)); 61.29 (CH$_2$OH (*trans*)); 66.89 (PhCH$_2$O); 126.41, 127.81, 128.04, 128.18, 128.37, 129.25, 129.33, 129.45, 130.82, 131.43, 136.03, 137.00, 137.26 (C=C, Ph); 156.66 (OCON); 168.52 (CON (*trans*)); 168.71 (CON (*cis*)). MS: 383 (MH$^+$, 100), 365 (14), 339 (88), 209 (75), 165 (88). HRMS for $C_{22}H_{27}N_2O_4$: calcd 383.1971, found 383.1960.

PhCH$_2$CH$_2$CH=CHCH$_2$CONHCH(CH$_2$Ph)CO$_2$Me (8d). 9.1:1 *cis*/*trans* mixture (after chromatography, CH_2Cl_2/ethanol 20:1), 58% yield. ^{1}H NMR: (*cis* isomer) 2.32 (m, 2H, PhCH$_2$C*H*$_2$); 2.64 (t, *J*=7.7 Hz, 2H, Ph C*H*$_2$CH$_2$); 2.91 (dd, *J*=7.5, 1.1 Hz, 2H, CH$_2$CO); 3.06 (dd, *J*=13.8, 5.8 Hz, 1H, CHC*H*$_2$Ph); 3.13 (dd, *J*=13.8, 5.8 Hz, 1H, CHC*H*$_2$Ph); 3.71 (s, 3H, OMe); 4.83 (dt, *J*=7.8, 5.7 Hz, 1H, NCH); 5.49 (dt, *J*=10.8, 7.4 Hz, 1H, =CH); 5.67 (dt, *J*=10.6, 7.2 Hz, 1H, CH=); 6.00 (d, *J*=7.3 Hz, 1H, NH); 7.04–7.30 (m, 10H, Ph). ^{13}C NMR: 29.31 (PhCH$_2$*C*H$_2$ (*cis*)); 34.16 (PhCH$_2$*C*H$_2$ (*trans*)); 35.10 (*C*H$_2$CO (*cis*)); 35.47 (Ph*C*H$_2$CH$_2$ (*cis*)); 35.59 (Ph*C*H$_2$CH$_2$ (*trans*)); 37.93 (Ph*C*H$_2$CH (*cis*)); 40.32 (*C*H$_2$CO (*trans*)); 52.22 (OMe (*cis*)); 53.13 (NCH (*cis*)); 122.09 (=CH (*cis*)); 122.96 (=CH (*trans*)); 126.04, 127.17, 128.42, 128.48, 128.59, 129.30 (Ph); 134.04 (CH= (*cis*)); 135.53 (CH= (*trans*)); 170.23 (CON (*cis*)); 170.6 (CON (*trans*)); 171.99 (CO$_2$ (*cis*)). MS: 352 (MH$^+$, 100), 320 (7), 292 (5), 272 (11), 180 (29), 91 (5).

PhCH$_2$CH$_2$CH=CHCH(CH$_2$Ph)CONHCH$_2$CO$_2$Me (8c). The acid (0.29 mmol) (see below) was stirred with 1,1-carbonyldiimidazole (0.34 mmol) in THF (5 ml) under argon atmosphere for 1.5 h. Then Gly-OMe (0.35 mmol) was added and the solution was stirred overnight. The solvent was evaporated to dryness and purification was carried out by chromatography (ether/hexane 1:4), affording the product as a 2.1:1 *trans*/*cis* mixture in 43% yield. ^{1}H NMR: 2.12 (dqd, *J*=14.2, 7.4, 1.6 Hz, 1H, PhCH$_2$C*H*$_2$ (*cis*)); 2.19 (dqd, *J*=14.9, 7.8, 1.5 Hz, 1H, PhCH$_2$C*H*$_2$ (*cis*)); 2.32 (dq, *J*=14.2, 6.5 Hz, 1H, PhCH$_2$C*H*$_2$ (*trans*)); 2.34 (dq, *J*=14.0, 6.3 Hz, 1H, PhCH$_2$C*H*$_2$ (*trans*)); 2.46 (t, *J*=7.8 Hz, 2H, PhC*H*$_2$CH$_2$ (*cis*)); 2.59 (dt, *J*=13.8, 7.8 Hz, 1H, PhC*H*$_2$CH$_2$ (*trans*)); 2.66 (dt, *J*=13.6, 8.4 Hz, 1H, PhC*H*$_2$CH$_2$ (*trans*)); 2.66 (dd, *J*=13.7, 8.2 Hz, 1H, CHC*H*$_2$Ph (*cis*)); 2.76 (dd, *J*=13.6, 7.9 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 3.07 (td, *J*=8.1, 6.4 Hz, 1H, C*H*CH$_2$ (*trans*)); 3.17 (dd, *J*=13.7, 6.3 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 3.19 (dd, *J*=13.6, 5.6 Hz, 1H, CHC*H*$_2$Ph (*cis*)); 3.32 (tdd, *J*=9.3, 5.6, 1.0 Hz, 1H, C*H*CH$_2$ (*cis*)); 3.73 (s, 3H, Me (*cis*)); 3.73 (s, 3H, Me (*trans*)); 3.87 (dd, *J*=18.4, 5.4 Hz, 1H, NCH$_2$ (*cis*)); 3.90 (dd, *J*=18.3, 5.3 Hz, 1H, NCH$_2$ (*cis*)); 3.91 (dd, *J*=18.4, 5.4 Hz, 1H, NCH$_2$ (*trans*)); 3.93 (dd, *J*=18.3, 5.2 Hz, 1H, NCH$_2$ (*trans*)); 5.43 (ddt, *J*=10.9, 9.9, 1.4 Hz, 1H, =CH (*cis*)); 5.44 (ddt, *J*=15.4, 8.4, 1.1 Hz, 1H, =CH (*trans*)); 5.50 (dt, *J*=15.4, 6.3 Hz, 1H, CH= (*trans*)); 5.59 (dtd, *J*=10.8, 7.5, 0.9 Hz, 1H, CH= (*cis*)); 5.64 (t, *J*=5.0 Hz, 1H, NH (*cis*)); 5.83 (t, *J*=5.1 Hz, 1H, NH (*trans*)); 7.05–7.26 (m, 10H, Ph). ^{13}C NMR: 29.34 (PhCH$_2$*C*H$_2$ (*cis*)); 34.01 (PhCH$_2$*C*H$_2$ (*trans*)); 35.24 (Ph*C*H$_2$CH$_2$ (*cis*)); 35.41 (Ph*C*H$_2$CH$_2$ (*trans*)); 38.10 (CH*C*H$_2$Ph); 41.26 (NCH$_2$); 46.98 (*C*HCH$_2$ (*cis*)); 52.23 (*C*HCH$_2$ (*trans*), OMe); 125.82 (=CH (*trans*)); 127.72 (=CH (*cis*)); 126.16, 128.22, 128.49, 129.22 (Ph); 133.01 (CH= (*cis*)); 134.19 (CH= (*trans*)); 139.34, 141.52 (Ph); 170.24, 172.93, 173.19 (COO, CON). MS: 352 (MH$^+$, 100), 260 (14). HRMS for $C_{22}H_{26}NO_3$: calcd 352.1913, found 352.1925.

Oxidation of the alcohol to the corresponding acid

Jones oxidation[17] of the alcohol afforded the corresponding acid. It was purified by a triple extraction procedure: extraction into organic phase (ether or ethyl acetate) directly from the acidic Jones' reaction, extraction back into sat. $NaHCO_3$ aqueous solution, acidification of the latter to pH 1 by conc. HCl and re-extraction into organic phase. Drying over $MgSO_4$, filtration and evaporation afforded the acid, which was transferred to the next reaction, either coupling with an amine or esterification, without further purification.

PhCH$_2$OCONHCH(CH$_2$Ph)CONHCH$_2$CH=CHCH$_2$-CO$_2$H (7a)

cis Isomer: 57% yield. ^{1}H NMR: 3.03 (m, 2H, CHC*H*$_2$Ph); 3.11 (d, *J*=7.2 Hz, 2H, CH$_2$CO$_2$); 3.76 (m, 2H, NCH$_2$); 4.40 (q, *J*=5.6 Hz, 1H, NCH); 5.04 (d, *J*=13.1 Hz, 1H, PhCH$_2$O); 5.07 (d, *J*=13.1 Hz, 1H, PhCH$_2$O); 5.41 (dt, *J*=10.6, 6.7 Hz, 1H, CH=); 5.64–5.70 (m, 2H, =CH+N*H*CH); 6.25 (t, *J*=4.5 Hz, 1H, N*H*CH$_2$); 7.14–7.34 (m, 10H, Ph). ^{13}C NMR: 32.79 (*C*H$_2$CO$_2$); 36.48 (NCH$_2$); 38.67 (CH*C*H$_2$Ph); 56.35 (NCH); 67.13 (PhCH$_2$O); 124.71, 127.06, 127.99, 128.23, 128.37, 128.53, 128.67, 129.27, 129.36, 136.23 (C=C, Ph); 156.14 (OCON); 171.25, 174.81 (CON, CO$_2$).

trans Isomer: 53% yield. ^{1}H NMR: 3.01 (d, *J*=6.9 Hz, 2H, CH$_2$CO$_2$); 3.03 (m, 2H, CHC*H*$_2$Ph); 3.75 (m, 2H, NCH$_2$); 4.45 (q, *J*=6.7 Hz, 1H, NCH); 5.01 (d, *J*=12.3 Hz, 1H, PhCH$_2$O); 5.06 (d, *J*=12.3 Hz, 1H, PhCH$_2$O); 5.39 (dt, *J*=15.6, 5.8 Hz, 1H, CH=); 5.51 (dt, *J*=15.0, 7.5 Hz, 1H, =CH); 5.85 (d, *J*=8.2 Hz, 1H, N*H*CH); 6.43 (s, 1H, N*H*CH$_2$); 7.17–7.33 (m, 10H, Ph). ^{13}C NMR: 37.13 (*C*H$_2$CO$_2$); 38.74 (CH*C*H$_2$Ph); 40.87 (NCH$_2$); 56.38

(NCH); 67.09 (PhCH$_2$CH$_2$); 124.28, 126.97, 127.92, 128.17, 128.49, 128.61, 129.29, 129.43, 136.34 (C=C, Ph); 156.190 (OCON); 171.179, 175.156 (CON, CO$_2$). MS: 397 (MH$^+$, 44), 353 (65), 289 (40), 243 (44), 191 (100). HRMS for $C_{22}H_{25}N_2O_5$: calcd 397.1763, found 397.1735.

PhCH$_2$OCONHCH$_2$CONHCH(CH$_2$Ph)CH=CHCH$_2$CO$_2$H (7b). 2:1 *trans*/*cis* mixture, 27% yield. ^{1}H NMR (acetone-d$_6$): 2.6–3.1 (m, 4H, CH$_2$CO$_2$+CHCH$_2$Ph); 3.64 (s, 2H, NCH$_2$); 4.58 (m, 1H, NCH (*trans*)); 4.75 (m, 1H, NCH (*cis*)); 4.95 (s, 2H, PhCH$_2$O); 5.45 (m, 2H, CH=CH); 6.42 (s, 1H, NH); 7.00–7.27 (m, 10H, Ph). ^{13}C NMR (acetone-d$_6$): 31.87 (CH$_2$CO$_2$ (*cis*)); 36.43 (CH$_2$CO$_2$ (*trans*)); 40.26 (CHCH$_2$Ph) (*cis*)); 40.45 (CHCH$_2$Ph) (*trans*)); 43.5 (NCH$_2$ (*cis*)); 43.58 (NCH$_2$ (*trans*)); 47.89 (NCH (*cis*)); 51.38 (NCH) (*trans*)); 65.56 (PhCH$_2$O); 122.81, 123.48, 125.66, 125.72, 127.29, 127.61, 127.66, 127.84, 128.97, 131.40, 132.65, 136.73, 137.50, 137.66 (C=C, Ph); 156.08 (OCON); 167.89 (CON); 171.44 (CO$_2$ (*cis*)); 171.50 (CO$_2$ (*trans*)). MS: 397 (MH$^+$, 54), 379 (20), 353 (94), 305 (16), 289 (54), 271 (75), 209 (16), 171 (100). HRMS for $C_{22}H_{25}N_2O_5$: calcd 397.1763, found 397.1730.

PhCH$_2$CH$_2$CH=CHCH(CH$_2$Ph)CO$_2$H (5c). 2.4:1 *trans*/*cis* mixture, 49% yield. ^{1}H NMR: 2.16 (ddtd, *J*=14.5, 9.0, 7.2, 1.4 Hz, 1H, PhCH$_2$CH$_2$ (*cis*)); 2.25 (ddtd, *J*=15.3, 8.5, 6.6, 1.6 Hz, 1H, PhCH$_2$CH$_2$ (*cis*)); 2.30 (qd, *J*=7.3, 0.7 Hz, 2H, PhCH$_2$CH$_2$ (*trans*)); 2.36 (ddd, *J*=13.7, 8.7, 6.7 Hz, 1H, PhCH$_2$CH$_2$ (*cis*)); 2.49 (ddd, *J*=13.7, 8.7, 6.4 Hz, 1H, PhCH$_2$CH$_2$ (*cis*)); 2.59 (dt, *J*=13.5, 7.4 Hz, 1H, PhCH$_2$CH$_2$ (*trans*)); 2.63 (dt, *J*=13.3, 7.4 Hz, 1H, PhCH$_2$CH$_2$ (*trans*)); 2.67 (dd, *J*=13.5, 8.5 Hz, 1H, CHCH$_2$Ph (*cis*)); 2.79 (dd, *J*=13.5, 7.5 Hz, 1H, CHCH$_2$Ph (*trans*)); 3.07 (dd, *J*=13.5, 7.5 Hz, 1H, CHCH$_2$Ph (*trans*)); 3.07 (dd, *J*=13.5, 6.8 Hz, 1H, CHCH$_2$Ph (*cis*)); 3.27 (dt, *J*=8.0, 7.6 Hz, 1H, CHCH$_2$Ph (*trans*)); 3.56 (dddd, *J*=10.0, 6.9, 1.7, 1.0 Hz, 1H, CHCH$_2$Ph (*cis*)); 5.41 (ddt, *J*=11.0, 10.0, 1.6 Hz, 1H, =CH (*cis*)); 5.46 (ddt, *J*=15.5, 8.5, 1.2 Hz, 1H, =CH (*trans*)); 5.53 (dt, *J*=15.5, 6.4 Hz, 1H, CH= (*trans*)); 5.56 (dtd, *J*=11.0, 7.4, 1.0 Hz, 1H, CH= (*cis*)); 7.03–7.27 (m, 10H, Ph). ^{13}C NMR: 29.33 (PhCH$_2$CH$_2$ (*cis*)); 34.14 (PhCH$_2$CH$_2$ (*trans*)); 35.24 (PhCH$_2$CH$_2$ (*cis*)); 35.43 (PhCH$_2$CH$_2$ (*trans*)); 38.38 (CHCH$_2$Ph); 45.94 (CHCH$_2$Ph (*cis*)); 50.82 (CHCH$_2$Ph (*trans*)); 125.78 (=CH (*trans*)); 125.83 (=CH (*cis*)); 126.31, 126.37, 126.43, 126.87, 128.22, 128.27, 128.35, 128.40, 129.06 (Ph); 132.82 (CH= (*cis*)); 133.66 (CH= (*trans*)); 138.43, 141.47 (Ph); 180.02 (CO$_2$ (*cis*)); 180.17 (CO$_2$ (*trans*)). MS: 281 (MH$^+$, 100), 263 (70), 235 (72), 131 (88), 91 (35). HRMS for $C_{19}H_{21}O_2$: calcd 281.1542, found 281.1543.

PhCH$_2$CH$_2$CH=CHCH$_2$CO$_2$H (5d). 9.1:1 *cis*/*trans* mixture, 87% yield. ^{1}H NMR: (*cis* isomer) 2.37 (q, *J*=7.7 Hz, 2H, PhCH$_2$CH$_2$); 2.68 (t, *J*=7.5 Hz, 2H, PhCH$_2$); 3.02 (d, *J*=6.4 Hz, 2H, CH$_2$CO$_2$); 5.51–5.70 (m, 2H, CH=CH); 7.05–7.30 (m, 5H, Ph). ^{13}C NMR: 29.31 (PhCH$_2$CH$_2$ (*cis*)); 32.48 (CH$_2$CO$_2$ (*cis*)); 34.19 ((PhCH$_2$CH$_2$ (*trans*)); 35.42 (PhCH$_2$ (*cis*)); 35.54 (PhCH$_2$ (*trans*)); 37.64 (CH$_2$CO$_2$ (*trans*)); 120.86 (=CH (*cis*)); 121.49 (=CH (*trans*)); 125.92, 128.32, 128.41 (Ph); 132.75 (CH= (*cis*)); 134.40 (CH= (*trans*)); 141.45 (Ph). MS: 191 (MH$^+$, 12), 173 (88), 145 (18), 131 (37), 91 (100).

Esterification

The acid (0.1 mmol) was suspended in ether (5 ml) and diazomethane (0.3 M solution in ether, 1 ml) was added until the acid was dissolved completely and the solution turned yellow. After stirring overnight, the solvent was evaporated to dryness. The product ester was purified by chromatography.

PhCH$_2$OCONHCH(CH$_2$Ph)CONHCH$_2$CH=CHCH$_2$-CO$_2$Me (8a)

cis Isomer: Chromatography (2:1 hexane/ethyl acetate). 52% yield. ^{1}H NMR: 3.02 (dd, *J*=13.5, 7.5 Hz, 1H, CHCH$_2$Ph); 3.08 (d, *J*=7.2 Hz, 2H, CH$_2$CO$_2$); 3.12 (dd, *J*=13.5, 5.8 Hz, 1H, CHCH$_2$Ph); 3.67 (s, 3H, Me); 3.79 (m, 2H, NHCH$_2$); 4.36 (q, *J*=6.1 Hz, 1H, CHCH$_2$Ph); 5.08 (bs, 2H, PhCH$_2$O); 5.35 (d, *J*=6 Hz, 1H, NHCH); 5.43 (dt, *J*=10.2, 7 Hz, 1H, CH=); 5.68 (dtt, *J*=10.6, 7.5, 1.5 Hz, 1H, =CH); 5.86 (t, *J*=5 Hz, 1H, NHCH$_2$); 7.22–7.37 (m, 10H, Ph). ^{13}C NMR: 32.65 (CH$_2$CO$_2$) 36.41 (NHCH$_2$); 38.77 (CHCH$_2$Ph); 52.07 (Me); 56.37 (CHCH$_2$Ph); 67.09 (PhCH$_2$O); 124.86 (CH=); 128.06, 128.25, 128.41, 128.56, 128.73, 129.27 (Ph); 129.33 (CH=); 136.24, 136.40 (Ph); 170.55, 171.79 (CON, CO$_2$). MS: 411 (MH$^+$, 55), 367 (84), 303 (50), 271 (100). HRMS for $C_{23}H_{27}N_2O_5$: calcd 411.1920, found 411.1930.

trans Isomer: Chromatography (2:1 hexane/ethyl acetate). 71% yield. ^{1}H NMR: 2.96 (d, *J*=7.1 Hz, 2H, CH$_2$CO$_2$); 2.98 (dd, *J*=13.0, 7.8 Hz, 1H, CHCH$_2$Ph); 3.07 (dd, *J*=13.0, 5.6 Hz, 1H, CHCH$_2$Ph); 3.63 (s, 3H, Me); 3.72 (m, 2H, NHCH$_2$); 4.32 (q, *J*=7.2 Hz, 1H, CHCH$_2$Ph); 5.02 (d, *J*=12.2 Hz, 1H, PhCH$_2$O); 5.04 (d, *J*=12.2 Hz, 1H, PhCH$_2$O); 5.35 (obscured, 1H, NHCH); 5.36 (dt, *J*=16.0, 5.3 Hz, 1H, CH=); 5.51 (dtt, *J*=15.4, 7.0, 1.5 Hz, 1H, =CH); 5.76 (t, *J*=5.2 Hz, 1H, NHCH$_2$); 7.15–7.32 (m, 10H, Ph). ^{13}C NMR: 37.32 (CH$_2$CO$_2$); 38.77 (CHCH$_2$Ph); 40.94 (NHCH$_2$); 51.89 (Me); 56.44 (CHCH$_2$Ph); 67.10 (PhCH$_2$O); 124.68 (CH=); 127.08, 128.07, 128.26, 128.56, 128.74, 129.34 (Ph); 129.45 (CH=); 136.10, 136.43 (Ph); 155.94 (OCON); 170.51, 171.81 (CON, CO$_2$). MS: 411 (MH$^+$, 50), 367 (97), 303 (100), 271 (88). HRMS for $C_{23}H_{27}N_2O_5$: calcd 411.1920, found 411.1920.

PhCH$_2$OCONHCH$_2$CONHCH(CH$_2$Ph)CH=CHCH$_2$CO$_2$Me (8b). 4.5:1 *trans*/*cis* mixture (after chromatography, ether), 76% yield. ^{1}H NMR: 2.76 (dd, *J*=16, 7 Hz, 1H, CHCH$_2$Ph (*cis*)); 2.83 (dd, *J*=13.5, 7.5 Hz, 1H, CHCH$_2$Ph (*trans*)); 2.86 (dd, *J*=13.5, 7.5 Hz, 1H, CHCH$_2$Ph (*trans*)); 2.90 (dd, *J*=16.5, 7.9 Hz, CHCH$_2$Ph (*cis*)); 2.91 (m, 1H, CH$_2$CO$_2$ (*cis*)); 3.03 (d, *J*=6.7 Hz, 2H, CH$_2$CO$_2$ (*trans*)); 3.08 (dd, *J*=18.0, 7.5 Hz, 1H, CH$_2$CO$_2$ (*cis*)); 3.63 (s, 3H, Me (*cis*)); 3.66 (s, 3H, Me (*trans*)); 3.79 (m, 2H, NCH$_2$ (*cis*+*trans*)); 4.75 (quint, *J*=6.9 Hz, 1H, NCH (*trans*)); 4.86 (quint, *J*=7 Hz, 1H, NCH (*cis*)); 5.12 (s, 2H, PhCH$_2$O (*cis*+*trans*)); 5.42 (m, 1H, NHCH$_2$); 5.43 (obscured, 1H, CH= (*cis*)); 5.54 (dd, *J*=14.6, 5.6 Hz, 1H, CH= (*trans*)); 5.63 (dt, *J*=14.5, 7.0 Hz, 1H, =CH (*trans*)); 5.66 (m, 1H, =CH (*cis*)); 6.11 (d, *J*=6.5 Hz, 1H, NHCH (*trans*)); 6.16 (d, *J*=7 Hz, 1H, NHCH (*cis*)); 6.98–7.36 (m, 10H, Ph). ^{13}C NMR: 32.76 (CH$_2$CO$_2$ (*cis*)); 37.28 (CH$_2$CO$_2$ (*trans*)); 40.98 (CHCH$_2$Ph); 44.66 (NCH$_2$);

48.06 (NCH (*cis*)); 51.43 (NCH (*trans*)); 51.76 (Me); 65.75 ($PhCH_2O$ (*cis*)); 67.11 ($PhCH_2O$ (*trans*)); 123.35, 125.52, 126.71, 128.13, 128.30, 128.44, 128.59, 129.47, 133.01, 136.90 (C=C, Ph); 156.53 (OCON); 168.09 (CON\$CO_2$ (*cis*)); 168.23, 171.65 (CON+CO_2 (*trans*)); 171.79 (CON\$CO_2$ (*cis*)). MS: 411 (MH^+, 86), 367 (100), 318 (12), 303 (63), 209 (51). HRMS for $C_{23}H_{27}N_2O_5$: calcd 411.1920, found 411.1940.

Epoxidation

Peptide (0.05 mmol), mCPBA 50% (0.06 mmol), K_2HPO_4 (0.07 mmol) were stirred in CH_2Cl_2 (1 ml) and H_2O (10 μl) overnight. The solution was washed successively with saturated $NaHCO_3$, 5% Na_2SO_3, saturated $NaHCO_3$, water and brine (1 ml each), and dried over $MgSO_4$. Evaporation to dryness afforded the product, which was purified by chromatography.

$PhCH_2OCONHCH(CH_2Ph)CONHCH_2CHOCHCH_2CO_2Me$ (9a)

cis Isomer: (1:0.82 diasteriomeric ratio). Purified by chromatography (ethyl acetate/$CHCl_3$/hexane 5:3:2), 55% yield. ^{1}H NMR: 2.44 (dd, *J*=16.4, 6.8 Hz, 1H, CH_2CO_2 (major)); 2.46 (dd, *J*=16.5, 6.8 Hz, 1H, CH_2CO_2 (minor)); 2.69 (dd, *J*=16.4, 6 Hz, 1H, CH_2CO_2 (minor)); 2.70 (dd, *J*=16.4, 6 Hz, 1H, CH_2CO_2 (major)); 2.92 (td, *J*=6, 4 Hz, 1H, CHO); 3.04 (dd, *J*=13.5, 7.5 Hz, 1H, CHC*H*$_2$Ph); 3.12 (m, 1H, CHC*H*$_2$Ph); 3.22 (td, *J*=6.5, 4.1 Hz, 1H, OCH (major)); 3.26 (td, *J*=6, 4 Hz, 1H, OCH (minor)); 3.31 (dt, *J*=14.4, 6.0 Hz, 1H, NCH_2 (major)); 3.37 (dt, *J*=14.1, 6.1 Hz, 1H, NCH_2 (major)); 3.38 (obscured, 2H, NCH_2 (minor)); 3.70 (s, 3H, Me (minor)); 3.71 (s, 3H, Me (major)); 4.42 (m, 1H, NCH); 5.08 (d, *J*=13.3 Hz, 1H, $PhCH_2O$); 5.10 (d, *J*=13.5 Hz, 1H, $PhCH_2O$); 5.39 (d, *J*=4.1, 1H, N*H*CH); 6.24 (bt, 1H, N*H*CH_2 (minor)); 6.28 (t, *J*=5.25 Hz, 1H, N*H*CH_2 (major)); 7.17–7.36 (m, 10H, Ph). ^{13}C NMR: 33.53 (*C*H_2CO_2); 37.86, 37.92 (NCH_2); 38.74 (CH*C*H_2Ph); 52.23, 52.32, 52.37(CHO\Me); 53.93 (OCH major); 54.00 (OCH minor); 56.46 (NCH); 67.18 ($PhCH_2O$); 127.15, 128.07, 128.26, 128.56 128.77, 129.13, 129.31, 129.81, 132.09, 133.60, 134.67, 136.26 (Ph); 155.5 (OCON); 168.74, 170.81, 171.19 (CON, CO_2). MS: 427 (MH^+, 54), 369 (11), 319 (19), 257 (17), 192 (20), 164 (22), 114 (21), 91 (100). HRMS for $C_{23}H_{27}N_2O_6$: calcd 427.1869, found 427.1870.

trans Isomer: (1:0.92 diasteriomeric ratio). Purified by chromatography (ethyl acetate/$CHCl_3$/hexane 2:2:1), 92% yield. ^{1}H NMR: 2.47 (dd, *J*=16.6, 6.5 Hz, 1H, CH_2CO_2 (major)); 2.49 (dd, *J*=16.5, 6.6 Hz, 1H, CH_2CO_2 (minor)); 2.53 (dd, *J*=16.5, 4.9 Hz, 1H, CH_2CO_2 (major)); 2.55 (dd, *J*=16.5, 4.7 Hz, 1H, CH_2CO_2 (minor)); 2.78 (m, 1H, CHO (minor)); 2.83 (m, 1H, CHO (major)); 2.90 (ddd, *J*=6.5, 5.0, 2.2 Hz, 1H, OCH (major)); 3.01–3.12 (m, CHC*H*$_2$Ph+OCH (minor)); 3.27 (dt, *J*=14.5, 5.8 Hz, 1H, NCH_2 (minor)); 3.30 (m, 1H, NCH_2 (major)); 3.54 (ddd, *J*=13.7, 5.5, 4.3 Hz, 1H, NCH_2 (minor)); 3.56 (dt, *J*=14.7, 5.8 Hz, 1H, NCH_2 (major)); 3.70 (s, 3H, Me); 4.42 (q, *J*=6.7 Hz, 1H, NCH); 5.07 (d, *J*=12.3 Hz, 1H, $PhCH_2O$); 5.08 (d, *J*=12.3 Hz, 1H, $PhCH_2O$); 5.47 (d, *J*=8.7, 1H, N*H*CH (major)); 5.49 (d, *J*=9.6, 1H, N*H*CH (minor)); 6.17 (t, *J*=6.0 Hz, 1H, N*H*CH_2 (minor)); 6.18 (t, *J*=6.0 Hz, 1H, N*H*CH_2 (major)); 7.15–7.35 (m, 10H, Ph). ^{13}C NMR: 36.84 (*C*H_2CO_2); 38.65 (CH*C*H_2Ph); 39.91, 40.07 (NCH_2); 52.02, 52.15 (OCH+Me); 55.93, 55.98 (CHO); 56.43 (NCH); 67.17 ($PhCH_2O$); 127.12, 128.06, 128.24, 128.55, 128.75, 129.28, 129.74, 130.18, 133.34, 136.08, 136.29 (Ph); 155.91 (OCON); 170.0, 171.32 (CON, CO_2). HRMS for $C_{23}H_{27}N_2O_6$: calcd 427.1869, found 427.1860.

$PhCH_2OCONHCH_2CONHCH(CH_2Ph)CHOCHCH_2CO_2Me$ (9b). 4.4:1 *trans*/*cis* mixture (after chromatography, ethyl acetate/$CHCl_3$/hexane 5:3:2), 34% yield. ^{1}H NMR: 2.36 (dd, *J*=17, 8 Hz, 1H, CH_2CO_2 (*cis*)); 2.41 (dd, *J*=17.0, 6.5 Hz, 1H, CH_2CO_2 (*trans*)); 2.54 (dd, *J*=17, 6 Hz, 1H, CH_2CO_2 (*cis*)); 2.59 (dd, *J*=16.0, 4.0 Hz, 1H, CH_2CO_2 (*trans*)); 2.84 (m, 2H, CHC*H*$_2$Ph (*cis*)); 2.88 (dd, *J*=13.0, 7.8 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 2.89 (bs, 1H, CHO (*trans*)); 2.94 (dd, *J*=13.0, 7.0 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 3.03 (dd, *J*=7, 4 Hz, 1H, CHO (*cis*)); 3.09 (bt, *J*=4 Hz, 1H, OCH (*trans*)); 3.31 (dt, *J*=8.0, 4.5 Hz, 1H, OCH (*cis*)); 3.67 (s, 3H, Me (*cis*)); 3.69 (s, 3H, Me (*trans*)); 3.79 (dd, *J*=16.5, 5.5 Hz, 1H, NCH_2 (*trans*)); 3.81 (dd, *J*=16.5, 5.1 Hz, 1H, NCH_2 (*trans*)); 3.82 (dd, *J*=16.5, 5.5 Hz, 1H, NCH_2 (*cis*)); 3.90 (dd, *J*=16.5, 6.0 Hz, 1H, NCH_2 (*cis*)); 3.99 (qd, *J*=8, 6 Hz, 1H, NCH (*cis*)); 4.47 (tdd, *J*=9.0, 7.5, 3.0 Hz, 1H, NCH (*trans*)); 5.14 (s, 2H, $PhCH_2O$); 5.33 (bt, *J*=5 Hz, 1H, N*H*CH_2 (*trans*)); 5.40 (bt, 1H, N*H*CH_2 (*cis*)); 6.01 (d, *J*=8.0 Hz, 1H, N*H*CH (*trans*)); 6.30 (d, *J*=7.2 Hz, 1H, N*H*CH (*cis*)); 7.12–7.37 (m, 10H, Ph). ^{13}C NMR: 36.79 (*C*H_2CO_2 (*trans*)); 39.06 (CH*C*H_2Ph (*trans*)); 44.62 (NCH_2 (*trans*)); 44.8 (NCH_2 (*cis*)); 49.00 (NCH (*trans*)); 49.73 (NCH (*cis*)); 51.70 (OCH (*trans*)); 52.03 (Me (*trans*)); 53.52 (OCH (*cis*)); 57.15 (CHO (*cis*)); 58.05 (CHO (*trans*)); 65.32 ($PhCH_2O$ (*trans*)); 126.93, 128.18, 128.32, 128.62, 128.68, 129.35, 136.64 (Ph (*trans*)); 127.05, 127.94, 129.51 (Ph (*cis*)); 168.68, 170.43 (CON, CO_2 (*trans*)). MS: 427 (MH^+, 100), 383 (11), 273 (33). HRMS for $C_{23}H_{27}N_2O_6$: calcd 427.1869, found 427.1820.

$PhCH_2CH_2CHOCHCH(CH_2Ph)CONHCH_2CO_2Me$ (9c). 8.7:4.9:4.6:1 *trans*(major)/*cis*(major)/*trans*(minor)/*cis*(minor) (after chromatography, hexane/ethyl acetate 2:1, which separated the major from the minor isomers), 58% yield.

Major isomers: ^{1}H NMR: 1.18 (dddd, *J*=14.2, 9.5, 7.2, 3.8 Hz, 1H, $PhCH_2CH_2$ (*cis*)); 1.37 (dddd, *J*=14.2, 9.2, 8.3, 5.5 Hz, 1H, $PhCH_2CH_2$ (*cis*)); 1.62 (dddd, *J*=14.2, 9.5, 6.6, 5.9 Hz, 1H, $PhCH_2CH_2$ (*trans*)); 1.67 (dddd, *J*=14.1, 9.6, 6.9, 4.5 Hz, 1H, $PhCH_2CH_2$ (*trans*)); 2.24 (td, *J*=8.8, 6.6 Hz, 1H, C*H*CH_2Ph (*trans*)); 2.32 (ddd, *J*=9.5, 8.7, 6.2 Hz, 1H, C*H*CH_2Ph (*cis*)); 2.46–2.54 (m, $PhCH_2CH_2$ (*cis*+*trans*), CHO (*trans*)); 2.58 (ddd, *J*=14.1, 9.5, 5.7 Hz, 1H, $PhCH_2CH_2$ (*trans*)); 2.65 (ddd, *J*=14.4, 9.0, 5.4 Hz, 1H, $PhCH_2CH_2$ (*cis*)); 2.76 (dd, *J*=13.9, 8.6 Hz, 1H, CHC*H*$_2$Ph (*cis*)); 2.78 (dd, *J*=13.9, 9.4 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 2.86 (dd, *J*=8.3, 2.2 Hz, 1H, OCH (*trans*)); 2.92 (q, *J*=4.1 Hz, 1H, CHO (*cis*)); 3.15 (dd, *J*=9.7, 4.2 Hz, 1H, OCH (*cis*)); 3.22 (dd, *J*=14.0, 6.3 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 3.26 (dd, *J*=13.9, 6.2 Hz, 1H, CHC*H*$_2$Ph) (*cis*)); 3.75 (s, 3H, Me (*cis*)); 3.76 (s, 3H, Me (*trans*)); 4.02 (dd, *J*=18.3, 5.1 Hz, 1H, NCH_2 (*trans*)); 4.04 (dd, *J*=18.3, 5.1 Hz, 1H, NCH_2 (*cis*));4.08 (dd, *J*=18.3, 5.5 Hz, 1H, NCH_2 (*cis*+*trans*)); 6.46 (t, *J*=5.0, 1H, NH (*cis*)); 6.47 (t,

J=5.0, 1H, NH (*trans*)); 7.05–7.28 (m, 10H, Ph). ^{13}C NMR: 29.10 (PhCH$_2$*C*H$_2$ (*cis*)); 31.61 (PhCH$_2$CH$_2$ (*trans*)); 32.40 (Ph*C*H$_2$CH$_2$ (*cis*)); 33.15 (PhCH$_2$*C*H$_2$ (*trans*)); 34.56 (CH*C*H$_2$Ph (*trans*)); 34.47 (CH*C*H$_2$Ph (*cis*)); 41.30 (NCH$_2$ (*trans*)); 41.39 (NCH$_2$ (*cis*)); 46.61 (*C*HCH$_2$Ph (*cis*)); 50.62 (*C*HCH$_2$Ph (*trans*)); 52.36 (OMe (*cis*+*trans*)); 57.67 (CHO (*cis*)); 58.18 (OCH (*cis*)); 59.04 (OCH (*trans*)); 59.36 (CHO (*trans*)); 126.07, 126.11, 126.60, 128.25, 128.31, 128.45, 128.56, 128.94, 129.23, 138.64, 140.90 (Ph); 170.18 (*cis*+*trans*), 171.98 (*trans*), 172.18 (*cis*) (CON, CO$_2$). MS: 368 (MH$^+$, 100), 350 (73). HRMS for $C_{22}H_{24}NO_4$: calcd 368.1862, found 368.1899.

Minor isomers: ^{1}H NMR: 1.82–1.89 (m, 2H, PhCH$_2$C*H*$_2$ (*trans*)); 2.29 (td, *J*=9.5, 4.7 Hz, 1H, (C*H*CH$_2$Ph (*cis*)); 2.46 (ddd, *J*=9.2, 6.2, 5.4 Hz, 1H, (C*H*CH$_2$Ph (*trans*)); 2.71 (ddd, *J*=13.9, 9.1, 7.3 Hz, 1H, PhC*H*$_2$CH$_2$ (*trans*)); 2.78 (ddd, *J*=13.7, 9.0, 6.3 Hz, 1H, PhC*H*$_2$CH$_2$ (*trans*)); 2.96 (dd, *J*=13.8, 5.0 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 2.95–2.99 (m, 2H, CHOCH (*trans*)); 3.09 (obscured, CHO (*cis*)); 3.10 (dd, *J*=13.8, 9.3 Hz, 1H, CHC*H*$_2$Ph (*trans*)); 3.10 (obscured, CHC*H*$_2$Ph (*cis*)); 3.15 (dd, *J*=12.0, 4.8 Hz, 1H, CHC*H*$_2$Ph (*cis*)); 3.27 (dd, *J*=9.1, 4.2 Hz, 1H, OCH (*cis*)); 3.72 (s, 3H, Me (*trans*)); 3.84 (dd, *J*=18.4, 4.8 Hz, 1H, NCH$_2$ (*trans*)); 4.01 (dd, *J*=18.3, 5.6 Hz, 1H, NCH$_2$ (*trans*)); 5.89 (t, *J*=5.6, 1H, NH (*trans*)); 7.16–7.29 (m, 10H, Ph). ^{13}C NMR: 30.19 (PhCH$_2$*C*H$_2$ (*cis*)); 32.05 (PhCH$_2$*C*H$_2$ (*trans*)); 32.86 (Ph*C*H$_2$CH$_2$ (*cis*)); 33.46 (Ph*C*H$_2$CH$_2$ (*trans*)); 35.53 (CH*C*H$_2$Ph (*trans*)); 37.19 (CH*C*H$_2$Ph (*cis*)); 40.99 (NCH$_2$ (*cis*)); 41.13 (NCH$_2$ (*trans*)); 48.68 (*C*HCH$_2$Ph (*cis*)); 50.76 (*C*HCH$_2$Ph (*trans*)); 52.36 (OMe (*trans*+*cis*)); 57.23 (*trans*), 57.69 (*trans*), 58.08 (*cis*), 58.94 (*cis*) (CHO+OCH); 126.08, 126.57, 128.39, 128.48, 128.55, 128.92, 141.04 (Ph); 169.98, 171.24 (CON, CO$_2$). MS: 368 (MH$^+$, 84), 351 (39), 350 (100); 297 (35). HRMS for $C_{22}H_{24}NO_4$: calcd 368.1862, found 368.1853.

PhCH$_2$CH$_2$CHOCHCH$_2$CONHCH(CH$_2$Ph)CO$_2$Me (9d). 10:9.3:1.1:1 *cis*(major)/*cis*(minor)/*trans*(major)/*trans*(minor) mixture. Chromatography (ethyl acetate/CHCl$_3$/hexane 1:2:5) partially separated the isomers, 72% yield. ^{1}H NMR: 1.74–1.88 (m, 2H, PhCH$_2$C*H*$_2$ (*cis* major+minor)); 2.24–2.32 (m, 2H, CH$_2$CO (*cis* major+minor); 2.50 (dd, *J*=10.7, 4.0 Hz, 1H, CH$_2$CO (*trans* minor)); 2.52 (dd, *J*=10.6, 3.9 Hz, 1H, CH$_2$CO (*trans* major)); 2.73 (dt, *J*=13.8, 8.1 Hz, 1H, PhC*H*$_2$CH$_2$ (*cis* major+minor)); 2.82 (ddd, *J*=8.8, 6.1, 2,0 Hz, 1H, PhC*H*$_2$CH$_2$ (*cis* major)); 2.81 (ddd, *J*=8.8, 6.1, 2.0 Hz, 1H, PhC*H*$_2$CH$_2$ (*cis* minor)); 2.90 (ddd, *J*=6.7, 3.9, 2.2 Hz, 1H, OCH (*trans*)); 2.93 (ddd, *J*=6.6, 4.2, 2.3 Hz, 1H, OCH (*trans*)); 3.03 (ddd, *J*=11.1, 5.7, 3.5 Hz, 1H, CHO (*cis* major)); 3.03 (ddd, *J*=5.8, 3.4, 2.6 Hz, 1H, CHO (*cis* minor)); 3.07 (dd, *J*=13.9, 6.2 Hz, 1H, CHC*H*$_2$Ph (*cis* major)); 3.07 (dd, *J*=13.8, 6.2 Hz, 1H, CHC*H*$_2$Ph (*cis* minor)); 3.15 (dd, *J*=13.9, 5.8 Hz, 1H, CHC*H*$_2$Ph (*cis* major)); 3.16 (dd, *J*=13.2, 5.9 Hz, 1H, CHC*H*$_2$Ph (*cis* minor)); 3.18 (dt, *J*=7.7, 4.4 Hz, 1H, OCH (*cis* major)); 3.24 (ddd, *J*=6.8, 5.7, 4.2 Hz, 1H, OCH (*cis* minor)); 3.68 (s, 3H, Me (*trans* minor)); 3.69 (s, 3H, Me (*trans* major)); 3.71 (s, 3H, Me (*cis* major)); 3.71 (s, 3H, Me (*cis* minor)); 4.87 (dt, *J*=7.0, 6.0 Hz, 1H, NCH (*cis* major)); 4.88 (dt, *J*=7.0, 6.0 Hz, 1H, NCH (*cis* minor)); 6.30 (d, *J*=7.8, 1H, NH (*cis* major)); 6.32 (d, *J*=8.0, 1H, NH (*cis* minor)); 6.37 (d, *J*=7.9, 1H, NH (*trans* major)); 6.38 (d, *J*=7.9, 1H, NH (*trans* minor)); 7.04–7.28 (m, 10H, Ph). ^{13}C NMR: 29.780 (PhCH$_2$*C*H$_2$ (*cis*)); 32.031 (PhCH$_2$CH$_2$ (*trans*)); 32.570 (Ph*C*H$_2$CH$_2$ (*cis*)); 33.424 (PhCH$_2$*C*H$_2$ (*trans*)); 35.286, 35.433 (*C*H$_2$CO (*cis*)); 37.888, 37.972 (CHC*H*$_2$Ph (*cis*)); 39.055 (*C*H$_2$CO (*trans*)); 52.321 (OMe); 53.255 (OCH (*cis*)); 53.401 (NCH); 54.723, 54.810 (OCH (*trans*)); 56.450 (CHO (*cis*)); 58.157, 58.216 (CHO (*trans*)); 126.140, 126.236, 127.160, 128.442, 128.548, 128.588, 129.234, 129.315, 135.820, 135.860, 140.931 (Ph); 169.411, 171.879 (CON, CO$_2$). MS: 368 (MH$^+$, 100), 350 (37), 180 (41). HRMS for $C_{22}H_{24}NO_4$: calcd 368.1862, found 368.1830.

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