Asymmetric Synthesis of 1,4-Disubstituted Tetrahydroioquinolines

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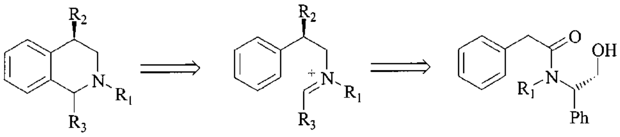
Bischler-Napieralski cyclisation of optically active β-substituted phenylethylamines **4a–c** followed by diastereoselective reduction led to 1,4-disubstituted tetrahydroisoquinolines **6a–c** and **8a–c**. The same methodology afforded the 4-benzyl pyrroloisoquinolines **10**.

Introduction

As part of our ongoing program investigating the use of optically pure phenylglycinol as a source of nitrogen and chirality[1] we were particularly interested in the synthesis of tetrahydroisoquinolines bearing substituents on the non-aromatic moiety. Indeed, a large variety of natural and unnatural derivatives in these series exert considerable pharmacological activity. Much attention has been paid to the synthesis of the C-1 substituted aporphine and related alkaloids in either racemic or optically pure fashions.[2] Amongst the biologically interesting polysubstituted tetrahydroisoquinolines three substitution patterns are notable: 1,3; 1,4 and 1,3,4. However, very few asymmetric syntheses have been reported for these structures.[3]

Our approach to the development of a general synthetic methodology for the construction of 1,3-disubstituted tetrahydroisoquinolines with the CN(*R*,*S*) method[4] was the first to give access to the enantiomeric C-1 substituted compounds and the four isomers of the 1,3-disubstituted tetrahydroisoquinolines in an optically pure form without limitation for the alkyl substituents. As far as we know there are no reports of the asymmetric synthesis of 1,4-disubstituted tetrahydroisoquinolines; the nearest relevant work being a synthesis of pyrroloisoquinolines bearing an aliphatic or aryl substituent at C-4.[5]

In this paper we provide an answer to the problem of the asymmetric synthesis of 1,4-disubstituted tetrahydroisoquinolines based upon a Bischler-Napieralski reaction of β-substituted phenylethylamines. The latter could be easily prepared following our method[6] of diastereoselective alkylation of amides derived from *R*-(–)phenylglycinol, followed by the reduction and removal of the chiral appendage (Scheme 1).



Scheme 1. Retrosynthetic scheme

Results and Discussion

Most of the biologically active structures bear substitutions in several positions of the condensed benzene ring of tetrahydroisoquinolines. Thus we prepared amides **1a–c** derived from *N*-methyl (*R*)-phenylglycinol (or its benzyl derivative) and 3,4-disubstituted phenylacetyl chloride to exemplify our methodology (Scheme 2).

The synthetic route followed was similar to that reported from this laboratory,[6] i.e. alkylation of the anion of **1a–c** (*s*BuLi, HMPA or DMPU) with iodomethane or benzyl bromide followed by reduction of the carbonyl group with $LiAlH_4$ in refluxing THF and hydrogenolysis of the chiral auxiliary. A single diastereomer was obtained for the alkylated amides **2a** and **2c** but, curiously, a 9:1 mixture was formed in the case of **2b**. However, the major diastereomer can be easily isolated and amine **4b** obtained in an optically pure form. Obtaining primary amines in excellent yield required special conditions in the case of **3c** [cyclohexene, $Pd(OH)_2$] to prevent incomplete deprotection as observed in our earlier studies.

Two general routes to tetrahydroisoquinolines have been devised from phenylethylamines. The first common approach is via an iminium salt which is cyclised according to a Pictet-Spengler reaction.[7]The second is the cyclization of an amide according to the Bischler-Napieralski reaction,[8] followed by the reduction of the resultant iminium salt. In both cases it was expected that the first stereogenic centre at C-4 would have an effect upon the outcome of the cyclization reaction (Pictet-Spengler) or the iminium reduction (Bischler-Napieralski).

As far as the Pictet-Spengler reaction was concerned, the formation of the desired product has not been observed from the secondary amines **4a** and **4b**, whatever the nature

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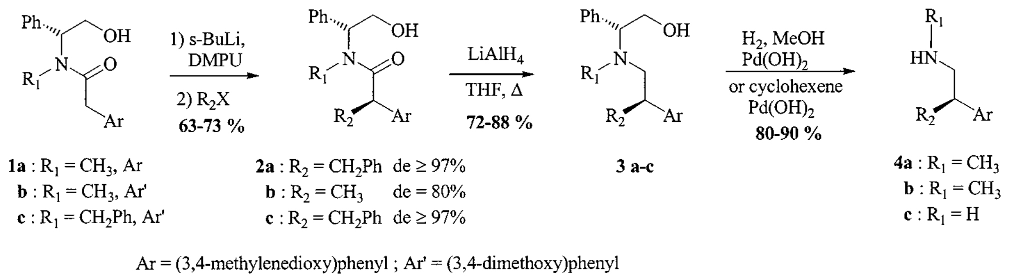
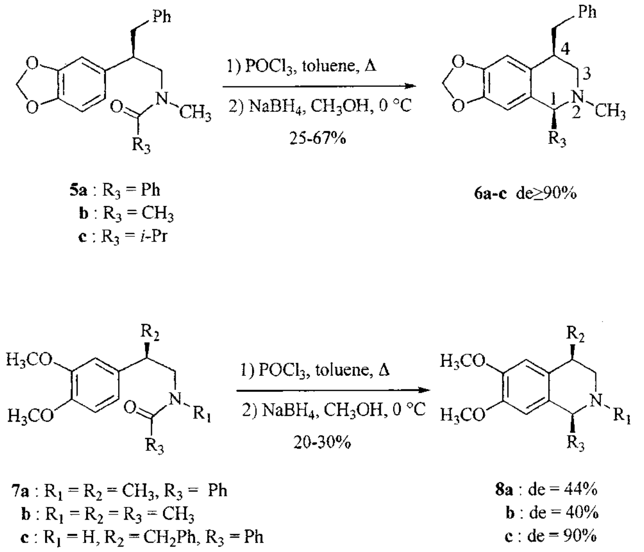


Scheme 2. Synthesis of β-phenylethylamines

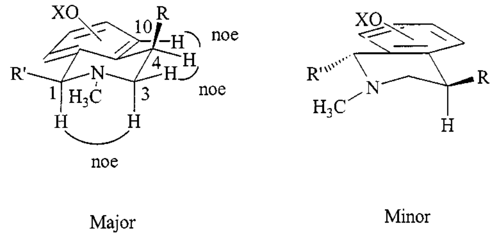
of the aldehydes (CH_3CHO, PhCHO) and the experimental conditions (*p*TSA, toluene, reflux TFA, CH_2Cl_2, reflux HCl, CH_3OH, room temp.). This lack of reactivity was surprising since it is well-known that the Pictet-Spengler reaction is quite a common method for the preparation of tetrahydroisoquinolines. Very recently, similar frustrating results have been reported in the attempted synthesis of 1,3-disusbstituted tetrahydroisoquinolines from the reaction of secondary amines with acetaldehyde.[9] However, condensations of formaldehyde and acetaldehyde occurred easily with primary amines. There is no explanation for this unexpected behaviour.

We then turned our attention to the Bischler-Napieralski conditions. We were pleased to observe a high diastereoselectivity for the reduction of the iminium intermediate in the (3,4-methylenedioxy)phenyl series **5 a–c** independently of the C-1 substituent (Scheme 3).



Scheme 3. Synthesis of tetrahydroisoquinolines **8a–c**

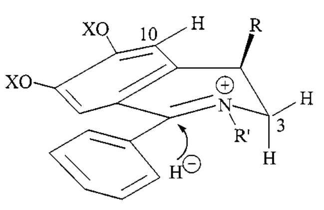
Yields related to the purified major diastereomer are low owing to degradation of the compound during the purification by flash chromatography on silica. The ^1H and ^{13}C NMR spectra of the crude product indicate only a mixture of two diastereomers and no other side product. The relative *cis* configuration of the newly created stereogenic centre was deduced from ^1H NMR studies of compound **6c** (Scheme 4).



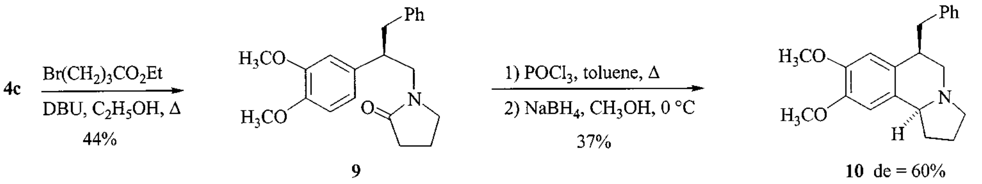
Scheme 4. Determination of the relative configuration of compound **6c**

The C-4 substituent clearly adopted an axial position as indicated by the values for $J_{H\text{-}3\text{–}H\text{-}4}$ (3.3 Hz). A NOESY experiment revealed correlations between C3–Hax and C1–H, indicative of an axial position for C1–H. This conclusion was confirmed by the chemical shifts of C1–H (δ = 4.04) and C10–H (δ = 6.12) which are in complete agreement with those previously reported.[10] So, the C-1 and C-4 substituents are mutually *cis* in the major diastereomer. In the ^1H NMR spectrum of the minor isomer, the C3–H axial proton appeared as a doublet (δ = 2.13, J = 10.6 and 11.3 Hz) indicative of an axial position for C4–H. The chemical shifts of C1–H (δ = 4.24) and C10-H (δ = 6.1) are in agreement with an equatorial position for the C-1 aromatic ring confirming the *trans* relationship between the two substituents.

Unexpectedly, the diastereoselectivity of the reduction step of the same reaction sequence was poor when applied to amides **7a** and **7b**, whereas it was satisfactory in the case of amide **7c** in the same (3,4-dimethoxy)phenyl series. The relative stereochemistry in the latter series was deduced from the results obtained for **6a–c**. This diastereoselectivity can be best explained considering the intermediate iminium moiety in which the C-4 substituent could adopt a pseudo-axial position to minimise steric interactions with C3–H and C10–H (Scheme 5).



Scheme 5. Preferential attack in the reduction of intermediate iminium



Scheme 6. Synthesis of pyrroloisoquinoline **10**

Consequently the hydride ion approach (opposite to the C-4 substituent) is under stereoelectronic control. The differences observed between the benzyl and methyl series could be due to a modification in the hindrance of these substituents which could slightly modify the conformation of the intermediate iminium and subsequently the selectivity of the hydride approach.

A final application of this methodology was conducted for the synthesis of a benzyl-substituted pyrroloisoquinoline, a series which was extensively investigated.[11]

Lactam **9** was obtained following a method previously described by us.[12] The $NaBH_4$ reduction of the Bischler-Napieralski reaction iminium afforded an 80:20 diastereomeric mixture (Scheme 6). In the ^{1}H-NMR spectrum of **10** C3–H_{ax} appeared as a broad doublet at $\delta = 2.34$, indicative of an equatorial position for C4–H as observed previously for the major isomer **6c**. A *cis* relationship was assigned for the C-1 and C-4 substituents of the major diastereomer according to the above mentioned mechanism of iminium reduction.

Conclusion

We have described the asymmetric Bischler-Napieralski synthesis of 1,4-disubstituted tetrahydroisoquinolines, including one example in the pyrroloisoquinoline series. During the reduction of the intermediate iminium, a moderate to good diastereoselectivity was observed. The synthetic pathway described above provides a general entry into a new series of tetrahydroisoquinolines. The ease of synthesis of enantiomerically pure β-substituted amines **4**, combined with the ability to vary the nature of the substituents, should enjoy a wide application in the preparation of enantiomerically pure polysubstituted isoquinolines.

Experimental Section

General Remarks: ^{1}H (300 MHz) and ^{13}C (75 MHz) was recorded with a AC-300 Bruker spectrometer. Mass spectra (CI) were recorded at 30 eV with a Nermag R10-10 spectrometer. Optical rotations were recorded with a Perkin–Elmer 141MC polarimeter. TLC was carried out on Merck silica gel 60 PF_{254}. Flash column chromatography was carried out on silica 60, 70–200 µm (SDS, France) or aluminium oxide 90, activity II–III (Merck). THF was dried using sodium/benzophenone and $LiAlH_4$ before use.

General Procedures (GP)

Synthesis of Amides 1a–c (GP1): To a solution of 1 equiv. of amine in chloroform (4 mL/mmol) was added a solution of 1.1 equivalents of sodium hydroxide in water (0.23 mL/mmol). The reaction mixture was cooled to 0 °C and 1.2 equiv. of acyl chloride was added dropwise. After stirring for between 30 min and 3 h. at 0 °C, a saturated aqueous solution of K_2CO_3 was added. The organic layer was separated and the aqueous layer extracted twice with dichloromethane. The combined organic extracts were dried with $MgSO_4$ and the solvent was removed. The amide was purified by flash column chromatography on silica gel.

Synthesis of Amides 2a–c (GP2): To a solution of 1 equiv. of amide **1** in dry tetrahydrofuran (15 mL/mmol) under nitrogen was added 5 equiv. of DMPU. The solution was then cooled to –78 °C and a solution of 2.5 equiv. of *sec*-butyllithium (1 M in cyclohexane) was added. After stirring for 15 min at –78 °C, 3 equiv. of electrophile were added, and the solution was stirred for 2 h. at –78 °C. A saturated aqueous solution of NH_4Cl was added for hydrolysis. The organic layer was separated and the aqueous layer extracted 3 times with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and the solvent was removed. The amide was purified by column chromatography on silica gel.

Synthesis of Amines 3a–c (GP3): To a suspension of 10 equiv. of $LiAlH_4$ in dry THF, under nitrogen, was added dropwise at ambient temperature a solution of 1 equiv. of amide **2** in dry THF (4.8 mL/mmol). The mixture was refluxed for 3 h. and then cooled to 0 °C. For each gram of $LiAlH_4$ was added carefully 1 mL of water followed by 1 mL of a 15% solution of NaOH in water and 3 mL of water. The mixture was allowed to warm to room temperature and then filtered through a Celite bed. The solid was washed with diethyl ether, and the solvent was removed. The amine was purified by column chromatography (silica or alumina gel).

Synthesis of Amines 4a–b (GP4): To 1 g of amine in 30 mL of methanol was added 500 mg of Pearlman's catalyst. The resulting mixture was stirred for 1.5 h under hydrogen. The mixture was then filtered through a Celite bed. The catalyst was washed with methanol and 2 mL of a 2 M solution of HCl in methanol was added to the filtrate. The solvent was removed. The solid crude mixture was washed several times with diethyl ether and then diluted in a saturated aqueous solution of K_2CO_3. This aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent was removed to give the free amine.

Synthesis of Tetrahydroisoquinolines 6a–c, 8a–c and 10 (GP5): To a solution of 1 equiv. of amide **6**, **8** or **10** in toluene (16 mL/mmol) was added dropwise 10 equiv. of phosphorus oxychloride. The mixture was heated at reflux for 3 h and then allowed to cooled to 0 °C. Water was added for hydrolysis. The organic layer was separated and the aqueous layer extracted three times with chloroform. The pH of the aqueous layer was adjusted to 6 with sodium hydroxide. The aqueous layer was concentrated and the residue washed with acetonitrile. This layer was added to the previous organic layers. The solvent was removed. The crude mixture was diluted in methanol (10 mL/mmol) and cooled to 0 °C. Sodium borohydride (20 equiv.) was added to the solution. After stirring for 30 min at 0 °C, water was added for hydrolysis and the mixture was extracted three times with chloroform. The combined organic layers were dried with $MgSO_4$. The solvent was removed. The tetrahydroisoquinoline was purified by column chromatography on silica gel.

Amide 1a: (*R*)-*N*-methylphenylglycinol (2.26 g, 15 mmol) was allowed to react with (3,4-methylendioxyphenyl)acetyl chloride according to GP1, yielding **1a** (3.41 g, 73%) after column chromatography on silica gel (ethyl acetate) as colourless crystals, m.p. 82 °C. – $[\alpha]_D^{22} = -93$ (c = 1.05, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3385 cm^{-1} (OH), 1620 (C=O). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS), two rotamers in a 70:30 ratio: δ = 2.65 (s, 3 H_{min}, NCH_3), 2.75 (s, 3 H_{maj}, NCH_3), 3.68 [s, 2 H, (CO)CH_2], 3.7–4.15 (m, 3 H_{maj} + 2 H_{min}, $NCHCH_2$), 5.15 (m, 1 H_{min}, NC*H*CH_2), 5.60 (s, 2 H_{maj}, OCH_2O), 5.85 (s, 2 H_{min}, OCH_2O), 6.5–7.4 (m, 8 H, aromatic H). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 28.2 (NCH_3), 31.03 (NCH_3), 40.5 [(CO)*C*H_2], 41.0 [(CO)*C*H_2], 57.9 (CH), 60.9 (CH_2OH), 61.1 (CH_2OH), 61.5 (CH), 100.8 (OCH_2O), 108.2, 109.3, 109.6, 121.8, 122.0, 126.9, 127.5, 128.2, 128.5 (aromatic CH), 136.6, 137.0, 146.3, 147.7 (aromatic C), 172.8 (C=O). – MS (CI, NH_3); 314 (MH^+). – $C_{18}H_{19}NO_4$(313.3): calcd. C 68.99, H 6.11, N 4.47; found C 69.05, H 6.24, N 4.36.

Amide 1b: (*R*)-*N*-methylphenylglycinol (1 g, 6.62 mmol) was allowed to react with (3,4-dimethoxyphenyl)acetyl chloride according to GP1, yielding **2** (1.57 g, 72%) after column chromatography on silica gel (CH_2Cl_2/MeOH 98:2 then 95:5) as a colourless oil. – $[\alpha]_D^{22} = -102$ (c = 0.55, CH_2Cl_2). – IR (film): $\tilde{\nu}$ = 3398 cm^{-1} (OH), 1617 (C=O). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS), two rotamers in a 70:30 ratio: δ = 2.63 (s, 3 H_{min}, NCH), 2.78 (s, 3 H_{maj}, NCH_3), 3.75–4.1 [m, 10 H, 2 OCH_3, (CO)CH_2, NCHC*H*$_2$], 5.21 (dd, J = 9.5, 4.4 Hz, 1 H_{min}, NCH), 5.90 (dd, J = 9.3, 5.2 Hz, 1 H_{maj}, NCH), 6.8–7.25 (m, 8 H, aromatic H). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 28.1 (NCH_3), 30.8 (NCH_3), 40.4 [(CO)*C*H_2], 40.9 [(CO)*C*H_2], 55.6 (2 OCH_3), 57.7 (CH), 60.9 (CH_2OH), 61.4 (CH), 111.1, 111.6, 112.1, 120.7, 121.1, 126.8, 127.0, 127.4, 127.6, 127.7, 128.4 (aromatic CH), 136.1, 137.0, 147.6, 148.9 (aromatic C), 172.8 (C=O).

Amide 1c: (*R*)-*N*-benzylphenylglycinol (4.47 g, 19.69 mmol) was allowed to react with (3,4-dimethoxyphenyl)acetyl chloride according to GP1, yielding **2** (5.05 g, 63%) after column chromatography on silica gel (ethyl acetate/cyclohexane 80:20 then ethyl acetate) as yellow crystals, m.p. 102 °C. – $[\alpha]_D^{22} = -45$ (c = 0.8, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3406 cm^{-1} (OH), 1633 (C=O). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS), two rotamers in a 75:25 ratio: δ = 3.64 [br. s, 2 H_{maj} + 2 H_{min}, (CO)CH_2], 3.83 (m, 6 H_{maj} + 6 H_{min} + 2 H_{min}, 2 OCH_3, C*H*$_2$OH), 4.05 (m, 2 H_{maj} + 1 H_{min}, C*H*$_2$OH, NC*H*H), 4.42 (d, J = 17.7 Hz, 1 H_{maj}, NCH*H*), 4.46 (d, J = 17.7 Hz, 1 H_{maj}, NC*H*H), 4.82 (d, J = 15.4 Hz, 1 H_{min}, NC*H*H), 5.29 (dd, J = 8.6, 5.0 Hz 1 H_{min}, NCH), 5.49 (dd, J = 7.5, 5.4 Hz, 1 H_{maj}, NCH), 6.67–6.92 (m, 3 H, aromatic H), 7.07–7.36 (m, 5 H, aromatic H) –^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 41.1, 41.3 [(CO)*C*H_2], 45.5, 49.6 (NCH_2), 55.7 (OCH_3), 61.8, 62.1 (NCH), 62.9 (CH_2OH), 111.1, 111.6, 120.8, 121.1, 125.9, 126.9, 127.4, 127.8, 128.0, 128.3, 128.5, 128.7 (aromatic CH), 136.9, 137.1, 138.9, 147.8, 148.9 (aromatic C), 173.2, 173.8 (C=O), $C_{25}H_{27}NO_4$ (405.5): calcd. C 74.05, H 6.71, N 3.45; found C 74.12, H 6.64, N 3.46.

Amide 2a: Amide **1a** (200 mg, 0.639 mmol) was allowed to react with benzyl bromide (228 μL, 1.91 mmol) according to GP2, yielding **2a** (187 mg, 72%) after column chromatography on silica gel (ethyl acetate/cyclohexane 30:70 then 50:50) as colourless crystals, m.p. 128 °C. – $[\alpha]_D^{22} = -102$ (c = 0.88, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3404 cm^{-1} (OH), 1624 (C=O). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS), two rotamers in a 70:30 ratio: δ = 2.51 (s, 3 H_{min}, NCH_3), 2.57 (s, 3 H_{maj}, NCH_3), 2.95 (dd, J = 13.1, 5.7 Hz, 1 H, C_6H_6CH*H*), 3.45 (dd, J = 13.2, 9.0 Hz, 1 H, C_6H_6C*H*H), 3.8–4.1 [m, 3 H, NCHC*H2*, (CO)CH], 4.37 (dd, J = 7.2, 7.2 Hz, 1 H, OH), 5.20 (dd, J = 9.3, 4.6 Hz, 1 H_{min}, NC*H*CH_2), 5.78 (dd, J = 8.8, 5.5 Hz, 1 H_{maj}, NC*H*CH_2), 5.9 (m, 2 H, OCH_2O), 6.6–7.3 (m, 8 H, aromatic H). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 28.3 (NCH_3), 31.0 (NCH_3), 41.3 (C_6H_6*C*H_2), 50.5 [(CO)*C*H], 50.9 [(CO)*C*H], 58.2 (N*C*HCH_2), 60.3 (N*C*HCH_2), 60.7 (CH_2OH), 61.5 (CH_2OH), 100.9 (OCH_2O), 108.2, 108.5, 121.2, 121.6, 126.0, 126.1, 127.0, 127.4, 127.5, 128.0, 128.2, 128.4, 129.0, 129.2 (aromatic CH), 132.9, 133.6, 136.3, 136.7, 139.6, 139.8, 146.5, 146.6, 147.9 (aromatic C), 174.1, 174.4 (C=O). – MS (CI, NH_3); 404 (MH^+). – $C_{18}H_{19}NO_4$ (403.5): calcd. C 74.42, H 6.24, N 3.48; found C 74.57, H 6.47, N 3.41.

Amide 2b: Compound **1b** (2.61 g, 7.93 mmol) was allowed to react with iodomethane (1.5 mL, 24.1 mmol) according to GP2, yielding **2b** (1.53 g) and a 2:1 mixture of **2b** and the minor diastereomer (680 mg) after column chromatography on silica gel (ethyl acetate/cyclohexane 50:50 then 80:20). The overall yield was 81% and the *de* was 80%. – Major diastereomer: $[\alpha]_D^{22} = -68$ (c = 0.95, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3405 cm^{-1} (OH), 1618 (C=O). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS), two rotamers in a 70:30 ratio: δ = 1.46 (d, J = 3.5 Hz, 3 H_{min}, CHC*H3*), 1.48 (d, J = 6.6 Hz, 3 H_{maj}, CHC*H*$_3$), 2.56 (s, 3 H_{min}, NCH_3), 2.66 (s, 3 H_{maj}, NCH_3), 3.20 (m, 1 H_{maj}, OH), 3.8–4.14 [m, 9 H, 2 OCH_3, (CO)CH, NCHC*H*$_2$], 4.35 (m, 1 H_{min}, OH), 5.30 (dd, J = 8.2, 5.2 Hz, 1 H_{min}, NC*H*CH_2), 5.90 (dd, J = 8.2, 5.4 Hz, 1 H_{maj}, NC*H*CH_2), 6.5–7.4 (m, 8 H, aromatic H). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 20.5 (CH*C*H_3), 20.8 (CH*C*H_3), 28.1 (NCH_3), 30.6 (NCH_3), 42.4 (*C*HCH_3), 43.3 (*C*HCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 58.1 (N*C*HCH_2), 60.3 (N*C*HCH_2), 60.4 (CH_2OH), 61.1 (CH_2OH), 110.1, 110.4, 111.1, 111.4, 119.4, 119.7, 127.0, 127.6, 128.2, 128.4 (aromatic CH), 133.8, 134.9, 136.3, 136.9, 147.6, 149.0 (aromatic C), 175.5 (C=O). – MS (CI, NH_3); 344 (MH^+).

Amide 2c: Amide **1c** (2.87 g, 7.08 mmol) was allowed to react with benzyl bromide (2.5 mL, 21 mmol) according to GP2, yielding **2c** (2.37 g, 68%) after column chromatography on silica gel (ethyl acetate/cyclohexane 30:70 then 50:50) as a white foam. – $[\alpha]_D^{22} = -18$ (c = 1.15, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3412 cm^{-1} (OH), 1636 (C=O). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS), two rotamers in a 75/25 ratio: δ = 2.86 [dd, J = 13.0, 4.8, 1 H_{maj}, (CO)CHC*H*H], 3.05 [dd, J = 13.0, 5.3, 1 H_{min}, (CO)CHCH*H*], 3.56 [m, 1H + 2 H_{min}, (CO)CHC*H*H, NC*H*H, C*H*HOH], 3.87 [m, 7 H + 2 H_{maj}, 2 OCH_3, C*H*HOH, (CO)CH, NC*H*H], 4.15 (m, 1 H_{maj}, CH*H*OH), 4.58 [m, 1 H_{maj} + 1 H_{min}, NCH*H*, (CO)CH], 4.68 (dd, J = 7.6 –3.7, 1 H_{maj}, NCH), 5.0 (d, J = 15.4, 1 H_{min}, NC*H*H), 5.35 (m, 1 H_{min}, NCH), 6.5–7.5 (m, 18 H, aromatic H). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 41.9 [(CO)CH*C*H_2], 42.0 [(CO)CH*C*H_2], 44.9 (NCH_2), 50.3 (NCH_2), 50.8 [(CO)*C*H], 52.2 [(CO)*C*H], 55.6 (2 OCH_3), 60.9 (NCH), 61.3 (CH_2OH), 63.6 (CH_2OH), 64.3 (NCH), 110.3, 110.7, 111.1, 111.2, 120.0, 120.4, 125.8–129.5 (aromatic CH), 131.3, 132.2, 136.0, 136.3, 136.7, 138.9, 139.5, 139.8, 148.0, 149.0 (aromatic C), 173.6, 174.7 (C=O). – MS (CI, NH_3); 496 (MH^+).

Amine 3a: 1.9 g (4.71 mmol) of amide **2a** were allowed to react according to GP3, yielding 1.7 g of **3a** (72%) after column chromatography on silica gel (ethyl acetate/cyclohexane 50:50) as a colourless oil. – $[\alpha]_D^{22} = -66$ (c = 1.12, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3421 cm^{-1} (OH). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS): δ = 1.97 (s, 3 H, NCH_3), 2.5–3.0 (m, 5 H, NCH_2CHCH_2), 3.43 (dd, J = 10.2, 4.6 Hz, 1 H, CH*H*OH), 3.60 (dd, J = 10.3, 4.6 Hz, 1 H, NCH), 3.74 (dd, J = 10.3, 10.3 Hz, 1 H, CH*H*OH), 5.90 (s, 2 H, OCH_2O), 6.4–7.3 (m, 8 H, aromatic H). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ =

35.4 (NCH_3), 41.0 ($NCH_2CH\mathit{C}H_2$), 46.1($NCH_2\mathit{C}HCH_2$), 60.2, 61.0 (NCH_2, CH_2OH), 69.5 (NCH), 100.7 (OCH_2O), 107.6, 108.0, 120.8, 125.7, 127.7, 127.9, 128.1, 128.6, 128.8 (aromatic CH), 135.5, 137.1, 139.9, 145.8, 147.6 (aromatic C). – MS (CI, NH_3); 390 (MH^+).

Amine 3b: Amide **2b** (1.43 g, 4.17 mmol) was allowed to react according to GP3, yielding **3b** (1.213 g, 88%) after column chromatography on alumina gel (ethyl acetate) as a colourless oil. – $[\alpha]^{22}_{D}$ = +2.5 (*c* = 1.05, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3402 cm^{-1} (OH). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS): δ = 1.25 (d, *J* = 6.8 Hz, 3 H, $CHC\mathit{H}_3$), 2.14 (s, 3 H, NCH_3), 2.55 (m, 2 H, NCH_2), 2.91 (m, 1 H, $NCH_2C\mathit{H}$), 3.55 (dd, *J* = 10.3, 4.8 Hz, 1 H, $CH\mathit{H}OH$), 3.72 (dd, *J* = 10.4, 4.7 Hz, 1 H, $C\mathit{H}CH_2OH$), 3.9 (m, 7 H, 2 OCH_3, $CH\mathit{H}OH$), 6.7–6.85 (m, 3 H, Har.), 7.1–7.35 (m, 5 H, Har.). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 19.9 ($CH\mathit{C}H_3$), 36.1, 37.4 (NCH_3, NCH), 55.8 (2 OCH_3), 60.2, 61.9 (NCH_2, CH_2OH), 69.2 (NCH), 110.5, 111.2, 118.8, 127.7, 128.0, 128.6 (aromatic CH), 135.4, 138.2, 147.4, 148.8 (aromatic C).

Amine 3c: Amide **2c** (2.97 g, 6 mmol) was allowed to react according to GP3, yielding **3c** (2.23 g, 77%) after column chromatography on silica gel (ethyl acetate/cyclohexane 30:70 then 50:50) as a colourless oil. – $[\alpha]^{22}_{D}$ = –91 (*c* = 1.1, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3447 cm^{-1} (OH). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS): δ = 2.59 (m, 2 H, $NC\mathit{H}HCHC\mathit{H}H$), 2.90 (m, 2 H, $NCH_2C\mathit{H}$, $NC\mathit{H}HCHCH_2$ or $NCH_2CHC\mathit{H}H$), 3.03 (dd, *J* = 13.2, 5.0 Hz, 1 H, $NC\mathit{H}HCHCH_2$ or $NCH_2CHC\mathit{H}H$), 3.17 (d, *J* = 13.5 Hz, 1 H, $NC\mathit{H}HC_6H_6$), 3.61 (dd, *J* = 10.3, 4.5 Hz, 1 H, $CH\mathit{H}OH$), 3.74 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.87 (m, 2 H, $NC\mathit{H}HC_6H_6$, NCH), 4.00 (dd, *J* = 10.3, 10.3 Hz, 1 H, $CH\mathit{H}OH$), 6.4–6.9 (m, 3 H, aromatic), 7.1–7.3 (m, 5 H, aromatic). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 41.1 ($NCH_2CH\mathit{C}H_2$), 46.9 ($NCH_2\mathit{C}HCH_2$), 55.1 ($N\mathit{C}H_2CHCH_2$ or $N\mathit{C}H_2C_6H_6$), 55.7 (2 OCH_3), 56.6 ($N\mathit{C}H_2CHCH_2$ or $N\mathit{C}H_2C_6H_6$), 60.7 (CH_2OH), 65.6 (NCH), 111.0, 111.3, 119.5, 125.2, 125.7, 127.2, 127.8, 128.0, 128.2, 128.4, 128.9, 129.1 (aromatic CH), 135.7, 135.9, 139.3, 140.2, 147.5, 148.5 (aromatic C). – MS (CI, NH_3); 482 (MH^+).

Amine 4a: Amine **3a** (1.3 g, 3.34 mmol) was allowed to react according to GP4, yielding **4a** as its hydrochloride salt (915 mg, 90%), which can be crystallised from a methanol/diethyl ether system, m.p. 156 °C. – $[\alpha]^{22}_{D}$ = –70 (HCl salt, *c* = 1.16, MeOH). – ^1H NMR of the HCl salt (300.13 MHz, CD_3OD): δ = 2.71 (s, 3 H, NCH_3), 2.95 (dd, *J* = 13.6, 8.6 Hz, 1 H, $NCH\mathit{H}CHCH_2$ or $NCH_2CHC\mathit{H}H$), 3.09 (dd, *J* = 13.4, 6.0 Hz, 1 H, $NCH\mathit{H}CHCH_2$ or $NCH_2CHC\mathit{H}H$), 3.32 (m, 2 H, $NCH_2C\mathit{H}$, $NCH\mathit{H}CHCH_2$ or $NCH_2CHC\mathit{H}H$), 3.44 (m, 1 H, $NCH\mathit{H}CHCH_2$ or $NCH_2CHC\mathit{H}H$), 6.02 (s, 2 H, OCH_2O), 6.75–6.86 (m, 3 H, aromatic H), 7.15–7.3 (m, 5 H, aromatic H). – ^{13}C NMR (75.43 MHz, CD_3OD): δ = 34.3 (NCH_3), 41.7 ($NCH_2CH\mathit{C}H_2$), 46.2 ($NCH_2\mathit{C}HCH_2$), 54.9 (NCH_2), 102.4 (OCH_2O), 108.9, 109.4, 122.8, 127.3, 129.3, 130.1 (aromatic CH), 134.1, 139.7, 148.5, 149.6 (aromatic C). – MS (CI, NH_3); 270 (MH^+). – $C_{17}H_{19}NO_2{\cdot}HCl{\cdot}0.5CH_4O$ (321.8): calcd. C 65.31, H 6.89, N 4.35; found C 65.03, H 6.55, N 4.35.

Amine 4b: Amine **3b** (1.16 g, 3.53 mmol) was allowed to react according to GP4, yielding **4b** (594 mg, 80%). Its hydrochloride salt crystallised from a methanol/diethyl ether system, m.p. 191 °C. – $[\alpha]^{22}_{D}$ = +13 (*c* = 1.75, $CHCl_3$). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS): δ = 1.22 (d, *J* = 6.9 Hz, 3 H, $CHC\mathit{H}_3$), 2.35 (s, 3 H, NCH_3), 2.68 (m, 2 H, NCH_2), 2.86 (m, 1 H, $NCH_2C\mathit{H}$), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.7–6.8 (m, 3 H, aromatic H). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 20.1 ($CH\mathit{C}H_3$), 36.5, 39.5 (NCH_3, $CH\mathit{C}H_3$), 55.8 (2 OCH_3), 59.5 (NCH_2), 110.5, 111.4, 118.9 (aromatic CH), 137.9, 147.5, 149.0 (aromatic C). – MS (CI, NH_3); 210 (MH^+). – $C_{12}H_{19}NO_2{\cdot}HCl{\cdot}0.25CH_4O$ (253.7): calcd. C 57.98, H 8.34, N 5.51; found C 58.01, H 7.91, N 5.81.

Amine 4c: Amine **3c** (2.196 g, 4.56 mmol) was allowed to react with 100 mL of cyclohexene and 2 g of Pearlman's catalyst. The mixture was refluxed during 24 h and then filtered through a Celite bed. The catalyst was washed with methanol and 10 mL of a 2 M solution of HCl in methanol was added to the filtrate. The solvent was removed. The solid crude mixture was washed several times with diethyl ether and then diluted with a saturated aqueous solution of K_2CO_3. This aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent was removed to give the free amine (1.1 g, 90%) as a pale yellow oil. Its hydrochloride salt crystallised from a methanol/diethyl ether system, m.p. 195 °C. $[\alpha]^{22}_{D}$ = –63 (HCl salt, *c* = 1, CH_3OH). – ^1H NMR (300.13 MHz, CD_3OD): δ = 2.95 (m, 5 H, NCH_2CHCH_2), 3.84 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.8–7.4 (m, 8 H, aromatic H). – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 40.8 ($NCH_2CH\mathit{C}H_2$), 46.3 ($N\mathit{C}H_2$), 50.5 ($NCH_2\mathit{C}H$), 55.6 (2 OCH_3) 110.9, 111.1, 119.6, 125.7, 127.9, 128.1, 128.8 (aromatic CH), 134.7, 139.7, 147.4, 148.7 (aromatic C). – MS (CI, NH_3); 272 (MH^+). – $C_{17}H_{21}NO_2{\cdot}HCl{\cdot}0.5CH_4O$ (323.8): calcd. C 64.90, H 7.46, N 4.32; found C 64.83, H 7.37, N 4.45.

Amide 7a: Amine **4b** (325 mg, 1.55 mmol) was allowed to react according to GP1 with benzoyl chloride, yielding **7a** (427 mg, 88%). – $[\alpha]^{22}_{D}$ = +50 (*c* = 0.8, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1633 cm^{-1} (CO). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS), two rotamers in a 70:30 ratio: δ = 1.13 (d, *J* = 5.7 Hz, 3 H_{min}, $CHC\mathit{H}_3$), 1.33 (d, *J* = 6.9 Hz, 3 H_{maj}, $CHC\mathit{H}_3$), 2.67 (s, 3 H_{maj}, NCH_3), 2.98 (m, 1 H_{min}, $NCH_2C\mathit{H}$), 3.07 (s, 3 H_{min}, NCH_3), 3.32 (m, 1 H_{min} + 1 H_{maj}, $NCH\mathit{H}$, $NCH_2C\mathit{H}$), 3.53 (m, 1 H_{min} + 1 H_{maj}, $NCH\mathit{H}$), 3.87 (m, 6 H + 1 H_{maj}, 2 OCH_3, $NC\mathit{H}H$), 6.3–7.3 (m, 8 H, aromatic H) – ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 18.3, 19.4 ($CH\mathit{C}H_3$), 33.4, 37.4, 37.9, 38.4 (NCH_3, $\mathit{C}HCH_3$), 54.3 (NCH_2), 55.7 (OCH_3), 58.7 (NCH_2), 109.6, 110.4, 111.0, 119.1, 126.5, 126.7, 128.0, 128.1, 128.9, 129.2, 129.7 (aromatic CH), 135.4, 136.7, 147.5, 148.8, 149.1, 149.3 (aromatic C), 169.8, 171.4 (CO).

Amide 7b: Amine **4b** (117 mg, 0.56 mmol) was allowed to react according to GP1 with acetyl chloride, yielding **7b** (110 mg, 78%) after column chromatography on silica gel (ethyl acetate). – $[\alpha]^{22}_{D}$ = +79 (*c* = 0.8, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1633 cm^{-1} (CO). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS), two rotamers in a 55:45 ratio: δ = 1.15 (d, *J* = 6.8 Hz, 3 H_{maj}, $CHC\mathit{H}_3$), 1.22 (d, *J* = 7.0 Hz, 3 H_{min}, $CHC\mathit{H}_3$), 1.76 [s, 3 H_{min}, $C(O)CH_3$], 1.94 [s, 3 H_{maj}, $C(O)CH_3$], 2.66 (s, 3 H_{maj}, NCH_3), 2.79 (s, 3 H_{min}, NCH_3), 2.92 (m, 1 H_{min}, $NCH_2C\mathit{H}$), 3.04 (m, 1 H_{maj}, $NCH_2C\mathit{H}$), 3.15 (dd, *J* = 13.1, 8.4 Hz, 1 H_{maj}, $NC\mathit{H}HCH$), 3.30 (m, 2 H_{min}, $NC\mathit{H}_2CH$), 3.67 (dd, *J* = 13.0, 6.9 Hz, 1 H_{maj}, $NC\mathit{H}HCH$), 3.78 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.6–6.8 (m, 3 H, aromatic H) –^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 18.2, 19.0 ($CH\mathit{C}H_3$), 20.9, 21.7 [$C(O)\mathit{C}H_3$], 33.8, 36.9, 37.5, 38.2 (NCH_3, $\mathit{C}HCH_3$), 54.9 (NCH_2), 55.7 (OCH_3), 58.5 (NCH_2), 110.3, 110.4, 111.0, 111.3, 118.9 (aromatic CH), 135.7, 136.9, 147.40, 147.8, 148.7, 148.9 (aromatic C), 170.5 (CO).

Amide 7c: Amine **4c** (170 mg, 0.627 mmol) was allowed to react according to GP1 with benzoyl chloride, yielding **7c** (170 mg, 72%). – $[\alpha]^{22}_{D}$ = +16 (*c* = 0.85, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1638 cm^{-1} (CO). – ^1H NMR (300.13 MHz, $CDCl_3$, TMS): δ = 2.97 (m, 2 H, $NCH_2CHC\mathit{H}_2$), 3.17 (m, 1 H, $NCH_2C\mathit{H}$), 3.50 (m, 1 H, $NC\mathit{H}H$), 3.76 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.93 (m, 1 H, $NCH\mathit{H}$), 5.94 (m, 1 H, NH), 6.5–7.5 (m, 13 H, aromatic H) –^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 40.9, 44.7 ($N\mathit{C}H_2CH\mathit{C}H_2$), 46.8

(NCH$_2$*C*H), 55.7 (OCH$_3$), 110.9, 111.1, 119.4, 126.0, 126.6, 128.1, 128.3, 131.2 (aromatic CH), 134.3, 134.4, 139.4, 147.7, 148.8 (aromatic C), 167.2 (CO).

Lactam 9: Amine **4c** (240 mg, 0.88 mmol) was heated at reflux in absolute ethanol (3 mL) with DBU (199 µL, 1.33 mmol) and methyl 5-bomovalerate (139 mL, 0.97 mmol) during 96 h. The solvent was then removed. The crude mixture was purified by column chromatography on silica gel (ethyl acetate/methanol 98:2 then 95:5) yielding **9** (132 mg, 44%) as a colourless oil. – $[\alpha]_D^{22}$ = –56 (*c* = 1.18, ethyl acetate). – IR (film): $\tilde{\nu}$ = 1680 cm^{-1} (CO). – ^{1}H NMR (300.13 MHz, CDCl$_3$, TMS): δ = 1.77 (m, 2 H, NCH$_2$C*H*$_2$), 2.22 (m, 2 H, NCOC*H*$_2$), 3.00 (m, 5 H, NCH$_2$C*H*C*H*$_2$, NC*H*$_2$CH$_2$), 3.49 (dd, *J* = 13.7, 9.0, 1 H, NC*H*HCH), 3.63 (dd, *J* = 13.6, 7.0, 1 H, NCH*H*CH), 6.6–6.7 (m, 3 H, aromatic H), 7.0–7.2 (m, 5 H, aromatic H) . – ^{13}C NMR (75.43 MHz, CDCl$_3$): δ = 17.6 (NCH$_2$*C*H$_2$), 30.7 (NCO*C*H$_2$), 41.1 (NCH$_2$CH*C*H$_2$), 45.1 (NCH$_2$CH), 47.2, 47.3 (CH$_2$NCH$_2$), 55.5 (OCH$_3$), 55.6 (OCH$_3$), 110.6, 119.6, 125.7, 127.9, 128.8 (aromatic CH), 134.0, 139.4, 147.3, 148.4 (aromatic C), 174.9 (CO). – MS (CI, NH$_3$); 340 (MH$^+$), 357 (MNH$_4^+$).

Tetrahydroisoquinoline 6a: Amide **5a** (200 mg, 0.53 mmol) was allowed to react according to GP5, yielding 123 mg of **6a** as a yellow oil and 4 mg of a 1:2 mixture of major and minor diastereomer (overall yield: 67%) after column chromatography on silica gel (ethyl acetate/cyclohexane 10:90). Major diastereomer: $[\alpha]_D^{22}$ = +61 (*c* = 0.92, CHCl$_3$). – ^{1}H NMR (300.13 MHz, CDCl$_3$, TMS): δ = 2.13 (s, 3 H, NCH$_3$), 2.50 (dd, *J* = 11.5, 3.3 Hz, 1 H, NCH*H*), 2.80 (dd, *J* = 11.6, 1.8 Hz, 1 H, NC*H*H), 2.85 (m, 1 H, NCH$_2$C*H*), 3.06 (dd, *J* = 13.2, 5.2 Hz, 1 H, NCH$_2$CHC*H*H), 3.33 (dd, *J* = 13.2, 10.3 Hz, 1 H, NCH$_2$CHC*H*H), 4.04 (s, 1 H, C*H*C$_6$H$_6$), 5.78 (s, 1 H, OCH*H*O), 5.80 (s, 1 H, OCH*H*O), 6.11 (s, 1 H, aromatic H), 6.52 (s, 1 H, aromatic H), 7.2–7.4 (m, 10 H, aromatic H). – ^{13}C NMR (75.43 MHz, CDCl$_3$): δ = 41.7 (NCH$_2$*C*H), 43.4 (NCH$_2$CH*C*H$_2$), 44.2 (NCH$_3$), 54.7 (NCH$_2$), 72.1 (NCH), 100.6 (OCH$_2$O), 108.0, 108.2, 126.0, 127.3, 128.3, 129.4 (aromatic CH) 138.1, 141.0, 144.5, 145.6, 145.8 (aromatic C). – MS (CI, NH$_3$); 358 (MH$^+$). – HR-MS (CI, CH$_4$) calcd. for C$_{24}$H$_{24}$NO$_2$ (MH$^+$) 358.1807; found 358.1803.

Tetrahydroisoquinoline 6b: Amide **5b** (173 mg, 0.55 mmol) was allowed to react according to GP5, yielding 40 mg of the major diastereomer (25%) as a yellow oil after column chromatography on silica gel (ethyl acetate/cyclohexane 20:80 then 50:50). – $[\alpha]_D^{22}$= –65 (*c* = 0.77, CHCl$_3$) . – ^{1}H NMR (300.13 MHz, CDCl$_3$, TMS): δ = 1.39 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$), 2.39 (s, 3 H, NCH$_3$), 2.41 (dd, *J* = 11.7, 4.1 Hz, 1 H, NC*H*H), 2.70 (dd, *J* = 11.7, 4.1 Hz, 1 H, NCH*H*), 2.88 (m, 1 H, NCH$_2$C*H*), 2.98 (m, 2 H, NCH$_2$CHC*H*$_2$), 3.36 (q, *J* = 6.3 Hz, 1 H, NC*H*CH$_3$), 5.89 (s, 2 H, OCH$_2$O), 6.55 (s, 1 H, aromatic H), 6.60 (s, 1 H, aromatic H), 7.2–7.4 (m, 5 H, aromatic H). – ^{13}C NMR (75.43 MHz, CDCl$_3$): δ = 20.6 (CH*C*H$_3$), 40.6 (NCH$_3$), 42.2 (NCH$_2$CH*C*H$_2$), 43.6 (NCH$_2$*C*HCH$_2$), 53.7 (NCH$_2$), 60.1 (*C*HCH$_3$), 100.6 (OCH$_2$O), 106.5, 107.9, 125.9, 128.2, 129.2 (aromatic CH), 131.4, 133.1, 140.8, 145.5, 145.9 (aromatic C) – MS (CI, NH$_3$); 296 (MH$^+$). – HR-MS (CI, CH$_4$) calcd. for C$_{19}$H$_{22}$NO$_2$ (MH$^+$) 296.1650; found 296.1636.

Tetrahydroisoquinoline 6c: Amide **5c** (65 mg, 0.19 mmol) was allowed to react according to GP5. After preparative thin layer chromatography on alumina gel (ethyl acetate/cyclohexane 10:90), 20 mg (33%) of the major diastereomer was isolated. – $[\alpha]_D^{22}$ = +9 (*c* = 0.77, CHCl$_3$). – ^{1}H NMR (300.13 MHz, CDCl$_3$, TMS): δ = 0.89 (d, *J* = 6.8 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.04 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.80 (m, 1 H, CH$_3$C*H*CH$_3$), 2.32 (s, 3 H, NCH$_3$), 2.56 (dd, *J* = 13.2, 5.7 Hz, 1 H, NC*H*H), 2.85 (m, 2 H, NCH, NCH$_2$CHC*H*H), 2.99 (m, 2 H, NCH$_2$C*H*CH*H*), 3.10 (dd, *J* = 13.2, 4.9 Hz, 2 H, NCH*H*), 5.89 (s, 1 H, OC*H*HO), 5.90 (s, 1 H, OCH*H*O), 6.54 (s, 1 H, aromatic H), 6.64 (s, 1 H, aromatic H), 7.1–7.3 (m, 5 H, aromatic H). – ^{13}C NMR (75.43 MHz, CDCl$_3$): δ = 20.6 (CH$_3$CH*C*H$_3$), 20.8 (*C*H$_3$CHCH$_3$), 33.2 (CH$_3$*C*HCH$_3$), 35.9 (NCH$_3$), 41.9 (NCH$_2$CH*C*H$_2$), 43.7 (NCH$_2$*C*H), 51.8 (NCH$_2$), 70.5 (NCH), 100.5 (OCH$_2$O), 107.9, 108.5, 126.0, 128.2, 129.2 (aromatic CH), 131.1, 140.1 (aromatic C) – MS (CI, NH$_3$); 324 (MH$^+$).

Tetrahydroisoquinoline 8a: Amide **7a** (163 mg, 0.52 mmol) was allowed to react according to GP5. After preparative thin layer chromatography, 31 mg (20%) of the major diastereomer was isolated. – $[\alpha]_D^{22}$ = +52 (*c* = 0.74, CHCl$_3$). – ^{1}H NMR (300.13 MHz, CDCl$_3$, TMS): δ = 1.50 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$), 2.20 (s, 3 H, NCH$_3$), 2.72 (dd, *J* = 11.5, 4.2 Hz, 1 H, NC*H*H), 2.80 (dd, *J* = 11.5, 3.0 Hz, 1 H, NCH*H*), 2.90 (m, 1 H, C*H*CH$_3$), 3.55 (s, 3 H, OCH$_3$), 3.85 (s, 3 H, OCH$_3$), 4.13 (s, 1 H, NC*H*), 6.09 (s, 1 H, aromatic H), 6.03 (s, 1 H, aromatic H), 7.2–7.4 (m, 5 H, aromatic H). – ^{13}C NMR (75.43 MHz, CDCl$_3$): δ = 23.2 (CH*C*H$_3$), 33.0 (NCH$_3$), 55.8 (*C*HCH$_3$), 44.4 (2 OCH$_3$), 58.5 (NCH$_2$), 71.2 (NCH), 110.4, 111.3, 127.3, 128.3, 129.6 (aromatic CH). – MS (IC, NH$_3$); 298 (MH$^+$). – HR-MS (CI, CH$_4$) calcd. for C$_{19}$H$_{24}$NO$_2$ (MH$^+$) 298.1807; found 298.1818.

Tetrahydroisoquinoline 8b: Amide **7b** (95 mg, 0.38 mmol) was allowed to react according to GP5. A 72:28 mixture of 2 inseparable diastereomers was obtained (71 mg). – ^{1}H NMR of the major diastereomer (300.13 MHz, CDCl$_3$, TMS): δ = 1.32 (d, *J* = 6.8 Hz, 3 H, NCHC*H*$_3$), 1.46 (d, *J* = 6.5 Hz, 3 H, CH$_2$CHC*H*$_3$), 2.55 (s, 3 H, NCH$_3$), 2.84 (m, 1 H, NCH*H*), 3.01 (m, 2 H, CH$_2$C*H*CH$_3$, NC*H*H), 3.70 (q, *J* = 6.8 Hz, 1 H, NCH), 3.85 (s, 3 H, OCH$_3$), 3.86 (s, 3 H, OCH$_3$), 6.55 (s, 1 H, aromatic H), 6.69 (s, 1 H, aromatic H), –^{13}C NMR (75.43 MHz, CDCl$_3$): δ = 19.6, 20.1 (NCH*C*H$_3$, NCH$_2$CH*C*H$_3$), 29.8 (NCH$_3$), 42.4 (NCH$_2$*C*HCH$_3$), 54.3 (NCH$_2$), 55.8 (OCH$_3$), 58.9 (NCH), 109.7, 110.0 (aromatic CH), 129.8, 130.1, 147.4, 147.7 (aromatic C). – MS (CI, NH$_3$); 236 (MH$^+$).

Tetrahydroisoquinoline 8c: Amide **7c** (137 mg, 0.365 mmol) was allowed to react according to GP5. After column chromatography on alumina gel (ethyl acetate/cyclohexane 50:50) 40 mg (30%) of the major diastereomer was obtained as a yellow oil. – $[\alpha]_D^{22}$ = –36 (*c* = 0.8, CHCl$_3$) –^{1}H NMR (300.13 MHz, CDCl$_3$, TMS): δ = 1.58 (m, 1 H, NH), 2.94 (m, 1 H, NCH$_2$C*H*), 3.10 (m, 4 H, NC*H*$_2$CHC*H*$_2$), 3.60 (s, 3 H, OCH$_3$), 3.71 (s, 3 H, OCH$_3$), 5.00 (s, 1 H, NCH), 6.19 (s, 1 H, aromatic H), 6.39 (s, 1 H, aromatic H), 7.2–7.35 (m, 10 H, aromatic H). – ^{13}C NMR (75.43 MHz, CDCl$_3$): δ = 39.8 (NCH$_2$*C*H), 42.7, 46.5 (NCH$_2$CH*C*H$_2$, N*C*H$_2$CHCH$_2$), 55.6 (OCH$_3$), 62.3 (NCH), 110.5, 111.6, 126.0, 127.4, 128.3, 128.4, 128.9, 129.5 (aromatic CH), 140.6, 144.8, 147.1 (aromatic C). – MS (CI, NH$_3$); 360 (MH$^+$). – HR-MS (CI, CH$_4$) calcd. for C$_{24}$H$_{26}$NO$_2$ (MH$^+$) 360.1963; found 360.1987.

Tetrahydroisoquinoline 10: Lactam **9** (132 mg, 0.39 mmol) was allowed to react according to GP5. After column chromatography on alumina gel (ethyl acetate/cyclohexane 10:90) 46 mg (37%) of the major isomer was obtained as a yellow oil. – $[\alpha]_D^{22}$ = –105 (*c* = 0.92, ethyl acetate). – ^{1}H NMR (300.13 MHz, CDCl$_3$, TMS): δ = 1.65–2.05 (m, 3 H, NCH$_2$C*H*$_2$CH*H*), 2.34 (m, 3 H, NCH*H*CH$_2$C*H*H, NCH*H*CH), 3.01 (m, 6 H, NCH, NCH*H*C*H*C*H*$_2$, NCH*H*C*H*$_2$), 3.74 (s, 3 H, OCH$_3$), 3.85 (s, 3 H, OCH$_3$), 6.53 (s, 1 H, aromatic H), 6.58 (s, 1 H, aromatic H), 7.20–7.32 (m, 5 H, aromatic H). – ^{13}C NMR (75.43 MHz, CDCl$_3$): δ = 21.7 (NCH$_2$*C*H$_2$), 29.5 (NCH*C*H$_2$), 41.2 (NCH$_2$*C*HCH$_2$), 43.6

(NCH$_2$CH*C*H$_2$), 52.3, 53.6 (CH$_2$NCH$_2$), 55.7 (OCH$_3$), 55.8 (OCH$_3$), 64.6 (NCH), 108.2, 111.6, 125.8, 128.2, 129.4, 130.4, 131.0 (aromatic CH), 141.1, 146.9, 147.0 (aromatic C). – MS (CI, NH$_3$); 324 (MH$^+$).

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