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One-pot enzymatic desymmetrization and Ugi MCR

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Abstract—A new approach to the synthesis of chiral peptidomimetics is reported. It combines an enzymatic desymmetrization of 3-phenylglutaric anhydrides with a subsequent Ugi multi-component reaction in a one-pot, two-step procedure. NMR and CD spectroscopy was used to assign the configurations of obtained products. Our synthetic method is very efficient and it can easily be extended to other types of multi-component reactions and can be used for the preparation of chiral peptidomimetic libraries.
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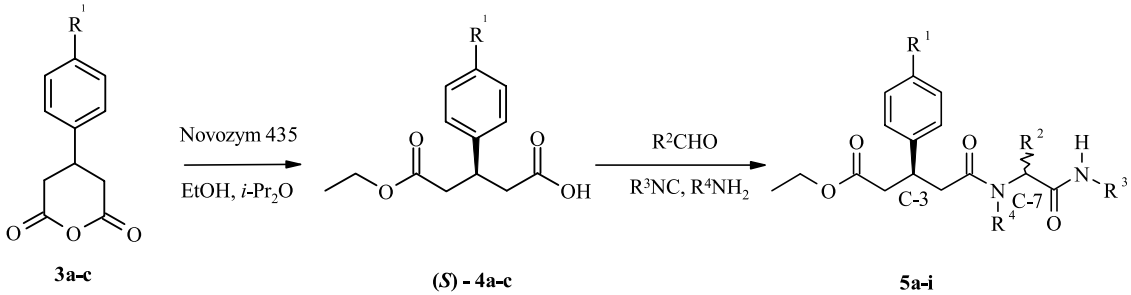
1. Introduction

Multi-component reactions (MCRs) are of great interest for medicinal chemistry.[1] MCRs can be efficiently used in the synthesis of chiral compounds.[2] They are also useful in peptidomimetic synthesis due to their ability to generate a large number of compounds efficiently in one or two synthetic steps.[3,4] Commonly used MCRs include the Ugi reaction.[5,6] These reactions are especially attractive as a one-pot tandem processes with other reactions.

Only a few examples can be found in the literature, in which one-pot, two-step and one-pot, three-step methodologies involving Ugi condensation were applied.[7–19] In the significant majority of these processes, the Ugi MCR is followed by a subsequent modification of the Ugi product, as acidic hydrolysis or hydroxyaminolysis[7] or post-condensation modifications leading to cyclic products.[8,9]

The generation of chiral combinatorial libraries by one-pot methodologies is much more challenging.[20] To gain access to the optically active reactants for MCRs at least one additional step is required. Routinely chiral compounds are obtained via stereoselective synthesis paths (including enzymatic resolution) or by chiral HPLC resolution of enantiomers. Unfortunately, constructing a combinatorial library for pharmaceutical purposes or asymmetric synthesis means that additional step(s) is/are involved.[21] In most cases, different types of chiral auxiliaries are used in these syntheses. This leads to substantial complication of the overall processes, since not all auxiliaries are cheap and readily available in both enantiomeric forms. Moreover, two additional steps are required for introduction and efficient removal of these groups. Recently, we announced a novel approach towards the synthesis of chiral combinatorial libraries.[22]

In this paper we present the results of our studies on the



Scheme 1. Combination of enzymatic desymmetrization with Ugi condensation.

Keywords: Enzyme; Desymmetrization; Peptidomimetic.
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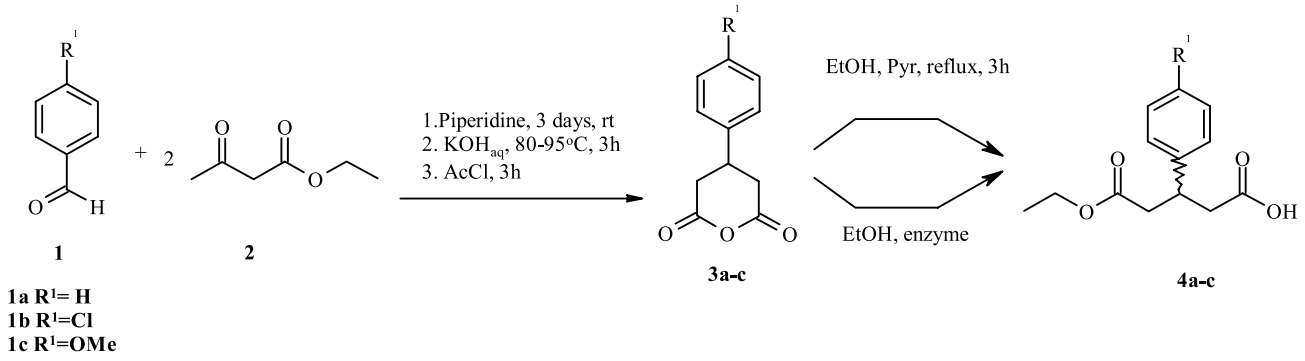

Scheme 2. The synthesis of monoesters **4**.

combination of multi-component reactions with enzymatic procedures (Scheme 1).

Our idea is based on the combination of enzymatic procedures with multi-component condensations as a one-pot, two-step reaction. We propose to use a *meso* reagent (**3**) as a substrate, which can be enzymatically desymmetrized into the desired optically active product (**4**). In this way, two steps: enzymatic reaction and subsequent reaction can be combined in one step. This two-step, one-pot approach is much simpler then the ones currently used, and application of chiral auxiliaries is omitted. We are unaware of precedent methodology combining an enzymatic procedure with an MCC.

2. Results

The 3-phenylglutaric anhydrides (**3**), required for the synthesis, were obtained according to the procedures described previously[23,24] from appropriate benzaldehydes (**1**) and ethyl acetylacetate (**2**) in yields of 41% for **3a**, 80% for **3b**, and 19% for **3c** (Scheme 2).

Since the carboxylic acid is one of the reactants in Ugi MCR, we decided to generate these chiral reagents from respective cyclic anhydrides **3**. Enzymatic desymmetrization of *meso*-anhydrides with alcohols is known in literature,[25–30] but it has been never applied for 3-phenylglutaric anhydrides.

For the preparation of chiral monoesters **4**, the following immobilized enzymes were used: Novozym 435 (CAL-B), Chirazyme L-2, c-f, c-3 lyso (CAL-B) and immobilized Amano PS lipase. Enzymes not only carried out the desymmetrization efficiently but the change of the enzyme provided access to different enantiomers (Table 1). The reactions reached full conversion within a few days and gave monoacids (**4**) in over 95% yields, while the same racemic esters were obtained in 91, 89, 63% for **4a**, **4b** and **4c**, respectively, according to the literature procedures.[23,24]

Absolute configurations of monoacids **4a** and **4b** were established by comparison to literature data (vide infra). We observed that while Novozym 435 and Chirazyme catalysed formation of (*S*)-**4a** monoacid (78 and 80% ee, respectively), the immobilized Amano PS lipase showed an opposite selectivity ((*R*)-enantiomer formed with 66% ee). Desymmetrization of anhydrides **3b** and **3c** led to the formation of respective monoacids with lower enantiomeric excess. According to our expectation, the enzyme changes the stereoselectivity and the kinetics of the desymmetrization reaction. An influence of substituent on phenyl ring is also observed. The presence of these substituents (4-Cl, for **4b** and 4-OMe, for **4c**) led to longer reaction time and lowered the optical purity.

Our initial idea of combination of Ugi four-component condensations with enzymatic desymmetrization was based on the assumption that both experimental procedures can be performed simultaneously, in the same solvent. Initially, we tried to perform the Ugi reaction in ethereal solvents, using racemic monoester **4a**, butylamine, 2-naphthaldehyde and ethyl isocyanoacetate as reagents (entry 1 in Table 2). The reaction did not occur. Addition of alcohol was necessary to complete the reaction. In the mixture of isopropyl ether and methanol (2:1, v/v) the reaction proceeded in 24 h and the desired product was obtained in 6% yield (entry 2 in Table 2). It is already known that aromatic aldehydes are not good substrates for Ugi reaction. For isovaleraldehyde, *n*-butylamine and benzyl isocyanate, the yield increased to 82% (entry 6 in Table 2). Interestingly, upon dilution of this

Table 1. Enzymatic desymmetrization of anhydrides **1**

Entry	Lipase	4a				4b				4c			
		Time (h)	Yield (%)	ee[20a] (%)	Conf.	Time (days)	Yield (%)	ee[20b] (%)	Conf.	Time (days)	Yield (%)	ee[20b] (%)	Conf.
1	Novozym 435	48	99	78	(*S*)	5	99	54	(*S*)	13	99	68	(*S*)
2	Chirazyme L-2	48	99	80	(*S*)	4	99	60	(*S*)	7	99	73	(*S*)
3	Amano PS immob.	48	95	66	(*R*)	4	99	14	(*R*)	7	99	52	(*S*)

Reagents and conditions: To the solution of anhydride **3** (0.05 mmol) in *iso*-propyl ether (1 mL) ethanol (0.075 mmol) was added, followed by respective lipase: Novozym 435–7.6 mg; Chirazyme L-2, c.-f., c-3, Amano PS—6.2 mg. The reaction was conducted until it reached full conversion and ee was determined by HPLC on Chiracel OD-H column.

Table 2. The synthesis of products **5a–i**

Entry	5	Acid 4	R^2	R^3	R^4	Solvent[a]	Ugi MCR		Enzymatic and Ugi reaction		
							Time (days)	Yield	Time (days)	Yield	$[\alpha]_D$ (benzene)
1	**5a**	**4a**	2-Naph	CH_2COOEt	*n*-Bu	A	4	0		—	
2	**5a**	**4a**	2-Naph	CH_2COOEt	*n*-Bu	B	1	6		—	
3	**5a**	(*S*)-**4a**	2-Naph	CH_2COOEt	*n*-Bu	B	1	6	2	6	
4	**5b**	(*S*)-**4a**	*p*-Br-Ph	Bn	*n*-Bu	B	17	32	15	31	−4.0 (*c* 1.29)
5	**5c**	(*S*)-**4a**	*i*-Bu	CH_2COOEt	*n*-Bu	B	9	49	9	49	−0.9 (*c* 1.30)
6	**5d**	**4a**	*i*-Bu	Bn	*n*-Bu	B	4	82		—	
7	**5d**	(*S*)-**4a**	*i*-Bu	Bn	*n*-Bu	B	5	81	2	65	−0.4 (*c* 1.31)
8	**5e**	(*S*)-**4b**	*i*-Bu	Bn	*n*-Bu	B	7	70	2	61	−4.9 (*c* 1.27)
9	**5f**	(*S*)-**4c**	*i*-Bu	Bn	*n*-Bu	B	7	72	2	78	−3.0 (*c* 1.28)
10	**5g**	(*S*)-**4a**	*i*-Bu	Bn	Bn	B	4	80	2	67	+9.0 (*c* 1.50)
11	**5h**	(*S*)-**4a**	*p*-Br-Ph	Bn	Bn	B	17	23	15	25	−13.8 (*c* 1.43)
12	**5i**	(*S*)-**4a**	2-Naph	CH_2COOEt	Bn	B	2	33		—	

[a] Solvents: A—*i*-Pr_2O, rt; B—*i*-Pr_2O/MeoH, 2:1, v/v, rt.

reaction mixture the yield of reaction decreased to 65% (concentrations of substrates are 0.042 and 0.170 M). Further, dilution decreased the yield to 44% and the reaction became poorly reproducible. In order to preserve reproducibility, all experiments were performed at concentration of substrates 0.1 M.

In the next experiments, we applied our two-step, one-pot approach based on combination of enzymatic desymmetrization of anhydrides **3** with subsequent Ugi MCR for the synthesis of compounds **5**. The same compounds were obtained in Ugi MCR with chiral or racemic acids **4**. The results are presented in Table 2.

In Ugi reaction with racemic acid **4a**, product **5a** was obtained in 6% yield (entry 3 in Table 2). The same yield was obtained when the reaction was repeated with chiral acid (*S*)-**4a** or when enzymatic desymmetrization was combined with Ugi MCR (entry 3 in Table 2). Better yields were obtained for *p*-bromobenzaldehyde as a substrate (entry 4 in Table 2) and our approach led to formation of the desired product in almost the same yield as for the two separate reactions. Optical rotation of compound **5b** proved that a chiral, nonracemic product **5c** was obtained. For isovaleraldehyde, the two-step approach leads to formation of a 1:1 diastereoisomeric mixture of products **5c** in 49% yield (entry 5 in Table 3). Our two-step but one-pot approach did not change the yield of reaction, and optical rotation of products proved that racemisation did not occur. It is interesting to note that Ugi reaction of racemic acid **4a** proceeds in 82% yield (entry 6 in Table 2). The same, but chiral product was obtained in lower, 67% yield, in two-step process. Our one-pot two-step process proceeds in 81% yield similar to that for Ugi reaction of racemic acid (entry 7 versus entry 6 in Table 3). Desymmetrization of 3-(4-chlorophenyl)-anhydride (**3b**) combined with Ugi condensation is also straightforward. The corresponding product **5e**, obtained in one-pot, two-step methodology, was formed in slightly lower yield (entry 8 in Table 3) in respect of the two-pot process.

It is evident from the data presented in Table 3, that the combination of enzymatic desymmetrization with Ugi MCR proceeds efficiently. In most cases, the yields of the one-pot, two-step procedure are similar to the yields of Ugi reaction performed on pure monoacid **4**.

We observed that all the products **5** consisted of a *syn*/*anti* diastereoisomeric mixture, in approximately 1:1 ratio on newly formed C-7 chiral centres, what was evident from NMR and HPLC data.

In the case of products **5c–f**, the diastereoisomers were separated by preparative TLC. Relative configurations at C-3 and C-7 carbons were assigned by ^{1}H NMR spectroscopy. The most distinctive ^{1}H NMR data of separated diastereoisomers of compounds **5c–f** are shown in Table 3.

The analysis of proton spectra led us to a conclusion that all less polar diastereoisomers of compounds **5c–f**-possess the same *anti* configuration, at C-3 and C-7 carbon atoms. Analogously, the more polar diastereoisomers possess relative *syn* configuration.

The most significant difference is observed for N*H* protons,

Table 3. The most distinctive ^{1}H NMR data for peptidomimetic **5c–f** diastereoisomers

Entry	Comp.	Chemical shifts δ (ppm) and coupling constant J_{gem} (Hz)			
		N*H*	NHCH_2R	CH_2CHPh	CH_3[a]
1	**5c** *anti*	6.55	3.76; 3.85 J_{gem}=18.0	2.66; 2.80 J_{gem}=15.4	0.84–0.96 (m)
2	**5c** *syn*	7.00	3.85; 3.98	2.60–2.80	0.79 (d, J=6.5)
3	**5d** *anti*	6.66	4.17; 4.33 J_{gem}=14.9	2.63; 2.75 J_{gem}=15.5	0.83–0.92 (m)
4	**5d** *syn*	6.95	4.35	2.64; 2.69	0.79 (d, J=6.5)
5	**5e** *anti*	6.67	4.18; 4.34 J_{gem}=14.8	2.63; 2.73 J_{gem}=16.6	0.84–0.92
6	**5e** *syn*	6.91	4.35	2.55–2.71	0.77 (d, J=6.5)
7	**5f** *anti*	6.68	4.17; 4.34 J_{gem}=14.9	2.59; 2.73 J_{gem}=15.4	0.82–0.92 (m)
8	**5f** *syn*	6.96	4.35	2.55–2.71	0.79 (d, J=6.5)

[a] For one of the CH_3 groups from *i*-Bu chain.

which are shifted downfield for all *syn* compounds ($\Delta\delta$ 0.28–0.45 ppm, Table 3). We postulate that intramolecular hydrogen bond formation can be responsible for this phenomenon. In case of opposite diastereoisomers such a bond is weakened due to steric repulsion. Spectral data suggest that the *syn* diastereoisomers can be folded analogously, as it is observed in β-turn mimetics,[31] while the *anti* diastereoisomers possess an open chain conformation.

2.1. Attempt to assign the absolute configurations by CD spectroscopy

An effort was also made to assign unambiguously the absolute configuration to compounds *syn*-**5d**, *anti*-**5d** and *syn*-**5c**, *anti*-**5c**. For this purpose, circular dichroism spectroscopy was chosen. UV and CD data of compounds **5c** and **5d** are presented in Table 4. As can be seen from the table, the less polar components of both reaction mixtures, namely compounds *syn*-**5c** and *syn*-**5d**, displayed the same shape of their CD curves in the 250–185 nm spectral range (Fig. 1).

Analogously, in the same spectral region (Table 4), CD curves of more polar components *anti*-**5d** and *anti*-**5c** are similar to each other, that is, the signs of particular Cotton effects (CEs) are the same with very similar amplitudes. In addition, their CD curves are in a mirror–image relationship to those of the less polar compounds. The only exception to this regularity presents the long-wavelength CE occurring at 268 nm being negative for all compounds investigated. This CE, associated with an electronic absorption observed at 257 nm, can be attributed to the ^1L_b benzene transition. According to the benzene sector rule, the negative sign of this CE points unambiguously to the (*S*) absolute configuration at the stereogenic centre contiguous to the benzene ring.[32] Thus, (3*S*,7*S*) configuration can be assumed for the *syn* diastereoisomer and (3*S*,7*R*) for the *anti* diastereoisomers. The presence of an additional phenyl substituent in compounds (3*S*,7*S*)-**5d** and (3*S*,7*R*)-**5d** (entries 1 and 2 in Table 4) does not affect this assignment because the sign of the ^1L_b CE depends exclusively upon the chirality of the chiral centre directly linked to the benzene ring. Thus, the configuration assignment made on the basis of the benzene sector rule corroborates nicely with the assignment previously done on the basis of NMR spectroscopy.

Independent determination of the absolute configuration at the second stereogenic centre, however, remains a much more difficult task. Different functional groups, present in the molecules, have their own contributions to the overall CD spectrum approximately at the same energy range. Thus, the most pronounced CE at ca. 230 nm poses a sum of contributions stemming from the amide, ester and phenyl groups. It has to be added that, due to the conformational mobility, different rotamers also contribute to the overall spectrum with their own CD. Therefore, the absolute configuration assignment to the second stereogenic centre (C-7) is impossible only on the basis of CD spectroscopy. Additional data is required to correlate the absolute configuration and the sign of the specific CD band. Nevertheless, on the basis of the same signs of the CE around 230 nm, we are able to state that the less and the more polar products have the same absolute configuration at the carbon atom directly attached to the tertiary amide nitrogen. Further study allowing the determination of the absolute configuration at this stereogenic centre is in progress in our laboratory.

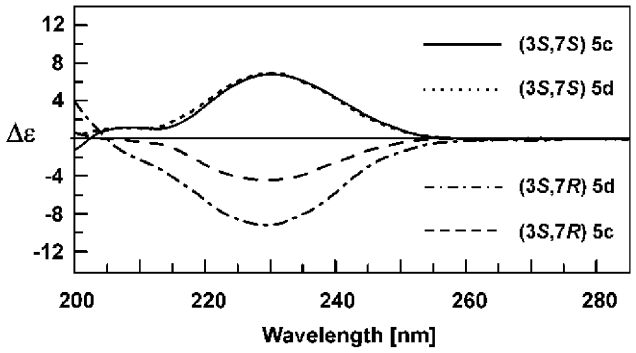

Figure 1. CD spectra of compounds (3*S*,7*S*)-**5d** (·····), (3*S*,7*S*)-**5c** (———), (3*S*,7*R*)-**5d** (–·–·–·–), and (3*S*,7*R*)-**5c** (– – – – – –) recorded in acetonitrile.

3. Conclusions

We developed a general, simple and efficient method for chiral peptidomimetic preparation. Combination of the enzymatic and Ugi reactions gave us access to the optically active compounds **5**. Both reactions can be performed separately or successively, without isolation of the intermediates. The latter approach evidently simplifies the overall process. In our opinion, the one-pot enzymatic desymmetrization followed by Ugi reaction can be readily extended to prepare chiral, Ugi-type combinatorial libraries starting from achiral substrates. This efficient process opens new options in organic chemistry. It can be easily extended to other types of reactions and used to generate chiral peptidomimetic libraries as well. According to our knowledge, this is the first example of combination of enzymatic procedures with multi-component conden-sations.

In enzymatic reactions, one can control the stereochemistry

Table 4. UV and CD data of compounds **5c** and **5d**—peptidomimetics obtained by Ugi reaction and diastereoisomers separations recorded in acetonitrile

Entry	Comp.	UV		CD			
		ε (λ)		$\Delta\varepsilon$ (λ)			
1	(3*S*,7*S*)-**5c** (*syn*)	280 (257)	15 900 (205^{sh})	+3.10 (193.0)	−0.46 (210.5)	−4.56 (228.5)	−0.05 (268.0)
2	(3*S*,7*R*)-**5c** (*anti*)	260 (257)	14 700 (205^{sh})	−0.69 (197.0)	+1.17 (207.0^{sh})	+6.92 (229.5)	−0.03 (268.0)
3	(3*S*,7*S*)-**5d** (*syn*)	450 (257)	24 500 (207^{sh})	+12.1 (191.5)	−2.40 (210.5^{sh})	−9.23 (229.5)	−0.03 (268.0)
4	(3*S*,7*R*)-**5d** (*anti*)	480 (257)	24 300 (207^{sh})	−1.68 (197.5)	+1.16 (209.5)	+6.96 (230.5)	−0.02 (268.0)

UV and CD values are given as ε (nm) and $\Delta\varepsilon$ (nm), respectively.

of C-3 carbon atom. Unfortunately, the C-7 center formed in the Ugi reaction cannot be controlled. The resulting mixtures of diastereoisomers can be readily separated using column chromatography.

An attempt was made to assign relative configuration in obtained products using NMR and CD spectroscopy. By proton NMR, the relative configurations of less polar diastereoisomers were assigned to be *anti*. Spectral data suggest that all more polar, *syn* diastereoisomers are folded, as it is analogously observed in β-turn mimetics. Currently, the absolute configurations of chiral products cannot be assigned using CD spectroscopy. Further studies into unambiguous configuration assignment by CD spectroscopy are in progress in our laboratory.

4. Experimental

4.1. General

NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard using a 200 MHz Varian Gemini 200 or a 500 MHz Bruker DRX 500 Avance spectrometers. Chemical shifts are reported in ppm and coupling constants (J) are given in Hertz (Hz). MS spectra were recorded on an API-365 (SCIEX) apparatus. IR spectra in $CHCl_3$ were recorded with a Perkin Elmer FT-IR Spectrum 2000 apparatus. Optical rotations were measured in 1 dm cell of 1 mL capacity using a Jasco DIP-360 polarimeter operating at 589 nm. HPLC analyses were performed on a LC-6A Shimadzu apparatus with an UV SPD-6A detector and a Chromatopac C-R6A analyser.

The determination of enantiomeric excess of monoesters **4** was performed on a Chiracel OD-H column 4.6 mm×250 mm (from Diacel Chemical Ind., Ltd) equipped with a pre-column (4 mm×10 mm, 5 μ). The determination of diastereoisomeric ratio of the Ugi products **5** was performed on a Kromasil SI 60 Å column (4.6 mm×250 mm) from Eka Chemicals.

CD spectra were measured using a JASCO J-715 spectropolarimeter in 1 cm and 1 mm cells in acetonitrile at concentrations approximately of 2×10^{-4} M. The elemental analyses were performed on a CHN Perkin–Elmer 240 apparatus. Melting points are uncorrected. All reactions were monitored by TLC on Merck silica gel plates 60 F_{254}. Preparative TLC was performed on 0.5 mm Kieselgel 60 F_{254} preparative plates. Column chromatography was performed on Merck silica gel 60/230–400 mesh.

Immobilized lipase Amano PS-C was purchased from Amano. Chirazyme L-2, c.-f., c-3, lyo. (*C. antarctica* lipase type B) was purchased from Roche. Novozym 435 was purchased from Novo Nordisk. All the chemicals were obtained from common chemical suppliers. The solvents were of analytical grade.

4.2. Chemistry

4.2.1. 3-Phenylglutaric acid anhydride (3a). The anhydride **3a** was obtained according to the literature procedures[23,24] in 40% yield as white crystals (EtOAc/hexane): mp 104–105 °C (lit. 104–105[33]); ^{1}H NMR δ 2.86 (dd, J=11.3, 17.2 Hz, 2H), 3.08 (dd, J=4.5, 17.2 Hz, 2H), 3.30–3.50 (m, 1H), 6.90–7.40 (m, 5H); ^{13}C NMR δ 34.7, 37.7, 126.8, 128.7, 129.9, 139.7, 166.6.

4.2.2. 3-(4-Chlorophenyl)glutaric acid anhydride 2b. The anhydride **3b** was prepared in 80% overall yield as white crystals (EtOAc/hexane): mp 126 °C (lit. 131–133[34]); R_f=0.36 ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR δ 2.82 (dd, J=11.4, 17.2 Hz, 2H), 3.08 (dd, J=4.5, 17.2 Hz, 2H), 3.34–3.50 (m, 1H), 6.91 (d, J=8.4 Hz, 2H), 7.12 (d, J=8.8 Hz, 2H); ^{13}C NMR δ 34.2, 37.6, 37.8, 128.1, 128.2, 130.1, 134.6, 138.0, 166.0; Anal. Calcd for $C_{11}H_9ClO_3$: C, 58.81; H, 4.04. Found: C, 58.19; H, 4.05.

4.2.3. 3-(4-Methoxyphenyl)glutaric acid anhydride 3c. The anhydride **3c** was prepared in 19% overall yield as white crystals (EtOAc/hexane): 155–156 °C (lit. 155–157[35]); R_f=0.60 (hexane/EtOAc, 6:4); ^{1}H NMR δ 2.82 (dd, J=11.2, 17.0 Hz, 2H), 3.08 (dd, J=4.5, 17.0 Hz, 2H), 3.31–3.44 (m, 1H), 3.81 (s, 1H), 6.91 (d, J=8.4 Hz, 2H), 7.12 (d, J=8.8 Hz, 2H); ^{13}C NMR δ ^{13}C NMR δ 33.3, 37.3, 55.3, 114.7, 127.3, 131.0, 159.1, 166.0; Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.90; H, 5.44.

4.3. General procedure for chemical synthesis of 3-arylglutaric acid monoethyl esters (4)

Model racemic monoethyl esters **4** were obtained by the procedure described before[24] in 91% yield for **4a** yield 89% for **4b**, 63% for **4c**, respectively. Spectral and physical data are in accordance with data obtained for chiral monoesters **4** obtained in enzymatic reaction.

4.4. General procedure of synthesis of chiral monoesters of 3-arylglutaric acids (4) with Novozym 435 in *iso*-propyl ether

To the solution of anhydride (**3**, 0.5 mmol) dissolved in *iso*-propyl ether (10 mL), lipase (75.0 mg) and absolute ethanol (0.80 mmol) were added. The reaction was carried out at room temperature and its progress was monitored by TLC ($CHCl_3$/MeOH/HCOOH, 100:2:0.05). The enzyme was filtered off and residue was concentrated to give a monoester **4** as colourless oil. The product was recrystallized from Et_2O/hexane (or EtOAc/hexane).

4.4.1. (*S*)-3-Phenylglutaric acid monoethyl ester, (*S*)-4a. The reaction reached full conversion after 43 h to give (*S*)-**4a** in 99% yield as a colourless oil. After crystallisation (Et_2O/hexane), the ester was obtained as white crystals in 66% yield. Mp 58–59 °C (lit. 59–60[24]); $[\alpha]_D^{20}$ −9.5 (*c* 1.10, benzene) (lit. $[\alpha]_D^{25}$ 9.47 (*c* 1.1, benzene) for (*R*)-enantiomer)[36]; HPLC analysis [hexane/*i*-PrOH/CH_3COOH, 185:14:1; λ=226 nm; 1.0 ml/min; $t_R(S)$=8.26 min, $t_R(R)$=8.95 min)] 78% ee; R_f=0.24 ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (t, J=7.1 Hz, 3H), 2.68–2.81 (m, 4H), 3.10–3.25 (m, 1H), 4.08 (q, J=7.1 Hz, 2H), 7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7, 38.6, 41.3, 61.1, 113.4, 127.8, 129.1, 142.8, 156.9, 172.1, 178.1; IR ($CHCl_3$) ν_{max}: 3513 (OH), 1727 (C=O) cm^{-1}; LSIMS (+), NBA, (*m/z*), 259

([M+Na]$^+$, 56%), 237 ([M+H]$^+$, 100%); LSIMS (+), NBA+NaOAc, (*m/z*), 281 ([M+2Na]$^+$, 100%), 259 ([M+Na]$^+$, 41%).

4.4.2. (*S*)-3-(4-Chlorophenyl)glutaric acid monoethyl ester, (*S*)-4b. The reaction reached full conversion after 4 days to give (*S*)-**4b** as an oil in 99% yield. After crystallisation, the ester was obtained as white crystals in 61% yield. Mp 56 °C (Et_2O/hexane); $[\alpha]_D^{20}$ −3.8 (*c* 0.90, $CHCl_3$); HPLC analysis [hexane/*i*-PrOH/CH_3COOH, 185:14:1; λ=226 nm; 1.0 ml/min; $t_R(S)$=9.0 min, $t_R(R)$=9.8 min]; R_f=0.27 ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (t, *J*=7.1 Hz, 3H), 2.69 (m, 4H), 3.60 (m, 1H), 4.03 (q, *J*=7.1 Hz, 2H), 7.15 (d, *J*=8.6 Hz, 2H), 7.34 (d, *J*=8.6 Hz, 2H), 10.7 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7, 38.0, 40.7, 41.1, 61.2, 115.1, 129.2, 129.3, 129.4, 133.3, 141.2, 171.8, 177.8; Anal. Calcd for $C_{13}H_{15}ClO_4$: C, 57.68; H, 5.59. Found: C, 57.59; H, 5.74.

4.4.3. (*S*)-3-(4-Methoxyphenyl)glutaric acid monoethyl ester, (*S*)-4c. The reaction reached full conversion after 19 days to give (*S*)-**4c** as an oil in 93% yield. After crystallisation (Et_2O/hexane), the ester was obtained as white crystals in 71% yield. Mp 75–77 °C (lit. 78[37]); $[\alpha]_D^{20}$ +8.3 (*c* 0.95, EtOH); HPLC analysis [hexane/*i*-PrOH/CH_3COOH 193:6:1; λ=226 nm; 0.7 ml/min; $t_R(S)$=26.5 min, $t_R(R)$=29.1 min] 69% ee; R_f=0.28 ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (t, *J*=7.2 Hz, 3H), 2.74 (m, 4H), 3.63 (m, 1H), 3.83 (s, 3H), 4.09 (q, *J*=7.2 Hz, 2H), 6.9 (d, *J*=7.0 Hz, 2H), 7.19 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 41.1, 41.1, 55.9, 60.9, 114.8, 129.4, 136.0, 159.4, 172.9, 174.8; Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.12; H, 6.81.

4.5. General procedure for synthesis of compounds 5

To a solution of monoester **4** (1.0 mmol) in *iso*-propyl ether/methanol mixture (2:1, v/v, 5 mL), aldehyde (1.1 mmol), amine (1.1 mmol) and isonitrile (1.0 mmol) were added subsequently at 0 °C. The reaction was allowed to warm up to room temperature and its progress was monitored by TLC. After the reaction was completed, the solvent was removed in vacuo and the residue was poured into 10 mL of EtOAc. The organic solution was washed consecutively with hydrochloric acid (1 M, 10 mL), sodium hydroxide (1 M, 10 mL), saturated sodium sulphite solution (10 mL) and brine (10 mL), and dried ($MgSO_4$). The solvent was evaporated and the product **5** was isolated by flash chromatography.

4.6. General experimental procedure for tandem enzymatic-Ugi reaction

To a solution of glutaric anhydride **3** (1.0 mmol) in 10 mL of *iso*-propyl ether, lipase (150 mg) and ethanol (1.50 mmol, 90 μL, 99.8% pure) were added. The reaction was carried out at room temperature and its progress was monitored by TLC. After all the substrate reacted, the enzyme was filtered off and washed with *iso*-propyl ether and concentrated to 1% of volume, then *iso*-propyl ether/methanol mixture (2:1, v/v, 5 mL) was added. Subsequently, the aldehyde (1.1 mmol), the amine (1.1 mmol) and the isonitrile (1.0 mmol) were added to the resulting solution cooled to 0 °C. The reaction was allowed to warm up to room temperature and its progress was monitored by TLC. When the reaction was completed, the solvent was removed in vacuo and the residue was poured into 10 mL of EtOAc. The organic solution was washed consecutively with hydrochloric acid (1 M, 10 mL), sodium hydroxide (1 M, 10 mL), saturated sodium sulphite solution (10 mL) and brine (10 mL), and dried ($MgSO_4$). The solvent was evaporated and the product was isolated by flash chromatography.

4.6.1. Compound 5a (*syn/anti* mixture). Yellow oil, R_f=0.24 (hexane/EtOAc/CH_3COOH, 7:3:0.17); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.80–1.50 (m, 13H), 2.40–2.90 (m, 4H), 3.15–3.30 (m, 2H), 3.47 (q, *J*=7.0 Hz, 2H), 3.70–3.90 (m, 1H), 4.00–4.10 (m, 2H), 4.47 (m, 2H), 5.83 (s, 1H, rotamers), 6.07 (s, 1H, rotamers), 6.23 (m, 1H, NH_{anti}), 6.46 (m, 1H, NH_{syn}), 6.8–7.8 (m, 12H). MS (ESI): *m/z*=583 ([M+Na]$^+$, 100%); (ESI-MS HR: *m/z* Calcd for $C_{33}H_{40}N_2O_6Na$: 583.2779. Found: 583.2783.

4.6.2. Compound 5b (*syn/anti* mixture). Yellow oil; R_f=0.32 (hexane/EtOAc, 7:3); $[\alpha]_D^{32}$ −4.0 (*c* 1.29, benzene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.71–0.81 (m, 3H), 1.12 (t, *J*=7.1 Hz, 3H), 1.00–1.50 (m, 4H), 2.68–2.90 (m, 4H), 3.10–3.30 (m, 2H), 3.68–3.90 (m, 1H), 3.93–4.15 (m, 2H), 4.44 (dd, *J*=5.9, 10.5 Hz, 2H), 5.62 (s, 1H, rotamers), 5.87 (s, 1H, rotamers), 6.45–6.60 (m, 1H, NH_{anti}), 6.83–6.90 (m, 1H, NH_{syn}), 7.04 (dd, *J*=8.6, 16.4 Hz, 2H), 7.15–7.30 (m, 10H), 7.37 (d, *J*=8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ:13.5, 14.0, 19.9, 31.6, 38.6, 38.8, 39.3, 39.4, 40.4, 43.6, 46.5, 60.3, 61.2, 62.7, 122.0, 126.7, 126.8, 127.0, 127.3, 127.5, 127.6, 128.5, 130.5, 130.6, 131.5, 134.2, 137.9, 142.8, 169.2, 171.7, 172.1; MS (ESI): *m/z*=617 ([M+Na]$^+$, 100%), 615 ([M+Na]$^+$; 76%); ESI-MS HR: *m/z* Calcd for $C_{32}H_{37}N_2O_4NaBr$: 617.1829. Found: *m/z*: 617.1796.

4.6.3. Compound 5c (*syn/anti* mixture). Reaction time: 9 days. The product was purified by flash chromatography to give two fractions R_{f1}=0.26—*anti*-diastereoisomer and R_{f2}=0.15—*syn*-diastereoisomer (hexane/EtOAc, 7:3) in 49% total yield as viscous transparent oil. $[\alpha]_{D\,syn/anti}^{34}$ −0.9 (*c* 1.30, benzene).

4.6.4. Compound (3*S*,7*R*)-5c (*anti*-diastereoisomer). Transparent oil; R_f=0.26 (hexane/EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84–0.096 (m, 9H) 1.15 (t, *J*=7.1 Hz, 3H), 1.26 (t, *J*=7.1 Hz, 3H), 1.25–1.32 (m, 2H), 1.35–1.45 (m, 2H), 1.48–1.56 (m, 2H), 1.75–1.81 (m, 1H), 2.66 (dd, *J*=7.7, 15.4 Hz, 1H), 2.71–2.77 (m, 2H), 2.80 (dd, *J*=7.1, 15.4 Hz, 1H), 3.05–3.20 (m, 2H), 3.76 (dd, *J*=5.7, 18.0 Hz, 1H), 3.85 (dd, *J*=6.0, 18.0 Hz, 1H), 3.77–3.82 (m, 1H), 4.04 (dq, *J*=2.6, 7.1 Hz, 2H), 4.17 (q, *J*=7.1 Hz, 2H), 4.96 (t, *J*=7.0 Hz, 1H), 6.55 (br s, 1H), 7.17–7–21 (m, 1H), 7.22–7.30 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 13.6, 14.0, 14.1, 20.2, 22.2, 22.5, 22.8, 24.7, 32.2, 36.7, 38.9, 39.7, 40.5, 41.1, 45.5, 60.4, 61.1, 126.8, 127.4, 128.5, 143.1, 169.4, 171.8, 172.7; MS (ESI): *m/z*=513 ([M+Na]$^+$, 64%), 491 ([M+H]$^+$, 100%), ESI-MS HR: *m/z* Calcd for $C_{27}H_{43}N_2O_6$: 491.3121. Found: *m/z*: 491.3134.

4.6.5. Compound (3*S*,7*S*)-5c (*syn* diastereoisomer). Transparent oil; R_f=0.15 (hexane/EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (d, J=6.5 Hz, 3H), 0.85 (d, J=6.6 Hz, 3H), 0.88–0.97 (m, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.24–1.32 (m, 2H), 1.35–1.55 (m, 4H), 1.68–1.75 (m, 1H), 2.60–2.80 (m, 4H), 3.05–3.20 (m, 2H), 3.73–3.84 (m, 1H), 3.85 (d, J=5.3 Hz, 1H), 3.98 (d, J=6.3 Hz, 1H), 4.00–4.08 (m, 2H), 4.17 (q, J=7.1 Hz, 2H), 4.97 (t, J=7.4 Hz, 1H), 7.00 (t, J=5.3 Hz, 1H), 7.17–7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.0, 14.1, 20.3, 22.1, 22.8, 24.5, 31.9, 36.5, 38.8, 39.6, 40.7, 41.1, 60.4, 61.1, 126.8, 127.2, 127.4, 128.5, 143.1, 169.5, 172.0, 172.1, 172.8; MS (ESI): m/z=513 ($[M+Na]^+$, 50%), 491 ($[M+H]^+$, 100%), ESI-MS HR: m/z Calcd for $C_{27}H_{43}N_2O_6$: 491.3121. Found: m/z: 491.3105.

4.6.6. Compound (3*S*,7*RS*)-5d. Reaction time: 2 days. The product was purified by flash chromatography (R_f=0.23, hexane/EtOAc, 8:2) and obtained as a colourless oil in 65% yield. The ^{1}H NMR spectrum was a superposition of 2 separate diastereoisomers. ESI-MS: m/z=517 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{42}N_2O_4Na$: 517.3037. Found: 517.3028; $[\alpha]^{26}_{D\,syn/anti}$ −0.4 (*c* 1.31, benzene). The diastereoisomers (in 1.1:1 ratio) were separated by preparative TLC (R_f= 0.16 and 0.15, hexane/*i*-PrOH, 95:5; 6 times reversed).

4.6.7. Compound (3*S*,7*R*)-5d (*anti*-diastereoisomer). Transparent oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83–0.92 (m, 9H), 1.14 (t, 3H, J=7.1 Hz), 1.17–1.33 (m, 4H) 1.36–1.48 (m, 1H), 1.49–1.61 (m, 1H), 1.69–1.84 (m, 1H), 2.63 (dd, J=7.5, 15.5 Hz, 1H), 2.66–2.72 (m, 2H), 2.75 (dd, J=7.3, 15.5 Hz, 1H), 3.05–3.15 (m, 2H), 3.73 (quintet, 1H, J=7.3 Hz), 4.01 (dq, J=3.6, 7.1 Hz, 2H), 4.17 (dd, J=5.6, 14.9 Hz, 1H), 4.33 (dd, J=6.4, 14.9 Hz, 1H), 4.94 (br s, 1H), 6.66 (br s, 1H), 7.13–7.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.0, 20.2, 22.2, 22.9, 24.7, 32.0, 36.7, 38.8, 39.7, 40.5, 43.2, 45.2, 60.4, 126.8, 126.9, 127.1, 127.2, 127.3, 127.5, 127.7, 128.4, 128.5, 128.6, 138.4, 143.0, 171.4, 171.8, 172.5; ESI-MS: m/z=517 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{42}N_2O_4Na$: 517.3037. Found: 517.3062.

4.6.8. Compound (3*S*,7*S*)-5d (*syn*-diastereoisomer). Transparent oil; R_f=0.23 (hexane/EtOAc, 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (d, J=6.5 Hz, 3H), 0.82–0.97 (m, 6H), 1.12 (t, J=7.1 Hz, 3H), 1.18–1.33 (m, 4H), 1.35–1.45 (m, 1H), 1.47–1.57 (m, 1H), 1.70–1.77 (m, 1H), 2.64 (dd, J=5.4, 7.3 Hz, 2H)), 2.69 (dd, J=7.3, 8.5 Hz, 2H), 3.05–3.15 (m, 2H), 3.75 (quintet, J=7.3 Hz, 1H), 3.98 (dq, J=4.3, 7.1 Hz, 2H), 4.35 (d, J=6.0 Hz, 2H), 4.94 (t, 1H, J=7.4 Hz), 6.95 (br s, 1H), 7.14–7.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.0, 20.2, 22.1, 22.2, 22.9, 24.6, 31.9, 36.6, 38.8, 39.5, 40.8, 43.3, 45.0, 60.4, 126.8, 127.1, 127.2, 127.7, 128.5, 128.6, 138.4, 140.1, 171.5, 172.0, 172.6; ESI-MS: m/z=518 517 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{42}N_2O_4Na$: 517.3037. Found: 517.3020.

4.6.9. Compound (3*S*,7*RS*)-5e. Reaction time: 2 days. The product was purified by flash chromatography (R_f=0.41, hexane/EtOAc, 7:3) and obtained in 61% yield as colourless oil that solidified. ^{1}H NMR spectrum was superposition of two separated diastereoisomers. ESI-MS: m/z=552 ($[M+Na]^+$, 5%), 551 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{41M2}O_4NaCl$: 551.2647. Found: 551.2650; $[\alpha]^{26}_{D\,syn/anti}$ −4.9 (*c* 1.27, benzene). The diastereoisomers (in 1.1:1 ratio) were separated by PTLC (R_f= 0.15 and 0.14, respectively, hexane/*i*-PrOH, 95:5; 8 times reversed).

4.6.10. Compound (3*S*,7*R*)-5e (*anti*-diastereoisomer). Colourless oil; R_f=0.41 (hexane/EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84–0.92 (m, 9H), 1.15 (t, 3H, J=7.1 Hz), 1.18–1.33 (m, 4H), 1.35–1.48 (m, 1H), 1.50–1.59 (m, 1H), 1.73–1.85 (m, 1H), 2.63 (dd, J=7.8, 15.6 Hz, 1H), 2.67–2.73 (m, 2H), 2.73 (dd, J=7.0, 15.6 Hz, 1H), 3.05–3.20 (m, 2H), 3.73 (quintet, J=7.3 Hz, 1H), 4.01 (dq, J=3.5, 7.1 Hz, 2H), 4.18 (dd, J=5.6, 14.8 Hz, 1H), 4.34 (dd, J=6.4, 14.8 Hz, 1H), 4.91 (t, J=6.0 Hz, 1H), 6.67 (br s, 1H), 7.13–7.19 (m, 4H), 7.20–7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.1, 20.2, 22.2, 22.8, 24.7, 32.0, 36.7, 38.1, 39.4, 40.4, 43.2, 45.2, 60.5, 127.2, 127.6, 128.5, 128.6, 128.7, 132.6, 138.3, 141.6, 171.3, 171.5, 172.2; ESI-MS: m/z=552 ($[M+Na]^+$, 6%), 551 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{41}N_2O_4NaCl$: 551.2647. Found: 551.2661.

4.6.11. Compound (3*S*,7*S*)-5e (*syn*-diastereoisomer). Colourless oil, R_f=0.41 (hexane/EtOAc, 7:3).^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (d, J=6.5 Hz, 3H), 0.84–0.90 (m, 6H), 1.14 (t, J=7.1 Hz, 3H), 1.17–1.34 (m, 4H), 1.35–1.44 (m, 1H), 1.49–1.57 (m, 1H), 1.67–1.74 (m, 1H), 2.55–2.71 (m, 4H), 3.08–3.15 (m, 2H), 3.74 (quintet, J=7.3 Hz, 1H), 3.99 (dq, J=7.1, 4.5 Hz, 2H), 4.35 (d, J=5.9 Hz, 2H), 4.92 (t, J=7.3 Hz, 1H), 6.91 (br s, 1H), 7.13 (dd, J=1.8, 6.6 Hz, 2H), 7.19–7.27 (m, 5H), 7.28–7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 13.9, 20.1, 22.0, 22.7,, 24.4, 31.8, 36.4, 38.0, 39.1, 40.5, 43.2, 44.7, 60.4, 127.1, 127.6, 128.3, 128.4, 128.5, 132.4, 138.2, 141.3, 171.2, 171.5, 172.1; ESI-MS: m/z=552 ($[M+Na]^+$, 6%), 551 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{41}N_2O_4NaCl$: 551.2647. Found: 551.2630.

4.6.12. Compound (3*S*,7*RS*)-5f. Reaction time: 2 days. The product was purified by flash chromatography (R_f=0.36, hexane/EtOAc, 7:3) and obtained as colourless oil in 78% yield. ^{1}H NMR spectrum was superposition of two separated diastereoisomers. ESI-MS: m/z=547 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{31}H_{44}N_2NaO_4$: 547.3137. Found: 547.3139; $[\alpha]^{26}_{D\,syn/anti}$ −3.0 (*c* 1.28, benzene). The diastereoisomers (in 2.4:1 ratio) were separated by PTLC (R_f=0.15 and 0.14, hexane/*i*-PrOH, 95:5; 11 times reversed).

4.6.13. Compound (3*S*,7*R*)-5f (*anti*-diastereoisomer). Colourless oil; R_f=0.36 (hexane/EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82–0.92 (m, 9H), 1.14 (t, J=7.1 Hz, 3H), 1.18–1.35 (m, 4H) 1.36–1.47 (m, 1H), 1.50–1.59 (m, 1H), 1.75–1.83 (m, 1H), 2.59 (dd, J=7.7, 15.4 Hz, 1H), 2.62–2.69 (m, 2H), 2.73 (dd, J=7.2, 15.4 Hz, 1H), 3.10 (t, J=8.1 Hz, 2H), 3.73 (s, 3H), 3.68–3.80 (m, 1H), 4.01 (dq, J=7.3, 4.0 Hz, 2H), 4.17 (dd, J=5.7, 14.9 Hz, 1H), 4.34 (dd, J=5.9, 14.8 Hz, 1H), 4.94 (t, J=7.0 Hz, 1H), 6.68 (br s, 1H), 6.77–6.82 (m, 2H), 7.09–7.19 (m, 2H), 7.20–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.1, 20.2,

22.2, 22.9, 24.7, 32.1, 36.7, 38.1, 39.9, 41.0, 43.2, 45.3, 55.2, 60.4, 113.9, 127.1, 127.2, 127.5, 127.7, 128.2, 128.3, 128.4, 128.5, 135.0, 138.4, 158.4, 171.5, 171.9, 172.7.

4.6.14. Compound (3*S*,7*S*)-5f (*syn*-diastereoisomer). Colourless oil; R_f=0.36 (hexane/EtOAc, 7:3); $[\alpha]_D^{26}$ −0.4 (*c* 1.31, benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (d, 3H, *J*=6.5 Hz), 0.83–0.90 (m, 6H), 1.14 (t, 3H, *J*=7.1 Hz), 1.17–1.34 (m, 4H), 1.35–1.45 (m, 1H), 1.49–1.57 (m, 1H), 1.68–1.76 (m, 1H), 2.55–2.71 (m, 4H), 3.07–3.15 (m, 2H), 3.76 (s, 3H), 3.74–3.67 (m, 1H), 3.94–4.05 (m), 4.35 (d, *J*= 6.0 Hz, 2H), 4.93 (t, *J*=7.3 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 6.96 (br s, 1H), 7.11 (d, *J*=8.7 Hz, 2H), 7.20–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.1, 20.3, 22.2, 22.9, 24.6, 32.0, 36.6, 38.1, 39.7, 41.0, 43.3, 45.0, 55.2, 60.4, 113.9, 127.2, 127.7, 128.2, 128.4, 128.5, 135.0, 138.4, 158.4, 171.5, 172.1, 172.8.

4.6.15. Compound (3*S*,7*RS*)-5g. Colourless oil; R_f=0.41 (hexane/EtOAc, 7:3); $[\alpha]_{D\,syn/anti}^{26}$ +9.0 (*c* 1.50, benzene); ^{1}H NMR (200 MHz, $CDCl_3$) (0.60–0.88 (m, 6H), 1.14 (dt, *J*=1.0, 7.1 Hz, 3H), 1.20–1.50 (m, 2H), 1.61–1.78 (m, 1H), 2.48–2.78 (m, 4H), 3.68–3.84 (m, 1H), 4.01 (dq, *J*=3.1, 7.1 Hz, 2H), 4.30–4.41 (m, 2H), 4.41–4.53 (m, 2H), 5.06 (dt, *J*=3.2, 7.0 Hz, 1H), 6.57 (t, *J*=5.7 Hz, 1H$_{anti}$), 6.95 (t, *J*=5.7 Hz, 1H$_{syn}$), 7.02–7.40 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) (14.1, 22.4, 22.6, 22.7, 25.0, 25.1, 36.9, 37.0, 38.6, 40.0, 40.1, 40.4, 40.7, 43.3, 48.3, 48.4, 56.0, 56.1, 60.3, 125.9, 126.7, 127.1, 127.2, 127.5, 127.9.128.3, 128.4, 128.6, 127.1, 137.2, 138.1, 142.7, 142.8, 170.3, 170.4, 171.5, 171.6, 173.7; MS (ESI): *m*/*z*= 551 ([M+Na]$^+$, 100%), 529 ([M+H]$^+$, 18%), ESI-MS HR *m*/*z* Calcd for $C_{33}H_{40}N_2O_4Na$: 551.2880. Found: *m*/*z:* 551.2877.

4.6.16. Compound (3*S*,7*RS*)-5h (*syn*/*anti* mixture). Yellow oil; R_f=0.20 (hexane/EtOAc, 7:3); $[\alpha]_{D\,syn/anti}^{26}$ +13.8 (*c* 1.43, benzene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, *J*=7.0 Hz, 3H), 2.48–2.85 (m, 4H), 3.68–3.90 (m, 1H), 4.01 (q, *J*=7.0 Hz, 2H), 4.30–4.70 (m, 4H), 5.63 (s, 1H, rotamers), 5.90 (s, 1H, rotamers), 6.23–6.38 (m, 1H$_{anti}$), 6.48–6.58 (m, 1H$_{syn}$), 6.80–7.50 (m, 19H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 32.0, 38.5, 39.4 39.9, 40.5, 43.6, 49.8, 50.5, 60.3, 60.4, 61.7, 63.0, 122.3, 122.4, 125.9, 126.6, 126.9, 127.1, 127.2, 127.4, 127.5, 128.3, 128.4, 128.7, 131.0, 131.4, 131.6, 136.4, 137.6, 142.6, 142.7, 171.6, 172.5, 172.8; MS (ESI): *m*/*z*=651 ([M+Na]$^+$, 100%), 649 ([M+Na]$^+$, 58%); ESI-MS HR *m*/*z* Calcd for $C_{35}H_{35}N_2O_4NaBr$: 651.1649. Found: 651.1651.

4.6.17. Compound (3*S*,7*RS*)-5i (*syn*/*anti* mixture). Yellow oil; R_f=0.33 (hexane/EtOAc/CH_3COOH, 7:3:0.17); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (dt, *J*=2.0, 7.1 Hz, 3H), 1.17 (dt, *J*=2.1, 7.1 Hz, 3H), 2.4–2.8 (m, 4H), 3.7 (m, 1H), 3.92 (m, 2H), 4.1 (m, 4H), 4.47 (m, 2H), 5.83 (s, 1H, rotamers), 6.07 (s, 1H, rotamers), 6.23 (m, 1H$_{syn}$, 6.46 (m, 1H, 1H$_{anti}$, 6.8–7.8 (m, 17H); MS (ESI): *m*/*z*=617 ([M+Na]$^+$, 100%), ESI-MS HR *m*/*z* Calcd for $C_{36}H_{38}N_2O_6Na$: 617.2627. Found: (*m*/*z*): 617.2643.

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