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

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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.

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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).

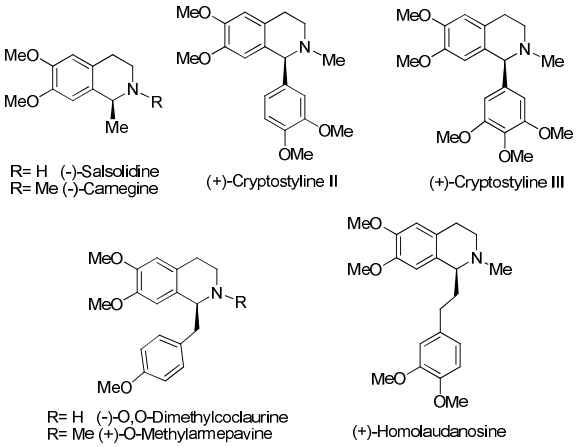
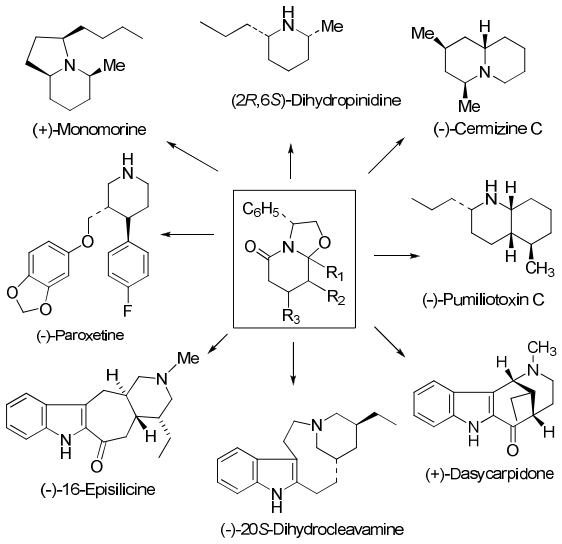


Figure 1. Selected 1-substituted tetrahydroisoquinoline alkaloids.

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



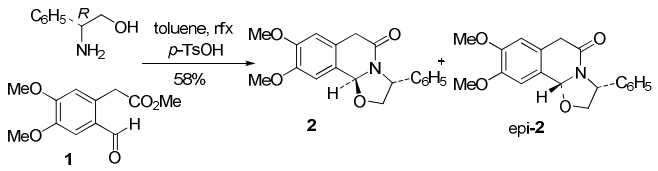
Scheme 1. Natural and bioactive products prepared from phenylglycinol-derived lactams.

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

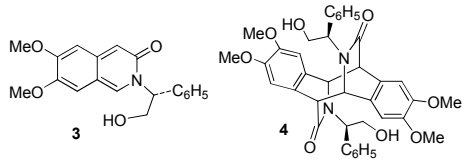
from an appropriate benzo-fused oxazolopiperidone lactam and the subsequent stereocontrolled introduction of the substituent at the 1-position of the tetrahydroisoquinoline ring by an asymmetric α-amidoalkylation reaction. [5]

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 the lactam epi-**2**, epimeric at the 2-position of the oxazolidine ring, were also formed.



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

In contrast with related *cis*-oxazolopiperidone lactams,[8] the 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** being formed instead. This dimer was formed in 49% yield after a 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 $BF_3.Et_2O$[9] resulted in failure, leading exclusively to isoquinolone **3**. However, treatment of lactam **2** with an excess (3 equiv.) of methylmagnesium chloride at 5 ºC stereoselectively led to the expected 1-substituted tetrahydroisoquinolone **5a** in 61% yield (Table 1).[10] Isoquinolone **3** was formed as a by-product (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 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]

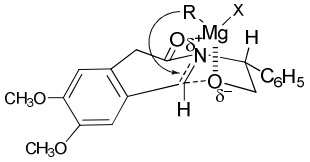


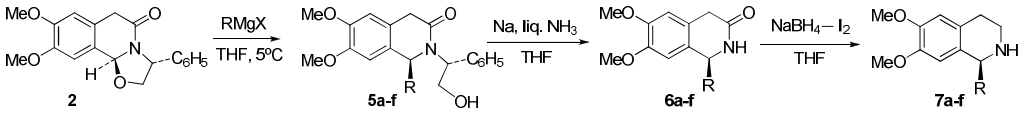
Figure 2. Stereochemical outcome of the α-amidoalkylation reaction.

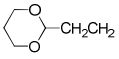
As in related *cis*-substituted oxazolopiperidones,[11] the minor *cis* lactam epi-**2** was more reluctant to undergo α-amidoalkylation[12] than the *trans* isomer **2** and, on treatment with MeMgCl, led to isoquinolone **3** as the major product (50%), 2-methyltetrahydroisoquinoline **5a** being formed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

Removal of the phenylethanol moiety from lactam **5a** was accomplished in excellent yield with sodium in liquid ammonia to give the *N*-unsubstituted lactam **6a**. A 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 to (*S*)-1-ethyl-1,2,3,4-tetrahydroisoquinoline **7b** in good overall yield, as in the above methyl series.

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	-

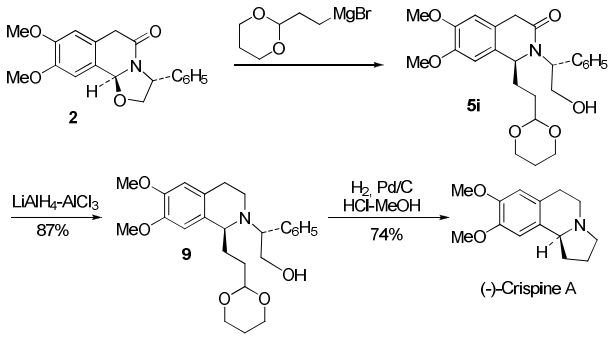
With the aim of demonstrating the potential of the methodology for the synthesis of 1-aryl-, 1-benzyl-, and 1-phenethyl tetrahydroisoquinoline alkaloids, we applied the above three-step sequence from lactam **2** using a variety of aryl-, benzyl-, and phenethylmagnesium halides. The results are summarized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

Although the reductive cleavage of the exocyclic benzylic C–N bond of the 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*-unsusbtituted lactams **6d** and **6e** in excellent yield. A 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 to (–)-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** to (–)-O,O-dimethylcoclaurine (**7f**).[18] Taking into account previous transformations, this synthesis also constitutes a formal synthesis of the alkaloids (+)-O-methylarmepavine,[18a,b] zanoxyline,[19] and (–)-demethylcoclaurine [(–)-higenamine].[18e]

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

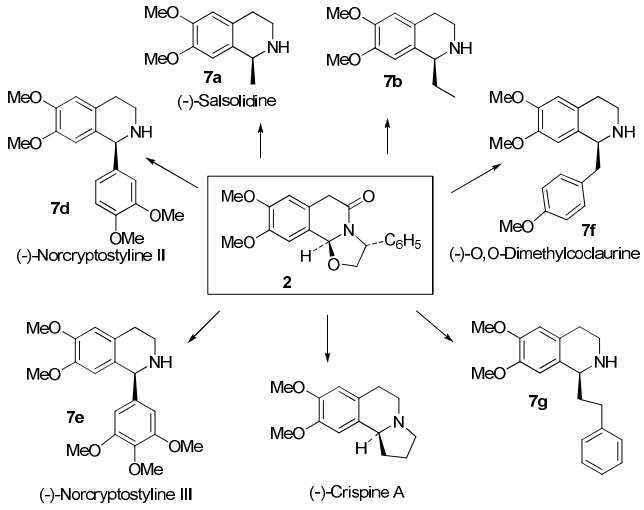
The procedure allows the preparation of tetrahydroisoquinolines and tetrahydroisoquinolones bearing a functionalized C-1 substituent, for instance allyl[21] or 2-(1,3-dioxan-2-yl)ethyl (Table 1, entries **h**, **i**),[22] which can open access to more complex tetrahydroisoquinoline alkaloids embodying an additional ring. This was exemplified with the synthesis of the pyrrolo[2,1-*g*]isoquinoline alkaloid crispine A. The three-carbon fragment required to assemble the pyrrolidine ring was incorporated in the α-amidoalkylation step by reaction of lactam **2** with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane (Scheme 3) to give **5i**. In this synthesis, the lactam carbonyl was reduced prior to debenzylation to give tetrahydroisoquinoline **9** in excellent yield. A 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 the common scaffold **2**.

Experimental Section

(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%). **2**: White solid; m.p. 135–137ºC (Et_2O). $[\alpha]^{22}_D$ = – 136.6 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.52 (d, *J* = 19.2 Hz, 1H, H-6), 3.73 (dd, *J* = 19.2, 2.2 Hz, 1H, H-6), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.02 (dd, *J* = 9.0, 7.5 Hz, 1H, H-2), 4.58 (dd, *J* = 9.0, 7.5 Hz, 1H, H-2), 5.38 (t, *J* = 7.5, 1H, H-3), 6.02 (d, *J* = 2.2 Hz, 1H, H-10b), 6.66 (s, 1H, H-10), 6.99 (s, 1H, H-7), 7.35 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. epi-**2**: $[\alpha]^{22}_D$ = + 62.5 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 3.45 (d, *J* = 18.9 Hz, 1H, H-6), 3.60 (dd, *J* = 18.9, 2.1 Hz, 1H, H-6), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.20 (dd, *J* = 9.0, 0.9 Hz, 1H, H-2), 4.47 (dd, *J* = 9.0, 6.3 Hz, 1H, H-2), 5.10 (d, *J* = 6.3 Hz, 1H, H-3), 5.90 (d, *J* = 2.1 Hz, 1H, H-10b), 6.71 (s, 1H, H-10), 7.10 (s, 1H, H-7), 7.15-7.25 (m, 5H, ArH) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$, 25ºC): 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 chromatographed (7:3 Et_2O–EtOAc to EtOAc) to afford **4** (47 mg, 49%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.48 (s, 6H, 2OCH_3), 3.64 (s, 6H, 2OCH_3), 4.27 (dd, *J* = 13.0, 2.8 Hz, 2H, 2CH_2OH), 4.43 (d, *J* = 10.8 Hz, 2H, 2CHCO), 4.44 (dd, *J* = 13.0, 3.6 Hz, 2H, 2CH_2OH), 4.79 (d, *J* = 11.2 Hz, 2H, 2CHNCO), 5.68 (s, 2H, 2CH_3OCCH), 5.73 (t, *J* = 2.9 Hz, 2H, CHAr), 6.26 (s, 2H, 2CH_3OCCH), 7.08 (d, *J* = 6.4 Hz, 4H, ArH), 7.14-7.23 (m, 6H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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 ºC) 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 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 (3M 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 yelow-green foam. **5a**: $[\alpha]^{22}_D$ = + 23.5 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1629, 3400 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.39 (d, *J* = 7.2 Hz, 3H, CH_3), 3.60 (d, *J* = 18.9 Hz, 1H, H-4), 3.76 (d, *J* = 18.9 Hz, 1H, H-4), 3.77 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.28 (q, *J* = 7.2 Hz, 1H, H-1), 4.29 (dd, *J* = 12.0, 8.4 Hz, 1H, CH_2OH), 4.30 (dd, *J* = 12.0, 5.2 Hz, 1H, CH_2OH), 5.70 (dd, *J* = 8.4, 5.2 Hz, 1H, CHAr), 6.38 (s, 1H, H-8), 6.66 (s, 1H, H-5), 7.18-7.30 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. $C_{20}H_{23}NO_4$ 1/4 CH_2Cl_2 (362.64): calcd. C 67.07, H 6.53, N 3.86; found C 67.13, H 6.65, N 3.81. **3**: IR (KBr): ν = 1652, 3269 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.31 (dd, *J* = 12.4, 7.2 Hz, 1H, CH_2OH), 4.42 (dd, *J* = 12.4, 4.4 Hz, 1H, CH_2OH), 6.12 (s, 1H, H-5), 6.26 (s, 1H, H-8), 6.47 (dd, *J* = 7.2, 4.4 Hz, 1H, CHAr), 6.59 (s, 1H, H-4), 7.33 (m, 5H, ArH), 7.95 (s, 1H, H-1) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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 (3M 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: $[\alpha]^{22}_D$ = + 34.4 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1630, 3388 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.72 (t, *J* = 7.2 Hz, 3H, CH_3), 1.66-1.77 (m, 1H, CH_2), 1.79-1.89 (m, 1H, CH_2), 3.57 (d, *J* = 18.0 Hz, 1H, H-4), 3.77 (s, 3H, OCH_3), 3.79 (d, *J* = 18.0 Hz, 1H, H-4), 3.86 (s, 3H, OCH_3), 4.00 (dd, *J* = 9.6, 3.2 Hz, 1H, H-1), 4.23 (dd, *J* = 11.6, 8.4 Hz, 1H, CH_2OH), 4.29 (dd, *J* = 11.6, 5.2 Hz, 1H, CH_2OH), 5.66 (dd, *J* = 8.4, 5.2 Hz, 1H, CHAr), 6.33 (s, 1H, H-8), 6.67 (s, 1H, H-5), 7.10-7.30 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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 (2M 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%).

5c: $[\alpha]^{22}_D$ = + 16.7 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1629, 3388 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 3.66 (d, *J* = 19.8 Hz, 1H, H-4), 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.84 (d, *J* = 19.8 Hz, 1H, H-4), 3.88-3.91 (m, 2H, CH_2OH), 5.26 (s, 1H, H-1), 5.96 (t, *J* = 6.6 Hz, 1H, CHAr), 6.41 (s, 1H, H-8), 6.58 (s, 1H, H-5), 7.15-7.30 (m, 10H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): 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%). **5d**: $[\alpha]^{22}_D$ = + 17.1 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1634, 3406 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.68 (d, *J* = 20.0 Hz, 1H, H-4), 3.73 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 3.87 (d, *J* = 20.0 Hz, 1H, H-4), 3.95 (dd, *J* = 11.6, 8.4 Hz, 1H, CH_2OH), 4.01 (dd, *J* = 11.6, 5.2 Hz, 1H, CH_2OH), 5.18 (s, 1H, H-1), 5.93 (dd, *J* = 8.4, 5.2 Hz, 1H, CHAr), 6.37 (s, 1H, H-2'), 6.58 (s, 1H, H-5'), 6.72 (s, 1H, H-6'), 6.75 (s, 1H, H-8), 6.76 (s, 1H, H-5), 7.12-7.15 (m, 2H, ArH), 7.26-7.32 (m, 3H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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%). **5e**: $[\alpha]^{22}_D$ = + 13.1 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1684, 2930 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 3.65 (d, *J* = 19.5 Hz, 1H, H-4), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.80 (masked d, H-4), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.17 (s, 1H, H-1), 3.98-4.08 (m, 2H, CH_2OH), 5.89 (dd, *J* = 8.7, 5.1 Hz, 1H, CHAr), 6.40 (s, 1H, H-2'), 6.46 (s, 2H, H-5, H-8), 6.62 (s, 2H, H-6'), 7.13-7.27 (m, 2H, ArH), 7.29-7.31 (m, 3H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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%). **5f**: $[\alpha]^{22}_D$ = + 41.5 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1630, 3393 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.84 (dd, *J* = 13.1, 8.5 Hz, 1H, CHCH_2Ar), 3.06 (dd, *J* = 13.1, 3.4 Hz, 1H, CHCH_2Ar), 3.10 (d, *J* = 19.4 Hz, 1H, H-4), 3.39 (d, *J* = 19.4 Hz, 1H, H-4), 3.51 (s, 3H, OCH_3C4'), 3.69 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.29 (dd, *J* = 8.5, 3.4 Hz, 1H, H-1), 4.35-4.44 (m, 2H, CH_2OH), 5.80 (s, 1H, H-5 or H-8), 5.85 (t, *J* = 6.5 Hz, 1H, CHAr), 6.53 (s, 1H, H-5 or H-8), 6.62 (s, 4H, H-2', H-3', H-5', H-6'), 7.25-7.35 (m, 5H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 37.2 (C-4), 41.9 (C1*C*H_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. $C_{27}H_{29}NO_5$.3/4 H_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 (5g): 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%). **5g**: $[\alpha]^{22}_D$ = +72.9 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1632, 3399 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.92-2.07 (m, 1H, CH_2), 2.10-2.18 (m, 1H, CH_2), 2.25-2.36 (m, 1H, CH_2Ar), 2.50-2.57 (m, 1H, CH_2Ar), 3.59 (d, *J* = 18.8 Hz, 1H, H-4), 3.78 (s, 3H, OCH_3), 3.81 (d, *J* = 18.8 Hz, 1H, H-4), 3.87 (s, 3H, OCH_3), 4.10 (dd, *J* = 9.2, 2.8 Hz, 1H, H-1), 4.18-4.23 (m, 2H, CH_2OH), 5.59 (dd, *J* = 7.6, 6.0 Hz, 1H, CHAr), 6.34 (s, 1H, H-8), 6.69 (s, 1H, H-5), 7.01 (d, *J* = 13.2 Hz, 2H, C-2', C-6'), 7.15 (m, 1H, H-4'), 7.20 (br s, 2H, C-3', C-5'), 7.24-7.26 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 31.5 (*C*H_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. $C_{27}H_{29}NO_4$.3/4 H_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%). **5h**: $[\alpha]^{22}_{D}$ = +16.8 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1637, 3386 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 2.18-2.33 (m, 1H, CH_2CH=), 2.39-2.60 (m, 1H, CH_2CH=), 3.54 (d, *J* = 19.5 Hz, 1H, H-4), 3.79 (d, *J* = 19.5 Hz, 1H, H-4), 3.76 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.26 (m, 1H, H-1), 4.28 (dd, *J* = 11.4, 7.8 Hz, 1H, CH_2OH), 4.30 (dd, *J* = 11.4, 5.7 Hz, 1H, CH_2OH), 4.90 (dd, *J* = 10.5, 1.8 Hz, 1H, CH_2=), 4.99 (td, *J* = 6.0, 1.8 Hz, 1H, CH_2=), 5.51 (m, 1H, CH=), 5.68 (dd, *J* = 7.8, 5.7 Hz, 1H, H-1), 6.31 (s, 1H, H-8), 6.65 (s, 1H, H-5), 7.22-7.38 (m, 5H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 37.6 (C-4), 40.8 (*C*H_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. $C_{22}H_{25}NO_4.1/2H_2O$ (411.5): calcd. C 70.05, H 7.10, N 3.40; found C 66.69, H 6.70, N 3.55. **10:** IR (KBr): ν = 1638, 3073, 3324 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.10-2.19 (m, 4H, 2CH_2CHCH_2), 2.38-2.53 (m, 2H, CHCH_2CHCH_2), 2.56 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 2.66 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 3.57 (dd, J = 10.8, 8.0 Hz, 1H, CH_2OH), 3.67 (dd, *J* = 10.8, 4.4 Hz, 1H, CH_2OH), 3.85 (s, 3H, OCH_3), 3.86 (dd, *J* = 8.0, 4.4 Hz, 1H, CHAr), 3.89 (s, 3H, OCH_3), 4.05 (t, *J* = 6.4 Hz, 1H, *CH*CH_2CHCH_2), 4.98-5.09 (m, 2H, CHCH_2CHCH_2), 5.10-5.15 (m, 4H, 2CH_2CHCH_2), 5.64-5.72 (m, 1H, CHCH_2C*H*CH_2), 5.74-5.84 (m, 2H, 2CH_2C*H*CH_2), 6.65 (s, 1H, CH_3OCC*H*), 6.85 (s, 1H, CH_3OCC*H*), 7.26-7.28 (m, 5H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 40.3 (CH*C*H_2CHCH_2), 40.4 (CH_2Ar), 43.7 (*C*H_2CHCH_2), 44.0 (*C*H_2CHCH_2), 55.1 (*C*HCH_2CHCH_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_2CH*C*H_2), 118.5 (CH_2CH*C*H_2), 118.6 (CH_2CH*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. $C_{28}H_{37}NO_4.1/2H_2O$ (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 2.5h), 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%). **5i:** $[\alpha]^{22}_{D}$ = +38.5 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1632, 3399 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.31 (dt, *J* = 13.6, 1.2 Hz, 2H, H-1'), 1.41-1.46 (m, 2H, OCH_2CH_2), 1.72-1.81 (m, 1H, H-2'), 1.92-2.06 (m, 1H, H-2'), 3.56 (d, *J* = 19.0 Hz, 1H, H-4), 3.68 (ddd, *J* = 15.2, 12.0, 3.6 Hz, 2H, CH_2CH_2O), 3.75 (s, 3H, OCH_3), 3.79 (d, *J* = 19.0 Hz, 1H, H-4), 3.85 (s, 3H, OCH_3), 4.03 (m, 2H, CH_2CH_2O), 4.40 (t, *J* = 4.8 Hz, 1H, CHO_2), 4.15 (dd, *J* = 10.0, 3.2 Hz, 1H, H-1), 4.23-4.32 (m, 2H, CH_2OH), 5.76 (dd, *J* = 8.0, 5.6 Hz, 1H, CHAr), 6.34 (s, 1H, H-8), 6.65 (s, 1H, H-5), 7.16 (d, *J* = 1.6 Hz, 1H, ArH), 7.18 (d, *J* = 2.0 Hz, 1H, ArH), 7.25-7.30 (m, 3H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 25.6 (C-1'), 30.3 (C-2'), 31.1 (*C*H_2CH_2O), 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 ($2CH_2CH_2O$), 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/liq. NH_3 Reaction: Into a three-necked round-bottomed equipped with a coldfinger condenser charged with dry ice-acetone was condensed NH_3 at –78 ºC. The temperature was raised to –33 ºC, 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 ºC for 1 min, the reaction was quenched by the addition of solid NH_4Cl until the blue color disappeared. The mixture was stirred at rt for 4h, poured into water, and extracted with Et_2O. The combined organic extracts were dried and concentrated to give a residue, which was chromatographed.

(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 marron residue was obtained. Flash chromatography (9:1 EtOAc-EtOH) afforded **6a** (110 mg, 85%) as a white solid. $[\alpha]^{22}_{D}$ = + 10.0 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1668, 3217 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.51 (d, *J* = 6.4 Hz, 3H, CH_3), 3.48 (d, *J* = 20.0 Hz, 1H, H-4), 3.60 (d, J = 20.0 Hz, 1H, H-4), 3.87 (s, 6H, $2OCH_3$), 4.60 (m, 1H, H-1), 6.60 (s, 1H, H-8), 6.61 (s, 1H, H-5), 6.90 (br s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. $[\alpha]^{22}_{D}$ = + 21.7 (*c* = 0.57, $CHCl_3$). IR (KBr): ν = 1654, 2972 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.92 (t, *J* = 8.0 Hz, 3H, CH_3), 1.81 (m, 2H, CH_2), 3.46 (d, *J* = 20.0 Hz, 1H, H-4), 3.62 (d, *J* = 20.0 Hz, 1H, H-4), 3.87 (s, 6H, $2OCH_3$), 4.44 (m, 1H, H-1), 6.60 (s, 1H, H-8), 6.62 (s, 1H, H-5), 7.70 (br s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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): ν = 1647, 2920 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.52 (d, *J* = 24.0 Hz, 1H, H-4), 3.66 (d, *J* = 24.0 Hz, 1H, H-4), 3.71 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.54 (s, 1H, H-1), 6.37 (s, 1H, H-2'), 6.65 (s, 1H, H-5'), 6.72 (s, 1H, H-6'), 6.83 (s, 1H, H-8), 6.84 (s, 1H, H-5),

7.05 (br s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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): ν = 1663, 2926 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 3.56 (d, *J* = 18.0 Hz, 1H, H-4), 3.71 (d, *J* = 18.0 Hz, 1H, H-4), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.25 (s, 1H, H-1), 6.41 (s, 2H, H-2', H-6'), 6.66 (s, 1H, H-8), 6.73 (s, 1H, H-5), 7.25 (br s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): 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. $[\alpha]^{22}_D$ = – 61.2 (*c* = 0.5, $CHCl_3$). IR (KBr): ν = 1630, 2934 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.87 (d, *J* = 20.0 Hz, 1H, H-4), 2.91 (dd, *J* = 13.5, 6.0 Hz, 1H, CH_2), 3.03 (dd, *J* = 13.5, 4.0 Hz, 1H, CH_2), 3.23 (d, *J* = 20.0 Hz, 1H, H-4), 3.77 (s, 1H, OCH_3), 3.83 (s, 1H, OCH_3), 3.86 (s, 1H, OCH_3), 4.68 (m, 1H, H-1), 6.49 (s, 1H, H-8), 6.55 (s, 1H, H-5), 6.76 (d, *J* = 8.2 Hz, 2H, H-2'), 6.86 (d, *J* = 8.2 Hz, 2H, H-3'), 6.95 (br s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. $[\alpha]^{22}_D$ = +16.0 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1674 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.03-2.09 (m, 2H, CH_2), 2.62-2.70 (m, 2H, CH_2Ar), 3.48 (d, *J* = 20.0 Hz, 1H, H-4), 3.64 (d, *J* = 20.0 Hz, 1H, H-4), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.60 (m, 1H, H-1), 6.60 (s, 2H, H-5, H-8), 7.14-7.19 (m, 3H, ArH), 7.25-7.28 (m, 2H, ArH), 7.43 (m, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. $[\alpha]^{22}_D$ = – 10.5 (*c* = 0.6, $CHCl_3$). IR (KBr): ν = 1667, 2918 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.45 (ddd, *J* = 14.0, 7.2, 7.2 Hz, 1H, CH_2), 2.57-2.61 (m, 1H, CH_2), 3.47 (d, *J* = 20.0 Hz, 1H, H-4), 3.60 (d, *J* = 20.0 Hz, 1H, H-4), 3.88 (s, 6H, 2OCH_3), 4.52 (m, 1H, H-1), 5.12-5.17 (m, 2H, =CH_2), 5.69-5.79 (m, 1H, CH=), 6.60 (s, 1H, H-8), 6.65 (s, 1H, H-5), 6.80 (br s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. $[\alpha]^{22}_D$ = + 2.3 (*c* = 0.53, $CHCl_3$). IR (KBr): ν = 1674, 3217 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.33 (dm, J = 13.2 Hz, 2H, H-2'), 1.61-1.84 (m, 2H, H-1'), 1.87-1.94 (m, 1H, C$H_2$$CH_2$O), 1.91-2.11 (m, 1H, C$H_2$$CH_2$O), 3.56 (d, *J* = 19.5 Hz, 1H, H-4), 3.60 (d, *J* = 19.5 Hz, 1H, H-4), 3.74 (td, *J* = 11.6, 0.8 Hz, 2H, CH_2CH_2O), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.09 (ddd, *J* = 11.6, 4.8, 1.2 Hz, 2H, CH_2CH_2O), 4.48-4.52 (br m, 1H, H-1), 4.56 (t, *J* = 4.8 Hz, 1H, CHO_2), 6.59 (s, 1H, H-8), 6.65 (s, 1H, H-5), 7.18 (s.a., 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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): ν = 1629, 2933 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.44 (s, 2H, CH_2CO), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.93 (s, 2H, CH_2Ar), 5.20 (s, 1H, NH_2), 5.90 (s, 1H, NH_2), 6.70 (s, 1H, H-3), 6.75 (s, 1H, H-6), 7.10-7.25 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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 ºC) suspension of $NaBH_4$ (2.5 equiv) in anhydrous THF, and the mixture was stirred at this temperature for 30 min. Then, a solution of lactam **6** (1 equiv) in THF was added to the solution (0 ºC). The resulting mixture was refluxed for 16 h and cooled to 0ºC. MeOH (4 mL) was slowy added, and the stirring was continued at room temperature for 30 min. The solvent was evaporated, and the resulting solid was digested with 2N NaOH (30 min). The resulting

suspension was extracted with CH_2Cl_2, the combined organic extracts were dried and concentrated, and the residue was chromatographed.

(–)-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). $[\alpha]^{22}_D$ = –58.5 (*c* = 0.50, EtOH) {lit.:[1b] $[\alpha]^{24}_D$ –62.5 (*c* 0.1, EtOH)}. IR (KBr): ν = 3217 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 1.43 (d, *J* = 6.5 Hz, 3H, CH_3), 1.78 (br s, 1H, NH), 2.60-2.68 (dt, *J* = 16.0, 4.8 Hz, 1H, H-4), 2.74-2.84 (ddd, *J*= 16.0, 8.4, 5.4 Hz, 1H, H-4), 2.99 (ddd, *J* = 13.0, 8.4, 4.8 Hz, 1H, H-3), 3.24 (ddd, J = 13.0, 4.8 Hz, 1H, H-3), 3.87 (s, 6H, 2OCH_3), 4.04 (q, *J* = 6.5 Hz, 1H, H-1), 6.57 (s, 1H, H-8), 6.62 (s, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 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 using a cartridge containing amine functionalized silica (7:3 hexane–EtOAc to EtOAc). $[\alpha]^{22}_D$ = –47.4 (*c* = 0.3, CH_2Cl_2) {lit.:[25] $[\alpha]^{22}_D$ –51.9 (*c* 2.1, CH_2Cl_2)}. IR (KBr): ν = 2930 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.02 (t, *J* = 7.6 Hz, 3H, CH_3), 1.67-1.78 (m, 1H, CH_2), 1.90 (dddd, *J* = 14.4, 7.2, 7.2, 3.2 Hz, 1H, CH_2), 2.40 (s, 1H, NH), 2.67 (dt, *J* = 16.2, 5.2 Hz, 1H, H-3), 2.77 (dt, *J* = 16.2, 6.0 Hz, 1H, H-3), 2.98 (ddd, *J* = 12.4, 7.6, 4.8 Hz, 1H, H-4), 3.24 (dt, *J* = 12.4, 5.2 Hz, 1H, H-4), 3.85 (s, 6H, 2OCH_3), 3.85 (m, 1H, H-1), 6.57 (s, 1H, H-8), 6.62 (s, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 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 yelow oil after flash chromatography using a cartridge containing amine functionalized silica (1:1 hexane–EtOAc). $[\alpha]^{22}_D$ = –33.8 (*c* = 0.36, $CHCl_3$) {lit.:[5a] $[\alpha]^{18}_D$ –37 (c 0.26, $CHCl_3$)}. IR (KBr): ν = 2923 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.75 (dt, *J* = 15.2, 4.4 Hz, 1H, H-4), 2.96 (ddd, *J* = 15.2, 4.8, 4.8 Hz, 1H, H-4), 3.06 (ddd, *J* = 13.2, 8.8, 4.8 Hz, 1H, H-3), 3.24 (ddd, *J* = 13.2, 4.8 Hz, 1H, H-3), 3.65 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 6H, OCH_3), 5.00 (s, 1H, H-1), 6.27 (s, 1H, H-8), 6.62 (s, 1H, H-5), 6.79 (s, 1H, H-2'), 6.80 (s, 1H, H-6'), 6.82 (s, 1H, H-5') ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 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 yelow oil after flash chromatography using a cartridge containing amine functionalized silica (7:3 Et_2O–EtOAc). $[\alpha]^{22}_D$ = – 45.7 (*c* = 0.11, $CHCl_3$) {lit.:[16a] $[\alpha]_D$ –37.0 ($CHCl_3$)}. IR (KBr): ν = 2919 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 2.74 (dt, *J* = 15.6, 4.5, 3.9 Hz, 1H, H-4), 2.90-3.00 (m, 1H, H-4), 3.07 (ddd, *J* = 11.7, 7.8, 3.9 Hz, 1H, H-3), 3.26 (dt, *J* = 11.7, 5.1, 4.5 Hz, 1H, H-3), 3.68 (s, 3H, OCH_3), 3.81 (s, 6H, 2CH_3O), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.01 (s, 1H, H-1), 6.26 (s, 1H, H-8), 6.47 (s, 2H, H-2', H-6'), 6.63 (s, 1H, H-5) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 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 yelow oil after flash chromatography using a cartridge containing amine functionalized silica (8:2 to 1:1 hexane–EtOAc). $[\alpha]^{22}_D$ = –11.8 (*c* = 0.5, $CHCl_3$) {lit.:[18c] $[\alpha]^{22}_D$ –19.9 (*c* 1, $CHCl_3$)}. IR (KBr): ν = 2932 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.64-2.79 (m, 1H, H-3), 2.73 (ddd, *J* = 11.6, 6.0, 6.0 Hz, 1H, H-4), 2.86 (dd, *J* = 14.0, 9.5 Hz, 1H, CH_2Ar), 2.91 (ddd, *J* = 12.0, 6.0, 5.6 Hz, 1H, H-3), 3.15 (dd, *J* = 14.0, 4.5 Hz, 1H, CH_2Ar), 3.20 (ddd, *J* = 11.6, 11.6, 5.6 Hz, 1H, H-4), 3.80 (s, 1H, OCH_3), 3.82 (s, 1H, OCH_3), 3.86 (s, 1H, OCH_3), 4.11 (dd, *J* = 9.5, 4.5 Hz, 1H, H-1), 6.59 (s, 1H, H-8), 6.63 (s, 1H, H-5), 6.86 (d, *J* = 8.5 Hz, 2H, H-3'), 7.16 (d, *J* = 8.5 Hz, 2H, H-5') ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 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 colourless oil after flash chromatography (SiO_2 previously washed with 8:2 Et_3N-EtOAc; 8:2 to 1:1 Et_2O–EtOAc as eluent). $[\alpha]^{22}_D$ = – 23.4 (*c* = 0.25, $CHCl_3$). IR (KBr): ν = 2955 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.04-2.17 (m, 2H, CH_2), 2.66-2.89 (m, 4H, CH_2Ar, H-4), 3.02 (ddd, *J* = 12.0, 7.2, 5.6 Hz, 1H, H-3), 3.27 (ddd, *J* = 12.0, 5.6, 5.6 Hz, 1H, H-3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.00 (dd, *J* = 8.0, 2.8 Hz, 1H, H-1), 6.57 (s, 2H, H-5, H-8), 7.17-7.31 (m, 5H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 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]-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 ºC 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 ºC 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 chromatographed (Et_2O to 1:1 Et_2O–EtOAc) to afford tetrahydroisoquinoline **9** (144 mg, 87%). $[\alpha]^{22}_D = -37.1$ (*c* = 1.03, $CHCl_3$). IR (KBr): ν = 3399 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.26-1.31 (m, 1H, C1CH_2), 1.49-1.52 (m, 1H, OCH_2CH_2), 1.53-1.62 (m, 1H, CH_2CHO_2), 1.76-1.82 (m, 1H, CH_2CHO_2), 1.83-1.93 (m, 1H, OCH_2CH_2), 1.97-2.09 (m, 1H, C1CH_2), 2.27 (s, 1H, OH), 2.43 (dd, *J* = 17.0, 5.0 Hz, 1H, H-4), 2.97 (ddd, J = 17.0, 12.0, 6.0 Hz, 1H, H-4), 3.20 (dd, *J* = 13.5, 6.0 Hz, 1H, H-3), 3.31 (dd, *J* = 13.5, 5.0 Hz, 1H, H-3), 3.37 (dd, *J* = 9.6, 4.4 Hz, 1H, H-1), 3.64-3.67 (m, 2H, 2OCH_2CH_2), 3.68-3.73 (m, 1H, CHAr), 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.81-3.86 (m, 2H, 2OCH_2CH_2), 3.95 (dd, *J* = 10.8, 6.0 Hz, 1H, CH_2OH), 4.05 (dd, *J* = 10.8, 4.8 Hz, 1H, CH_2OH,), 4.40 (t, *J* = 4.8 Hz, 1H, CHO_2), 6.28 (s, 1H, H-8), 6.55 (s, 1H, H-5), 7.28-7.29 (m, 5H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): 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 days. The catalyst was removed by filtration, the solvent was concentrated under vacuum, and the resulting oil was chromatographed using a cartridge containing amine functionalized silica (1:1 hexane-EtOAc) to give crispine A (45 mg, 74%). $[\alpha]^{22}_D = -100.1$ (*c* = 0.32, $CHCl_3$) {lit.:[26] $[\alpha]^{22}_D$ –96 (*c* 0.25, $CHCl_3$)}. IR (KBr): ν = 2922 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.69-1.78 (m, 1H, H-1), 1.82-1.99 (m, 2H, H-2), 2.30-2.38 (m, 1H, H-1), 2.63 (ddd, *J* = 17.0, 8.0, 8.0 Hz, 1H, H-6), 2.69 (m, 1H, H-5), 2.74 (m, 1H, H-3), 3.00 (ddd, *J* = 12.4, 9.6, 5.6 Hz, 1H, H-3), 3.07 (ddd, *J* = 17.0, 8.0, 4.0 Hz, 1H, H-6), 3.18 (dddd, *J* = 17.2, 11.2, 6.4, 2.8 Hz, 1H, H-5), 3.49 (m, 1H, H-10b), 3.85 (s, 6H, OCH_3), 6.57 (s, 1H, H-10), 6.61 (s, 1H, H-7) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): 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.

Acknowledgments

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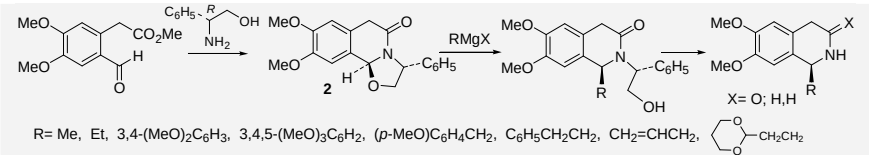

Tricyclic (*R*)-phenylglycinol–derived lactam **2** has proven to be a versatile scaffold that provides general access to enantiopure 1-substituted tetrahydroisoquinoline derivatives as well as more complex alkaloids, e.g. (–)-crispine A, bearing the tetrahydroisoquionoline moiety.

M. Amat,* V. Elias, N. Llor, F. Subrizi, E. Molins, J. Bosch ……..... Page No. – Page No.

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

Keywords: Alkaloids / Tetrahydroisoquinolines / Lactams / Phenylglycinol / α-Amidoalkylation