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A General Methodology for the Enantioselective Synthesis of 1-Substituted Tetrahydroisoquinoline Alkaloids

Mercedes Amat,*[a] Viviane Elias,[a] Núria Llor,[a] Fabiana Subrizi,[a] Elies Molins,[b] and Joan Bosch[a]

Dedicated to Prof. Dr. Antonio García Martínez on the occasion of his retirement

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Starting from tricyclic lactam **2**, which is easily accessible by cyclocondensation of δ-oxoester **1** with (*R*)-phenylglycinol, a three-step synthetic route to enantiopure 1-substituted tetrahydroisoquinolines, including 1-alkyl-, 1-aryl-, and 1-benzyl-tetrahydroisoquinoline alkaloids, as well as the tricyclic alkaloid (–)-crispine A, has been developed. The key step is a stereoselective α-amidoalkylation reaction using the appropriate Grignard reagent.

Introduction

The tetrahydroisoquinoline ring system is present in numerous structurally diverse natural products exhibiting a wide range of biological and pharmacological activities.[1] In particular, simple 1-substituted tetrahydroisoquinolines are of great interest not only as alkaloids themselves but also as useful key intermediates in the synthesis of more complex alkaloids. This has stimulated the development of a number of methodologies aimed at the enantioselective synthesis of 1-substituted tetrahydroisoquinoline derivatives[2] (Figure 1).

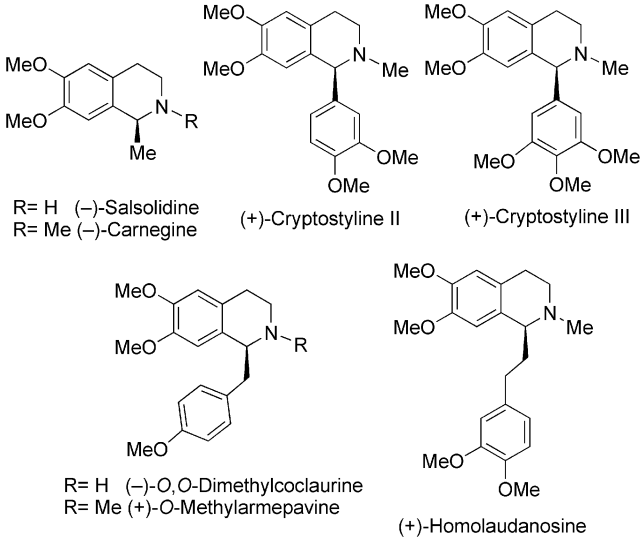
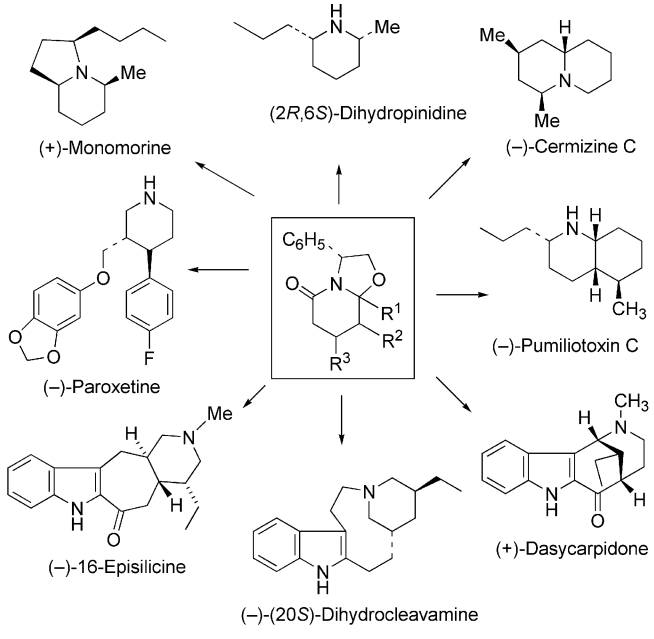


Figure 1. Selected 1-substituted tetrahydroisoquinoline alkaloids.

In previous work, we demonstrated that phenylglycinol-derived oxazolopiperidone lactams are versatile scaffolds that allow the regio- and stereocontrolled introduction of substituents at different positions of the piperidine ring,



Scheme 1. Natural and bioactive products prepared from phenylglycinol-derived lactams.

[a] Laboratory of Organic Chemistry, Faculty of Pharmacy, and Institute of Biomedicine (IBUB), University of Barcelona, Av. Joan XXIII s/n, 08028 Barcelona, Spain
Fax: +34-934-024-539
E-mail: amat@ub.edu
[b] Institut de Ciència de Materials de Barcelona (CSIC), Campus UAB, 08193 Cerdanyola, Spain

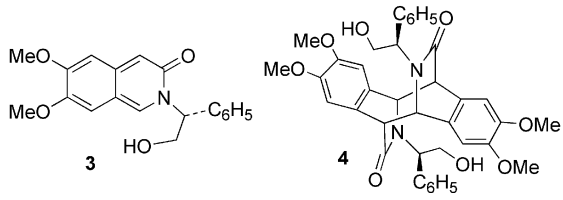
thus providing access to enantiopure substituted piperidines bearing virtually any type of substitution pattern, as well as to quinolizidine, indolizidine, decahydroquinoline, and complex piperidine-containing indole alkaloids[3] (Scheme 1).

Results and Discussion

To further expand the synthetic potential of phenylglycinol-derived oxazolopiperidone lactams, we report here a general methodology for the enantioselective synthesis of 1-substituted tetrahydroisoquinoline alkaloids. The application of our enantiomeric scaffolding strategy[4] would simply require starting from an appropriate benzo-fused oxazolopiperidone lactam and the subsequent stereocontrolled introduction of the substituent at the 1-position of the tetrahydroisoquinoline ring by an asymmetric α-amidoalkylation reaction.[5]

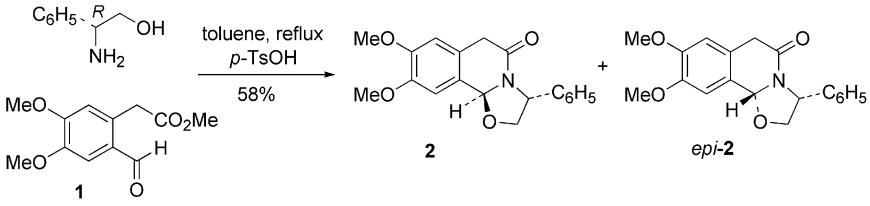
Tricyclic lactam **2** was envisaged as the pivotal intermediate of our synthesis. It was prepared in 52% yield by cyclocondensation of aldehyde ester **1**[6] with (*R*)-phenylglycinol in refluxing toluene in the presence of a catalytic amount of *p*-TsOH (Scheme 2). The absolute configuration of lactam **2** was unambiguously determined by X-ray crystallographic analysis.[7] Minor amounts (6%) of lactam *epi*-**2**, epimeric at the 2-position of the oxazolidine ring, were also formed.

In contrast with related *cis*-oxazolopiperidone lactams,[8] minor *cis* lactam *epi*-**2** did not undergo epimerization under acidic conditions (1.2 N HCl, MeOH, r.t); isoquinolone **3** and trace amounts of dimer **4** were formed instead. This dimer was formed in 49% yield after prolonged acidic treatment (1.2 N HCl, MeOH, reflux, 66 h) of isoquinolone **3**.



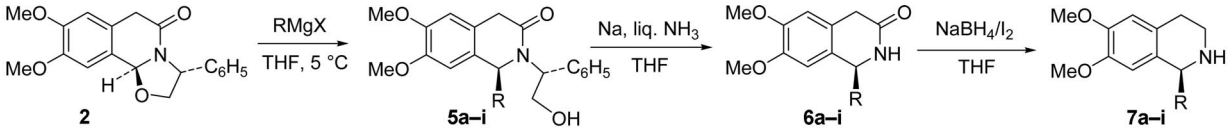
Initial attempts to carry out the α-amidoalkylation reaction with a higher order cyanocuprate [$Me_2Cu(CN)Li_2$] in the presence of $BF_3{\cdot}Et_2O$[9] resulted in failure, leading exclusively to isoquinolone **3**. However, treatment of lactam **2** with an excess amount (3 equiv.) of methylmagnesium chloride at 5 °C stereoselectively led to the expected 1-substituted tetrahydroisoquinolone **5a** in 61% yield (Table 1).[10] Isoquinolone **3** was formed as a byproduct (17%). Higher temperatures resulted in the formation of increasing amounts of **3**, whereas when the reaction was carried out at a lower temperature the starting lactam was recovered to a considerable extent.

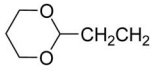
The observed retention of the configuration of the reactive methine carbon can be rationalized by considering that



Scheme 2. Preparation of key tricyclic lactam **2**.

Table 1. Enantioselective synthesis of 1-substituted tetrahydroisoquinolines.



	R	X	Yield of **5** [%]	Yield of **6** [%]	Yield of **7** [%]
a	Me	Cl	61	85	70
b	Et	Br	82	92	60
c	C_6H_5	Cl	67	–	–
d	3,4-$(MeO)_2C_6H_3$	Br	54	77	69
e	3,4,5-$(MeO)_3C_6H_2$	Br	49	87	58
f	(*p*-MeO)$C_6H_4CH_2$	Cl	63	85	59
g	$C_6H_5CH_2CH_2$	Br	67	79	77
h	CH_2=$CHCH_2$	Br	42	90	–
i		Br	45	92	–

the Grignard reagent coordinates with the oxygen atom of the oxazolidine ring and that the subsequent intramolecular delivery of the alkyl group occurs on the same face of the C–O bond of the incipient acyl iminium salt (Figure 2).[11]

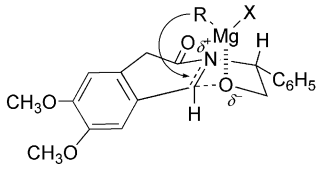


Figure 2. Stereochemical outcome of the α-amidoalkylation reaction.

As in related *cis*-substituted oxazolopiperidones,[11] minor *cis* lactam *epi*-**2** was more reluctant to undergo α-amidoalkylation[12] than *trans* isomer **2** and, upon treatment with MeMgCl, led to isoquinolone **3** as the major product (50%); 2-methyltetrahydroisoquinoline **5a** was formed in low yield (35%).

Removal of the phenylethanol moiety from lactam **5a** was accomplished in excellent yield with sodium in liquid ammonia to give *N*-unsubstituted lactam **6a**. Subsequent reduction with borane generated in situ from $NaBH_4$ and iodine completed the enantioselective synthesis of (–)-salsolidine (**7a**).[13] Taking into account previous correlations, this synthesis also constitutes a formal synthesis of the alkaloid (–)-carnegine.[14]

The above protocol provides general access to 1-alkyl-substituted tetrahydroisoquinolines. Thus, reaction of lactam **2** with ethylmagnesium bromide stereoselectively afforded (82% yield) lactam **5b**, which was then debenzylated and converted into (*S*)-1-ethyl-1,2,3,4-tetrahydroisoquinoline **7b** in good overall yield, as in the above methyl series.

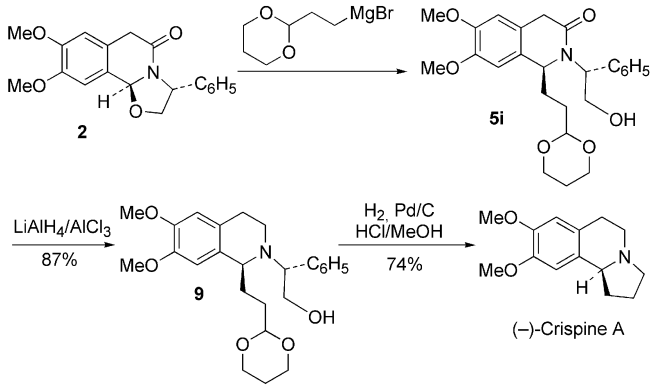
With the aim of demonstrating the potential of the methodology for the synthesis of 1-aryl-, 1-benzyl-, and 1-phenethyltetrahydroisoquinoline alkaloids, we applied the above three-step sequence from lactam **2** using a variety of aryl-, benzyl-, and phenethylmagnesium halides. The results are summarized in Table 1 (Entries c–g). In all cases the α-amidoalkylation reaction took place stereoselectively to give a single 1-substituted tetrahydroisoquinolone derivative (i.e., **5c**–**g**).[15]

Although the reductive cleavage of the exocyclic benzylic C–N bond of 2-phenyl derivative **5c** with Na/liq. NH_3 occurred with concomitant cleavage of the doubly benzylic endocyclic C–N bond to give 2-benzyl-4,5-dimethoxyphenylacetamide (**8**), a similar reduction from the methoxyphenyl-substituted tetrahydroisoquinolones **5d** and **5e** satisfactorily led to the respective *N*-unsubstituted lactams **6d** and **6e** in excellent yield. Subsequent reduction of the lactam carbonyl of **6d** led to (–)-norcryptostyline II (**7d**), which constitutes a formal synthesis of the alkaloid (+)-cryptostyline II.[16] Similarly, lactam **6e** was converted into (–)-norcryptostyline III (**7e**), a known precursor of the alkaloid (+)-cryptostyline III.[17]

The same set of sequential reductions (Na/liq. NH_3 and then $NaBH_4/I_2$) was used to convert 2-benzyl derivative **5f** into (–)-*O*,*O*-dimethylcoclaurine (**7f**).[18] Taking into account previous transformations, this synthesis also constitutes a formal synthesis of the alkaloids (+)-*O*-methylarmepavine,[18a,18b] zanoxyline,[19] and (–)-demethylcoclaurine [(–)-higenamine].[18d]

Similarly, the usefulness of this methodology in the synthesis of 1-phenethyltetrahydroisoquinolines was demonstrated by the preparation of **7g**[20] from α-amidoalkylation product **5g**.

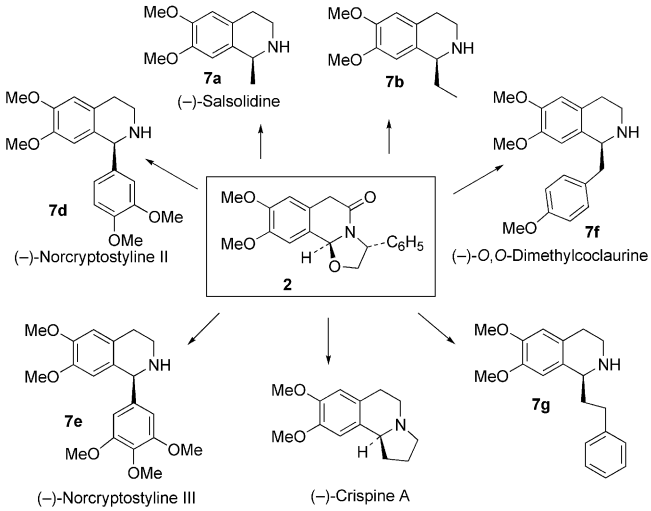
The procedure allows the preparation of tetrahydroisoquinolines and tetrahydroisoquinolones bearing a functionalized C-1 substituent, for instance allyl[21] or 2-(1,3-dioxan-2-yl)ethyl (Table 1, Entries h and i),[22] which can open access to more complex tetrahydroisoquinoline alkaloids embodying an additional ring. This was exemplified with the synthesis of the pyrrolo[2,1-*g*]isoquinoline alkaloid crispine A. The three-carbon fragment required for the construction of the pyrrolidine ring was incorporated in the α-amidoalkylation step. Thus, reaction of lactam **2** with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane (Scheme 3) gave 1-substituted tetrahydroisoquinolone. In this synthesis, the lactam carbonyl was reduced prior to debenzylation to give tetrahydroisoquinoline **9** in excellent yield. Subsequent catalytic hydrogenation under acidic conditions brought about the hydrogenolysis of the exocyclic benzylic C–N bond, deprotection of the acetal function, and closure of the pyrrolidine ring by reductive amination, directly leading to crispine A[23] in 74% yield.



Scheme 3. Enantioselective synthesis of (–)-crispine A.

Conclusions

Tricyclic (*R*)-phenylglycinol-derived lactam **2** has proven to be a useful scaffold that provides general access to enantiopure 1-substituted tetrahydroisoquinoline derivatives, including 1-alkyl-, 1-aryl-, and 1-benzyltetrahydroisoquinoline alkaloids as well as more complex alkaloids bearing the tetrahydroisoquinoline moiety (Scheme 4). The enantioselective synthesis of 1-benzyltetrahydroisoquinolines is of particular interest because these derivatives not only play a pivotal role in the biosynthesis of numerous alkaloids with a variety of skeletal types (e.g., aporphines, cularines, protoberberines, and pavines) but have also been used as key synthetic precursors of such alkaloids.[24]



Scheme 4. Enantiopure 1-substituted tetrahydroisoquinolines prepared from common scaffold **2**.

Experimental Section

General: Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm) or (when indicated) by using a cartridge containing amine-functionalized silica. Melting points were taken with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HMRS; LC/MSD TOF Agilent Technologies) were performed by Serveis Científico-Tècnics, Barcelona. Microanalyses (Carlo Erba 1106 analyzer) were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona. Only noteworthy IR absorptions (Perkin-Elmer 1600) are listed. NMR spectra were recorded with either a Varian Gemini-300 (300 and 75.4 MHz for ^1H and ^{13}C, respectively) or Mercury-400 (400 and 100.6 MHz for ^1H and ^{13}C, respectively) spectrometer.

(3*R*,10b*S*)-8,9-Dimethoxy-5-oxo-3-phenyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (2): To a mixture of aldehyde-ester **1**[6] (993 mg, 4.2 mmol) and (*R*)-phenylglycinol (690 mg, 5.0 mmol) in anhydrous toluene (45 mL) containing 4 Å molecular sieves was added a catalytic amount of *p*-TsOH. The mixture was heated at reflux for 18 h with azeotropic elimination of water produced by a Dean–Stark apparatus. The resulting suspension was concentrated under reduced pressure to give a yellow foam. Flash chromatography (Et_2O to EtOAc) afforded lactam **2** (710 mg, 52%) and the 10b-epimer *epi*-**2** (82 mg, 6%). Data for **2**: White solid; m.p. 135–137 °C (Et_2O). $[a]_D^{22}$ = –136.6 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.52 (d, *J* = 19.2 Hz, 1 H, 6-H), 3.73 (dd, *J* = 19.2, 2.2 Hz, 1 H, 6-H), 3.88 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.02 (dd, *J* = 9.0, 7.5 Hz, 1 H, 2-H), 4.58 (dd, *J* = 9.0, 7.5 Hz, 1 H, 2-H), 5.38 (t, *J* = 7.5 Hz, 1 H, 3-H), 6.02 (d, *J* = 2.2 Hz, 1 H, 10b-H), 6.66 (s, 1 H, 10-H), 6.99 (s, 1 H, 7-H), 7.35 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 36.9 (C-6), 56.0 (OCH_3), 56.1 (OCH_3), 58.6 (C-3), 72.7 (C-2), 87.8 (C-10b), 107.7 (C-10), 109.8 (C-7), 122.5 (C-6a), 123.1 (C-10a), 126.0 (C-*o*), 127.7 (C-*p*), 128.8 (C-*m*), 139.3 (C-*i*), 148.4 (C-8), 149.7 (C-9), 166.2 (CO) ppm. HRMS: calcd. for $C_{19}H_{19}NO_4$ [M + H]$^+$ 326.1386; found 326.1382. $C_{19}H_{19}NO_4$ (325.36): calcd. C 70.14, H 5.89, N 4.31; found C 70.27, H 5.87, N 4.08. Data for *epi*-**2**: $[a]_D^{22}$ = +62.5 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.45 (d, *J* = 18.9 Hz, 1 H, 6-H), 3.60 (dd, *J* = 18.9, 2.1 Hz, 1 H, 6-H), 3.90 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.20 (dd, *J* = 9.0, 0.9 Hz, 1 H, 2-H), 4.47 (dd, *J* = 9.0, 6.3 Hz, 1 H, 2-H), 5.10 (d, *J* = 6.3 Hz, 1 H, 3-H), 5.90 (d, *J* = 2.1 Hz, 1 H, 10b-H), 6.71 (s, 1 H, 10-H), 7.10 (s, 1 H, 7-H), 7.15–7.25 (m, 5 H, ArH) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$, 25 °C): δ = 38.1 (C-6), 55.9 (OCH_3), 56.0 (OCH_3), 58.6 (C-3), 74.8 (C-2), 87.3 (C-10b), 106.5 (C-10), 110.1 (C-7), 123.0 (C-6a), 125.0 (C-10a), 125.9 (C-*o*), 127.4 (C-*p*), 128.4 (C-*m*), 140.5 (C-*i*), 148.0 (C-8), 149.2 (C-9), 165.2 (CO) ppm. HRMS: calcd. for $C_{19}H_{19}NO_4$ [M + H]$^+$ 326.1386; found 326.1382.

Dimer 4: A solution of 1.2 M HCl in MeOH (6 mL) was added to a solution of isoquinolone **3** (96 mg, 0.3 mmol) in MeOH (1 mL). The mixture was heated at reflux for 66 h. The solvent was removed, and the resulting solid was diluted with EtOAc. The solution was washed with saturated aqueous Na_2CO_3. The organic phase was dried and concentrated to give a residue, which was purified by chromatography (7:3 Et_2O/EtOAc to EtOAc) to afford **4** (47 mg, 49%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.48 (s, 6 H, 2 OCH_3), 3.64 (s, 6 H, 2 OCH_3), 4.27 (dd, *J* = 13.0, 2.8 Hz, 2 H, 2 CH_2OH), 4.43 (d, *J* = 10.8 Hz, 2 H, 2 CHCO), 4.44 (dd, *J* = 13.0, 3.6 Hz, 2 H, 2 CH_2OH), 4.79 (d, *J* = 11.2 Hz, 2 H, 2 CHNCO), 5.68 (s, 2 H, 2 CH_3OCCH), 5.73 (t, *J* = 2.9 Hz, 2 H, CHAr), 6.26 (s, 2 H, 2 CH_3OCCH), 7.08 (d, *J* = 6.4 Hz, 4 H, ArH), 7.14–7.23 (m, 6 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 55.9 (OCH_3), 56.0 (OCH_3), 56.9 (CHCO), 58.5 (CHNCO), 58.7 (CHAr), 62.1 (CH_2OH), 108.6 (CH_3OCCH), 110.3 (CH_3OCCH), 127.7 (C-*p*), 128.4 (C-*o*), 128.7 (*C*CHCO), 128.9 (C-*m*), 131.5 (*C*CHN), 136.4 (C-*i*), 147.5 (CH_3OC), 147.9 (CH_3OC), 176.0 (CO) ppm. HRMS: calcd. for $C_{38}H_{38}N_2O_8$ [M + H]$^+$ 651.2706; found 651.2697.

General Procedure for the α-Amidoalkylation Reaction: The Grignard reagent (3.0 equiv.) was added to a cooled (5 °C) solution of oxazolopiperidone **2** (1 equiv.) in THF, and the mixture was stirred at this temperature until the disappearance of the starting material was observed by TLC. The reaction was quenched by the addition of water, and the mixture was extracted with EtOAc. The combined extracts were dried and concentrated to give the 1-substituted tetrahydroisoquinolones after flash chromatography.

(1*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-1-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (5a): Following the above general procedure (reaction time 1.5 h), from lactam **2** (100 mg, 0.31 mmol) and methylmagnesium chloride (3 M in THF, 0.31 mL, 0.92 mmol) in THF (12.5 mL) a brown oil was obtained. Flash chromatography (7:3 Et_2O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5a** (64 mg, 61%) as a yellow oil and isoquinolone **3** (17 mg, 17%) as a yellow-green foam. Data for **5a**: $[a]_D^{22}$ = +23.5 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1629, 3400 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.39 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.60 (d, *J* = 18.9 Hz, 1 H, 4-H), 3.76 (d, *J* = 18.9 Hz, 1 H, 4-H), 3.77 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.28 (q, *J* = 7.2 Hz, 1 H, 1-H), 4.29 (dd, *J* = 12.0, 8.4 Hz, 1 H, CH_2OH), 4.30 (dd, *J* = 12.0, 5.2 Hz, 1 H, CH_2OH), 5.70 (dd, *J* = 8.4, 5.2 Hz, 1 H, CHAr), 6.38 (s, 1 H, 8-H), 6.66 (s, 1 H, 5-H), 7.18–7.30 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 23.2 (CH_3), 37.3 (C-4), 55.6 (OCH_3), 56.0 (OCH_3), 56.1 (C-1), 60.8 (CHAr), 63.3 (CH_2OH), 107.7 (C-8), 110.3 (C-5), 123.1 (C-4a), 127.6 (C-*o*), 128.1 (C-*p*), 128.7 (C-*m*), 130.5 (C-8a), 136.8 (C-*i*), 148.3 (C-7), 147.8 (C-6), 171.7 (CO) ppm. HRMS: calcd. for $C_{20}H_{23}NO_4$ [M + H]$^+$ 342.1699; found 342.1695. $C_{20}H_{23}NO_4 \cdot 1/4CH_2Cl_2$ (362.64): calcd. C 67.07, H 6.53, N 3.86; found C 67.13, H 6.65, N 3.81. Data for **3**: IR (KBr): $\tilde{\nu}$ = 1652, 3269 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.82 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.31 (dd, *J* = 12.4, 7.2 Hz, 1 H, CH_2OH), 4.42 (dd, *J* = 12.4, 4.4 Hz, 1 H,

CH_2OH), 6.12 (s, 1 H, 5-H), 6.26 (s, 1 H, 8-H), 6.47 (dd, J = 7.2, 4.4 Hz, 1 H, CHAr), 6.59 (s, 1 H, 4-H), 7.33 (m, 5 H, ArH), 7.95 (s, 1 H, 1-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 55.7 (OCH_3), 55.8 (OCH_3), 60.7 (CHAr), 62.9 (CH_2OH), 100.6 (C-7), 103.6 (C-5), 107.6 (C-4), 114.2 (C-8a), 127.9 (C-*m*), 128.1 (C-*p*), 128.9 (C-*o*), 135.3 (C-1), 137.4 (C-*i*), 140.6 (C-6), 147.7 (C-7), 155.0 (C-4a), 160.5 (CO) ppm. EM (IQ+): *m*/*z* (%) = 326 (47), 325 (5), 206 (13), 138 (27), 122 (12) 121 (100).

(1*S*)-1-Ethyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (5b): Following the general procedure (reaction time 6 h), from lactam **2** (400 mg, 1.23 mmol) in THF (10 mL) and ethylmagnesium bromide (3 M in Et_2O, 1.23 mL, 3.68 mmol) a residue was obtained. Flash chromatography (1:1 Et_2O/EtOAc) gave **5b** (354 mg, 82%) as a yellow oil: $[\alpha]_D^{22}$ = +34.4 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1630, 3388 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.72 (t, J = 7.2 Hz, 3 H, CH_3), 1.66–1.77 (m, 1 H, CH_2), 1.79–1.89 (m, 1 H, CH_2), 3.57 (d, J = 18.0 Hz, 1 H, 4-H), 3.77 (s, 3 H, OCH_3), 3.79 (d, J = 18.0 Hz, 1 H, 4-H), 3.86 (s, 3 H, OCH_3), 4.00 (dd, J = 9.6, 3.2 Hz, 1 H, 1-H), 4.23 (dd, J = 11.6, 8.4 Hz, 1 H, CH_2OH), 4.29 (dd, J = 11.6, 5.2 Hz, 1 H, CH_2OH), 5.66 (dd, J = 8.4, 5.2 Hz, 1 H, CHAr), 6.33 (s, 1 H, 8-H), 6.67 (s, 1 H, 5-H), 7.10–7.30 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 10.2 (CH_3), 29.1 (CH_2), 37.5 (C-4), 55.9 (OCH_3), 56.1 (OCH_3), 61.3 (C-1), 61.5 (CHAr), 63.4 (CH_2OH), 109.3 (C-8), 110.3 (C-5), 123.7 (C-4a), 127.7 (C-*o*), 127.8 (C-*p*), 127.8 (C-8a), 129.9 (C-*m*), 136.8 (C-*i*), 147.2 (C-7), 148.3 (C-6), 171.9 (CO) ppm. HRMS: calcd. for $C_{21}H_{25}NO_4$ [M + H]$^+$ 356.1862; found 356.1872. $C_{21}H_{25}NO_4$·1/4$CHCl_3$ (385.28): calcd. C 66.25, H 6.61, N 3.64; found C 66.13, H 6.64, N 3.53.

(1*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1-phenyl-1,2,3,4-tetrahydroisoquinoline (5c): Following the general procedure (reaction time 1 h), from lactam **2** (500 mg, 1.54 mmol) in THF (10 mL) and phenylmagnesium chloride (2 M in THF, 2.3 mL, 4.61 mmol) a residue was obtained. Flash chromatography (Et_2O/EtOAc increasing polarity and 9:1 EtOAc/EtOH) gave **5c** (415 mg, 67%) as a yellow oil and **3** (125 mg, 25%). Data for **5c**: $[\alpha]_D^{22}$ = +16.7 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1629, 3388 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.66 (d, J = 19.8 Hz, 1 H, 4-H), 3.71 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.84 (d, J = 19.8 Hz, 1 H, 4-H), 3.88–3.91 (m, 2 H, CH_2OH), 5.26 (s, 1 H, 1-H), 5.96 (t, J = 6.6 Hz, 1 H, CHAr), 6.41 (s, 1 H, 8-H), 6.58 (s, 1 H, 5-H), 7.15–7.30 (m, 10 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 37.2 (C-4), 55.8 (OCH_3), 55.9 (OCH_3), 59.9 (C-1), 62.2 (CH_2OH), 62.5 (CHAr), 108.6 (C-8), 110.0 (C-5), 122.3 (C-4a), 126.0 (C-*o*), 127.4 (C-*p*), 127.8 (C-*p*), 128.1 (C-*m*), 128.3 (C-*o*), 128.5 (C-8a), 128.8 (C-*m*), 136.7 (C-*i*), 143.0 (C-*i*), 147.8 (C-6), 148.0 (C-7), 171.9 (CO) ppm. HRMS: calcd. for $C_{25}H_{25}NO_4$ [M + H]$^+$ 404.1862; found 404.1875.

(1*S*)-1-(3,4-Dimethoxyphenyl)-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (5d): Following the general procedure (reaction time 15 min), from lactam **2** (150 mg, 0.46 mmol) in THF (10 mL) and 3,4-dimethoxyphenylmagnesium bromide (0.5 M in THF, 2.8 mL, 1.4 mmol) a residue was obtained. Flash chromatography (1:1 Et_2O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5d** (115 mg, 54%) as a yellow foam and **3** (50 mg, 33%). Data for **5d**: $[\alpha]_D^{22}$ = +17.1 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1634, 3406 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.68 (d, J = 20.0 Hz, 1 H, 4-H), 3.73 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.83 (s, 3 H, CH_3O), 3.86 (s, 3 H, CH_3O), 3.87 (d, J = 20.0 Hz, 1 H, 4-H), 3.95 (dd, J = 11.6, 8.4 Hz, 1 H, CH_2OH), 4.01 (dd, J = 11.6, 5.2 Hz, 1 H, CH_2OH), 5.18 (s, 1 H, 1-H), 5.93 (dd, J = 8.4, 5.2 Hz, 1 H, CHAr), 6.37 (s, 1 H, 2′-H), 6.58 (s, 1 H, 5′-H), 6.72 (s, 1 H, 6′-H), 6.75 (s, 1 H, 8-H), 6.76 (s, 1 H, 5-H), 7.12–7.15 (m, 2 H, ArH), 7.26–7.32 (m, 3 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 37.4 (C-4), 55.8 (OCH_3), 55.9 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 60.4 (C-1), 62.5 (CHAr), 62.6 (CH_2OH), 108.1 (C-8), 109.5 (C-5), 110.1 (C-2′), 111.3 (C-5′), 118.3 (C-6′), 122.4 (C-4a), 127.9 (C-*p*), 128.4 (C-*o*), 128.6 (C-8a), 128.6 (C-*m*), 134.4 (C-1′), 136.2 (C-*i*), 147.9 (C-6), 148.5 (C-4′), 148.6 (C-7), 149.2 (C-3′), 171.6 (CO) ppm. HRMS: calcd. for $C_{27}H_{29}NO_6$ [M + H]$^+$ 464.2073; found 464.2081. $C_{27}H_{29}NO_6$·1/4$CHCl_3$ (493.37): calcd. C 66.34, H 5.98, N 2.84; found C 66.65, H 6.33, N 2.49.

(1*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5e): Following the general procedure (reaction time 20 min), from lactam **2** (500 mg, 1.54 mmol) in THF (10 mL) and 3,4,5-trimethoxyphenylmagnesium bromide (0.5 M in THF, 9.2 mL, 4.61 mmol) a residue was obtained. Flash chromatography (Et_2O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5e** (370 mg, 49%) as a yellow foam and **3** (135 mg, 27%). Data for **5e**: $[\alpha]_D^{22}$ = +13.1 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1684, 2930 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.65 (d, J = 19.5 Hz, 1 H, 4-H), 3.75 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.80 (masked d, 4-H), 3.81 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 5.17 (s, 1 H, 1-H), 3.98–4.08 (m, 2 H, CH_2OH), 5.89 (dd, J = 8.7, 5.1 Hz, 1 H, CHAr), 6.40 (s, 1 H, 2′-H), 6.46 (s, 2 H, 5-H, 8-H), 6.62 (s, 2 H, 6′-H), 7.13–7.27 (m, 2 H, ArH), 7.29–7.31 (m, 3 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 37.3 (C-4), 55.8 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 56.2 (OCH_3), 60.8 (C-1), 62.8 (CH_2OH), 63.0 (CHAr), 103.3 (C-2′, C-6′), 108.1 (C-8), 110.0 (C-5), 122.7 (C-4a), 128.1 (C-*p*), 128.4 (C-*o*), 128.6 (C-8a), 128.6 (C-*m*), 136.1 (C-1′), 137.0 (C-*i*), 137.4 (C-4′), 147.9 (C-6), 148.6 (C-7), 153.4 (C-5′, C-3′), 172.0 (CO) ppm. HRMS: calcd. for $C_{28}H_{31}NO_7$ [M + H]$^+$ 494.2179; found 494.2183. $C_{28}H_{31}NO_7$·1/4$CHCl_3$ (523.40): calcd. C 64.83, H 6.02, N 2.68; found C 64.69, H 6.26, N 2.42.

(1*S*)-[(*R*)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-1-(*p*-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline (5f): Following the general procedure (reaction time 15 min), from lactam **2** (150 mg, 0.46 mmol) in THF (10 mL) and 4-methoxybenzylmagnesium chloride (0.25 M in THF, 5.5 mL, 1.4 mmol) a residue was obtained. Flash chromatography (3:7 hexane/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5f** (129 mg, 63%) as a white foam and **3** (37 mg, 25%). Data for **5f**: $[\alpha]_D^{22}$ = +41.5 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1630, 3393 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.84 (dd, J = 13.1, 8.5 Hz, 1 H, CHCH_2Ar), 3.06 (dd, J = 13.1, 3.4 Hz, 1 H, CHCH_2Ar), 3.10 (d, J = 19.4 Hz, 1 H, 4-H), 3.39 (d, J = 19.4 Hz, 1 H, 4-H), 3.51 (s, 3 H, OCH_3C-4′), 3.69 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.29 (dd, J = 8.5, 3.4 Hz, 1 H, 1-H), 4.35–4.44 (m, 2 H, CH_2OH), 5.80 (s, 1 H, 5-H or 8-H), 5.85 (t, J = 6.5 Hz, 1 H, CHAr), 6.53 (s, 1 H, 5-H or 8-H), 6.62 (s, 4 H, 2′-H, 3′-H, 5′-H, 6′-H), 7.25–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 37.2 (C-4), 41.9 (C-1CH_2), 55.2 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 61.4 (C-1), 61.6 (CHAr), 63.6 (CH_2OH), 109.2 (C-8), 109.7 (C-5), 113.5 (C-2′, C-6′), 124.2 (C-4a), 127.2 (C-8a), 127.9 (C-o), 128.0 (C-*p*), 128.8 (C-*m*), 131.1 (C-*m*), 131.1 (C-3′, C-5′), 136.9 (C-*i*), 146.8 (C-6), 148.2 (C-7), 158.5 (C-4′), 172.3 (CO) ppm. HRMS: calcd. for $C_{27}H_{29}NO_5$ [M + H]$^+$ 448.2124; found 448.2130. $C_{27}H_{29}NO_5$·3/4H_2O (461.04): calcd. C 70.34, H 6.67, N 3.04; found C 70.03, H 6.42, N 2.87.

(1*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (5 g): Following the general procedure (reaction time 40 min), from lactam **2** (400 mg,

1.23 mmol) in THF (10 mL) and phenethylmagnesium chloride (1 M in THF, 3.69 mL, 3.69 mmol) a residue was obtained. Flash chromatography (8:2 Et_2O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5g** (353 mg, 67%) as a white foam and **3** (68 mg, 17%). Data for **5g**: $[\alpha]_D^{22}$ = +72.9 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1632, 3399 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.92–2.07 (m, 1 H, CH_2), 2.10–2.18 (m, 1 H, CH_2), 2.25–2.36 (m, 1 H, CH_2Ar), 2.50–2.57 (m, 1 H, CH_2Ar), 3.59 (d, *J* = 18.8 Hz, 1 H, 4-H), 3.78 (s, 3 H, OCH_3), 3.81 (d, *J* = 18.8 Hz, 1 H, 4-H), 3.87 (s, 3 H, OCH_3), 4.10 (dd, *J* = 9.2, 2.8 Hz, 1 H, 1-H), 4.18–4.23 (m, 2 H, CH_2OH), 5.59 (dd, *J* = 7.6, 6.0 Hz, 1 H, CHAr), 6.34 (s, 1 H, 8-H), 6.69 (s, 1 H, 5-H), 7.01 (d, *J* = 13.2 Hz, 2 H, C-2′, C-6′), 7.15 (m, 1 H, 4′-H), 7.20 (br. s, 2 H, C-3′, C-5′), 7.24–7.26 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 31.5 (CH_2Ar), 37.6 (C-4), 37.7 (CH_2), 56.0 (OCH_3), 56.1 (OCH_3), 59.4 (C-1), 61.7 (CHAr), 63.3 (CH_2OH), 109.1 (C-8), 110.5 (C-5), 123.9 (C-4a), 126.1 (C-4′), 127.8 (C-*p*), 127.8 (C-*m*), 128.1 (C-*o*), 128.3 (C-8a), 128.5 (C-2′, C-6′), 128.6 (C-3′, C-5′), 136.7 (C-*i*), 140.6 (C-1′), 147.3 (C-6), 148.4 (C-7), 171.9 (CO) ppm. HRMS: calcd. for $C_{27}H_{29}NO_4$ [M + H]$^+$ 432.2175; found 432.2180. $C_{27}H_{29}NO_4 \cdot 3/4H_2O$ (445.04): calcd. C 72.87, H 6.91, N 3.15; found C 72.95, H 6.87, N 2.95.

(1*S*)-1-Allyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (5h): Following the general procedure (reaction time 2 h), from lactam **2** (200 mg, 0.6 mmol) in THF (10 mL) and allylmagnesium bromide (1 M in Et_2O, 1.85 mL, 1.85 mmol) a yellow oil was obtained. Flash chromatography (95:5 *tert*-butyl methyl ether/EtOAc) gave **5h** (92 mg, 42%) as a white oil and 1-(2-allyl-2-hydroxy-4-pentenyl)-2-{1-[2-hydroxy-(1*R*)-phenylethylamino]-3-butenyl}-4,5-dimethoxybenzene (**10**; 103 mg, 39%). Data for **5h**: $[\alpha]_D^{22}$ = +16.8 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1637, 3386 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.18–2.33 (m, 1 H, CH_2CH=), 2.39–2.60 (m, 1 H, CH_2CH=), 3.54 (d, *J* = 19.5 Hz, 1 H, 4-H), 3.79 (d, *J* = 19.5 Hz, 1 H, 4-H), 3.76 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.26 (m, 1 H, 1-H), 4.28 (dd, *J* = 11.4, 7.8 Hz, 1 H, CH_2OH), 4.30 (dd, *J* = 11.4, 5.7 Hz, 1 H, CH_2OH), 4.90 (dd, *J* = 10.5, 1.8 Hz, 1 H, CH_2=), 4.99 (td, *J* = 6.0, 1.8 Hz, 1 H, CH_2=), 5.51 (m, 1 H, CH=), 5.68 (dd, *J* = 7.8, 5.7 Hz, 1 H, 1-H), 6.31 (s, 1 H, 8-H), 6.65 (s, 1 H, 5-H), 7.22–7.38 (m, 5 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 37.6 (C-4), 40.8 (CH_2CH=), 55.8 (OCH_3), 56.0 (OCH_3), 60.1 (C-1), 61.3 (CHAr), 63.2 (CH_2OH), 109.0 (C-8), 110.0 (C-5), 118.9 (CH_2=), 123.6 (C-4a), 127.6 (C-*p*), 127.7 (C-*o*), 128.4 (C-*m*), 128.6 (C-8a), 133.0 (CH=), 136.8 (C-*i*), 147.1 (C-7), 148.2 (C-6), 171.8 (CO) ppm. HRMS: calcd. for $C_{22}H_{25}NO_4$ [M + H]$^+$ 368.1862; found 368.1873. $C_{22}H_{25}NO_4 \cdot 1/2H_2O$ (411.5): calcd. C 70.05, H 7.10, N 3.40; found C 66.69, H 6.70, N 3.55. Data for **10**: IR (KBr): $\tilde{\nu}$ = 1638, 3073, 3324 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.10–2.19 (m, 4 H, 2 CH_2CHCH$_2$), 2.38–2.53 (m, 2 H, CHCH_2CHCH$_2$), 2.56 (d, *J* = 14.8 Hz, 1 H, CH_2Ar), 2.66 (d, *J* = 14.8 Hz, 1 H, CH_2Ar), 3.57 (dd, *J* = 10.8, 8.0 Hz, 1 H, CH_2OH), 3.67 (dd, *J* = 10.8, 4.4 Hz, 1 H, CH_2OH), 3.85 (s, 3 H, OCH_3), 3.86 (dd, *J* = 8.0, 4.4 Hz, 1 H, CHAr), 3.89 (s, 3 H, OCH_3), 4.05 (t, *J* = 6.4 Hz, 1 H, *CH*CH$_2$CHCH$_2$), 4.98–5.09 (m, 2 H, CHCH$_2$CHCH_2), 5.10–5.15 (m, 4 H, 2 CH$_2$CHCH_2), 5.64–5.72 (m, 1 H, CHCH$_2$C*H*CH$_2$), 5.74–5.84 (m, 2 H, 2 CH$_2$C*H*CH$_2$), 6.65 (s, 1 H, CH$_3$OCC*H*), 6.85 (s, 1 H, CH$_3$OCC*H*), 7.26–7.28 (m, 5 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 40.3 (CH*C*H$_2$CHCH$_2$), 40.4 (CH_2Ar), 43.7 (*C*H$_2$CHCH$_2$), 44.0 (*C*H$_2$CHCH$_2$), 55.1 (*C*HCH$_2$CHCH$_2$), 55.6 (OCH_3), 55.7 (OCH_3), 61.5 (CHAr), 66.3 (CH_2OH), 73.3 (*C*OH), 110.1 (C-3), 114.8 (C-6), 117.3 (CHCH$_2$CH*C*H$_2$), 118.5 (CH$_2$CH*C*H$_2$), 118.6 (CH$_2$CH*C*H$_2$), 127.0 (C-2), 127.3 (C-*m*), 127.4 (C-*p*), 128.4 (C-*o*), 133.8 (CH$_2$*C*HCH$_2$), 133.9 (CH$_2$*C*HCH$_2$), 135.0 (C-1), 135.2 (CHCH$_2$*C*HCH$_2$), 140.9 (C-*i*), 146.9 (C-4), 147.5 (C-5) ppm. HRMS: calcd. for $C_{28}H_{37}NO_4$ [M + H]$^+$ 452.2801; found 452.2784. $C_{28}H_{37}NO_4 \cdot 1/2H_2O$ (460.61): calcd. C 73.01, H 8.32, N 3.04; found C 73.24, H 8.13, N 2.75.

(1*S*)-1-[2-(1,3-Dioxan-2-yl)ethyl]-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (5i): Following the general procedure (reaction time 2.5 h), from lactam **2** (400 mg, 1.23 mmol) in THF (20 mL) and 2-(1,3-dioxan-2-yl)ethylmagnesium bromide (0.5 M in THF, 7.4 mL, 3.69 mmol) a yellow solid was obtained. Flash chromatography (1:1 Et_2O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5i** (246 mg, 45%) as a yellow foam and **3** (121 mg, 30%). Data for **5i**: $[\alpha]_D^{22}$ = +38.5 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1632, 3399 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.31 (dt, *J* = 13.6, 1.2 Hz, 2 H, 1′-H), 1.41–1.46 (m, 2 H, OCH$_2$CH_2), 1.72–1.81 (m, 1 H, 2′-H), 1.92–2.06 (m, 1 H, 2′-H), 3.56 (d, *J* = 19.0 Hz, 1 H, 4-H), 3.68 (ddd, *J* = 15.2, 12.0, 3.6 Hz, 2 H, CH$_2$CH_2O), 3.75 (s, 3 H, OCH_3), 3.79 (d, *J* = 19.0 Hz, 1 H, 4-H), 3.85 (s, 3 H, OCH_3), 4.03 (m, 2 H, CH$_2$CH_2O), 4.40 (t, *J* = 4.8 Hz, 1 H, CHO_2), 4.15 (dd, *J* = 10.0, 3.2 Hz, 1 H, 1-H), 4.23–4.32 (m, 2 H, CH_2OH), 5.76 (dd, *J* = 8.0, 5.6 Hz, 1 H, CHAr), 6.34 (s, 1 H, 8-H), 6.65 (s, 1 H, 5-H), 7.16 (d, *J* = 1.6 Hz, 1 H, ArH), 7.18 (d, *J* = 2.0 Hz, 1 H, ArH), 7.25–7.30 (m, 3 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 25.6 (C-1′), 30.3 (C-2′), 31.1 (*C*H$_2$CH$_2$O), 37.6 (C-4), 55.9 (OCH_3), 56.0 (OCH_3), 58.9 (C-1), 60.3 (CHAr), 63.1 (CH_2OH), 66.7 (2 CH$_2$*C*H$_2$O), 101.6 (CHO_2), 109.4 (C-8), 110.4 (C-5), 123.8 (C-4a), 127.7 (C-*p*), 127.8 (C-*o*), 128.1 (C-8a), 128.5 (C-*m*), 136.8 (C-*i*), 147.2 (C-6), 148.3 (C-7), 171.9 (CO) ppm. HRMS: calcd. for $C_{25}H_{31}NO_6$ [M + H]$^+$ 442.2223; found 442.2219.

General Procedure for Na/liquid NH_3 Reaction: Into a three-necked, round-bottomed flask equipped with a cold-finger condenser charged with dry ice/acetone was condensed NH_3 at –78 °C. The temperature was raised to –33 °C, and a solution of lactam **5** in THF was added. Then, sodium metal was added in small portions until the blue color persisted. After the mixture was stirred at –33 °C for 1 min, the reaction was quenched by the addition of solid NH_4Cl until the blue color disappeared. The mixture was stirred at room temperature for 4 h, poured into water, and extracted with Et_2O. The combined organic extracts were dried and concentrated to give a residue, which was purified by chromatography.

(1*S*)-6,7-Dimethoxy-1-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (6a): Operating as described in the general procedure, from **5a** (200 mg, 0.59 mmol) in THF (7 mL) and NH_3 (50 mL) a clear maroon residue was obtained. Flash chromatography (9:1 EtOAc/EtOH) afforded **6a** (110 mg, 85%) as a white solid. $[\alpha]_D^{22}$ = +10.0 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1668, 3217 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.51 (d, *J* = 6.4 Hz, 3 H, CH_3), 3.48 (d, *J* = 20.0 Hz, 1 H, 4-H), 3.60 (d, *J* = 20.0 Hz, 1 H, 4-H), 3.87 (s, 6 H, 2 OCH_3), 4.60 (m, 1 H, 1-H), 6.60 (s, 1 H, 8-H), 6.61 (s, 1 H, 5-H), 6.90 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 24.4 (CH_3), 35.4 (C-4), 51.3 (C-1), 56.0 (OCH_3), 56.1 (OCH_3), 108.2 (C-8), 110.4 (C-5), 122.8 (C-4a), 127.8 (C-8a), 148.0 (C-6), 148.4 (C-7), 171.5 (CO) ppm. HRMS: calcd. for $C_{12}H_{15}NO_3$ [M + H]$^+$ 222.1124; found 222.1122. $C_{12}H_{15}NO_3$ (221.25): calcd. C 65.14, H 6.83, N 6.33; found C 64.89, H 6.76, N 6.16.

(1*S*)-1-Ethyl-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (6b): Operating as described in the general procedure, from **5b** (230 mg, 0.65 mmol) in THF (4 mL) and NH_3 (30 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **6b** (140 mg, 92%) as a white oil. $[\alpha]_D^{22}$ = +21.7 (*c* = 0.57, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1654, 2972 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92

(t, J = 8.0 Hz, 3 H, CH_3), 1.81 (m, 2 H, CH_2), 3.46 (d, J = 20.0 Hz, 1 H, 4-H), 3.62 (d, J = 20.0 Hz, 1 H, 4-H), 3.87 (s, 6 H, 2 OCH_3), 4.44 (m, 1 H, 1-H), 6.60 (s, 1 H, 8-H), 6.62 (s, 1 H, 5-H), 7.70 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 9.1 (CH_3), 31.7 (CH_2), 35.2 (C-4), 55.9 (OCH_3), 56.0 (OCH_3), 57.2 (C-1), 108.8 (C-8), 110.3 (C-5), 123.2 (C-4a), 126.2 (C-8a), 147.8 (C-7), 148.4 (C-6), 171.9 (CO) ppm. HRMS: calcd. for $C_{13}H_{17}NO_3$ [M + H]$^+$ 236.1286; found 236.1280.

(1*S*)-1-[3,4-(Dimethoxyphenyl)]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (6d): Operating as described in the general procedure, from **5d** (215 mg, 0.46 mmol) in THF (3 mL) and NH_3 (35 mL) a residue was obtained. Flash chromatography (2:8 to 1:9 hexane/EtOAc) afforded **6d** (121 mg, 77%) as a yellow foam. IR (KBr): $\tilde{\nu}$ = 1647, 2920 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.52 (d, J = 24.0 Hz, 1 H, 4-H), 3.66 (d, J = 24.0 Hz, 1 H, 4-H), 3.71 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 5.54 (s, 1 H, 1-H), 6.37 (s, 1 H, 2′-H), 6.65 (s, 1 H, 5′-H), 6.72 (s, 1 H, 6′-H), 6.83 (s, 1 H, 8-H), 6.84 (s, 1 H, 5-H), 7.05 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 35.5 (C-4), 55.6 (OCH_3), 55.7 (OCH_3), 55.8 (OCH_3), 59.6 (C-1), 109.5 (C-8), 110.0 (C-5), 110.1 (C-2′), 110.9 (C-5′), 119.7 (C-6′), 123.0 (C-4a), 126.1 (C-8a), 134.2 (C-1′), 147.7 (C-6), 148.5 (C-4′), 148.8 (C-7), 149.3 (C-3′), 170.8 (CO) ppm. HRMS: calcd. for $C_{19}H_{21}NO_5$ [M + H]$^+$ 344.1498; found 344.1491.

(1*S*)-6,7-Dimethoxy-3-oxo-1-[3,4,5-(trimethoxyphenyl)]-1,2,3,4-tetrahydroisoquinoline (6e): Operating as described in the general procedure, from **5e** (150 mg, 0.30 mmol) in THF (2 mL) and NH_3 (30 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **6e** (98 mg, 87%) as a yellow foam. IR (KBr): $\tilde{\nu}$ = 1663, 2926 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.56 (d, J = 18.0 Hz, 1 H, 4-H), 3.71 (d, J = 18.0 Hz, 1 H, 4-H), 3.72 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.25 (s, 1 H, 1-H), 6.41 (s, 2 H, 2′-H, 6′-H), 6.66 (s, 1 H, 8-H), 6.73 (s, 1 H, 5-H), 7.25 (br. s, 1 H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 38.8 (C-4), 55.8 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 60.0 (C-1), 60.1 (OCH_3), 104.3 (C-8), 105.4 (C-2′, C-6′), 113.9 (C-5), 125.4 (C-4a), 131.2 (C-4′), 131.3 (C-8a), 133.4 (C-1′), 147.7 (C-6), 148.1 (C-7), 153.1 (C-3′, C-5′), 173.7 (CO) ppm. HRMS: calcd. for $C_{20}H_{23}NO_6$ [M + H]$^+$ 374.1603; found 374.1592.

(1*S*)-6,7-Dimethoxy-1-(*p*-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline (6f): Operating as described in the general procedure, from **5f** (95 mg, 0.21 mmol) in THF (2 mL) and NH_3 (30 mL) a residue was obtained. Flash chromatography (EtOAc to 95:5 EtOAc/EtOH) afforded **6f** (58 mg, 85%) as a yellow foam. $[\alpha]_D^{22}$ = –61.2 (c = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1630, 2934 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.87 (d, J = 20.0 Hz, 1 H, 4-H), 2.91 (dd, J = 13.5, 6.0 Hz, 1 H, CH_2), 3.03 (dd, J = 13.5, 4.0 Hz, 1 H, CH_2), 3.23 (d, J = 20.0 Hz, 1 H, 4-H), 3.77 (s, 1 H, OCH_3), 3.83 (s, 1 H, OCH_3), 3.86 (s, 1 H, OCH_3), 4.68 (m, 1 H, 1-H), 6.49 (s, 1 H, 8-H), 6.55 (s, 1 H, 5-H), 6.76 (d, J = 8.2 Hz, 2 H, 2′-H), 6.86 (d, J = 8.2 Hz, 2 H, 3′-H), 6.95 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 35.0 (C-4), 44.5 (CH_2), 55.2 (OCH_3), 55.9 (C-1), 56.0 (OCH_3), 57.3 (OCH_3), 108.9 (C-8), 110.1 (C-5), 113.8 (C-3′), 123.9 (C-4a), 125.2 (C-2′), 127.8 (C-8a), 131.8 (C-1′), 147.7 (C-6), 148.4 (C-7), 158.5 (C-4′), 172.3 (CO) ppm. HRMS: calcd. for $C_{19}H_{21}NO_4$ [M + H]$^+$ 328.1549; found 328.1532.

(1*S*)-6,7-Dimethoxy-3-oxo-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (6g): Operating as described in the general procedure, from **5g** (100 mg, 0.23 mmol) in THF (2 mL) and NH_3 (25 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **6g** (56 mg, 79%) as a white foam. $[\alpha]_D^{22}$ = +16.0 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1674 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.03–2.09 (m, 2 H, CH_2), 2.62–2.70 (m, 2 H, CH_2Ar), 3.48 (d, J = 20.0 Hz, 1 H, 4-H), 3.64 (d, J = 20.0 Hz, 1 H, 4-H), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.60 (m, 1 H, 1-H), 6.60 (s, 2 H, 5-H, 8-H), 7.14–7.19 (m, 3 H, ArH), 7.25–7.28 (m, 2 H, ArH), 7.43 (m, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 31.2 (CH_2Ar), 35.4 (C-4), 40.5 (CH_2), 55.7 (C-1), 56.0 (OCH_3), 56.1 (OCH_3), 108.7 (C-8), 110.5 (C-5), 123.2 (C-4a), 126.1 (C-8a), 126.3 (C-4′), 128.3 (C-3′), 128.5 (C-2′), 140.9 (C-1′), 147.9 (C-6), 148.5 (C-7), 171.7 (CO) ppm. HRMS: calcd. for $C_{19}H_{21}NO_3$ [M + H]$^+$ 312.1599; found 312.1598.

(1*S*)-1-Allyl-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (6h): Operating as described in the general procedure, from **5h** (80 mg, 0.22 mmol) in THF (2 mL) and NH_3 (25 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **6h** (48.3 mg, 90%) as a yellow foam. $[\alpha]_D^{22}$ = –10.5 (c = 0.6, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1667, 2918 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.45 (ddd, J = 14.0, 7.2, 7.2 Hz, 1 H, CH_2), 2.57–2.61 (m, 1 H, CH_2), 3.47 (d, J = 20.0 Hz, 1 H, 4-H), 3.60 (d, J = 20.0 Hz, 1 H, 4-H), 3.88 (s, 6 H, 2 OCH_3), 4.52 (m, 1 H, 1-H), 5.12–5.17 (m, 2 H, =CH_2), 5.69–5.79 (m, 1 H, CH=), 6.60 (s, 1 H, 8-H), 6.65 (s, 1 H, 5-H), 6.80 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 35.4 (C-4), 43.2 (CH_2), 55.5 (C-1), 55.9 (OCH_3), 56.0 (OCH_3), 108.6 (C-8), 110.4 (C-5), 119.9 (=CH_2), 123.3 (C-4a), 125.6 (C-8a), 132.7 (CH=), 147.9 (C-6), 148.5 (C-7), 171.2 (CO) ppm. HRMS: calcd. for $C_{14}H_{17}NO_3$ [M + H]$^+$ 248.1288; found 248.1278.

(1*S*)-1-[2-(1,3-Dioxan-2-yl)ethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (6i): Operating as described in the general procedure, from **5i** (114 mg, 0.26 mmol) in THF (2 mL) and NH_3 (30 mL) a residue was obtained. Flash chromatography (9:1 EtOAc/EtOH) afforded **6i** (78.5 mg, 92%) as a white solid. $[\alpha]_D^{22}$ = +2.3 (c = 0.53, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1674, 3217 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.33 (dm, J = 13.2 Hz, 2 H, 2′-H), 1.61–1.84 (m, 2 H, 1′-H), 1.87–1.94 (m, 1 H, C$H_2$$CH_2$O), 1.91–2.11 (m, 1 H, C$H_2$$CH_2$O), 3.56 (d, J = 19.5 Hz, 1 H, 4-H), 3.60 (d, J = 19.5 Hz, 1 H, 4-H), 3.74 (td, J = 11.6, 0.8 Hz, 2 H, CH_2CH_2O), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.09 (ddd, J = 11.6, 4.8, 1.2 Hz, 2 H, CH_2CH_2O), 4.48–4.52 (br. m, 1 H, 1-H), 4.56 (t, J = 4.8 Hz, 1 H, CHO_2), 6.59 (s, 1 H, 8-H), 6.65 (s, 1 H, 5-H), 7.18 (s.a., 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 25.7 (C$H_2$$CH_2$O), 30.5 (C-1′), 33.0 (C-2′), 35.3 (C-4), 55.6 (C-1), 55.9 (OCH_3), 56.0 (OCH_3), 66.8 (CH_2O), 101.6 (CHO_2), 108.8 (C-8), 110.4 (C-5), 123.1 (C-4a), 126.6 (C-8a), 147.8 (C-6), 148.3 (C-7), 171.4 (CO) ppm. HRMS: calcd. for $C_{17}H_{23}NO_5$ [M + H]$^+$ 322.1655; found 322.1650.

2-Benzyl-4,5-dimethoxyphenylacetamide (8): Operating as described in the general procedure, from **5c** (100 mg, 1.17 mmol) in THF (2 mL) and NH_3 (30 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **8** (20 mg, 28%). IR (KBr): $\tilde{\nu}$ = 1629, 2933 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.44 (s, 2 H, CH_2CO), 3.81 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.93 (s, 2 H, CH_2Ar), 5.20 (s, 1 H, NH_2), 5.90 (s, 1 H, NH_2), 6.70 (s, 1 H, 3-H), 6.75 (s, 1 H, 6-H), 7.10–7.25 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 38.8 (CH_2Ar), 40.2 (CH_2CO), 55.9 (OCH_3), 56.0 (OCH_3), 113.8 (C-3), 114.2 (C-6), 125.5 (C-1), 126.3 (C-*p*), 128.5 (C-*m*), 128.6 (C-*o*), 131.6 (C-2), 140.3 (C-*i*), 147.8 (C-4), 148.3 (C-5), 173.9 (CO) ppm. HRMS: calcd. for $C_{17}H_{19}NO_3$ [M + H]$^+$ 286.1443; found 286.1437.

General Procedure for the $NaBH_4$–I_2 Reduction Reactions: A solution of iodine (1 equiv.) in THF was slowly added to a cooled (0 °C) suspension of $NaBH_4$ (2.5 equiv.) in anhydrous THF, and the mix-

ture was stirred at this temperature for 30 min. Then, a solution of lactam **6** (1 equiv.) in THF was added to the solution (0 °C). The resulting mixture was heated at reflux for 16 h and cooled to 0 °C. MeOH (4 mL) was slowly added, and the stirring was continued at room temperature for 30 min. The solvent was evaporated, and the resulting solid was digested with 2 N NaOH (30 min). The resulting suspension was extracted with CH_2Cl_2, the combined organic extracts were dried and concentrated, and the residue was purified by chromatography.

(–)-Salsolidine (7a): Following the above general procedure, from lactam **6a** (100 mg, 0.45 mmol) in THF (5 mL), $NaBH_4$ (42.6 mg, 1.13 mmol) in THF (5 mL), and I_2 (114 mg, 0.45 mmol) in THF (4 mL), tetrahydroisoquinoline **7a** (65 mg, 70%) was obtained as an oil after flash chromatography (9:1 EtOAc/EtOH). $[\alpha]_D^{22} = -58.5$ ($c = 0.50$, EtOH) {lit.[1b] $[\alpha]_D^{24} = -62.5$ ($c = 0.1$, EtOH)}. IR (KBr): $\tilde{\nu} = 3217\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.43$ (d, $J = 6.5$ Hz, 3 H, CH_3), 1.78 (br. s, 1 H, NH), 2.60–2.68 (dt, $J = 16.0$, 4.8 Hz, 1 H, 4-H), 2.74–2.84 (ddd, $J = 16.0$, 8.4, 5.4 Hz, 1 H, 4-H), 2.99 (ddd, $J = 13.0$, 8.4, 4.8 Hz, 1 H, 3-H), 3.24 (ddd, $J = 13.0$, 4.8 Hz, 1 H, 3-H), 3.87 (s, 6 H, 2 OCH_3), 4.04 (q, $J = 6.5$ Hz, 1 H, 1-H), 6.57 (s, 1 H, 8-H), 6.62 (s, 1 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): $\delta = 22.8$ (CH_3), 29.5 (C-4), 41.8 (C-3), 51.2 (C-1), 55.8 (OCH_3), 55.9 (OCH_3), 109.0 (C-8), 111.7 (C-5), 126.8 (C-4a), 132.5 (C-8a), 147.2 (C-7), 147.3 (C-6) ppm.

(1*S*)-1-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7b): Following the above general procedure, from lactam **6b** (91 mg, 0.39 mmol) in THF (10 mL), $NaBH_4$ (36 mg, 1.1 mmol) in THF (4 mL), and I_2 (99 mg, 0.39 mmol) in THF (4 mL), tetrahydroisoquinoline **7b** (52 mg, 60%) was obtained as an oil after flash chromatography by using a cartridge containing amine-functionalized silica (7:3 hexane/EtOAc to EtOAc). $[\alpha]_D^{22} = -47.4$ ($c = 0.3$, CH_2Cl_2) {ref.[25] $[\alpha]_D^{22} = -51.9$ ($c = 2.1$, CH_2Cl_2)}. IR (KBr): $\tilde{\nu} = 2930\ cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 1.02$ (t, $J = 7.6$ Hz, 3 H, CH_3), 1.67–1.78 (m, 1 H, CH_2), 1.90 (dddd, $J = 14.4$, 7.2, 7.2, 3.2 Hz, 1 H, CH_2), 2.40 (s, 1 H, NH), 2.67 (dt, $J = 16.2$, 5.2 Hz, 1 H, 3-H), 2.77 (dt, $J = 16.2$, 6.0 Hz, 1 H, 3-H), 2.98 (ddd, $J = 12.4$, 7.6, 4.8 Hz, 1 H, 4-H), 3.24 (dt, $J = 12.4$, 5.2 Hz, 1 H, 4-H), 3.85 (s, 6 H, 2 OCH_3), 3.85 (m, 1 H, 1-H), 6.57 (s, 1 H, 8-H), 6.62 (s, 1 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): $\delta = 10.9$ (CH_3), 29.0 (CH_2), 29.4 (C-4), 41.1 (C-3), 55.8 (OCH_3), 56.0 (OCH_3), 56.7 (C-1), 109.2 (C-8), 111.7 (C-5), 127.1 (C-4a), 131.0 (C-8a), 147.2 (C-7), 147.3 (C-6) ppm. HRMS: calcd. for $C_{13}H_{19}NO_2$ $[M + H]^+$ 222.1494; found 222.1488.

(–)-Norcryptostyline II (7d): Following the above general procedure, from lactam **6d** (90 mg, 0.26 mmol) in THF (3 mL), $NaBH_4$ (24.8 mg, 0.66 mmol) in THF (4 mL), and I_2 (66.5 mg, 0.26 mmol) in THF (3 mL), tetrahydroisoquinoline 7**d** (58 mg, 69%) was obtained as a yellow oil after flash chromatography by using a cartridge containing amine-functionalized silica (1:1 hexane/EtOAc). $[\alpha]_D^{22} = -33.8$ ($c = 0.36$, $CHCl_3$) {ref.[5a] $[\alpha]_D^{18} = -37$ ($c = 0.26$, $CHCl_3$)}. IR (KBr): $\tilde{\nu} = 2923\ cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 2.75$ (dt, $J = 15.2$, 4.4 Hz, 1 H, 4-H), 2.96 (ddd, $J = 15.2$, 4.8, 4.8 Hz, 1 H, 4-H), 3.06 (ddd, $J = 13.2$, 8.8, 4.8 Hz, 1 H, 3-H), 3.24 (ddd, $J = 13.2$, 4.8 Hz, 1 H, 3-H), 3.65 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.87 (s, 6 H, OCH_3), 5.00 (s, 1 H, 1-H), 6.27 (s, 1 H, 8-H), 6.62 (s, 1 H, 5-H), 6.79 (s, 1 H, 2′-H), 6.80 (s, 1 H, 6′-H), 6.82 (s, 1 H, 5′-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): $\delta = 29.1$ (C-4), 42.1 (C-3), 55.8 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 61.3 (C-1), 110.7 (C-2′), 110.9 (C-5′), 111.4 (C-8), 111.8 (C-5), 121.3 (C-6′), 127.4 (C-4a), 129.8 (C-8a), 136.9 (C-*i*), 147.0 (C-6), 147.7 (C-4′), 148.4 (C-7), 149.0 (C-3′) ppm. HRMS: calcd. for $C_{19}H_{23}NO_4$ $[M + H]^+$ 330.1705; found 330.1691.

(–)-Norcryptostyline III (7e): Following the above general procedure, from lactam **6e** (92 mg, 0.25 mmol) in THF (3 mL), $NaBH_4$ (23.3 mg, 0.62 mmol) in THF (4 mL), and I_2 (70.8 mg, 0.25 mmol) in THF (3 mL), tetrahydroisoquinoline **7e** (52 mg, 58%) was obtained as a yellow oil after flash chromatography by using a cartridge containing amine-functionalized silica (7:3 Et_2O/EtOAc). $[\alpha]_D^{22} = -45.7$ ($c = 0.11$, $CHCl_3$) {ref.[16a] $[\alpha]_D = -37.0$ ($CHCl_3$)}. IR (KBr): $\tilde{\nu} = 2919\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 2.74$ (dt, $J = 15.6$, 4.5, 3.9 Hz, 1 H, 4-H), 2.90–3.00 (m, 1 H, 4-H), 3.07 (ddd, $J = 11.7$, 7.8, 3.9 Hz, 1 H, 3-H), 3.26 (dt, $J = 11.7$, 5.1, 4.5 Hz, 1 H, 3-H), 3.68 (s, 3 H, OCH_3), 3.81 (s, 6 H, 2 CH_3O), 3.85 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.01 (s, 1 H, 1-H), 6.26 (s, 1 H, 8-H), 6.47 (s, 2 H, 2′-H, 6′-H), 6.63 (s, 1 H, 5-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): $\delta = 27.9$ (C-4), 41.5 (C-3), 55.8 (OCH_3), 56.0 (OCH_3), 56.2 (OCH_3), 60.8 (OCH_3), 61.2 (C-1), 106.4 (C-2′, C-6′), 110.8 (C-8), 111.3 (C-5), 126.7 (C-4a), 129.8 (C-8a), 137.7 (C-1′), 147.4 (C-6), 148.2 (C-7), 153.2 (C-3′, C-4′, C-5′) ppm. HRMS: calcd. for $C_{20}H_{25}NO_5$ $[M + H]^+$ 360.1809; found 360.1809.

(–)-*O*,*O*-Dimethylcoclaurine (7f): Following the above general procedure, from lactam **6f** (200 mg, 0.6 mmol) in THF (3 mL), $NaBH_4$ (58 mg, 1.5 mmol) in THF (4 mL), and I_2 (152 mg, 0.8 mmol) in THF (3 mL), tetrahydroisoquinoline **7f** (111 mg, 59%) was obtained as a yellow oil after flash chromatography by using a cartridge containing amine-functionalized silica (8:2 to 1:1 hexane/EtOAc). $[\alpha]_D^{22} = -11.8$ ($c = 0.5$, $CHCl_3$) {ref.[18c] $[\alpha]_D^{22} = -19.9$ ($c = 1$, $CHCl_3$)}. IR (KBr): $\tilde{\nu} = 2932\ cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 2.64$–2.79 (m, 1 H, 3-H), 2.73 (ddd, $J = 11.6$, 6.0, 6.0 Hz, 1 H, 4-H), 2.86 (dd, $J = 14.0$, 9.5 Hz, 1 H, CH_2Ar), 2.91 (ddd, $J = 12.0$, 6.0, 5.6 Hz, 1 H, 3-H), 3.15 (dd, $J = 14.0$, 4.5 Hz, 1 H, CH_2Ar), 3.20 (ddd, $J = 11.6$, 11.6, 5.6 Hz, 1 H, 4-H), 3.80 (s, 1 H, OCH_3), 3.82 (s, 1 H, OCH_3), 3.86 (s, 1 H, OCH_3), 4.11 (dd, $J = 9.5$, 4.5 Hz, 1 H, 1-H), 6.59 (s, 1 H, 8-H), 6.63 (s, 1 H, 5-H), 6.86 (d, $J = 8.5$ Hz, 2 H, 3′-H), 7.16 (d, $J = 8.5$ Hz, 2 H, 5′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): $\delta = 29.5$ (C-4), 40.7 (CH_2Ar), 41.5 (C-3), 55.3 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 56.9 (C-1), 109.4 (C-8), 111.8 (C-5), 114.0 (C-3′), 127.3 (C-4a), 130.3 (C-2′), 130.5 (C-1′), 131.0 (C-8a), 147.0 (C-7), 147.4 (C-6), 158.3 (C-4′) ppm. HRMS: calcd. for $C_{19}H_{23}NO_3$ $[M + H]^+$ 314.1756; found 314.1743.

(1*S*)-6,7-Dimethoxy-1-phenylethyl-1,2,3,4-tetrahydroisoquinoline (7g): Following the above general procedure, from lactam **6g** (250 mg, 0.8 mmol) in THF (3 mL), $NaBH_4$ (76 mg, 2.0 mmol) in THF (4 mL), and I_2 (203 mg, 0.8 mmol) in THF (3 mL), tetrahydroisoquinoline **7g** (183 mg, 77%) was obtained as a colorless oil after flash chromatography (SiO_2 previously washed with 8:2 Et_3N/EtOAc; 8:2 to 1:1 Et_2O/EtOAc as eluent). $[\alpha]_D^{22} = -23.4$ ($c = 0.25$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 2955\ cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 2.04$–2.17 (m, 2 H, CH_2), 2.66–2.89 (m, 4 H, CH_2Ar, 4-H), 3.02 (ddd, $J = 12.0$, 7.2, 5.6 Hz, 1 H, 3-H), 3.27 (ddd, $J = 12.0$, 5.6, 5.6 Hz, 1 H, 3-H), 3.82 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.00 (dd, $J = 8.0$, 2.8 Hz, 1 H, 1-H), 6.57 (s, 2 H, 5-H, 8-H), 7.17–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): $\delta = 29.1$ (CH_2Ar), 32.4 (C-4), 38.1 (CH_2), 40.9 (C-3), 55.1 (C-1), 55.8 (OCH_3), 56.0 (OCH_3), 109.2 (C-8), 111.8 (C-5), 125.9 (C-4′), 127.0 (C-4a), 128.4 (C-2′, C-3′), 128.5 (C-8a), 142.2 (C-4′), 147.3 (C-6), 147.4 (C-7) ppm. HRMS: calcd. for $C_{19}H_{23}NO_2$ $[M + H]^+$ 298.1807; found 298.1802.

(1*S*)-1-[2-(1,3-Dioxan-2-yl)ethyl]-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9): $LiAlH_4$ (96 mg, 2.54 mmol) was slowly added to a suspension of $AlCl_3$ (113 mg, 0.85 mmol) in THF (6 mL) at –78 °C and the mixture was stirred for 2 h. Then, a solution of tetrahydroisoquinolone **5i** (170 mg,

0.39 mmol) in anhydrous THF (6 mL) was slowly added. The stirring was continued at –78 °C for 20 h, and the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated to give a residue, which was purified by chromatography (Et_2O to 1:1 Et_2O/EtOAc) to afford tetrahydroisoquinoline **9** (144 mg, 87%). $[\alpha]_D^{22}$ = –37.1 (*c* = 1.03, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3399 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.26–1.31 (m, 1 H, C1CH_2), 1.49–1.52 (m, 1 H, OCH_2CH_2), 1.53–1.62 (m, 1 H, CH_2CHO_2), 1.76–1.82 (m, 1 H, CH_2CHO_2), 1.83–1.93 (m, 1 H, OCH_2CH_2), 1.97–2.09 (m, 1 H, C1CH_2), 2.27 (s, 1 H, OH), 2.43 (dd, *J* = 17.0, 5.0 Hz, 1 H, 4-H), 2.97 (ddd, *J* = 17.0, 12.0, 6.0 Hz, 1 H, 4-H), 3.20 (dd, *J* = 13.5, 6.0 Hz, 1 H, 3-H), 3.31 (dd, *J* = 13.5, 5.0 Hz, 1 H, 3-H), 3.37 (dd, *J* = 9.6, 4.4 Hz, 1 H, 1-H), 3.64–3.67 (m, 2 H, 2 OCH_2CH_2), 3.68–3.73 (m, 1 H, CHAr), 3.75 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.81–3.86 (m, 2 H, 2 OCH_2CH_2), 3.95 (dd, *J* = 10.8, 6.0 Hz, 1 H, CH_2OH), 4.05 (dd, *J* = 10.8, 4.8 Hz, 1 H, CH_2OH), 4.40 (t, *J* = 4.8 Hz, 1 H, CHO_2), 6.28 (s, 1 H, 8-H), 6.55 (s, 1 H, 5-H), 7.28–7.29 (m, 5 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 22.5 (CH_2CH_2O), 25.6 (C-4), 30.7 (C-1′), 32.1 (C-2′), 39.0 (C-3), 55.6 (OCH_3), 55.7 (OCH_3), 57.6 (C-1), 64.0 (CH_2OH), 64.5 (CHAr), 66.6 (OCH_2CH_2), 102.1 (CHO_2), 110.5 (C-8), 111.3 (C-5), 125.4 (C-4a), 127.4 (C-*p*), 128.2 (C-*o*), 128.6 (C-*m*), 130.3 (C-8a), 140.9 (C-*i*), 146.9 (C-6), 147.1 (C-7) ppm. HRMS: calcd. for $C_{25}H_{33}NO_5$ $[M + H]^+$ 428.2437; found 428.2424.

(*S*)-(–)-Crispine A: A solution of tetrahydroisoquinoline **9** (110 mg, 0.26 mmol) in EtOH (12 mL) and 1.0 M aqueous HCl (0.5 mL) containing 10% Pd/C (15 mg) was hydrogenated with vigorous stirring at room temperature and atmospheric pressure for 3 d. The catalyst was removed by filtration, the solvent was concentrated under vacuum, and the resulting oil was purified by chromatography with a cartridge containing amine-functionalized silica (1:1 hexane/EtOAc) to give crispine A (45 mg, 74%). $[\alpha]_D^{22}$ = –100.1 (*c* = 0.32, $CHCl_3$) {ref.[26] $[\alpha]_D^{22}$ = –96 (*c* = 0.25, $CHCl_3$)}. IR (KBr): $\tilde{\nu}$ = 2922 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.69–1.78 (m, 1 H, 1-H), 1.82–1.99 (m, 2 H, 2-H), 2.30–2.38 (m, 1 H, 1-H), 2.63 (ddd, *J* = 17.0, 8.0, 8.0 Hz, 1 H, 6-H), 2.69 (m, 1 H, 5-H), 2.74 (m, 1 H, 3-H), 3.00 (ddd, *J* = 12.4, 9.6, 5.6 Hz, 1 H, 3-H), 3.07 (ddd, *J* = 17.0, 8.0, 4.0 Hz, 1 H, 6-H), 3.18 (dddd, *J* = 17.2, 11.2, 6.4, 2.8 Hz, 1 H, 5-H), 3.49 (m, 1 H, 10b-H), 3.85 (s, 6 H, OCH_3), 6.57 (s, 1 H, 10-H), 6.61 (s, 1 H, 7-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 22.3 (C-2), 27.9 (C-6), 30.6 (C-3), 48.2 (C-3), 53.1 (C-5), 55.9 (OCH_3), 56.0 (OCH_3), 62.8 (C-10b), 108.8 (C-10), 111.3 (C-7), 126.1 (C-6a), 130.5 (C-10a), 147.3 (C-8), 147.4 (C-9) ppm. HRMS: calcd. for $C_{14}H_{19}NO_2$ $[M + H]^+$ 234.1494; found 234.1486.

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[1] a) J. D. Phillipson, M. F. Roberts, M. H. Zenk (Eds.), *The Chemistry and Biology of Isoquinoline Alkaloids*, Springer, Berlin, **1985**; b) Atta-ur-Rahman (Ed.), *Handbook of Natural Products Data*, Elsevier, Amsterdam, **1994**, vol. 3; c) D. Jack, R. Williams, *Chem. Rev.* **2002**, 1669–1730; d) P. M. Dewick in *Medicinal Natural Products*, Wiley, Chichester, **2002**, pp. 315–346; e) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444–463 and previous reviews in this series.

[2] For reviews, see: a) E. Anakabe, D. Badía, L. Carrillo, E. Reyes, J. L. Vicario, "Chiral β-Amino alcohols and Derivatives in the Asymmetric Synthesis of Tetrahydroisoquinolines" in *Targets in Heterocyclic Systems* (Eds.: O. A. Attanasi, D. Spinelli), Italian Society of Chemistry, **2002**, vol. 6, pp. 270–311; b) J. L. Vicario, D. Badía, L. Carrillo, J. Etxebarria, *Curr. Org. Chem.* **2003**, *7*, 1775–1792; c) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370; d) E. L. Larghi, M. Amongero, A. B. J. Bracca, T. S. Kaufman, *Arkivoc* **2005**, *12*, 98–153; e) Z. Czarnocki, A. Siwicka, J. Szawkato, *Curr. Org. Chem.* **2005**, *2*, 301–331.

[3] For reviews on the use of amino alcohol derived oxazolopiperidone lactams, see: a) A. I. Meyers, G. P. Brengel, *Chem. Commun.* **1997**, 1–8; b) M. D. Groaning, A. I. Meyers, *Tetrahedron* **2000**, *56*, 9843–9873; c) C. Escolano, M. Amat, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 8198–8207; d) S. N. Gaskell, L. J. Duffy, S. M. Allin, *Nat. Prod. Commun.* **2008**, *3*, 1825–1838; for more recent work, see: e) M. Amat, O. Bassas, N. Llor, M. Cantó, M. Pérez, E. Molins, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 7872–7881; f) M. Amat, M. M. M. Santos, O. Bassas, N. Llor, C. Escolano, A. Gómez-Esqué, E. Molins, S. M. Allin, V. McKee, J. Bosch, *J. Org. Chem.* **2007**, *72*, 5193–5201; g) M. Amat, R. Griera, R. Fabregat, J. Bosch, *Angew. Chem. Int. Ed.* **2008**, *47*, 3348–3351; h) M. Amat, A. Gómez-Esqué, C. Escolano, M. M. M. Santos, E. Molins, J. Bosch, *J. Org. Chem.* **2009**, *74*, 1205–1211; i) M. Amat, N. Llor, B. Checa, E. Molins, J. Bosch, *J. Org. Chem.* **2010**, *75*, 178–189; j) M. Amat, M. Pérez, S. Proto, T. Gatti, J. Bosch, *Chem. Eur. J.*, DOI: 10.1002/chem.201000421.

[4] T. C. Coombs, M. D. Lee IV, H. Wong, M. Armstrong, B. Cheng, W. Chen, A. F. Moretto, L. S. Liebeskind, *J. Org. Chem.* **2008**, *73*, 882–888.

[5] For related approaches from oxazolotetrahydroisoquinolines, see: a) M. Yamato, K. Hashigaki, N. Qais, S. Ishikawa, *Tetrahedron* **1990**, *46*, 5909–5920; b) K. Hashigaki, K. Kan, N. Qais, Y. Takeuchi, M. Yamato, *Chem. Pharm. Bull.* **1991**, *39*, 1126–1131; c) A.-C. Carbonnelle, V. Gott, G. Roussi, *Heterocycles* **1993**, *36*, 1763–1769; d) K. Umetsu, N. Asao, *Tetrahedron Lett.* **2008**, *49*, 2722–2725.

[6] J. M. Gardiner, M. R. Bryce, P. A. Bates, M. B. Hursthouse, *J. Org. Chem.* **1990**, *55*, 1261–1266.

[7] CCDC-770769 (for **2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[8] a) M. Amat, J. Bosch, J. Hidalgo, M. Cantó, M. Pérez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque, *J. Org. Chem.* **2000**, *65*, 3074–3084; b) M. Amat, C. Escolano, A. Gómez-Esqué, O. Lozano, N. Llor, R. Griera, E. Molins, J. Bosch, *Tetrahedron: Asymmetry* **2006**, *17*, 1581–1588; c) M. Amat, M. Pérez, A. T. Minaglia, D. Passarella, J. Bosch, *Tetrahedron: Asymmetry* **2008**, *19*, 2406–2410.

[9] M. Amat, N. Llor, J. Hidalgo, C. Escolano, J. Bosch, *J. Org. Chem.* **2003**, *68*, 1919–1928.

[10] The use of MeMgBr resulted in a lower yield (42%) of α-amidoalkylation product **5a**.

[11] For related α-amidoalkylation reactions from oxazolopiperidone lactams, see: M. Amat, C. Escolano, N. Llor, M. Huguet, M. Pérez, J. Bosch, *Tetrahedron: Asymmetry* **2003**, *14*, 1679–1683; see also ref.[8b]

[12] This behavior can be explained in terms of the stereoelectronic effect: P.-Q. Huang, *Synlett* **2006**, 1133–1149.

[13] For a review, see: a) T. S. Kaufman, *Tetrahedron: Asymmetry* **2004**, *15*, 1203–1237; for more recent work, see: b) T. Kanemitsu, Y. Yamashita, K. Nagata, T. Itoh, *Synlett* **2006**, 1595–1597; c) F. Werner, N. Blank, T. Opatz, *Eur. J. Org. Chem.* **2007**, 3911–3915; d) C. Li, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208–13209.

[14] For a review, see: A. B. J. Bracca, T. S. Kaufman, *Tetrahedron* **2004**, *60*, 10575–10610.

[15] The α-amidoalkylation failed when *p*-methoxyphenylzinc iodide was used, lactam **2** was recovered along with variable amounts of isoquinolone **3**.
[16] For previous enantioselective syntheses, see: a) A. Brossi, S. Teitel, *Helv. Chim. Acta* **1971**, *54*, 1564–1571; b) M. J. Munchhof, A. I. Meyers, *J. Org. Chem.* **1995**, *60*, 7086–7087; c) H. Suzuki, S. Aoyagi, C. Kibayashi, *Tetrahedron Lett.* **1995**, *36*, 6709–6712; see also ref.[5a,5d]
[17] For previous enantioselective syntheses, see: a) G. Gosmann, D. Guillaume, H.-P. Husson, *Tetrahedron Lett.* **1996**, *37*, 4369–4372; b) V. Samano, J. A. Ray, J. B. Thompson, R. A. Mook Jr., D. K. Jung, C. S. Koble, M. T. Martin, E. C. Bigham, C. S. Regitz, P. L. Feldman, E. E. Boros, *Org. Lett.* **1999**, *1*, 1993–1996; see also ref.[16a]
[18] For previous enantioselective syntheses, see: a) N. Yamazaki, H. Suzuki, S. Aoyagi, C. Kibayashi, *Tetrahedron Lett.* **1996**, *37*, 6161–6164; b) R. Pedrosa, C. Andrés, J. M. Iglesias, *J. Org. Chem.* **2001**, *66*, 243–250; c) P. Allef, H. Kunz, *Heterocycles* **2007**, *74*, 421–436; d) M. K. Pyo, D.-H. Lee, D.-H. Kim, J.-H. Lee, J.-C. Moon, K. C. Chang, H. S. Yun-Choi, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4110–4114; see also ref.[13c]
[19] S. V. Kini, M. M. V. Ramana, *Tetrahedron Lett.* **2004**, *45*, 4171–4173.
[20] For the enantioselective synthesis of the enantiomer, see: K. Th. Wanner, I. Praschak, *Heterocycles* **1989**, *29*, 29–33.
[21] In this series, the polyallylated compound 1-(2-allyl-2-hydroxy-4-pentenyl)-2-{1-[2-hydroxy-(1*R*)-phenylethylamino]-3-butenyl}-4,5-dimethoxybenzene (**10**) was isolated as a byproduct (39%).
[22] Treatment of lactam **2** with allyltrimethylsilane in the presence of $TiCl_4$ or with 2-(1,3-dioxolan-2-yl)ethylzinc iodide led to isoquinolone **3**, and the starting lactam was partly recovered in the latter case.
[23] For previous enantioselective syntheses, see: a) T. R. Wu, M. Chong, *J. Am. Chem. Soc.* **2006**, *128*, 9646–9647; b) J. Szawkato, S. J. Czarnocki, A. Zawadzka, K. Wojtasiewicz, A. Leniewski, J. K. Maurin, Z. Czarnocki, J. Drabowicz, *Tetrahedron: Asymmetry* **2007**, *18*, 406–413; c) S. M. Allin, S. N. Gaskell, J. M. R. Towler, P. C. B. Page, B. Saha, M. J. McKenzie, W. P. Martin, *J. Org. Chem.* **2007**, *72*, 8972–8975; d) T. Kanemitsu, Y. Yamashita, K. Nagata, T. Itoh, *Heterocycles* **2007**, *74*, 199–203; e) G.-H. Hou, J.-H. Xie, P.-C. Yan, Q.-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 1366–1367.
[24] a) T. Kametani in *The Total Synthesis of Natural Products* (Ed.: J. ApSimon), Wiley, New York, **1977**, vol. 3, pp. 1–272; b) M. J. Munchhof, A. I. Meyers, *J. Org. Chem.* **1996**, *61*, 4607–4610; see also ref.[1a,1d]
[25] R. P. Polniaszek, C. R. Kaufman, *J. Am. Chem. Soc.* **1989**, *111*, 4859–4863.
[26] I. W. Southon, J. Buckingham, *Dictionary of Alkaloids*, Chapman and Hall, London, **1989**, p 261.

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