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PAPER

Diversity oriented and chemoenzymatic synthesis of densely functionalized pyrrolidines through a highly diastereoselective Ugi multicomponent reaction†

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A highly diastereoselective Ugi reaction involving a chiral cyclic imine, two enantiomerically pure isocyanides and various carboxylic acids was employed for the synthesis of polyfunctionalized pyrrolidines. Both chiral substrates have been efficiently prepared by chemoenzymatic methodologies from readily available achiral substrates. This highly convergent approach can find an application in the fragment-based drug discovery process.

Introduction

Fragment-based drug discovery (FBDD)[1,2] represents a fast growing screening methodology in medicinal chemistry, whose concept was proposed in 1981.[3] This approach was conceived as an efficient alternative to the hit-to-lead process based on high throughput screening (HTS). In HTS the activity of very large collections of quite complex molecules is assayed on a specific target, usually a protein. However, this method is hampered by the need for large libraries, because the number of different structures grows exponentially as the number of heavy (non-hydrogen) atoms increases. On the contrary, in FBDD small libraries (1000–2000 molecules) of low-weight molecules (MW < 250 Da) may be sufficient for disclosing fragments able to give single-site interactions. This weak binding activity towards the protein is studied employing several biophysical techniques, such as NMR or X-ray crystallography. In this way it is possible to evaluate the key weak interactions and to modulate them by an appropriate choice of the decorations on single fragments. Moreover, after finding different fragments able to interact with neighbouring portions of the target, they can be combined (linked or merged) in order to check if a match of activity occurs. Indeed, the fragment can be used as a seed for growing, through rationally designed chemical transformations, a larger molecule, to give additional and more efficient interactions. With respect to HTS, FBDD therefore allows a more thorough exploration of the chemical space.

However, after finding active fragments, an efficient and convergent methodology for joining them, possibly to a rigid scaffold, is needed. We would like to present here a general strategy designed towards this goal.

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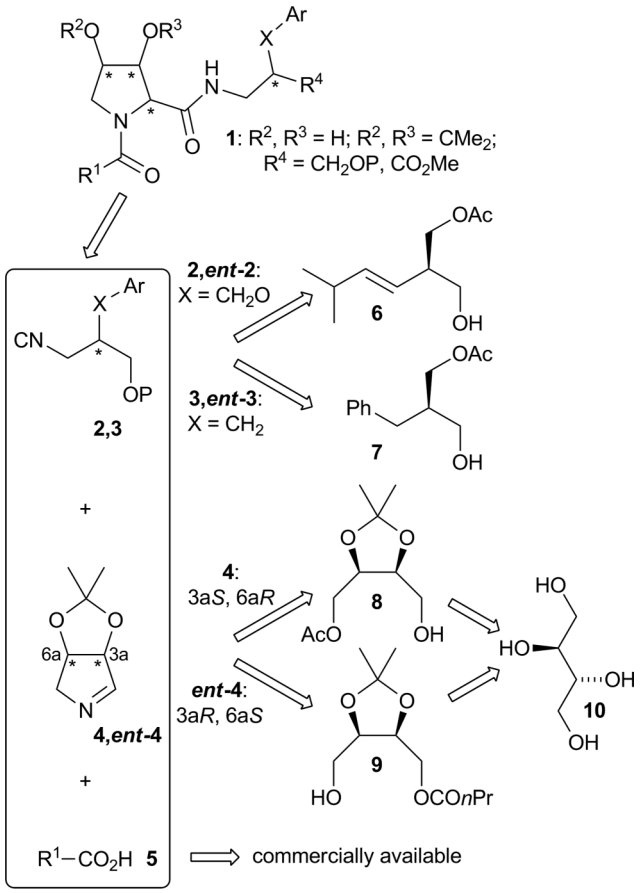
In recent years our group has been involved in several projects aimed at the development of diversity oriented syntheses of pyrrolidine based scaffolds through multicomponent Ugi reaction, either in the classical version[4,5] or in the intramolecular variant.[6,7]

The Ugi reaction is well known as a very useful method for the highly convergent synthesis of peptide moieties with an acyclic backbone:[8–10] these structures are, however, not so interesting as drug candidates because they are not conformationally restricted enough for a potent interaction with biological targets. On the contrary, cyclic scaffolds, such as for example pyrrolidines, display more interesting pharmacophoric properties. These structures can also be regarded as possible scaffolds in FBDD. Linking this cyclic structure, preferably through a one-pot procedure, with two other fragments, decorated with appropriate functional groups, would then offer the chance to join fragments displaying weak activity, gaining rapid access to interesting drug candidates.

A possibility to reach this goal is represented by the intramolecular Ugi reaction[11] in which a cyclic imine is reacted with an isocyanide and a carboxylic acid (Ugi–Joullié reaction), affording, for example, compounds **1**, as depicted in retrosynthetic Scheme 1.

The isocyanide and the carboxylic acid represent the two fragments that carry the pharmacophoric groups, and thus they should be relatively complex, being endowed with functional groups and/or stereogenic centres.

A huge variety of carboxylic acids **5**, provided with complex structures and stereogenic centres, is readily accessible from commercial sources, often in both enantiomeric forms. The availability of functionalised and/or chiral isocyanides is, on the contrary, much more limited. The commonly used commercially available isocyanides are unfunctionalised, making these structures not pharmacophoric at all. For this reason, we decided to develop an enantioselective synthesis of both enantiomers of isocyanides **2** and **3**, endowed with 2 important characteristics: 1) a protected OH to be used as H bond acceptor or donor (in the deprotected form); this group can moreover be regarded as a synthetic equivalent of a carboxylic acid, which can be exploited for



Scheme 1 The retrosynthetic plan.

electrostatic interactions; 2) an aryl group, bonded to a C or an O atom, to be used for π interactions.

The absolute configuration is clearly crucial for a correct interaction with the biological target. We envisaged that both enantiomers of **2** or **3** could be obtained from a common chiral building block, that is monoacetates **6** or **7**, respectively.

The main problem when using this approach is, however, the poor stereoselectivity usually encountered during the formation of the new stereogenic carbon induced by the pre-existing one(s) on the chiral imine.[7,12–15] Only very few high inducing chiral imines have been reported so far.[12,16] For our purposes we selected imines **4** and ***ent*-4**, on the basis of two considerations: a) the already demonstrated possibility to attain a complete diastereoselection during the MCR, thanks to the conformational rigidity of this bicyclic system;[17] b) the presence of the acetonide moiety, which can be regarded as an additional source of diversity in the final compounds. As far as it concerns the first point, it is worth noting that the obtainment of complete stereoselection in the Ugi reaction of chiral pyrrolines is not general: in more flexible systems, even with a stereogenic centre α to the imine carbon, diastereoselectivity is poor or incomplete.[7,13,15,17,18]

With regard to the second point, deblocking of the acetal would leave a highly polar, sugar-like scaffold. It has been recently stressed that often Ugi-based libraries have the drawback of being too unpolar.[19] The presence in **1** of three blocked alcoholic moieties allows us to modulate the polarity of the final products. Imine **4** has been already prepared, but only in racemic form.[17] We envisioned desymmetrized diols **8** and **9** as possible precursors of enantiomerically pure **4** and ***ent*-4**.

One of the milestones of this project is the possibility to also explore the stereochemical diversity, because the two inputs of the MCR are chiral, while the third one (**5**) can be either chiral or achiral. For this reason we focussed our attention on the development of methods able to produce both enantiomers of either the isocyanides or the imines. Our results can therefore be seen as an efficient exploration of the chemical space because four out of eight stereoisomers can readily be assembled through the same methodology by an appropriate combination of stereoisomeric isocyanides and imines, in a Diversity Oriented approach.

Results and Discussion

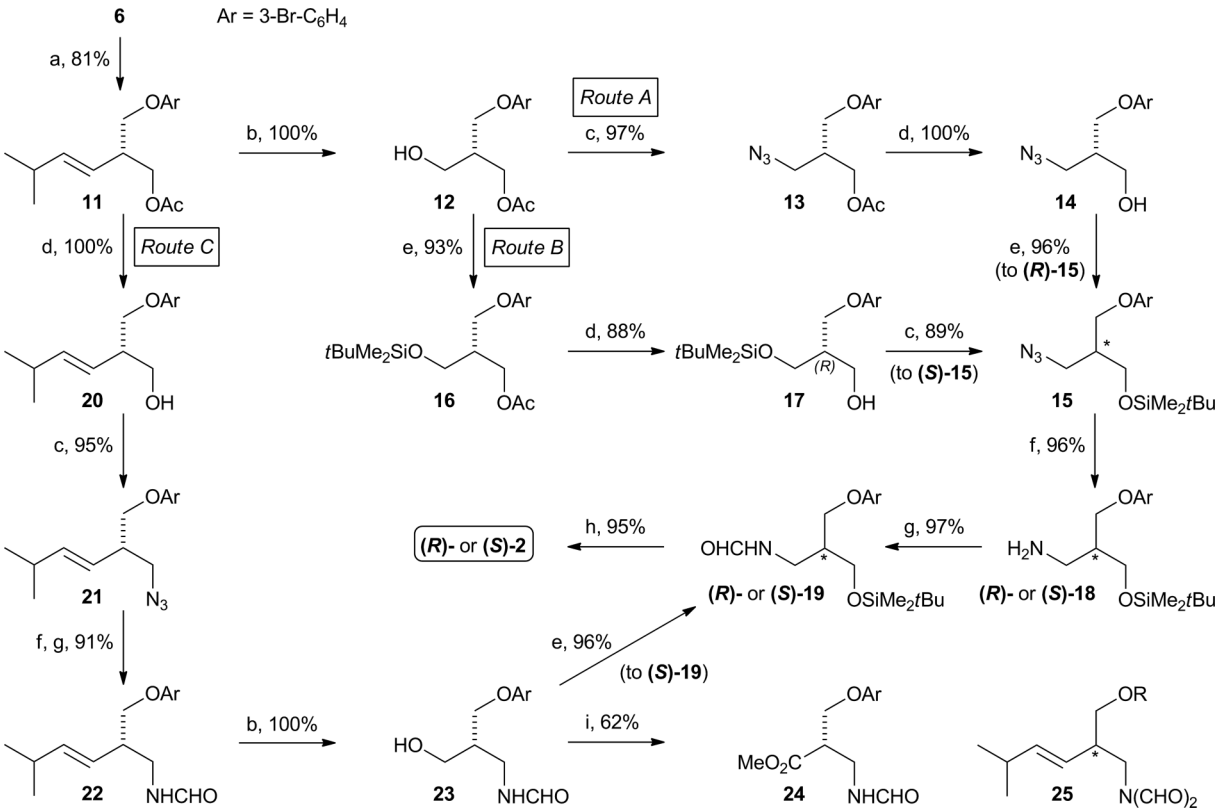
An attractive approach for obtaining these new compounds is represented by chemoenzymatic syntheses, in particular those exploiting the desymmetrization of prochiral (to give **6** and **7**) or *meso* compounds (to give **8** and **9**).

The synthesis of monoacetates **6** and **7** was already optimized in our group and they have been used as chiral building blocks for several applications;[20–23] however, none of them involved an MCR. They have both been obtained through a very efficient monoacetylation of the corresponding diols promoted by vinyl acetate in the presence of lipase from Porcine pancreas (PPL, **6**, e.e. ≥ 98%) or from *Pseudomonas cepacia* (PCL, **7**, e.e. > 95%) supported on celite, according to our previously reported protocol.[22,23]

The enantiodivergency of these monoacetates should allow the independent conversion of them into both enantiomers of the desired isocyanides through an appropriate choice of the order of introduction of the needed functionalities.

For the synthesis of **2**, the route depicted in Scheme 2 was followed. Compound **6**, a synthetic equivalent of desymmetrized trishydroxymethylmethane (THYM*),[20] was converted, under Mitsunobu conditions, into the key aryl ether **11**. Three branch routes depart from this intermediate, two of them leading to (***S*)-2** (Route B and C) and one to (***R*)-2** (Route A). A stereoconservative ozonolysis–reduction procedure afforded **12** (Routes A and B). This intermediate was converted into both enantiomers of azide **15** by two complementary pathways of equal length: in Route A the free OH of **12** was directly converted into the azide, whereas in Route B it was protected and the azide was later installed on the other arm. The Staudinger reduction gave amine **18**, which was in turn acylated with formic acid by means of DCC, a method that was shown to be superior to others (*i.e.* treatment with 2,4,5-trichlorophenyl formate). Finally, dehydration of formamides **19** furnished the desired isocyanides in excellent overall yield (67% (***R*)-2**, 52% (***S*)-2**) after 9 synthetic steps from **6**.

A slightly more efficient synthesis of (***S*)-2** from the common intermediate **11** (Route C) was attained just postponing the ozonolysis and introducing first the nitrogen atom precursor of the isocyanide moiety. In this case the overall yield (8 steps from **6**) was 64%. In order to explore the possibility to obtain **2** or its enantiomer by a shorter sequence, we also tried to transform both **6** and **20** into bisformamides **25** (R = Ac or Ar), by treatment with sodium diformylimide of the corresponding mesylates,[24] having in mind to selectively hydrolyze one formyl group. While the nucleophilic substitution gave about 62% overall yield in both



Scheme 2 *Reagents and conditions*: a) di-*t*-butylazodicarboxylate, PPh_3, CH_2Cl_2, r.t.; b) i. O_3; CH_2Cl_2/MeOH 2 : 3, –78 °C; ii. $NaBH_4$, –78 °C; c) i. MsCl, Et_3N, CH_2Cl_2, –30 °C; ii. NaN_3, DMF, 50 °C; d) 0.2 M KOH (MeOH), 0 °C; e) *t*BuMe$_2$SiCl, imidazole, DMF, r.t.; f) PPh_3, THF/H_2O, r.t. then 50 °C; g) HCO_2H, DCC, CH_2Cl_2, r.t.; h) $POCl_3$, Et_3N, CH_2Cl_2, –30 °C; i) i. Jones reagent, Me_2CO, 0 °C; ii. CH_2N_2, THF, 0 °C.

cases, removal of the formyl group worked well only when R = Ar, while when R = Ac only the diol precursor of **6** was identified in the crude. On the other hand the formation of formamide *via* the corresponding azide always gave excellent overall yields and thus this slightly longer approach was definitely more efficient.

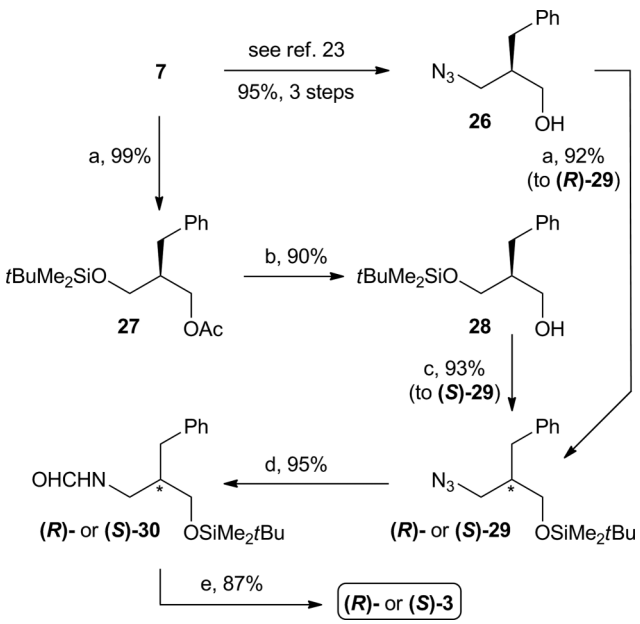
In order to enhance the diversity of the chiral isocyanides available by our strategy we also studied the oxidation of **23** into **24**, which was isolated in moderate (62%) yield. Also because of a not trivial isolation procedure, we preferred in this work to delay the oxidation until after the MCR, as described later.

Following a similar synthetic sequence we were able to transform monoacetate **7** into both enantiomers of **3**, again in excellent yield (72% (***R***)-**3**, 68% (***S***)-**3**) after 7 synthetic steps from **7** (Scheme 3).

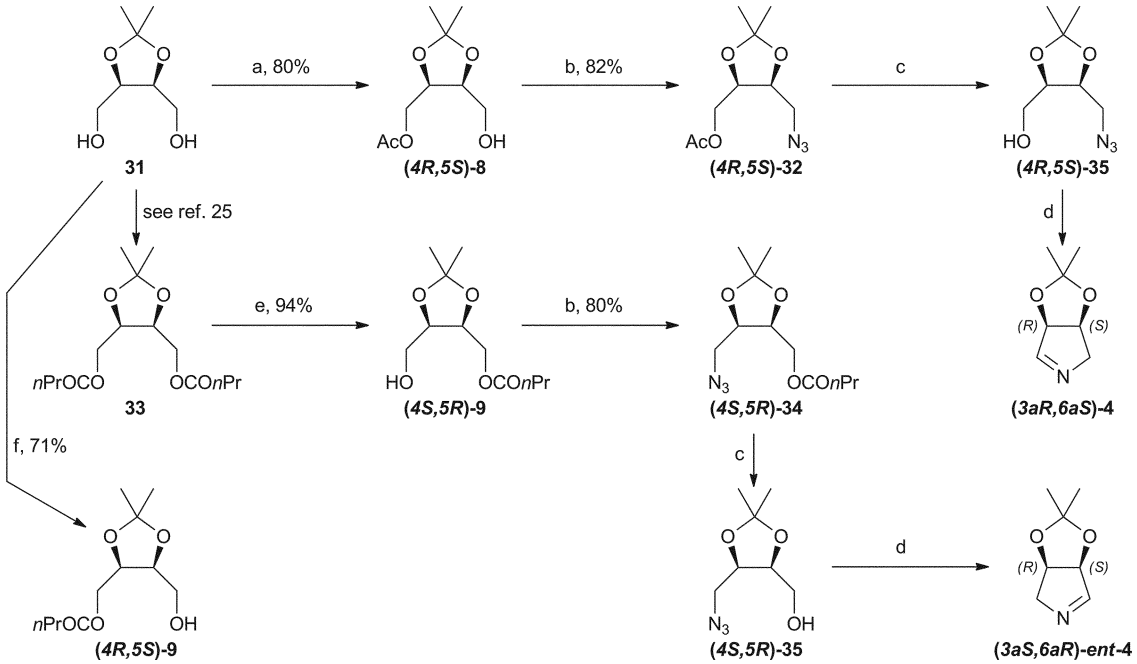
The absence of racemization in all the routes described in Schemes 2 and 3 has been demonstrated by analysis of the Ugi products (see later). Moreover, stereointegrity was demonstrated, at the level of formamides **30**, by ^{1}H NMR of the Mosher esters obtained after silyl protection removal.

We then turned to the enantioselective preparation of both enantiomers of cyclic imines **4** and ***ent*-4** (Scheme 4). For this purpose we planned to exploit the enzymatic desymmetrization of *meso* diol **31**, which can be obtained in three straightforward steps from *meso*-erythritol.[25]

The enzymatic monoacetylation of diol **31** and the enzymatic hydrolysis of its diesters have been previously reported. However, under the reported conditions,[25,26] the e.e.s, although good, were not as high as desired by us. Thus we screened other enzymes and conditions. We found that Amano PS lipase was the best



Scheme 3 *Reagents and conditions*: a) *t*BuMe$_2$SiCl, imidazole, DMF, r.t.; b) 0.2 M KOH (MeOH), 0 °C; c) i. MsCl, Et_3N, CH_2Cl_2, –30 °C; ii. NaN_3, DMF, 50 °C; d) i. PPh_3, THF/H_2O, 50 °C; ii. HCO_2H, DCC, CH_2Cl_2, r.t.; e) $POCl_3$, Et_3N, CH_2Cl_2, –30 °C.



Scheme 4 *Reagents and conditions*: a) vinyl acetate, Amano PS lipase, 20 °C; b) i. MsCl, Et_3N, CH_2Cl_2, −18 °C; ii. NaN_3, DMF, 100 °C; c) 1 M KOH (MeOH), 0 °C; d) i. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 −78 °C; ii. PPh_3, THF, 50 °C; e) 1 M phosphate buffer (pH 7)/H_2O 2 : 1, Amano PS lipase, 0 °C; f) vinyl butyrate, Amano PS lipase, r.t.

Table 1 Monohydrolysis of dibutyrate **33**

Entry	Enzyme	Quantity (g enzyme/g **33**)	Temp.	Time (min)	Yield	e.e.
1	Amano AK	0.20	0 °C	45	66%	82%
2	Amano AY	0.20	0 °C	70	<35%[a]	not det.
3	PPL	0.20	0 °C	40	51%	31%
4	Lipozyme RM	0.16	0 °C	1440	<20%[b]	not det.
5	Lipozyme TM	0.16	0 °C	240	<20%[b]	not det.
6	Amano AS	0.25	0 °C	240	no reaction	—
7	Amano PS	0.40	25 °C	40	85%	91%
8	Amano PS	0.12	0 °C	60	94%	97%

[a] This reaction showed a poor substrate selectivity, leading to nearly equal mixtures of dibutyrate, monobutyrate and diol at 50% conversion. [b] This reaction showed a very poor substrate selectivity, leading mainly dibutyrate, monobutyrate and diol at 50% conversion.

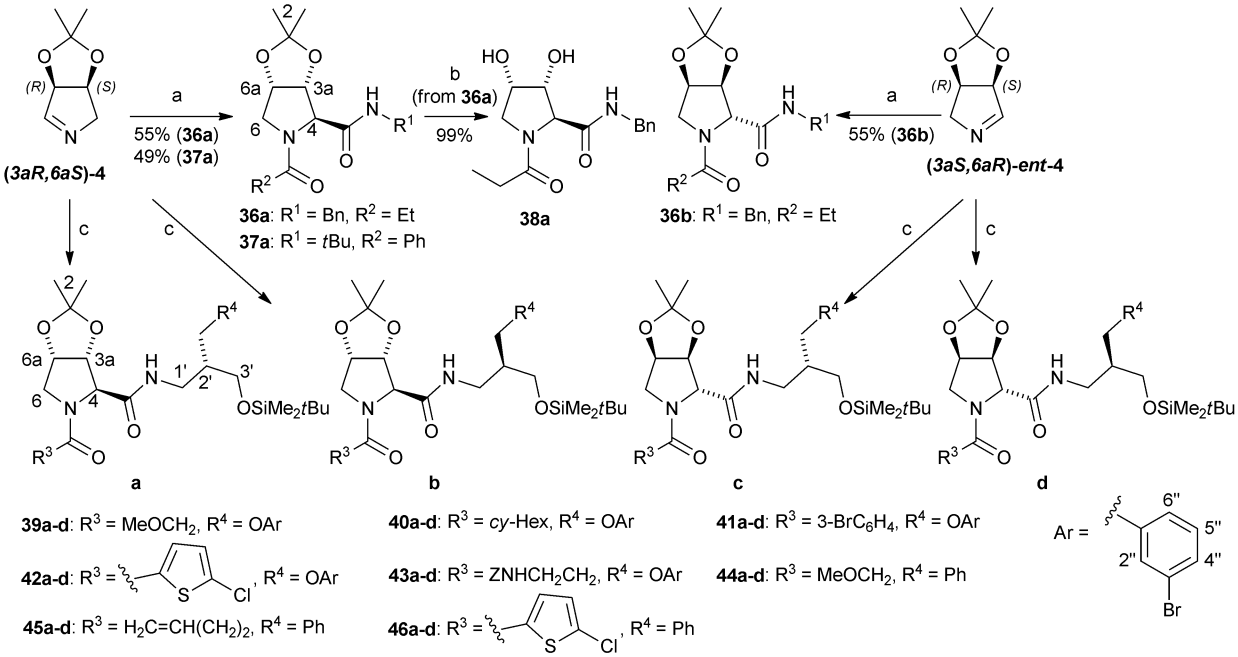
performing one in the acetylation of **31** using vinyl acetate as solvent (e.e. 97%).

For the synthesis of the opposite enantiomer, monohydrolysis of the diacetate of **31** was not fully satisfactory. Thus we studied the monohydrolysis of dibutyrate **33**. Table 1 reports the results obtained with various enzymes and various conditions. Once again, the best enzyme was Amano PS lipase, and we found an improvement in e.e. by performing the reaction at 0 °C with a lower amount of catalyst. The enantiomeric (+) monobutyrate could be obtained as well by monobutyrylation of diol **31** with vinyl butyrate. The reaction was, however, much slower than that in vinyl acetate, and the e.e. slightly lower as well.

Having in hand the two chiral building blocks **8** and **9**, we converted them, by an identical sequence, into azido esters **32** and **34**, by mesylation and S_N2 with sodium azide. Saponification afforded the moderately volatile enantiomeric azidoalcohols (***4R*,*5S*)-35** and (***4S*,*5R*)-35**. For this reason the sequence of transformations from **32** and **34** to the Ugi adducts was carried out without isolation or purification of the intermediates. The crude alcohols **35** were subjected to Swern oxidation to the corresponding aldehydes, followed by Staudinger/aza-Wittig with PPh_3 to give the imines **4** and ***ent*-4**. They were used as such (without the need to remove Ph_3PO) in the Ugi reaction with commercial or chiral isocyanides and a variety of carboxylic acids.

First we performed an Ugi reaction with two commercially available isocyanides to give Ugi adducts **36a**,**b** and **37a** (Scheme 5). The yields reported in Scheme 5 are determined from the starting azidoacetate **32** or azidobutyrate **34** (the isocyanide and carboxylic acid were used in slight excess) and thus must be considered quite good (4 steps). At room temperature, ^1H and ^{13}C showed the presence of two distinct sets of signals, in 95 : 5 (**36**) or 90 : 10 (**37**) ratio (in $CDCl_3$). In d_6-DMSO the ratios changed, becoming about 2 : 1.

Moreover, at 120 °C, complete coalescence of the two sets of signals occurred. This clearly demonstrated that the two sets are due to rotamers around the tertiary amide bond. In both conformers the vicinal coupling constants J_{3a-4} (≅0) demonstrate unambiguously the *trans* relative configuration. Actually, in **36a**



Scheme 5 *Reagents and conditions*: a) R^1NC, R^2CO_2H, MeOH, r.t.; b) HF, $CH_3CN–H_2O$, –10 °C; c) **2** or **3**, R^3CO_2H, MeOH, r.t.

the dihedral angle is expected to be ≅100°, whereas in the *cis* epimer it should be around 20°.[17] No signals attributable to the *cis* diastereoisomers could be detected. Thus, under the detections limits, the diastereoselectivity of the Ugi reaction turned out to be complete (>98%). In the case of **36** the reaction was carried out on both enantiomeric imines and chiral HPLC analysis showed in both cases an e.e. comparable to that of the starting monoacetate **8** or monobutyrate **9**.

Then we coupled the two enantiomeric imines **4** with both enantiomers of chiral isocyanides **2** and **3** and six different carboxylic acids. In principle it is possible to independently prepare 4 stereoisomers for each combination of 6 acids and 2 isocyanides: this means 48 different products.

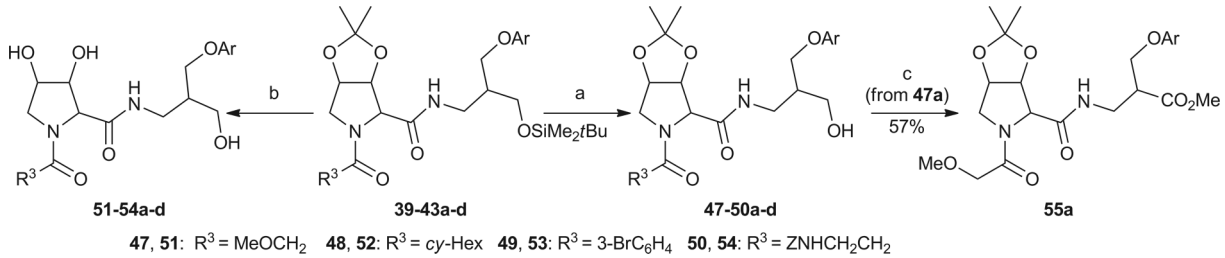
However, we prepared only a selection of them in order to demonstrate the feasibility of the method. The results are reported in Table 2. The yields are this time calculated from the isocyanide, that was used as the limiting agent. Once again, no *cis* isomer was detected. In the case of compounds **39** all four possible stereoisomers were prepared, by appropriate combination of isocyanides and imines. Interestingly, the ^1H and ^{13}C NMR of diastereoisomeric pairs were nearly superimposable, not allowing the measurement of a precise diastereomeric ratio. However, in chiral HPLC analysis, they give four well separated peaks. In all cases, the d.r. was around 95% or higher (see the experimental part). This analysis also allowed us to indirectly prove the enantiomeric purity of starting isocyanides **2** or **3** and to rule out any possible racemization during the Ugi reaction. From the d.r.s listed in the experimental part we could figure out an e.e of at least 95% for both **2** and ***ent*-2**. Accordingly, also the stereoisomeric purity of the imines was preserved, as in the reaction with achiral isocyanides. A similar analysis was carried out for compounds **42a** and **42c** too, with an analogous outcome. For **44a** and **44b** the ^1H and ^{13}C spectra indicated a d.r ≥ 95%.

As for **36** and **37**, also compounds **39–46** showed, in $CDCl_3$, a strong preference for one of the two rotamers, the ratios ranging from 86 : 14 to >97 : 3 (**42a–42c** and **46c** seem to be present as a single rotamer).

Further exploration of chemical diversity can be carried out by manipulation of the additional functional groups present in these adducts (Scheme 6). For example, removal of the silyl protection leads to alcohols **47–50**. We prepared, in high yields, some of these compounds (Table 1). Moreover, both silyl and acetal protections can be simultaneously removed, by treatment with a strong acid. This deprotection was first demonstrated on **36a** to give **38a** (Scheme 5). Under the same conditions, triols **51–54** have been obtained in good to excellent yields. These compounds

Table 2 Yields for the synthesis of compounds **39–54**

Starting isocyanide	R^3	Yield of Ugi reaction				Yield of silyl removal		Yield of silyl and acetal removal	
2	$MeOCH_2$	**39a**: 56%	**39b**: 54%	**39c**: 57%	**39d**: 80%	**47a**: 56%		**51a**: 59%	**51c**: 61%
2	*cy*-Hex	**40a**: 73%		**40c**: 73%		**48a**: 94%	**48c**: 94%	**52a**: 88%	
2	$3\text{-}BrC_6H_4$	**41a**: 69%		**41c**: 73%		**49a**: 91%	**49c**: 95%	**53a**: 93%	
2	5-Cl-2-thienyl	**42a**: 56%		**42c**: 58%					
2	$ZNHCH_2CH_2$	**43a**: 74%		**43c**: 80%		**50a**: 100%	**50c**: 100%	**54a**: 100%	
3	$MeOCH_2$	**44a**: 68%	**44b**: 55%						
3	$H_2C{=}CH(CH_2)_2$			**45c**: 56%					
3	5-Cl-2-thienyl			**46c**: 67%					



Scheme 6 *Reagents and conditions*: a) HF, CH_3CN–H_2O, –10 °C; b) CF_3CO_2H, H_2O, THF; c) i) Jones reagent; ii) CH_2N_2.

are, as expected, rather polar. Moreover, the conformation of the pyrrolidine ring is no longer fixed by the fused acetal, and thus the tridimensional structure is modified, as demonstrated by the different coupling constants, compared to **39–50**.

Thus, the small library of compounds listed in Table 2 (29 molecules) represents a real diversity-oriented collection, where not only the substituents (decorations) have been varied, but also the scaffold itself and the stereochemistry.

The free alcohol in **47–50** can also be converted into a carboxylic acid. This was demonstrated for **47a**, that gave, after oxidation and esterification with diazomethane, ester **55a**.

Conclusions

The present work demonstrates the possibility to use the Ugi reaction for the convergent synthesis of conformationally biased peptidomimetics where all the inputs (including the isocyanide) carry pharmacologically relevant appendages. Moreover, a full control of relative and absolute configuration has been achieved by appropriately combining chiral, enantiomerically pure isocyanides and imines obtained by a chemoenzymatic route, also thanks to the high diastereoselectivity of Ugi reactions of rigid cyclic imines **4**. Application of this strategy for the fragment-based assembly of biologically active substances is in progress.

Experimental section

NMR spectra were taken at r.t. in $CDCl_3$ or d_6-DMSO at 300 MHz (^{1}H), and 75 MHz (^{13}C), using as internal standards: for ^{1}H NMR in $CDCl_3$: TMS; for ^{1}H NMR in DMSO: the central peak of DMSO (2.506); for ^{13}C in $CDCl_3$ the central peak of $CDCl_3$ (at 77.02 ppm); for ^{13}C NMR in DMSO: the central peak of DMSO (39.43). Chemical shifts are reported in ppm (δ scale), coupling constants are reported in Hertz. Peak assignments were also made with the aid of gCOSY and gHSQC experiments. In ABX systems, the proton A is considered upfield and B downfield. GC-MS were carried out using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170 °C. Only $m/z > 33$ were detected. All analyses were performed (unless otherwise stated) with a constant He flow of 1.0 mL min^{-1} with initial temp. 100 °C, init. time 2 min, rate 20 °C min^{-1}, final temp. 290 °C, inj. temp. 250 °C, det. temp. 280 °C. HR-MS were recorded employing ESI+ or ESI– ionization method. IR spectra were recorded as $CHCl_3$ solutions. TLC analyses were carried out on silica gel plates and viewed at UV (254 nm) or developed by dipping into a solution of $(NH_4)_4MoO_4$·4 H_2O (21 g) and $Ce(SO_4)_2$·4 H_2O (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming or, when specified, with ninhydrin (900 mg of ninhydrin in 300 mL *n*BuOH and 9 mL AcOH) or 2% aqueous $KMnO_4$, followed by warming. R_f were measured after an elution of 7–9 cm. Column chromatographies were done with the "flash" methodology using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. In the extractive work-up, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere. Amano enzymes used were a kind gift of Amano-Mitsubishi Italia.

(*R*,*E*)-2-[(3-Bromophenoxy)methyl-5-methylhex-3-enyl acetate 11

A solution of **6**[22] (1.32 g, 3.87 mmol) in dry CH_2Cl_2 (9 mL) was cooled to 0 °C and treated with 3-bromophenol (1.00 g, 5.80 mmol), PPh_3 (1.52 g, 5.80 mmol) and di-*t*-butylazodicarboxylate (1.35 g, 5.86 mmol), stirred for 25 min at the same temperature and then 1.7 h at room temperature. After solvent removal the mixture was chromatographed with PE/Et_2O 95 : 1 to 9 : 1 to give **11** (1.96 g, 81%) as a colourless oil. R_f 0.60 (PE/AcOEt 90 : 10). $[\alpha]_D$ –14.1 (*c* 1.4, $CHCl_3$). IR: $\nu_{max}(CHCl_3)$/cm^{-1} 2951, 2864, 1727, 1586, 1460, 1378, 1254, 1017, 972. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.98 (6 H, d, *J* 6.9, $(CH_3)_2CH$), 2.05 (3 H, s, $COCH_3$), 2.28 (1 H, centre of m, $(CH_3)_2CH$), 2.80 (1 H, centre of m, $CH(CH_2O–)_2$), 3.94 (2 H, d, *J* 6.0, CH_2OAr), 4.17 and 4.21 (2 H, AB part of an ABX syst., J_{AB} 9.9, J_{AX} 5.1, J_{BX} 5.1, CH_2OAc), 5.33 (1 H, ddd, *J* 1.2, 7.8, 15.3, $(CH_3)_2CHCH{=}CH$), 5.60 (1 H, ddd, *J* 0.6, 6.6, 15.3, $(CH_3)_2CHCH = CH$), 6.83 (1 H, ddd, *J* 1.2, 2.1, 7.8, *H*-6′), 7.05–7.16 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): 20.9 ($COCH_3$), 22.4 ($(CH_3)_2CH$), 31.2 ($(CH_3)_2CH$), 41.5 ($CH(CH_2O–)_2$), 64.4 (CH_2OAc), 68.4 (CH_2OAr), 113.7 (*C*-6′), 117.7 (*C*-2′), 122.8 (*C*-3′), 122.9 ($(CH_3)_2CHCH = CH$), 123.9 (*C*-4′), 130.5 (*C*-5′), 141.6 ($(CH_3)_2CHCH{=}CH$), 159.6 (*C*-1′), 171.0 ($C{=}O$). GC-MS (usual method but with initial temp. 70 °C, rate 10 °C min^{-1}, final temp. 280 °C): R_t: 15.14 min; m/z (EI): 342 (M^+ (^{81}Br), 0.19), 340 (M^+ (^{79}Br), 0.20), 169 (7.3), 109 (44), 95 (6.0), 93 (9.6), 81 (16), 79 (5.7), 67 (40), 55 (12), 43 (100), 41 (14). m/z (ESI+) 363.0572 ($M + Na^+$). $C_{16}H_{21}BrO_3Na$ requires 363.0572.

(*R*)-3-Acetoxy-2-((3-bromophenoxy)methyl)propanol 12

A solution of **11** (3.11 g, 9.11 mmol) in dry CH_2Cl_2/MeOH (1 : 1.5, 83 mL) was cooled to –78 °C and submitted to ozonolysis (120 L h^{-1} ozone flow) until a pearl grey colour appeared (about 40 min). Me_2S (3.75 mL, 51.04 mmol) was added, followed after 1 min,

by $NaBH_4$ (1.38 g, 36.48 mmol). The temperature was allowed to increase up to −3 °C in 2.5 h. The reaction was quenched with saturated NH_4Cl solution. After extraction with Et_2O, the organic layers were washed with brine and concentrated. Chromatography with PE/AcOEt 7 : 3 + MeOH (0.5 to 1%) afforded **12** as a pale yellow oil (2.76 g, 100%). R_f 0.24 (PE/AcOEt 80 : 20 + 1% MeOH). $[\alpha]_D$ −2.55 (*c* 1.4, $CHCl_3$). IR: $\nu_{max}(CHCl_3)/cm^{-1}$ 3609, 3024, 2962, 2881, 1726, 1587, 1465, 1197, 1019. δ_H (300 MHz; $CDCl_3$, 25 °C): 2.04 (1 H, centre of m, O*H*), 2.09 (3 H, s, COCH_3), 2.36 (1 H, septet, *J* 5.7, C*H*(CH_2O–)$_3$), 3.78 (2 H, centre of m, CH_2OH), 4.04 (2 H, d, *J* 6.0, CH_2OAr), 4.30 (2 H, d, *J* 6.0, CH_2OAc), 6.84 (1 H, ddd, *J* 1.2, 2.4, 7.8, *H*-6′), 7.07–7.17 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): 20.8 (CO*C*H_3), 40.7 (*C*H(CH_2O–)$_3$), 60.5 (*C*H_2OH), 62.2 (*C*H_2OAc), 66.1 (*C*H_2OAr), 113.5 (*C*-6′), 117.6 (*C*-2′), 122.7 (*C*-3′), 124.0 (*C*-4′), 130.5 (*C*-5′), 159.3 (*C*-1′), 171.4 (*C*═O). GC-MS: R_t: 7.91 min; *m*/*z* (EI): 304 (M^+ (^{81}Br), 1.1), 302 (M^+ (^{79}Br), 1.1), 174 (24), 172 (25), 132 (8.5), 131 (100), 71 (19), 65 (5.5), 61 (6.1), 43 (96). *m*/*z* (ESI+) 325.0047 (M + Na^+). $C_{12}H_{15}BrO_4Na$ requires 325.0051.

(*R*)-1-Acetoxy-3-azido-2-((3-bromophenoxy)methyl)propane 13

a) Mesylate formation: alcohol **12** (825 mg, 2.72 mmol) was dissolved in dry CH_2Cl_2 (9 mL), cooled to −30 °C, and treated with Et_3N (493 µL, 3.54 mmol) and methanesulphonyl chloride (253 µL, 3.26 mmol) and stirred for 1.8 h until the reaction was complete (as determined by TLC with PE/AcOEt 60 : 40 + 1% MeOH). Quenching with saturated NH_4Cl was followed by an extraction with Et_2O. After treatment with brine the organic phases were evaporated to dryness. **b**) Azide formation: crude mesylate [R_f 0.38 (PE/Et_2O 60 : 40 + 1% MeOH)] was taken up in dry DMF (9 mL), treated with NaN_3 (354 mg, 5.44 mmol) and heated at 50 °C for 20.5 h. After cooling, the mixture was treated with H_2O and Et_2O and extracted. The organic phase was washed with water (twice) and then with brine. After solvent removal the crude was purified by chromatography (PE/AcOEt 90 : 10 to 85 : 15) to give pure **13** as a pale yellow oil (866 mg, 97%). R_f 0.49 (PE/Et_2O 70 : 30). $[\alpha]_D \approx 0$ (*c* 2.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3004, 2886, 2102, 1731, 1587, 1464, 1192. δ_H (300 MHz; $CDCl_3$, 25 °C): 2.09 (3 H, s, COCH_3), 2.41 (1 H, septet, *J* 6.0, C*H*(CH_2–)$_3$), 3.57 (2 H, d, *J* 6.3, CH_2N_3), 3.97 and 4.00 (2 H, AB part of an ABX syst., J_{AB} 7.6, J_{AX} 4.1, J_{BX} 3.7, CH_2OAr), 4.21 and 4.21 (2 H, AB part of an ABX syst., J_{AB} 11.5, J_{AX} 6.2, J_{BX} 6.2, CH_2OAc), 6.84 (1 H, ddd, *J* 1.5, 2.7, 7.8, *H*-6′), 7.06–7.18 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): 20.8 (CO*C*H_3), 38.4 (*C*H(CH_2–)), 49.7 (*C*H_2N_3), 62.3 (*C*H_2OAc), 65.6 (*C*H_2OAr), 113.4 (*C*-6′), 117.6 (*C*-2′), 122.8 (*C*-3′), 124.2 (*C*-4′), 130.6 (*C*-5′), 159.1 (*C*-1′), 170.7 (*C*═O). GC-MS: R_t: 8.13 min; *m*/*z* (EI): 329 (M^+ (^{81}Br), 0.086), 327 (M^+ (^{79}Br), 0.080), 174 (6.0), 172 (6.5), 156 (14), 68 (24), 65 (5.4), 63 (5.1), 56 (5.3), 44 (11), 43 (100), 42 (7.1), 41 (31). *m*/*z* (ESI+) 350.0133 (M + Na^+). $C_{12}H_{14}BrN_3O_3Na$ requires 350.0116.

(*S*)-3-Azido-2-((3-bromophenoxy)methyl)propanol 14

A pre-cooled solution of KOH (0.2 M in MeOH, 17 mL) was added at 0 °C to **13** (645 mg, 1.97 mmol) and the mixture was stirred at the same temperature for 1 h. After quenching with saturated NH_4Cl, MeOH was removed under reduced pressure and the aqueous phases were extracted with Et_2O and washed with brine. The crude was purified by chromatography (PE/AcOEt 45 : 35 to 6 : 4) to give **14** as a pale yellow oil (562 mg, 100%). R_f 0.25 (PE/Et_2O 80 : 20). $[\alpha]_D \approx 0$ (c 2.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3604, 3038, 2959, 2881, 2101, 1587, 1464, 1188, 1020. δ_H (300 MHz; $CDCl_3$, 25 °C): 1.83 (1 H, t, *J* 4.8, O*H*), 2.26 (1 H, septet, *J* 5.8, C*H*(CH_2-)$_3$), 3.59 (2 H, d, *J* 6.0, CH_2N_3), 3.82 (2 H, broad t, *J* 5.0, CH_2OH), 4.02 and 4.04 (2 H, AB part of an ABX syst., J_{AB} 9.4, J_{AX} 6.0, J_{BX} 5.3, CH_2OAr), 6.84 (1 H, ddd, *J* 1.5, 2.4, 7.8, *H*-6′), 7.07–7.18 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): 40.9 (*C*H(CH_2–)), 50.0 (*C*H_2N_3), 61.3 (*C*H_2OH), 66.4 (*C*H_2OAr), 113.4 (*C*-6′), 117.7 (*C*-2′), 122.8 (*C*-3′), 124.2 (*C*-4′), 130.6 (*C*-5′), 159.2 (*C*-1′). GC-MS: R_t: 7.89 min; *m*/*z* (EI): 287 (M^+ (^{81}Br), 1.6), 285 (M^+ (^{79}Br), 1.6), 201 (14), 200 (8.7), 199 (13), 198 (7.3), 178 (12), 175 (7.5), 174 (94), 173 (11), 172 (100), 157 (14), 155 (13), 145 (9.8), 143 (9.2), 120 (20), 119 (5.2), 94 (7.4), 93 (27), 92 (6.6), 86 (14), 76 (8.8), 75 (9.3), 68 (6.6), 65 (29), 64 (11), 63 (17), 57 (9.8), 56 (9.1), 55 (8.9), 54 (7.5), 50 (5.8), 44 (6.0), 42 (12), 41 (27), 39 (16), 38 (5.9). *m*/*z* (ESI−) 284.0028 (M − H^+). $C_{10}H_{11}BrN_3O_2$ requires 284.0035.

(*R*)- and (*S*)-1-Azido-3-(*tert*-butyl)dimethylsilyloxy-2-((3-bromophenoxy)methyl)propane 15

a) From **14**: a solution of **14** (462 mg, 1.61 mmol) in dry DMF (6.5 mL) was treated, at r.t., with imidazole (189 mg, mmol) and *t*-butyldimethylsilyl chloride (316 mg, 2.10 mmol). After 4 h the crude was diluted with water and Et_2O and extracted. The collected organic layers were washed with water and finally with brine. After solvent removal, chromatography with PE + Et_2O from 0.5% to 3% afforded (***R***)-**15** as a colourless oil (621 mg, 96%). **b**) From **17**: compound **17** was transformed into the corresponding mesylate [R_f 0.41 (PE/Et_2O 60 : 40)] and then into azide (***S***)-**15**, following the procedure reported for compound **13** in 89% yield. R_f 0.51 (PE/Et_2O 98 : 2). (***R***)-**15**: $[\alpha]_D$ −1.49 (*c* 1.1, $CHCl_3$). (***S***)-**15**: $[\alpha]_D$ +0.03 (*c* 1.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3047, 2925, 2854, 2100, 1586, 1461, 1251, 1191, 1092, 1027. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.050, 0.054 (2 × 3 H, 2 s, CH_3Si), 0.89 (9 H, s, (CH_3)$_3$CSi), 2.22 (1 H, septet, *J* 5.9, C*H*(CH_2-)$_3$), 3.51 (2 H, d, *J* 6.3, CH_2N_3), 3.73 and 3.73 (2 H, AB part of an ABX syst., J_{AB} 10.3, J_{AX} 5.5, J_{BX} 5.5, CH_2OSi), 3.94 and 3.98 (2 H, AB part of an ABX syst., J_{AB} 9.4, J_{AX} 6.2, J_{BX} 6.2, CH_2OAr), 6.83 (1 H, ddd, *J* 1.5, 2.7, 8.1, *H*-6′), 7.05–7.18 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H_3Si), 18.2 (*C*(CH_3)$_3$), 25.8 ((CH_3)$_3$C), 41.4 (*C*H(CH_2–)), 49.8 (*C*H_2N_3), 60.7 (*C*H_2OSi), 66.0 (*C*H_2OAr), 113.4 (*C*-6′), 117.8 (*C*-2′), 122.8 (*C*-3′), 124.0 (*C*-4′), 130.5 (*C*-5′), 159.5 (*C*-1′). GC-MS: R_t: 9.10 min; *m*/*z* (EI): 344 (M^+ (^{81}Br) − 56, 3.1), 342 (M^+ (^{79}Br) − 56, 3.2), 231 (22), 229 (22), 174 (7.2), 172 (7.5), 143 (5.7), 142 (29), 115 (7.1), 112 (8.5), 99 (5.7), 89 (5.1), 86 (5.1), 76 (6.1), 75 (28), 73 (27), 68 (9.0), 65 (6.3), 59 (20), 57 (7.7), 45 (8.7), 43 (7.3), 42 (100), 41 (20), 39 (8.1). *m*/*z* (ESI+) 422.0889 (M + Na^+). $C_{16}H_{26}BrN_3O_2SiNa$ requires 422.0875.

(*R*)-1-Acetoxy-3-(*tert*-butyl)dimethylsilyloxy-2-((3-bromophenoxy)methyl)propane 16

Compound **16** was prepared from **12**, following the procedure reported for compound **15**. Chromatography with PE/Et_2O 95 : 5 gave **16** as a pale yellow oil in 93% yield. R_f 0.53 (PE/Et_2O 90 : 10). $[\alpha]_D$ +3.22 (*c* 0.99, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3000, 2886,

1730, 1587, 1519, 1466, 1415, 1188, 1028. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.04 (6 H, s, CH_3Si), 0.88 (9 H, s, (CH_3)$_3$CSi), 2.07 (3 H, s, COCH_3), 2.33 (1 H, septet, *J* 5.9, CH(CH$_2$–)$_3$), 3.75 and 3.75 (2 H, AB part of an ABX syst., J_{AB} 10.4, J_{AX} 5.7, J_{BX} 5.7, CH_2OSi), 3.98 and 4.01 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 5.6, J_{BX} 6.1 CH_2OAr), 4.20 and 4.20 (2 H, AB part of an ABX syst., J_{AB} 11.5, J_{AX} 6.2, J_{BX} 6.2 CH_2OAc), 6.83 (1 H, ddd, *J* 1.2, 2.4, 7.8, *H*-6′), 7.05–7.17 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): –5.6 (*C*H$_3$Si), 18.2 (*C*(CH$_3$)$_3$), 20.9 (CO*C*H$_3$), 25.8 ((*C*H$_3$)$_3$C), 40.8 (*C*H(CH$_2$–)), 60.4 (*C*H$_2$OSi), 62.4 (*C*H$_2$OAc), 65.6 (*C*H$_2$OAr), 113.5 (*C*-6′), 117.7 (*C*-2′), 122.8 (*C*-3′), 123.8 (*C*-4′), 130.5 (*C*-5′), 159.6 (*C*-1′), 171.0 (*C*=O). GC-MS: R_t: 9.18 min; *m*/*z* (EI): 361 (M$^+$ (^{81}Br) – 57, 24), 359 (M$^+$ (^{79}Br) – 57, 23), 302 (8.2), 301 (47), 300 (8.1), 299 (45), 271 (16), 269 (14), 259 (13), 257 (12), 245 (5.4), 243 (6.1), 232 (7.4), 231 (54), 230 (7.5), 229 (52), 227 (5.6), 225 (6.0), 220 (20), 219 (5.4), 192 (5.5), 187 (5.7), 185 (5.9), 157 (7.9), 155 (7.3), 146 (22), 145 (19), 135 (5.7), 131 (7.5), 119 (5.5), 117 (100), 115 (16), 105 (6.1), 99 (9.1), 89 (12), 85 (6.9), 77 (10), 76 (13), 75 (80), 74 (5.9), 73 (38), 71 (6.4), 59 (16), 57 (6.0), 45 (6.3), 43 (90), 41 (15). *m*/*z* (ESI+) 439.0925 (M + Na$^+$). $C_{18}H_{29}BrO_4SiNa$ requires 439.0916.

(*S*)-3-(*tert*-Butyl)dimethylsilyloxy-2-((3-bromophenoxy)methyl)-propanol 17

Compound **17** was prepared from **16**, following the procedure reported for compound **14**. Chromatography with PE/Et$_2$O 60 : 40 gave **16** as a yellow oil in 88% yield. R_f 0.24 (PE/Et$_2$O 80 : 20). $[\alpha]_D$ +3.29 (*c* 1.1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3605, 3020, 2887, 1580, 1525, 1476, 1415, 1164, 1025. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.06 and 0.08 (2 × 3 H, 2 s, CH_3Si), 0.89 (9 H, s, (CH_3)$_3$CSi), 2.18 (1 H, centre of m, CH(CH$_2$–)$_3$), 2.47 (1 H, dd, *J* 5.4, 6.0, O*H*) 3.81–3.94 (2 H, m, CH_2OH), 3.89 (2 H, d, *J* 5.1, CH_2OSi), 4.04 and 4.07 (2 H, AB part of an ABX syst., J_{AB} 9.4, J_{AX} 5.8, J_{BX} 6.7 CH_2OAr), 6.84 (1 H, ddd, *J* 1.2, 2.4, 7.8, *H*-6′), 7.04–7.17 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): –5.60, –5.58 (*C*H$_3$Si), 18.2 (*C*(CH$_3$)$_3$), 25.8 ((*C*H$_3$)$_3$C), 42.5 (*C*H(CH$_2$–)), 63.0, 63.3 (*C*H$_2$OSi and *C*H$_2$OH), 66.4 (*C*H$_2$OAr), 113.4 (*C*-6′), 117.8 (*C*-2′), 122.8 (*C*-3′), 123.9 (*C*-4′), 130.5 (*C*-5′), 159.6 (*C*-1′), 171.0 (*C*=O). GC-MS: R_t: 8.75 min; *m*/*z* (EI): 361 (M$^+$ (^{81}Br) – 57, 3.8), 359 (M$^+$ (^{79}Br) – 57, 4.0), 301 (18), 299 (17), 271 (6.8), 269 (6.2), 259 (5.8), 257 (5.3), 231 (22), 229 (22), 220 (5.8), 187 (5.2), 185 (5.4), 157 (5.9), 155 (5.4), 147 (5.2), 146 (39), 145 (29), 131 (9.5), 115 (15), 105 (17), 89 (11), 77 (12), 76 (15), 75 (100), 74 (5.3), 73 (27), 71 (6.3), 61 (5.6), 59 (13), 57 (7.1), 47 (6.5), 45 (9.2), 43 (9.9), 41 (35), 39 (6.2). *m*/*z* (ESI+) 397.0798 (M + Na$^+$). $C_{16}H_{27}BrO_3SiNa$ requires 397.0811.

(*R*)- or (*S*)-1-Amino-3-(*tert*-butyl)dimethylsilyloxy-2-((3-bromophenoxy)methyl)propane 18

A solution of (*R*)- or (*S*)-**15** (610 mg, 1.52 mmol) in dry THF (10 mL) was treated at 0 °C with PPh_3 (599 mg, 2.28 mmol) and water (55 µL, 3.04 mmol). After evolution of N_2 finished, the reaction was allowed to stir at r.t. for 22 h. In order to complete the hydrolysis of the intermediate phosphazene an equivalent amount of water was added and the mixture was heated at 50 °C for 5 h. The mixture was partitioned between water and Et$_2$O and extracted. The organic layers were washed with brine, concentrated and chromatographed with CH_2Cl_2/MeOH 95 : 5 + 3% Et$_3$N to give **18** as a yellow oil (546 mg, 96%). The preparation of formamide **19** can be performed also without the purification of intermediate **18**, without affecting the overall yield. R_f 0.48 [CH_2Cl_2/MeOH 90 : 10 + 2% Et$_3$N, ninhydrin]. (*R*)-**18**: $[\alpha]_D$ –2.85 (*c* 1.0, $CHCl_3$). (*S*)-**18**: $[\alpha]_D$ +3.06 (*c* 1.1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3674, 3614, 3018, 2923, 2853, 1587, 1462, 1189, 1089, 1039. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.039, 0.045 (2 × 3 H, 2 s, CH_3Si), 0.88 (9 H, s, (CH_3)$_3$CSi), 2.06 (1 H, septet, *J* 5.8, CH(CH$_2$–)$_3$), 2.89 (2 H, d, *J* 6.3, CH_2NH$_2$), 3.76 (2 H, d, *J* 5.4, CH_2OSi), 3.98 and 4.02 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 5.8, J_{BX} 6.2, CH_2OAr), 6.84 (1 H, ddd, *J* 1.2, 2.4, 8.1, *H*-6′), 7.05–7.16 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): –5.2, –5.6 (*C*H$_3$Si), 18.2 (*C*(CH$_3$)$_3$), 25.8 ((*C*H$_3$)$_3$C), 40.9 (*C*H$_2$NH$_2$), 43.3 (*C*H(CH$_2$–)), 61.7 (*C*H$_2$OSi), 66.8 (*C*H$_2$OAr), 113.3 (*C*-6′), 117.7 (*C*-2′), 122.7 (*C*-3′), 123.7 (*C*-4′), 130.4 (*C*-5′), 159.7 (*C*-1′). GC-MS: R$_t$: 8.65 min; *m*/*z* (EI): 360 (M$^+$ (^{81}Br) – 15, 1.8), 358 (M$^+$ (^{79}Br) – 15, 1.7), 320 (5.1), 319 (18), 318 (100), 316 (100), 271 (5.1), 259 (7.3), 243 (6.4), 232 (5.7), 231 (38), 230 (5.9), 229 (36), 174 (5.9), 172 (6.4), 159 (8.4), 158 (8.9), 157 (7.8), 155 (7.3), 151 (5.5), 150 (5.5), 146 (5.9), 145 (12), 144 (65), 139 (6.8), 137 (7.1), 135 (8.7), 131 (6.5), 130 (5.7), 116 (5.2), 115 (19), 114 (12), 104 (18), 99 (12), 93 (5.1), 89 (15), 88 (13), 85 (13), 77 (9.1), 76 (21), 75 (84), 74 (45), 73 (78), 71 (5.1), 70 (75), 68 (5.0), 65 (5.8), 64 (5.1), 63 (7.0), 61 (9.0), 60 (8.2), 59 (44), 58 (12), 57 (15), 56 (34.8), 47 (11), 45 (17), 43 (21), 42 (5.5), 41 (53), 39 (11). *m*/*z* (ESI+) 374.1148 (M + H$^+$). $C_{16}H_{29}BrNO_2Si$ requires 374.1151.

(*R*)- or (*S*)-1-(*tert*-Butyl)dimethylsilyloxy-2-((3-bromophenoxy)-methyl)-3-formylaminopropane 19

a) From (*R*)- or (*S*)-**18**: a solution of **18** (512 mg, 1.37 mmol) in dry CH_2Cl_2 (12 mL) was cooled to 0 °C and treated with *N*,*N*′-dicyclohexylcarbodiimide (460 mg, 2.23 mmol) and formic acid (85 µL, 2.25 mmol). After 10 min the reaction was stirred at r.t. until complete (3 h). The crude was concentrated and taken up with Et$_2$O/AcOEt 7 : 3 to remove most of the 1,3-dicyclohexylurea by filtration. After solvent removal chromatography with PE/Me$_2$CO 8 : 2 gave **19** (534 mg, 97%) as a pale yellow oil. **b**) From **23**: compound (*S*)-**19** was prepared from **23**, following the procedure reported for compound **15** in 100% yield. R_f 0.35 (PE/Et$_2$O 80 : 20). (*R*)-**19**: $[\alpha]_D$ –10.9 (*c* 1.0, $CHCl_3$). (*S*)-**19**: $[\alpha]_D$ +14.1 (*c* 1.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3431, 2997, 2926, 2854, 1680, 1588, 1463, 1386, 1217, 1086. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers a and b are visible, in a 81 : 19 a : b ratio): 0.04, 0.05 (2 × 3 H, 2 s, CH_3Si, a + b), 0.88 (9 H, s, (CH_3)$_3$CSi, a + b), 2.14 (1 H, septet, *J* 5.7, CH(CH$_2$–)$_3$, b), 2.23 (1 H, septet, *J* 5.8, CH(CH$_2$–)$_3$, a), 3.43–3.59 (2 H, m, CH_2NH, a + b), 3.73 and 3.75 (2 H, AB part of an ABX syst., J_{AB} 10.3, J_{AX} 5.9, J_{BX} 4.8, CH_2OSi, b), 3.79 (2 H, d, *J* 5.1, CH_2OSi, a), 3.91 and 3.94 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 6.5, J_{BX} 5.5, CH_2OAr, b), 3.95 and 3.99 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 5.6, J_{BX} 6.4, CH_2OAr, b), 5.88 (1 H, broad s, N*H*, b), 6.23 (1 H, broad s, N*H*, a) 6.82 (1 H, ddd, *J* 1.5, 2.4, 7.8, *H*-6′, a, which is partially overlapped with b), 7.04–7.17 (3 H, m, other aromatics, a + b), 8.02 (1 H, d, *J* 12.0, C*H*O, b), 8.18 (1 H, d, *J* 1.5, C*H*O, a). δ_C (75 MHz; $CDCl_3$, 25 °C): –5.58, –5.56 (*C*H$_3$Si, a + b), 18.2 (*C*(CH$_3$)$_3$, a + b), 25.8 ((*C*H$_3$)$_3$C, a + b), 38.4 (a), 40.7 (b) (*C*H$_2$NH), 40.4 (a), 41.7 (b) (*C*H(CH$_2$–)), 61.1 (b), 62.6 (a) (*C*H$_2$OSi), 66.3 (b), 67.0 (a)

(CH_2OAr), 113.28 (b), 113.33 (a) (*C*-6′), 117.78 (b), 117.83 (a) (*C*-2′), 122.80 (a), 122.85 (b) (*C*-3′), 124.1 (a), 124.3 (b) (*C*-4′), 130.57 (a), 130.63 (b) (*C*-5′), 159.2 (b), 159.4 (a) (*C*-1′), 161.2 (a), 164.8 (b) (*C*═*O*). GC-MS: R_t: 10.09 min; *m*/*z* (EI): 388 (M^+ (^{81}Br) – 15, 0.50), 386 (M^+ (^{79}Br) – 15, 0.50), 347 (8.9), 346 (45), 345 (9.3), 344 (45), 271 (5.5), 269 (5.0), 232 (5.1), 231 (39), 230 (6.2), 229 (38), 173 (5.1), 172 (15), 157 (6.0), 155 (6.2), 151 (5.5), 150 (6.2), 159 (5.3), 145 (7.6), 139 (7.3), 137 (7.9), 135 (10), 131 (6.1), 117 (7.8), 116 (27), 115 (19), 102 (26), 99 (13), 98 (19), 91 (5.4), 89 (19), 88 (6.5), 86 (6.6), 85 (13), 77 (14), 76 (17), 75 (100), 74 (10), 73 (71), 71 (7.2), 70 (21), 65 (5.6), 63 (6.3), 61 (9.1), 60 (5.7), 59 (39), 58 (80), 57 (15), 56 (11), 55 (6.6), 47 (9.3), 45 (15), 44 (5.1), 43 (16), 42 (7.3), 41 (42), 39 (11). *m*/*z* (ESI+) 424.0925 (M + Na^+). $C_{17}H_{28}BrNO_3SiNa$ requires 424.0920.

(*R*)- or (*S*)-1-(*tert*-Butyl)dimethylsilyloxy-2-((3-bromophenoxy)-methyl)-3-isocyanopropane 2

A solution of (***R***)- or (***S***)-**19** (123 mg, 306 μmol) in dry CH_2Cl_2 (2.5 mL) was cooled to −30 °C and treated with Et_3N (196 μL, 1.41 mmol) and $POCl_3$ (43 μL, 459 mmol). The colourless solution became brick red in about 1 h. After 5.5 h, quenching with 5% $NaHCO_3$ was followed by extraction with Et_2O/AcOEt 1 : 1. The organic phases were washed with brine, concentrated and chromatographed with PE/Me_2CO 98 : 2 to 8 : 2 to give **2** as a colourless oil (112 mg, 95%). R_f 0.40 (PE/Et_2O 95 : 5). (***R***)-**2**: $[\alpha]_D$ +0.23 (*c* 1.0, $CHCl_3$). (***S***)-**2**: $[\alpha]_D$ −0.30 (*c* 1.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3020, 2999, 2152, 1584, 1466, 1423, 1189, 1026. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.07 (2 × 3 H, 2 s, CH_3Si), 0.89 (9 H, s, $(CH_3)_3CSi$), 2.36 (1 H, septet, *J* 5.8, $CH(CH_2–)_3$), 3.64 (2 H, d, *J* 6.0, CH_2NC), 3.75 and 3.80 (2 H, AB part of an ABX syst., J_{AB} 10.4, J_{AX} 6.0, J_{BX} 5.2, CH_2OSi), 3.96 and 4.03 (2 H, AB part of an ABX syst., J_{AB} 9.4, J_{AX} 6.7, J_{BX} 5.5, CH_2OAr), 6.83 (1 H, ddd, *J* 1.8, 2.4, 7.8, *H*-6′), 7.05–7.18 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (CH_3Si), 18.2 ($C(CH_3)_3$), 25.8 ($(CH_3)_3C$), 40.0 (CH_2NC), 40.9 ($CH(CH_2–)$), 60.1 (CH_2OSi), 65.4 (CH_2OAr), 113.3 (*C*-6′), 117.8 (*C*-2′), 122.8 (*C*-3′), 124.3 (*C*-4′), 130.6 (*C*-5′), 157.3 (N*C*), 159.1 (*C*-1′). GC-MS: R_t: 8.82 min; *m*/*z* (EI): 370 (M^+ (^{81}Br) - 15, 0.26), 368 (M^+ (^{79}Br) – 15, 0.23), 329 (8.5), 328 (44), 327 (8.5), 326 (43), 301 (6.5), 299 (6.7), 271 (12), 269 (11), 259 (11), 257 (10), 233 (5.0), 232 (14), 231 (100), 230 (15), 229 (96), 220 (7.7), 187 (23), 185 (24), 180 (6.0), 179 (5.5), 157 (14), 155 (14), 151 (5.1), 150 (9.4), 149 (7.9), 146 (6.5), 139 (9.7), 137 (9.6), 135 (12), 131 (6.0), 127 (9.9), 115 (13), 114 (24), 99 (9.4), 89 (6.7), 86 (5.0), 85 (11), 84 (39), 78 (5.4), 77 (7.3), 76 (20), 75 (34), 74 (6.0), 73 (46), 71 (11), 64 (5.2), 63 (6.7), 59 (25), 58 (10), 57 (12), 55 (5.7), 53 (5.1), 47 (6.6), 45 (12), 43 (14), 41 (37), 39 (10). *m*/*z* (ESI+) 406.0795 (M + Na^+). $C_{17}H_{26}BrNO_2SiNa$ requires 406.0814.

(*S*,*E*)-2-((3-Bromophenoxy)methyl)-5-methylhex-3-en-1-ol 20

Compound **20** was prepared from **11**, following the procedure reported for compound **14**. Chromatography with PE/Et_2O 75 : 25 gave **20** as a colourless oil in 100% yield. R_f 0.23 (PE/Et_2O 80 : 20). $[\alpha]_D$ −32.1 (*c* 2.1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3606, 3002, 2955, 2870, 1589, 1463, 1193, 1020. δ_H (300 MHz; $CDCl_3$, 25 °C): 1.00 (6 H, d, *J* 6.9, $(CH_3)_2CH$), 1.70 (1 H, t, *J* 6.2, O*H*), 2.31 (1 H, centre of m, $(CH_3)_2CH$), 2.70 (1 H, centre of m, $CH(CH_2O–)_2$), 3.74 (2 H, centre of m, CH_2OH), 3.97 and 4.00 (2 H, AB part of an ABX syst., J_{AB} 9.2, J_{AX} 7.6, J_{BX} 5.0, CH_2OAr), 5.33 (1 H, ddd, *J* 1.2, 8.1, 15.3, $(CH_3)_2CHCH═CH$), 5.65 (1 H, ddd, *J* 0.9, 6.6, 15.6, $(CH_3)_2CHCH = CH$), 6.84 (1 H, ddd, *J* 1.5, 2.4, 7.8, *H*-6′), 7.06–7.16 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): 22.4, 22.5 ($(CH_3)_2CH$), 31.3 ($(CH_3)_2CH$), 44.6 ($CH(CH_2O–)_2$), 63.8 (CH_2OAc), 69.3 (CH_2OAr), 113.6 (*C*-6′), 117.8 (*C*-2′), 122.8 (*C*-3′), 123.3 ($(CH_3)_2CHCH = CH$), 124.0 (*C*-4′), 130.5 (*C*-5′), 142.2 ($(CH_3)_2CHCH═CH$), 159.6 (*C*-1′). GC-MS (usual method but with initial temp. 70 °C, rate 10 °C min^{-1}, final temp. 280 °C): R_t: 14.36 min; *m*/*z* (EI): 300 (M^+ (^{81}Br), 2.5), 298 (M^+ (^{79}Br), 2.1), 174 (37), 172 (40), 157 (8.4), 155 (7.3), 126 (22), 110 (8.4), 109 (96), 108 (9.5), 96 (12), 95 (30), 93 (18), 83 (34), 82 (23), 81 (61), 80 (5.3), 79 (18), 77 (11), 76 (9.4), 75 (6.5), 71 (16), 70 (9.3), 69 (37), 68 (8.6), 67 (100), 65 (12), 64 (5.6), 63 (7.9), 59 (11), 57 (37), 56 (8.5), 55 (85), 54 (5.4), 53 (18), 43 (69), 41 (75), 39 (23). *m*/*z* (ESI+) 321.0472 (M + Na^+). $C_{14}H_{19}BrO_2Na$ requires 321.0466.

(*S*,*E*)-1-Azido-2-((3-bromophenoxy)methyl)-5-methylhex-3-ene 21

Compound **20** was transformed into the corresponding mesylate [R_f 0.89 (CH_2Cl_2/Et_2O 90 : 10); 0.12 (PE/Me_2CO 90 : 10] and then into azide **21**, following the procedure reported for compound **13**. Chromatography with PE/CH_2Cl_2 95 : 5 to 75 : 25 gave **21** as a colourless oil in 95% yield. R_f 0.46 (PE/CH_2Cl_2 90 : 10). $[\alpha]_D$ −20.3 (*c* 1.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3020, 2953, 2868, 2099, 1590, 1463, 1194, 1021. δ_H (300 MHz; $CDCl_3$, 25 °C): 1.002, 0.999 (6 H, 2 d, *J* 6.6 and 6.6, $(CH_3)_2CH$), 2.30 (1 H, centre of m, $(CH_3)_2CH$), 2.72 (1 H, centre of m, $CH(CH_2O–)_2$), 3.44 and 3.49 (2 H, AB part of an ABX syst., J_{AB} 11.5, J_{AX} 5.7, J_{BX} 5.2, CH_2N_3), 3.90 and 3.94 (2 H, AB part of an ABX syst., J_{AB} 9.4, J_{AX} 7.2, J_{BX} 5.3, CH_2OAr), 5.35 (1 H, ddd, *J* 1.2, 8.1, 15.3, $(CH_3)_2CHCH═CH$), 5.66 (1 H, ddd, *J* 1.2, 6.6, 15.9, $(CH_3)_2CHCH = CH$), 6.83 (1 H, ddd, *J* 1.2, 2.7, 7.8, *H*-6′), 7.05–7.17 (3 H, m, other aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): 22.21, 22.23 ($(CH_3)_2CH$), 31.2 ($(CH_3)_2CH$), 42.5 ($CH(CH_2O–)_2$), 52.7 (CH_2N_3), 68.6 (CH_2OAr), 113.5 (*C*-6′), 117.8 (*C*-2′), 122.8 (*C*-3′), 123.3 ($(CH_3)_2CHCH = CH$), 124.0 (*C*-4′), 130.6 (*C*-5′), 142.0 ($(CH_3)_2CHCH═CH$), 159.4 (*C*-1′). GC-MS (usual method but with initial temp. 70 °C, rate 10 °C min^{-1}, final temp. 280 °C): R_t: 14.94 min; *m*/*z* (EI): 325 (M^+ (^{81}Br), 0.30), 323 (M^+ (^{79}Br), 0.32), 174 (15), 172 (16), 157 (8.4), 155 (7.2), 110 (10), 109 (19), 108 (9.8), 96 (12), 95 (35), 94 (7.1), 93 (10), 82 (19), 81 (48), 80 (18), 79 (18), 77 (9.9), 76 (8.3), 75 (6.3), 70 (10), 69 (16), 68 (23), 67 (51), 65 (12), 64 (6.4), 63 (9.4), 56 (15), 55 (100), 54 (9.9), 53 (20), 50 (5.5), 43 (32), 42 (11), 41 (72), 39 (25). *m*/*z* (ESI+) 346.0543 (M + Na^+). $C_{14}H_{18}BrN_3ONa$ requires 346.0531.

N-((*S*,*E*)-2-((3-Bromophenoxy)methyl)-5-methylhex-3-enyl)-formamide 22

Compound **21** was transformed into the corresponding primary amine following the procedure reported for compound **18**. R_f 0.45 (CH_2Cl_2/MeOH 90 : 10 + 2% Et_3N, ninhydrin). The crude was directly transformed into **22** following the procedure reported for compound **19**. Chromatography with CH_2Cl_2 + 1.5% MeOH gave **22** as an ivory foam. R_f 0.39 (CH_2Cl_2 + 2% MeOH). $[\alpha]_D$ −33.1 (*c* 1.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3437, 3029, 2954, 2869, 1683, 1590, 1573, 1464, 1190. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers a and b are visible, in a 79 : 21 a : b ratio): 0.998, 0.995

(6 H, 2 d, *J* 6.9 and 6.6, $(CH_3)_2CH$, a + b), 2.28 (1 H, centre of m, $(CH_3)_2CH$, a + b), 2.57–2.74 (1 H, m, $CH(CH_2)_2$, a + b), 3.28–3.65 (2 H, m, CH_2NH, a + b), 3.83 and 3.86 (2 H, AB part of an ABX syst., J_{AB} 9.4, J_{AX} 8.3, J_{BX} 1.4, CH_2OAr, b), 3.87 and 4.00 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 7.3, J_{BX} 5.0, CH_2OAr, a), 5.25 (1 H, ddd, *J* 1.2, 8.4, 15.6, $(CH_3)_2CHCH{=}CH$, b), 5.29 (1 H, ddd, *J* 0.9, 8.1, 15.3, $(CH_3)_2CHCH{=}CH$, a), 5.64 (1 H, ddd, *J* 0.6, 6.6, 15.9, $(CH_3)_2CHCH = CH$, a), 5.65 (1 H, ddd, *J* 0.6, 6.3, 15.6, $(CH_3)_2CHCH = CH$, b), 5.76 (1 H, broad s, N*H*, a + b), 6.83 (1 H, ddd, *J* 1.2, 2.4, 7.8, *H*-6′, a + b), 7.05–7.18 (3 H, m, other aromatics, a+b), 8.02 (1 H, d, *J* 11.7, C*H*O, b), 8.20 (1 H, d, *J* 1.2, C*H*O, a). δ_C (75 MHz; $CDCl_3$, 25 °C): 22.2, 22.3, 22.4 ($(CH_3)_2CH$, a + b), 31.1 (a), 31.2 (b) ($(CH_3)_2CH$), 39.8 (a), 43.2 (b) (CH_2NH), 42.1 (a), 43.3 (b) ($CH(CH_2)_2$), 68.6 (b), 70.0 (a) (CH_2OAr), 113.4 (b), 113.5 (a) (C-6′), 117.68 (b), 117.72 (a) (C-2′), 122.6 (b), 123.6 (a) ($(CH_3)_2CHCH{=}CH$), 122.76 (a), 122.83 (b) (C-3′), 124.1 (a), 124.2 (b) (C-4′), 130.57 (a), 130.62 (b) (C-5′), 142.1 (a), 142.9 (b) ($(CH_3)_2CHCH{=}CH$), 159.1 (b), 159.3 (a) (C-1′), 161.2 (a), 164.8 (b) (C=O). GC-MS (usual method but with initial temp. 70 °C, rate 10 °C min^{-1}, final temp. 280 °C): R_t: 9.17 min; *m*/*z* (EI): 327 (M^+ (^{81}Br), 0.51), 325 (M^+ (^{79}Br), 0.58), 174 (10), 172 (11), 155 (7.4), 154 (34), 153 (16), 110 (12), 109 (100), 108 (32), 98 (9.0), 96 (17), 95 (24), 93 (20), 84 (6.2), 82 (5.6), 81 (46), 79 (13), 77 (7.7), 76 (5.0), 69 (7.6), 68 (5.0), 67 (42), 65 (6.9), 59 (13), 58 (45), 56 (5.7), 55 (25), 53 (10), 46 (8.3), 43 (15), 41 (31), 39 (12). *m*/*z* (ESI+) 348.0576 ($M + Na^+$). $C_{15}H_{20}BrNO_2Na$ requires 310.0055.

(*R*)-2-((3-Bromophenoxy)methyl)-3-formylamino-1-propanol 23

Compound **23** was prepared from **22**, following the procedure reported for compound **12**. Chromatography with PE/Et_2O 75 : 25 gave **23** as a colourless oil in 100% yield. R_f 0.40 (PE/Me_2CO 50 : 50 + 1% EtOH). $[\alpha]_D$ −17.5 (*c* 1.1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3433, 3000, 2878, 1676, 1588, 1496, 1465, 1190, 1023. δ_H(300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers a and b are visible, in a 91 : 9 a : b ratio): 2.20 (1 H, centre of m, $CH(CH_2)_3$, a + b), 3.31 (1 H, t, *J* 6.6, O*H*, a + b), 3.51 (2 H, t, *J* 6.3, CH_2NH, b), 3.58 (2 H, t, *J* 6.3, CH_2NH, a), 3.62–3.83 (2 H, m, CH_2OH, a + b), 3.93 and 4.01 (2 H, AB part of an ABX syst., J_{AB} 9.4, J_{AX} 7.5, J_{BX} 5.7, CH_2OAr, a, which is partially overlapped with b), 6.12 (1 H, broad s, N*H*, a + b), 6.83 (1 H, ddd, *J* 1.5, 2.7, 7.8, *H*-6′, a, which is partially overlapped with b), 7.05–7.18 (3 H, m, other aromatics, a + b), 8.03 (1 H, d, *J* 12.3, C*H*O, b), 8.25 (1 H, d, *J* 1.8, C*H*O, a). δ_C (75 MHz; $CDCl_3$, 25 °C): 36.8 (CH_2NH, a + b), 40.9 (a), 41.4 (b) ($CH(CH_2)$), 60.4 (a), 60.8 (b) (CH_2OH), 66.5 (b), 67.2 (a) (CH_2OAr), 113.3 (C-6′, a + b), 117.7 (C-2′, a + b), 122.8 (C-3′, a + b), 124.1 (a), 124.3 (b) (C-4′), 130.6 (C-5′, a + b), 159.1 (b), 159.3 (a) (C-1′), 162.7 (a), 165.3 (b) (C=O). GC-MS: R_t: 9.11 min; *m*/*z* (EI): 174 (M^+ (^{81}Br) − 101, 7.2), 172 (M^+ (^{79}Br) − 101, 7.1), 117 (6.6), 116 (100), 98 (5.6), 86 (6.2), 71 (6.8), 70 (6.1), 65 (5.4), 59 (6.2), 58 (47), 56 (5.6), 46 (8.7), 43 (6.7), 41 (18), 39 (6.1). *m*/*z* (ESI+) 310.0042 ($M + Na^+$). $C_{11}H_{14}BrO_3Na$ requires 310.0055.

(*S*)-Methyl 2-((3-bromophenoxy)methyl)-3-formylaminopropanoate 24

a) Oxidation to carboxylic acid: a solution of **23** (110 mg, 382 µmol) in dry acetone (stored on dry $CuSO_4$) was cooled to 0 °C and treated dropwise with Jones reagent (prepared from 10 g CrO_3, 8.6 mL 96% H_2SO_4, 14 mL H_2O, and brought up to 40 mL with H_2O) until the yellow-brown colour persisted. After 2 h 5% $NH_4H_2PO_4$ solution saturated with NaCl was added. The pH of the aqueous phase was adjusted to 2 by careful addition of HCl. The extraction was performed with AcOEt/MeOH 90 : 10. The organic layers were washed with 5% Na_2SO_3 solution saturated with NaCl and concentrated. R_f 0.31 (PE/Me_2CO 50 : 50, developed with $KMnO_4$). **b**) Methyl ester formation: crude acid was dissolved in dry THF (5 mL) to give a yellowish solution. After cooling to 0 °C, diazomethane solution was added dropwise until the peculiar yellow colour persisted. The excess of CH_2N_2 was eliminated by addition of few drops of AcOH. The solvent was evaporated and AcOH was removed azeotropically by addition of *n*-heptane. Chromatography with PE/Me_2CO 70 : 30 to 50 : 50 afforded **24** as a yellow oil (75 mg, 62%). R_f 0.38 (PE/Me_2CO 50 : 50, developed with $KMnO_4$). $[\alpha]_D$ +4.12 (*c* 2.1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3436, 3035, 2989, 2974, 1730, 1686, 1587, 1501, 1466, 1192. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers a and b are visible, in a 85 : 15 a : b ratio): 3.02 (1 H, centre of m, $CHCH_2NH$, b), 3.10 (1 H, ddt, J_t 4.8, J_d 5.2, J_d 8.2 $CHCH_2NH$, a), 3.62–3.84 (2 H, m, CH_2NH, a + b), 3.76 (3 H, s, OCH_3, a), 3.78 (3 H, s, OCH_3, b), 4.19 and 4.23 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 4.4, J_{BX} 5.5, CH_2OAr, a, which is partially overlapped with b), 6.01 (1 H, broad s, N*H*, b), 6.18 (1 H, broad s, N*H*, a), 6.83 (1 H, ddd, *J* 1.8, 2.4, 7.2, *H*-6′, a, which is partially overlapped with b), 7.05–7.18 (3 H, m, other aromatics, a + b), 8.05 (1 H, d, *J* 11.7, C*H*O, b), 8.19 (1 H, d, *J* 1.2, C*H*O, a). δ_C (75 MHz; $CDCl_3$, 25 °C): 36.6 (a), 39.7 (b) (CH_2NH), 44.8 (a), 45.9 (b) ($CHCH_2NH$), 52.4 (a), 52.6 (b) (OCH_3), 66.2 (b), 66.7 (a) (CH_2OAr), 113.4 (b), 113.5 (a) (C-6′), 117.9 (b), 118.0 (a) (C-2′), 122.8 (a), 123.2 (b) (C-3′), 124.5 (a), 124.8 (b) (C-4′), 130.6 (a), 130.7 (b) (C-5′), 158.6 (b), 158.9 (a) (C-1′), 161.3 (a), 164.7 (b) (HC=O), 171.2 (b), 172.3 (a) (CO_2Me). GC-MS: R_t: 8.89 min; *m*/*z* (EI): 317 (M^+ (^{81}Br), 0.26), 315 (M^+ (^{79}Br), 0.26), 145 (10), 144 (100), 112 (44), 87 (9.7), 84 (7.7), 63 (6.2), 59 (9.9), 58 (28), 56 (11), 55 (19), 41 (6.0), 58 (2.3), 56 (0.3), 46 (0.4), 43 (0.3), 41 (0.9). *m*/*z* (ESI+) 337.9996 ($M + Na^+$). $C_{12}H_{14}BrNO_4Na$ requires 338.0004.

(*S*)-1-Acetoxy-2-benzyl-3-(*tert*-butyl)dimethylsilyloxypropane 27

Compound **27** was prepared from known monoacetate **7**,[23] following the procedure reported for compound **15**. Chromatography with PE/Et_2O 95 : 5 gave **27** as a colourless oil in 99% yield. R_f 0.50 (PE/Et_2O 90 : 10). $[\alpha]_D$ +6.07 (*c* 1.8, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3670, 3627, 3028, 2990, 2946, 2920, 2852, 1725, 1432, 1382, 1363, 1188, 1085, 1020. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.023, 0.019 (6 H, s, CH_3Si), 0.90 (9 H, s, $(CH_3)_3CSi$), 2.04 (3 H, s, $COCH_3$), 2.10 (1 H, centre of m, $CH(CH_2)_3$), 2.60 and 2.71 (2 H, AB part of an ABX syst., J_{AB} 13.5, J_{AX} 7.2, J_{BX} 7.8, CH_2Ph), 3.52 and 3.57 (2 H, AB part of an ABX syst., J_{AB} 10.0, J_{AX} 5.5, J_{BX} 4.7, CH_2OSi), 4.05 and 4.05 (2 H, AB part of an ABX syst., J_{AB} 11.1, J_{AX} 5.8, J_{BX} 5.8, CH_2OAc), 7.16–7.22 (5 H, m, Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6, −5.5 (CH_3Si), 18.3 ($C(CH_3)_3$), 20.9 ($COCH_3$), 25.9 ($(CH_3)_3C$), 34.2 (CH_2Ph), 42.2 ($CH(CH_2)$), 61.8 (CH_2OSi), 64.3 (CH_2OAc), 126.0 (CH *para* of Ph), 128.3 (CH *meta* of Ph), 129.1 (CH *ortho* of Ph), 139.8 (C *ipso* of Ph), 171.1 (C=O). GC-MS: R_t: 7.46 min; *m*/*z* (EI): 265 (M^+ − 57, 2.0), 131 (5.1), 131 (47), 118 (10), 117 (100), 105 (5.1), 91 (31), 75 (40), 73

(11), 43 (18). *m/z* (ESI+) 323.2048 (M + H$^+$). $C_{18}H_{31}O_3Si$ requires 323.2042.

(*S*)-2-Benzyl-3-(*tert*-butyl)dimethylsilyloxypropanol 28

Compound **28** was prepared from **27**, following the procedure reported for compound **14**. Chromatography with PE/Et_2O 95 : 5 to 80 : 20 gave **28** as a yellow oil in 90% yield. R_f 0.47 (PE/Et_2O 80 : 20). $[\alpha]_D$ −26.3 (*c* 1.0, $CHCl_3$). IR: ν_{max}($CHCl_3$)/cm^{-1} 3610, 3480, 2997, 2945, 2925, 2889, 1496, 1418, 1189, 1105, 1041. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.053, 0.047 (6 H, s, CH_3Si), 0.90 (9 H, s, (CH_3)$_3$CSi), 2.01 (1 H, centre of m, CH(CH_2-)$_3$), 2.62 and 2.62 (2 H, AB part of an ABX syst., J_{AB} 13.9, J_{AX} 7.6, J_{BX} 7.6, CH_2Ph), 2.77 (1 H, broad t, *J* 4.6, O*H*), 3.62 and 3.77 (2 H, AB part of an ABX syst., J_{AB} 9.8, J_{AX} 6.6, J_{BX} 4.0, CH_2OSi), 3.70 (2 H, centre of m, CH_2OH), 7.13–7.31 (5 H, m, Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H$_3$Si), 18.1 (*C*(CH$_3$)$_3$), 25.8 ((*C*H$_3$)$_3$C), 34.1 (*C*H$_2$Ph), 43.8 (*C*H(CH$_2$-)), 65.8 (*C*H$_2$OSi), 66.2 (*C*H$_2$OH), 126.0 (*C*H *para* of Ph), 128.3 (*C*H *meta* of Ph), 129.0 (*C*H *ortho* of Ph), 140.0 (*C ipso* of Ph). GC-MS: R_t: 7.00 min; *m/z* (EI): 265 (M$^+$ − 15, 0.037), 132 (11), 131 (100), 129 (7.1), 117 (6.3), 105 (30), 92 (5.5), 91 (54), 75 (56), 73 (8.1). *m/z* (ESI+) 281.1936 (M + H$^+$). $C_{16}H_{29}O_2Si$ requires 281.1937.

(*R*)- or (*S*)-1-Azido-2-benzyl-3-(*tert*-butyl)dimethylsilyloxypropane 29

a) From **26**: compound (*R*)-**29** was prepared from known compound **26**,[23] following the procedure reported for compound **15**. Chromatography with PE to PE/Et_2O 95 : 5 gave (*R*)-**29** as a colourless oil in 92% yield. **b**) From **28**: compound **28** was transformed into the corresponding mesylate [R_f 0.82 (CH_2Cl_2/Et_2O/PE 1 : 0.5 : 1); 0.12 (PE/Me_2CO 90 : 10] and then into azide (*S*)-**29**, following the procedure reported for compound **13** to give (*S*)-**29** in 93% yield. R_f 0.29 (PE). (*R*)-**29**: $[\alpha]_D$ −9.53 (*c* 2.6, $CHCl_3$). (*S*)-**29**: $[\alpha]_D$ +9.99 (*c* 2.1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 2999, 2929, 2852, 2099, 1463, 1191, 1107. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.04 (6 H, s, CH_3Si), 0.91 (9 H, s, (CH_3)$_3$CSi), 1.98 (1 H, septet, *J* 6.2, CH(CH$_2$–)$_3$), 2.59 and 2.67 (2 H, AB part of an ABX syst., J_{AB} 13.6, J_{AX} 7.4, J_{BX} 7.5, CH_2Ph), 3.28 and 3.30 (2 H, AB part of an ABX syst., J_{AB} 12.1, J_{AX} 6.6, J_{BX} 4.8, CH_2N$_3$), 3.46 and 3.54 (2 H, AB part of an ABX syst., J_{AB} 10.0, J_{AX} 5.8, J_{BX} 4.4, CH_2OSi), 7.16–7.32 (5 H, m, Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.52, −5.50 (*C*H$_3$Si), 18.3 (*C*(CH$_3$)$_3$), 25.9 ((*C*H$_3$)$_3$C), 34.7 (*C*H$_2$Ph), 43.0 (*C*H(CH$_2$–)), 51.7 (*C*H$_2$N$_3$), 62.1 (*C*H$_2$OSi), 126.1 (*C*H *para* of Ph), 128.4 (*C*H *meta* of Ph), 129.1 (*C*H *ortho* of Ph), 139.6 (*C ipso* of Ph). GC-MS: R$_t$: 7.29 min; *m/z* (EI): 277 (M$^+$ − 28, 0.38), 249 (5.7), 248 (30), 220 (14), 218 (12), 193 (5.5), 191 (19), 190 (13), 159 (5.2), 144 (8.1), 136 (6.0), 135 (39), 132 (5.4), 130 (5.8), 129 (10), 128 (17), 118 (7.1), 117 (48), 116 (32), 115 (20), 105 (8.5), 104 (5.3), 102 (6.4), 101 (6.3), 100 (6.3), 92 (8.3), 91 (100), 90 (6.1), 89 (58), 86 (36), 77 (8.0), 76 (7.7), 75 (100), 74 (9.0), 73 (36), 65 (7.8), 61 (7.3), 59 (32), 57 (8.0), 47 (7.6), 45 (11), 41 (9.0). *m/z* (ESI+) 278.1936 (M + H$^+$ − N$_2$). $C_{16}H_{28}NOSi$ requires 278.1940.

(*R*)- or (*S*)-2-Benzyl-3-(*tert*-butyl)dimethylsilyloxy-1-formylaminopropane 30

Compounds (*R*)- and (*S*)-**29** were transformed into the corresponding primary amines following the procedure reported for compound **18**. R_f 0.46 (CH_2Cl_2/MeOH 95 : 5 + 2% Et_3N, ninhydrin). The crude were directly transformed into (*R*)- and (*S*)-**30**, respectively, following the procedure reported for compound **19**. Chromatography with PE/Et_2O gave **30** as a pale yellow foam. R_f 0.48 (PE/Et_2O 40 : 60). (*R*)-**30**: $[\alpha]_D$ +0.90 (*c* 2.1, $CHCl_3$). (*S*)-**30**: $[\alpha]_D$ −0.24 (*c* 1.8, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3393, 3006, 2924, 2856, 1680, 1493, 1463, 1386, 1187, 1069. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers a and b are visible, in a 78 : 22 a : b ratio): 0.032, 0.038 (6 H, s, CH_3Si, a), 0.043, 0.049 (6 H, s, CH_3Si, b), 0.91 (9 H, s, (CH_3)$_3$CSi, a), 0.92 (9 H, s, (CH_3)$_3$CSi, b), 1.88–2.08 (1 H, centre of m, CH(CH$_2$-)$_3$, a + b), 2.59 and 2.64 (2 H, AB part of an ABX syst., J_{AB} 13.3, J_{AX} 6.7, J_{BX} 7.8, CH_2Ph, a, which is partially overlapped with b), 3.23–3.66 (3 H, m, CH_2NH, a + b and CH_2OSi, b), 3.53 and 3.66 (2 H, AB part of an ABX syst., J_{AB} 10.2, J_{AX} 6.0, J_{BX} 3.9, CH_2OSi, a), 5.89 (1 H, broad s, N*H*, b), 6.36 (1 H, broad s, N*H*, a), 7.14–7.33 (5 H, m, Ph, a + b), 7.94 (1 H, d, *J* 12.0, C*H*O, b), 8.14 (1 H, d, *J* 1.5, C*H*O, a). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H$_3$Si, a + b), 18.1 (*C*(CH$_3$)$_3$, a + b), 25.9 ((*C*H$_3$)$_3$C, a + b), 34.8 (b), 35.5 (a) (*C*H$_2$Ph), 41.3 (a), 42.7 (b) (*C*H$_2$NH), 41.6 (a), 43.0 (b) (*C*H(CH$_2$–)), 63.0 (b), 65.2 (a) (*C*H$_2$OSi), 126.2 (a), 126.4 (b) (*C*H *para* of Ph), 128.4 (a), 128.6 (b) (*C*H *meta* of Ph), 128.9 (b), 129.0 (a) (*C*H *ortho* of Ph), 139.2 (b), 139.5 (a) (*C ipso* of Ph), 161.0 (a), 164.9 (b) (*C*═*O*). GC-MS: R_t: 8.52 min; *m/z* (EI): 292 (M$^+$ − 15, 1.6), 252 (5.1), 251 (21), 250 (100), 175 (8.2), 135 (5.1), 131 (16), 130 (21), 129 (15), 117 (22), 116 (25), 115 (14), 105 (7.0), 104 (6.1), 103 (8.5), 102 (67), 92 (8.9), 91 (99), 89 (19), 77 (8.2), 76 (5.8), 75 (78), 74 (6.2), 73 (30), 65 (7.3), 61 (5.5), 59 (13), 58 (7.1), 57 (6.2), 47 (5.7), 45 (6.8), 41 (6.9). *m/z* (ESI+) 308.2036 (M + H$^+$). $C_{17}H_{30}NO_2Si$ requires 308.2046.

Mosher's ester obtained from 30

a) Silyl ether removal: a solution of **30** (30 mg, 97.6 μmol) in dry CH_3CN (1 mL) was cooled to −10 °C and treated with 40% aqueous HF (50 μL). After stirring for 20 min at the same temperature, the reaction was quenched with $NaHCO_3$ (5% solution saturated with NaCl) and extracted with Et_2O. After solvent removal, the crude was used as such for the following acylation. R_f 0.21 (AcOEt, ninhydrin); **b**) Mosher's ester formation: 25% of the above prepared crude (24.4 μmol, based on **30**) was dissolved in dry CH_2Cl_2 (500 μL), cooled to 0 °C, and treated with *N*,*N*-dimethylamino pyridine (9.0 mg, 73.2 μmol) and either (*R*)- or (*S*)-Mosher chloride (6.0 μL, 32.1 μmol). The solution was allowed to stir at r.t. for 30 min. Then the crude was directly purified by preparative TLC, to give the desired ester in 70% overall yield. R_f 0.34 (PE/AcOEt 4 : 6). The comparison between the proton spectra of the diastereomeric esters, in particular signals due to CH_2OCOC(OMe)(CF_3)Ph, demonstrate that the initial e.e. of **7** was maintained.

(*R*)- or (*S*)-2-Benzyl-1-(*tert*-butyl)dimethylsilyloxy-3-isocyanopropane 3

Compounds (*R*)- and (*S*)-**3** were prepared from (*R*)- and (*S*)-**30**, respectively, following the procedure reported for compound **2**. Chromatography with PE to PE/Et_2O 97 : 3 gave **30** as a pale yellow oil. R_f 0.44 (PE/AcOEt 97 : 3). (*R*)-**3**: $[\alpha]_D$ −19.3 (*c* 2.2, $CHCl_3$). (*S*)-**3**: $[\alpha]_D$ +19.2 (*c* 2.2, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3001, 2945, 2923, 2884, 2852, 2151, 1506, 1468, 1413, 1189, 1122,

1029. δ_H (300 MHz; $CDCl_3$, 25 °C): 0.06, 0.07 (6 H, s, CH_3Si), 0.91 (9 H, s, (CH_3)$_3$CSi), 2.08 (1 H, centre of m, CH(CH_2–)$_3$), 2.62 and 2.71 (2 H, AB part of an ABX syst., J_{AB} 13.7, J_{AX} 8.1, J_{BX} 7.0, CH_2Ph), 3.41 (2 H, centre of m, CH_2NC), 3.56 and 3.67 (2 H, AB part of an ABX syst., J_{AB} 10.3, J_{AX} 6.8, J_{BX} 4.1, CH_2OSi), 7.18–7.34 (5 H, m, Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.5 (*C*H_3Si), 18.2 (*C*(CH$_3$)$_3$), 25.8 ((*C*H$_3$)$_3$C), 34.1 (*C*H$_2$Ph), 41.7 (*C*H$_2$NC), 42.4 (*C*H(CH$_2$-)), 61.7 (*C*H$_2$OSi), 126.5 (*C*H *para* of Ph), 128.6 (*C*H *meta* of Ph), 129.0 (*C*H *ortho* of Ph), 138.6 (*C ipso* of Ph), 156.5 (N*C*) (signal very difficult to detect). GC-MS: R_t: 7.12 min; *m*/*z* (EI): 273 (M^+ − 15, 0.33), 233 (5.5), 232 (28), 205 (11), 132 (3.3), 131 (29), 129 (14), 117 (7.1), 115 (9.4), 114 (8.2), 92 (9.7), 91 (100), 89 (9.1), 84 (14), 77 (5.5), 76 (5.5), 75 (69), 73 (12), 65 (6.2), 59 (6.5), 41 (5.3). *m*/*z* (ESI+) 290.1933 ($M + H^+$). $C_{17}H_{28}NOSi$ requires 290.1940.

(4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate 8

Diol **31** (2.01 g, 12.4 mmol) was dissolved in vinyl acetate (30 mL) and treated with Amano PS lipase (1.05 g), and stirred at 20 °C under nitrogen for 20 h. Then it was filtered, washing the filter with CH_2Cl_2, evaporated to dryness and chromatographed (PE/AcOEt 50 : 50 to 30 : 70), to give pure **42** as a colourless liquid (2.02 g, 80%). $[\alpha]_D$ +19.9 (*c* 2, $CHCl_3$). Lit.[25] +16.6. The e.e. (97%) was determined by benzoylation and by HPLC analysis on Daicel Chiralpak AD 250 × 4.6 column, after standardization with a racemic sample. Flow: 0.8 mL min^{-1}.; isocratic elution with *n*-hexane/*i*-PrOH 97 : 3; temp.: 35 °C. R_t 13.19 min (4*R*,5*S*) and 14.20 min (4*S*,5*R*). All other analytical-spectroscopic data were in accord with those already reported.[25]

(4*R*,5*S*)-5-(Azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate 32

a) Mesylate formation: monoacetate (**4*R*,5*S*)-8** (1.90 g, 9.30 mmol) was dissolved in dry CH_2Cl_2 (30 mL), cooled to −18 °C, and treated with Et_3N (3.90 mL, 27.9 mmol) and methanesulphonyl chloride (1.08 mL, 13.95 mmol). After 15 min the reaction was complete (as determined by TLC with PE/Et_2O/CH_2Cl_2 1 : 1 : 1). It was poured into saturated $NaHCO_3$ (40 mL) and extracted 4 times with Et_2O. **b**) Azide formation: the organic phases were evaporated to dryness, taken up in dry DMF (8 mL), treated with NaN_3 (1.515 g, 23.3 mmol) and heated at 100 °C for 42 h. After cooling, the mixture was treated with H_2O (60 mL), saturated aqueous NH_4Cl (40 mL), and Et_2O (50 mL). The phases were separated, and the organic phase evaporated to dryness and chromatographed (PE/Et_2O 75 : 25 to 50 : 50) to give pure **32** as a colourless liquid (1.75 g, 82%). R_f 0.47 (PE/Et_2O 50 : 50). Found: C, 47.35; H, 6.7; N, 18.0%. $C_9H_{15}N_3O_4$ requires C, 47.16; H, 6.60; N, 18.33%. $[\alpha]_D$ −22.4 (*c* 2, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 2968, 2103, 1737, 1372, 1186, 1039. δ_H (300 MHz; $CDCl_3$): 1.39 (3 H, s, CH_3CCH$_3$), 1.51 (3 H, s, CH_3CCH$_3$), 2.11 (3 H, s, CH_3C═O), 3.37 and 3.42 (2 H, AB part of an ABX syst., J_{AB} 12.9, J_{AX} 4.2, J_{BX} 6.6, CH_2N$_3$), 4.12 and 4.23 (2 H, AB part of an ABX syst., J_{AB} 11.7, J_{AX} 6.7, J_{BX} 4.6, CH_2OAc), 4.30–4.41 (2 H, m, C*H*–O). δ_C (75 MHz; $CDCl_3$): 20.9 (*C*H$_3$C═O), 25.2, 27.7 (*C*H$_3$–C–*C*H$_3$), 50.4 (*C*H$_2$N$_3$), 62.4 (*C*H$_2$OAc), 74.4, 75.6 (*C*HO), 109.6 ((CH$_3$)$_2$)*C*, 170.6 (*C*═*O*). GC-MS: R_t: 6.08 min; *m*/*z* (EI): 214 (M^+ − 15, 1.8%); 173 (2.0); 115 (41); 113 (3.8); 84 (22); 59 (8.2); 43 (100); 42 (6.4); 41 (6.7).

(4*S*,5*R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl butanoate 9

A suspension of known dibutyrate **33**[25] (2.50 g, 8.27 mmol) in H_2O (30 mL) was treated with 1 M pH 7 phosphate buffer (K_2HPO_4/KH_2PO_4) (60 mL), cooled to 0 °C, and treated with Amano PS lipase (375 mg). The suspension was stirred at 0 °C for 1 h. The mixture was saturated with NaCl, diluted with AcOEt and filtered through a celite cake, washing thoroughly with AcOEt. The phases were separated and the organic phase dried, evaporated to dryness, and chromatographed (PE/AcOEt 6 : 4) to give pure **9** as a colourless liquid (1.81 g, 94%). $[\alpha]_D$ −14.3 (*c* 2.5, $CHCl_3$). Lit:[25] −11.1. The e.e. (97%) was determined by GC of the corresponding Mosher's ester, after standardization on a racemic sample. The monobutyrate was esterified with (*R*)-Mosher's chloride, and analyzed on a HP-1 column. (0.33 μ, 0.201 mm i.d., 12 m). Flow: 1 mL min^{-1}; isothermal at 170 °C. R_t 19.58 min. R_t of the other diastereomer: 19.03 min. All other analytical spectroscopic data were in accord with those already reported.[25]

(4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl butanoate 9

A solution of diol **31** (100 mg, 616 μmol) in dry THF (1.5 mL) was treated with vinyl butyrate (390 μl, 3.08 mmol) and Amano PS lipase (50 mg). The mixture was stirred for 14 days and then filtered, washing the filter with CH_2Cl_2, evaporated to dryness and chromatographed (PE/AcOEt 60 : 40), to give pure **9** as a colourless liquid (100 mg, 71%). $[\alpha]_D$ +13.9 (*c* 2, $CHCl_3$). The e.e., determined as above, was 95%.

(4*S*,5*R*)-5-(Azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl butanoate 34

It was prepared from (**4*S*,5*R*)-9** following the same procedure used for (**4*R*,5*S*)-32**. The isolated yield after chromatography was 80%. R_f 0.51 (PE/Et_2O 70 : 30). Found: C, 51.4; H, 7.5; N, 16.2%. $C_{11}H_{19}N_3O_4$ requires C, 51.35; H, 7.44; N, 16.33%. $[\alpha]_D$ +23.1 (*c* 2, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 2964, 2106, 1729, 1373, 1255, 1165, 1080. δ_H (300 MHz; $CDCl_3$): 0.95 (3 H, t, CH_3CH$_2$), 1.39 (3 H, s, CH_3CCH$_3$), 1.51 (3 H, s, CH_3CCH$_3$), 1.67 (2 H, sextet, *J* 7.4, CH_2CH$_3$), 2.34 (2 H, t, *J* 7.4, CH_2C═O), 3.30–3.48 (2 H, m, CH_2N$_3$), 4.10–4.28 (2 H, m, CH_2OC═O), 4.30–4.40 (2 H, m, C*H*–O). δ_C (75 MHz; $CDCl_3$): 13.6 (*C*H$_3$CH$_2$), 18.3 (*C*H$_2$CH$_3$), 25.2, 27.7 (*C*H$_3$–C–*C*H$_3$), 35.9 (*C*H$_2$C═O), 50.4 (*C*H$_2$N$_3$), 62.0 (*C*H$_2$OC═O), 74.5, 75.7 (*C*HO), 109.5 ((CH$_3$)$_2$)*C*, 173.2 (*C*═*O*). GC-MS: R$_t$: 5.80 min; *m*/*z* (EI): 242 (M^+ − 15, 6.9%); 201 (5.0); 143 (100); 113 (11); 102 (4.8); 101 (4.8); 84 (56); 71 (58); 59 (11); 58 (6.3); 55 (6.9); 43 (79); 42 (9.8); 41 (16).

(3a*R*,4*S*,6a*S*)-*N*-Benzyl-2,2-dimethyl-5-propionyltetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrole-4-carboxamide 36a

a) Hydrolysis of acetate: a solution of azidoacetate (**4*R*,5*S*)-32** (1.75 g, 7.63 mmol) in absolute MeOH (35 mL) was cooled to 0 °C and treated with 1 M KOH in MeOH (13.0 mL, 13.0 mmol). After 20 min the mixture was quenched with saturated aqueous

NH_4Cl (60 mL) and extracted four times with Et_2O (80 + 40 + 30 + 20 mL). The organic extracts were dried over Na_2SO_4, and concentrated to dryness. The residue was taken up with Et_2O and dried again on Na_2SO_4, filtered, evaporated and briefly (30 min) stripped at 1 mbar to give crude azidoalcohol (**4*R*,5*S*)-35** (1.344 g, 94%), that was used as such for the next reaction. **b**) Oxidation to aldehyde: dimethyl sulfoxide (183 µL, 2.58 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to −70 °C. The solution was treated with a 1.63 M solution of $(COCl)_2$ in CH_2Cl_2 (1.33 mL, 2.17 mmol. After 10 min, a solution of crude alcohol (**4*R*,5*S*)-35** (193 mg, 1.03 mmol) in CH_2Cl_2 (5 mL) was added. After 10 min, Et_3N (677 µL, 4.86 mmol) was finally added. The temperature was allowed to rise to −60 °C in 1 h. The oxidation to the azidoaldehyde was complete by TLC (PE/AcOEt 1 : 1; R_f **35**: 0.35; R_f azidoaldehyde: 0.52). Thus the mixture was poured into 5% aqueous $(NH_4)H_2PO_4$ (35 mL) + 2 M HCl (2 mL). Extraction with Et_2O, washings with saturated NaCl, and evaporation gave the rather volatile azidoaldehyde as an oil. **c**) Imine formation: it was taken up at once in dry THF (5 mL), treated with freshly activated powdered 3 Å mol. sieves (50 mg) and triphenylphosphine (325 mg, 1.241 mmol) and immediately heated at 50 °C for 24 h. After cooling, the mixture was diluted with CH_2Cl_2, filtered and cautiously evaporated (the imine **4** is rather volatile) to dryness. **d**) Ugi reaction: the residue was taken up in dry MeOH (6 mL), and treated with propionic acid (93 µL, 1.24 mmol) and benzyl isocyanide (151 µL, 1.24 mmol). The solution was stirred at r.t. for 48 h, and then evaporated to dryness. The crude product was taken up in AcOEt, washed with saturated aqueous $NaHCO_3$, evaporated again, and chromatographed (PE/AcOEt 45 : 55 to 30 : 70) to give pure compound **36a** as a foam (201 mg, 55% from **32**). R_f 0.31 (PE/AcOEt 30 : 70). $[\alpha]_D$ −83.8 (*c* 2, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3673, 3615, 2977, 1670, 1629, 1521, 1420, 1375, 1205, 1156, 1036. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 95 : 5 ratio. Only the signals of major rotamer are reported): 1.13 (3 H, t, *J* 7.5, CH_3CH_2), 1.33 (3 H, s, $(CH_3)_2C$), 1.42 (3 H, s, $(CH_3)_2C$), 2.26 (1 H, dq, J_d 15.9, J_q 7.5, $CHHCH_3$), 2.40 (1 H, dq, J_d 15.9, J_q 7.5, $CHHCH_3$), 3.62 (1 H, dd, *J* 4.8, 12.0, *H*-6), 3.76 (1 H, d, *J* 12.0, *H*-6), 4.30–4.48 (2 H, m, CH_2Ph), 4.82 (1 H, s, *H*-4), 4.89 (1 H, t, *J* 5.1, *H*-6a), 5.13 (1 H, d, *J* 5.7, *H*-3a), 7.15 (1 H, broad s, N*H*), 7.20–7.35 (5 H, m, aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): 9.0 (CH_3CH_2), 24.8, 26.8 (CH_3CCH_3), 27.6 (CH_2CH_3), 43.3 (CH_2Ph), 53.0 (*C*-6), 65.4 (*C*-4), 79.7 (*C*-6a), 80.7 (*C*-3a), 111.9 (*O*–*C*–O), 127.36, 127.43 (×2), 128.6 (aromatic *C*H), 138.0 (aromatic quat.), 169.3, 173.7 (*C*=*O*). GC-MS: R_t: 9.80 min; *m*/*z* (EI): 332 (M^+, 8.2), 274, (9.7), 199 (6.2), 198 (9.5), 142 (100), 124 (6.5), 106 (8.2), 91 (26), 85 (5.8), 84 (11), 68 (16), 57 (22), 43 (6.3). *m*/*z* (ESI+) 355.1645 ($M + Na^+$). $C_{18}H_{24}N_2O_4Na$ requires 355.1634.

(3a*S*,4*R*,6a*R*)-*N*-Benzyl-2,2-dimethyl-5-propionyltetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrole-4-carboxamide 36b

A solution of azidobutyrate **34** (1.47 g, 5.73 mmol) in MeOH (20 mL) was cooled at 0 °C and treated with 4 M NaOH (2.50 mL, 10 mmol). The mixture was stirred at 0 °C for 4 h. The work-up was made as above to afford crude azidoalcohol (**4*S*,5*R*)-35**. From 1/10 of this alcohol, the same procedure described for the enantiomer gave pure **36b** as a foam (103 mg, 54% from **34**). $[\alpha]_D$ +84.8 (*c* 2, $CHCl_3$).

HPLC Analysis of 36a and 36b

The two enantiomers were analyzed at chiral HPLC (Daicel Chiralpak AD 250 × 4.6 mm, 0.8 mL min^{-1}, Vinj = 20 µl, *T* = 35 °C, eluent: *n*-hexane/*i*-PrOH 85 : 15; flow: 0.8 mL min^{-1}). R_t: **36a**: 20.19, **36b**: 12.32 min. Analysis indicated for **36a** an e.e. of 97% and for **36b** an e.e. of 96%.

(3a*R*,4*S*,6a*S*)-5-Benzoyl-*N*-(*tert*-butyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrole-4-carboxamide 37a

It was prepared in 49% overall yield (from **32**) following the same procedure used for **36a**, but employing benzoic acid and *tert*-butyl isocyanide. Thick oil. R_f 0.49 (PE/AcOEt 50 : 50). $[\alpha]_D$ +144.9 (*c* 2, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3419, 2962, 2926, 1670, 1614, 1520, 1415, 1367, 1293, 1195, 1150, 1045. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 90 : 10 ratio. Only the signals of major rotamer are reported): 1.32 (3 H, s, $(CH_3)_2C$), 1.36 (9 H, s, $C(CH_3)_3$), 1.46 (3 H, s, $(CH_3)_2C$), 3.63 and 3.81 (2 H, AB part of an ABX syst., J_{AB} 13.4, J_{AX} 4.2, J_{BX} 0, *H*-6), 4.78 (1 H, dd, *J* 4.2, 6.0, *H*-6a), 4.90 (1 H, s, *H*-4), 5.19 (1 H, d, *J* 6.0, *H*-3a), 5.30 (1 H, s, N*H*), 7.37–7.52 (5 H, m, aromatics). δ_C (75 MHz; $CDCl_3$, 25 °C): 24.7, 26.7 (CH_3CCH_3), 51.4 ($C(CH_3)_3$), 54.6 (*C*-6), 66.2 (*C*-4), 79.6 (*C*-6a), 80.6 (*C*-3a), 111.8 (O–*C*–O), 127.2 (×2), 128.5 (×2), 130.4 (aromatic *C*H), 135.1 (aromatic quat.), 168.1, 170.5 (*C*=*O*). *m*/*z* (ESI+) 355.1645 ($M + Na^+$). $C_{18}H_{24}N_2O_4Na$ requires 355.1634.

General procedure for the synthesis of Ugi adducts 39–46

Imine **4** or ***ent*-4** were prepared from azidoacetate **32** or azidobutyrate **34**, as described for the synthesis of **36a** and **36b**. Then the crude imine (500 µmol, estimated on the amount of starting azidoalcohol **35**) was dissolved in dry MeOH (2.5 mL) and treated with powdered 4 Å mol. sieves (50 mg), the appropriate carboxylic acid (400 µmol), and finally with a solution of isocyanides **2** or **3** (330 µmol) in MeOH (1 mL). The solution was stirred at r.t. for 48 h, and then evaporated to dryness. The crude product was taken up in AcOEt, washed with saturated aqueous $NaHCO_3$, evaporated again, and chromatographed (PE/AcOEt). The yields reported are based on the isocyanide (limiting agent).

Compound 39a

Thick oil. Yield: 56%. R_f 0.48 (PE/AcOEt 30 : 70). $[\alpha]_D$ −46.0 (*c* 2.4, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3000, 2875, 1669, 1588, 1521, 1463, 1375, 1191, 1027, 921. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 87 : 13 ratio. Only the signals of major rotamer are reported): 0.036, 0.043 (2 × 3 H, 2 s, CH_3Si), 0.89 (9 H, s, $(CH_3)_3CSi$), 1.32 (3 H, s, $(CH_3)_2C$), 1.42 (3 H, s, $(CH_3)_2C$), 2.17 (1 H, septet, *J* 5.9, *H*-2′), 3.35–3.44 (2 H, m, *H*-1′), 3.40 (3 H, s, OCH_3), 3.57 (1 H, dd, *J* 4.7, 12.4, *H*-6), 3.71 (2 H, d, *J* 5.4, *H*-3′), 3.84 (1 H, d, *J* 12.4, *H*-6), 3.88–3.98 (2 H, m, CH_2OAr), 4.09 and 4.01 (2 H, AB syst., *J* 14.3, CH_2OCH_3), 4.74 (1 H, s, *H*-4), 4.86 (1 H, t, *J* 5.2, *H*-6a), 5.04 (1 H, d, *J* 6.0, *H*-3a), 6.85 (1 H, ddd, *J* 0.9, 1.8, 7.8, *H*-6″), 6.90 (1 H, broad t, N*H*), 7.04–7.09 (2 H, m, *H*-2″, *H*-4″), 7.13 (1 H, t, *J* 8.0, *H*-5″). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.5 (CH_3Si), 18.2 ($C(CH_3)_3$), 24.7, 26.8 (CH_3CCH_3), 25.9 ($(CH_3)_3C$), 38.8 (*C*-1′), 41.1 (*C*-2′), 51.9 (*C*-6), 59.0 (OCH_3), 61.6 (*C*-3′), 65.8 (*C*-4), 66.7 (CH_2OAr), 71.6 (CH_2OCH_3), 79.7 (*C*-6a), 80.2 (*C*-3a),

111.9 (*O*–*C*–O), 113.5 (*C*-6″), 117.8 (*C*-2″), 122.7 (*C*-3″), 123.9 (*C*-4″), 130.5 (*C*-5″), 159.6 (*C*-1″), 168.9, 169.1 (*C*=*O*). *m*/*z* (ESI+) 637.2010 (M + Na^+). $C_{27}H_{43}BrN_2O_7SiNa$ requires 637.1921.

Compound 39b

Thick oil. Yield: 54%. R_f 0.48 (PE/AcOEt 30 : 70). $[\alpha]_D$ −28.3 (*c* 2.4, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3000, 2875, 1669, 1588, 1521, 1463, 1375, 1191, 1027, 921. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 86 : 14 ratio. Only the signals of major rotamer are reported): 0.04 (6 H, s, CH_3Si), 0.89 (9 H, s, (CH_3)$_3$CSi), 1.32 (3 H, s, (CH_3)$_2$C), 1.42 (3 H, s, (CH_3)$_2$C), 2.18 (1 H, septet, *J* 5.9, *H*-2′), 3.35–3.44 (2 H, m, *H*-1′), 3.40 (3 H, s, OCH_3), 3.60 (1 H, dd, *J* 4.8, 12.6, *H*-6), 3.66–3.78 (2 H, m, *H*-3′), 3.84 (1 H, d, *J* 12.4, *H*-6), 3.88–3.98 (2 H, m, CH_2OAr), 4.09 and 4.01 (2 H, AB syst., *J* 14.3, CH_2OCH$_3$), 4.73 (1 H, s, *H*-4), 4.86 (1 H, t, *J* 5.2, *H*-6a), 5.04 (1 H, d, *J* 6.0, *H*-3a), 6.85 (1 H, ddd, *J* 0.9, 1.8, 7.8, *H*-6″), 6.92 (1 H, broad t, N*H*), 7.04–7.09 (2 H, m, *H*-2″, *H*-4″), 7.12 (1 H, t, *J* 8.0, *H*-5″). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.5 (*C*H_3Si), 18.2 (*C*(CH$_3$)$_3$), 24.7, 26.8 (*C*H$_3$C*C*H$_3$), 25.9 ((*C*H$_3$)$_3$C), 38.8 (*C*-1′), 40.9 (*C*-2′), 51.9 (*C*-6), 59.0 (O*C*H$_3$), 61.7 (*C*-3′), 65.9 (*C*-4), 66.7 (*C*H$_2$OAr), 71.6 (*C*H$_2$OCH$_3$), 79.8 (*C*-6a), 80.2 (*C*-3a), 111.9 (*O*-*C*-O), 113.4 (*C*-6″), 117.8 (*C*-2″), 122.7 (*C*-3″), 123.9 (*C*-4″), 130.5 (*C*-5″), 159.6 (*C*-1″), 169.0 (2 *C*=*O*). *m*/*z* (ESI+) 615.2110 (M + H^+). $C_{27}H_{44}BrN_2O_7Si$ requires 615.2101.

Compound 39c

Thick oil. Yield: 57%. R_f 0.48 (PE/AcOEt 30 : 70). $[\alpha]_D$ +27.5 (*c* 2, $CHCl_3$). *m*/*z* (ESI+) 615.2110 (M + H^+). $C_{27}H_{44}BrN_2O_7Si$ requires 615.2101. All the other spectroscopic data were identical with those of its enantiomer **39b**.

Compound 39d

Thick oil. Yield: 80%. R_f 0.48 (PE/AcOEt 30 : 70). $[\alpha]_D$ +45.4 (*c* 2, $CHCl_3$). *m*/*z* (ESI+) 615.2107 (M + H^+). $C_{27}H_{44}BrN_2O_7Si$ requires 615.2101. All the other spectroscopic data were identical with those of its enantiomer **39a**.

HPLC analysis of stereoisomers 39a–d

HPLC was performed on Daicel Chiralpak AD 250 × 4.6 mm, 1.0 mL min^{-1}, V_{inj} = 10 μL, *T* = 35 °C, flow: 0.8 mL min^{-1}; eluent: 0–15 min *n*-hexane/*i*-PrOH 9 : 1 → 30 min *n*-hexane/*i*-PrOH 8 : 2. R_t: **39a**: 13.27 min, **39b**: 17.81 min, **39c** 7.94 min, **39d** 7.46 min. From these chromatograms we deduced the following d.r.s:

39a: a:b:c:d = 96.6 : 2.5 : 0.9 : 0
39b: a:b:c:d = 2.7 : 95.9 : 0 : 1.4
39c: a:b:c:d = 1.7 : 0 : 96.2 : 2.1
39d: a:b:c:d = 0 : 1.9 : 2.7 : 95.4.

Compound 40a

Thick oil. Yield: 73%. R_f 0.38 (PE/AcOEt 70 : 30). $[\alpha]_D$ −52.7 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3685, 3430, 3090, 2990, 2925, 2854, 1667, 1588, 1516, 1436, 1375, 1192, 1152, 1128, 1095. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 94 : 6 ratio. Only the signals of major rotamer are reported): 0.029, 0.034 (2 × 3 H, 2 s, CH_3Si), 0.87 (9 H, s, (CH_3)$_3$CSi), 1.32 (3 H, s, (CH_3)$_2$C), 1.40 (3 H, s, (CH_3)$_2$C), 1.13–1.30 (2 H, m), 1.43–1.56 (2 H, m), 1.57–1.88 (6 H, m), 2.14 (1 H, septet, *J* 5.9, *H*-2′), 2.31 (1 H, tt, *J* 3.3, 11.4, C*H*C=O), 3.25–3.49 (2 H, m, *H*-1′), 3.54 (1 H, dd, *J* 4.8, 12.6, *H*-6), 3.67 and 3.69 (2 H, AB part of an ABX syst., J_{AB} 10.2, J_{AX} 5.9, J_{BX} 4.9, *H*-3′), 3.83 (1 H, d, *J* 12.6, *H*-6), 3.88 and 3.93 (2 H, AB part of an ABX syst., J_{AB} 9.2, J_{AX} 5.1, J_{BX} 6.4, CH_2OAr), 4.75 (1 H, s, *H*-4), 4.85 (1 H, t, *J* 5.1, *H*-6a), 5.10 (1 H, d, *J* 6.0, *H*-3a), 6.84 (1 H, ddd, *J* 1.3, 2.4, 8.0, *H*-6″), 6.98 (1 H, t, *J* 5.8, N*H*), 7.04–7.09 (2 H, m, *H*-2″, *H*-4″), 7.13 (1 H, t, *J* 8.1, *H*-5″). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H_3Si), 18.1 (*C*(CH$_3$)$_3$), 24.7, 26.6 (*C*H$_3$C*C*H$_3$), 25.7 ((*C*H$_3$)$_3$C), 25.4, 25.56, 25.61, 28.5, 28.8 (cyclohexyl *C*H$_2$), 38.2 (*C*-1′), 41.2 (*C*-2′), 41.9 (cyclohexyl *C*H), 52.4 (*C*-6), 61.3 (*C*-3′), 65.1 (*C*-4), 66.4 (*C*H$_2$OAr), 79.5 (*C*-6a), 80.2 (*C*-3a), 111.6 (*O*-*C*-O), 113.4 (*C*-6″), 117.7 (*C*-2″), 122.6 (*C*-3″), 123.7 (*C*-4″), 130.3 (*C*-5″), 159.5 (*C*-1″), 169.4, 175.8 (*C*=*O*). *m*/*z* (ESI+) 653.2634 (M + H^+). $C_{31}H_{50}BrN_2O_6Si$ requires 653.2622.

Compound 40c

Thick oil. Yield: 73%. R_f 0.38 (PE/AcOEt 70 : 30). $[\alpha]_D$ +32.8 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3685, 3430, 3090, 2990, 2925, 2854, 1667, 1588, 1516, 1436, 1375, 1192, 1152, 1128, 1095. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 94 : 6 ratio. Only the signals of major rotamer are reported): 0.030, 0.032 (2 × 3 H, 2 s, CH_3Si), 0.87 (9 H, s, (CH_3)$_3$CSi), 1.32 (3 H, s, (CH_3)$_2$C), 1.40 (3 H, s, (CH_3)$_2$C), 1.13–1.30 (2 H, m), 1.43–1.56 (2 H, m), 1.57–1.88 (6 H, m), 2.16 (1 H, septet, *J* 6.0, *H*-2′), 2.32 (1 H, tt, *J* 3.3, 11.4, C*H*C=O), 3.24–3.50 (2 H, m, *H*-1′), 3.56 (1 H, dd, *J* 4.7, 12.2, *H*-6), 3.68 and 3.70 (2 H, AB part of an ABX syst., J_{AB} 10.2, J_{AX} 5.4, J_{BX} 5.4, *H*-3′), 3.84 (1 H, d, *J* 12.2, *H*-6), 3.88 and 3.93 (2 H, AB part of an ABX syst., J_{AB} 9.2, J_{AX} 5.3, J_{BX} 6.3, CH_2OAr), 4.75 (1 H, s, *H*-4), 4.85 (1 H, t, *J* 5.1, *H*-6a), 5.11 (1 H, d, *J* 6.0, *H*-3a), 6.84 (1 H, ddd, *J* 1.2, 2.4, 8.0, *H*-6″), 7.01 (1 H, t, *J* 6.0, N*H*), 7.04–7.09 (2 H, m, *H*-2″, *H*-4″), 7.13 (1 H, t, *J* 8.1, *H*-5″). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H_3Si), 18.2 (*C*(CH$_3$)$_3$), 24.7, 26.7 (*C*H$_3$C*C*H$_3$), 25.8 ((*C*H$_3$)$_3$C), 25.4, 25.6, 25.7, 28.5, 28.9 (cyclohexyl *C*H$_2$), 38.3 (*C*-1′), 41.1 (*C*-2′), 41.9 (cyclohexyl *C*H), 52.4 (*C*-6), 61.3 (*C*-3′), 65.1 (*C*-4), 66.4 (*C*H$_2$OAr), 79.5 (*C*-6a), 80.2 (*C*-3a), 111.7 (*O*-*C*-O), 113.4 (*C*-6″), 117.7 (*C*-2″), 122.6 (*C*-3″), 123.7 (*C*-4″), 130.4 (*C*-5″), 159.6 (*C*-1″), 169.4, 175.8 (*C*=*O*). *m*/*z* (ESI+) 653.2630 (M + H^+). $C_{31}H_{50}BrN_2O_6Si$ requires 653.2622.

Compound 41a

Thick oil. Yield: 69%. R_f 0.35 (PE/AcOEt 70 : 30). $[\alpha]_D$ −57.3 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3655, 3426, 2927, 2850, 1673, 1620, 1589, 1432, 1280, 1194, 1150, 1048. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 92 : 8 ratio. Only the signals of major rotamer are reported): 0.038, 0.043 (2 × 3 H, 2 s, CH_3Si), 0.88 (9 H, s, (CH_3)$_3$CSi), 1.32 (3 H, s, (CH_3)$_2$C), 1.46 (3 H, s, (CH_3)$_2$C), 2.21 (1 H, septet, *J* 5.8, *H*-2′), 3.46 (2 H, t, *J* 6.2, *H*-1′), 3.61 (1 H, dd, *J* 4.1, 12.6, *H*-6), 3.72 and 3.74 (2 H, AB part of an ABX syst., J_{AB} 10.3, J_{AX} 5.7, J_{BX} 5.1, *H*-3′), 3.80 (1 H, d, *J* 12.6, *H*-6), 3.94 and 3.99 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 5.7, J_{BX} 5.7, CH_2OAr), 4.78 (1 H, dd, *J* 4.1, 5.9, *H*-6a), 4.91 (1 H, s, *H*-4), 5.16 (1 H, d, *J* 5.9, *H*-3a), 6.85 (1 H, ddd, J 1.2, 2.4, 8.0, *H*-6″), 6.99 (1 H, t, J 5.9, N*H*), 7.03–7.17 (3 H, m, *H*-2″, *H*-4″, *H*-5″), 7.27 (1 H, t, *J* 7.6, *H meta* to Br),

7.37 (1 H, dt, J_t 1.3, J_d 7.7, *H para* to Br), 7.58 (1 H, ddd, *J* 1.2, 2.1, 7.8, *H para* to C═O), 7.63 (1 H, t, *J* 1.6, *H ortho* to Br and C═O). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H_3Si), 18.1 (*C*$(CH_3)_3$), 24.6, 26.7 (*C*H_3C*C*H_3), 25.7 ((*C*H_3)$_3$C), 38.7 (*C*-1′), 41.0 (*C*-2′), 54.6 (*C*-6), 61.4 (*C*-3′), 65.9 (*C*-4), 66.7 (*C*H_2OAr), 79.4 (*C*-6a), 80.6 (*C*-3a), 111.9 (*O*–*C*–O), 113.3 (*C*-6″), 117.8 (*C*-2″), 122.5, 122.6 (*C*-3″ and quat. bromobenzoic group), 123.8 (*C*-4″), 125.7 (*C para* to Br), 129.9 (*C*H *meta* to Br), 130.4 (*C*-5″ and *C meta* to Br and C═O), 133.4 (*C para* to C═O), 136.7 (quat. bromobenzoic group), 159.4 (*C*-1″), 168.7, 168.9 (*C*═*O*). *m*/*z* (ESI+) 725.1252 (M + H$^+$). $C_{31}H_{43}Br_2N_2O_6Si$ requires 725.1257.

Compound 41c

Thick oil. Yield: 73%. R_f 0.35 (PE/AcOEt 70 : 30). $[\alpha]_D$ +43.4 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3773, 3675, 3610, 3424, 3200, 3104, 2947, 2853, 1671, 1625, 1590, 1525, 1463, 1420, 1246, 1157, 1044, 921. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 92 : 8 ratio. Only the signals of major rotamer are reported): 0.04 (6 H, s, CH_3Si), 0.88 (9 H, s, (CH_3)$_3$CSi), 1.32 (3 H, s, (CH_3)$_2$C), 1.46 (3 H, s, (CH_3)$_2$C), 2.22 (1 H, septet, *J* 5.8, *H*-2′), 3.37–3.56 (2 H, m, *H*-1′), 3.64 (1 H, dd, *J* 4.2, 12.6, *H*-6), 3.72 and 3.74 (2 H, AB part of an ABX syst., J_{AB} 10.3, J_{AX} 5.7, J_{BX} 5.1, *H*-3′), 3.80 (1 H, d, *J* 12.6, *H*-6), 3.93 and 3.99 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 5.7, J_{BX} 6.0, CH_2OAr), 4.79 (1 H, dd, *J* 4.1, 5.9, *H*-6a), 4.90 (1 H, s, *H*-4), 5.15 (1 H, d, *J* 5.9, *H*-3a), 6.85 (1 H, ddd, *J* 1.2, 2.4, 8.0, *H*-6″), 7.02 (1 H, t, *J* 5.9, N*H*), 7.03–7.17 (3 H, m, *H*-2″, *H*-4″, *H*-5″), 7.27 (1 H, t, *J* 7.6, *H meta* to Br), 7.37 (1 H, dt, J_t 1.3, J_d 7.7, *H para* to Br), 7.58 (1 H, ddd, *J* 1.2, 2.1, 7.8, *H para* to C═O), 7.63 (1 H, t, *J* 1.6, *H ortho* to Br and C═O). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H_3Si), 18.2 (*C*$(CH_3)_3$), 24.7, 26.7 (*C*H_3C*C*H_3), 25.8 ((*C*H_3)$_3$C), 38.9 (*C*-1′), 40.9 (*C*-2′), 54.6 (*C*-6), 61.6 (*C*-3′), 65.9 (*C*-4), 66.7 (*C*H_2OAr), 79.5 (*C*-6a), 80.8 (*C*-3a), 112.0 (*O*-*C*-O), 113.3 (*C*-6″), 117.8 (*C*-2″), 122.6, 122.7 (*C*-3″ and quat. bromobenzoic group), 123.9 (*C*-4″), 125.8 (*C para* to Br), 130.0 (*C*H *meta* to Br), 130.4 (*C*-5″ and *C meta* to Br and C═O), 133.5 (*C para* to C═O), 136.7 (quat. bromobenzoic group), 159.5 (*C*-1″), 168.8, 168.9 (*C*═*O*). *m*/*z* (ESI+) 725.1275 (M + H$^+$). $C_{31}H_{43}Br_2N_2O_6Si$ requires 725.1257.

Compound 42a

Thick oil. Yield: 56%. R_f 0.35 (PE/AcOEt 70 : 30). $[\alpha]_D$ −70.6 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 2926, 2854, 1730, 1673, 1589, 1521, 1424, 1241, 1152, 1127, 1047. δ_H (300 MHz; $CDCl_3$, 25 °C) (only one amide rotamer is visible): 0.02, 0.03 (2 × 3 H, 2 s, CH_3Si), 0.87 (9 H, s, (CH_3)$_3$CSi), 1.32 (3 H, s, (CH_3)$_2$C), 1.42 (3 H, s, (CH_3)$_2$C), 2.18 (1 H, septet, *J* 5.8, *H*-2′), 3.43 (2 H, t, *J* 6.3, *H*-1′), 3.70 (2 H, d, *J* 6.4, *H*-3′), 3.80–4.00 (2 H, m, CH_2OAr), 4.15 (1 H, d, *J* 12.0, *H*-6), 4.82–5.00 (2 H, m, *H*-6a, *H*-4), 5.07 (1 H, d, *J* 5.9, *H*-3a), 6.82 (1 H, dt, J_t 2.1, J_d 7.5, *H*-6″), 6.88 (1 H, d, *J* 3.9, *H ortho* to Cl), 6.94 (1 H, t, *J* 5.7, N*H*), 7.02–7.15 (3 H, m, *H*-2″, *H*-4″, *H*-5″), 7.21 (1 H, d, *J* 3.9, *H meta* to Cl). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H_3Si), 18.2 (*C*$(CH_3)_3$), 24.8, 26.9 (*C*H_3C*C*H_3), 25.8 ((*C*H_3)$_3$C), 38.9 (*C*-1′), 41.0 (*C*-2′), 54.6 (*C*-6), 61.6 (*C*-3′), 66.75, 66.84 (*C*-4 and *C*H_2OAr), 80.0 (*C*-6a and *C*-3a), 112.2 (*O*–*C*–O), 113.5 (*C*-6″), 117.8 (*C*-2″), 122.7 (*C*-3″), 123.9 (*C*-4″), 126.6 (*C*H *ortho* to Cl), 130.0 (*C*H *meta* to Cl), 130.5 (C-5″), 136.0, 136.1 (quat. thienyl group), 159.5 (*C*-1″), 161.7, 168.9 (*C*═*O*). *m*/*z* (ESI+) 687.1300 (M + H$^+$). $C_{29}H_{41}ClN_2O_6SSi$ requires 687.1327.

Compound 42c

Thick oil. Yield: 58%. R_f 0.35 (PE/AcOEt 70 : 30). $[\alpha]_D$ +51.7 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3002, 2928, 2854, 1674, 1589, 1505, 1424, 1190, 1151, 1126, 1058. δ_H (300 MHz; $CDCl_3$, 25 °C) (only one amide rotamer is visible): 0.03 (6 H, s, CH_3Si), 0.87 (9 H, s, (CH_3)$_3$CSi), 1.33 (3 H, s, (CH_3)$_2$C), 1.42 (3 H, s, (CH_3)$_2$C), 2.19 (1 H, septet, *J* 6.0, *H*-2′), 3.30–3.57 (2 H, m, *H*-1′), 3.70 and 3.73 (2 H, AB part of an ABX syst., J_{AB} 10.2, J_{AX} 5.4, J_{BX} 5.4, *H*-3′), 3.80–4.00 (2 H, m, CH_2OAr), 4.16 (1 H, d, *J* 12.0, *H*-6), 4.89–4.98 (2 H, m, *H*-6a, *H*-4), 5.07 (1 H, d, *J* 6.0, *H*-3a), 6.82 (1 H, dt, J_t 2.1, J_d 7.2, *H*-6″), 6.88 (1 H, d, *J* 3.9, *H ortho* to Cl), 6.95 (1 H, t, *J* 5.7, N*H*), 7.02–7.15 (3 H, m, *H*-2″, *H*-4″, *H*-5″), 7.22 (1 H, d, *J* 3.9, *H meta* to Cl). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.57, −5.54 (*C*H_3Si), 18.2 (*C*$(CH_3)_3$), 24.8, 26.8 (*C*H_3C*C*H_3), 25.9 ((*C*H_3)$_3$C), 38.9 (*C*-1′), 40.8 (*C*-2′), 54.6 (*C*-6), 61.7 (*C*-3′), 66.6, 66.8 (*C*-4 and *C*H_2OAr), 80.0 (*C*-6a and *C*-3a), 112.1 (*O*-*C*-O), 113.4 (*C*-6″), 117.8 (*C*-2″), 122.7 (*C*-3″), 123.9 (*C*-4″), 126.6 (*C*H *ortho* to Cl), 130.0 (*C*H *meta* to Cl), 130.5 (*C*-5″), 136.0, 136.1 (quat. thienyl group), 159.5 (*C*-1″), 161.6, 168.9 (*C*═*O*). *m*/*z* (ESI+) 687.1320 (M + H$^+$). $C_{29}H_{41}ClN_2O_6SSi$ requires 687.1327.

HPLC analysis of stereoisomers 42a–42c

HPLC was performed on Daicel Chiralpak AD 250 × 4.6 mm, 1.0 mL min^{-1}, V_{inj} = 20 µL, *T* = 25 °C, flow: 0–15 min: 0.8 mL min^{-1}; 15–30 min: 1.0 mL min^{-1}; eluent: 0–15 min *n*-hexane/*i*-PrOH 9 : 1 → 30 min *n*-hexane/*i*-PrOH 85 : 15). R_t: **42a**: 24.38 min, **42c**: 13.25 min, From these chromatograms we deduced the following d.r.s: **42a**: 95.3%; **42c**: 93.8%.

Compound 43a

Thick oil. Yield: 74%. R_f 0.37 (PE/AcOEt 50 : 50). $[\alpha]_D$ −34.3 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3683, 3434, 3006, 2855, 1711, 1670, 1588, 1506, 1435, 1249, 1091. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 91 : 9 ratio. Only the signals of major rotamer are reported): 0.039, 0.045 (2 × 3 H, 2 s, CH_3Si), 0.88 (9 H, s, (CH_3)$_3$CSi), 1.31 (3 H, s, (CH_3)$_2$C), 1.40 (3 H, s, (CH_3)$_2$C), 2.16 (1 H, septet, *J* 5.8, *H*-2′), 2.41 (1 H, broad dt, J_t 5.4, J_d 16.5, C*H*HCH$_2$NHZ), 2.59 (1 H, broad dt, J_t 6.0, J_d 16.5, C*H*HCH$_2$NHZ), 3.31–3.53 (4 H, m, *H*-1′ and CH_2NHZ), 3.57 (1 H, dd, *J* 4.6, 12.2, *H*-6), 3.65–3.77 (3 H, m, *H*-3′ and *H*-6), 3.85–4.03 (2 H, m, CH_2OAr), 4.66 (1 H, s, *H*-4), 4.83 (1 H, dd, *J* 4.6, 5.7, *H*-6a), 4.96 (1 H, d, *J* 5.7, *H*-3a), 5.07 (2 H, s, CH_2Ph), 5.49 (1 H, broad t, ZN*H*), 6.80–6.91 (2 H, m, *H*-6″ and N*H*), 7.02–7.15 (3 H, m, *H*-2″, *H*-4″, *H*-5″), 7.30–7.40 (5 H, m, C*H* of Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H_3Si), 18.1 (*C*$(CH_3)_3$), 24.6, 26.7 (*C*H_3C*C*H_3), 25.7 ((*C*H_3)$_3$C), 34.1 (*C*H_2*C*H_2NHZ), 36.5 (*C*H_2NHZ), 38.7 (*C*-1′), 40.9 (*C*-2′), 52.8 (*C*-6), 61.6 (*C*-3′), 65.8 (*C*-4), 66.5 (*C*H_2Ph), 66.7 (*C*H_2OAr), 79.4 (*C*-6a), 81.0 (*C*-3a), 111.9 (*O*-*C*-O), 113.3 (*C*-6″), 117.7 (*C*-2″), 122.6 (*C*-3″), 123.8 (*C*-4″), 127.9 (×3), 128.3 (×2) (*C*H benzyl), 130.4 (*C*-5″), 136.4 (quat. benzyl), 159.4 (*C*-1″), 156.3, 169.2, 171.2 (*C*═*O*). *m*/*z* (ESI+) 748.2626 (M + H$^+$). $C_{35}H_{51}BrN_3O_8Si$ requires 748.2629.

Compound 43c

Thick oil. Yield: 80%. R_f 0.37 (PE/AcOEt 50 : 50). $[\alpha]_D$ +20.6 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3670, 3603, 3439, 3042, 2948, 2742,

2394, 1711, 1669, 1589, 1501, 1434, 1190, 1033. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 91 : 9 ratio. Only the signals of major rotamer are reported): 0.04 (6 H, s, CH_3Si), 0.88 (9 H, s, (CH_3)$_3$CSi), 1.30 (3 H, s, (CH_3)$_2$C), 1.41 (3 H, s, (CH_3)$_2$C), 2.16 (1 H, septet, *J* 5.8, H-2′), 2.41 (1 H, broad dt, J_t 5.6, J_d 16.6, C*H*HCH$_2$NHZ), 2.60 (1 H, broad dt, J_t 5.8, J_d 16.6, C*H*HCH$_2$NHZ), 3.31–3.53 (4 H, m, *H*-1′ and CH_2NHZ), 3.59 (1 H, dd, *J* 4.8, 12.0, *H*-6), 3.66–3.78 (3 H, m, *H*-3′ and *H*-6), 3.84–4.03 (2 H, m, CH_2OAr), 4.65 (1 H, s, *H*-4), 4.83 (1 H, t, *J* 5.5, *H*-6a), 4.97 (1 H, d, *J* 6.0, *H*-3a), 5.07 (2 H, s, CH_2Ph), 5.50 (1 H, broad t, ZN*H*), 6.85 (1 H, ddd, *J* 1.2, 2.4, 7.8, *H*-6″), 6.92 (1 H, t, *J* 5.7, N*H*), 7.02–7.15 (3 H, m, *H*-2″, *H*-4″, *H*-5″), 7.30–7.40 (5 H, m, C*H* of Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6 (*C*H$_3$Si), 18.1 (*C*(CH$_3$)$_3$), 24.6, 26.7 (*C*H$_3$C*C*H$_3$), 25.8 ((*C*H$_3$)$_3$C), 34.1 (*C*H$_2$CH$_2$NHZ), 36.5 (*C*H$_2$NHZ), 38.8 (*C*-1′), 40.8 (*C*-2′), 52.8 (*C*-6), 61.8 (*C*-3′), 65.8 (*C*-4), 66.5 (*C*H$_2$Ph), 66.7 (*C*H$_2$OAr), 79.4 (*C*-6a), 80.9 (*C*-3a), 111.9 (*O*-*C*-O), 113.3 (*C*-6″), 117.8 (*C*-2″), 122.6 (*C*-3″), 123.8 (*C*-4″), 128.0 (×3), 128.4 (×2) (*C*H benzyl), 130.4 (*C*-5″), 136.4 (quat. benzyl), 159.5 (*C*-1″), 156.3, 169.2, 171.2 (*C*═*O*). *m*/*z* (ESI+) 748.2610 (M + H$^+$). $C_{35}H_{51}BrN_3O_8Si$ requires 748.2629.

Compound 44a

Yellow oil. Yield: 68%. R_f 0.32 (PE/AcOEt 50 : 50). $[\alpha]_D$ −40.7 (*c* 1.7, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3671, 3607, 3427, 2927, 2888, 2851, 1667, 1515, 1433, 1188, 1086, 1046. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 85 : 15 ratio. Only the signals of major rotamer are reported): 0.02, 0.04 (6 H, s, CH_3Si), 0.91 (9 H, s, (CH_3)$_3$CSi), 1.33 (3 H, s, (CH_3)$_2$C), 1.42 (3 H, s, (CH_3)$_2$C), 1.96 (1 H, centre of m, *H*-2′), 2.54 and 2.65 (2 H, AB part of an ABX syst., J_{AB} 13.5, J_{AX} 6.5, J_{BX} 8.2, CH_2Ph), 3.28 (2 H, centre of m, *H*-1′), 3.41 (3 H, s, OCH_3), 3.53 and 3.66 (2 H, AB part of an ABX syst., J_{AB} 10.2, J_{AX} 6.0, J_{BX} 3.9, *H*-3′), 3.61 (1 H, dd, *J* 4.8, 12.3, *H*-6), 3.84 (1 H, d, *J* 12.3, *H*-6), 4.03 and 4.11 (2 H, AB syst., *J* 14.1, CH_2OCH$_3$), 4.72 (1 H, s, *H*-4), 4.87 (1 H, t, *J* 5.1, *H*-6a), 5.03 (1 H, d, *J* 5.7, *H*-3a), 6.80 (1 H, broad t, *J* 6.0, N*H*), 7.15–7.31 (5 H, m, Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.54, −5.51 (*C*H$_3$Si), 18.2 (*C*(CH$_3$)$_3$), 24.8, 26.8 (*C*H$_3$C*C*H$_3$), 25.9 ((*C*H$_3$)$_3$C), 35.2 (*C*H$_2$Ph), 41.2 (*C*-1′), 42.5 (*C*-2′), 51.9 (*C*-6), 59.0 (O*C*H$_3$), 63.2 (*C*-3′), 65.9 (*C*-4), 71.6 (*C*H$_2$OCH$_3$), 79.8 (*C*-6a), 80.3 (*C*-3a), 111.9 (*O*-*C*-O), 126.1 (*C*H *para* of Ph), 128.4 (*C*H *meta* of Ph), 129.1 (*C*H *ortho* of Ph), 139.9 (*C ipso* of Ph), 168.9, 169.0 (*C*═*O*). *m*/*z* (ESI+) 521.3038. (M + H$^+$). $C_{27}H_{45}N_2O_6Si$ requires 521.3047.

Compound 44b

White solid. M.p. 96.8–97.8 °C (PE/AcOEt/CH_2Cl_2). Yield: 55%. R_f 0.50 (PE/AcOEt 30 : 70). $[\alpha]_D$ −46.2 (*c* 2.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3673, 3609, 3439, 3005, 2971, 2929, 2888, 1664, 1505, 1473, 1417, 1191, 1031, 923. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 87 : 13 ratio. Only the signals of major rotamer are reported): 0.01, 0.02 (6 H, s, CH_3Si), 0.89 (9 H, s, (CH_3)$_3$CSi), 1.31 (3 H, s, (CH_3)$_2$C), 1.41 (3 H, s, (CH_3)$_2$C), 1.96 (1 H, centre of m, *H*-2′), 2.54 and 2.62 (2 H, AB part of an ABX syst., J_{AB} 13.7, J_{AX} 6.6, J_{BX} 8.2, CH_2Ph), 3.27 (2 H, centre of m, *H*-1′), 3.40 (3 H, s, OCH_3), 3.45 and 3.52 (2 H, AB part of an ABX syst., J_{AB} 10.2, J_{AX} 5.5, J_{BX} 4.4, *H*-3′), 3.61 (1 H, dd, *J* 4.5, 12.3, *H*-6), 3.84 (1 H, d, *J* 12.3, *H*-6), 4.03 and 4.11 (2 H, AB syst., *J* 14.1, CH_2OCH$_3$), 4.69 (1 H, s, *H*-4), 4.86 (1 H, t, *J* 5.2, *H*-6a), 5.01 (1 H, d, *J* 6.0, *H*-3a), 6.83 (1 H, broad t, *J* 5.4, N*H*), 7.13–7.28 (5 H, m, Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6, −5.5 (*C*H$_3$Si), 18.2 (*C*(CH$_3$)$_3$), 24.7, 26.8 (*C*H$_3$C*C*H$_3$), 25.9 ((*C*H$_3$)$_3$C), 35.1 (*C*H$_2$Ph), 41.1 (*C*-1′), 42.3 (*C*-2′), 52.0 (*C*-6), 59.0 (O*C*H$_3$), 63.3 (*C*-3′), 65.8 (*C*-4), 71.7 (*C*H$_2$OCH$_3$), 79.8 (*C*-6a), 80.3 (*C*-3a), 111.9 (O–*C*–O), 126.0 (*C*H *para* of Ph), 128.3 (*C*H *meta* of Ph), 129.1 (*C*H *ortho* of Ph), 139.8 (*C ipso* of Ph), 168.8, 168.9 (*C*═*O*). GC-MS (usual method but final temp. 290 °C for 4 min): R_t: 12.50 min; *m*/*z* (EI): 464 (M$^+$ -56, 14), 463 (48), 215 (12), 214 (73), 186 (39), 156 (11), 142 (12), 140 (6.0), 131 (18), 130 (8.3), 129 (5.9), 128 (5.0), 117 (8.5), 115 (7.3), 105 (5.5), 100 (6.4), 91 (38), 89 (5.3), 80 (7.6), 75 (36), 74 (5.5), 73 (23), 59 (9.1), 57 (5.7), 56 (6.9), 55 (6.0), 45 (100), 44 (22), 43 (14), 41 (9.8), 40 (9.1), 39 (5.3), 45 (21), 41 (21). *m*/*z* (ESI+) 521.3038. (M + H$^+$). $C_{27}H_{45}N_2O_6Si$ requires 521.3047. Comparison of ^{1}H and ^{13}C NMR of **44a** and **44b** showed that d.r. must be ≥95% in both cases (diagnostic are the signals of *H*-4 and *H*-1′ at ^{1}H NMR and of *C*-2′ at ^{13}C NMR).

Compound 45c

Colourless oil. Yield: 56%. R_f 0.62 (PE/AcOEt 65 : 35). $[\alpha]_D$ +50.6 (*c* 1.1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3671, 3610, 3428, 2973, 2926, 2853, 1664, 1638, 1511, 1416, 1174, 1157, 1044. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 93 : 7 ratio. Only the signals of major rotamer are reported): 0.026, 0.032 (6 H, s, CH_3Si), 0.90 (9 H, s, (CH_3)$_3$CSi), 1.29 (3 H, s, (CH_3)$_2$C), 1.42 (3 H, s, (CH_3)$_2$C), 1.96 (1 H, centre of m, *H*-2′), 2.29–2.51 (4 H, m, (CH_2)$_2$CO), 2.54 and 2.64 (2 H, AB part of an ABX syst., J_{AB} 13.7, J_{AX} 6.4, J_{BX} 8.2, CH_2Ph), 3.26 (2 H, centre of m, H-1′), 3.46 and 3.52 (2 H, AB part of an ABX syst., J_{AB} 10.2, J_{AX} 5.1, J_{BX} 4.5, *H*-3′), 3.65 (1 H, dd, *J* 4.8, 12.0, *H*-6), 3.78 (1 H, d, *J* 12.0, *H*-6), 4.71 (1 H, s, *H*-4), 4.87 (1 H, t, *J* 5.2, *H*-6a), 4.98–5.08 (3 H, m, *H*-3a and CH_2 = CH), 5.84 (1 H, centre of m, CH$_2$═C*H*), 6.88 (1 H, broad t, *J* 5.4, N*H*), 7.13–7.30 (5 H, m, Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.54, −5.49 (*C*H$_3$Si), 18.2 (*C*(CH$_3$)$_3$), 24.8, 26.8 (*C*H$_3$C*C*H$_3$), 25.9 ((*C*H$_3$)$_3$C), 28.8, 33.3 ((*C*H$_2$)$_2$CO), 35.1 (*C*H$_2$Ph), 40.9 (*C*-1′), 42.4 (*C*-2′), 53.0 (*C*-6), 63.1 (*C*-3′), 65.5 (*C*-4), 79.6 (*C*-6a), 80.6 (*C*-3a), 111.8 (*O*–*C*–O), 115.5 (*C*H$_2$═CH), 126.0 (*C*H *para* of Ph), 128.3 (*C*H *meta* of Ph), 129.1 (*C*H *ortho* of Ph), 136.9 (CH$_2$═*C*H), 139.9 (*C ipso* of Ph), 169.2, 172.1 (*C*═*O*). *m*/*z* (ESI+) 531.3246. (M + H$^+$). $C_{29}H_{47}N_2O_5Si$ requires 531.3254.

Compound 46c

Colourless oil. Yield: 67%. R_f 0.76 (PE/AcOEt 50 : 50). $[\alpha]_D$ +76.7 (*c* 1.9, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3670, 3612, 3419, 2989, 2967, 2929, 1668, 1420, 1194, 1125, 1057, 1027. δ_H (300 MHz; $CDCl_3$, 50 °C) (only one amide rotamer is visible either at 25 or 50 °C): 0.01, 0.03 (6 H, s, CH_3Si), 0.89 (9 H, s, (CH_3)$_3$CSi), 1.32 (3 H, s, (CH_3)$_2$C), 1.42 (3 H, s, (CH_3)$_2$C), 1.96 (1 H, centre of m, *H*-2′), 2.54 and 2.63 (2 H, AB part of an ABX syst., J_{AB} 13.7, J_{AX} 6.5, J_{BX} 8.0, CH_2Ph), 3.30 (2 H, t, *J* 5.8, *H*-1′), 3.48 and 3.54 (2 H, AB part of an ABX syst., J_{AB} 9.4, J_{AX} 5.2, J_{BX} 3.2, *H*-3′), 3.85 (1 H, broad s, *H*-6; at 25 °C: 3.90 (1 H, dd, *J* 4.5, 12.0)), 4.18 (1 H, broad d, *J* 9.0, *H*-6; at 25 °C: 4.17 (1 H, d, *J* 12.0)), 4.88–4.91 (2 H, m, *H*-4 and *H*-6a; at 25 °C: 4.90 (1 H, s, *H*-4), 4.94 (1 H, t, *J* 5.2, *H*-6a)), 5.05 (1 H, d, *J* 5.7, *H*-3a), 6.74 (1 H, broad s, N*H*),

6.89 (1 H, d, *J* 3.9, *H ortho* to Cl), 7.10–7.26 (6 H, m, Ph and *H meta* to Cl). δ_C (75 MHz; $CDCl_3$, 25 °C): −5.6, −5.5 (CH_3Si), 18.3 ($C(CH_3)_3$), 24.9, 26.9 (CH_3CCH_3), 25.9 ($(CH_3)_3C$), 35.1 (CH_2Ph), 41.1 (*C*-1′), 42.3 (*C*-2′), 54.7 (*C*-6), 63.4 (*C*-3′), 66.8 (*C*-4), 80.1 (*C*-6a and *C*-3a), 112.1 (*O*-*C*-O), 126.1 (*CH para* of Ph), 126.6 (*CH ortho* to Cl), 128.3 (*CH meta* of Ph), 129.0 (*CH ortho* of Ph), 130.0 (*CH meta* to Cl), 136.0, 136.2 (quat. thienyl group), 139.8 (*C ipso* of Ph), 161.7, 168.7 (*C*═*O*). *m*/*z* (ESI+) 593.2285. (M + Na^+). $C_{29}H_{42}ClN_2O_5SSi$ requires 593.2272.

General procedure for the deblocking of TBDMS protection to give compounds 47–50

A solution of Ugi adducts **39**, **40**, **41** or **43** in CH_3CN (18–28 mM) was cooled at −10 °C and treated with 40% aqueous HF (50 µL per mL of acetonitrile). The reactions were stirred at −10 °C until complete (1.5–2.5 h) and then quenched with 5% aq $NaHCO_3$ solution saturated with NaCl(s), and diluted with AcOEt. The phases were separated and the organic phase dried, evaporated to dryness and chromatographed (PE/AcOEt 8 : 2 to AcOEt/MeOH 95 : 5 depending on the specific compound) to give pure **47–50**.

Compound 47a

Thick oil. Yield: 56%. R_f 0.57 (AcOEt/MeOH 95 : 5). $[\alpha]_D$ −31.2 (*c* 1.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3673, 3604, 3422, 2984, 1663, 1589, 1506, 1420, 1190, 1049, 919. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 91 : 9 ratio. Only the signals of major rotamer are reported): 1.32 (3 H, s, $(CH_3)_2C$), 1.43 (3 H, s, $(CH_3)_2C$), 2.17 (1 H, septet, *J* 5.3, *H*-2′), 3.35–3.47 (1 H, m, *H*-1′), 3.41 (3 H, s, OCH_3), 3.47–3.75 (4 H, m, *H*-1′, *H*-6 and *H*-3′), 3.84 (1 H, d, *J* 12.3, *H*-6), 3.89 and 3.94 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 7.2, J_{BX} 5.9, CH_2OAr), 4.03 and 4.10 (2 H, AB syst., *J* 14.3, CH_2OCH_3), 4.78 (1 H, s, *H*-4), 4.89 (1 H, t, *J* 5.1, *H*-6a), 5.01 (1 H, d, *J* 6.0, *H*-3a), 6.83 (1 H, ddd, *J* 1.2, 2.4, 7.9, *H*-6″), 7.04–7.09 (2 H, m, *H*-2″, *H*-4″), 7.13 (1 H, t, *J* 7.9, *H*-5″), 7.24 (1 H, broad t, *J* 6.3, N*H*). δ_C (75 MHz; $CDCl_3$, 25 °C): 24.7, 26.8 (CH_3CCH_3), 37.8 (*C*-1′), 41.2 (*C*-2′), 52.0 (*C*-6), 59.1 (OCH_3), 60.3 (*C*-3′), 65.9 (*C*-4), 67.2 (CH_2OAr), 71.4 (CH_2OCH_3), 79.7 (*C*-6a), 80.3 (*C*-3a), 112.1 (*O*-*C*-O), 113.4 (*C*-6″), 117.7 (*C*-2″), 122.8 (*C*-3″), 124.0 (*C*-4″), 130.6 (*C*-5″), 159.4 (*C*-1″), 169.3, 170.5 (*C*═*O*). *m*/*z* (ESI+) 523.1076 (M + Na^+). $C_{21}H_{29}BrN_2O_7Na$ requires 523.1056.

Compound 48a

Thick oil. Yield: 94%. R_f 0.36 (PE/AcOEt 70 : 30). $[\alpha]_D$ −30.1 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3652, 3430, 3005, 2933, 2854, 1658, 1624, 1589, 1430, 1372, 1278, 1239, 1192, 1155, 1045, 992, 975. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 90 : 10 ratio. Only the signals of major rotamer are reported): 1.13–1.30 (2 H, m), 1.33 (3 H, s, $(CH_3)_2C$), 1.41 (3 H, s, $(CH_3)_2C$), 1.43–1.56 (2 H, m), 1.57–1.88 (6 H, m), 2.17 (1 H, broad septet, H-2′), 2.35 (1 H, tt, *J* 3.3, 11.4, C*H*C═O), 3.30–3.73 (5 H, m, *H*-1′, *H*-3′, *H*-6), 3.82–3.95 (3 H, m, *H*-6, CH_2OAr), 4.77 (1 H, s, *H*-4), 4.87 (1 H, t, *J* 5.1, *H*-6a), 5.09 (1 H, d, *J* 6.0, *H*-3a), 6.84 (1 H, ddd, *J* 1.5, 2.4, 7.8, *H*-6″), 7.04–7.09 (2 H, m, *H*-2″, *H*-4″), 7.13 (1 H, t, *J* 8.1, *H*-5″), 7.22 (1 H, t, *J* 6.0, N*H*). δ_C (75 MHz; $CDCl_3$, 25 °C): 24.8, 26.7 (CH_3CCH_3), 25.5, 25.6, 25.7, 28.6, 29.0 (cyclohexyl CH_2), 37.5 (*C*-1′), 41.2 (*C*-2′), 42.0 (cyclohexyl *C*H), 52.6 (*C*-6), 60.2 (*C*-3′), 65.3 (*C*-4), 67.2 (CH_2OAr), 79.6 (*C*-6a), 80.4 (*C*-3a), 111.9 (*O*-*C*-O), 113.5 (*C*-6″), 117.7 (*C*-2″), 122.7 (*C*-3″), 124.0 (*C*-4″), 130.5 (*C*-5″), 159.4 (*C*-1″), 171.0, 176.2 (*C*═*O*). *m*/*z* (ESI+) 539.1765 (M + H^+). $C_{25}H_{36}BrN_2O_6$ requires 539.1757.

Compound 48c

Thick oil. Yield: 94%. R_f 0.36 (PE/AcOEt 70 : 30). $[\alpha]_D$ +50.3 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3672, 3601, 3430, 2966, 2927, 2853, 1660, 1622, 1589, 1513, 1428, 1374, 1191, 1043, 991. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 90 : 10 ratio. Only the signals of major rotamer are reported): 1.13–1.30 (2 H, m), 1.33 (3 H, s, $(CH_3)_2C$), 1.42 (3 H, s, $(CH_3)_2C$), 1.43–1.56 (2 H, m), 1.57–1.88 (6 H, m), 2.09 (1 H, broad signal, *H*-2′), 2.36 (1 H, tt, *J* 3.0, 11.4, C*H*C═O), 3.38 (1 H, dt, J_t 5.1, J_d 13.8, *H*-1′), 3.47–3.71 (4 H, m, *H*-1′, *H*-3′, *H*-6), 3.82–3.97 (3 H, m, *H*-6, CH_2OAr), 4.77 (1 H, s, *H*-4), 4.88 (1 H, t, *J* 5.3, *H*-6a), 5.04 (1 H, d, *J* 6.3, *H*-3a), 6.83 (1 H, ddd, *J* 1.5, 2.4, 7.8, *H*-6″), 7.04–7.09 (2 H, m, *H*-2″, *H*-4″), 7.13 (1 H, t, *J* 8.1, *H*-5″), 7.30 (1 H, t, *J* 6.0, N*H*). δ_C (75 MHz; $CDCl_3$, 25 °C): 24.7, 26.7 (CH_3CCH_3), 25.5, 25.59, 25.62, 28.5, 28.9 (cyclohexyl CH_2), 37.6 (*C*-1′), 41.3 (*C*-2′), 42.0 (cyclohexyl *C*H), 52.7 (*C*-6), 60.1 (*C*-3′), 65.4 (*C*-4), 67.3 (CH_2OAr), 79.6 (*C*-6a), 80.5 (*C*-3a), 111.9 (*O*-*C*-O), 113.4 (*C*-6″), 117.7 (*C*-2″), 122.7 (*C*-3″), 123.9 (*C*-4″), 130.5 (*C*-5″), 159.4 (*C*-1″), 170.9, 176.2 (*C*═*O*). *m*/*z* (ESI+) 539.1769 (M + H^+). $C_{25}H_{36}BrN_2O_6$ requires 539.1757.

Compound 49a

Thick oil. Yield: 91%. R_f 0.61 (AcOEt). $[\alpha]_D$ −51.8 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3672, 3599, 3424, 2971, 1663, 1621, 1589, 1562, 1516, 1465, 1413, 1222, 1041. δ_H (300 MHz; d_6-DMSO, 25 °C) (2 amide rotamers a and b are visible, in a 63 : 37 a : b ratio): 1.66 (a + b) (3 H, s, $(CH_3)_2C$), 1.79 (a), 1.81 (b) (3 H, s, $(CH_3)_2C$), 2.41 (b) (1 H, septet, *J* 5.8, *H*-2′), 2.51 (a) (1 H, septet, *J* 5.9, *H*-2′), 3.52–4.00 (5 H, m, 2 *H*-1′, 2 *H*-3′, *H*-6), 3.75–4.00 (3 H, m, 1 *H*-6, CH_2OAr), 4.60–4.85 (3 H, m, *H*-4, *H*-6a, *H*-3a), 6.88–7.00 (1 H, m, *H*-6″), 7.07–7.30 (3 H, m), 7.35–7.52 (2 H, m), 7.60–7.75 (2 H, m). δ_C (75 MHz; d_6-DMSO, 25 °C): 24.5 (b), 24.6 (a), 26.57 (b), 26.61 (a) (CH_3CCH_3), 37.6 (b), 37.7 (a) (*C*-1′), 41.0 (b), 41.3 (a) (*C*-2′), 51.6 (b), 54.8 (a) (*C*-6), 61.4 (*C*-3′), 65.9 (a), 68.7 (b) (*C*-4), 66.7 (a+b) (CH_2OAr), 78.0 (b), 79.9 (a) (*C*-6a), 82.2 (a), 83.8 (b) (*C*-3a), 111.0 (b), 111.1 (a) (*O*–*C*–O), 113.91 (a), 113.95 (b) (*C*-6″), 117.2 (b), 117.3 (a) (*C*-2″), 121.6 (a), 121.7 (b), 122.1 (a + b) (*C*-3″ and *C*-Br), 123.3 (a + b) (*CH ortho* to Br), 125.3 (b), 126.2 (a) (*C*-4″), 128.9 (b), 129.8 (a) (*C*-5″), 130.7 (a), 130.8 (b), 131.1 (a + b), (*CH para* to Br, *CH meta* to Br, and *CH meta* to Br and C═O), 132.7 (b), 133.0 (a) (*C para* to C═O), 137.6 (a), 138.2 (b) (*C*-C═O), 159.7 (a + b) (*C*-1″), 167.7 (a), 168.2 (b), 168.5 (b), 168.6 (*C*═*O*). *m*/*z* (ESI+) 611.0377 (M + H^+). $C_{25}H_{29}Br_2N_2O_6$ requires 611.0392.

Compound 49c

Thick oil. Yield: 95%. R_f 0.61 (AcOEt). $[\alpha]_D$ +53.2 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3672, 3601, 3430, 2966, 2927, 1660, 1622, 1589, 1513, 1428, 1374, 1191, 1043. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 91 : 9 ratio. Only the signals of major rotamer are reported): 1.33 (3 H, s, $(CH_3)_2C$), 1.47 (3 H, s, $(CH_3)_2C$), 2.17 (1 H, broad septet, *J* 5.8, *H*-2′), 3.32–3.74 (5 H, m,

2 *H*-1′, 1 *H*-6, *H*-3′), 3.82 (1 H, d, *J* 12.6, *H*-6), 3.90 and 3.97 (2 H, AB part of an ABX syst., J_{AB} 9.3, J_{AX} 6.9, J_{BX} 6.0, CH_2OAr), 4.80 (1 H, dd, *J* 4.1, 5.9, *H*-6a), 4.96 (1 H, s, *H*-4), 5.13 (1 H, d, *J* 5.9, *H*-3a), 6.82 (1 H, ddd, *J* 1.5, 2.4, 7.7, *H*-6″), 7.03–7.16 (3 H, m, *H*-2″, *H*-4″, *H*-5″), 7.29 (1 H, t, *J* 7.6, *H meta* to Br), 7.22 (1 H, broad t, N*H*), 7.37 (1 H, dt, J_t 1.3, J_d 7.8, *H para* to Br), 7.60 (1 H, ddd, *J* 1.2, 1.8, 7.8, *H para* to C═O), 7.64 (1 H, t, *J* 1.5, *H ortho* to Br and C═O). δ_C (75 MHz; $CDCl_3$, 25 °C): 24.7, 26.7 (*C*H_3C*C*H_3), 38.1 (*C*-1′), 41.1 (*C*-2′), 54.8 (*C*-6), 60.5 (*C*-3′), 66.0 (*C*-4), 67.3 (*C*H_2OAr), 79.5 (*C*-6a), 81.1 (*C*-3a), 112.1 (*O*-*C*-O), 113.3 (*C*-6″), 117.7 (*C*-2″), 122.6, 122.7 (*C*-3″ and quat. bromobenzoic group), 124.0 (C-4″), 125.8 (*C para* to Br), 130.1 (*C*H *meta* to Br), 130.3, 130.5 (*C*-5″ and *C meta* to Br and C═O), 133.7 (*C para* to C═O), 136.6 (quat. bromobenzoic group), 159.3 (*C*-1″), 169.1, 170.1 (*C*═*O*). *m*/*z* (ESI+) 611.0384 (M + H^+). $C_{25}H_{29}Br_2N_2O_6$ requires 611.0392.

Compound 50a

Thick oil. Yield: 100%. R_f 0.23 (PE/AcOEt 50 : 50). $[\alpha]_D$ −16.2 (*c* 1, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3683, 3424, 2995, 2935, 2868, 1721, 1660, 1590, 1506, 1429, 1372, 1243, 1148, 1126, 1055. δ_H (300 MHz; $CDCl_3$, 50 °C) (2 amide rotamers are visible, in a 94 : 6 ratio. Only the signals of major rotamer are reported): 1.31 (3 H, s, (CH_3)$_2$C), 1.41 (3 H, s, (CH_3)$_2$C), 2.15 (1 H, broad septet, *H*-2′), 2.40–2.68 (2 H, m, CH_2CH_2NHZ), 3.30–3.70 (4 H, m, H-1′, CH_2NHZ, 1 *H*-6, *H*-3′), 3.75 (1 H, d, *J* 12.3, *H*-6), 3.79–3.95 (2 H, m, CH_2OAr), 4.73 (1 H, s, *H*-4), 4.84 (1 H, t, *J* 4.8, *H*-6a), 4.96 (1 H, d, *J* 6.0, *H*-3a), 5.07 (2 H, s, CH_2Ph), 5.54 (1 H, broad peak, ZN*H*), 6.78–6.90 (2 H, m, *H*-6″), 7.00–7.20 (4 H, m, *H*-2″, *H*-4″, *H*-5″, N*H*), 7.30–7.40 (5 H, m, C*H* of Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): 24.6, 26.7 (*C*H_3C*C*H_3), 34.3 (*C*H_2CH_2NHZ), 36.6 (*C*H_2NHZ), 38.1 (*C*-1′), 40.9 (*C*-2′), 52.9 (*C*-6), 60.7 (*C*-3′), 65.8 (*C*-4), 66.7 (*C*H_2Ph), 67.2 (*C*H_2OAr), 79.4 (*C*-6a), 81.0 (*C*-3a), 112.1 (*O*-*C*-O), 113.4 (*C*-6″), 117.8 (*C*-2″), 122.7 (*C*-3″), 124.1 (*C*-4″), 127.9 (×3), 128.5 (×2) (*C*H benzyl), 130.5 (*C*-5″), 136.3 (quat. benzyl), 159.3 (*C*-1″), 156.4, 170.4, 171.5 (*C*═*O*). *m*/*z* (ESI+) 634.1746 (M + H^+). $C_{29}H_{37}BrN_3O_8$ requires 634.1764.

Compound 50c

Thick oil. Yield: 100%. R_f 0.23 (PE/AcOEt 50 : 50). $[\alpha]_D$ +34.1 (*c* 1, $CHCl_3$). IR: ν_{max}($CHCl_3$)/cm^{-1} 3670, 3599, 3434, 2968, 1711, 1658, 1589, 1502, 1436, 1375, 1190, 1042. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 89 : 11 ratio. Only the signals of major rotamer are reported): 1.30 (3 H, s, (CH_3)$_2$C), 1.40 (3 H, s, (CH_3)$_2$C), 2.12 (1 H, broad septet, J 5.4, *H*-2′), 2.38–2.66 (2 H, m, CH_2CH_2NHZ), 3.30–3.70 (4 H, m, *H*-1′, CH_2NHZ, 1 *H*-6, *H*-3′), 3.75 (1 H, d, *J* 12.0, *H*-6), 3.79–3.95 (2 H, m, CH_2OAr), 4.72 (1 H, s, *H*-4), 4.82 (1 H, t, *J* 5.1, *H*-6a), 4.95 (1 H, d, *J* 5.7, *H*-3a), 5.07 (2 H, s, CH_2Ph), 5.61 (1 H, t, *J* 6.0, ZN*H*), 6.78–6.90 (2 H, m, *H*-6″), 7.00–7.09 (2 H, m, *H*-2″, *H*-4″), 7.12 (1 H, t, *J* 7.8, *H*-5″), 7.21 (1 H, t, *J* 5.8, N*H*), 7.30–7.40 (5 H, m, C*H* of Ph). δ_C (75 MHz; $CDCl_3$, 25 °C): 24.6, 26.7 (*C*H_3C*C*H_3), 34.3 (*C*H_2CH_2NHZ), 36.6 (*C*H_2NHZ), 38.0 (*C*-1′), 41.0 (*C*-2′), 53.0 (*C*-6), 60.5 (*C*-3′), 65.9 (*C*-4), 66.6 (*C*H_2Ph), 67.2 (*C*H_2OAr), 79.3 (*C*-6a), 81.1 (*C*-3a), 112.1 (*O*–*C*–O), 113.3 (*C*-6″), 117.6 (*C*-2″), 122.7 (*C*-3″), 123.9 (*C*-4″), 128.1 (×3), 128.4 (×2) (*C*H benzyl), 130.5 (*C*-5″), 136.3 (quat. benzyl), 159.3 (*C*-1″), 156.4, 170.4, 171.5 (*C*═*O*). *m*/*z* (ESI+) 634.1751 (M + H^+). $C_{29}H_{37}BrN_3O_8$ requires 634.1764.

General procedure for the deblocking of cyclic acetal to give compounds 38a and 51–54

The Ugi adducts **36a** or **39–41** or **43** (150 μmol) were dissolved in THF (1.5 mL) and water (750 μL) and treated with CF_3COOH (750 μL). The reactions were stirred at r.t. until complete by TLC (21–144 h). Then the crudes were diluted with benzene/EtOH/CH_2Cl_2, evaporated in order to remove H_2O and finally chromatographed (typically with AcOEt/MeOH 95 : 5 to 8 : 2) to give pure products **38a** or **51–54**.

Compound 38a

White foam. Yield: 99%. R_f 0.37 (AcOEt/MeOH 90 : 10). $[\alpha]_D$ +13.3 (*c* 0.84, $CHCl_3$). δ_H (300 MHz; d_6-DMSO, 30 °C) (2 amide rotamers a and b are visible, in a 71 : 29 ratio): 0.88 (b) (0.87 H, t, *J* 7.4, CH_3CH$_2$) 0.98 (a) (2.13 H, t, *J* 7.5, CH_3CH$_2$), 1.85 (b) (0.29 H, dq, J_d 16.2, J_q 7.5, C*H*HCH$_3$), 2.10 (b) (0.29 H, dq, J_d 16.2, J_q 7.5, C*H*HCH$_3$), 2.26 (a) (1.42 H, q, *J* 7.5, C*H*HCH$_3$), 3.25–3.37 (a + b) (1 H, m, *H*-6), 3.47 (b) (0.29 H, dd, *J* 5.9, 11.6, *H*-6), 3.69 (a) (0.71 H, dd, *J* 6.6, 9.6, *H*-6), 3.91 (a) (0.71 H, q, *J* 2.7, *H*-3a), 3.99 (b) (0.29 H, q, *J* 4.4, *H*-3a), 4.04 (b) (0.29 H, t, *J* 5.4, *H*-6a), 4.07–4.17 (1.71 H, m, *H*-4 (a + b), *H*-6a (a)), 4.21–4.37 (a + b) (2 H, m, CH_2Ph), 4.99 (b) (0.29 H, d, *J* 4.8, O*H*), 5.07 (a) (0.71 H, d, *J* 5.7, O*H*), 5.20 (a) (0.71 H, d, *J* 4.8, O*H*), 5.32 (b) (0.29 H, d, *J* 4.8, O*H*), 7.17–7.37 (5 H, m, aromatics), 8.41 (a) (0.71 H, t, *J* 6.0, N*H*), 8.78 (b) (0.29 H, t, *J* 6.0, N*H*). δ_C (75 MHz; d_6-DMSO, 30 °C): 8.6 (a), 8.7 (b) (*C*H_3CH$_2$), 25.8 (b), 26.4 (a) (*C*H_2CH$_3$), 41.7 (a), 42.2 (b) (*C*H_2Ph), 50.10 (a), 50.14 (b) (*C*-6), 66.1 (b), 66.2 (a), 68.6 (b), 69.8 (a) (*C*-4, *C*-6a), 73.8 (a), 75.9 (b) (*C*-3a), 126.4 (a + b), 126.7 (a) (×2), 127.2 (b) (×2), 128.0 (a) (×2), 128.1 (b) (×2) (aromatic *C*H), 139.1 (b), 139.4 (a) (aromatic quat.), 169.8 (a), 170.1 (b), 171.9 (a+b) (*C*═*O*). *m*/*z* (ESI+) 315.1313 (M + Na^+). $C_{15}H_{20}N_2O_4Na$ requires 315.1321.

Compound 51a

Thick oil. Yield: 59%. R_f 0.34 (CH_2Cl_2/EtOH 80 : 20). $[\alpha]_D$ −15.9 (*c* 1.0, $CHCl_3$). δ_H (300 MHz; d_6-DMSO, 25 °C) (2 amide rotamers a and b are visible, in a 77 : 23 ratio): 2.05 (a + b) (1 H, septet, *J* 5.7, *H*-2′), 3.15–3.30 (a + b) (3 H, m, 2 *H*-1′ + *H*-6), 3.19 (b) (0.69 H, s, OCH_3), 3.27 (a) (2.31 H, s, OCH_3), 3.48 (a + b) (2 H, q, *J* 5.1, *H*-3′), 3.56–3.66 (a + b) (1 H, m, *H*-6), 3.83–4.15 (a + b) (7 H, m, CH_2Ar, CH_2OMe, *H*-4, *H*-3a, *H*-6a), 4.59 (a) (0.77 H, t, *J* 5.4, O*H*), 4.66 (b) (0.23 H, t, *J* 5.3, O*H*), 5.04 (b) (0.23 H, d, *J* 5.1, O*H*), 5.10 (a) (0.77 H, d, *J* 5.4, O*H*), 5.24 (a) (0.77 H, d, *J* 5.1, O*H*), 5.34 (b) (0.23 H, d, *J* 5.4, O*H*), 6.92–6.98 (a + b) (1 H, m, *H*-4″), 7.07–7.15 (a + b) (2 H, m, *H*-2″ and *H*-6′), 7.20–7.28 (a + b) (1 H, m, *H*-5′), 8.08 (a) (0.77 H, t, *J* 6.0, N*H*), 8.24 (b) (0.23 H, t, *J* 5.7, N*H*). δ_C (75 MHz; d_6-DMSO, 25 °C; only the signals of major rotamer are shown): 37.3 (*C*-1′), 41.1 (*C*-2′), 49.3 (*C*-6), 58.2 (O*C*H_3), 59.1 (*C*-3′), 66.4 (*C*-4), 66.4 (*C*H_2OAr), 70.0 (*C*-6a), 71.4 (*C*H_2OCH$_3$), 73.5 (*C*-3a), 114.0 (*C*-6″), 117.2 (*C*-2″), 122.0 (*C*-3″), 123.2 (*C*-4″), 131.1 (*C*-5″), 159.7 (*C*-1″), 168.0, 169.9 (*C*═*O*). *m*/*z* (ESI+) 483.0745 (M + Na^+). $C_{18}H_{25}BrN_2O_7Na$ requires 483.0743.

Compound 51c

Thick oil. Yield: 61%. R_f 0.34 (CH_2Cl_2/EtOH 80 : 20). $[\alpha]_D$ −9.35 (*c* 2.0, $CHCl_3$). δ_H(300 MHz; d_6-DMSO, 25 °C) (2 amide rotamers a and b are visible, in a 77 : 23 ratio): 2.03 (a + b) (1 H, septet, *J* 6.0, *H*-2′), 3.15–3.30 (a + b) (3 H, m, 2 *H*-1′ + *H*-6), 3.20 (b) (0.69 H, s, OCH_3), 3.28 (a) (2.31 H, s, OCH_3), 3.35–3.43 (a + b) (2 H, m, *H*-3′), 3.56–3.66 (a + b) (1 H, m, *H*-6), 3.83–4.17 (a + b) (7 H, m, CH_2Ar, CH_2OMe, *H*-4, *H*-3a, *H*-6a), 4.35–4.80 (1 H, broad peak, O*H*), 4.90–5.50 (2 H, broad peak, O*H*), 6.92–6.98 (a + b) (1 H, m, *H*-4″), 7.07–7.15 (a + b) (2 H, m, *H*-2″ and *H*-6′), 7.23 (b) (0.23 H, t, *J* 8.6, *H*-5′), 7.24 (a) (0.77 H, t, *J* 8.9, *H*-5′), 8.07 (a) (0.77 H, t, *J* 5.8, N*H*), 8.26 (b) (0.23 H, t, *J* 5.7, N*H*). δ_C (75 MHz; d_6-DMSO, 25 °C; only the signals of major rotamer are shown): 37.2 (*C*-1′), 41.1 (*C*-2′), 49.3 (*C*-6), 58.2 (O*C*H_3), 59.0 (*C*-3′), 66.0 (*C*-4), 66.6 (*C*H_2OAr), 70.0 (*C*-6a), 70.2 (*C*H_2OCH$_3$), 73.5 (*C*-3a), 113.9 (*C*-6″), 117.3 (*C*-2″), 122.0 (*C*-3″), 123.2 (*C*-4″), 131.1 (*C*-5″), 159.7 (*C*-1″), 168.0, 169.9 (*C*═*O*). *m*/*z* (ESI+) 461.0917 (M + H^+). $C_{18}H_{26}BrN_2O_7$ requires 461.0923.

Compound 52a

Thick oil. Yield: 88%. R_f 0.37 (AcOEt/MeOH 90 : 10). $[\alpha]_D$ −158.8 (*c* 1.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3669, 3597, 3418, 3003, 2928, 1667, 1590, 1516, 1418, 1180, 1139, 1026. δ_H (300 MHz; d_6-DMSO, 25 °C) (2 amide rotamers a and b are visible, in a 70 : 30 ratio): 1.13–1.30 (2 H, m), 1.43–1.56 (2 H, m), 1.57–1.88 (6 H, m), 2.03 (1 H, broad signal, *H*-2′), 2.35 (1 H, broad signal, C*H*C═O), 3.10–3.35 (a + b) (3 H, m, 2 *H*-1′ + *H*-6), 3.35–3.43 (3 H, m, *H*-3′ (a + b), *H*-6 (b)), 3.72 (a) (0.7 H, dd, *J* 6.0, 9.9, *H*-6), 3.83–4.15 (a + b) (4 H, m, CH_2Ar, *H*-3a, *H*-6a), 3.98 (a) (0.7 H, d, *J* 3.3, *H*-4), 4.16 (b) (0.3 H, d, J 3.3, *H*-4), 4.60 (a) (0.70 H, t, *J* 5.3, O*H*), 4.68 (b) (0.3 H, t, *J* 5.3, O*H*), 5.01 (b) (0.3 H, d, *J* 5.1, O*H*), 5.07 (a) (0.7 H, d, J 5.4, O*H*), 5.22 (a) (0.7 H, d, *J* 5.1, O*H*), 5.34 (b) (0.3 H, d, *J* 5.1, O*H*), 6.92–6.98 (a + b) (1 H, m, *H*-4″), 7.06–7.15 (a + b) (2 H, m, *H*-2″ and *H*-6′), 7.19–7.28 (a+b) (1 H, m, *H*-5′), 7.93 (a) (0.7 H, t, *J* 5.8, N*H*), 8.41 (b) (0.3 H, t, *J* 5.6, N*H*). δ_C (75 MHz; d6-DMSO, 25 °C; only the signals of major rotamer are shown): 25.1 (×2), 25.5, 28.4, 28.5 (cyclohexyl CH_2), 37.3 (*C*-1′), 41.1 (*C*-2′), 41.2 (*C*H cyclohexyl), 50.5 (*C*-6), 59.3 (*C*-3′), 65.9 (*C*-4), 66.3 (*C*H_2OAr), 70.0 (*C*-6a), 73.9 (*C*-3a), 114.1 (*C*-6″), 117.2 (*C*-2″), 122.0 (*C*-3″), 123.2 (*C*-4″), 131.1 (*C*-5″), 159.8 (*C*-1″), 170.4, 174.1 (*C*═*O*). *m*/*z* (ESI+) 521.1245 (M + Na^+). $C_{22}H_{31}BrN_2O_6Na$ requires 521.1263.

Compound 53a

Thick oil. Yield: 93%. R_f 0.37 (AcOEt/MeOH 90 : 10). $[\alpha]_D$ −32.3 (*c* 1.0, $CHCl_3$). IR: ν_{max}($CHCl_3$)/cm^{-1} 3671, 3598, 3402, 2998, 1663, 1589, 1527, 1466, 1416, 1207, 1168, 1024. δ_H (300 MHz; d_6-DMSO, 25 °C)(2 amide rotamers a and b are visible, in a 75 : 25 ratio): 1.79 (b) (0.25 H, septet, *J* 5.8, *H*-2′), 2.07 (a) (0.75 H, septet, *J* 6.0, *H*-2′), 2.88–3.09 (b) (0.5 H, m, *H*-1′), 3.15–3.35 (2.5 H, m, 2 *H*-1′ (a) + 1 *H*-6 (a + b)), 3.38–3.55 (2 H, m, *H*-3′), 3.58–3.85 (a + b) (1.5 H, m, *H*-6 (a + b), CH_2OAr (b)), 3.85–4.20 (3.5 H, m, CH_2OAr (a), *H*-3a (a + b), *H*-6a (a + b)), 4.16 (a) (0.75 H, d, *J* 5.1, *H*-4), 4.49 (b) (0.25 H, d, *J* 5.7, *H*-4), 4.55 (b) (0.25 H, t, *J* 5.3, O*H*), 4.62 (a) (0.75 H, t, *J* 5.3, O*H*), 5.09 (a) (0.75 H, d, *J* 4.8, O*H*), 5.15 (b) (0.25 H, d, *J* 5.4, O*H*), 5.35 (a) (0.75 H, d, *J* 5.1, O*H*), 5.38 (b) (0.25 H, d, *J* 5.1, O*H*), 6.92–6.98 (a + b) (1 H, m, *H*-4″), 7.03–7.32 (a + b) (4 H, m, *H*-2″, *H*-6″, *H*-5″, *H meta* to Br), 7.37–7.47 (a + b) (1 H, m, *H para* to Br), 7.49–7.57 (a + b) (1 H, m, *H para* to C═O), 7.69 (a) (0.75 H, t, *J* 1.5, *H ortho* to Br and C═O), 7.71 (b) (0.25 H, t, *J* 1.5, *H ortho* to Br and C═O), 8.06 (b) (0.25 H, t, *J* 5.8, N*H*), 8.16 (a) (0.75 H, t, *J* 5.6, N*H*). δ_C (75 MHz; d_6-DMSO, 25 °C; only the signals of major rotamer are shown): 37.3 (*C*-1′), 41.2 (*C*-2′), 54.0 (*C*-6), 59.2 (*C*-3′), 65.6 (*C*-4), 66.4 (*C*H_2OAr), 70.1 (*C*-6a), 74.5 (*C*-3a), 114.0 (*C*-6″), 117.2 (*C*-2″), 121.5, 122.0 (*C*-3″ and *C*-Br), 123.2 (*C*-4″), 126.3 (*C*H *ortho* to Br), 129.9, 130.5, 131.0, 131.1 (*C*-5″, *C*H *para* to Br, *C*H *meta* to Br, and *C*H *meta* to Br and C═O), 132.9 (*C para* to C═O), 137.9 (*C*-C═O), 159.7 (*C*-1″), 167.3, 170.2 (*C*═*O*). *m*/*z* (ESI+) 571.0074 (M + H^+). $C_{22}H_{25}Br_2N_2O_6$ requires 571.0079.

Compound 54a

Thick oil. Yield: 100%. R_f 0.46 (AcOEt/MeOH 80 : 20). $[\alpha]_D$ −12.9 (*c* 1.0, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3673, 3598, 3400 (broad), 2999, 2881, 1671, 1589, 1511, 1435, 1191, 1135, 1028. δ_H (300 MHz; d_6-DMSO, 25 °C) (2 amide rotamers a and b are visible, in a 77 : 23 ratio): 1.95–2.15 (a + b) (1 H, m, *H*-2′), 2.24–2.48 (a + b) (2 H, m, CH_2CH_2NH), 3.10–3.33 (a + b) (5.23 H, m, 2 *H*-1′, 1 *H*-6 (a), 2 *H*-6 (b), CH_2NHZ), 3.47 (a + b) (2 H, t, *J* 5.3, *H*-3′), 3.65 (a) (1 H, dd, *J* 6.3, 9.6, *H*-6), 3.83–4.15 (5 H, m, *H*-6 (b), CH_2OAr (a + b), *H*-3a (a + b), *H*-6a (a + b), *H*-4), 4.61 (a) (0.77 H, t, *J* 5.3, O*H*), 4.65 (b) (0.23 H, t, *J* 5.3, O*H*), 4.98 (b) (0.46 H, s, CH_2Ph), 5.01 (a) (1.54 H, s, CH_2Ph), 5.05 (b) (0.23 H, d, *J* 5.1, O*H*), 5.11 (a) (0.77 H, d, *J* 5.7, O*H*), 5.26 (a) (0.77 H, d, *J* 5.1, O*H*), 5.36 (b) (0.23 H, d, *J* 5.1, O*H*), 6.81 (b) (0.23 H, broad s, N*H*), 6.92–6.98 (a + b) (1 H, m, *H*-4″), 7.05–7.18 (a + b) (2 H, m, *H*-2″, *H*-6″), 7.19 (b) (0.23 H, t, *J* 8.3, *H*-5′), 7.24 (a) (0.77 H, t, *J* 8.3, *H*-5′), 7.28–7.41 (5.77 H, m, *H* of benzyl (a + b), N*H* (a)), 8.05 (a) (0.77 H, t, *J* 6.0, N*H*), 8.32 (b) (0.23 H, t, *J* 5.8, N*H*). δ_C (75 MHz; d_6-DMSO, 25 °C; only the signals of major rotamer are shown): 33.6 (*C*H_2CO), 36.4 (*C*H_2NHZ), 37.4 (*C*-1′), 41.1 (*C*-2′), 50.4 (*C*-6), 59.2 (*C*-3′), 65.2 (Ph*C*H_2), 66.0 (*C*-4), 66.5 (*C*H_2OAr), 69.9 (*C*-6a), 70.4 (*C*-3a), 113.9 (*C*-6″), 117.3 (*C*-2″), 122.0 (*C*-3″), 123.2 (*C*-4″), 127.7 (×3), 128.3 (*C*H benzyl), 131.1 (*C*-5″), 137.1 (quat. benzyl), 156.0 (*C*═*O* urethane), 159.7 (*C*-1″), 169.6, 170.1 (*C*═*O*). *m*/*z* (ESI+) 616.1251 (M + Na^+). $C_{26}H_{32}BrN_3O_8Na$ requires 616.1270.

Ester 55a

A solution of alcohol **47a** (29.5 mg, 59.8 µmol) in acetone (1.5 mL), cooled to 0 °C, was treated slowly with Jones reagent (80 µl). After 1.2 h the reaction was quenched with 1 M KH_2PO_4, diluted with CH_2Cl_2/MeOH 9 : 1 and extracted. The organic layer was then washed with brine containing some 10% Na_2SO_3. The residue was taken up in THF (1 mL), cooled to 0 °C, and treated dropwise with a freshly prepared ethereal CH_2N_2 solution until the yellow colour persisted. The mixture was treated with AcOH (50 µL) and then evaporated to dryness. The crude was finally purified through a preparative TLC eluted with AcOEt to obtain a colourless oil (17.4 mg, 57%). R_f 0.49 (AcOEt). $[\alpha]_D$ −81.4 (*c* 0.5, $CHCl_3$). IR: ν_{max} ($CHCl_3$)/cm^{-1} 3671, 3604, 3447, 2962, 2886, 1735, 1672, 1588, 1505, 1420, 1188, 1028. δ_H (300 MHz; $CDCl_3$, 25 °C) (2 amide rotamers are visible, in a 89 : 11 ratio. Only the signals of major rotamer are reported): 1.32 (3 H, s, (CH_3)$_2$C), 1.42 (3 H, s,

(CH_3)$_2$C), 2.17 (1 H, dq, J_q 5.7, J_d 6.8, *H*-2′), 3.42 (3 H, s, OCH_3), 3.50–3.62 (1 H, m, 1 *H*-1′ + 1 *H*-6), 3.65–3.78 (1 H, m, *H*-1′), 3.73 (3 H, s, OCH_3), 3.85 (1 H, d, *J* 12.3, *H*-6), 4.05 and 4.12 (2 H, AB syst., *J* 14.3, CH_2OCH$_3$), 4.11 and 4.15 (2 H, AB part of an ABX syst., J_{AB} 9.5, J_{AX} 2.7, J_{BX} 2.6, CH_2OAr), 4.77 (1 H, s, *H*-4), 4.85 (1 H, t, *J* 5.3, *H*-6a), 5.05 (1 H, d, *J* 6.0, *H*-3a), 6.84 (1 H, ddd, *J* 1.5, 2.4, 7.5, *H*-6″), 6.97–7.17 (4 H, m, *H*-2″, *H*-4″, *H*-5′, N*H*). δ_C (75 MHz; $CDCl_3$, 25 °C) (only the signals of major rotamer are reported): 24.7, 26.7 (*C*H$_3$C*C*H$_3$), 37.8 (*C*-1′), 44.9 (*C*-2′), 51.2, (*C*-6), 52.4 (O*C*H$_3$), 59.1 (O*C*H$_3$), 65.5 (*C*-4), 66.3 (*C*H$_2$OAr), 71.6 (*C*H$_2$OCH$_3$), 79.7 (*C*-6a), 79.9 (*C*-3a), 111.9 (*O*-*C*-O), 113.6 (*C*-6″), 118.0 (*C*-2″), 122.8 (*C*-3″), 124.4 (*C*-4″), 130.6 (*C*-5″), 159.0 (*C*-1″), 169.0, 169.4, 171.8 (*C*=*O*). *m*/*z* (ESI+) 551.1019 (M + Na$^+$). $C_{22}H_{29}BrN_2O_8Na$ requires 551.1005.

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