Stereoselective Total Synthesis of Enantiomerically Pure 1-Trifluoromethyl Tetrahydroisoquinoline Alkaloids

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Enantiomerically pure 1-trifluoromethyl-tetrahydroisoquinoline alkaloid analogues, in which C-1 is a quaternary stereogenic centre, have been synthesized by stereoselective intramolecular Pictet-Spengler reaction of the *N*-arylethyl γ-trifluoro-β-iminosulfoxide (*R*)-**3**, and subsequent elaborations of the sulfinyl auxiliary. The absolute stereochemistry of the stereogenic centre was determined by X-ray diffraction on the α-phenylpropionic ester (1*R*,2′*S*)-**10**.

The stereocontrolled synthesis of quaternary stereogenic centres is a major accomplishment in modern organic chemistry[1]. Particularly challenging is the stereoselective approach to structures bearing a trifluoromethyl-substituted tertiary aminic function, owing to the additional difficulties connected with the selective introduction of fluorine, and to the biological interest of α-trifluoromethyl−amino compounds, such as amino acids, amino alcohols, and amino sugars[2].

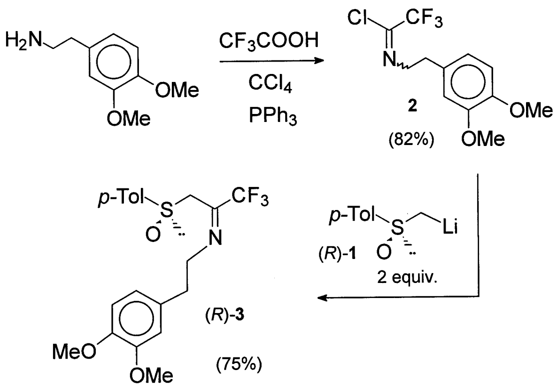
The potential biological interest of synthetic 1-trifluoromethyl analogues of tetrahydroisoquinoline alkaloids, which have never been described in enantiomerically pure form, stimulated us to undertake the synthesis of these intriguing frameworks. In fact, only one report describing the preparation of racemic 1-methoxycarbonyl-1-trifluoromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline appeared in literature[3]. It is worth noting that fluorine-free natural tetrahydroisoquinolines in which C-1 is a quaternary stereogenic centre have been reported to feature very interesting biological properties. In spite of this, only a handful of enantioselective syntheses of compounds belonging to the class of 1,1-disubstituted tetrahydroisoquinoline alkaloids have been accomplished[4]. Among them, recent reports by the group of Corey described the stereoselective synthesis of the spyro-tetrahydroisoquinoline unit of the antitumor marine-derived molecule ecteinascidin 743[5].

Results and Discussion

Our strategy for the stereoselective construction of the quaternary α-trifluoromethyltetrahydroisoquinoline framework takes advantage of the sulfinyl group, used as a removable stereocontrolling agent, as well as an activating moiety for the introduction of an oxygen functionality, such as a hydroxyl or a carbonyl[6].

The β-iminosulfoxide (*R*)-**3** was envisioned to function as the key intermediate (Scheme 1)[7]. This compound was obtained by condensation between 2 equiv. of lithiated methyl *p*-tolylsulfoxide (*R*)-**1** and the trifluoroacetimidoyl chloride **2**, which was prepared by the Uneyama's one-pot procedure[8] from 2-(3,4-dimethoxyphenyl)ethylamine, trifluoroacetic acid (TFA), and CCl_4, in the presence of PPh_3. The excess of sulfoxide (*R*)-**1** was recovered unchanged in almost quantitative yield by flash chromatography of the crude reaction mixture.

Scheme 1. Preparation of the β-iminosulfoxide (*R*)-**3**



The β-iminosulfoxide (*R*)-**3**, a crystalline compound that can be stored for several months at 4°C without decomposition, exists as a single imine geometric isomer, most probably with (*Z*) geometry, namely with the sulfinylmethyl and the *N*-arylethyl groups in *cis* configuration with respect to the C=N bond, in analogy with closely related *N*-substituted γ-trifluoro-β-iminosulfoxides, which have been recently investigated[9]. The targeted 1-trifluoromethyltetrahydroisoquinoline framework was obtained by intramolecular Pictet-Spengler reaction[10] of the β-iminosulfoxide (*R*)-**3**

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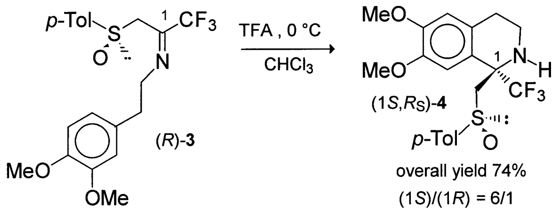
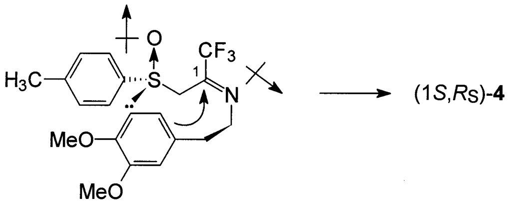
(Scheme 2), promoted by an excess of TFA in $CHCl_3$ at 0°C. The desired 1-trifluoromethyl-1-sulfinylmethyltetrahydroisoquinoline **4** was produced in 74% yield and in diastereomeric ratio $(1S,R_S)/(1R,R_S) = 6:1$, determined by ^{19}F-NMR and HPLC analysis of the crude reaction mixture.

Scheme 2. The Pictet-Spengler reaction



The reaction is irreversible and kinetically controlled, as demonstrated by the fact that increasing the reaction time from ca. 20 min to 1 hour, no change of diastereoselectivity was observed. Further evidence was obtained by re-submitting both the pure diastereomers $(1R,R_S)$- and $(1S,R_S)$-**4** to the exact reaction conditions for 1 hour: as expected, no interconversion between diastereoisomers, and therefore no epimerization of the stereocentre C-1, was observed by ^{1}H- and ^{19}F-NMR analysis of the crude reaction mixtures. The good diastereoselectivity of this intramolecular Pictet-Spengler reaction could possibly be explained considering that, due to the *cis* geometry of the C=N bond of the substrate (*R*)-**3**, the electronrich 3,4-dimethoxyphenyl group and the stereogenic *p*-tolylsulfinyl group should be spatially close to each other. Thus the sulfinyl auxiliary can exert a strong stereodirecting effect on the ring closure (Figure 1), through the reactive conformation which minimizes the dipole-dipole interactions between the S=O and C=N bonds[11]. The attack of the 3,4-dimethoxyphenyl group is thus induced to the less hindered *Re* face of the stabilized carbocation C-1 formed via protonation of the imine nitrogen of (*R*)-**3** by TFA.

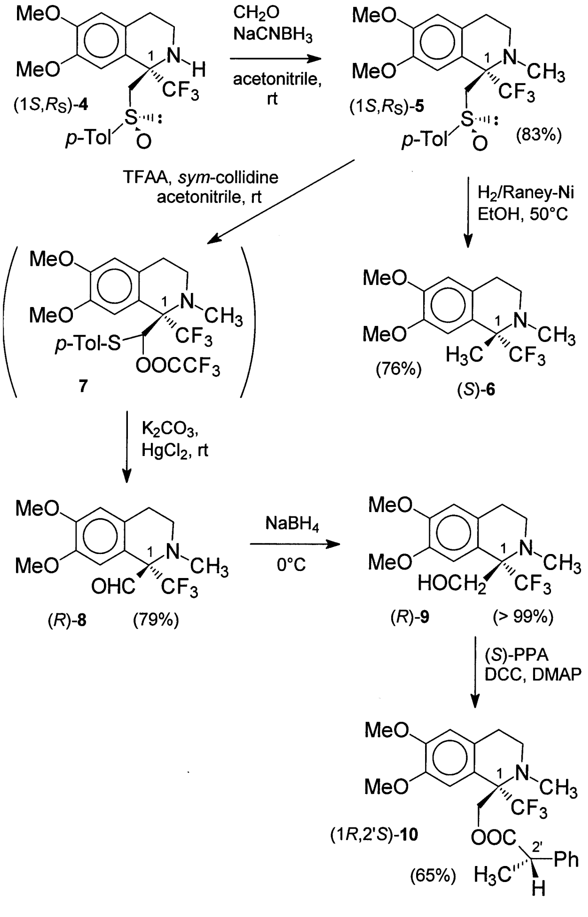
Figure 1. A model for the diastereofacial selectivity



On the other hand, the high reactivity of the β-iminosulfoxide (*R*)-**3**, which is somewhat unusual for the Pictet-Spengler reaction of ketimines[12], can be attributed to the electronwithdrawing effect of the trifluoromethyl group, which strongly increases the electrophilic character of the iminic carbon C-1.

Next, the major diastereomeric sulfoxide $(1S,R_S)$-**4** was submitted to *N*-methylation (Scheme 3). The desired transformation was successfully achieved according to the Borch reductive procedure, by treatment of $(1S,R_S)$-**4** with aqueous formaldehyde and $NaCNBH_3$ in acetonitrile (83%)[13].

Scheme 3. Synthesis of the sulfur-free 1-trifluoromethyl tetrahydroisoquinoline alkaloid analogs



With the *N*-methyl β-aminosulfoxide $(1S,R_S)$-**5** in hand we addressed the preparation of sulfur free analogues of 1-trifluoromethyltetrahydroisoquinoline alkaloids. Hydrogenolysis of the sulfinyl auxiliary with Raney-Ni/H_2 provided 1-trifluoromethylcarnegine (*S*)-**6** in 76% yield[14].

Substitution of the sulfinyl group of $(1S,R_S)$-**5** with an oxygen functionality was achieved by means of the Pummerer rearrangement[15]. Treatment of $(1S,R_S)$-**5** with trifluoroacetic anhydride and *sym*-collidine in acetonitrile at 0°C produced the expected intermediate α-trifluoroacetoxysulfide **7**, which was not isolated, but hydrolized in situ to the desired aldehyde (*R*)-**8** by treatment with $K_2CO_3/HgCl_2$ at room temperature (79% overall yield). The aldehyde (*R*)-**8**, which is a stable compound that can be stored neat at 4°C for several months and handled at room temperature without any decomposition, was reduced in quantitative yields with $NaBH_4$ at 0°C, affording *N*-methyl-1-trifluoromethylcalycotomine (*R*)-**9**[16]. Esterification of (*R*)-**9** with both enantiomers of α-phenylpropionic acid and analysis of the resulting crude reaction mixtures by ^{1}H- and ^{19}F NMR evidenced its enantiomeric purity. Finally, the stereochemistry of the quaternary trifluoromethyl substituted stereogenic centre C-1 was unequivocally determined by X-ray diffraction of a single crystal of (1*R*,2′*S*)-**10**, obtained by esterification of *N*-methyl-1-trifluoromethylcalycotomine (*R*)-**9** with (+)-(*S*)-α-phenylpropionic acid (65% yield).

Figure 2. ORTEP view of **10** showing the atomic labelling scheme. 20% Thermal ellipsoids for non-hydrogen atoms are shown

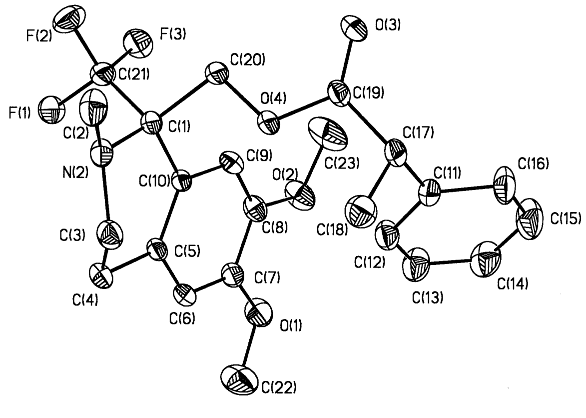


Table 1. Selected bond lengths and angles of **10**

Bond lengths [Å]			
C(1)−C(21)	1.524(4)	N(2)−C(3)	1.453(4)
C(1)−C(10)	1.542(4)	C(3)−C(4)	1.496(4)
C(1)−C(20)	1.552(3)	C(4)−C(5)	1.493(4)
C(1)−N(2)	1.467(4)		
Bond angle [°]			
N(2)−C(1)−C(10)	113.3(2)	C(5)−C(10)−C(1)	121.3(2)
N(2)−C(3)−C(4)	110.4(3)	C(3)−N(2)−C(1)	116.7(2)
C(5)−C(4)−C(3)	109.2(2)	C(3)−N(2)−C(2)	109.4(3)
C(10)−C(5)−C(4)	120.0(2)	C(1)−N(2)−C(2)	117.3(2)
Torsion angles [°]			
C(20)−C(1)−N(2)−C(3)	−105.8(3)	N(2)−C(1)−C(10)−C(5)	9.7(3)
C(21)−C(1)−N(2)−C(2)	−89.6(3)	C(10)−C(1)−N(2)−C(3)	20.3(3)
C(20)−C(1)−N(2)−C(2)	26.8(3)	C(1)−N(2)−C(3)−C(4)	−55.9(3)
C(21)−C(1)−C(10)−C(5)	−106.1(3)	N(2)−C(3)−C(4)−C(5)	59.8(3)
C(20)−C(1)−C(10)−C(5)	138.0(2)	C(3)−C(4)−C(5)−C(10)	−31.4(4)
C(12)−C(11)−C(17)−C(19)	−66.3(4)	C(4)−C(5)−C(10)−C(1)	−2.9(4)
C(11)−C(17)−C(19)−O(4)	88.3(3)		

A view of (1*R*,2′*S*)-**10** is shown in Figure 2, while selected molecular dimensions are reported in Table 1. Bond lengths and angles values fall in the expected range[17]. The six-member ring adopts an envelope conformation with C(3) displaced out of the mean plane of the other five atoms by 0.678 Å. This ring conformation would not seem the most likely, but it was already reported in a natural compound with a similarly constrained ring[18]. C(2) and C(20) are quite close (2.843 Å), due to the narrow endocyclic torsion angle around the C(1)−N(2) bond (20.3°).

The N(2) atom is pyramidal and there is no evidence of significant inversion disorder. This is probably due to steric interactions with the trifluoromethyl group: in fact relatively close intramolecular C2···F2 non-bonded distances (2.956 Å) are observed even in this more favourable arrangement.

Concluding Remarks

We have reported the first strategy for the stereocontrolled total synthesis of enantiopure 1-trifluoromethyltetrahydroisoquinoline units. This protocol features both good stereoselectivity and chemical yields, providing a practical entry to an unprecedented class of alkaloid analogues, like 1-trifluoromethylcarnegine (*S*)-**6** and *N*-methyl 1-trifluoromethylcalycotomine (*R*)-**9**, whose biological properties are currently under investigation.

Experimental Section

General: ^{1}H, ^{19}F, and ^{13}C nuclear magnetic resonance samples were prepared as dilute solutions in $CDCl_3$ and spectra recorded on Bruker spectrometers: ARX 400, AC 250L, or AC 200. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as internal standard (δ_H and δ_C = 0.00) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as external standard (δ_F = −162.90) for ^{19}F nuclei. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m. − $[\alpha]_D^{20}$ values were taken on a Jasco-Dip and on a W. Kernchen Propol polarimeters. − IR spectra were registered on a Perkin Elmer System 2000 FT-IR spectrophotometer. − Mass spectra were registered on a Hitachi-Perkin-Elmer ZAB 2F instrument. Run times (t_r) of diastereomers **4** were determined on a Waters 600E HPLC instrument, using LiChrosorb Si60 (5 μm) prepacked columns (Merck) and HPLC-grade *n*-hexane/ethyl acetate as eluents. − Anhydrous THF was distilled from sodium and benzophenone. In all other cases commercially available reagent-grade solvents were employed without purification. Reactions performed in dry solvents were carried out in nitrogen atmosphere. − Melting points are uncorrected and were obtained on a capillary apparatus. − Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230−400 ASTM mesh) was employed for column chromatography. − Combustion microanalyses were performed by Redox SNC, Cologno M. (Milano).

Synthesis of N-[2-(3,4-Dimethoxyphenyl)ethyl]-2,2,2-trifluoroacetimidoyl Chloride **2**: In a cooled (0°C) two necked flask equipped with a condenser and a loading funnel, were charged respectively triphenylphosphine (10.36 g, 39.5 mmol), carbon tetrachloride (6.35 ml, 65.8 mmol), triethylamine (2.2 ml, 15.8 mmol), and trifluoroacetic acid (0.98 ml, 13.15 mmol) under stirring. The reaction mixture was stirred 10 min at the same temperature. Then, 2.72 ml (15.8 mmol) of 2-(3,4-dimethoxyphenyl)ethylamine dissolved in 6.35 ml of carbon tetrachloride, were added dropwise and the resulting reaction mixture was heated at reflux for 3 h. After evaporation of the solvent, the solid residue was extracted with *n*-hexane (15 ml), the suspension filtered and the solid phase washed again with *n*-hexane (4 × 10 ml). The collected organic phases were evaporated and the residue purified by flash-chromatography (F.C.) (eluent mixture *n*-hexane/ethyl acetate from 9:1 to 7:3) giving 3.2 g (82% yield) of product **2** as a viscous oil: R_f (*n*-hexane/ethyl acetate, 70:30) 0.56. − ^{1}H NMR ($CDCl_3$) δ 6.83−6.74 (m, 3 H), 3.90-3.80 (m, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.96 (t, *J* = 7.3 Hz, 2 H). − ^{13}C NMR ($CDCl_3$) δ 148.8, 147.7, 132.3 (q, *J* = 42.8 Hz), 131.0, 120.7, 116.4 (q, *J* = 276.4 Hz), 112.0, 111.2, 55.8, 55.6, 55.0, 34.7. − ^{19}F NMR ($CDCl_3$) δ −72.8 (s). − IR (neat) ṽ (cm^{-1}): 2939, 1702, 1518, 1264, 1157.

Synthesis of 2-N-[2-(3,4-Dimethoxyphenyl)ethyl]imino-1-(p-tolyl)sulfinyl-3,3,3-trifluoropropane (*R*)-**3**: A solution of trifluoroacetimidoyl chloride **2** (1.94 g, 6.55 mmol) in THF (5 ml) was added dropwise at −78 °C to a solution of the lithium derivative of methyl-*p*-tolylsulfoxide (*R*)-**1** (2.02 g, 13.1 mmol) [generated in THF (20 ml), at the same temperature, by action of LDA, preformed by treatment of 2.04 ml (14.4 mmol) of diisopropylamine with 5.76 ml (14.4 mmol) of a 2.5 M *n*-hexane solution of *n*-butyllithium] stirred under nitrogen. After 10 min at the same temperature the reaction was quenched with an excess of an aqueous solution of ammonium chloride, the layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic layers were dried over anhydrous sodium sulfate and, after removal of the solvent under reduced pressure, the crude was purified by F.C. (*n*-hexane/ethyl acetate from 30:20 to 45:55 with 10% of triethylamine), giving 2.03 g of (*R*)-**3** (75% yield) and 1.0 g of sulfoxide (*R*)-**1** used in excess (99%). (*R*)-**3**: R_f (1:1 *n*-hexane/ethyl acetate with 10% of triethylamine) 0.57; m.p. ($i\mathrm{Pr_2O}$) 105−106°C; $[\alpha]_D^{20}$ +130.1 (*c* 0.86, $\mathrm{CHCl_3}$). − ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.48 (d, *J* = 8 Hz, 2 H), 7.33 (d, *J* = 8 Hz, 2 H), 6.79−6.67 (m, 3 H), 3.88−3.75 (m, 1H), 3.84 (s, 6 H), 3.75 (d, *J* = 13.1 Hz, 1 H), 3.68−3.54 (m, 1 H), 3.43 (d, *J* = 13.1 Hz, 1 H), 2.99−2.81 (m, 2 H), 2.42 (s, 3 H). − ^{13}C NMR ($\mathrm{CDCl_3}$) δ 149.5 (q, *J* = 34.2 Hz), 148.6, 147.4, 142.6, 139.6, 131.4, 130.1, 123.6, 120.6, 118.9 (q, *J* = 279 Hz), 112.1, 111.0, 55.7, 55.5, 54.5, 54.0, 35.6, 21.3. − ^{19}F NMR ($\mathrm{CDCl_3}$) δ −73.1 (s). − IR (KBr) ṽ (cm^{-1}): 2938, 1523, 1238, 1196, 1050. − MS (EI) (*m/z*): 413 (32) [M$^+$], 397 (55), 151 (100), 91 (58). − $\mathrm{C_{20}H_{22}F_3NO_3S}$: C 58.09, H 5.37, N 3.39; found: C 58.08, H 5.39, N 3.42.

Synthesis of the 6,7-Dimethoxy-1-(p-tolylsulfinyl)methyl-1-trifluoromethyl-1,2,3,4-tetrahydroisoquinolines ($1S,R_S$)- *and* ($1R,R_S$)-**4**: The starting material (s.m.) (*R*)-**3** (1 g, 2.42 mmol) was dissolved in chloroform (4 ml) and the solution was cooled at 0°C. Trifluoroacetic acid (1.49 ml, 19.35 mmol) was added in one portion to the solution, under stirring. The reaction mixture was left at 0°C until disappearance of the s.m., as revealed by t.l.c. analysis (70:30 *n*-hexane/ethyl acetate with 10% of triethylamine), for a standard time of 20−30 min, then it was quenched with an ammonia aqueous solution (ca. 15%) until pH 8 was reached. The layers were separated, the organic one was washed first with water, then with brine and finally dried over anhydrous sodium sulfate. Afterwards, the solvent was removed under reduced pressure and the crude, containing a 6:1 mixture of diastereomers (1*S*)/(1*R*), was purified by F.C. (*n*-hexane/ethyl acetate from 75:25 to 65:35 with 10% of triethylamine), giving diastereomerically pure products ($1S,R_S$)- and ($1R,R_S$)-**4** (74% overall yield).

($1S,R_S$)-**4** *(major):* t_r 13 min and 34 sec (45:55 *n*-hexane/ethyl acetate, 1.2 ml/min); R_f (1:1 *n*-hexane/ethyl acetate with 10% of triethylamine) 0.5; m.p. ($i\mathrm{Pr_2O}$/ethyl acetate) 139−142°C; $[\alpha]_D^{20}$ +38.4 (*c* 0.41, $\mathrm{CHCl_3}$). − ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.57 (d, *J* ca. 8 Hz, 2 H), 7.32 (d, *J* ca. 8 Hz, 2 H), 6.79 (br signal, 1H), 6.64 (s, 1 H), 3.87 (s, 3H), 3.84 (s, 3 H), 3.43 (d, *J* = 13.3 Hz, 1 H), 3.29 (d, *J* = 13.3 Hz, 1 H), 3.27−3.11 (m, 2 H), 2.96−2.67 (m, 2H), 2.69 (br s, 1 H), 2.41 (s, 3 H). − ^{13}C NMR ($\mathrm{CDCl_3}$) δ 149.2, 147.4, 142.2, 141.8, 130.04, 129.95, 126.7 (q, *J* = 290.3 Hz), 124.2, 121.5, 111.9, 110.0, 65.8, 61.2 (q, *J* = 25.4 Hz), 56.2, 55.8, 39.0, 29.2, 21.4. − ^{19}F NMR ($\mathrm{CDCl_3}$) δ −74.1 (s). − IR (KBr) ṽ (cm^{-1}): 3433, 1524, 1384, 1146. − MS (EI) (*m/z*): 414 (22) [M$^+$+1], 139 (100), 140 (24). − $\mathrm{C_{20}H_{22}F_3NO_3S}$: C 58.09, H 5.37, N 3.39; found: C 58.03, H 5.14, N 3.16.

($1R,R_S$)-**4** *(minor):* t_r 9 min and 36 sec (45:55 *n*-hexane/ethyl acetate, 1.2 ml/min); R_f (1:1 *n*-hexane/ethyl acetate with 10% of triethylamine) 0.55; oil; $[\alpha]_D^{20}$ +79.16 (*c* 1.9, $\mathrm{CHCl_3}$). − ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.34 and 7.27 (m, 4 H), 6.72 (s, 1 H), 6.67 (br signal, 1 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 3.47 (d, *J* = 13.5 Hz, 1 H), 3.28 (br signal, 1 H), 3.22 (d, *J* = 13.5 Hz, 1 H), 3.07−2.67 (m, 4 H), 2.40 (s, 3 H). − ^{13}C NMR ($\mathrm{CDCl_3}$) δ 149.2, 147.4, 141.9, 141.4, 131.7, 130.0, 126.4 (q, *J* = 290.2 Hz), 123.8, 121.1, 112.1, 110.0, 67.2, 60.8 (q, *J* = 25.9 Hz), 56.0, 55.9, 39.5, 29.2, 21.3. − ^{19}F NMR ($\mathrm{CDCl_3}$) δ −75.8 (s).

Reductive Methylation of ($1S,R_S$)-**4**. − *Synthesis of the N-Methyl-6,7-dimethoxy-1-(p-tolylsulfinyl)methyl-1-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline* ($1S,R_S$)-**5**: To a solution of s.m. ($1S,R_S$)-**4** (745 mg, 1.8 mmol), dissolved in acetonitrile (8 ml), were added 1.8 ml (23.43 mmol) of a 36% aqueous solution of formaldehyde and 155 mg (2.34 mmol) of sodium cyanoborohydride, under stirring. After 30 min at r.t., the pH was adjusted to neutrality by dropwise addition of glacial acetic acid. The reaction mixture was allowed to stay overnight under stirring at r.t. A mixture of a 2 N aqueous solution of sodium hydroxide (8 ml) and chloroform (5 ml) was added to the residue obtained after evaporation of acetonitrile. The layers were separated and the aqueous one was washed with chloroform (3 × 15 ml). The collected organic layers, washed with brine, were dried over anhydrous sodium sulfate, and the residue obtained after solvent evaporation was purified by F.C. (benzene/acetone from 85:15 to 70:30) giving 638 mg (83% yield) of ($1S,R_S$)-**5**: R_f (benzene/acetone, 40:10) 0.38; m.p. ($i\mathrm{Pr_2O}$) 134−136°C; $[\alpha]_D^{20}$ −51.5 (*c* 0.3, $\mathrm{CHCl_3}$). − ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.57 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.01 (br signal, 1 H), 6.65 (s, 1 H), 3.92 (d, *J* = 13.7 Hz, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.54 (d, *J* = 13.7 Hz, 1 H), 3.36−3.20 (m, 1 H), 3.14−3.01 (m, 1 H), 2.85−2.78 (m, 1 H), 2.75−2.65 (m, 1 H), 2.41 (s, 3 H), 2.22 (q, J_{HF} = 3.1 Hz, 3 H). − ^{13}C NMR ($\mathrm{CDCl_3}$) δ 149.2, 147.1, 142.6, 141.6, 129.9, 129.8, 126.9 (q, *J* = 299.7 Hz), 124.8, 121.3, 111.6 (q, *J* = 3.7 Hz), 111.2, 63.72 (q, *J* = 3.1 Hz), 63.70 (q, *J* = 22.2 Hz), 56.2, 55.7, 47.5, 39.4, 28.9, 21.4. − ^{19}F NMR ($\mathrm{CDCl_3}$) δ −67.4 (br signal). − IR (KBr) ṽ (cm^{-1}): 2958, 1523, 1220, 1135.5, 1103.4. − MS (EI) (*m/z*): 428 (15) [M$^+$+1], 358 (32), 274 (36), 219 (100). − $\mathrm{C_{21}H_{24}F_3NO_3S}$: C 59.00, H 5.66, N 3.28; found: C 58.88, H 5.66, N 3.33.

Synthesis of 1-Trifluoromethylcarnegine (*S*)-**6**: To the s.m. ($1S,R_S$)-**5** (109 mg, 0.25 mmol), dissolved in absolute ethanol (3 ml), was added Raney-Ni (ca. 0.8 g) in a refrigerant equipped flask. The slurry was heated at 50 °C and vigorously stirred under hydrogen atmosphere. After 35 min t.l.c. analysis (*n*-hexane/ethyl acetate, 70:30) showed the complete disappearance of s.m. Raney-Ni was filtered on a Celite pad and washed twice with ethyl acetate. The solvent was removed under reduced pressure and the crude was purified by F.C. (*n*-hexane/ethyl acetate from 85:15 to 70:30), giving 55 mg (76% yield) of (*S*)-**6**: R_f (*n*-hexane/ethyl acetate, 40:10) 0.38; m.p. ($i\mathrm{Pr_2O}$) 85−87°C; $[\alpha]_D^{20}$ −37.1 (*c* 0.15, $\mathrm{CHCl_3}$). − ^{1}H NMR ($\mathrm{CDCl_3}$) δ 6.90 (br signal, 1 H), 6.58 (s, 1 H), 3.86 (s, 6 H), 3.28−3.16 (m, 1 H), 2.90−2.70 (m, 3 H), 2.62 (s, 3 H), 1.65 (s, 3 H). − ^{13}C NMR ($\mathrm{CDCl_3}$) δ 148.5, 147.0, 129.4, 128.0 (q, *J* = 292.1 Hz), 125.5, 111.4, 111.0, 62.3 (q, *J* = 24.0 Hz), 56.1, 55.7, 48.5, 39.7, 28.0, 20.0. − ^{19}F NMR ($\mathrm{CDCl_3}$) δ −72.5 (br signal). − IR (KBr) ṽ (cm^{-1}): 1612.5, 1520, 1141, 1109. − MS (EI) (*m/z*): 289 (3) [M$^+$], 220 (100), 204 (40). − $\mathrm{C_{14}H_{18}F_3NO_2}$: C 58.11, H 6.27, N 4.84; found: C 58.28, H 6.35, N 4.71.

Synthesis of N-Methyl-6,7-dimethoxy-1-formyl-1-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (*R*)-**8**: To a cooled (0°C) solution of s.m. ($1S,R_S$)-**5** (670 mg, 1.57 mmol) and *sym*-collidine (457 µl, 3.45 mmol) in 15 ml of acetonitrile, stirred under nitrogen atmosphere, 444 µl (3.14 mmol) of trifluoroacetic anhydride were added dropwise. After ca. 20 min (reaction monitored by t.l.c. using *n*-hexane/ethyl acetate, 70:30), the pH was adjusted approximatively to neutrality with solid potassium carbonate, and then 639 mg (2.35

mmol) of mercuric chloride were added to the suspension. After 2.5 h at r.t. (the reaction was monitored by t.l.c. during this time) the reaction mixture was centrifuged, the solid phase washed with acetonitrile (2 × 5 ml) and the collected organic phases evaporated under reduced pressure. The crude was purified by flash-chromatography (*n*-hexane/ethyl acetate from 80:20 to 70:30) giving 376 mg (79% yield) of (*R*)-**8**: R_f (*n*-hexane/ethyl acetate, 70:30) 0.45; m.p. (iPr$_2$O) 88−91°C; $[\alpha]_D^{20}$ +132.7 (*c* 0.41, CHCl$_3$). − ^{1}H NMR (CDCl$_3$) δ 9.06 (q, *J* = 3.93 Hz, 1H), 6.70 (s, 1 H), 6.64 (br signal, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.37−3.25 (m, 1 H), 3.11−2.94 (m, 2 H), 2.82−2.74 (m, 1 H), 2.71 (q, *J* = 2.8 Hz, 3 H). − ^{13}C NMR (CDCl$_3$) δ 193.9, 149.9, 147.2, 130.2, 125.7 (q, *J* = 296.4 Hz), 115.6, 112.0, 111.8 (q, *J* = 3.7 Hz), 71.9 (q, *J* = 22.2 Hz), 56.0, 55.8, 46.2, 41.5, 28.6. − ^{19}F NMR (CDCl$_3$) δ −65.1 (br signal). − IR (KBr) ṽ (cm^{-1}): 2962, 1735, 1518, 1144. − MS (EI) (*m/z*): 303 (1) [M$^+$], 274 (100), 275 (15). − $C_{14}H_{16}F_3NO_3$: C 55.43, H 5.32, N 4.62; found: C 55.13, H 5.32, N 4.48.

Synthesis of N-Methyl-1-trifluoromethylcalycotomine (*R*)-**9**: To a solution of s.m. (*R*)-**8** (100 mg, 0.33 mmol) in ethanol (5 ml) cooled at 0°C, 14 mg (0.37 mmol) of sodium borohydride were added portionwise. After 5 min the reaction mixture was concentrated under reduced pressure, then a 1 N aqueous solution of HCl was added until almost neutral pH was reached, and the resulting mixture was extracted with ethyl acetate (3 × 10 ml). The collected organic layers were washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The residue obtained after removal of the solvent was purified by F.C. (*n*-hexane/ethyl acetate from 30:20 to 1:1), giving a quantitative yield of the reduction product (*R*)-**9**: R_f (*n*-hexane/ethyl acetate, 70:30) 0.13; m.p. (iPr$_2$O) 92−94°C; $[\alpha]_D^{20}$ −107.1 (*c* 0.21, CHCl$_3$). − ^{1}H NMR (CDCl$_3$) δ 6.94 (br signal, 1 H), 6.60 (s, 1 H), 4.17 (d, *J* = 11.0 Hz, 1 H), 4.02 (d, *J* = 11.0 Hz, 1 H), 3.86 (s, 6 H), 3.40−3.30 (m, 1 H), 3.05−2.91 (m, 2 H), 2.74−2.64 (m, 1 H), 2.71 (q, *J* = 2.8 Hz, 3 H), 2.39 (br signal, 1 H). − ^{13}C NMR (CDCl$_3$) δ 149.0, 147.3, 130.6, 127.3 (q, *J* = 295.7 Hz), 121.5, 111.3, 110.5 (q, *J* = 3.7 Hz), 66.3 (q, *J* = 22.18 Hz), 61.0, 56.0, 55.7, 47.7, 39.2, 28.7. − ^{19}F NMR (CDCl$_3$) δ −66.9 (br signal). − IR (KBr) ṽ (cm^{-1}): 3531, 2939, 1523, 1132. − MS (EI) (*m/z*): 306 (3) [M$^+$+1], 305 (2) [M$^+$], 274 (100). − $C_{14}H_{18}F_3NO_3$: C 55.06, H 5.95, N 4.59; found: C 55.46, H 6.12, N 4.23.

Synthesis of the (+)-(S)-α-Phenylpropionic Ester of N-Methyl-1-trifluoromethylcalycotomine (1*R*,2′*S*)-**10**: To a solution of s.m. (*R*)-**9** (30 mg, 0.1 mmol) in dry dichloromethane (1.5 ml) stirred at r.t., were added respectively 15 mg of (+)-(*S*)-α-phenylpropionic acid (0.1 mmol), 21 mg (0.1 mmol), of DCC and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine. A t.l.c. control (*n*-hexane/ethyl acetate, 30:20) after 30 min showed the absence of s.m. The reaction mixture was diluted with diethyl ether, filtered, the solid residue washed with ether, and the solvent was removed under reduced pressure. The crude was purified by F.C. (40:10 *n*-hexane/ethyl acetate) giving 28.5 mg of product (1*R*,2′*S*)-**10** (65% yield): $[\alpha]_D^{20}$ +16.4 (*c* 0.57, CHCl$_3$). − ^{1}H NMR (CDCl$_3$) δ 7.23−7.17 (m, 3 H), 7.05−7.02 (m, 2 H), 6.82 (br signal, 1 H), 6.59 (s, 1 H), 4.92 (d, *J* = 7.7 Hz, 1 H), 4.60 (d, *J* = 7.7 Hz, 1 H), 3.90 (s, 3 H), 3.76 (s, 3 H), 3.56 (q, *J* = 4.4 Hz, 1 H), 3.01−2.96 (m, 1 H), 2.86−2.72 (m, 2 H), 2.67−2.59 (m, 1 H), 2.56 (s, 3 H), 1.34 (d, *J* = 4.6 Hz, 3 H). − ^{19}F NMR (CDCl$_3$) δ −72.8 (br signal).

X-ray Crystal Structure Determination of (1*R*,2′*S*)-**10**[19]: Crystals of (1*R*,2′*S*)-**10**, suitable for X-ray diffraction were obtained by crystallization from diisopropyl ether. *Crystal data*: $C_{23}H_{26}O_4F_3N$, *M* = 437.45. Monoclinic, *a* = 17.923(2), *b* = 7.301(1), *c* = 17.794(1) Å, β = 103.77(1)°, *V* = 2261.5(4) Å^3, space group *C*2, *Z* = 4, D_x = 1.285 Mg/m^3, μ = 0.879 mm^{-1}, *F*(000) = 920. Colorless prismatic crystal, dimensions: 0.8 × 0.6 × 0.3 mm.

Data Collection: Siemens P4 diffractometer, θ−2θ scan technique, graphite monochromated Cu-*K*α radiation; 3401 reflections measured (5.12<θ<57.28, +*h*, +*k*, +*l* and −*h*, −*k*, −*l*), 3035 unique. 3 standard reflections measured every 100 reflections showed no significant decay. Data were corrected for Lorentz and polarization effects, while no absorption correction was deemed necessary.

Structure Analysis and Refinement: The crystal structure was solved by direct methods (SHELXTL[20]), and refined by full-matrix least squares on F^2 values (SHELXL-97[21]). Non-hydrogen atoms were refined with anisotropic temperature factors. Hydrogen atoms were included at calculated positions and refined in the riding mode. Final value of the residual *R* and *wR*2 [for 2998 reflections with $I>2\sigma(I)$] were respectively 0.0424 and 0.1244. The highest peak in final difference-Fourier map was 0.167 eÅ^{-3}. The refined value of Flack's *x* parameter[22] was 0.10(19) and suggests the correct absolute configuration, known because enantiomerically pure (*S*)-α-phenylpropionic acid was used in the synthesis. In the absence of substantial anomalous scatterers this confirms the good quality of the data.

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