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Stereoselective Synthesis of *cis*-1,3-Dimethyltetrahydroisoquinolines. Formal Synthesis of Naphthylisoquinoline Alkaloids

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Dedicated to Prof. Miguel A. Miranda on the occasion of his 60th birthday

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A synthetic route to enantiopure *cis*-1,3-dimethyltetrahydroisoquinolines **9**, synthetic precursors of naphthylisoquinoline alkaloids, has been developed. The synthesis relies on the use of a phenylglycinol-derived lactam, **2**, as the starting enantiopure scaffold. After stereoselective opening of the oxazolidine ring, the C-3 methyl substituent was installed taking advantage of the lactam carbonyl group by stereoselective hydrogenation of an α-methyl enamide generated via a vinyl triflate.

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Introduction

The naphthylisoquinoline alkaloids[1] constitute a remarkable group of structurally diverse natural products with an unprecedented origin,[2] arising from acetate and malonate units rather than aromatic amino acids. Their characteristic substitution pattern includes a stereogenic biaryl axis and an unusual methyl substituent at the 3-position of the isoquinoline ring. They exhibit a broad spectrum of important biological activities, among them antimalarial, antileishmanial, antitrypanosomal, antitumor, and anti-HIV. Many of these alkaloids incorporate a 6,8-dioxygenated 1,3-dimethyltetrahydroisoquinoline moiety, in some cases with a 1,3-*cis* relative configuration, *e.g.* ancistrocline, ancistrobrevines A and D, korupensamine D, and ancistrotectorine (Figure 1). A few naphthalene-devoid 1,3-dimethyltetrahydroisoquinolines also occur in nature,[3] *e.g.* gentrymine A, the free heterocyclic half of ancistrobrevine D.

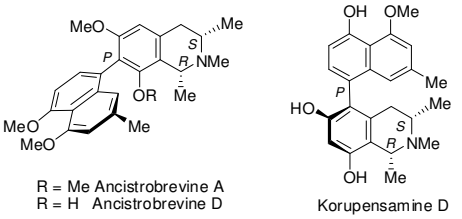
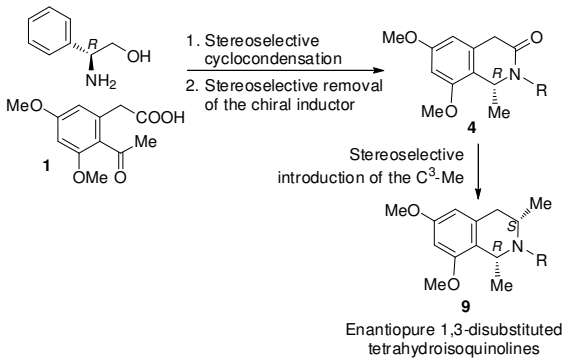


Figure 1. Naphthylisoquinoline alkaloids.

These alkaloids are usually assembled by the bond formation between the naphthalene and tetrahydroisoquinoline rings in the key synthetic step, so the development of efficient procedures for the stereocontrolled construction of these heterocyclic building blocks has received considerable attention. However, all previous synthetic approaches to *cis*-1,3-dimethyltetrahydroisoquinolines **9** involve the reduction ($NaBH_4$ or H_2, Pd/C) of the corresponding 3,4-dihydro derivatives,[4] usually prepared via a Bischler-Napieralski cyclization.[4a-d,f,g]

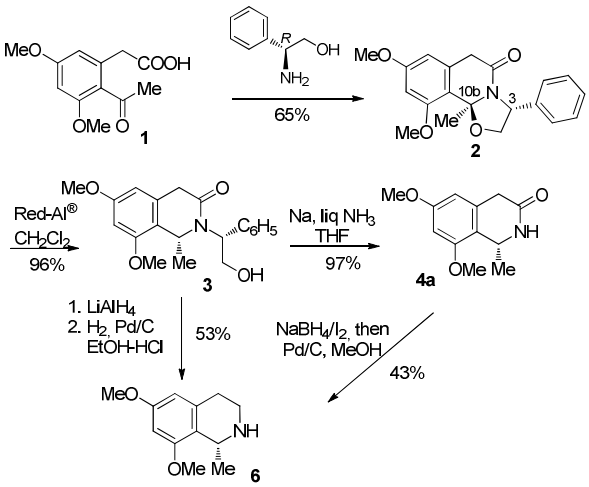
Results and Discussion

We herein report a practical procedure for the synthesis of enantiopure *cis*-1,3-dimethyltetrahydroisoquinolines. From the stereochemical standpoint, the synthesis involves two crucial steps: i) the stereoselective preparation of an enantiopure 1-methyl-3-oxotetrahydroisoquinoline derivative **4** by cyclocondensation of δ-keto acid **1** with (*R*)-phenylglycinol,[5] followed by removal of the chiral inductor from the resulting tricyclic lactam; and ii) the stereoselective introduction of the C-3 methyl substituent taking advantage of the lactam carbonyl group (Scheme 1).



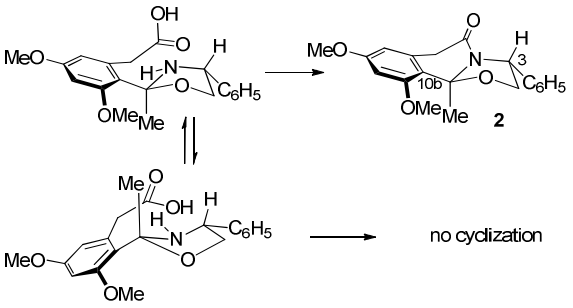
Scheme 1. Synthetic strategy.

In the reaction with 1,5-dicarbonyl derivative **1**,[6] (*R*)-phenylglycinol acts as a chiral latent form of ammonia, in a process that mimics the presumed biosynthetic origin of acetogenin isoquinoline alkaloids.[7] The cyclocondensation reaction furnished a single tricyclic lactam **2** (Scheme 2), whose absolute configuration was unambigously established by X-ray crystallographic analysis.[8]



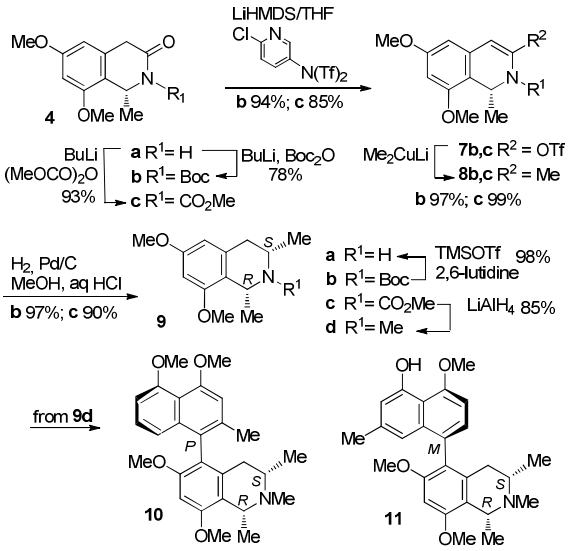
Scheme 2. Preparation of the key 1-methyl-3-oxotetrahydroisoquinoline intermediate **4a.**

A tentative explanation of the *trans* 3-H/10b-Me relative configuration is that the initially formed imine is in equilibrium with two diastereoisomeric oxazolidines and that the irreversible final lactamization occurs faster from the oxazolidine that allows a less hindered approach of the ester group to the nitrogen, as depicted in Scheme 3.



Scheme 3. Lactamization step.

The reductive opening of the oxazolidine ring was performed with Red-Al® and also took place in excellent yield with complete stereoselectivity (retention of configuration)[9] to give bicyclic lactam **3**. Subsequent treatment with sodium in liquid ammonia brought about the cleavage of the exocyclic C-N bond to give the key tetrahydroisoquinolone intermediate **4a**. A further reduction of **4a** with $NaBH_4/I_2$, followed by treatment with Pd/C in MeOH to cleave[10] the resulting *N*-epimeric mixture of amino-borane complexes, led to amine **6**, which was also prepared by $LiAlH_4$ reduction of **3** followed by debenzylation of the resulting tertiary amine **5**.

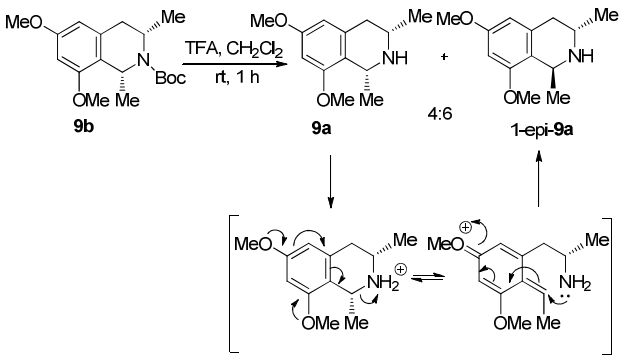


Scheme 4. Access to enantiopure *cis*-1,3-dimethyltetrahydroisoquinolines. Formal synthesis of the naphthylisoquinoline alkaloids **10**[17] and **11**.[18]

The stereoselective introduction of the C-3 substituent from lactam **4a** would be accomplished by hydrogenation of an α-substituted enamide generated by alkylation of the lactam carbonyl, once this was activated as a vinyl triflate.[11] To this end, lactam **4a** was converted to the *N*-protected derivatives **4b** and **4c** (Scheme 4). The *N*-acyl substituent would not only act as a protecting group but also increase the facial selectivity of the hydrogen uptake. The conversion of lactams **4b** and **4c** into the corresponding vinyl triflates **7b** and **7c** was satisfactorily accomplished with LiHMDS and Comins' triflating reagent.[12] A subsequent alkylation with lithium methylcuprate (generated *in situ* from MeLi and CuI), with final quenching with methyl iodide,[11] afforded the methylated enamides **8b** and **8c** in 72% and 81% overall yield, respectively, from **4a**.

Finally, catalytic hydrogenation of **8b** and **8c** under slightly acidic conditions (MeOH, 1.5 equiv of aq HCl, rt, 1 atm) using Pd/C as the catalyst took place with complete facial selectivity, leading to the respective *N*-acyl-1,3-*cis*-dimethyltetrahydroisoquinolines **9b** and **9c** in high yield.[13,14]

Unexpectedly, deprotection of the *N*-Boc derivative **9b** with TFA led to a 4:6 epimeric mixture of *cis* and *trans* derivatives **9a** and 1-*epi*-**9a**, presumably via a retro-Michael ring opening process favored by the methoxy groups, as outlined in Scheme 5.[15]



Scheme 5. Epimerization of 6,8-dioxygenated *cis*-1,3-disubstituted tetrahydroisoquinolines.

This problem was overcome by using TMSOTf/2,6-lutidine[16] (see Scheme 4), which allowed the *N*-Boc to be removed in high yield, leading to the *N*-unsubstituted 1,3-*cis* derivative **9a**, an early intermediate in a previous synthesis of korupensamine D.[4c,d] On the other hand, $LiAlH_4$ reduction of the *N*-methoxycarbonyl derivative **9c** led to the *N*-methyl-*cis*-tetrahydroisoquinoline **9d**. Comparison of the sign of the [α] value of **9d** with the one previously reported for this compound[17] confirmed the 1*R*,3*S* absolute configuration of our synthetic material. Taking into account previous transformations, the synthesis of tetahydroisoquinoline **9d** constitutes a formal synthesis of *O*-methylancistrocline (**10**)[17] and 5-*epi*-4'-*O*-demethyl-ancistrobertsonine C (**11**).[18]

Conclusions

In summary, we have reported a new strategy for the synthesis of enantiopure *cis*-1,3-dimethyltetrahydroisoquinolines based on the use of phenylglycinol-derived tricyclic lactam **2** as the starting enantiopure scaffold. After stereoselective opening of the oxazolidine ring, the *cis*-1,3 relative configuration is installed by stereoselective hydrogenation of an α–methyl enamide generated via a vinyl triflate.

Given that a variety of enantiopure 1-substituted 3-oxotetrahydroisoquinolines are easily available by cyclocondensation of 2-formylphenylacetic esters with phenylglycinol followed by α-amidoalkylation of the resulting tricyclic lactams,[19] the methodology here developed opens a general synthetic route to enantiopure *cis*-1,3-disubstituted tetrahydroisoquinolines.

Experimental Section

(3*R*,10b*S*)-8,10-Dimethoxy-10b-methyl-5-oxo-3-phenyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[2,3-*a*] isoquinoline (2). A solution of compound **1** (1.15 g, 4.81 mmol) and (*R*)-phenylglycinol (790 mg, 2.26 mmol) in toluene (40 mL) was refluxed for 22 h in a Dean-Stark system. The solvent was removed under reduced pressure and the residue was purified by flash chromatography under silica (hexane to 7:3 hexane-EtOAc) to afford compound **2** (1.06 g, 65%) as a brown solid. $[\alpha]^{22}_D = -211.1$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.72 (s, 3H, CH_3), 3.71 (d, *J* = 19.0 Hz, 1H, H-6), 3.77 (d, *J* = 19.0 Hz, 1H, H-6), 3.81 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 4.11 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2), 4.59 (t, *J* = 8.4 Hz, 1H, H-2), 5.33 (t, *J* = 8.0 Hz, 1H, H-3), 6.30 (d, *J* = 2.4 Hz, 1H, H-9), 6.45 (d, *J* = 2.4 Hz, 1H, H-7), 7.30 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 24.9 (CH_3), 37.9 (C-6), 55.3 (CH_3O), 56.0 (C-3), 58.2 (CH_3O), 70.4 (C-2), 95.1 (C-10b), 98.4 (C-9), 103.1 (C-7), 118.3 (C-6a), 125.6 (C-*m*), 127.2 (C-*p*), 128.6 (C-*o*), 132.3 (C-10a), 139.4 (C-*i*), 157.4 and 160.6 (C-*i*), 166.2 (CO) ppm. IR (KBr): ν = 1514, 1610, 1660, 2256, 2977 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{20}H_{21}NO_4$ $[M + H]^+$: 340.1549; found 340.1543.

(1*R*)-2-[(*R*)-2-Hydroxy-1-phenylethyl]-6,8-dimethoxy-1-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (3). Red-Al® (2 mL of a 65% solution in toluene, 6.5 mmol) was slowly added (10 min) to a cooled solution (– 78°C) of lactam **2** (220 mg, 0.65 mmol) in anhydrous CH_2Cl_2 (2 mL). The resulting solution was stirred at 0 °C for 1 h and poured into crushed-ice. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated. Flash chromatography (2:8 Et_2O-EtOAc) afforded compound **3** (212 mg, 96%) as a white solid. $[\alpha]^{22}_D = +13.9$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.10 (d, *J* = 6.4 Hz, 3H, CH_3), 3.56 (d, *J* = 18.8 Hz, 1H, H-4), 3.73 (s, 3H, CH_3O), 3.75 (d, *J* = 18.8 Hz, 1H, H-4), 3.77 (s, 3H, CH_3O), 4.10 (dd, *J* = 12.0, 4.4 Hz, 1H, C*H*$_2$OH), 4.28 (dd, *J* = 12.0, 7.6 Hz, 1H, C*H*$_2$OH), 4.71 (q, *J* = 6.4 Hz, 1H, H-1), 5.15 (dd, *J* = 7.6, 4.4 Hz, 1H, CHAr), 6.25 (d, *J* = 2.0 Hz, 1H, H-7), 6.30 (d, *J* = 2.0 Hz, 1H, H-5), 7.24-7.34 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 19.9 (CH_3), 38.2 (C-4), 51.0 (C-1), 55.3 ($2CH_3O$), 63.2 (CH_2OH), 63.7 (CHAr), 96.7 (C-7), 102.8 (C-5), 118.5 (C-4a), 127.5 (C-*p*), 127.8 (C-*o*), 128.4 (C-*m*), 133.4 (C-8a), 136.9 (C-*i*), 155.1 and 160.0 (C-*i*), 170.6 (CO) ppm. IR (KBr): ν = 1513, 1629, 2240, 3400 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{20}H_{23}NO_4$ $[M + H]^+$: 342.1699; found 342.1703.

(*R*)-6,8-Dimethoxy-1-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (4a). Into a three-necked round-bottomed flask equipped with a cold-finger condenser charged with dry ice-acetone was condensed NH_3 (35 mL) at –78 °C. The temperature was raised to –33 °C, and a solution of lactam **3** (322 mg, 0.94 mmol) in THF (3 mL) was added. Then, sodium metal was added in small portions until the blue color persisted. 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 CH_2Cl_2. The combined organic extracts were dried and concentrated to give a clear residue, which was purified by chromatography (EtOAc) to afford **4a** (201 mg, 97%) as a white solid; m. p. 168–171 ºC. $[\alpha]^{22}_D = -31.5$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.38 (d, *J* = 6.9 Hz, 3H, CH_3), 3.45 (d, *J* = 20.0 Hz, 1H, H-4), 3.65 (d, *J* = 20.0 Hz, 1H, H-4), 3.79 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 4.75-4.82 (m, 1H, H-1), 6.25 (d, *J* = 2.2 Hz, 1H, H-7), 6.34 (d, *J* = 2.2 Hz, 1H, H-5), 7.44 (br. s, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 23.4 (CH_3), 35.8 (C-4), 47.2 (C-1), 55.2 (CH_3O), 55.3 (CH_3O), 96.8 (C-7), 103.1 (C-5), 117.4 (C-4a), 132.9 (C-8a), 156.0 and 159.8 (C-*i*), 171.3 (CO) ppm. IR (KBr): ν = 1517, 1668, 2966, 3217 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{12}H_{15}NO_3$ $[M + H]^+$: 222.1124; found 222.1121.

(*R*)-2-(*tert*-Butoxycarbonyl)-6,8-dimethoxy-1-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (4b). *n*-BuLi (1.6 M in hexane, 0.28 mL, 0.45 mmol) was added to a solution of lactam **4a** (100 mg, 0.45 mmol) in THF (5 mL) at –78°C. After stirring for 20 min, the mixture was transferred *via cannula* into a cooled (–78°C) solution of di-*tert*-butyldicarbonate (142 mg, 0.68 mmol) in THF (2 mL). After stirring for 40 min, a saturated aqueous solution of NH_4Cl was added. The aqueous layer was extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (hexane to 7:3 hexane-EtOAc) to afford compound **4b** (112 mg, 78%) as a white oil. $[\alpha]^{22}_D = -55.4$ (*c* = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.41 (d, *J* = 6.6 Hz, 3H, CH_3), 1.56 [s, 9H, $C(CH_3)_3$], 3.58 (d, *J* = 19.5 Hz, 1H, H-4), 3.79 (s, 3H, CH_3O), 3.80 (d, *J* = 19.5 Hz, 1H, H-4), 3.83 (s, 3H, CH_3O), 5.64 (q, *J* = 6.6 Hz, 1H, H-1), 6.25 (d, *J* = 1.8 Hz, 1H, H-7), 6.36 (d, *J* = 1.8 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 20.3 (CH_3), 27.9 [$C(CH_3)_3$], 39.7 (C-4), 49.3

(C-1), 55.3 (2CH_3O), 82.9 [*C*(CH_3)$_3$], 96.7 (C-5), 102.6 (C-7), 117.9 (C-8a), 132.6 (C-4a), 152.0 (C-*i*), 155.5 (NCO), 160.1 (C-*i*), 169.4 (CO) ppm. IR (KBr): ν = 1441, 1502, 1606, 1710, 1776, 2957 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{17}H_{23}NO_5$ [M + H]$^+$: 322.1653; found 322.1649.

(*R*)-6,8-Dimethoxy-2-(methoxycarbonyl)-1-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (4c). Operating as in the above preparation of **4b**, from lactam **4a** (285 mg, 1.29 mmol) in THF (10 mL), *n*-BuLi (1.6 M in hexane, 0.81 mL, 1.29 mmol), and dimethyl dicarbonate (210 mg, 1.55 mmol) in THF (7 mL), tetrahydroisoquinoline **4c** (335 mg, 93%) was obtained as a white oil after flash chromatography (7:3 hexane-EtOAc). [α]$^{22}_D$ = – 65.4 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.42 (d, *J* = 6.4 Hz, 3H, CH_3), 3.62 (d, *J* = 19.2 Hz, 1H, H-4), 3.79 (s, 3H, CH_3O), 3.82 (d, *J* = 19.2 Hz, 1H, H-4), 3.83 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 5.73 (q, *J* = 6.4 Hz, 1H, H-1), 6.26 (d, *J* = 1.6 Hz, 1H, H-7), 6.36 (d, *J* = 1.6 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 20.3 (CH_3), 39.7 (C-4), 50.5 (C-1), 53.9 (CO_2CH_3), 55.4 (2CH_3O), 96.9 (C-5), 102.7 (C-7), 117.7 (C-8a), 132.4 (C-4a), 154.4 (NCO), 155.6 and 160.4 (C-*i*), 169.6 (CO) ppm. IR (KBr): ν = 1439, 1503, 1606, 1710, 1776, 2843, 2956 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{14}H_{17}NO_5$ [M + H]$^+$: 280.1177; found 280.1179.

(1*R*)-6,8-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (6). *Method A.* A solution of iodine (114 mg, 0.45 mmol) in THF (2 mL) was slowly added to a cooled (0 ºC) suspension of $NaBH_4$ (42.7 mg, 1.13 mmol) in anhydrous THF (2.5 mL), and the mixture was stirred at this temperature for 5 min (until the solution became colorless). Then, a solution of lactam **4a** (100 mg, 0.45 mmol) in THF (2 mL) was added to the solution (0 ºC). The resulting mixture was refluxed for 20 h and cooled to 0ºC. MeOH (5 mL) was slowly added, and the stirring was continued at rt for 30 min. The solvent was evaporated, and the resulting solid was digested with 2 N aqueous KOH (30 min). The resulting suspension was extracted with CH_2Cl_2 and the combined organic extracts were dried and concentrated. The resulting residue was dissolved in MeOH (2 mL) and stirred for 12 h in the presence of 5% Pd/C (15 mg, 55% wet). The suspension was filtered, and the filtrate was concentrated. Column chromatography (SiO_2 previously washed with TEA; 95:5 CH_2Cl_2–MeOH to 90:5:5 CH_2Cl_2–MeOH–TEA as eluent) of the residue afforded an oil (61 mg), which was dissolved in CH_2Cl_2 (8 mL). The solution was washed with saturated aqueous $NaHCO_3$, dried, filtered, and evaporated to afford **6** as a yellow oil (40 mg, 43%).

Method B. $LiAlH_4$ (90 mg, 2.4 mmol) was added to a solution of lactam **3** (200 mg, 0.6 mmol) in THF (5 mL) at 0°C. The mixture was stirred at rt for 2.5 h, cooled to 0°C, and quenched with MeOH, water, and 10% aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. Column chromatography (15:85 hexane/EtOAc) of the residue afforded **(1*R*)-2-[(*R*)-2-hydroxy-1-phenylethyl]-6,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline** (**5**; 110 mg, 56%) as a dark yellow oil. [α]$^{22}_D$ = –39.2 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.36 (d, *J* = 6.8 Hz, 3H, CH_3), 2.58 (m, 2H, H-4), 2.65 (m, 1H, H-3), 3.10 (m, 1H, H-3), 3.75 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 3.84 (m, 2H, C*H*$_2$OH), 3.88 (m, 1H, CHAr), 4.23 (q, *J* = 6.4 Hz, 1H, H-1), 6.19 (s, 1H, H-7), 6.27 (s, 1H, H-5), 7.24-7.34 (m, 5H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 20.3 (CH_3), 27.9 (C-4), 39.7 (C-3), 49.0 (C-1), 55.1 (CH_3O), 55.2 (CH_3O), 62.0 (CH_2OH), 64.7 (CHAr), 96.4 (C-5), 103.9 (C-7), 120.9 (C-8a), 127.6 (C-*p*), 128.2 (C-*o*), 128.7 (C-*m*), 136.5 (C-4a), 138.7 (C-*i*), 157.3 and 158.5 (C-*i*) ppm. IR (KBr): ν = 3417, 2936 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{20}H_{25}NO_3$ [M + H]$^+$: 328.1907; found: 328.1904. A solution of the above amine (110 mg, 0.34 mmol) in EtOH (7.4 mL), 1 N aqueous HCl (739 µl), and 5% Pd/C (226 mg, 55% wet) was hydrogenated at room temperature and atmospheric pressure for 6 h. The catalyst was removed by filtration, the solvent was evaporated, and the resulting residue was washed with 1 N aqueous HCl and extracted with Et_2O. The aqueous phase was basified with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a residue, which was chromatographed (SiO_2 previously washed with TEA; 95:5 CH_2Cl_2–MeOH to 90:5:5 CH_2Cl_2–MeOH–TEA as eluent) to afford **6** (66 mg, 94%) as a dark yellow oil. [α]$^{22}_D$ = + 10.3 (*c* = 1.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.39 (d, *J* = 6.6 Hz, 3H, CH_3), 2.40 (br. s, 1H, NH), 2.66 (dt, *J* = 16.5, 3.9 Hz, 1H, H-4), 2.80 (dq, *J* = 16.5, 10.2, 6.3 Hz, 1H, H-4), 3.03 (dq, *J* = 13.2, 5.7, 3.3 Hz, 1H, H-3), 3.21 (dq, *J* = 13.2, 9.9, 5.1 Hz, 1H, H-3), 3.77 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 4.24 (q, *J* = 6.6 Hz, 1H, H-1), 6.22 (d, *J* = 2.4 Hz, 1H, H-7), 6.29 (d, *J* = 2.4 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 20.8 (CH_3), 29.7 (C-4), 37.9 (C-3), 46.3 (C-1), 55.0 (CH_3O), 55.1 (CH_3O), 96.3 (C-5), 104.3 (C-7), 121.7 (C-8a), 136.0 (C-4a), 157.1 and 158.5 (C-*i*) ppm. IR (KBr): ν = 2935, 1606 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{12}H_{17}NO_2$ [M + H]$^+$: 208.1332; found: 208.1332.

(*R*)-2-(*tert*-Butoxycarbonyl)-6,8-dimethoxy-1,3-dimethyl-1,2-dihydroisoquinoline (8b). LiHMDS (1 M in THF, 0.47 mL, 0.47 mmol) was slowly added to a solution of lactam **4b** (100 mg, 0.31 mmol) in THF (1 mL) at –78°C. After stirring for 3.5 h, a cooled solution (– 78°C) of 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (183 mg, 0.47 mmol) in THF (4 mL) was added *via cannula*, and the mixture was stirred at rt for 16 h. EtOAc (35 mL) was added, and the organic layer was washed with water, dried, filtered, and concentrated. The resulting residue was chromatographed (95:5 hexane-EtOAc) to give **(*R*)-2-(*tert*-butoxycarbonyl)-6,8-dimethoxy-1-methyl-3-(trifluoromethylsulphonyloxy)-1,2-dihydro-isoquinoline** (**7b**; 130 mg, 94%) as a yellow oil. [α]$^{22}_D$ = – 30.3 (*c* = 1.85, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.24 (d, *J* = 7.0 Hz, 3H, CH_3), 1.50 [s, 9H, C(CH_3)$_3$], 3.80 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 5.80 (q, *J* = 7.0 Hz, 1H, H-1), 6.10 (s, 1H, H-4), 6.32 (d, *J* = 2.4 Hz, 1H, H-7), 6.40 (d, *J* = 2.4 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 18.3 (CH_3), 27.9 [C(*C*H$_3$)$_3$], 49.7 (C-1), 55.4 (CH_3O), 55.5 (CH_3O), 83.3 [*C*(CH_3)$_3$], 98.6 (C-7), 102.1 (C-5), 106.3 (C-4), 117.3 (C-8a), 116.8 (*C*F$_3$), 118.4 (q, *J* = 320.9 Hz, C*F*$_3$), 129.7 (C-3), 139.1 (C-4a), 151.4 (NCO), 155.4 and 160.0 (C-*i*) ppm. IR (KBr): ν = 1459, 1501, 1607, 1718, 1770, 2976 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{18}H_{22}F_3NO_7S$ [M + H]$^+$: 454.1147; found 454.1142. MeLi (1.6 M in THF, 47 µl, 0.76 mmol) was added to a suspension of CuI (102.8 mg, 0.54 mmol) in THF (2.3 mL) at 0°C. After stirring for 20 min, the mixture was transferred *via cannula* into a cooled (0°C) solution of the above triflate (70 mg, 0.15 mmol) in THF (1.2 mL). The mixture was stirred for 3.5 h, quenched with MeI (29 µl, 0.462 mmol), and stirred at rt for 40 min. The solvent was

evaporated, the residue was taken up with EtOAc (30 mL) and washed with a saturated aqueous solution of NH_4Cl. The organic layer was dried, filtered, and concentrated. Flash chromatography (CH_2Cl_2) of the residue afforded **8b** (48.4 mg, 97%) as a green oil. $[\alpha]^{22}_D$ = – 331.1 (*c* = 0.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.15 (d, *J* = 6.8 Hz, 3H, CH_3), 1.49 [s, 9H, $C(CH_3)_3$], 2.21 (s, 3H, CCH_3), 3.77 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 5.68 (q, *J* = 6.8 Hz, 1H, H-1), 5.83 (s, 1H, H-4), 6.18 (d, *J* = 2.4 Hz, 1H, H-7), 6.29 (d, *J* = 2.4 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 18.3 (CH_3), 22.4 (CCH_3), 28.3 [$C(CH_3)_3$], 46.8 (C-1), 55.3 (CH_3O), 55.4 (CH_3O), 80.8 [$C(CH_3)_3$], 96.6 (C-7), 100.1 (C-5), 112.8 (C-4), 116.8 (C-8a), 132.3 (C-3), 135.4 (C-4a), 152.8 (NCO), 155.2 and 159.5 (C-8) ppm. IR (KBr): ν = 1441, 1603, 1640, 1712, 2956 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{18}H_{25}NO_4$ $[M + H]^+$: 320.1862; found 320.1856.

(*R*)-6,8-Dimethoxy-2-(methoxycarbonyl)-1,3-dimethyl-1,2-dihydroisoquinoline (8c). Operating as in the above preparation of **7b**, from a solution of lactam **4c** (300 mg, 1.07 mmol) in THF (3.5 mL), LiHMDS (1 M in THF, 1.61 mL, 1.61 mmol) and 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine in THF (12.5 mL), **(*R*)-6,8-dimethoxy-2-(methoxycarbonyl)-1-methyl-3-(trifluoromethylsulfonyloxy)-1,2-dihydroisoquinoline** (**7c**; 375 mg, 85%) was obtained as a yellow oil after flash chromatography (hexane to 85:15 hexane-EtOAc). $[\alpha]^{22}_D$ = –157.6 (*c* = 1.18, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.28 (d, *J* = 6.4 Hz, 3H, CH_3), 3.79 (s, 3H, CO_2CH_3), 3.82 (s, 6H, $2CH_3O$), 5.84 (q, *J* = 6.4 Hz, 1H, H-1), 6.17 (s, 1H, H-4), 6.33 (d, *J* = 2.0 Hz, 1H, H-7), 6.41 (d, *J* = 2.0 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 18.2 (CH_3), 50.2 (C-1), 53.6 (CO_2CH_3), 55.4 (CH_3O), 55.5 (CH_3O), 98.8 (C-7), 102.3 (C-5), 106.9 (C-4), 116.8 (C-8a), 116.9 (CF_3), 118.4 (q, *J* = 320.1 Hz, CF_3), 129.5 (C-3), 138.4 (C-4a), 153.3 (NCO), 155.3 and 160.0 (C-8) ppm. IR (KBr): ν = 1439, 1502, 1612, 1729, 1776, 2850, 2927, 2956 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{15}H_{16}F_3NO_7S$ $[M + H]^+$: 412.0677; found 412.0672. Following the procedure reported in the preparation of **8b**, from the above vinyl triflate (270 mg, 0.66 mmol) in THF (5 mL), MeLi (1.6 M in THF, 2 mL, 3.2 mmol), CuI (438 mg, 2.3 mmol) in THF (10 mL), and MeI (0.12 mL, 1.97 mmol), compound **8c** (180 mg, 99%) was obtained after flash chromatography (CH_2Cl_2). $[\alpha]^{22}_D$ = – 327.7 (*c* = 1.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.18 (d, *J* = 6.4 Hz, 3H, CH_3), 2.24 (s, 3H, CCH_3), 3.75 (s, 3H, CH_3O), 3.77 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 5.71 (q, *J* = 6.4 Hz, 1H, H-1), 5.89 (d, *J* = 1.2 Hz, 1H, H-4), 6.18 (d, *J* = 2.4 Hz, 1H, H-7), 6.29 (d, *J* = 2.4 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 18.3 (CH_3), 21.8 (CCH_3), 47.2 (C-1), 52.7 (CO_2CH_3), 55.3 ($2CH_3O$), 96.8 (C-5), 100.4 (C-7), 113.6 (C-4), 116.5 (C-8a), 132.1 (C-3), 135.1 (C-4a), 154.2 (NCO), 155.1 (C-6), 159.6 (C-8) ppm. IR (KBr): ν = 1321, 1442, 1603, 1643, 1713, 2842, 2957 cm^{-1}. HRMS (ESI-TOF) calcd. for $C_{15}H_{19}NO_4$ $[M + H]^+$: 278.1388; found 278.1387.

(1*R*,3*S*)-2-(*tert*-Butoxycarbonyl)-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydro isoquinoline (9b). A solution of **8b** (43 mg, 0.14 mmol) in MeOH (8 mL), 2 N aqueous HCl (105 µl), and 5% Pd/C (21 mg, 55% wet) was hydrogenated at rt and atmospheric pressure for 6 h. The catalyst was removed by filtration and the solvent was evaporated. The resulting residue was diluted in CH_2Cl_2 (15 mL) and the solution was washed with water. The organic layer was dried and concentrated to give **9b** (44 mg, 97%). $[\alpha]^{22}_D$ = – 29.9 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.33 (d, *J* = 6.6 Hz, 3H, CH_2CHCH_3), 1.40 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 1.48 [s, 9H, $C(CH_3)_3$], 2.68 (dd, *J* = 15.9, 6.9 Hz, 1H, H-4), 2.94 (dd, *J* = 15.9, 6.9 Hz, 1H, H-4), 3.78 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 3,.80 (br. s, 1H, H-3), 5.68 (q, *J* = 6.6 Hz, 1H, H-1), 6.26 (d, *J* = 2.4 Hz, 1H, H-7), 6.32 (d, *J* = 2.4 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 14.1 (CH_2CHCH_3), 22.6 ($CHCH_3$), 28.5 [$C(CH_3)_3$], 31.9 (C-4), 35.4 (C-1), 46.8 (C-3), 55.2 (CH_3O), 55.3 (CH_3O), 79.2 [$C(CH_3)_3$], 96.6 (C-7), 112.8 (C-5), 132.3 (C-8a), 154.8 (C-4a), 156.3 (NCO), 159.1 (2C-*i*) ppm. IR (KBr): ν = 1458, 1609, 1690, 2853, 2925, 2940 cm^{-1}. EM (IQ^+): m/z (%) = 306 (11), 265 (6), 264 (35), 251 (15), 250 (100), 220 (10), 207 (5), 206 (39), 191(4), 190 (9), 176 (4), 57 (11). HRMS (ESI-TOF) calcd. for $C_{18}H_{28}NO_4$ $[M + H]^+$: 322.2013; found 322.1999.

(1*R*,3*S*)-6,8-Dimethoxy-2-(methoxycarbonyl)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (9c). Operating as described in the preparation of **9b**, from **8c** (100 mg, 0.36 mmol) in MeOH (10 mL), 2 N aqueous HCl (270 µl), 5% of Pd/C (35 mg, 55% wet), compound **9c** (90 mg, 90%) was obtained. $[\alpha]^{22}_D$ = + 13.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.27 (d, *J* = 6.8 Hz, 3H, CH_2CHCH_3), 1.34 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 2.62 (dd, *J* = 16.0, 6.4 Hz, 1H, H-4), 2.87 (dd, *J* = 16.0, 6.8 Hz, 1H, H-4), 3.65 (s, 3H, CO_2CH_3), 3.71 (s, 3H, CH_3O), 3.72 (s, 3H, CH_3O), 4.31 (br. s, 1H, H-3), 5.31 (br. s, 1H, H-1), 6.19 (d, *J* = 2.4 Hz, 1H, H-7), 6.25 (d, *J* = 2.4 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 20.6 ($CHCH_3$), 21.7 (CH_2CHCH_3), 35.2 (C-4), 45.9 (C-1), 46.3 (C-3), 52.4 (CO_2CH_3), 55.2 ($2CH_3O$), 96.4 (C-5), 104.1 (C-7), 118.9 (C-8a), 134.7(C-4a), 156.2 (NCO), 159.2 (2C-*i*) ppm. HRMS (ESI-TOF) calcd. for $C_{15}H_{21}NO_4$ $[M + H]^+$: 280.1543; found 280.1548.

(1*R*,3*S*)-6,8-Dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (9a). 2,6-Lutidine (56 mg, 0.48 mmol) and TMSOTf (65 µl, 0.36 mmol) were sequentially added to a solution of tetrahydroisoquinoline **9b** (37 mg, 0.12 mmol) in dry CH_2Cl_2 (308 µl), and the mixture was stirred at 0°C for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, dried, and concentrated to give **9a** as yellow oil (27 mg, 98%). $[\alpha]^{22}_D$ = + 73.0 (*c* = 0.44, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.23 (d, *J* = 6.4 Hz, 3H, CH_2CHCH_3), 1.44 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 1.70 (br. s, 1H, NH), 2.46 (dd, *J* = 15.2, 11.2 Hz, 1H, H-4), 2.63 (dd, *J* = 15.6, 2.4 Hz, 1H, H-4), 2.88 (m, 1H, H-3), 3.78 (s, 6H, $2CH_3O$), 4.24 (q, *J* = 6.4 Hz, 1H, H-1), 6.21 (d, *J* = 2.0 Hz, 1H, H-7), 6.32 (d, *J* = 2.4 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ 22.2 (CH_2CHCH_3), 22.7 ($CHCH_3$), 39.7 (C-4), 48.3 (C-1), 49.4 (C-3), 55.0 (CH_3O), 55.2 (CH_3O), 96.7 (C-5), 104.4 (C-7), 121.1 (C-8a), 137.9 (C-4a), 157.9 and 158.5 (C-*i*) ppm. HRMS (ESI-TOF) calcd. for $C_{13}H_{19}NO_2$ $[M + H]^+$: 222.1489; found 222.1489.

(1*R*,3*S*)-6,8-Dimethoxy-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (9d). $LiAlH_4$ (20 mg, 0.53 mmol) was added to a solution of the carbamate **9c** (35 mg, 0.13 mmol) in THF (1.3 mL) at 0°C. The mixture was stirred at rt for 1 h and then

heated to reflux. After 3.5 h, it was cooled to 0 °C and quenched with water. After evaporation of the volatile components, the residue was diluted with CH_2Cl_2 and washed with brine. The organic extract was dried, filtered, and concentrated to give **9d** (26 mg, 85%) as pale yellow oil. $[\alpha]^{22}_D$ = + 123 (*c* = 1.0, $CHCl_3$) [Lit[17] $[\alpha]^{19}_D$ = + 120 (*c* = 1.08, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR, 25 ºC): δ = 1.21 (d, *J* = 6.4 Hz, 3H, CH_2CHCH_3), 1.36 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 2.42 (masked m, 1H, H-3), 2.45 (s, 3H, NCH_3), 2.53 (dd, *J* = 15.2, 10.4, 0.8 Hz, 1H, H-4), 2.68 (ddd, *J* = 15.2, 2.0 Hz, 1H, H-4), 3.62 (q, *J* = 6.4 Hz, 1H, H-1),3.78 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 6.22 (d, *J* = 2.4 Hz, 1H, H-7), 6.31 (d, *J* = 2.4 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 21.2 (CH_3), 22.5 (CH_3), 39.1 (CH_3), 41.1 (C-4), 55.0 (CH_3O), 55.1 (CH_3O), 55.2 (C-1), 56.9 (C-3), 96.5 (C-5), 103.5 (C-7), 121.2 (C-8a), 137.6 (C-4a), 157.0 and 158.4 (C-*i*) ppm. HRMS (ESI-TOF) calcd. for $C_{14}H_{21}NO_2$ $[M + H]^+$: 236.1645; found 236.1639.

Methyl *N*-[2-(3,5-dimethoxy-2-ethylphenyl)-1-methylethyl]carbamate (12). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC): δ = 1.08 (t, *J* = 7.2 Hz, 3H, CH_3CH_2); 1.14 (d, *J* = 6.4 Hz, 3H, $CHCH_3$); 2.59 (dd, *J* = 13.6, 8.4 Hz, 1H, H-2); 2.63 (q, *J* = 7.2 Hz, 2H, CH_3CH_2); 2.92 (dd, *J* = 13.6, 5.6 Hz, 1H, H-2); 3.65 (s, 3H, CO_2CH_3); 3.77 (s, 3H, CH_3O); 3.79 (s, 3H, CH_3O); 3.93 (br. a, 1H, H-1); 4.63 (br. s, 1H, NH), 6.29 (d, *J* = 2.4 Hz, 1H, H-6'); 6.35 (d, *J* = 2.4 Hz, 1H, H-4') ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 ºC): δ = 14.6 (CH_3CH_2); 18.8 (CH_3CH_2); 20.4 ($CHCH_3$); 40.1 (C-2); 48.0 (C-1); 51.8 (CO_2CH_3); 55.2 (CH_3O); 55.3 (CH_3O); 96.8 (C-4'); 106.3 (C-6'); 124.0 (C-2'); 137.3 (C-1'); 156.3 (NHCO); 158.0 (C-3'); 158.6 (C-5'). EM (IQ^+) m/z (%): 283 (14), 282 (96), 280 (4), 253 (1), 250 (6).

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of compounds **2**-**9** and **12**, and X-ray crystallographic data for compound **2**.

Acknowledgments

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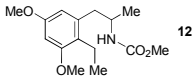
[14] a) Reduction of the double bond of enamides **8b** and **8c** with Et_3SiH/ TFA[14b] (rt, 3 h) was not satisfactory from the stereochemical standpoint as it led to mixtures of *cis*/*trans* isomers (with Boc deprotection from **8b**). This was initally attributed to a low facial selectivity in the generation of the C-3 stereocenter. However, epimerization at C-1 can also occur in the presence of TFA (see below in the main text). The isolation (33%) of the ring opening product **12** in the reduction of **8c** confirms this interpretation. b) For the stereoselective reduction of 1,2-dihydroisoquinolines to *cis*-1,3-substituted tetrahydroisoquinolines under ionic hydrogenation conditions, see: P. Magnus, K. S. Matthews, V. Lynch, *Org. Lett*. **2003**, *5*, 2181–2184.



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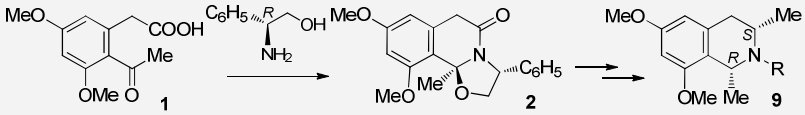

An efficient stereoselective synthesis of enantiopure *cis*-1,3-dimethyltetrahydro-isoquinolines **9,** synthetic precursors of naphthylisoquinoline alkaloids, from the easily accessible phenylglycinol-derived tricyclic lactam **2** is reported.

((Key Topic))

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Stereoselective Synthesis of *cis*-1,3-Dimethyltetrahydroisoquinolines. Formal Synthesis of Naphthylisoquinoline alkaloids

Keywords: Asymmetric synthesis / Lactams / Nitrogen heterocycles / Alkaloids / Total synthesis