JOC The Journal of Organic Chemistry

Article

Synthesis of Tetrahydroisoquinoline Alkaloids and Related Compounds Through the Alkylation of Anodically Prepared alpha-Amino nitriles.

Lotfi Benmekhbi, Fadila Louafi, Thierry Roisnel, and Jean-Pierre Hurvois

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01419 • Publication Date (Web): 13 Jul 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

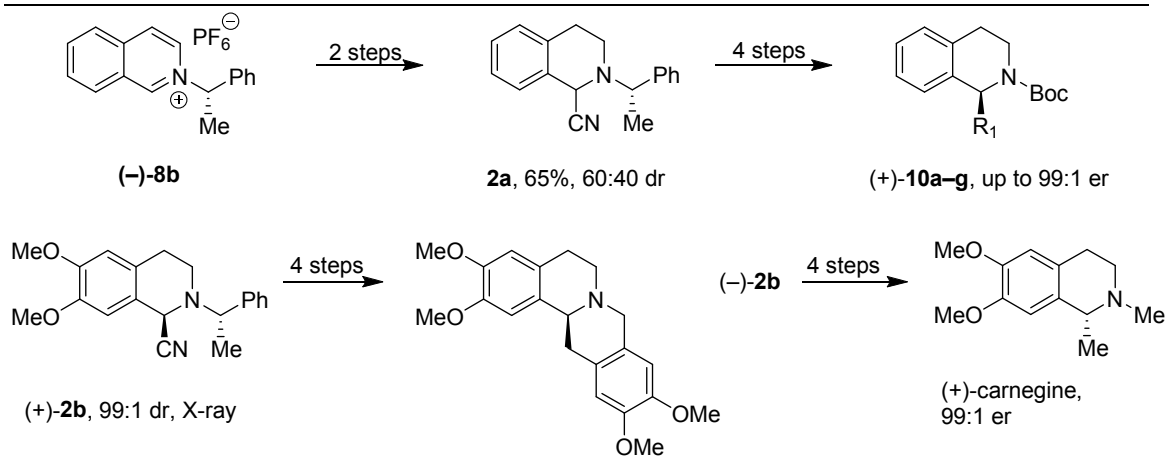
Synthesis of Tetrahydroisoquinoline Alkaloids and Related Compounds Through the Alkylation of Anodically Prepared α-Amino nitriles.

Lotfi Benmekhbi,[§] Fadila Louafi,[†] Thierry Roisnel,[‡] Jean-Pierre Hurvois.[‡]*

[§]Laboratoire de Chimie des Matériaux, Faculté des Sciences Exactes, Université de Constantine1, route de Ain El Bey, 25000 Constantine, Algérie

[†]Unité de Recherche CHEMS, Faculté des Sciences Exactes, Université de Constantine1, route de Ain El Bey, 25000 Constantine, Algérie

[‡]Sciences Chimiques de Rennes, UMR 6226, CNRS–Université de Rennes 1, 2 Avenue Léon Bernard, 35043, Rennes Cedex, France.



α-Amino nitrile **2a** was conveniently prepared in two individual steps from chiral hexafluorophosphate salt isoquinolinium (–)-**8b** including anodic cyanation as an efficient mean to activate the sp^3 C1–H bond of the THIQ nucleus. The lithiation of **2a** was carried out in THF at –80 °C in the presence of LDA to produce a stable α-amino carbanion which was condensed on a large variety of alkyl halides. The resulting quaternary α-amino nitriles were subjected to a stereoselective reductive decyanation in ethanol in the presence of $NaBH_4$ as the hydride donor to yield *N*-Boc-1-alkyl-THIQs (+)-**10a–g** in up to 97:3 er's after removal of the chiral auxiliary group. Examination of the ORTEP view of THIQ (+)-**1f** revealed that the newly created

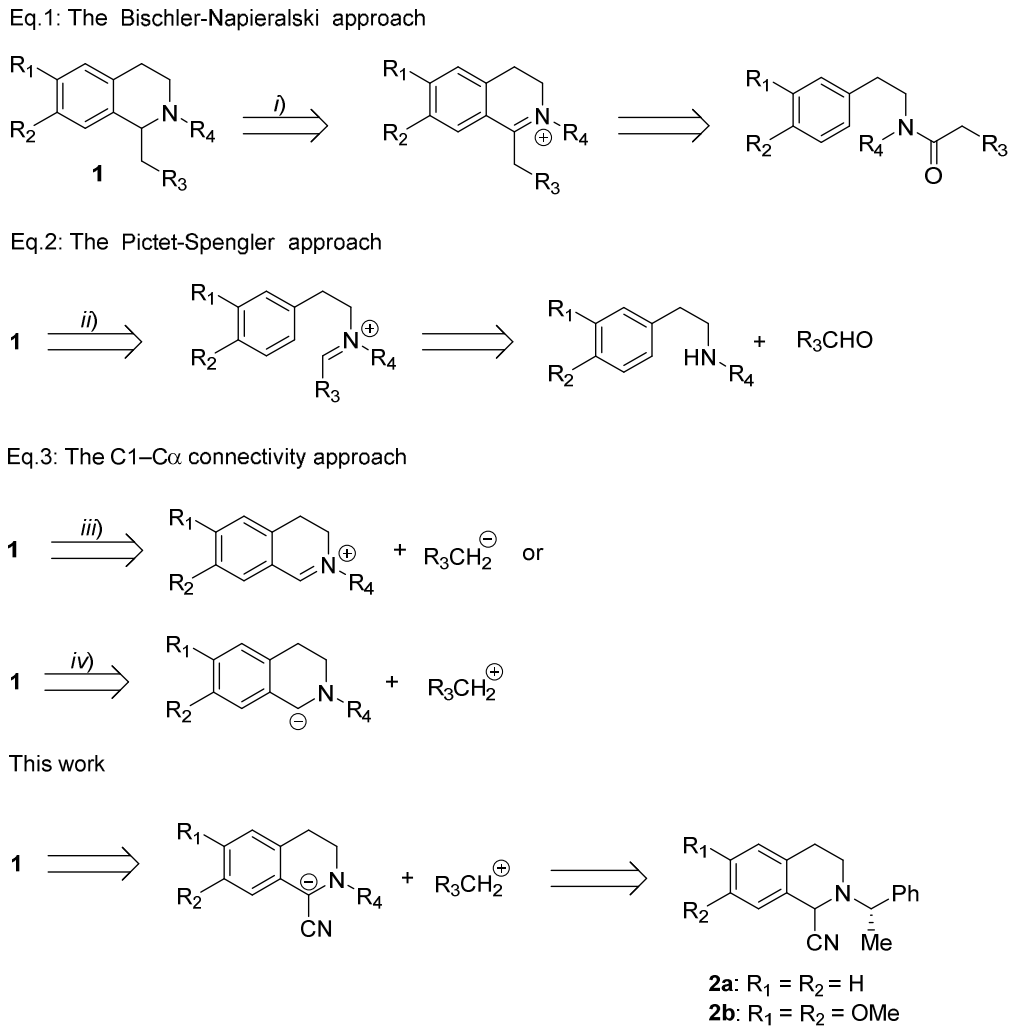
stereogenic center had an absolute *S* configuration. Likewise, (–)-xylopinine was synthesized in four work-up steps in an overall 63% yield from α-amino nitrile (+)-**2b**. In this process, crystallization of an enantioenriched mixture (90:10) of (–)-norlaudanosine with 1 equiv of (–)-*N*-acetyl-*L*-leucine afforded the leucinate salt (+)-**13** (99:1 dr). Similarly, (+)-salsolidine was displaced from its (–)-DBTA salt (–)-**12** in 99:1 er, which was determined by proton and carbon NMR spectroscopy in the presence of thiophosphinic acid (+)-**14** as the chiral solvating agent.

INTRODUCTION

Isoquinolines form a large group of compounds which are found in nature and in pharmaceuticals.[1] 1-Alkyl-tetrahydroisoquinolines (1-alkyl-THIQs, **1**) are a subclass of isoquinolines occurring in at least 20 families of the plant kingdom.[2] Apart from their significance in biosynthesis,[3] these compounds also display a broad range of interesting biological activities. For example, numerous 1-benzyl-THIQs were shown to act as ligands of calcium activated potassium channels.[4] They also shown to selectively inhibit the Orexin system which is involved in feeding behavior and insomnia.[5] Many derivatives showed potentiation of NMDA glutamate receptors which play a prominent role in brain processes such as neuronal plasticity and synaptic communication.[6] So, approaches allowing the stereoselective syntheses of 1-alkyl-THIQs are of great value and rely on one of three strategies that are drawn on scheme 1.[7]

The first approach (Eq.1, *i*) is based on diastereoselective hydride reduction of the C1–N2 double bond of 1-alkyl-3,4-dihydroisoquinolinium salts which are readily prepared by a Bischler–Napieralski cyclization.[8] Similarly, asymmetric transfer hydrogenation with chiral Ru,[9] Rh,[10] or Ir complexes[11] has become a well-established method that allowed an efficient control of the absolute configuration of the C1 carbon. Asymmetric Pictet–Spengler cyclization (Eq.2, *ii*) between a β-arylethylamine and an aldehyde, in which the control of the absolute configuration of the C1 carbon atom is performed during the cyclization process, has also been successfully employed for the synthesis of THIQ alkaloids; it is worthy of note that enantioselective approaches have been recently reported.[12] However, both approaches are not completely satisfactory since they required the presence of

electron-rich aryl groups (*ie*. R_1 = R_2 = OMe) in the molecule for the construction of the future C8a–C1 bond.



Scheme 1. General approaches for stereoselective syntheses of 1-alkyl-THIQs.

This problem can be avoided by using the bond disconnection between the THIQ ring and the C1 substituent. This so-called C1–Cα connectivity approach (Eq.3) can be achieved through the diastereo-[13] or enantioselective additions[14] of carbon nucleophiles on the azomethine bond of the isoquinoline ring (Eq.3, *iii*) or through the alkylation of dipole-stabilized anions obtained from the deprotonation of THIQs (Eq.3, *iv*) in which the chiral auxiliary is appended by the N2 or C3 atoms.[15] However, the condensation of such α-amino-organolithium species with alkyl halides has proven to be somewhat problematic due to the presence of an unwanted single electron or elimination processes which limit this approach to a restricted number of electrophiles.[16] To overcome this drawback, the use of lithiated 1-cyano-stabilized

THIQs seemed a promising possibility which has been little studied to date.[17] This is surprising since in the last decade, several catalytic,[18] visible-light photoredox approaches,[19] and stoichiometric oxidants such as DDQ,[20] $PhI(OAc)_2$,[21] 1-cyano-3(1*H*)-1,2-benziodoxols,[22] have been utilized for the synthesis of 2-aryl-tetrahydroisoquinoline-1-carbonitriles. However, the above-mentioned methods have a limited substrate scope due to the fact that cleavage of the *N*-aryl bond (R_4 = Ph) in the late stage of the syntheses could only be achieved under Birch type conditions.[23]

On the other hand, examples of oxidation of tertiary aliphatic amines are scarce. As far as the α-cyanation of natural products is concerned, Sundberg reported the synthesis of 3-cyanocatharantine in the presence of DDQ and 3 equiv of TMSCN, and a photoredox catalytic version of this study has been recently reported by Stephenson.[24] 12-Cyanogalanthamine was obtained by Hametner by the successive treatment of galanthamine with *N*-bromosuccinimide and KCN.[25]

In this area of research, we reported the synthesis of the pyrroloisoquinoline alkaloid (+)-crispine A from a stable THIQ α-amino nitrile, prepared by electrochemical means.[26] Yet, anodic cyanation and alkylation of metallated α-amino nitriles seemed to be a quite general approach for the formation of new carbon to carbon bonds in the C1 position of the THIQ nucleus.[27] In addition, the presence of an α-phenylethylamine group (α-PEA) linked to the nitrogen atom allowed an efficient 1-3-stereoinduction during the reductive decyanation process. The objectives of the present study were two-fold. Firstly, we wish to widen the scope of our electrochemical approach for the synthesis of natural optically active THIQs derivatives such as (+)-salsolidine or (–)-xylopinine (figure 1); secondly, to investigate the chemistry of α-amino nitrile **2a** which complements the existing methods reported for the synthesis of pyrrolo[2,1-a]-isoquinoline (–)-**3** and tetrahydroberberine (–)-**4**, analogous to (–)-crispine and (–)-xylopinine, respectively.

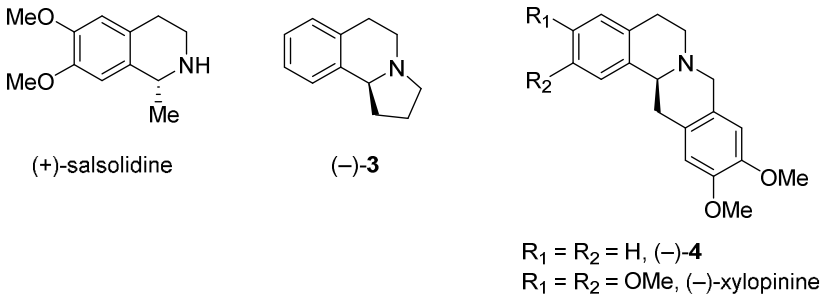
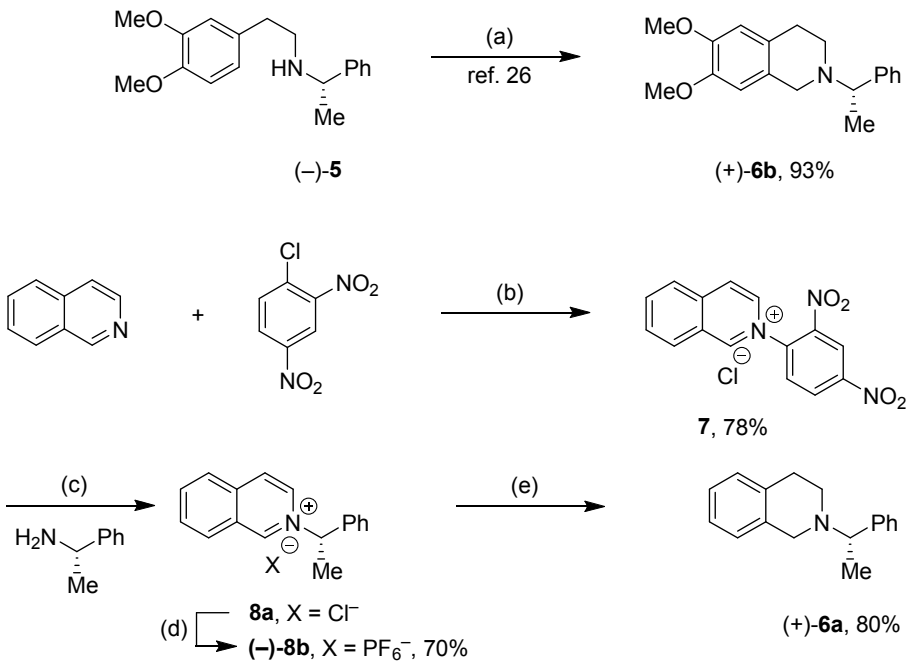


Figure 1. Natural and synthetic THIQs.

RESULTS AND DISCUSSION

Synthesis of THIQs (+)-6a,b. We set the intermediary THIQs (+)-**6a,b** as initial synthetic targets according to the two distinct protocols depicted in scheme 2. The synthesis of THIQ (+)-**6b** was carried out according to the procedure which has been reported in a previous work from this laboratory.[26a] Thus, treatment of β-phenylethylamine (–)-**5** in the presence of a mixture of formic acid, and para-formaldehyde proved to be the most straightforward access to synthesize the expected THIQ (+)-**6b** which was obtained in an overall 75% yield. In lieu of an impracticable Pictet-Spengler cyclization necessitating alkoxy or hydroxyl substituents on the aromatic ring, we decided to utilize chiral isoquinolinium salt **8a** which was formerly employed by Marazano in a stereoselective access to 1-alkyl-THIQs.[28] Thus, the treatment of Zincke salt **7** with (*S*)-(–)-α-PEA in dichloromethane in the presence of 1.2 equiv of diethylamine for 48 h, provided the intermediary pyridinium chloride salt **8a**. For subsequent chemical manipulations, the chloride salt **8a** was displaced from its chloride counterpart upon the addition of a concentrated solution of HPF_6 onto an aqueous solution of **8a** to yield the hexafluorophosphate (–)-**8b** which was recovered in an overall 70% yield from **7**. The borohydride reduction of isoquinolinium salts is a well-established method,[29] and in a first trial, the hexafluorophosphate salt (–)-**8b** was stirred in ethanol at ambient temperature in the presence of three fold excess of sodium borohydride. Unfortunately, the ^{1}H NMR analysis of the reaction mixture revealed the presence of the intermediary 1,2-dihydroisoquinoline as the major compound and varying amounts of unidentified products. In a second trial, the same experiment was carried out in the presence of 2 equiv of acetic acid to afford the expected THIQ (+)-**6a** in yields ranging from 50% and 65%.

Scheme 2. Syntheses of THIQs (+)-6a,b[a]

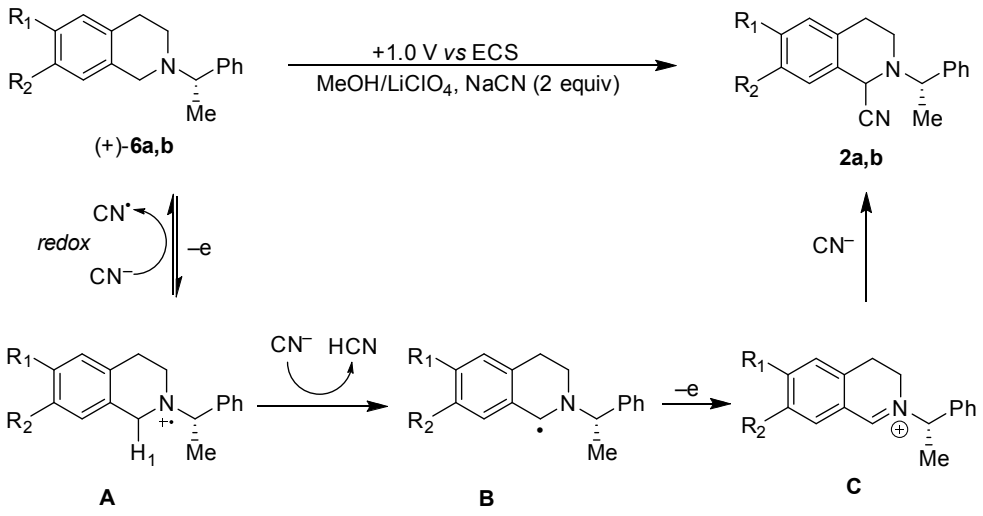


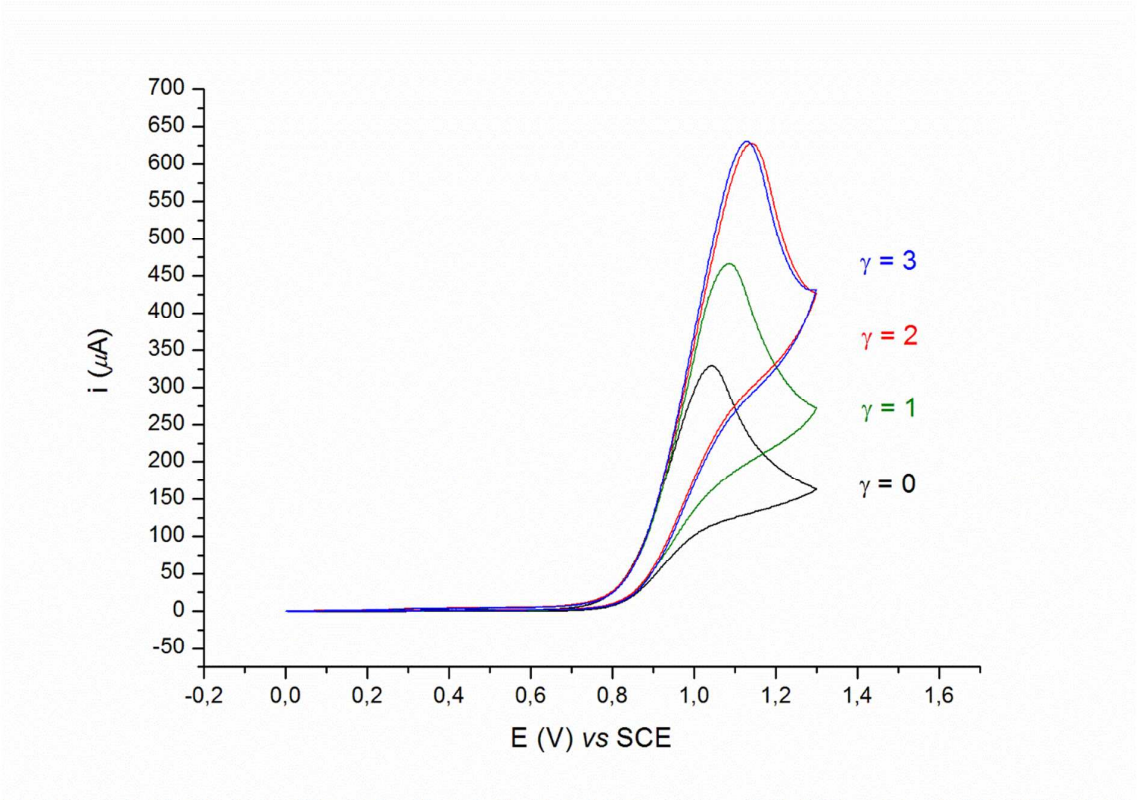
[a] Reagents and conditions: (a) HCO_2H, $(CH_2O)_n$, 50 °C, 12 h; (b) isoquinoline, 1-chloro-2,4-dinitrobenzene, 60 °C, 2 h, then acetone, reflux, 2 h; (c) (–)-α-PEA, Et_2NH, CH_2Cl_2, rt, 48 h; (d) 37% HPF_6; (e) $NaBH_3CN$, THF, rt, 12 h.

Unfortunately, close examination of the ^1H NMR spectra of derivatives still revealed the presence of oligomeric compounds which could not be removed by column chromatography. Finally, the best yields and reaction rates were obtained when the reduction was performed in the presence of 2 equiv of $NaBH_3CN$ to afford cleanly and reproducibly the THIQ (+)-**6a** {$[\alpha]^{22}_D$ = +9.2 (*c* 0.5, $CHCl_3$)} in 80% yield.

Analytical study of THIQs (+)-6a,b. The electrochemical behavior of THIQ (+)-**6a,b** was studied by cyclic voltammetry and details are reported in table 1. The polarization curves were recorded at a vitreous carbon electrode at a scan rate of 50 mVs^{-1} on a 20 mM solution of THIQs (+)-**6a,b** in methanol containing $LiClO_4$ (0.1 M) as the supporting electrolyte and NaCN as the trapping agent. The first voltammogram was recorded on a 20 mM solution of THIQ (+)-**6a** (γ = 0, table 1), and the feature of primary interest in the voltammogram is the presence of a well-defined irreversible bielectronic system which was recorded at E_p = +1.0 V.

Table 1. (Top) Redox and proton transfer options for aminium radical cations A and synthesis of α-amino nitrile 2a. (Bottom) Cyclic Voltammograms of THIQ (+)-6a in the absence (γ = 0) and in the presence (γ = 1–3) of NaCN[a]





Entry	no	E_p (V)	γ = 1 (i_p/i_p^0)	γ = 2 (i_p/i_p^0)	γ = 3 (i_p/i_p^0)
1	(+)-**6a**	+1.00	1.42	1.90	1.90
2	(+)-**6b**	+0.90	1.72	2.50	3.00

[a]$MeOH/LiClO_4 \cdot 3H_2O$ (0.1 M), glassy carbon electrode, v = 0.05 V s^{-1}: γ = 0 : THIQ (+)-**6a** (20 mM) alone; γ = 1 plus NaCN (20 mM); γ = 2: plus NaCN (40 mM); γ = 3: plus NaCN (60 mM).

The addition of incremental amounts of sodium cyanide (up to 2 equiv) to the previous solution caused an increase of the anodic current which is no longer under diffusion control.[30] The effect of cyanide on the voltammetric profile of (+)-**6a** is attributed to the presence of a typical catalytic current due to the return of the aminium radical cation **A** to its neutral form which occurred during the homogeneous redox process (table 1, top) in which the cyanide anion is now oxidized at a lower potential than that required for its direct oxidation at the electrode surface.[31] The magnitude of such process is given by the value of the i_p/i_p^0 ratio (where i_p and i_p^0 represent the anodic currents in the presence and in the absence of sodium cyanide, respectively). At low concentrations of sodium cyanide (up to 40 mM) the i_p/i_p^0 ratio turned to be 1.90 indicating that the redox process predominantly occurred. In contrast, further addition of sodium cyanide did not modify the i_p/i_p^0 ratio providing evidence that acid properties of radical cation **A** dominate at this concentration. As a result, deprotonation at C1 yields the neutral aminyl radical **B** which is immediately oxidized at the electrode surface to form the stable iminium cation **C**.[32]

A similar behavior was observed for THIQ (+)-**6b** (Table 1, entry 2). The values of the i_p/i_p^0 ratios indicate that electron donating substituents on the aromatic ring did not significantly modified the redox properties of our substrates, and it was also concluded that the initial electron transfer involved the amine moiety.

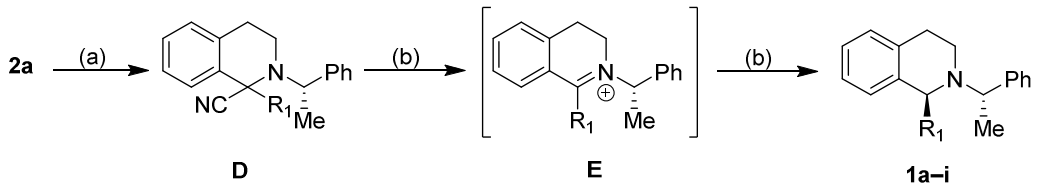
Anodic cyanation of THIQs (+)-6a,b. The electrolysis of THIQ (+)-**6a** was carried out at a vitreous carbon electrode in an undivided batch cell at a controlled potential of +1.0 V in the presence of 2.5 molar excess of sodium cyanide and 0.5 equiv of acetic acid to balance the excess of base that was produced at the cathode surface. After the consumption of 2.1 F per mole of substrate, the cyclic voltammogram recorded on the resulting solution showed the disappearance of the first oxidation peak, and aqueous work-up and filtration of the crude reaction mixture on a silica column afforded α-amino nitrile **2a** which was obtained in 81% yield as a mixture (60/40) of diastereoisomers. Slow crystallization of this mixture in a diethyl ether/petroleum ether biphasic system afforded single crystals which were found to be suitable for an X-ray diffraction study, and from the ORTEP view of (+)-**2a** (Figure S 13 in the Supporting Information) we were able to determine the absolute configuration of the C1 carbon atom of the major diastereoisomer as *R*.

The electrolysis of (+)-**6b** was carried out under conditions similar to those used for **6a**. After work-up, α-amino nitrile (+)-**2b** was obtained as a colorless powder in 70% yield after a rapid crystallization of the crude reaction mixture in ethanol. Interestingly, a slow crystallization of this powder in the same solvent afforded a single crystal which was suitable for an X-ray diffraction study. The ORTEP view is shown in Figure S 23 in the Supporting Information. As the absolute configuration of the exocyclic benzylic carbon is known to be *S*, the *R* absolute configuration of the newly created stereogenic center at C1 is simply deduced from examination of the structure. In addition, the determination of the Flack parameters values [–0.03 (6)] calculated from the Friedel pairs reflection for each structure confirmed the absolute configuration of (+)-**2b** in the solid state.

Syntheses of 1-alkyl-THIQs 1a-i. With the required α-amino nitriles in hand, we set to synthesize 1-alkyl-THIQs **1a–e** displaying an alkyl chain with an increasing length, and the results are collected in Table 2. The deprotonation sequence was carried out on a frozen (–80 °C) THF solution of a diastereoisomeric (60/40) mixture of α-amino nitrile **2a** by the slow addition of 1.5 equiv of LDA (prepared from diisopropylamine and 2.5 M of BuLi) upon which the resulting solution turned rapidly deep red. The solution was warmed up to –20 °C over a 2 h period, before being cooled down to –80 °C. The commercially available alkyl iodides were added at that temperature on the anion solution to afford the unstable quaternary α-amino nitriles **D** which were used in the next step without further purification. To control the diastereoselectivity of the hydride incorporation, the reductive decyanation was best achieved when an excess (4 equiv) of $NaBH_4$ was introduced onto a solution of **D** in ethanol at –20 °C. Work-up and a filtration over a silica column afforded THIQs **1a–e** in yields ranging from 72% to 40% (Table 2, entries 1–5). Upon comparing entries 3 and 4, one sees that the size of the alkyl chain has an influence on the yield. Entry 5, clearly showed the effect of the length of the alkyl chain, and a prolonged stirring was however required to complete the reaction with 1-iodoundecane. It is also worth mentioning that the parent THIQ (+)-**6b**, which resulted from the reductive decyanation of unreacted α-amino nitrile **2b**, was recovered in 20% yield. The stereoselectivity of the reductive decyanation process has been determined from the careful examination of the ^1H NMR spectra. For compound (–)-**1d**, a doublet of

doublet (J = 8.3, 4.2 Hz, 0.88 H) attributable to the 3-Hb proton of the major diastereoisomer was recorded at δ = 3.50, whereas the similar system was recorded at δ = 3.95 for 3-Hb proton of the minor diastereoisomer indicating that these two derivatives are present in a 90:10 ratio. Comparing entries 1–5 also revealed that the length of the alkyl chain has little effect on the stereochemical outcome of the reductive decyanation procedure. To extend the scope of our methodology, we also decided to evaluate the reactivity of benzyl bromides displaying one or two methoxy substituents on the aromatic ring. Thus, the treatment of the anion solution of **2a** with 1-(bromomethyl)-4-methoxybenzene afforded the corresponding bifunctional α-amino nitrile **D** which was reduced as above to provide the THIQ (+)-**1f** in 75% yield and in a 95:5 dr which could be improved to 99:1 dr by a slow crystallization in ethanol. To our satisfaction, an X-ray study performed on one of these crystals revealed the stereochemical outcome of the decyanation process. The ORTEP view (Figure S 43 in the SI) clearly shows that the newly created stereogenic center at C1 was *S* indicating that incorporation of the hydride had occurred on the least hindered *Re* face or the intermediary iminium **E**. From Table 2, it is also seen that when 4-(bromomethyl)-1,2-dimethoxybenzene was selected as the electrophile, the THIQ (+)-**1g** was obtained in 70% yield and in a 99:1 dr after crystallization.[33] As an extension of the previous reaction sequence, we sought to introduce a three carbon chain tethered by a potential cyclizing group with the aim of synthesizing pyrroloisoquinoline (–)-**4**. Alkylation of the anion solution of **2a** with 2-(2-iodopropoxy)-tetrahydropyran or 2-(2-iodoethyl)-1,3-dioxolane as the alkylating agents, afforded the THIQ (–)-**1h** and (–)-**1i**, respectively. Analyses of the ^{1}H and the ^{13}C NMR spectrum were straightforward. For example, in the case of THIQ (–)-**1i**, the CH proton of the *O*,*O*'-acetal protecting group (J = 4.6 Hz) resonated as a triplet signal (J = 4.6 Hz) at δ = 4.71 in the major *S*,*S* diastereoisomer. The same signal was recorded at δ = 4.92 and comparison of the relative integration of these two characteristic protons showed that reductive decyanation occurred in a 97:3 dr. The nature of the iminium species has an effect on the stereochemical outcome of the reductive decyanation, as the best dr's were obtained in the presence of oxygenated chains at C1 as shown by entries 6–9. Gratifyingly, THIQs (–)-**1h**,**i** could be obtained as sole products (99:1 dr's) after a careful filtration over silica column.

Table 2. Syntheses of THIQs 1a–i[a]



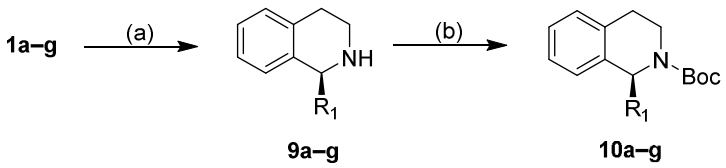
entry	no.	R_1	yield (%)	dr
1	(–)-**1a**	CH_3	72	90:10
2	(–)-**1b**	C_3H_7	73	90:10
3	(–)-**1c**	C_5H_{11}	71	88:12
4	(–)-**1d**	C_7H_{15}	60	90:10
5[b]	(–)-**1e**	$C_{11}H_{23}$	40	85:15
6[c]	(+)-**1f** (X-ray)	4-(MeO)-Ph-CH_2	75	95:5
7[c]	(+)-**1g** (X-ray)	3,4-$(MeO)_2$-Ph-CH_2	70	95:5
8	(–)-**1h**	$(CH_2)_3$-O-THP	70	95:5
9	(–)-**1i**	$(CH_2)_2$-1,3-dioxolane	70	97:3

[a]Reagents and conditions: Procedure A: (a) LDA, THF, –80 °C to 0 °C, 2 h, then RX, –80 °C to –10 °C; (b) $NaBH_4$, EtOH, 20 °C, 12 h. [b]THIQ (+)-**6b** was recovered in 20% yield. [c]THIQs (+)-**1f,g** were obtained as single diastereoisomers after a slow crystallization in ethanol.

Synthesis of *N*-Boc THIQs (+)-10a–g. Benzyl groups are commonly employed to protect secondary amines and as shown below, they proved to be useful when a substrate had to be subjected to basic conditions. In contrast to catalytic hydrogenolysis of simple benzylamines which are generally carried out in the presence of a low Pd/C catalyst loading, debenzylation of substrates containing the more sterically demanding α-PEA group are generally performed under more elevated hydrogen pressure and catalyst loading. Examining the structure of THIQs **1a–g**, one can see that a non-selective cleavage of the endocyclic C1–N2 bond could occur in competition with removal of the chiral auxiliary. The first experiment was carried out with 10% Pd/C (20% in mass) under a hydrogen pressure of 5 bars and with THIQ (–)-**1b** as the substrate. After treatment, the expected THIQ (–)-**9b** was obtained in a low 10% yield accompanied by unreacted starting material. It was also found in a second experiment that higher catalyst loading (up to 30%) resulted in

a non-selective cleavage of the C8a–C1 bond. Finally, the best yields and reaction rates were obtained upon a 48 h stirring of THIQs **1a–g** in ethanol under an H_2 atmosphere of 5 bars in the presence of Pearlman's catalyst (20% in mass).

Table 3. Syntheses of *N*-Boc-THIQs (+)-10a–g[a]



9a–g 10a–g

entry	no.	R_1	yield (%)	entry	no.	yield (%)
1	(–)-**9a**	CH_3	80	10	(+)-**10a**	80
2	(–)-**9b**	C_3H_7	73	11	(+)-**10b**	85
3	(–)-**9c**	C_5H_{11}	70	12	(+)-**10c**	75
4	(–)-**9d**	C_7H_{15}	80	13	(+)-**10d**	73
5	(–)-**9e**	$C_{11}H_{23}$	75	14	(+)-**10e**	75
8	(–)-**9f**	4-(MeO)-Ph-CH_2	70	18	(+)-**10f**	80
9	(–)-**9g**	3,4-$(MeO)_2$-Ph-CH_2	80	19	(+)-**10g**	78

[a]Reagents and conditions: Procedure B: (a) 20% $Pd(OH)_2/C$, H_2 (5 bar), EtOH, 48 h. Procedure C: (b) $(Boc)_2O$, Hünig's base, acetonitrile, reflux, 4 h, then NaOH 4 M/THF, rt, 2 h.

We could observe clean reductions with yields ranging from 73% to 80% (Table 3) and to prevent oxidation with ambient air, these derivatives were converted into the corresponding *N*-Boc-THIQs (+)-**10a–g** by treatment with Boc_2O in the presence of Hünig's base in refluxing acetonitrile. In all cases, ^1H NMR analysis revealed the presence of two rotamers which strongly affect the interpretation of the spectra. For example, in the spectrum of (+)-**10g** in $CDCl_3$ at 296 K, the signals for the rotamers of the H1 proton exhibit resonance signals at δ = 5.14 and δ = 5.33 and were found to exist in a 65:35 ratio.

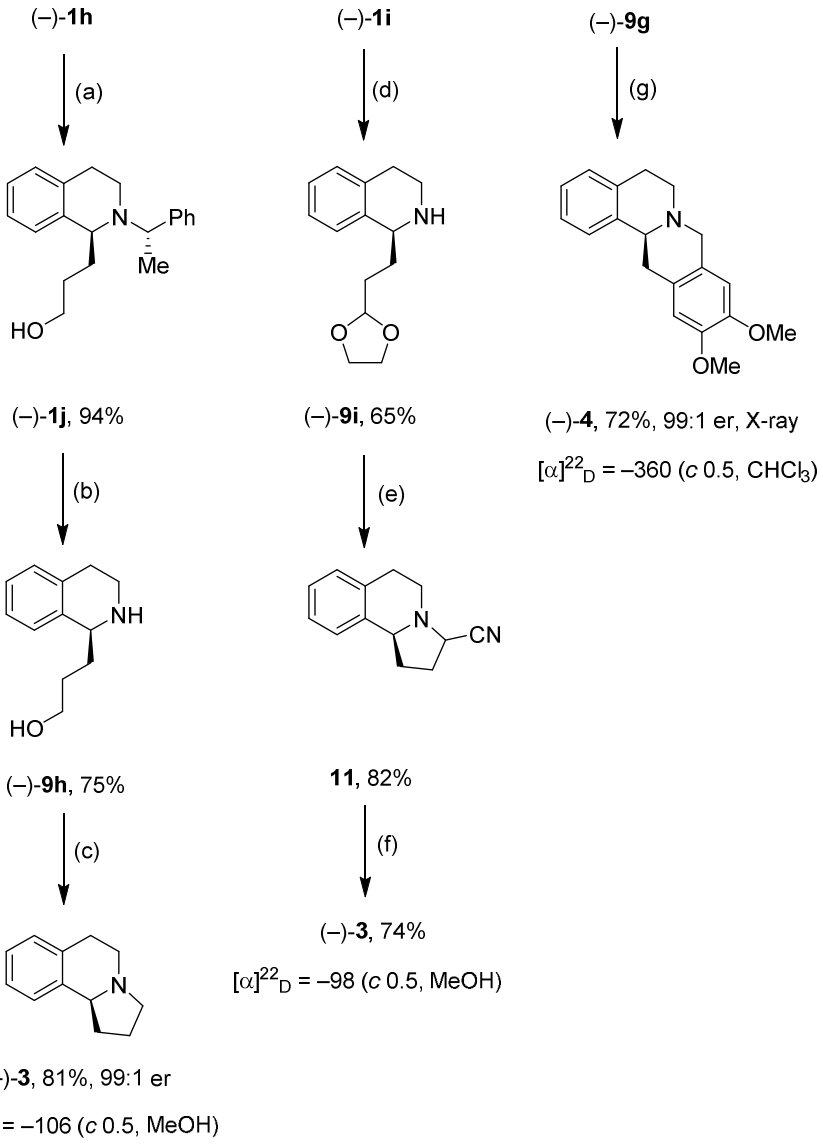
Synthesis of pyrroloisoquinoline (–)-3 and tetrahydroberberine (–)-4. From the requisite THIQ (–)-**1h** in hand, we first turned our attention to the synthesis of pyrroloisoquinoline (–)-**3**. Previous studies from this laboratory and others, showed that the third pyrrolidine ring could be constructed by the intramolecular displacement of a terminal chloride leaving group by the deprotected amine. As shown below, the

synthesis of the requisite amino alcohol (–)-**9h** (scheme 3) was carried out in a three step procedure. The acid catalyzed deprotection of O-THP protected THIQ (–)-**1h** was carried out without event by stirring it at 20 °C in a 1:1 mixture of THF and 2 N HCl. The amino alcohol (–)-**1j** was obtained in 94% yield as an oily residue {$[\alpha]^{22}_{D}$ – 57 (c 1.0, $CHCl_3$} and its ^{13}C NMR, well resolved, displayed a set of 8 independent resonance line in the region δ = 20–35, providing evidence that this compound exists as a single diastereoisomer. Removal of the chiral auxiliary was initiated with hydrogenolysis of the *N*-α-PEA group using $Pd(OH)_2$ as the catalyst under H_2 atmosphere, a procedure that proved inefficient in that case. The starting material was recovered in nearly quantitative yield and a prolonged stirring (up to 72 h) did not modified the conversion. To circumvent these drawbacks, we utilized a protocol described by Polniaszek.[34] Thus, the catalyst (10% Pd/C) was pretreated under an H_2 atmosphere of 6 bar in a 10:2 mixture of ethanol and 10 M HCl for 12 h, prior to the addition of amino alcohol (–)-**1j**. The resulting solution was stirred for an additional 72 h period under the same H_2 pressure to afford the expected (–)-**9h** in 75% yield as a viscous oily residue after column chromatography. Chlorination of the pendant alcohol was accomplished by refluxing (–)-**9h** in CH_2Cl_2 in the presence of a two-fold excess of $SOCl_2$ according to the protocol described by Xu.[35] The intermediary hydrochloride salt was not isolated but was stirred in a biphasic system (Et_2O/2M NaOH) to afford (–)-**3** in 81% yield. The spectroscopic data, the magnitude and the sign of the optical rotation of our sample {$[\alpha]^{22}_{D}$ –106 (*c* 0.5, MeOH)} matched in all aspects with those previously reported in the literature.[36]

To complement the previous synthetic efforts, an alternate procedure for the formation of the pyrrolidine ring was sought. This approach is based on the formation of an unstable iminium ion which could be prepared from THIQ (–)-**9i** through the condensation of the terminal aldehyde group and the deprotected N2. In this sequence, the hydrogenolysis of THIQ (–)-**1i** should be carried out first under non acidic conditions, and we found that Pearlman's catalyst was the reactant of choice. Following the previous procedure, THIQ (–)-**9i** was obtained in a satisfactorily 65% yield as an oily residue which should be stored at –20 °C to avoid aerial carbonatation.[37] Deprotection of the *O*,*O*'-dioxolane moiety was carried out by stirring (–)-**9i** in a degassed mixture of THF and 10% HCl over a 24 h period and after the removal of the organic solvent, the pH of the remaining solution was raised up to 4.5

upon the addition of solid AcONa. Then, the resulting emerald green solution was treated with an excess of sodium cyanide, causing the precipitation of α-amino nitrile **11** as a 1:1 mixture of diastereoisomers. For our purposes, this mixture was dissolved in ethanol and treated with $NaBH_4$ for removal of the cyanide group. Because it appeared difficult to remove it under standard conditions, the crude reaction mixture was refluxed for an additional three hours period to afforded (–)-**3** in an overall 60% yield from (–)-**9i**.

Scheme 3. Syntheses of pyrroloisoquinoline (–)-3 and tetrahydroberberine (–)-4[a]



[a]Reagents and conditions: (a) THF/HCl 2 N, 1:1, rt, 12 h; (b) 10% Pd/C, EtOH/ HCl 10 N, 10:2, H_2 (6 bar); then, (–)-**1h**, H_2 (6 bar), rt, 72 h; (c) $SOCl_2$, reflux, 3 h; (d) 20% $Pd(OH)_2$/C, H_2 (5 bar), EtOH, 48

h; (e) THF/HCl 2 N, rt, 24 h; then AcONa, pH = 4.5; then NaCN, rt, 2 h; (f) $NaBH_4$, EtOH, 24 h, rt; then reflux, 3 h; (g) HCO_2H/35% HCHO, reflux, 2 h.

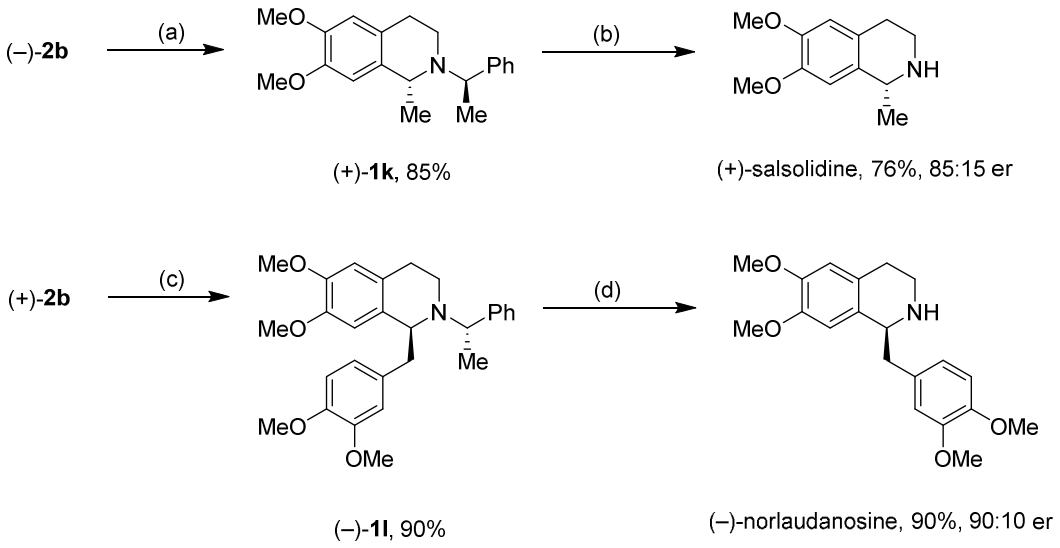
The optical rotation of this sample {$[\alpha]^{22}_D$ –98 (*c* 0.5, MeOH)} was consistent with that reported above, confirming the chiral conservation in both the synthetic approaches.

To extent this approach further, we performed the synthesis of the tetracyclic compound (–)-**4** by refluxing its precursor (+)-**9g** in a mixture of 35% formalin and formic acid for 2 h. After an aqueous work-up, the tetrahydroberberine (–)-**4** was obtained as a solid {$[\alpha]^{22}_D$ –360 (*c* 0.5, $CHCl_3$), mp 146–148 °C)} in 72% yield after column chromatography.[38] A further X-ray study which was performed on a single crystal of (–)-**4** confirmed the proposed structure.

Stereoselective syntheses of THIQs alkaloids. These encouraging results prompted us to expand the scope of our study to the synthesis of naturally occurring THIQs such as (+)-salsolidine or (–)-norlaudanosine.[39,40] The synthetic scheme for preparation of (+)-salsolidine involved the alkylation of α-amino nitrile (–)-**2b** which was prepared from THIQ (–)-**6b** by anodic cyanation. Thus, treatment of (–)-**2b** according to protocol A with iodomethane as the alkylating agent (Scheme 4), afforded THIQ (+)-**1k** (85%) in a 85:15 dr which was determined from examination of the ^{1}H NMR spectrum in C_6D_6. Similarly, the preparation of THIQ (–)-**1l**, the advanced precursor of (–)-norlaudanosine, proceeded in 90% yield (90:10 dr) from the alkylation–reduction sequence of enantiomeric α-amino nitrile (+)-**2b** with 4-(bromomethyl)-1,2-dimethoxybenzene as the electrophile. Unfortunately, the diastereomeric ratio of these two precursors could not be increased by fractionate crystallization and as shown in scheme 4, selective removal of the *N*-α-PEA group by hydrogenolysis afforded enantiomerically enriched (+)-salsolidine (85:15 er) and (–)-norlaudanosine (90:10 er) in 64% and 81% overall yields from enantiomeric α-amino nitriles **2b**, respectively. At this point, it should also be noted that neither variation of the temperature nor modification of the hydride source could improve the stereoselectivity of the reductive decyanation. In literature, the optical resolution of THIQ racemates can be traced back to 1938, when Späth reported the cocrystallization of salsolidine with chiral tartaric acid.[41] This approach is simple and effective and prompted us to screen a series of carboxylic acids that would hopefully afford the expected alkaloids as single enantiomers. After several experiments, it was

found that addition of (–)-DBTA to an enantioenriched mixture of (+)-salsolidine (85:15 er) afforded the corresponding diastereoisomeric salts in nearly quantitative yield.

Scheme 4. Stereoselective synthesis of (+)-salsolidine and (–)-norlaudanosine[a]



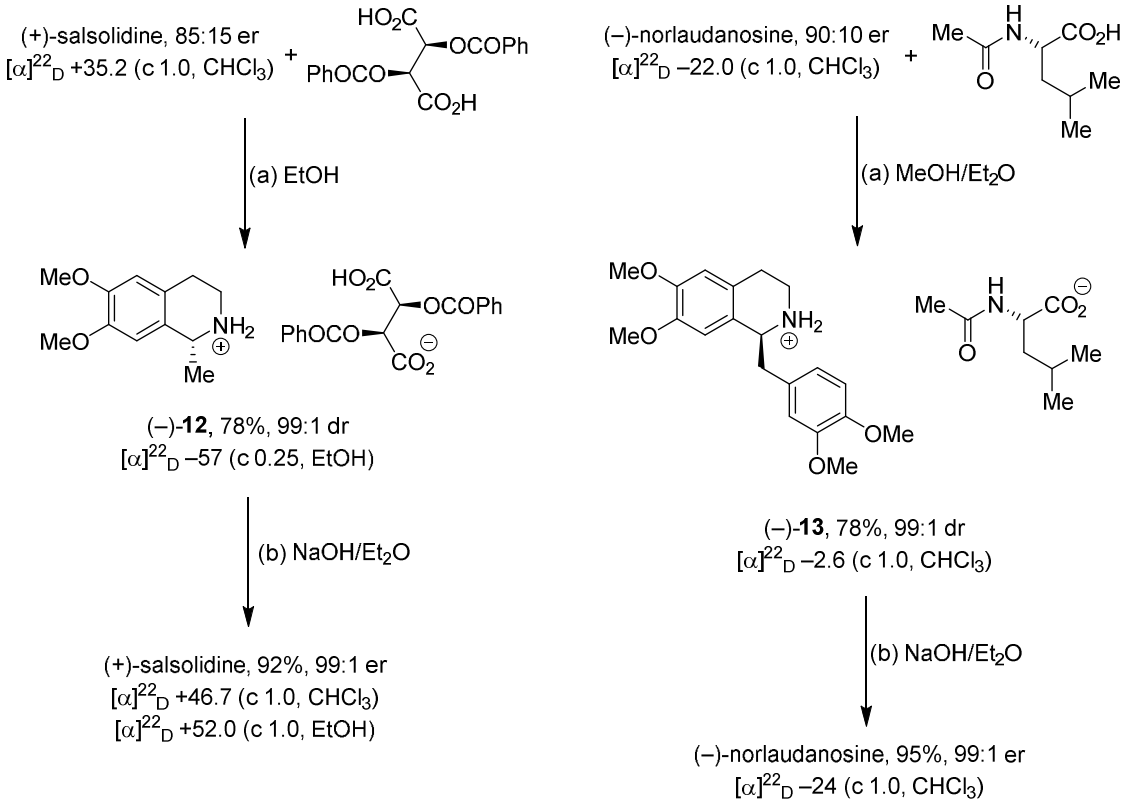
[a]Reagents and conditions: Procedure A: (a) LDA, THF, –80 °C to 0 °C, 2 h, then CH_3I, –80 °C to –10 °C, then: $NaBH_4$, EtOH, 20 °C, 12 h. (b) 10% Pd/C, EtOH/ 10% HCl (10:2), H_2 (7 bar), 48 h. (c) Procedure A but with 4-(bromomethyl)-1,2-dimethoxybenzene. (d) Procedure B: 20% $Pd(OH)_2$/C, H_2 (5 bar), EtOH, 48 h.

Gratifyingly, *a single crystallization* of this mixture in ethanol afforded the tartaric salt (–)-**12** in 78% yield and the ^{1}H NMR attested of the 1:1 stoichiometry of this complex (Scheme 5). A base treatment (Et_2O/10% NaOH) of this salt, afforded enantiopure (+)-salsolidine which was obtained as an oil. The optical rotation of our synthetic sample {$[\alpha]^{22}_D$ +46.7 (*c* 1, $CHCl_3$)} matched the values reported in the literature {$[\alpha]^{22}_D$ +51 (*c* 1, EtOH)}.[39h] The access to enantiopure (–)-norlaudanosine was carried out to the similar crystallization process but with (–)-*N*-acetyl-$_L$-leucine as the resolving agent according to the protocol formerly reported by Corrodi and Hardegger.[42] The expected leucinate salt (–)-**13** was obtained in 78% yield (99:1 dr) and a basic treatment of this salt afforded (–)-norlaudanosine in a 99:1 er.

Determination of enantiomeric ratios of THIQ alkaloids by proton and carbon NMR spectroscopy. We encountered problems with baseline return during

chromatographic separation of THIQs enantiomers and therefore turned to NMR to determine the optical purity of our samples. In contrast to chiral derivatizing agents which rely on bond formation with the substrate, chiral solvating agents (CSAs) do not require chemical manipulations thus facilitating the sample recovery. Previous studies from this laboratory and others, have shown that CSAs which are able to bind to enantiomers through Brønsted–Lowry acid/base interactions could form diastereoisomeric salts which could be differentiated by NMR spectroscopy. Thus, we turned to the utilization (*R*)-(+)-*tert*-butylphosphinothioic acid (+)-**14** as CSA to determine the enantiomeric ratios of our samples of (+)-salsolidine and (–)-norlaudanosine by proton and carbon spectroscopy (Scheme 6). The addition of 1.5 equiv of (+)-**14** to an enantioenriched mixture (85:15 er) of (+)-salsolidine dissolved in C_6D_6 resulted in the formation of the thiophosphinic salts (*R*,R_P)-**15** and (*S*,R_P)-**15**.

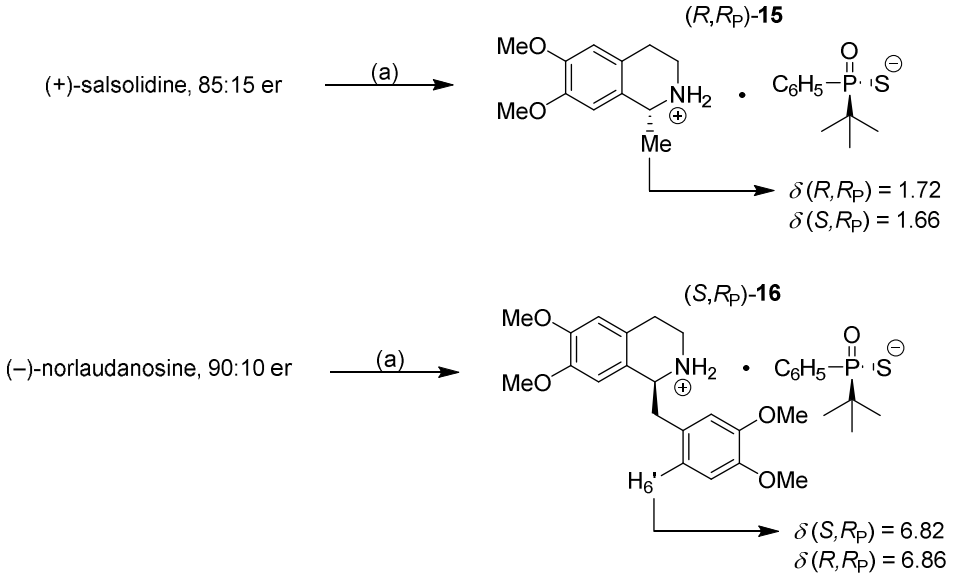
Scheme 5. Approaches for obtaining enantiopure (+)-salsolidine and (–)-norlaudanosine from enantiomerically enriched mixtures



As expected and observed, the C1-Me resonance signal in the proton NMR spectrum of the major diastereoisomer (*R*,R_P)-**15** resonated as a doublet signal (*J* =

6.7 Hz) at δ = 1.72, whereas the C1-Me group in the minor diastereoisomer exhibited a similar doublet signal at δ = 1.66. The magnitude of the $\Delta\delta$ (0.06) allowed the enantiomeric ratio to be determined from the further integration of these two signals which proved to be 85:15 dr. This result also indicated that no racemization occurred during the removal of the chiral auxiliary in the parent THIQ (+)-**1k**, and when a similar experiment was carried out on optically pure (+)-salsolidine, a single doublet was observed at δ = 1.72, indicating that our synthetic alkaloid had a >98:2 *er*. As expected, an analogous experiment performed with enantioenriched (–)-norlaudanosine (90:10 er) provided a well resolved spectrum in which the H-6' proton resonated as a characteristic doublet of doublet (J = 8.1, 1.7 Hz) at δ = 6.82 in the major complex (S,R_P)-**16**.

Scheme 6. Determination of the enantiomeric ratios of (+)-salsolidine and (–)-norlaudanosine by proton NMR spectroscopy[a]

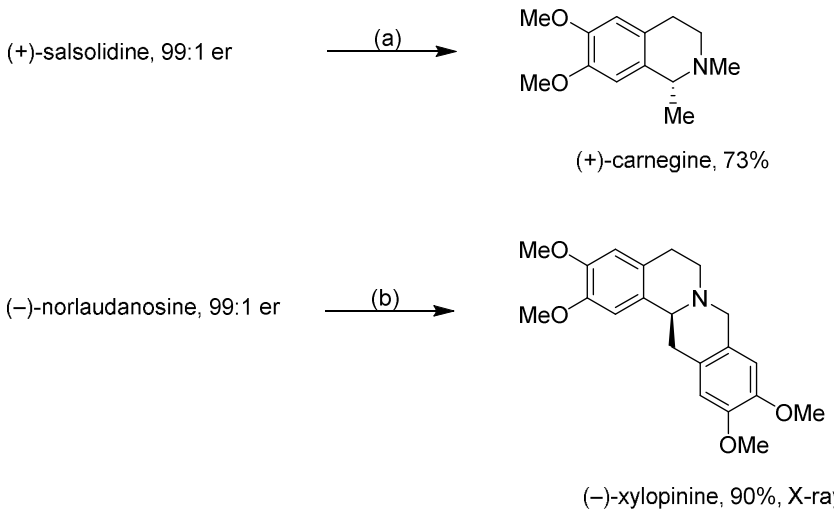


[a]Reagents and conditions: (*R*)-(+)-*tert*-butylphenylphosphanylthioic acid, (+)-**14**, C_6D_6.

Conversely, the H-6' proton signal resonated downfield at δ = 6.90 in the minor complex (R,R_P)-**16** indicating that both molecules could be efficiently discriminated in this way. Finally, when a similar experiment was carried out on optically pure (–)-norlaudanosine, a single resonance signal ascertained to the H-6' proton in (S,R_P)-**16** was recorded at δ = 6.82, providing the final proof that our sample was enantiomerically pure.

Synthesis of (+)-carnegine and (–)-xylopinine. Finally, methylation of the free nitrogen atom of (+)-salsolidine was carried out according to the protocol first described by Borch (Scheme 7).[43] Thus, addition of an excess of sodium cyanoborohydride on a solution of (+)-salsolidine (99:1 er) and aqueous formaldehyde in acetonitrile at pH = 7, afforded (+)-carnegine in 73 % yield after work-up and purification of the crude reaction mixture on a silica gel column. The specific optical rotation of our sample of (+)-carnegine proved to be $[\alpha]^{22}_{D}$ +18 (*c* 1.0, EtOH), which is in close agreement to that reported in the literature {$[\alpha]^{22}_{D}$ +23.5 (*c* 1.5, EtOH)}.[44] The synthesis of (–)-xylopinine, the prototypical member of the tetrahydroberberines which was isolated from *Xylopia Discreta*, seemed to be also an interesting possibility.[45] This, can be cleanly achieved by refluxing (–)-norlaudanosine (displaced from its leucinate salt (–)-**13**) for two hours in a mixture of 35% formaldehyde in formic acid.

Scheme 7. Synthesis of (+)-carnegine and (–)-xylopinine[a]



[a]Reagents and conditions: (a) aq. HCHO (35%), $NaBH_3CN$, pH = 7, CH_3CN, 15 min; (b) HCO_2H/aq. HCHO (35%), reflux, 2 h.

Basic treatment and purification of the crude reaction mixture by silica gel chromatography, afforded (–)-xylopinine as a white solid in a combined 90% yield from (+)-**12** with specific optical rotation and spectral data identical to that reported for the natural product. Additionally, an X-ray study which was carried out on a single

crystal of (–)-xylopinine confirmed the proposed structure and provided the final proof that the Pictet-Spengler type cyclization process occurred regioselectively to form the C8–C8a bond, the so-called “berberine” bridge.

Conclusion

In summary, we have found that LDA is able to deprotonate an isoquinoline based chiral non racemic α-amino nitrile in THF. The resulting α-amino cyano carbanion is condensed on a set of alkyl halides and the intermediary quaternary α-amino nitriles thus obtained are submitted to a reductive decyanation procedure to yield a series of 1-alkyl-THIQs in excellent yields with diatereoisomeric ratios ranging from 85:15 to 97:3. The same chemistry was applied successfully to the synthesis of THIQs (+)-salsolidine and (–)-norlaudanosine which was cyclized into (–)-xylopinine whose X-ray crystallography study was reported for the first time in the literature. Our efforts are currently directed toward the application of this strategy to the asymmetric synthesis of more complex molecule containing a THIQ nucleus. These results will be reported on due course.

Experimental section

General Techniques: Purification by column chromatography was performed with 70–230 mesh silica gel. TLC analyses were carried out on alumina sheets precoated with silica gel 60 F254; R_f values are given for guidance. The ^{1}H NMR spectra were recorded with a 500 MHz, a 400 MHz or a 300 MHz spectrometer. The ^{13}C NMR spectra were recorded with a 125 MHz, a 100 MHz or a 75 MHz spectrometer. Positive-ion mass spectra were recorded on an orthogonal acceleration quadrupole time-of-flight mass spectrometer equipped with a standard electrospray probe. Melting points were measured on a Kofler apparatus, the values reported in °C, and were uncorrected. Optical rotations were recorded at 20 °C in a 1 dm cell. For air-sensitive reactions, the glassware was oven-dried (90 °C) for 24 h and cooled under a stream of argon before use. All commercially available reagents were used as supplied and THF was distilled over sodium benzophenone ketyl. Diisopropylamine was distilled from solid potassium hydroxide.

Electrochemical techniques. Cyclic voltammetry experiments were carried out on a potentiostat using a three-electrode device with a glassy carbon (GCE, diameter = 2 mm) as the working electrode, a saturated calomel electrode (SCE) as

the reference and a platinum wire as the auxiliary electrode. The experiments were carried out in methanol containing $LiClO_4 \cdot 3H_2O$ (0.1 mol L^{-1}) as the supporting electrolyte. Preparative electrolysis were carried out at a controlled potential in a single compartment cell which was described previously.[46] The solution was stirred with a magnetic stirring bar and the electrolysis was stopped after the consumption of 2.1 F/mole.

2-(2,4-dinitro-phenyl)-isoquinolinium chloride, 7.[47] A 200-mL Schlenk tube fitted with a magnetic stirring bar was successively charged with 10 mL (11.00 g, 85.09 mmol) of isoquinoline and 17.10 g (84.42 mmol) of finely powdered 1-chloro-2,4-dinitrobenzene. The resulting suspension was stirred vigorously and heated at 60 °C for 10 minutes. The resulting orange solid paste was warmed at that temperature for an additional 1 h and 5 mL of acetone were added to the reaction mixture. The resulting suspension was refluxed for 6 h and the solid was filtered over a sintered glass funnel and was taken up with a minimum of acetone to afford 21.80 g (78%) of the isoquinolinium chloride **7**. Orange powder, mp = 200–202 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.18 (td, *J* = 7.2, 1.1 Hz, 1 H), 8.45 (td, *J* = 7.2, 1.1 Hz, 1 H), 8.56 (d, *J* = 8.0 Hz, 1 H), 8.63 (d, *J* = 8.7 Hz, 1 H), 8.69 (d, *J* = 8.2 Hz, 1 H), 8.90 (d, *J* = 7.0 Hz, 1 H), 9.04 (dd, *J* = 8.6, 2.5 Hz, 1 H), 9.15 (d, *J* = 2.5 Hz, 1 H), 9.19 (dd, *J* = 6.8, 2.1 Hz, 1 H), 10.77 (s, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 121.5 (t), 125.3 (t), 126.7 (q), 127.6 (t), 130.2 (t), 131.6 (t), 131.8 (t), 132.2 (t), 135.4 (t), 137.9 (q), 138.8 (t), 139.0 (q), 143.1 (q), 148.9 (q), 152.2 (t). HRMS (ESI$^+$, CH_3OH, $C_{15}H_{10}N_3O_4$, $[M]^+$) calcd for 296.0671, found 296.0670. Anal. Calcd for $C_{15}H_{10}ClN_3O_4$ (331.71): C, 54.31; H, 3.04; N, 12.67. Found: C, 54.15; H, 3.07; N, 12.55.

(*S*)-(–)-2-(1-Phenylethyl)-isoquinolinium hexafluorophosphate, (–)-8b, new compound. A 200 mL Schlenk fitted with a magnetic stirring bar was successively charged with 100 mL of CH_2Cl_2, 5.0 g (15.07 mmol) of Zincke salt **7**, 1.87 mL (1.32 g, 18.07 mmol, 1.2 equiv.) of diethylamine and 2.31 mL (2.22 g, 18.33 mmol, 1.2 equiv.) of (*S*)-(–)-1-phenylethylamine. The red solution was stirred at 20 °C for 48 h and the solvent was evaporated under reduced pressure to afford a solid gum which was taken up with 50 mL of water containing 5-10 drops of a 35% ammonia solution. The 2,4-dinitroaniline was filtered off and the aqueous phase was extracted with 20 mL of AcOEt (× 3). The combined organic layers were discarded and the isoquinolinium

chloride (**8a**) solution was treated for 12 h with 5 mL of a 37% solution of hexafluorophosphoric acid. The resulting suspension was extracted with 30 mL of dichloromethane (× 3) and the combined organic phases were washed with water until neutral pH. The organic phases were dried over $MgSO_4$ and concentrated to afford 4.03 g (70%) of isoquinolinium hexafluorophosphate salt (–)-**8b** as a viscous oil which solidified upon cooling. Slightly orange solid, mp = 106–108 °C (CH_2Cl_2). $[\alpha]^{22}_D$ = –78 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.12 (d, *J* = 7.0 Hz, 3 H), 6.17 (q, *J* = 7.0 Hz, 1 H), 7.26–7.39 (m, 3 H), 7.48–7.50 (m, 2 H), 7.86 (t, *J* = 8.1 Hz, 1 H), 8.02–8.08 (m, 2 H), 8.21 (d, *J* = 6.9 Hz, 1 H), 8.35 (d, *J* = 6.9 Hz, 1 H), 8.46 (d, *J* = 8.3 Hz, 1 H), 9.81 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 20.3 (p), 71.1 (t), 126.9 (t) 127.1 (t), 127.5 (t), 127.8 (q), 129.7 (t), 130.1 (t), 131.2 (t), 131.7 (t), 132.1 (t), 136.3 (q), 137.58 (t), 137.6(q), 147.7 (t). HRMS (ESI^+, CH_3OH, $C_{17}H_{16}N$, $[M]^+$) calcd for 234.1283, found 234.1282.

(*S*)-(+)-2-(phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (+)-6a, new compound. A 200 mL Schlenk tube fitted with a magnetic stirring bar was charged with 20 mL of THF and 2.0 g (5.27 mmol) of hexafluorophosphate salt (–)-**8b**. Then, $NaBH_3CN$ (0.66 g, 10.50 mmol, 2.0 equiv.) was added by portions to the resulting suspension and the reaction mixture was stirred under argon for 12 h at 20 °C. The solvent was removed under reduced pressure and the resulting paste was taken up with 20 mL of water containing 5 drops of a 35% ammonia solution. The resulting suspension was extracted with 50 mL of dichloromethane (× 2) and the organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to afford a crude oil which was transferred to a chromatographic column (diethyl ether/petroleum ether, 3:7). The combined fractions were evaporated to afford the THIQ (+)-**6a** (1.0 g, 80%) as a colorless oil. $[\alpha]^{22}_D$ = +9.2 (*c* 0.5, $CHCl_3$). R_f = 0.7 (diethyl ether/petroleum ether, 3:7). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.47 (d, *J* = 6.9 Hz, 3 H), 2.56–2.63 (m, 1 H), 2.73–2.90 (m, 3 H), 3.53 (q, *J* = 6.9 Hz, 1 H), 3.54 (d, *J* = 16.0 Hz, 1 H), 3.79 (d, *J* = 16.0 Hz, 1 H), 6.93–6.96 (m, 1 H), 7.02–7.08 (m, 3 H), 7.23 (tt, *J* = 5.3, 2.3 Hz, 1 H), 7.28–7.32 (m, 2 H), 7.34–7.37 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.1 (p), 29.3 (s), 48.0 (s), 53.5 (s), 64.4 (t), 125.5 (t), 125.9 (t), 126.7 (t), 126.9 (t), 127.5 (t), 128.3 (t), 128.6 (t), 134.6 (q), 135.2 (q), 144.3 (q). HRMS (ESI^+, CH_3CN, $C_{17}H_{20}N$, $[M + H]^+$)

calcd for 238.1590, found 238.1590. Anal. Calcd for $C_{17}H_{19}N$ (379.28): C, 86.03; H, 8.07; N, 5.90. Found: C, 86.18; H, 7.94; N, 5.90.

(1*R*,2*S*)-(+)-2-(1-Phenyl-ethyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile, (+)-2a, new compound. A 500 mL undivided electrolysis cell equipped with a planar vitreous carbon electrode (diameter 100 mm, Carbone Lorraine®) and a magnetic stirrer, was successively charged with 300 mL of methanol, 2.0 g (8.42 mmol) of THIQ (+)-**6a**, 3.0 g of $LiClO_4$, 0.82 g (16.73 mmol, 2.0 equiv.) of NaCN and 0.19 mL (0.19 g, 3.32 mmol, 0.4 equiv.) of acetic acid. The working potential was adjusted to +1.0 V/SCE and after the consumption of 1700 C (2.1 F/mol), the electrolysis was stopped. Then, 150 mL of water were added to the solution (**Caution**: *$LiClO_4$ may lead to severe explosions when the material is evaporated to dryness. NaCN was destroyed by adding an excess of $KMnO_4$ onto the aqueous phase. Due to the possible release of HCN, the electrolysis should be carried out under a well ventilated hood*) and methanol was evaporated under reduced pressure at +50 °C. The aqueous phase was extracted with dichloromethane (50 mL × 3) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was diluted in 10 mL of dichloromethane and poured into a chromatographic column (30 × 3.5 cm) prepared with 30 g of silica and 3:7 petroleum ether/diethyl ether. The combined fraction were concentrated to afford α-amino nitrile **2a** (1.78 g, 81%) as a mixture (6:4) of diastereoisomers. A further slow crystallization (3 weeks) of this mixture in a biphasic system (petroleum ether/diethyl ether 5:1) afforded a single crystal of (+)-**2a** whose absolute configuration was determined by X-ray diffraction. Colorless plate, mp = 104–106 °C (petroleum ether/diethyl ether). $[\alpha]^{22}_D$ = +21.5 (*c* 1.0, C_6H_6, 99 (*R*,*S*):1 (*S*,*S*) dr); $[\alpha]^{22}_D$ = –58.0 (*c* 1.0, C_6H_6, 60 (*R*,*S*):40 (*S*,*S*) dr). *Due to a slow epimerization of C1(R) in benzene, the optical rotation of the sample should be recorded within a 5 min period*. R_f = 0.9 (diethyl ether/petroleum ether, 3:7). ^{1}H NMR (C_6D_6, 400 MHz) δ = 1.20 (d, *J* = 6.6 Hz, 3 H), 2.06 (dd, *J* = 12.6, 4.2 Hz, 1 H), 2.42–2.55 (m, 2 H), 2.60–2.66 (m, 1 H), 3.66 (q, *J* = 6.6 Hz, 1 H), 4.89 (s, 1 H), 6.75 (dm, *J* = 7.3 Hz, 1 H), 6.90 (td, *J* = 8.4, 1.5 Hz, 1 H), 6.93–6.99 (m, 2 H), 7.05–7.09 (m, 1 H), 7.12–7.19 (m, 4 H). ^{13}C NMR (C_6D_6, 400 MHz) δ = 21.4 (p), 28.2 (s), 44.9 (s), 52.4 (t), 62.3 (t), 116.5 (q), 126.2 (t), 127.0 (t), 127.2 (t), 127.4 (t), 128.0 (t), 128.6 (t), 129.2 (t), 130.3 (q), 134.8 (q), 144.7 (q). ^{1}H NMR (isomeric mixture, 60 (*R,S*):40

(*S,S*), C_6D_6, 400 MHz) δ = 1.18 (d, *J* = 6.6 Hz, 1.8 H); 1.20 (d, *J* = 6.6 Hz, 1.2 H); 2.06 (dd, *J* = 12.6, 4.2 Hz, 0.6 H); 2.34 (dd, *J* = 16.6, 2.6 Hz, 0.4 H); 2.42–2.66 (m, 2.2 H); 2.76 (ddd, *J* = 17.1, 11.6, 6.2 Hz, 0.4 H); 2.98 (ddt, = 11.9, 6.3, 1.6 Hz, 0.4 H); 3.66 (q, *J* = 6.6 Hz, 0.6 H), 3.76 (q, *J* = 6.6 Hz, 0.4 H); 4.52 (s, 0.4 H); 4.90 (s, 0.6 H); 6.28 (d, *J* = 8.3 Hz, 0.4 H); 6.71–6.76 (m, 1 H); 6.79 (d, *J* = 3.7 Hz, 0.4 H); 6.88–7.00 (m, 2.2 H), 7.05–7.10 (m, 1 H); 7.12–7.20 (m, 3.2 H); 7.32–7.36 (m, 0.8 H). ^{1}H NMR (isomeric mixture, 60 (*R,S*):40 (*S,S*), $CDCl_3$, 500 MHz) δ = 1.47 (d, *J* = 6.6 Hz, 1.8 H), 1.50 (d, *J* = 6.6 Hz, 1.2 H), 2.56–2.63 (m, 1 H), 2.77 (td, *J* = 11.9, 4.0 Hz, 0.4 H), 2.83–2.91 (m, 1.8 H), 3.11 (ddd, *J* = 17.4, 11.6, 6.2 Hz, 0.4 H), 3.47 (dd = 11.9, 6.3 Hz, 0.4 H), 3.73 (q, *J* = 6.6 Hz, 0.6 H), 3.80 (q, *J* = 6.6 Hz, 0.4 H), 4.49 (s, 0.4 H), 5.18 (s, 0.6 H), 6.96 (d, *J* = 8.3 Hz, 0.4 H), 7.10–7.40 (m, 8.6 H). ^{13}C NMR (isomeric mixture, 60 (*R,S*):40 (*S,S*), $CDCl_3$, 125 MHz) δ = 21.7 & 21.8 (p), 28.5 & 28.9 (s), 42.6 & 45.0 (s), 52.6 & 54.1 (t), 61.9 & 62.4 (t), 116.8 & 117.1 (q), 126.3 (t), 126.5 (t), 127.1 (t), 127.2 (t), 127.4 (t, 2 C), 127.5 (t), 127.8 (t), 128.3 (t), 128.4 (t), 128.7 (t), 128.9 (t), 129.1 (t), 129.4 (t), 129.8 & 130.3 (q), 134.5 & 134.9 (q), 143.1 &144.4 (q). HRMS (ESI^+, CH_3OH, $C_{18}H_{18}N_2Na$, $[M + Na]^+$) calcd for 285.1368, found 285.1361. Anal. Calcd for $C_{18}H_{18}N_2$ ($C_{18}H_{18}N_2$): C, 82.41; H, 6.92; N, 10.68. Found: C, 82.47; H, 6.89; N, 10.38.

(1*R*,1'*S*)-(+)-6,7-dimethoxy-2(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile, (+)-2b. The synthesis was as reported for (+)-**2a** (*vide supra*) but with 2.0 g (6.72 mmol) of (+)-(*S*)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (+)-**6b**. After the consumption of 1430 C (2.2 F/mol), 100 mL of water were added to the electrolysis solution. Methanol was evaporated under reduced pressure and the aqueous phase was extracted twice with 100 mL of diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated. The crude reaction mixture was crystallized in a minimum of boiling ethanol containing 0.1 g of sodium cyanide to afford 1.58 g (73%) of (+)-**2b** as a white solid: mp 163–165 °C; $[\alpha]^{22}_D$ +40 (c 1.0, C_6D_6). Spectral data were reported in ref.[26a]. A single crystal was obtained upon a slow crystallization in ethanol and was studied by X-ray crystallography.

(1*S*,1'*R*)-(–)-6,7-dimethoxy-2(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile, (–)-2b. The synthesis was as reported for (+)-**2a** but with (–)-(*R*)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline to afford (–)-**2b** as a white solid: $[\alpha]^{22}_{D}$ –38 (c 1.0, C_6D_6).

Procedure A: synthesis of THIQs **1a–i** from α-amino nitrile **2a**.

(1*S*,1'*S*)-(–)-1-methyl-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (–)-1a.[13a] An oven dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was flushed with argon, and was successively charged with 10 mL of dry THF and 1.6 g (6.10 mmol) of α-amino nitrile **2b** as a 60:40 mixture of diastereoisomers. The flask was then cooled to –80 °C and 10 mL of a LDA solution in dry THF [prepared from 1.20 mL (0.86 g, 8.54 mmol) of diisopropylamine and 2.90 mL (7.25 mmol, 1.18 equiv.) of butyllithium (2.5 M solution in hexane)] were slowly added by syringe. The anion solution turned rapidly red and was allowed to warm to –20 °C over a 2 h period and was then cooled to –80 °C. Then, 1.71 g (0.75 mL, 12.04 mmol, 2.0 equiv.) of iodomethane was added dropwise and the reaction mixture was allowed to warm to –20 °C for 3 h. The contents of the flask were poured into a mixture of 100 mL of diethyl ether and 15 mL of water containing 0.25 g of NaCN. The organic layer was washed with 10 mL of water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield a crude oily residue which was used in the next step without further purification. The oily residue was dissolved in 10 mL of ethanol and poured in a 100-mL, one-necked flask, equipped with a rubber septum. The flask is cooled to –20 °C, and 0.92 g (24.40 mmol) of $NaBH_4$ was added in portions. Stirring was continued for 1 h at that temperature, and the solution was allowed to reach room temperature overnight. The solvents were evaporated under reduced pressure, and the crude material was taken-up with 20 mL of a 15% ammonia solution and the aqueous layer was extracted twice with 25 ml of dichloromethane. The combined organic layers were washed with 25 mL of water, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The crude oily residue was diluted with 5 mL of dichloromethane and poured into a chromatographic column (50 × 2.5 cm), prepared with 40 g of silica and 1:1 diethyl ether/petroleum ether. The combined fractions were

evaporated, to afford 1.1 g (72% based on α-amino nitrile **2b**) of (–)-**1a**. Yellow viscous oil. R_f = 0.70 (diethyl ether/petroleum ether, 3:7). $[\alpha]^{22}_D$ –21 (*c* 1.0, $CHCl_3$, 90 (*S*,*S*):10 (*R*,*S*) dr). ^{1}H NMR (isomeric mixture, 90 (*S*,*S*):10 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 300 MHz) δ = 1.32 (d, *J* = 6.9 Hz, 3 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 2.47–2.63 (dm, *J* = 14.0 Hz, 1 H), 2.80–3,00 (m, 3 H), 3.75 (q, *J* = 6.9 Hz, 1 H), 4.06 (q, *J* = 6.9 Hz, 1 H), 6.98–7.38 (m, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 19.4 (p), 21.3 (p), 26.5 (s), 39.9 (s), 53.6 (t), 59.5 (t), 125.5 (t), 125.7 (t), 126.7 (t), 127.2 (t), 127.8 (t), 128.3 (t), 128.9 (t), 134.6 (q), 140.5 (q), 146.6 (q). HRMS (EI^+, $C_{18}H_{21}N$, $[M]^+$) calcd for 251.1674, found 251.1679. Anal. Calcd for $C_{18}H_{21}N$ (251.37): C, 86.01; H, 8.42; N, 5.57. Found: C, 85.90; H, 8.25; N, 5.87.

(1*S*,1'*S*)-(–)-1-propyl-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (–)-1b, new compound. The synthesis of THIQ (–)-**1b** (1.24 g, 73%, 90:10 dr) was carried out according to procedure A, but with 1.18 mL (2.06 g, 12.20 mmol, 2.0 equiv.) of 1-iodopropane as the alkylating agent. The crude oily residue was diluted with 5 mL of dichloromethane and poured into a chromatographic column (50 × 2.5 cm), prepared with 40 g of silica and 2:8 diethyl ether/petroleum ether. Orange oil, $[\alpha]^{22}_D$ = –35 (*c* 1.0, $CHCl_3$, 90 (*S*,*S*):10 (*R*,*S*) dr). R_f = 0.8 (diethyl ether/petroleum ether, 20:80). ^{1}H NMR (isomeric mixture, 90 (*S*,*S*):10 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 300 MHz) δ = 0.80 (t, *J* = 7.4 Hz, 3 H), 1.02–1.15 (m, 1 H), 1.20–1.28 (m, 2 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 1.70–1.80 (m, 1 H), 2.57 (dt, *J* = 13.0, 3.6 Hz, 1 H), 2.96 (ddd, *J* = 16.5, 10.4, 6.9 Hz, 1 H), 3.15–3.22 (m, 2 H), 3.60 (dd, *J* = 8.3, 4.2 Hz, 1 H), 3.75 (q, *J* = 6.9 Hz, 1 H), 6.85–6.90 (m, 1 H), 7.02–7.10 (m, 3 H), 7.20–7.30 (m, 5 H). ^{13}C NMR (isomeric mixture, 90 (*S*,*S*):10 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 75 MHz) δ = 14.7 (p), 20.2 (p), 21.5 (s), 24.4 (s), 26.1 (s), 39.7 (s), 58.9 (t), 59.1 (t), 126.0 (t), 127.2 (t), 128.1 (t), 128.7 (t), 129.3 (t), 135.3 (q), 140.0 (q), 146.9 (q). HRMS (ESI^+, MeOH, $C_{20}H_{26}N$, $[M + H]^+$) calcd for 280.2065, found 280.2064. Anal. Calcd for $C_{20}H_{25}N$ (279.42): C, 85.97; H, 9.02; N, 5.01. Found C, 86.15; H, 9.04; N, 4.94.

(1*S*,1'*S*)-(–)-1-pentyl-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (–)-1c, new compound. The synthesis of THIQ (–)-**1c** (1.33 g, 71%, 88:12 dr) was carried out according to procedure A, but with 2.46 g, (12.42 mmol, 2.0 equiv.) of 1-iodopentane as the alkylating agent. The crude oily residue was diluted with 5 mL of

dichloromethane and poured into a chromatographic column (50 × 2.5 cm), prepared with 40 g of silica and 2:8 diethyl ether/petroleum ether. Orange oil, $[\alpha]^{22}_{D}$ = –30 (*c* 0.5, $CHCl_3$, 88 (*S*,*S*):12 (*R*,*S*) dr). R_f = 0.8 (diethyl ether/petroleum ether, 2:8). ^{1}H NMR (isomeric mixture, 88 (*S*,*S*):12 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 400 MHz) δ = 0.82 (t, *J* = 7.4 Hz, 3 H), 1.02–1.15 (m, 2 H), 1.20–1.28 (m, 3 H), 1.32–1.49 (m, 2 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 1.70–1.80 (m, 1 H), 2.49 (dt, *J* = 13.0, 3.6 Hz, 1 H), 2.91 (ddd, *J* = 16.5, 10.4, 6.9 Hz, 1 H), 3.15–3.22 (m, 2 H), 3.50 (dd, *J* = 8.3, 4.2 Hz, 1 H), 3.75 (q, *J* = 6.9 Hz, 1 H), 6.85–6.89 (m, 1 H), 7.02–7.12 (m, 3 H), 7.18–7.30 (m, 5 H). ^{13}C NMR (isomeric mixture, 88 (*S*,*S*):12 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 100 MHz) δ = 14.1 (p), 21.0 (p), 22.7 (s), 23.9 (s), 26.1 (s), 31.9 (s), 36.8 (s), 39.0 (s), 58.54 (t), 58.58 (t), 126.7 (t), 127.6 (t), 128.1 (t), 128.2 (t), 128.7 (t), 134.8 (q), 139.6 (q), 146.5 (q). HRMS, (ESI^+, MeOH, $C_{22}H_{30}N$, $[M + H]^+$) calcd for 308.2378, found 308.2373. Anal. Calcd for $C_{22}H_{29}N$ (307.48): C, 85.94; H, 9.51; N, 4.56. Found: C, 86.19; H, 9.73; N, 4.67.

(1*S*,1'*S*)-(–)-1-heptyl-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (–)-1d, new compound. The synthesis of THIQ (–)-**1d** (1.23 g, 60%, 87:13 dr) was carried out according to procedure A, but with 2.75 g, (12.20 mmol, 2.0 equiv.) of 1-iodoheptane as the alkylating agent. The crude oily residue was diluted with 5 mL of dichloromethane and poured into a chromatographic column (50 × 2.5 cm), prepared with 40 g of silica and 2:8 diethyl ether/petroleum ether. Orange oil, $[\alpha]^{22}_{D}$ = –23 (*c* 0.5, $CHCl_3$, 87 (*S*,*S*):13 (*R*,*S*) dr). R_f = 0.85 (diethyl ether/petroleum ether, 2:8). ^{1}H NMR (isomeric mixture, 87 (*S*,*S*):13 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 400 MHz) δ = 0.86 (t, *J* = 7.4 Hz, 3 H), 1.02–1.15 (m, 2 H), 1.16–1.35 (m, 8 H), 1.37 (d, *J* = 6.9 Hz, 3 H), 1.40–1.48 (m, 1 H), 1.70–1.80 (m, 1 H), 2.50 (dt, *J* = 13.0, 3.6 Hz, 1 H), 2.91 (ddd, *J* = 16.5, 10.4, 6.9 Hz, 1 H), 3.15–3.22 (m, 2 H), 3.52 (dd, *J* = 8.3, 4.2 Hz, 1 H), 3.75 (q, *J* = 6.9 Hz, 1 H), 6.85–6.89 (m, 1 H), 7.02–7.12 (m, 3 H), 7.18–7.30 (m, 5 H). ^{13}C NMR (isomeric mixture, 87 (*S*,*S*):13 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 100 MHz) δ = 14.1 (p), 20.9 (p), 22.7 (s), 24.0 (s), 26.5 (s), 29.3 (s), 29.7 (s), 31.9 (s), 36.9 (s), 39.1 (s), 58.6 (t), 125.5 (t) 125.6 (t), 126.7 (t), 127.6 (t), 128.1 (t), 128.2 (t), 128.7 (t), 134.8 (q), 139.7 (q), 146.5 (q). HRMS (ESI^+, MeOH, $[M + H]^+$, $C_{24}H_{34}N$) calcd for 336.2685, found 336.2686. Anal. Calcd for $C_{24}H_{33}N$ (335.53): C, 85.91; H, 9.91; N, 4.17. Found: C, 85.72; H, 9.84; N, 4.27.

(1*S*,1'*S*)-(–)-1-undecyl-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (–)-1e, new compound. The synthesis of THIQ (–)-**1e** (0.95 g, 40%, 85:15 dr) was carried out according to slightly procedure A but with a 4 h stirring at 0 °C) and with 3.44 g (12.20 mmol, 2.0 equiv.) of 1-iodoundecane as the alkylating agent. THIQ (+)-**6b** was recovered in 20% yield after purification of the crude material by column chromatography (petroleum ether/diethyl ether, 80:20). Orange oil, $[\alpha]^{22}_{D}$ = –11 (*c* 1.0, $CHCl_3$, isomeric mixture, 85 (*S*,*S*):15 (*R*,*S*) dr). R_f = 0.8 (petroleum ether/diethyl ether, 80:20). ^{1}H NMR (isomeric mixture, 85 (*S*,*S*):15 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 400 MHz) δ = 0.88 (t, *J* = 7.4 Hz, 3 H), 1.02–1.15 (m, 1 H), 1.16–1.35 (m, 17 H), 1.37 (d, *J* = 6.9 Hz, 3 H), 1.40–1.48 (m, 1 H), 1.70–1.80 (m, 1 H), 2.50 (dt, *J* = 13.0, 3.6 Hz, 1 H), 2.91 (ddd, *J* = 16.5, 10.4, 6.9 Hz, 1 H), 3.15–3.22 (m, 2 H), 3.52 (dd, *J* = 8.3, 4.2 Hz, 1 H), 3.75 (q, *J* = 6.9 Hz, 1 H), 6.85–6.89 (m, 1 H), 7.02–7.12 (m, 3 H), 7.18–7.30 (m, 5 H). ^{13}C NMR (isomeric mixture, 85 (*S*,*S*):15 (*R*,*S*) dr, major diastereoisomer, $CDCl_3$, 100 MHz) δ = 14.2 (p), 21.0 (p), 22.7 (s), 24.0 (s), 26.5 (s), 29.4 (s), 29.71 (s), 29.75 (s), 32.0 (s), 36.9 (s), 39.1 (s), 58.6 (t), 125.5 (t), 125.6 (t), 126.7 (t), 127.7 (t), 128.1 (t), 128.2 (t), 128.8 (t), 134.9 (q), 139.6 (q), 146.5 (q). HRMS (ESI$^+$, MeOH, $[M + H]^+$) $C_{28}H_{42}N$ calcd for 392.3311, found 392.3310. Anal. Calcd for $C_{28}H_{41}N$ (391.64): C, 85.87; H, 10.55; N, 3.58. Found: C, 85.74; H, 10.41; N, 3.66.

(1*S*,1'*S*)-(+)-1-(4-methoxybenzyl)-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (+)-1f.[13a] The synthesis of THIQ (+)-**1f** (1.63 g, 75%, 95:5 dr) was carried out according to procedure A, but with 1.84 g, (9.15 mmol, 1.5 equiv.) of 1-(bromomethyl)-4-methoxybenzene as the alkylating agent. A slow crystallization of THIQ (+)-**1f** in ethanol afforded single crystals which were analyzed by X-ray diffraction. Colourless crystals, mp = 82–84 °C (ethanol). R_f = 0.4 (petroleum ether/diethyl ether, 8:2). $[\alpha]^{22}_{D}$ = +57 (*c* 1.0, $CHCl_3$, 99:1 dr), lit.[13a] = +12 (0.6, $CHCl_3$, 90 (*S,S*):10 (*R,S*) dr). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.33 (d, *J* = 6.5 Hz, 3 H), 2.51 (ddd, *J* = 16.8, 6.8, 1.9 Hz, 1 H), 2.69 (dd, *J* = 13.6, 6.3 Hz, 1 H), 2.93 (ddd, *J* = 16.8, 11.5, 6.0 Hz, 1 H), 3.02 (dd, *J* = 13.6, 7.8 Hz, 1 H), 3.21 (dm, *J* = 13.8 Hz, 1 H), 3.33 (ddd, *J* = 13.8, 11.6, 4.7 Hz, 1 H), 3.73 (q, *J* = 6.6 Hz, 1 H), 3.77 (t, *J* = 6.8 Hz, 1 H), 3.80 (s, 3 H), 6.60 (d, *J* = 7.6 Hz, 1 H), 6.75 (dm, *J* = 8.7 Hz, 2 H), 6.85 (dm, *J* = 8.7

Hz, 2 H), 6.95–7.05 (m, 3 H), 7.08–7.15 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.8 (p), 24.2 (s), 39.4 (s), 41.7 (s), 55.3 (p), 59.1 (t), 60.9 (t), 113.2 (t), 125.2 (t), 125.9 (t), 126.4 (t), 127.3 (t), 128.0 (t), 128.6 (t), 128.8 (t), 130.7 (t), 132.1 (q), 135.0 (q), 138.2 (q), 146.1 (q), 157.8 (q). HRMS (ESI$^+$, CH_3OH/CH_2Cl_2, 90:10, $C_{25}H_{28}NO$, $[M + H]^+$) calcd for 358.2171, found 358.2170. Anal. Calcd for $C_{25}H_{27}NO$ (357.49): C, 83.99; H, 7.61; N, 3.92. Found: C, 84.27; H, 7.85; N, 3.96.

(1*S*,1'*S*)-(+)-1-(3,4-dimethoxybenzyl)-2(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (+)-1g.[13a] The synthesis of THIQ (+)-**1g** (1.65 g, 70%, 94:6 dr) was carried out according to procedure A, but with 1.97 g, (8.54 mmol, 1.4 equiv.) of 4-(bromomethyl)-1,2-dimethoxybenzene as the alkylating agent. The crude oily residue was diluted with 5 mL of dichloromethane and poured into a chromatographic column (50 × 2.5 cm), prepared with 30 g of silica and 8:2 petroleum ether/diethyl ether. A slow crystallization of THIQ (+)-**1g** in ethanol afforded single crystals which were analyzed by X-ray diffraction. Colourless crystals, mp = 88–90 °C (ethanol). R_f = 0.3 (petroleum ether/diethyl ether, 8:2). $[\alpha]^{22}_D$ = +14.0 (*c* 1.0, $CHCl_3$, 99:1 dr). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.34 (d, *J* = 6.5 Hz, 3 H), 2.51 (dm, *J* = 17.0 Hz, 1 H), 2.72 (dd, *J* = 13.6, 6.5 Hz, 1 H), 2.93 (ddd, *J* = 17.0, 11.5, 5.8 Hz, 1 H), 3.02 (dd, *J* = 13.6, 7.2 Hz, 1 H), 3.21 (dm, *J* = 13.8 Hz, 1 H), 3.31 (ddd, *J* = 13.8, 11.6, 4.7 Hz, 1 H), 3.67 (s, 3 H), 3.74 (q, *J* = 6.6 Hz, 1 H), 3.79 (t, *J* = 6.8 Hz, 1 H), 3.86 (s, 3 H), 6.33 (d, *J* = 1.9 Hz, 1 H), 6.51 (dd, *J* = 8.1, 1.9 Hz, 1 H), 6.60 (d, *J* = 7.6 Hz, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 6.95–7.05 (m, 3 H), 7.06–7.11 (m, 2 H), 7.12–7.16 (m, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.5 (p), 24.3 (s), 39.6 (s), 42.5 (s), 55.6 (p), 55.9 (p), 59.1 (t), 61.0 (t), 110.7 (t), 112.9 (t), 121.8 (t), 125.2 (t), 125.9 (t), 126.5 (t), 127.4 (t), 128.0 (t), 128.6 (t), 128.8 (t), 132.6 (q), 135.0 (q), 138.0 (q), 146.2 (q), 147.2 (q), 148.3 (q). HRMS (ESI$^+$, CH_3OH/CH_2Cl_2, 9:1, $C_{26}H_{30}NO_2$, $[M + H]^+$) calcd for 388.2276, found 388.2275. Anal. Calcd for $C_{26}H_{29}NO_2$ (387.52): C, 80.59; H, 7.54; N, 3.61. Found: C, 80.19; H, 7.52; N, 3.65.

(1*S*,1'*S*)-(–)-2-(1-phenylethyl)-1(3-((tetrahydro-2*H*-pyran-2-yl)oxy)propyl)-1,2,3,4-tetrahydroisoquinoline, (–)-1h, new compound. The synthesis of THIQ (–)-**1h** (1.62 g, 70%, 95:5 dr) was carried out according to procedure A, but with 2.47 g, (9.15 mmol, 1.5 equiv.) of 2-(3-iodopropoxy)-tetrahydro-2*H*-pyran as the alkylating

agent. The minor (1*R*,1'*S*)-**1h** diastereoisomer eluted at R_f = 0.5 (petroleum ether/diethyl ether, 8:2) and was separated by column chromatography. THIQ (–)-**1h** (1.54 g) was recovered in 65% yield. Viscous yellow oil. R_f = 0.3 (petroleum ether/diethyl ether, 8:2). $[\alpha]^{22}_D$ = –16.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.38 (d, *J* = 6.5 Hz, 3 H), 1.40–1.85 (m, 10 H), 2.55 (dt, *J* = 16.8, 3.5 Hz, 1 H), 2.91 (ddd, *J* = 16.8, 9.7, 7.2 Hz, 1 H), 3.15–3.28 (m, 3 H), 3.42–3.47 (m, 1 H), 3.54–3.65 (m, 2 H), 3.72–3.82 (m, 2 H), 4.46–4.50 (m, 1 H), 6.90 (dd, *J* = 7.0, 2.0 Hz, 1 H), 7.05–7.11 (m, 3 H), 7.18–7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz, splitting signals indicated with an asterisk (*) are due to the presence of the tetrahydropyranyl group) δ = 19.6* & 19.7* (s), 20.6 (p), 23.9 (s), 25.5 (s), 26.5* & 26.6* (s), 30.73* & 30.75* (s), 33.2* & 33.3* (s), 38.9 (s), 58.28* & 58.37* & 58.40* (t), 62.2* & 62.3* (s), 67.6* & 67.7* (s), 98.73* & 98.75* (t), 125.57 (t), 125.64 (t), 126.7 (t), 127.6 (t), 128.2 (t), 128.7 (t), 134.9 (q), 139.3 (q), 146.29 & 146.31 (q). HRMS (ESI^+, $C_{25}H_{34}NO_2$, [M + H^+]) calcd for 380.2589, found 380.2589. Anal. Calcd for $C_{25}H_{33}NO_2$ (379.54): C, 79.11; H, 8.76; N, 3.69. Found: C, 79.51; H, 8.76; N, 3.93.

(1*S*,1'*S*)-(–)-1-(2-(1,3-dioxolan-2-yl)ethyl-2-((*S*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (–)-1i, new compound. The synthesis of THIQ (–)-**1i** (1.44 g, 70%, 97:3 dr) was carried out according to procedure A, but with 2.08 g, (9.15 mmol, 1.5 equiv.) of 2-(2-iodoethyl)-[1,3]-dioxolane as the alkylating agent. Trace amount (up to 2%) of the minor (1*R*,1'*S*)-**1i** diastereoisomer were separated by column chromatography. Highly viscous yellow oil, R_f = 0.3 (petroleum ether/diethyl ether, 8/2); $[\alpha]^{22}_D$ = –13.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.37 (d, *J* = 6.5 Hz, 3 H), 1.56–1.62 (m, 2 H), 1.80–1.90 (m, 2 H), 2.50 (dt, *J* = 16.8, 3.7 Hz, 1 H), 2.90 (dt, *J* = 16.8, 8.2 Hz, 1 H), 3.15–3.19 (m, 2 H), 3.57 (dd, *J* = 8.4, 4.3 Hz, 1 H), 3.73–3.79 (m, 3 H), 3.87–3.90 (m, 2 H), 4.71 (t, *J* = 4.6 Hz, 1 H), 6.90 (dd, *J* = 5.8, 2.0 Hz, 1 H), 7.05–7.20 (m, 3 H), 7.18–7.30 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.5 (p), 23.9 (s), 30.53 (s), 30.61 (s), 38.8 (s), 58.1 (t), 58.3 (t), 64.76 (s), 64.77 (s), 104.6 (t), 125.6 (t), 125.7 (t), 126.7 (t), 127.6 (t), 128.1 (t), 128.2 (t), 128.8 (t), 134.9 (q), 139.0 (q), 146.24 (q). HRMS (ESI^+, $C_{22}H_{28}NO_2$, [M + H^+]) calcd for 338.2115, found 338.2116. Anal. Calcd for $C_{22}H_{27}NO_2$ (337.46): C, 78.30; H, 8.06; N, 4.15. Found C, 78.17; H, 8.01, N, 4.20.

Procedure B: Synthesis of THIQs (+)-**9a–g**.

(*S*)-(–)-1-methyl-1,2,3,4-tetrahydroisoquinoline, (–)-9a. A 50-mL low-pressure hydrogenator was charged with 10 mL of ethanol, 0.08 g (20% in mass) of 20% $Pd(OH)_2/C$ and 0.38 g (1.5 mmol) of THIQ (–)-**1a**. Air was removed from the reactor by alternatively filling it with hydrogen and venting it three times. The hydrogen pressure (3.75×10^3 Torr, 5 bars) was applied, and the suspension was stirred for 48 h at room temperature. The suspension was filtered over a small pad of Celite, and the vessel was washed with ethanol. The filtrate was concentrated under reduced pressure, and the resulting paste was dissolved in 10 mL of water. The solution was cooled in an ice bath and was basified with solid KOH. The white oily residue was extracted twice with 50 mL of dichloromethane, and the combined organic layers were washed with 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator. The crude oily residue was diluted with 5 mL of dichloromethane and poured into a chromatographic column (20 × 2.0 cm), prepared with 10 g of silica and 95:5 dichloromethane/methanol. The unreacted THIQ (–)-**1a** (0.040 g, 10%) was eluted first, followed by 1.76 g (80%) of THIQ (–)-**9a**. Yellow oil. $[\alpha]^{22}_D$ = –51 (*c* 1.8, $CHCl_3$, 90:10 er), lit.[48] = +75 (*c* 1.0, $CHCl_3$, 99:1 er, this value is referred to the *R* enantiomer). R_f = 0.2 (dichloromethane/methanol, 8:2). ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.45 (d, *J* = 6.7 Hz, 3 H), 2.04–2.06 (s, br. 1 H), 2.74 (dt, *J* = 16.0, 4.6 Hz, 1 H), 2.83–2.90 (ddd, *J* = 16.0, 8.7, 5.5 Hz, 1 H), 3.00 (ddd, *J* = 13.0, 8.8, 4.7 Hz, 1 H), 3.25 (dt, *J* = 13.0, 5.1 Hz, 1 H), 4.10 (q, *J* = 6.7 Hz, 1 H), 7.05–7.15 (m, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 22.6 (p), 29.8 (s), 41.6 (s), 51.5 (t), 125.89 (t), 125.90 (t), 126.0 (t), 129.2 (t), 134.8 (q), 140.2 (q). HRMS ($C_{10}H_{12}N$, EI, $[M–H]^+$) calcd for 146.0970, found 146.0983. Anal. Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.51. Found: C, 81.00; H, 8.80; N, 9.45.

(*S*)-(–)-1-propyl-1,2,3,4-tetrahydroisoquinoline, (–)-9b.[49] The synthesis of THIQ (–)-**9b** (0.19 g, 73%, 90:10 er) was carried out according to procedure B. The unreacted THIQ (–)-**1b** (0.029 g) was recovered in 7% yield after column chromatography (dichloromethane/methanol, 8:2). Yellow oil. $[\alpha]^{22}_D$ = –35 (*c* 1.0, $CHCl_3$, 90:10 er). R_f = 0.2 (dichloromethane/methanol, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.97 (t, *J* = 7.3 Hz, 3 H), 1.40–1.60 (m, 2 H), 1.70–1.88 (m, 2 H), 2.75 (dt, *J*

= 13.0, 5.1 Hz, 1 H), 2.80–2.90 (m, 1 H), 3.00 (ddd, *J* = 12.6, 7.6, 5.1 Hz, 1 H), 3.25 (dt, *J* = 12.6, 6.8 Hz, 1 H), 3.45–3.55 (s, br. 1 H), 4.02 (dd, *J* = 8.8, 3.9 Hz, 1 H), 7.05–7.15 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.2 (p), 19.3 (s), 29.5 (s), 38.5 (s), 40.7 (s), 55.4 (t), 125.9 (t), 126.0 (t), 126.2 (t), 129.2 (t), 134.7 (q), 139.0 (q). HRMS ($C_{12}H_{18}N$, ESI$^+$, MeOH, [M + H]$^+$) calcd for 176.1439, found 176.1436. Anal. Calcd for $C_{12}H_{17}N$ (175.27): C, 82.23; H, 9.78; N, 7.99. Found: C 81.99; H 9.73; N 7.99.

(*S*)-(–)-1-pentyl-1,2,3,4-tetrahydroisoquinoline, (–)-9c.[50] The synthesis of THIQ (–)-**9c** (0.21 g, 70%, 88:12 er) was carried out according to procedure B. The unreacted THIQ (–)-**1c** (0.055 g) was recovered in 12% yield after column chromatography (dichloromethane/methanol, 8:2). Yellow oil. $[\alpha]^{22}_D$ = –90 (*c* 1.0, $CHCl_3$, 88:12 er). R_f = 0.3 (dichloromethane/methanol, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.90 (t, *J* = 7.3 Hz, 3 H), 1.25–1.50 (m, 6 H), 1.68–1.76 (m, 1 H), 1.79–1.88 (m, 1 H), 2.00–2.09 (s, br., 1 H), 2.75 (dt, *J* = 13.0, 5.1 Hz, 1 H), 2.78–2.88 (m, 1 H), 2.98 (ddd, *J* = 12.6, 7.6, 5.1 Hz, 1 H), 3.22 (dt, *J* = 12.6, 6.8 Hz, 1 H), 3.95 (dd, *J* = 8.8, 3.9 Hz, 1 H), 7.05–7.15 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.1 (p), 22.7 (s), 25.9 (s), 30.0 (s), 32.04 (s), 36.5 (s), 41.1 (s), 55.8 (t), 125.7 (t), 125.8 (t), 126.1 (t), 129.2 (t), 135.1 (q), 139.8 (q). HRMS ($C_{14}H_{22}N$, ESI$^+$, MeOH, [M + H]$^+$) calcd for 204.1747, found 204.1746. Anal. Calcd for $C_{14}H_{21}N$ (203.32): C, 82.70; H, 10.41; N, 6.89. Found: C 82.28; H 10.31; N 6.90.

(*S*)-(–)-1-heptyl-1,2,3,4-tetrahydroisoquinoline, (–)-9d, new compound. The synthesis of THIQ (–)-**9d** (0.27 g, 80%, 87:13 er) was carried out according to procedure B and was purified by column chromatography (dichloromethane/methanol, 8:2). Yellow oil. $[\alpha]^{22}_D$ = –62 (*c* 1.0, $CHCl_3$, 87:13 er). R_f = 0.4 (dichloromethane/methanol, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.88 (t, *J* = 7.3 Hz, 3 H); 1.25–1.50 (m, 10 H), 1.68–1.76 (m, 1 H), 1.79–1.88 (m, 1 H), 2.05–2.09 (s, br., 1 H), 2.75 (dt, *J* = 13.0, 5.1 Hz, 1 H), 2.78–2.88 (m, 1 H), 2.98 (ddd, *J* = 12.6, 7.6, 5.1 Hz, 1 H), 3.22 (dt, *J* = 12.6, 6.8 Hz, 1 H), 3.95 (dd, *J* = 8.8, 3.9 Hz, 1 H), 7.05–7.15 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.1 (p), 22.7 (s), 26.2 (s), 29.3 (s), 29.8 (s), 30.0 (s), 31.9 (s), 36.5 (s), 41.1 (s), 55.8 (t), 125.7 (t), 125.8 (t), 126.1 (t), 129.2 (t), 135.1 (q), 139.7 (q). HRMS ($C_{16}H_{26}N$, ESI$^+$, MeOH, [M + H]$^+$) calcd for

232.2060, found 232.2062. Anal. Calcd for $C_{16}H_{25}N$ (231.38): C, 83.06; H, 10.89; N, 6.05. Found: C 82.70; H 10.70; N 6.03.

(*S*)-(–)-1-undecyl-1,2,3,4-tetrahydroisoquinoline, (–)-9e, new compound. The synthesis of THIQ (–)-**9e** (0.32 g, 75%, 85:15 er) was carried out according to procedure B. The unreacted THIQ (–)-**1e** (0.047 g) was recovered in 8% yield after column chromatography (dichloromethane/methanol, 8:2). Yellow oil. $[\alpha]^{22}_{D}$ = –47 (*c* 1.0, $CHCl_3$, 85:15 er). R_f = 0.6 (dichloromethane/methanol, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.88 (t, *J* = 7.3 Hz, 3 H), 1.20–1.50 (m, 18 H), 1.68–1.77 (m, 1 H), 1.79–1.88 (m, 1 H), 2.00–2.09 (s, br., 1 H), 2.75 (dt, *J* = 13.0, 5.1 Hz, 1 H), 2.78–2.88 (m, 1 H), 2.98 (ddd, *J* = 12.6, 7.6, 5.1 Hz, 1 H), 3.22 (dt, *J* = 12.6, 6.8 Hz, 1 H), 3.95 (dd, *J* = 8.8, 3.9 Hz, 1 H), 7.05–7.15 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.1 (p), 22.7 (s), 26.2 (s), 29.4 (s), 29.64 (s), 29.65 (s), 29.66 (s), 29.68 (s), 29.8 (s), 30.0 (s), 31.9 (s), 36.5 (s), 41.1 (s), 55.8 (t), 125.7 (t), 125.8 (t), 126.1 (t), 129.2 (t); 135.1 (q), 139.7 (q). HRMS ($C_{20}H_{34}N$, ESI^+, MeOH, $[M + H]^+$) calcd for 288.2685, found 288.2684. Anal. Calcd for $C_{20}H_{33}N$ (287.49): C, 83.56; H, 11.57; N, 4.87. Found: C 83.00; H 11.40; N 4.85.

(*S*)-(–)-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline, (–)-9f, new compound. The synthesis of THIQ (–)-**9f** (0.27 g, 70%, 99:1 er) was carried out according to procedure B. *Because of a rapid oxidation upon air contact, the analyses of THIQ (–)-**9f** should be performed promptly after chromatographic purification* (dichloromethane/methanol, 9:1). Yellow oil. R_f = 0.3 (dichloromethane/methanol, 9:1). $[\alpha]^{22}_{D}$ = –30.0 (*c* 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.35-2.55 (s, br., 1 H), 2.73–2.98 (m, 4 H), 3.16–3.25 (m, 2 H), 3.78 (s, 3 H), 4.15 (dd, *J* = 9.8, 3.9 Hz, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.08–7.25 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.6 (s), 40.6 (s), 41.5 (s), 55.2 (p), 57.3 (t), 113.9 (t), 125.7 (t), 126.17 (t), 126.22 (t), 129.3 (t), 130.3 (t), 130.9 (q), 135.2 (q), 138.5 (q), 158.3 (q). HRMS ($C_{17}H_{20}NO$, ESI^+, MeOH, $[M + H]^+$) calcd for 254.1545, found 254.1543. Anal. Calcd for $C_{17}H_{19}NO$ (253.34): C, 80.60; H, 7.56; N, 5.53. Found: C 80.30; H 7.55; N 5.50.

(*S*)(–)-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline, (–)-9g, new compound. The synthesis of THIQ (–)-**9g** (0.34 g, 80%, 99:1 er) was carried out according to procedure B. *Because of a rapid oxidation upon air contact, the analyses of THIQ (–)-**9g** should be performed promptly after chromatographic purification* (dichloromethane/methanol, 9:1). Yellow oil. R_f = 0.3 (dichloromethane/methanol, 9:1). $[\alpha]^{22}_D$ = –19.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.55–2.65 (s, br., 1 H), 2.73–2.84 (m, 2 H), 2.86–2.95 (m, 2 H), 3.16–3.25 (m, 2 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.15 (dd, *J* = 9.8, 3.9 Hz, 1 H), 6.72 (d, *J* = 1.6 Hz, 1 H), 6.80 (m, 2 H), 7.08–7.25 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.7 (s), 40.8 (s), 41.9 (s), 55.8 (p), 55.9 (p), 57.1 (t), 111.4 (t), 112.5 (t), 121.4 (t), 125.7 (t), 126.2 (t), 129.3 (t), 131.2 (q), 135.2 (q), 138.2 (q), 147.7 (q), 149.0 (q). HRMS ($C_{18}H_{22}NO_2$, ESI$^+$, MeOH, $[M + H]^+$) calcd for 284.1645, found 284.1644. Anal. Calcd for $C_{18}H_{21}NO_2$ (283.37): C, 76.29; H, 7.47; N, 4.94. Found: C 76.00; H 7.40; N 4.90.

Procedure C. Synthesis of **THIQs (+)-10a-g.**

(*S*)-(+)-*tert*-Butyl-1-methyl-3,4-dihydroisoquinoline-2-(1*H*)-carboxylate, (+)-10a, new compound.[51] An oven dried, 50-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was successively charged with 20 mL of dry acetonitrile, 0.12 g (0.81 mmol) of THIQ (–)-**9a**, 1.0 mL (0.74 g, 5.72 mmol) of *N,N*-diisopropylethylamine and 0.32 g (1.46 mmol) of di-*tert*-butyldicarbonate. The reaction mixture was refluxed for 4 h and the solvent was evaporated. The residue was next stirred for 2 h in a biphasic mixture of THF (10 mL) and NaOH 4 M (10 mL) to remove the di-*tert*-butyldicarbonate in excess. The THF was evaporated under reduced pressure and the aqueous phase was extracted with 50 mL of diethyl ether. The ethereal layer was dried over $MgSO_4$, concentrated, and the crude reaction mixture was poured into a chromatographic column (20 × 2.0 cm) prepared with 10 g of silica and 6:4 diethyl ether/petroleum ether. The combined fractions were evaporated to yield 0.16 g (80%) of THIQ (+)-**10a.** Yellow oil. $[\alpha]^{22}_D$ = +44 (*c* 0.5, $CHCl_3$, 90:10 er). R_f = 0.6 (petroleum ether/diethyl ether, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.46 (d, *J* = 6.8 Hz, 3 H), 1.52 (s, 9 H), 2.72 (dt, *J* = 16.0, 3.6 Hz, 1 H), 2.80–3.00 (m, 1 H), 3.10–3.30 (m, 1 H), 3.90–4.02 (m, 1 H), 5.00–5.30 (m, 1 H), 7.08–7.19 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ = 22.0 (p), 28.5 (p),

29.0 (s), 36.7 & 38.1 (br., s), 49.9 & 50.6 (br., t), 79.6 (q), 126.1 (t), 126.2 (t), 126.9 (t), 128.9 (t), 134.2 (q), 138.67 & 138.95 (br., q), 154.5 (q). HRMS ($C_{15}H_{21}NO_2Na$, ESI^+, MeOH, $[M + Na]^+$) calcd for 270.1464, found 270.1465. Anal. Calcd for $C_{15}H_{21}NO_2$ (247.34): C, 72.84; H, 8.56; N, 5.66. Found: C, 72.88; H, 8.60; N, 5.64.

(*S*)-(+)-*tert*-Butyl-1-propyl-3,4-dihydroisoquinoline-2-(1H)-carboxylate, (+)-10b, new compound. The synthesis of THIQ (+)-**10b** (0.2 g, 85%, 90:10 er) was carried out according to procedure C and was purified by column chromatography (petroleum ether/diethyl ether, 8:2). $[\alpha]^{22}_D$ = +50 (*c* 0.5, $CHCl_3$, 90:10 er). R_f = 0.4 (petroleum ether/diethyl ether, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ = 0.93–1.00 (t, *J* = 7.1 Hz, 3 H), 1.40–1.50 (m, 2 H), 1.47 (s, 9 H), 1.60–1.70 (m, 1.3 H), 1.72–1.85 (m, 0.7 H), 2.70–2.80 (m, 1 H), 2.80–3.00 (m, 1 H), 3.10–3.20 (m, 0.6 H), 3.20–3.40 (m, 0.4 H), 3.85–4.00 (m, 0.4 H), 4.10–4.25 (m, 0.6 H), 4.95–5.10 (m, 0.6 H), 5.10–5.20 (m, 0.4 H), 7.05–7.17 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.0 (p), 19.7 (s), 28.5 (p), 28.4 & 28.6 (s), 36.7 & 38.5 (s), 39.1 & 39.4 (s), 54.0 & 54.5 (t), 79.3 & 79.6 (q), 125.9 (t), 126.3 (t), 127.0 & 127.3 (t), 128.6 & 129.0 (t), 134.1 & 134.4 (q), 138.4 & 138.6 (q), 155.0 (q). HRMS ($C_{17}H_{25}NO_2Na$, ESI^+, MeOH, $[M + Na]^+$) calcd for 298.1778, found 298.1778. Anal. Calcd for $C_{17}H_{25}NO_2$ (275.39): C, 74.14; H, 9.15; N, 5.09. Found: C, 74.00; H, 9.10; N, 5.05.

(*S*)-(+)-*tert*-Butyl-1-pentyl-3,4-dihydroisoquinoline-2-(1*H*)-carboxylate, (+)-10c, new compound. The synthesis of THIQ (+)-**10c** (0.3 g, 75%, 88:12 er) was carried out according to procedure C and was purified by column chromatography (petroleum ether/diethyl ether, 8:2). Yellow oil. $[\alpha]^{22}_D$ = +148 (*c* 0.5, $CHCl_3$, 90:10 er). R_f = 0.8 (petroleum ether/diethyl ether, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ = 0.80–0.95 (m, br., 3 H); 1.25–1.50 (m, br., 6 H), 1.47 (s, 9 H), 1.60–1.70 (m, br., 1 H), 1.70–1.85 (m, br., 1 H), 2.65–2.75 (m, br., 1 H), 2.80–3.00 (m, br., 1 H), 3.10–3.35 (m, br., 1 H), 3.90–4.00 (m, br.,0.5 H), 4.12–4.28 (m, 0.5 H), 4.95–5.05 (m, 0.5 H), 5.05–5.20 (m, 0.5 H), 7.05–7.17 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.0 (p), 22.7 (s); 26.1 & 26.3 (s), 28.5 (p), 28.3 & 28.6 (s), 31.71 (s), 36.6 & 36.9 (s), 37.2 & 38.4 (s), 54.1 & 54.8 (t), 79.3 & 79.7 (q), 125.9 (t), 126.3 (t), 127.0 & 127.4 (t), 128.7 & 129.0 (t), 134.1 & 134.4 (q), 138.4 & 138.7 (q), 155.0 (q). HRMS ($C_{19}H_{29}NO_2Na$,

ESI$^+$, MeOH, [M + Na]$^+$) calcd for 326.2090, found 326.2090. Anal. Calcd for $C_{19}H_{29}NO_2$ (303.44): C, 75.21; H, 9.63; N, 4.62. Found: C, 75.16; H, 9.67; N, 4.65.

(*S*)-(+)-*tert*-Butyl-1-heptyl-3,4-dihydroisoquinoline-2-(1*H*)-carboxylate, (+)-10d, new compound. The synthesis of THIQ (+)-**10d** (0.3 g, 73%, 87:13 er) was carried out according to procedure C and was purified by column chromatography (petroleum ether/diethyl ether, 8:2). Yellow oil. $[\alpha]^{22}_D$ = +132 (*c* 1.0, $CHCl_3$, 87:13 er). R_f = 0.8 (petroleum ether/diethyl ether, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.80–0.90 (m, 3 H), 1.25–1.50 (m, 10 H), 1.47 (s, 9 H), 1.60–1.85 (m, 2 H), 2.65–2.75 (m, 1 H), 2.80–3.00 (m, 1 H), 3.10–3.20 (m, 0.6 H), 3.20–3.30 (m, 0.4 H), 3.90–4.00 (m, 0.4 H), 4.15–4.22 (m, 0.6 H), 4.95–5.05 (m, 0.6 H), 5.10–5.15 (m, 0.4 H), 7.05–7.20 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.1 (p), 22.7 (s), 26.5 & 26.6 (s), 28.4 & 28.65 (s), 28.50 (p), 29.3 (s), 29.5 (s), 31.9 (s), 36.7 & 36.9 (s), 37.3 & 38.4 (s), 54.2 & 54.9 (t), 79.3 & 79.7 (q), 125.9 (t), 126.3 (t), 127.0 & 127.3 (t), 128.7 & 129.0 (t), 134.1 & 134.4 (q), 138.4 & 138.7 (q), 155.0 (q). HRMS ($C_{21}H_{33}NO_2Na$, ESI$^+$, MeOH, [M + Na]$^+$) calcd for 354.2404, found 354.2404. Anal. Calcd for $C_{21}H_{33}NO_2$ (331.49): C, 76.09; H, 10.03; N, 4.23. Found: C, 76.02; H, 10.04; N, 4.25.

(*S*)-(+)-*tert*-Butyl-1-undecyl-3,4-dihydroisoquinoline-2-(1*H*)-carboxylate, (+)-10e, new compound. The synthesis of THIQ (+)-**10e** (0.25 g, 75%, 85:15 er) was carried out according to procedure C and was purified by column chromatography (petroleum ether/diethyl ether, 8:2). Yellow oil. $[\alpha]^{22}_D$ = +46 (*c* 0.5, $CHCl_3$, 85:15 er). R_f = 0.8 (petroleum ether/diethyl ether, 8:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.88 (t, *J* = 7.5 Hz, 3 H), 1.25–1.45 (m, 18 H), 1.47 (s, 9 H), 1.60–1.85 (m, 2 H), 2.70 (m, 1 H), 2.80–3.00 (m, 1 H), 3.10–3.20 (m, 0.6 H), 3.20–3.30 (m, 0.4 H), 3.90–4.00 (m, 0.4 H), 4.15–4.23 (m, 0.6 H), 4.98–5.05 (m, 0.6 H), 5.10–5.20 (m, 0.4 H); 7.05–7.20 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.1 (p), 22.7 (s), 26.5 & 26.6 (s), 28.4 & 28.65 (s), 28.5 (p), 29.3 (s), 29.56 (s), 29.64 (s), 29.69 (s), 31.9 (s), 36.6 & 36.9 (s), 37.3 & 38.5 (s), 54.2 & 54.9 (t), 79.3 & 79.7 (q), 125.9 (t), 126.3 (t); 127.0 & 127.4 (t), 128.7 & 129.0 (t), 134.1 & 134.4 (q), 138.4 & 138.7 (q), 155.0 (q). HRMS ($C_{25}H_{41}NO_2Na$, ESI$^+$, MeOH, [M + Na]$^+$) calcd for 410.3030, found 410.3030. Anal. Calcd for $C_{25}H_{41}NO_2$ (387.60): C, 77.47; H, 10.66; N, 3.61. Found: C, 77.51; H, 10.80; N, 3.57.

(*S*)-(+)-*tert*-Butyl-1-(4-methoxybenzyl)-3,4-dihydroisoquinoline-2-(1*H*)-carboxylate, (+)-10e, new compound. The synthesis of THIQ (+)-**10e** (0.25 g, 80%, 99:1 er) was carried out according to procedure C and was purified by column chromatography (petroleum ether/diethyl ether, 8:2). Yellow oil. R_f = 0.4 (petroleum ether/diethyl ether, 8:2). $[\alpha]^{22}_D$ = +39 (*c* 1.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ = 1.25 (s, 6 H) & 1.43 (s, 3 H), 2.55 (dt, *J* = 15.0 Hz, 4.0 Hz, 0.35 H) & 2.65 (dt, *J* = 15.0, 4.0 Hz, 0.65 H), 2.70–2.80 (m, 0.35 H), 2.82–3.08 (m, 2.65 H), 3.20–3.32 (m, 1 H), 3.71–3.82 (m, 0.35 H), 3.76 (s, 3 H), 4.14–4.19 (m, 0.65 H), 5.14 (t, *J* = 6.4 Hz, 0.65 H), 5.33 (t, *J* = 6.4 Hz, 0.35 H), 6.76–7.20 (m, 8 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.2 & 28.5 (p), 28.6 & 28.7 (s), 37.1 & 39.4 (s), 41.8 & 42.1 (s), 55.2 & 55.3 (p), 55.9 & 56.7 (t), 79.4 & 79.5 (q), 113.5 & 113.8 (t), 125.8 (t), 126.5 & 126.6 (t), 127.3 & 127.6 (t), 128.4 & 129.0 (t), 130.56 & 130.64 (t), 134.6 & 134.7 (q), 137.0 (q), 154.5 & 154.7 (q), 158.2 & 158.4 (q). HRMS ($C_{22}H_{27}NO_3Na$, ESI$^+$, MeOH, [M + Na]$^+$) calcd for 376.1883, found 376.1885. Anal. Calcd for $C_{22}H_{27}NO_3$ (353.46): C, 74.76; H, 7.70; N, 3.96. Found: C, 74.72; H, 7.68; N, 3.94.

(*S*)-(+)-*tert*-Butyl-1-(3,4-dimethoxybenzyl)-3,4-dihydroisoquinoline-2-(1*H*)-carboxylate, (+)-10f, new compound. The synthesis of THIQ (+)-**10f** (0.35 g, 78%, 99:1 er) was carried out according to procedure C and was purified by column chromatography (petroleum ether/diethyl ether, 8:2). Yellow oil. R_f = 0.4 (petroleum ether/diethyl ether, 8:2). $[\alpha]^{22}_D$ = +50 (*c* 1.80, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ = 1.25 (s, 6 H) & 1.43 (s, 3 H), 2.55 (dt, *J* = 15.0 Hz, 4.0 Hz, 0.35 H) & 2.65 (dt, *J* = 15.0, 4.0 Hz, 0.65 H), 2.70–2.80 (m, 0.35 H), 2.82–3.08 (m, 2.65 H), 3.20–3.32 (m, 1 H), 3.71–3.75 (m, 0.35 H) & 4.09–4.15 (m, 0.65 H), 3.72 (s, 1 H) & 3.78 (s, 2 H), 3.83 (s, 1 H) & 3.84 (s, 2 H), 5.14 (t, *J* = 6.4 Hz, 0.65 H), 5.33 (t, *J* = 6.4 Hz, 0.35 H), 6.47 (s, 0.35 H) & 6.53 (s, 0.65 H), 6.60 (d, *J* = 8.0 Hz, 0.35 H) & 6.63 (d, *J* = 8.0 Hz, 0.65 H), 6.72 (d, *J* = 8.0 Hz, 0.35 H) & 6.78 (d, *J* = 8.0 Hz, 0.65 H), 6.88 (d, *J* = 7.2 Hz, 0.35 H) & 7.00 (d, *J* = 7.2 Hz, 0.65 H), 7.05–7.20 (m, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.3 & 28.5 (p), 28.6 (s), 37.4 & 39.6 (s), 42.1 & 42.6 (s), 55.7 & 55.8 (p), 55.9 & 56.0 (p), 56.9 (t), 79.4 (q), 110.9 & 111.3 (t), 112.9 (t), 121.72 & 121.81 (t), 125.8 (t), 126.5 & 126.6 (t), 127.4 & 127.6 (t), 128.3 & 129.0 (t), 130.8 & 131.1 (q), 134.7 & 134.9 (q), 136.9 (q), 147.6 & 147.8 (q), 148.4 & 148.7 (q), 154.6 & 154.8 (q). HRMS ($C_{23}H_{29}NO_4Na$, ESI$^+$, MeOH, [M + Na]$^+$) calcd for 406.1989, found

406.1989. Anal. Calcd for $C_{23}H_{29}NO_4$ (383.48): C, 72.04; H, 7.62; N, 3.65. Found: C, 72.02; H, 7.60; N, 3.60.

(–)-3-((*S*)-2-(-1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-propan-1-ol, (–)-1j, new compound. Compound (–)-**1h** (1.5 g, 3.95 mmol) was dissolved in 20 mL of a mixture (1:1) of THF and HCl 2 M. The solution was stirred for 12 h and the organic solvent was evaporated under reduced pressure to yield an aqueous phase which was basified by the addition of NaOH pellets until the precipitation of a crude oily residue. This residue was extracted with 20 mL of dichloromethane (× 3) and the combined organic phases were dried over $MgSO_4$ and concentrated to yield a viscous oil which was purified by column chromatography (petroleum ether/diethyl ether, 1:1) to yield 1.10 g (94%) of (–)-**1j** Colorless viscous oil. R_f = 0.3 (petroleum ether/diethyl ether, 1:1). $[\alpha]^{22}_D$ = –57 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.38–1.50 (m, 1 H), 1.44 (d, *J* = 6.5 Hz, 3 H), 1.62–1.86 (m, 3 H), 2.55 (dm, *J* = 16.5 Hz, 1 H), 3.02 (ddd, *J* = 16.5, 10.9, 7.5 Hz, 1 H), 3.30–3.38 (m, 2 H), 3.40–3.50 (m, 2 H), 3.64–3.68 (m, 1 H), 3.71 (q, *J* = 6.5 Hz, 1 H), 6.82 (dm, *J* = 7.0 Hz, 1 H), 7.05–7.14 (m, 3 H), 7.20–7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.8 (p), 22.3 (s), 30.8 (s), 36.5 (s), 38.3 (s), 58.4 (t), 59.3 (t), 63.4 (s), 126.0 (t), 126.1 (t), 127.3 (t), 128.0 (t), 128.3 (t), 128.4 (t), 128.8 (t), 133.8 (q), 137.8 (q), 144.2 (q). HRMS ($C_{20}H_{26}NO$, [M + H^+]) calcd for 296.2014, found: 296.2008. Anal. Calcd for $C_{20}H_{25}NO$ (295.2): C, 81.31; H, 8.53; N, 4.74; found C, 81.18; H, 8.76; N, 4.83.

(*S*)-(–)-3-(1,2,3,4-tetrahydroisoquinolin-1-yl)-propan-1-ol, (–)-9h, new compound. In a low-pressure hydrogenator were successively added 0.07 g of 10% Pd-C (20% in weight) and 10 mL of ethanol containing 2 mL of 10% HCl. Air was removed from the reactor by alternately filling it with hydrogen and venting it three times. The solution was stirred during a 12 h period under a 6 bars (5.50 × 10^3 Torr) hydrogen pressure. Then, the reaction vessel was open, and THIQ (–)-**1j** (0.35 g, 1.18 mmol, 99:1 dr) was dissolved in the reaction mixture. The mixture was stirred for 72 h at 20 °C under a 6 bars (5.50 × 10^3 Torr) hydrogen pressure. The suspension was filtered over a small pad of Celite, and the vessel was washed thoroughly with ethanol. The filtrate was concentrated *in vacuo* and the resulting paste was dissolved in 10 mL of water. The solution was cooled in an ice bath and basified with solid KOH. The white oily residue was extracted with dichloromethane (50 mL × 3) and the combined

organic layers were dried over $MgSO_4$ and concentrated. The oily residue was purified by column chromatography (dichloromethane/methanol, 8:2). The less polar THIQ (–)-**1j** (0.05 g) was eluted first followed by THIQ (–)-**9h** (0.17 g, 75%) as a viscous yellow oil. Analyses should be carried out immediately after chromatographic purification. THIQs (–)-**9h** is sensitive to aerial oxidation and should be kept under argon at –20 °C for storage. R_f = 0.2 (dichloromethane/methanol, 8:2). $[\alpha]^{22}_D$ = –35 (*c* 1.8, $CHCl_3$), lit.[52] $[\alpha]^{22}_D$ = +55 (*c* 1.0, MeOH, 95% ee, this value is referred to the *R* enantiomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.65–1.81 (m, 2 H), 1.96–2.22 (m, 2 H), 2.75 (dt, *J* = 16.6, 6.0 Hz, 1 H), 2.86 (dt, *J* = 16.6, 6.0 Hz, 1 H), 2.80 (ddd, *J* = 11.9, 6.7, 5.2 Hz, 1 H), 3.22 (ddd, *J* = 11.9, 6.7, 5.2 Hz, 1 H), 3.54 (ddd, *J* = 11.1, 7.5, 3.6 Hz, 1 H), 3.64 (ddd, *J* = 11.1, 6.2, 3.8 Hz, 1 H), 3.80–3.98 (br. 2 H), 4.03 (t, *J* = 6.0 Hz, 1 H), 7.05–7.17 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.1 (s), 30.3 (s), 35.3 (s), 39.8 (s), 55.6 (t), 62.7 (s), 126.1 (t), 126.2 (t), 126.4 (t), 129.3 (t), 134.6 (q), 138.2 (q). HRMS ($C_{12}H_{18}NO$, ESI^+, MeOH, $[M + H]^+$) calcd for 192.1385, found 192.1386. Anal. Calcd for $C_{12}H_{17}NO$ (191.27): C, 74.35; H, 8.96; N, 7.32. Found: C 74.30; H 8.90; N 7.28.

(*S*)-1-(2-(1,3-dioxolan-2-yl)-ethyl)-1,2,3,4-tetrahydroisoquinoline, (–)-9i, new compound. The synthesis of THIQ (–)-**9i** (0.23 g, 65%, 99:1 er) was carried out according to procedure B. The unreacted THIQ (–)-**1i** (0.06 g) was recovered in 12% yield after column chromatography (dichloromethane/methanol, 9:1). *Because of a rapid oxidation and/or carbonatation upon air contact, the analyses of THIQ (–)-**9i** should be performed promptly after chromatographic purification*. Yellow oil. R_f = 0.2 (dichloromethane/methanol, 9:1). $[\alpha]^{22}_D$ = –53 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.80–1.97 (m, 2 H), 1.98–2.10 (m, 1 H), 2.78 (dt, *J* = 16.3, 5.3 H, 1 H), 2.83–2.92 (m, 1 H), 3.03 (ddd, *J* = 12.6, 7.6, 5.1 Hz, 1 H), 3.20–3.30 (m, 1 H), 3.20–3.30 (br., 2 H), 3.80–3.90 (m, 2 H), 3.93–4.00 (m, 2 H), 4.10 (dd, *J* = 7.0, 2.6 Hz, 1 H), 4.92 (t, *J* = 4.5 Hz, 1 H), 7.00–7.15 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.3 (s), 30.0 (s), 30.1 (s), 40.7 (s), 55.3 (t), 64.9 (s), 65.0 (s), 104.4 (t), 126.0 (t), 126.2 (t), 126.3 (t), 129.2 (t), 134.7 (q), 138.2 (q). HRMS ($C_{14}H_{20}NO_2$, ESI^+, MeOH, $[M + H]^+$) calcd for 234.1488, found 234.1490. Anal. Calcd for $C_{14}H_{19}NO_2$ (233.31): C, 72.07; H, 8.21; N, 6.00. Found: C 71.60; H 8.10; N 6.04.

(10b*S*)-1,2,3,5,610b-hexahydropyrrolo[2,1-*a*]-isoiquinoline-3-carbonitrile, 11, new compound. A 200-mL, one necked Schlenk tube was successively charged with 0.20 g (0.86 mmol) of THIQ (–)-**9i**, 10 mL of THF and 10 mL of an aqueous HCl 2 M. The resulting solution was degassed by a bubbling of argon and stirred at ambient temperature over a 24 h period. The organic solvent was evaporated under reduced pressure and solid AcONa was added to the resulting clear aqueous solution until pH = 4.5. Then, 0.5 g of NaCN was added by portions until the complete precipitation of an oily residue which was extracted with diethyl ether and stirred in the biphasic system for an additional 2 h period. The aqueous phase was discarded, and the ethereal phase was washed with a saturated Na_2CO_3 solution, dried over $MgSO_4$, and concentrated *in vacuo* to yield α-amino nitrile **11** (0.14 g, 82%) as a yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz, isomeric mixture, 1:1) δ = 1.75–1.82 (m, 0.5 H), 1.86–1.92 (m, 0.5 H), 2.20–2.45 (m, 2.5 H), 2.46–2.55 (m, 0.5 H), 2.64 (td, *J* = 11.7, 5.0 Hz, 0.5 H), 2.82–2.98 (m, 1.5 H), 3.10–3.28 (m, 1.5 H), 3.32–3.42 (m, 1 H), 3.49 (ddd, *J* = 10.5, 7.0, 1.8 Hz, 0.5 H), 3.83 (t, *J* = 8.1 Hz, 0.5 H), 4.08 (dd, *J* = 8.3, 3.0 Hz, 0.5 H), 7.02–7.09 (m, 1 H), 7.12–7.19 (m, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.3 (s), 28.37 (s), 28.40 (s), 28.44 (s), 29.1 (s), 29.2 (s), 45.8 (s), 47.6 (s), 52.9 (t), 53.1 (t), 60.9 (t), 63.5 (t), 118.4 (q), 119.8 (q), 125.0 (t), 125.6 (t), 126.0 (t), 126.1 (t), 126.5 (t), 126.8 (t), 128.57 (t), 128.65 (t), 133.6 (q), 133.8 (q), 137.2 (q), 137.6 (q). HRMS ($C_{13}H_{14}N_2Na$, ESI$^+$, MeOH, [M + Na]$^+$) calcd for 221.1055, found 221.1055. Anal. Calcd for $C_{13}H_{14}N_2$ (198.26): C, 78.75; H, 7.12; N, 14.13. Found: C, 78.68; H, 7.20; N, 14.10.

(*S*)-(–)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]-isoquinoline, (–)-3. *From THIQ (–)-**9h**.* A 200-mL, three necked Schlenk tube fitted with a reflux condenser and a magnetic stirring bar is successively charged with 10 mL of dichloromethane and 0.12 mL (0.19 g, 1.65 mmol, 2.1 equiv.) of $SOCl_2$. The resulting solution was heated at reflux and 5 mL of dichloromethane containing 0.15 g (0.78 mmol) of THIQ (–)-**9h** were added dropwise over a 30 min period. The solution was stirred for an additional 3 h period upon which the solvent was evaporated *in vacuo* to yield a green paste which was stirred overnight at room temperature in 10 mL of a 2 M NaOH solution and 20 mL of diethyl ether. The organic phase was separated, dried over $MgSO_4$ and concentrated in vacuo. The yellow oily residue was purified by column

chromatography (dichloromethane/MeOH, 8:2) to afford 0.11 g (81%) of pyrroloisoquinoline (–)-**3**. Yellow oil. R_f = 0.4 (dichloromethane/methanol, 8/2). $[\alpha]^{22}_D$ = –118 (*c* 0.5, $CHCl_3$, 99:1 er), $[\alpha]^{22}_D$ –106 (*c* 0.5, MeOH), lit.[53] $[\alpha]^{22}_D$ –101.7 (*c* 2.0, MeOH)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.72–1.80 (m, 1 H), 1.85–2.10 (m, 2 H), 2.34–2.43 (m, 1 H), 2.55 (q, *J* = 7.9 Hz, 1 H), 2.67 (ddd, *J* = 15.0, 10.2, 5.0 Hz, 1 H), 2.60 (dm, *J* = 15.07 Hz, 1 H), 3.08–3.18 (m, 2 H); 3.23 (ddd, *J* = 11.1, 6.3, 2.8 Hz, 1 H), 3.45 (dd, *J* = 9.0, 7.6 Hz, 1 H), 7.08–7.20 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.2 (s), 28.7 (s), 30.2 (s), 48.6 (s), 53.4 (s), 63.5 (t), 125.6 (t), 125.7 (t), 126.0 (t), 128.4 (t), 134.2 (q), 139.0 (q). HRMS ($C_{12}H_{16}N$, ESI^+, MeOH, $[M + H]^+$) calcd for 174.1283, found 174.1291. Anal. Calcd for $C_{12}H_{15}N$ (173.25): C, 83.19; H, 8.73; N, 8.08. Found: C, 82.98; H, 8.70; N, 8.05.

*From α-amino nitrile **11**.* A 50-mL, one necked flask was charged with 10 mL of ethanol, 0.10 g (0.50 mmol) of α-amino nitrile **11** and 0.076 g (2.0 mmol) of $NaBH_4$. The solution was stirred at ambient temperature for 24 h and heated at reflux for 3 h. The solvent was evaporated and the resulting mixture was taken-up with a 5% ammonia solution and extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated to yield an oily residue which was purified by column chromatography (dichloromethane/methanol, 8:2) to afford (–)-**3** (0.065 g, 74%) as a yellow oil. $[\alpha]^{22}_D$ –98 (*c* 0.5, MeOH). The spectroscopic data were in keeping with those reported above.

(*S*)-(–)-10,11-dimethoxy-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2a]isoquinoline, (–)-4, new compound.[54] A 50-mL, one necked flask was charged with 3 mL 35% aqueous formaldehyde solution, 4.2 g of formic acid and 0.20 g (0.70 mmol) of THIQ (–)-**9g**. The resulting solution was refluxed for 2 h and cooled by the addition of 10 mL of water. The solution was basified with solid sodium carbonate and the resulting oily residue was extracted with 50 mL of dichloromethane. The organic phases were dried over magnesium sulfate and concentrated. The crude residue was diluted in 3 mL of dichloromethane and poured on a chromatographic column prepared with 10 g of silica and diethyl ether. The combined fraction were evaporated to yield 0.15 g (72%) of THIQ (–)-**4** as a viscous oil which solidified as a white solid upon cooling. This solid was dissolved in 10 mL of

boiling ethanol and the resulting solution was allowed to cool to ambient temperature slowly over a 72 h period to yield a single crystal which was analyzed by X-ray diffraction. Colorless plate, mp = 146–148 °C (ethanol). R_f (diethyl ether) = 0.4. $[\alpha]^{22}_D$ –360 (*c* 0.5, $CHCl_3$, 99:1 er). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.59–2.67 (m, 1 H), 2.71–2.90 (m, 2 H), 3.11–3.25 (m, 2 H), 3.27 (dd, *J* = 15.9, 3.8 Hz, 1 H), 3.62–3.70 (m, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.93 (d, *J* = 15.0 Hz, 1 H), 6.57 (s, 1 H), 6.64 (s, 1 H), 7.11–7.27 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.5 (s), 36.2 (s), 51.1 (s), 55.91 (p), 55.96 (p), 58.2 (s), 59.9 (t), 109.1 (t), 111.5 (t), 125.4 (t), 126.0 (t), 126.1 (t), 126.3 (q), 126.4 (q), 128.9 (t), 134.5 (q), 138.0 (q), 147.4 (q), 147.6 (q). HRMS ($C_{19}H_{22}NO_2$, ESI$^+$, MeOH, $[M + H]^+$) calcd for 296.1645, found 296.1647. Anal. Calcd for $C_{19}H_{21}NO_2$ (295.38): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.16; H, 7.15; N, 4.72.

(1*R*,1'*R*)-(+)-6,7-dimethoxy-1-methyl-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (+)-1k, new compound. The synthesis of THIQ (+)-**1k** (1.24 g, 85%, 85:15 dr)) was carried out according to procedure A, but with 1.74 mL (3.96 g, 27.95 mmol) of iodomethane as the alkylating agent and (+)-**2b** as the α-amino nitrile. Orange oil, $[\alpha]^{22}_D$ = +8.9 (*c* 1.0, $CHCl_3$, 85 (*R,R*):15 (*S,R*) dr), $[\alpha]^{22}_D$ = +10.9 (*c* 1.0, EtOH, 85 (*R,R*):15 (*S,R*) dr). R_f = 0.4 (diethyl ether/petroleum ether, 50:50). ^{1}H NMR (isomeric mixture, 85 (*R,R*):15 (*S,R*) dr, major diastereoisomer, C_6D_6, 300 MHz) δ = 1.42 (d, *J* = 6.7 Hz, 6 H), 2.67 (dt, *J* = 16.0, 3.2 Hz, 1 H), 2.86 (ddd, *J* = 16.4, 10.0, 6.2 Hz, 1 H), 3.0–3.2 (m, 2 H), 3.50 (s, 3 H), 3.57 (s, 3 H), 3.86 (q, *J* = 6.7 Hz, 1 H), 4.11 (q, *J* = 6.7 Hz, 1 H), 6.41 (s, 1 H), 6.57 (s, 1 H), 7.20–7.30 (m, 3 H), 7.40–7.50 (m, 2 H). ^{13}C NMR (isomeric mixture, 85 (*R,R*):15 (*S,R*) dr, major diastereoisomer, C_6D_6, 75 MHz) δ = 20.0 (p), 21.4 (p), 25.8 (s), 40.0 (s), 53.6 (t), 55.6 (p), 59.5 (t), 111.7 (t), 112.7 (t), 126.8 (t), 127.3 (t), 129.5 (t), 132.5 (q), 147.4 (q), 148.41 (q), 148.45 (q).

(*R*)-(+)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*R*)-(+)-salsolidine. A low-pressure hydrogenator was successively charged with 0.25 g of 10% Pd/C (20% in weight), 10 mL of ethanol containing 2 mL of 10% HCl and 1.24 g (3.98 mmol, 85:15 dr) of THIQ (+)-**1k**. Air was removed from the reactor by alternately filling it with hydrogen and venting it three times. The solution was stirred during a 48 h period under a 7 bar (5.25×10^3 Torr) hydrogen pressure. The suspension was

filtered over a small pad of Celite, and the vessel was washed thoroughly with ethanol. The filtrate was concentrated under reduced pressure and the resulting paste was dissolved in 10 mL of water and the resulting aqueous solution was cooled in an ice bath and basified with solid KOH. The white oily residue was extracted with dichloromethane (50 mL × 3) and the combined organic layers were dried over $MgSO_4$ and concentrated to yield an oily residue was purified by column chromatography (dichloromethane/methanol, 95:5) to afford 0.63 g (76%) of (*R*)-(+)-salsolidine. $[\alpha]^{22}_D$ = +35.2 (*c* 1.0, $CHCl_3$, 85:15 er), $[\alpha]^{22}_D$ = +40.0 (*c* 1.0, EtOH, 85:15 er). Colorless oil. R_f = 0.4 (dichloromethane/methanol, 8:2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.45 (d, *J* = 6.7 Hz, 3 H), 2.66 (td, *J* = 16.0, 4.7 Hz, 1 H), 2.80 (ddd, *J* = 16.0, 8.7, 4.7 Hz, 1 H), 3.01 (ddd, *J* = 12.8, 8.70, 4.7 Hz, 1 H), 3.26 (dt, *J* = 12.8, 4.7 Hz, 1 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.05 (q, *J* = 6.7 Hz, 1 H), 6.58 (s, 1 H), 6.64 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 22.8 (p), 29.5 (s), 41.8 (s), 51.2 (t), 55.9 (p), 56.00 (p), 109.1 (t), 111.8 (t), 126.8 (q), 132.5 (q), 147.26 (q), 147.34 (q).

(*R*)-(+)-salsolidine•(–)-(*R*,*R*)-*O*,*O*'-dibenzoyl-$_L$-tartaric acid, (–)-12, new compound. To a solution of partially resolved (*R*)-(+)-salsolidine (0.63 g, 3.04 mmol, 85:15 er) in 20 mL of ethanol were added 1.14 g (3.18 mmol) of (–)-(*R*,*R*)-*O*,*O*'-dibenzoyl-$_L$-tartaric acid [(–)-DBTA] and the solution was stirred for 1 h and concentrated to afford a white residue which was taken-up in cold ethanol to afford 1.60 g (93%) of (*R*)-(+)-salsolidine•(–)-(*R*,*R*)-*O*,*O*'-dibenzoyl-$_L$-tartaric acid salt (88:12 dr) as a white powder. This powder (0.50 g, 88:12 dr) was dissolved in 20 mL of hot ethanol and the solution was allowed to cool at ambient temperature over a 48 h period. The precipitate was filtered over a sintered glass funnel to give 0.40 g (78%) of (*R*)-(+)-salsolidine•(–)-(*R*,*R*)-*O*,*O*'-dibenzoyl-$_L$-tartaric acid (99:1 dr) salt (–)-**12**, as colorless crystals, mp = 182 °C. $[\alpha]^{22}_D$ = –57 (*c* 0.25, EtOH, 99:1 dr). ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 1.46 (d, *J* = 6.7 Hz, 3 H), 2.70–2.90 (m, 2 H), 3.08–3.17 (m, 1 H), 3.23–3.29 (m, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 4.35 (q, *J* = 6.7 Hz, 1 H), 5.71 (s, 2 H), 6.66 (s, 1 H), 6.73 (s, 1 H), 7.54 (t, *J* = 7.8 Hz, 4 H), 7.66 (t, *J* = 7.7 Hz, 2 H), 8.00 (d, *J* = 7.6 Hz, 4 H), 8–10 (br. 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 19.1 (p), 24.6 (s), 38.0 (s), 49.5 (t), 55.4 (p), 55.6 (p), 72.8 (t), 109.4 (t), 111.5 (t), 123.6 (q), 125.9 (q), 128.6 (t), 129.2 (t), 129.6 (q), 133.4 (t), 147.6 (q), 147.9 (q), 164.9 (q), 168.3 (q). HRMS ($C_{12}H_{18}NO_2$, ESI$^+$, MeOH, [M]$^+$) calcd for 208.1332, found

208.1331; ($C_{42}H_{49}N_2O_{12}$, ESI$^+$, [2 M$^+$, A$^-$]$^+$ calcd for 773.3280, found 773.3280. Anal. Calcd for $C_{30}H_{31}NO_{10}$ (565.56): C, 63.71; H, 5.52; N, 2.48. Found: C, 63.20; H, 5.50; N, 2.50.

(*R*)-(+)-salsolidine from tartrate salt (–)-12. Tartrate salt (–)-**12** (0.50 g, 0.88 mmol) was stirred in a two-phase system (Et_2O/NaOH 10%) for 1 h under an argon atmosphere. The aqueous phase was discarded and the organic phase was washed with water until neutral pH. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to afford 0.17 g (92%) of (+)-salsolidine as a viscous oil. $[\alpha]^{22}_D$ = +46.7 (*c* 1.0, $CHCl_3$, 99:1 er), $[\alpha]^{22}_D$ = +52.4 (*c* 1.0, EtOH, 99:1 er).

(*R*)-(+)-salsolidine (85:15 er)•(*R*)-(+)-14. (*R*)-(+)-salsolidine (0.025 g, 120 μmol, 85:15 er), (*R*)-(+)-**14** (0.043 g, 200 μmol) and C_6D_6 (0.7 mL) were mixed in a 5 mm NMR tube. The ^{1}H and ^{13}C NMR data were collected on a 500 MHz spectrometer. *Signals attributed to the minor (S)-(+)-salsolidine•(R)-(+)-**14** complex (S,R_P)-**15** are indicated with an asterisk (*).* ^{1}H NMR (C_6D_6, 500 MHz, γ = 1.55) δ = 1.43 (d, $^3J_{PH}$ = 15.9 Hz, 13.9 H, γ = 1.55), 1.66 (d, *J* = 6.7 Hz, 0.45 H),* 1.72 (d, *J* = 6.7 Hz, 3 H), 2.43 (dt, *J* = 16.7, 5.1 Hz, 1 H), 2.51 (dt, *J* = 16.7, 5.1 Hz, 0.15 H)*, 2.86–2.92 (m, 1 H), 3.03–3.07 (m, 1 H), 3.24–3.32 (m, 1 H), 3.45 (s, 6 H), 4.51 (q, *J* = 6.7 Hz, 1 H), 6.18 (s, 1 H), 6.25 (s, 0.15 H)*, 6.26 (s, 0.15 H)*, 6.28 (s, 1 H), 7.20–7.30 (m, 4.5 H, γ = 1.5), 8.29–8.32 (m, 3 H, γ = 1.5). ^{13}C NMR (C_6D_6, 125 MHz, γ = 1.55) δ = 19.3 (p), 25.2 (p), 36.3 [q, (d, $^1J_{PC}$ = 75.0 Hz)], 39.9 (s), 50.6 (t), 55.3 (p), 55.4 (p), 109.4 (t), 109.5 (t)*, 111.9 t), 124.1 (q), 126.0 (q), 127.1 [t, (d, $^3J_{PC}$ = 10.0 Hz)], 129.8 (t), 133.2 [t, (d, $^2J_{PC}$ = 11.0 Hz)], 138.5 [q, (d, $^1J_{PC}$ = 89.0 Hz)], 148.95 (q), 148.99 (q)*, 149.33 (q), 149.37 (q)*.

(*R*)-(+)-salsolidine (99:1 er)•(*R*)-(+)-14, (*R*,R_P)-15. (*R*)-(+)-salsolidine (0.02 g, 96.7 μmol, 98:2 er), (*R*)-(+)-**14** (100 μmol) and C_6D_6 (0.7 mL) were mixed in a 5 mm NMR tube. The ^{1}H and ^{13}C NMR data were collected on a 500 MHz spectrometer. ^{1}H NMR (C_6D_6, 500 MHz, γ = 1.0) δ = 1.39 (d, $^3J_{PH}$ = 15.6 Hz, 9 H, γ = 1.0), 1.72 (d, *J* = 6.7 Hz, 3 H), 2.45 (dt, *J* = 16.7, 5.1 Hz, 1 H), 2.86–2.92 (m, 1 H), 3.03–3.07 (m, 1 H), 3.24–3.32 (m, 1 H), 3.47 (s, 3 H), 3.48 (s, 3 H), 4.47 (q, *J* = 6.7 Hz, 1 H), 6.25 (s, 1 H), 6.39

(s, 1 H), 7.20–7.30 (m, 3.10 H, γ = 1.03), 8.29–8.32 (m, 2.06 H, γ = 1.03). ^{13}C NMR (C_6D_6, 125 MHz, γ = 1.0) δ = 19.7 (p), 25.4 (p), 26.0 (s), 37.0 [q, (d, $^1J_{PC}$ = 75.0 Hz)], 40.2 (s), 50.6 (t), 55.3 (p), 55.5 (p), 109.6 (t), 112.0 (t), 124.7 (q), 127.1 [t, (d, $^3J_{PC}$ = 10.0 Hz)], 127.3 (q), 129.4 [t, (d, $^4J_{PC}$ = 2.5 Hz)], 133.2 [t, (d, $^2J_{PC}$ = 11.0 Hz)], 139.5 [q, (d, $^1J_{PC}$ = 89.0 Hz)], 148.8 (q), 149.2 (q).

(1*S*,1'*S*)-(+)-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (+)-1l, new compound.[55] The synthesis of THIQ (+)-**1l** (1.33 g, 80%, 90:10 dr) was carried out according to procedure A, but with 1.23 g (5.32 mmol, 1.5 equiv.) of 4-(bromomethyl)-1,2-dimethoxybenzene as the alkylating agent and was purified by column chromatography (diethyl ether/petroleum ether, 1:1)]. $[\alpha]^{22}_D$ = +10 (*c* 1.0, $CHCl_3$, 90:10 dr). R_f = 0.2 (diethyl ether/petroleum ether, 1:1)]. ^{1}H NMR (isomeric mixture, 90:10, major diastereoisomer, $CDCl_3$, 300 MHz) δ = 1.37 (d, *J* = 6.5 Hz, 3 H), 2.43 (dm, *J* = 16.3, Hz, 1 H), 2.70 (dd, *J* = 13.3, 7.7 Hz, 1 H), 2.89 (ddd, *J* = 16.5, 11.0, 6.4 Hz, 1 H), 3.04 (dd, *J* = 13.2, 6.1 Hz, 1 H), 3.20–3.30 (m, 2 H), 3.54 (s, 3 H), 3.67–3.79 (m, 2 H), 3.69 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 5.89 (s, 1 H), 6.37 (d, *J* = 1.8 Hz, 1 H), 6.49 (dd, *J* = 8.1, 1.8 Hz, 1 H), 6.59 (s, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 7.11–7.20 (m, 5 H). ^{13}C NMR (isomeric mixture, 90:10, major diastereoisomer, $CDCl_3$, 75 MHz) δ = 21.9 (p), 23.9 (s), 39.8 (s), 42.2 (s), 55.6 (p), 55.69 (p), 55.76 (p), 55.9 (p), 59.1 (t), 60.7 (t), 110.8 (t), 111.3 (t), 111.5 (t), 112.9 (t), 121.9 (t), 126.5 (t), 127.4 (t), 128.1 (t), 129.6 (q), 132.8 (q), 146.3 (q), 146.5 (q), 147.2 (q), 148.4 (q).

(*S*)-(–)-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (–)-norlaudanosine, The synthesis of (–)-norlaudanosine (0.61 g, 90%, 90:10 er) was carried out according to procedure B. The unreacted THIQ (+)-**1l** (0.01 g) was recovered in 5% yield after column chromatography (dichloromethane/methanol, 95:5). Yellow oil. $[\alpha]^{22}_D$ = –22 (*c* 1.0, $CHCl_3$, 90:10 er). R_f = 0.25 (dichloromethane/methanol, 95:5). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.60–2.75 (m, 2 H), 2.80–2.94 (m, 2 H), 3.10–3.25 (m, 2 H), 3.79 (s, 3 H), 3.81 (s, 6 H), 3.83 (s, 3 H), 4.10 (dd, *J* = 8.9, 4.3 Hz, 1 H), 6.56 (s, 1 H), 6.62 (s, 1 H), 6.73–6.81 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 29.5 (s), 40.9 (s), 42.2 (s), 55.80 (p), 55.82 (p), 55.88 (p),

55.95 (p), 56.8 (t), 109.4 (t), 111.3 (t), 111.8 (t), 112.4 (t), 121.4 (t), 127.4 (q), 130.4 (q), 131.4 (q), 145.0 (q), 147.4 (q), 147.6 (q), 148.9 (q).

(*S*)-(–)-norlaudanosine•(–)-*N*-acetyl-$_L$-leucine, (–)-13.[42] To a solution of 0.40 g (1.16 mmol, 90:10 er) of (–)-norlaudanosine in 4 mL of methanol and 6 mL of diethyl ether, was added 0.20 g (1.16 mmol) of (–)-*N*-acetyl-$_L$-leucine. The solution was kept standing in a closed vessel at –20 °C for 12 h and the precipitate was collected over a sintered glass funnel to afford 0.45 g (83% based on isomer content) of (–)-norlaudanosine•(–)-*N*-acetyl-$_L$-leucine [(–)-**13**]. Colorless needles, mp = 184–186° C. $[\alpha]^{22}_D$ = –2.6 (*c* 1.0, $CHCl_3$, 99:1 dr), $[\alpha]^{22}_D$ = +5.7 (*c* 1.0, EtOH, 99:1 dr). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.83 (d, *J* = 6.2 Hz, 6 H), 1.30–1.65 (m, 3 H), 1.90 (s, 3 H), 2.80–3.10 (m, 3 H), 3.20–3.32 (m, 3 H), 3.60 (s, 3 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.23–4.30 (m, 1 H), 4.51 (t, *J* = 6.5 Hz, 1 H), 6.20 (s, 1 H), 6.45 (d, *J* = 7.8 Hz, 1 H), 6.58 (s, 1 H), 6.70–6.73 (m, 3 H). 8.65 (s, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 22.1 (p), 23.1 (p), 23.3 (p), 25.0 (t), 26.1 (s), 38.8 (s), 40.7 (s), 42.2 (s), 53.0 (t), 55.4 (p), 55.7 (p), 55.8 (p), 55.9 (p), 109.8 (t), 111.3 (t), 112.9 (t), 122.0 (t), 124.6 (q), 125.4 (q), 129.1 (q), 147.2 (q), 148.1 (q), 148.3 (q), 149.0 (q), 169.7 (q), 176.5 (q). HRMS ($C_{20}H_{26}NO_4$, ESI$^+$, MeOH, $[M + H]^+$) calcd for 344.1862, found 344.1859. Anal. Calcd for $C_{28}H_{40}N_2O_7$ (516.62): C, 64.10; H, 7.80; N, 5.42. Found: C, 64.29; H, 7.80; N, 5.45.

(*S*)-(–)-norlaudanosine from leucinate salt (–)-13. Leucinate salt (–)-**13** (0.10 g, 0.19 mmol) was stirred in a two-phase system (Et_2O/NaOH 10%) for 1 h under an argon atmosphere. The aqueous phase was discarded and the organic phase was washed with water until neutral pH. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to afford 0.063 g (95%) of (–)-norlaudanosine as a viscous oil. $[\alpha]^{22}_D$ = –24 (*c* 1.0, $CHCl_3$, 99:1 er), lit.[40c] $[\alpha]^{22}_D$ = –21.9 (*c* 1.0, $CHCl_3$, 99:1 er).

(*S*)-(–)-norlaudanosine (90:10 er)•(*R*)-(+)-14. (*S*)-(–)-norlaudanosine (0.02 g, 58.2 μmol, 90:10 er), (*R*)-(+)-**14** (0.014 g, 64.1 μmol) and C_6D_6 (0.7 mL) were mixed in a 5 mm NMR tube. The ^{1}H and ^{13}C NMR data were collected on a 500 MHz spectrometer. *Signals corresponding to the minor (R)-(+)-norlaudanosine•(R)-(+)-**14***

*complex (R,R_P)-**16** are indicated with an asterisk (*).* ^{1}H NMR (C_6D_6, 500 MHz, γ = 1.07) δ = 1.47 (d, $^3J_{PH}$ = 15.6 Hz, 10 H, γ = 1.07), 2.60–2.65 (m, 2 H), 3.10–3.20 (m, 4 H), 3.37 (s, 0.3 H)*, 3.39 (s, 3 H), 3.46 (s, 3 H), 3.49 (s, 3 H), 3.50 (s, 0.3 H)*, 3.62 (s, 3 H), 3.68 (s, 0.3 H)*, 4.85–4.90 (m, 1 H), 6.27–6.30 (m, 2 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 6.82 (d, *J* = 8.1, 1.7 Hz, 1 H), 6.86 (d, *J* = 8.1, 1.7 Hz, 0.1 H)*, 6.94 (s, 1 H), 7.04 (s, 0.1 H)*, 7.20–7.30 (m, 3.30 H, γ = 1.10), 8.30–8.40 (m, 2.2 H, γ = 1.10). ^{13}C NMR (C_6D_6, 125 MHz, γ = 1.07) δ = 25.3 (p), 25.9 (s), 36.4 [q, (d, $^1J_{PC}$ = 75.0 Hz)], 39.07 (s), 39.15 (s)*, 40.7 (s)*, 40.8 (s), 55.25 (p), 55.28 (p), 55.47 (p), 55.57 (p), 55.6 (t), 110.6 (t)*, 110.8 (t), 112.0 (t), 112.3 (t), 113.9 (t), 122.1 (t), 124.7 (q), 125.6 (q), 127.1 [t, (d, $^3J_{PC}$ = 10.0 Hz)], 129.4 (q), 129.8 (t), 133.2 [t, (d, $^2J_{PC}$ = 11.0 Hz)], 139.0 [q, (d, $^1J_{PC}$ = 89.0 Hz)], 148.2 (q), 149.1 (q), 149.2 (q), 150.2 (q).

(*S*)-(–)-norlaudanosine (99:1 er)•(*R*)-(+)-14. (*S*)-(–)-norlaudanosine (0.025 g, 72.8 μmol, 99:1 er), (*R*)-(+)-**14** (0.016 g, 74.7 μmol, γ = 1.03) and C_6D_6 (0.7 mL) were mixed in a 5 mm NMR tube. The ^{1}H and ^{13}C NMR data were collected on a 500 MHz spectrometer. ^{1}H NMR (C_6D_6, 500 MHz, γ = 1.05) δ = 1.46 (d, $^3J_{PH}$ = 15.6 Hz, 9 H, γ = 1.05), 2.60–2.65 (m, 2 H), 3.10–3.20 (m, 4 H), 3.39 (s, 3 H), 3.47 (s, 3 H), 3.49 (s, 3 H), 3.62 (s, 3 H), 4.85–4.90 (m, 1 H), 6.30–6.31 (m, 2 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 6.82 (dd, *J* = 8.1, 1.7 Hz, 1 H), 6.95 (s, 1 H), 7.20–7.30 (m, 3 H), 8.30–8.40 (m, 2 H). ^{13}C NMR (C_6D_6, 125 MHz, γ = 1.05) δ = 25.4 (p), 26.1 (s), 36.4 [q, (d, $^1J_{PC}$ = 75.0 Hz)], 39.1 (s), 40.9 (s), 55.25 (p), 55.28 (p), 55.47 (p), 55.57 (p), 55.6 (t), 110.8 (t), 112.0 (t), 112.3 (t), 113.9 (t), 122.1 (t), 124.9 (q), 125.7 (q), 127.1 [t, (d, $^3J_{PC}$ = 10.0 Hz)], 129.5 (q), 129.7 (q), 133.2 [t, (d, $^2J_{PC}$ = 11.0 Hz)], 139.0 [q, (d, $^1J_{PC}$ = 89.0 Hz)], 148.1 (q), 149.1 (q), 149.2 (q), 150.2 (q).

(*R*)-6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline, (*R*)-(+)-carnegine. A 50-mL, one necked flask is charged with 0.48 g (2.31 mmol) of (*R*)-(+)-salsolidine (99:1 er), 10 mL of acetonitrile and 10 mL of a 35% aqueous formaldehyde solution. To the previous solution was added 0.23 g (3.36 mmol) of sodium cyanoborohydride. The reaction mixture was stirred for 15 min while glacial acetic acid was added to maintain the pH near neutrality. The solvents were evaporated under reduced pressure and 10 mL of a 2 M KOH solution was added to the residue. The mixture was extracted with 50 mL of diethyl ether and the ethereal

layer was dried over magnesium sulfate and concentrated under reduced pressure to afford 0.36 g of crude (*R*)-(+)-carnegine as a crude oil. The crude residue was diluted in 3 mL of dichloromethane and poured on a chromatographic column prepared with 10 g of silica and 1:1 dichloromethane/methanol. The combined fraction were evaporated to yield 0.37 g (73%) of (*R*)-(+)-carnegine. $[\alpha]^{22}_{D}$ = +20 (*c* 0.5, $CHCl_3$, 99:1 er), $[\alpha]^{22}_{D}$ = +18 (*c* 1.0, EtOH, 99:1 er), lit.[44] +23.5 (*c* 1.5, EtOH). Colorless oil. R_f = 0.5 (dichloromethane/methanol, 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.37 (d, *J* = 6.7 Hz, 3 H), 2.47 (s, 3 H), 2.61 (ddd, *J* = 11.7, 7.1, 4.8 Hz, 1 H), 2.74–2.79 (m, 2 H), 3.01 (ddd, *J* = 12.8, 8.70, 4.7 Hz, 1 H), 4.05 (q, *J* = 6.7 Hz, 1 H), 3.84 (s, 6 H), 6.56 (s, 1 H), 6.58 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 19.7 (p), 27.6 (s), 42.9 (p), 48.9 (s), 55.8 (p), 55.9 (p), 58.6 (t), 109.1 (t), 111.2 (t), 125.9 (q), 131.7 (q), 147.19 (q), 147.22 (q). HRMS ($C_{12}H_{16}NO_2$, EI$^+$, $[M - CH_3]^+$) calcd for 206.1181, found 206.1196.

(*S*)-(–)-2,3,10,11-tetramethoxy-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2*a*]-isoquinoline, (*S*)-(–)-xylopinine. Leucinate salt (–)-**13** (0.25 g, 0.48 mmol) was stirred in a two-phase system (Et_2O/NaOH 10%) for 1 h under an argon atmosphere. The aqueous phase was discarded and the organic phase was washed with water until neutral pH. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to afford 0.16 g (96%) of (–)-norlaudanosine as a viscous oil. This oil was placed in a 50-mL, one necked flask which was charged with 1.3 mL of a 35% aqueous formaldehyde solution and 2.15 mL of formic acid. The resulting solution is refluxed for 2 h and cooled by the addition of 10 mL of water. The solution was basified with solid sodium carbonate and the resulting oily residue was extracted with 50 mL of dichloromethane. The organic phases were dried over magnesium sulfate and concentrated. The crude residue was diluted in 3 mL of dichloromethane and poured on a chromatographic column prepared with 10 g of silica and diethyl ether. The combined fraction were evaporated to yield 0.15 g (90%) of (*S*)-(–)-xylopinine. This solid was dissolved in 10 mL of boiling ethanol and the resulting solution was allowed to cool to ambient temperature slowly over a 72 h period to yield a single crystal which was analyzed by X-ray diffraction. Colorless plates, mp = 188–190 °C (ethanol). R_f (diethyl ether) = 0.2. $[\alpha]^{22}_{D}$ –275 (*c* 1 $CHCl_3$, 99:1 er), lit.[45b] $[\alpha]^{22}_{D}$ –280 (*c* 0.19 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.61–2.68 (m, 2 H), 2.83 (dd, *J* = 15.3, 11.5 Hz, 1 H), 3.11–3.17 (m, 2 H), 3.24 (dd, *J* = 15.3, 3.7

Hz, 1 H), 3.58 (dd, *J* = 11.1, 3.5 Hz, 1 H), 3.67 (d, *J* = 14.8 Hz, 1 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.94 (d, *J* = 14.8 Hz, 1 H), 6.58 (s, 1 H), 6.62 (s, 1 H), 6.66 (s, 1 H), 6.74 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 29.1 (s), 36.4 (s), 51.4 (s), 55.8 (p), 55.91 (p), 55.96 (p), 56.0 (p), 58.3 (s), 59.6 (t), 108.6 (t), 109.05 (t), 111.37 (t), 111.41 (t), 126.3 (q), 126.4 (q), 126.8 (q), 129.8 (q), 147.41 (q), 147.44 (q), 147.49 (q), 147.6 (q). HRMS (EI^+, $[M]^+$, $C_{21}H_{25}NO_4$) calcd for 355.1783, found 355.1794. Anal. Calcd for $C_{21}H_{25}NO_4$ (355.43): C, 70.96; H, 7.09; N, 3.94. Found: C, 71.00; H, 7.10; N, 3.96.

Single Crystal X-ray Analysis of Collection and Refinement Results of derivatives.

The structures were solved by direct methods with SIR-97[56], which revealed the non-hydrogen atoms of the molecules. Refinement was performed by full-matrix least-square techniques based on F^2 with SHELXL-97[57] with the aid of the WINGX[58] program. All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. Figures were drawn with ORTEP-3 for Windows.[59] The absolute configuration of derivative (+)-**2a** was estimated by the determination of Flack parameters [–0.03(6)] values calculated from Friedel pair reflections for each structure. CCDC-1431995 [(+)-**2b**], CCDC-1431996 [(+)-**1g**], CCDC-1431997 [(+)-**1f**], CCDC-1431998 [(–)-**4**], CCDC-1046886 [(+)-**2a**], CCDC-807858 [(–)-xylopinine], contain the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif

Crystal data, X-ray data collection and refinement results of derivative (+)-2a: $C_{20}H_{22}N_2O_2$, *M* = 322.40, orthorhombic, space group $P2_1$, $P2_1$, $P2_1$, *a* = 7.0779(2), *b* = 9.2640(3), *c* = 26.1004(7) Å, α = 90°, β = 90°, γ = 90°, *V* = 1711.39(9) Å^{-3}, *Z* = 4, D_x = 1.251 Mg m^{-3}, μ = 0.647 cm^{-1}, λ (Cu-Kα) = 1.54184 Å, F(000) = 688, *T* = 150(2) K. The sample (0.48×0.24×0.15 mm) was studied on a diffractometer with graphite monochromatized Cu-Kα radiation. The data collection (Θ_{max} = 74.48°, range of *HKL* : H –8→8, K –11→10, L –32→32) gave 18672 reflections with 3488 unique reflections from which 3141 with $I > 2.0\sigma(I)$.

Crystal data, X-ray data collection and refinement results of derivative (+)-2b: $C_{18}H_{18}N_2$, M = 262.34, orthorhombic, space group $P2_1$, $P2_1$, $P2_1$, a = 7.0231(4), b = 7.1476(3), c = 29.3182(16) Å, α = 90°, β = 90°, γ = 90°, V = 1471.72(13) Å^{-3}, Z = 4, D_x = 1.184 Mg m^{-3}, μ = 0.70 cm^{-1}, λ (Mo–$K\alpha$) = 0.71073 Å, F(000) = 560, T = 100(2) K. The sample (0.57×0.52×0.49 mm) was studied on a diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.46°, range of *HKL* : H –8→5, K –7→9, L –38→35) gave 7366 reflections with 1937 unique reflections from which 1801 with $I > 2.0\sigma(I)$.

Crystal data, X-ray data collection and refinement results of derivative (+)-1f: $C_{25}H_{27}NO$, M = 357.48, monoclinic, space group $P2_1$, a = 6.2810(2), b = 19.8359(7), c = 7.8253(3) Å, α = 90°, β = 91.333(2)°, γ = 90°, V = 1034.75(14) Å^{-3}, Z = 2, D_x = 1.218 Mg m^{-3}, μ = 0.73 cm^{-1}, λ (Mo–$K\alpha$) = 0.71073 Å, F(000) = 384, T = 120(2) K. The sample (0.46×0.43×0.38 mm) was studied on a diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.47°, range of *HKL* : H –8→8, K –23→25, L –9→10) gave 9426 reflections with 2273 unique reflections from which 2077 with $I > 2.0\sigma(I)$.

Crystal data, X-ray data collection and refinement results of derivative (+)-1g: $C_{26}H_{29}NO_2$, M = 387.5, monoclinic, space group $P2_1$, a = 6.2620(5), b = 8.1188(6), c = 20.3785(16) Å, α = 90°, β = 92.859(2)°, γ = 90°, V = 1034.75(14) Å^{-3}, Z = 2, D_x = 1.244 Mg m^{-3}, μ = 0.78 cm^{-1}, λ (Mo–$K\alpha$) = 0.71073 Å, F(000) = 416, T = 100(2) K. The sample (0.57×0.45×0.41 mm) was studied on a diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.48°, range of *HKL* : H –6→8, K –9→10, L –26→26) gave 7767 reflections with 2534 unique reflections from which 2433 with $I > 2.0\sigma(I)$.

Crystal data, X-ray data collection and refinement results of derivative (–)-4 $C_{19}H_{21}NO_2$, M = 295.37, orthorhombic, space group $P2_1$, $P2_1$, $P2_1$, a = 5.0889(2), b = 13.9187(6), c = 21.5365(9) Å, α = 90°, β = 90°, γ = 90°, V = 1525.45(11) Å^{-3}, Z = 4, D_x = 1.286 Mg m^{-3}, μ = 0.83 cm^{-1}, λ (Mo–$K\alpha$) = 0.71073 Å, F(000) = 632, T = 100(2) K. The sample (0.53×0.17×0.09 mm) was studied on a diffractometer with graphite

monochromatized Mo Kα radiation. The data collection (Θ_{max} = 27.48°, range of *HKL* : H –6→6, K –17→13, L –19→27) gave 8316 reflections with 2047 unique reflections from which 1694 with $I > 2.0\sigma(I)$.

Crystal data, X-ray data collection and refinement results of derivative (–)-xylopinine: $C_{21}H_{25}NO_4$, *M* = 355.42, orthorhombic, space group $P2_1$, $P2_1$, $P2_1$, *a* = 7.9409(6), *b* = 9.0559(5), *c* = 25.8657(16) Å, α = 90°, β = 90°, γ = 90°, *V* = 1860.1(2) $Å^{-3}$, *Z* = 4, D_x = 1.269 Mg m^{-3}, μ = 0.87 cm^{-1}, λ (Mo–*K*α) = 0.71073 Å, F(000) = 760, *T* = 100(2) K. The sample (0.48×0.32×0.26 mm) was studied on a diffractometer with graphite monochromatized Mo–*K*α radiation. The data collection (Θ_{max} = 27.44°, range of *HKL* : H –10→9, K –11→7, L –33→26) gave 8390 reflections with 2433 unique reflections from which 2177 with $I > 2.0\sigma(I)$.

ASSOCIATED CONTENT

Supporting Information

Proton and carbon NMR spectra of derivatives **1–16,** ORTEP views, CIF files of derivatives (+)-**2a**, (+)-**2b,** (+)-**1f,g**, (–)-**4** and (–)-xylopinine and determination of enantiomeric ratios of (+)-salsolidine, (+)-norlaudanosine by proton and carbon NMR are provided in the supporting information. This material is available free of charge at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

E-mail: jean-pierre.hurvois@univ-rennes1.fr

ACKNOWLEDGMENTS

This work was supported by the Programme Franco-Algérien de Formation Supérieure en France (PROFAS). The authors would also thank the members of the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) for technical assistance.

Note

The authors declare no competing financial interest.

REFERENCES

[1] (a) Roesh, E. S. In *Privileged Scaffolds in Medicinal Chemistry : Design, Synthesis, Evaluation*; Bräser, S. Ed.; RSC Drug Discovery Series N° 50, The Royal Society of Chemistry, 2016, p147. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

[2] Bentley, K. W. In *The Isoquinoline Alkaloids*; Bharavi, B. R. Ed.; Harwood Academic Publishers, 1998, Vol. 1.

[3] Beecher, C. W. W.; Kelleher, W. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W. Ed.; John Wiley and Sons, New-York, 1988, vol.6, Chapter 4, p 297.

[4] Graulich, A.; Scuvée-Moreau, J.; Alleva, L.; Lamy, C.; Waroux, O.; Seutin, V.; Liégeois, J.-F. *J. Med. Chem.* **2006**, *49*, 7208.

[5] (a) Boss, C.; Brisbare-Roch, C.; Jenck, F. *J. Med. Chem.* **2009**, *52*, 897. (b) Perrey, D. A.; German, N. A.; Gilmour, B. P.; Li, J.-X.; Harris, D. L.; Thomas, B. F.; Zhang, Y. *J. Med. Chem.* **2013**, *56*, 6901. (c) Roecker, A. J.; Cox, C. D.; Coleman, P. J. *J. Med. Chem.* **2016**, *59*, 504.

[6] Freel, R. M. S.; Ogden, K. K.; Strong, K. L.; Khatri, A.; Chepiga, K. M.; Jensen, H. S.; Traynelis, S. F.; Liotta, D. C. *J. Med. Chem.* **2013**, *56*, 5351.

[7] For a review, see : Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

[8] (a) Wang, Y.-C.; Georghiou, P. E. *Org. Lett.* **2002**, *4*, 2675. (b) Piwowarczyk, K.; Zawadzka, A.; Roszkowski, P.; Swawkało, J.; Leniewski, A.; Maurin, J. K.; Kranz, D.; Czarnocki, Z. *Tetrahedron: Asymmetry*, **2008**, *19*, 309. (c) Zein, A. L.; Dawe, L. N.; Georghiou, P. E. *J. Nat. Prod.* **2010**, *73*, 1427. (d) Zein, A. L.; Dakhil, O. O.; Dawe, L. N.; Georghiou, P. E. *Tetrahedron Lett.* **2010**, *51*, 177. For biocatalytic approaches utilizing imine reductases see: (e) Huber, T.; Schneider, L.; Präg, A.; Gerhardt, S.; Einsle, O.; Müller, M. *ChemCatChem.* **2014**, *6*, 2248.

[9] (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T., Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227. (c) Martins, J. E. D.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2009**, *11*, 847. (d) Soni, R.; Jolley, K. E.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2013**, *15*, 5110. (e) Přech, J.; Václavík, J.; Šot, P.; Pecháček, J.; Vilhanová, B.; Januščák, J.; Syslová, K.; Pažout, R.; Maixner, J.; Zápal, J.; Kuzma, M.; Kačer, P. *Catalysis Communication*, **2013**, *36*, 67

[10] (a) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841. (b) Mutharu, D. S.; Martins, J. E. D.; Wills, M. *Chem. Asian J.* **2008**, *3*, 1374.

[11] (a) Morimoto, T.; Achiwa, K.; *Tetrahedron: Asymmetry*, **1995**, *6*, 2661. (b) Guiu, E.; Claver, C.; Benet-Buchholz, Castillón, S. *Tetrahedron: Asymmetry*, **2004**, *15*, 3365. (c) Xie, J.-H.; Yan, P.-C.; Zhang, Q.-Q.; Yuan, K. X.; Zhou, Q.-L. *ACS Catal.* **2012**, *2*, 561

[12] For diastereoselective approaches, see: (a) Czarnocki, Z.; Maclean, D. B.; Szarek, W. A. *J. Chem. Soc. Chem. Commun.* **1985**, 1318. (b) Pedrosa, R.; Andrés, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243. (c) Gremen, C.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **2001**, *42*, 8885. (d) Comins, D. L.; Thakker, P. M.; Baevsky, M. F. *Tetrahedron*, **1997**, *48*, 16327. (e) Aubry, S.; Pellet-Rostaing, S.; Fenet, B.; Lemaire, M. *Tetrahedron Lett.* **2006**, *4*, 1319. (f) Fishlock, D.; Williams, R. M. *J. Org. Chem.*

2008, *73*, 9594. For enantioselective approaches, see: (g) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 10558.

[13] (a) Youte, J.-J.; Barbier, D.; Al-Mourabit, A.; Gnecco, D.; Marazano, C. *J. Org. Chem*. **2004**, *69*, 2737. (b) Qiu, X.-L.; Zhu, J.; Wu, G.; Lee, W.-H.; Chamberlin, A. R. *J. Org. Chem*. **2009**, *74*, 2018. (c) Soriano, M. D. P. C.; Shankaraiah, N.; Santos, L. S. *Tetrahedron Lett*. **2010**, *51*, 1770. (d) Mastranzo, V. M.; Yuste, F.; Ortiz, B.; Sánchez-Obregón, R.; Toscano, R. A.; Garcia Ruano, J. L. *J. Org. Chem.* **2011**, *76*, 5036. (e) Reddy, N. S. S.; Reddy, B. J. M.; Reddy, B. V. S. *Tetrahedron Lett.* **2013**, *54*, 4228.

[14] (a) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700. (b) Wang, S.; Seto, C. T. *Org. Lett*. **2006**, *8*, 3979. (c) Itoh, T; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett*. **2006**, *8*, 1295. (d) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc*. **2006**, *128*, 14010. (e) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 9646.

[15] (a) Seebach, D.; Lohman, J.-J.; Syfrig, M. A.; Yoshifuji, M. *Tetrahedron*, **1983**, *39*, 1963. (b) Rein, K; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211. (c) Monsees, A.; Laschat, S.; Dix, I.; Jones, P. G. *J. Org. Chem*. **1998**, *63*, 10018. (d) Adam, S.; Pannecoucke, X.; Combret, J.-C.; Quirion, J.-C. *J. Org. Chem*. **2001**, *66*, 8744.

[16] Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.

[17] For a review, see : Opatz, T. *Synthesis*, **2009**, *12*, 1941.

[18] (a) Han, W.; Ofial, A. R. *Chem. Commun*. **2009**, 5024. (b) Alagiri, K.; Prabhu, K. R. *Org. Biomol. Chem*. **2012**, *10*, 835. (c) Zhang, G.; Ma, Y.; Cheng, G.; Liu, D.; Wang, R. *Org. Lett.* **2014**, *16*, 656. (d) Panwar, V.; Ray, S. S.; Jain, S. L. *Tetrahedron Lett*. **2015**, *56*, 4184.

[19] (a) Hari, D. P.; König, B. *Org. Lett*. **2011**, *13*, 3852. (b) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun*. **2011**, *47*, 12709. (c) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94. (d) To, W.-P.; Liu, Y.; Lau, T.-C.; Che, C.-M. *Chem. Eur. J.* **2013**, *19*, 5654.

[20] Su, W.; Yu, J.; Li, Z.; Jiang, Z. *J. Org. Chem.* **2011**, *76*, 9144.

[21] Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem*. **2009**, *74*, 7464.

[22] Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett*. **1995**, *36*, 7975.

[23] For the dearomatization process of *N*-aryl-piperidine systems, see : (a) Girard, N.; Hurvois, J.-P.; Moinet, C.; Toupet, L. *Eur. J. Org. Chem*. **2005**, 2269. (b) Girard, N.; Gautier, C.; Malassene, R.; Hurvois, J.-P.; Moinet, C. Toupet, L. *Synlett*, **2004**, *11*, 2005.

[24] (a) Sundberg, R. J.; Hunt, P. J.; Desos, P.; Gadamasetti, K. G. *J. Org. Chem.* **1991**, *56*, 1689. (b) BeattyJ. W.; Stephenson, C. R. J. *J. Am. Chem. Soc*. **2014**, *136*, 10270.

[25] Hametner, C.; Hemetsberger, M.; Treu, M.; Mereiter, K.; Jordis, U.; Frölich, J. *Eur. J. Org. Chem*. **2005**, 404.

[26] (a) Louafi, F.; Moreau, J.; Shahane, S.; Golhen, S.; Roisnel, T.; Sinbandhit, S.; Hurvois, J.-P. *J. Org. Chem.* **2011**, *76*, 9720. For recent work devoted to anodic cyanation of nitrogen containing compounds, see: (b) Libendi, S. S.; Demizu, Y.; Onomura, O. *Org. Biomol. Chem*. **2009**, *7*, 351. (c) Tajima, T.; Nakajima, A. *J. Am. Chem. Soc.* **2008**, *130*, 10496. (d) E. W. Liu, W.; Ma, Y.; Yin, Y.; Zhao, Y. *Bull. Chem. Soc. Jpn*. **2006**, *79*, 577.

[27] Hart, D. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W. Ed.; John Wiley and Sons, New-York, 1988, vol.6, Chapter 3, p 227.

[28] Nguyen, T. M.; Sanchez-Salvatori, M. del R.; Wypych, J.-C.; Marazano, C. *J. Org. Chem.* **2007**, *72*, 5916.

[29] Hudlický, M. In *Reductions in Organic Chemistry ;* ACS Monograph 188, 2d Ed. 1996.

[30] For a review on the fundamental aspects and developments of redox catalysis, see: Francke, R.; Little, R. D. *Chem. Soc. Rev.* **2014**, *43*, 2492.

[31] Stable radical cation salts such as those derived from *p*-substituted triarylamines proved to be efficient oxidants of cyanide anions. For a detailed study, see: (a) Papouchado, L.; Adams, R. N. Feldberg, S. W. *J. Electroanal. Chem*. **1969**, *21*, 408. For a review on synthetic applications of stable radical cation salts, see: (b) Jia, X.; *Synthesis*, **2016**, *48*, 18.

[32] Fu, Y.; Liu, L.; Wang, Y.-M.; Guo, Q.-X. *J. Am. Chem. Soc*. **2005**, *127*, 7227.

[33] The ORTEP view of (+)-**1g** again revealed that this adduct has an absolute configuration of (1*S*, 1'*S*).

[34] Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc*. **1989**, *111*, 4859.

[35] Xu, F.; Simmons, B.; Reamer, R. A.; Corley, E.; Murry, J.; Tschaen, D. *J. Org. Chem*. **2008**, *73*, 312.

[36] Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem*. **1995**, *60*, 7152.

[37] The close examination of the ^{1}H NMR spectrum revealed the presence of an additional triplet signal at δ = 5.00. The same phenomenon was also observed in the ^{13}C NMR spectrum. A characteristic resonance line recorded at δ = 166.4 was attributed to the presence of $H^{13}CO_3^-$ and $^{13}CO_3^{2-}$. Because the interchange of these two species is fast on the NMR time scale, a single signal was recorded for the two. For a rapid survey of the literature data on CO_2 capture, see: (a) Lepaumier, H.; Picq, D.; Carrette, P.-L. *Ind. Eng. Chem. Res*. **2009**, *48*, 9061. (b) Chen, C.; Yang, S.-T.; Ahn, W.-S.; Ryoo, R. *Chem. Commun*. **2009**, 3627. For an NMR study of CO_2 activation, see : (c) O'Leary, M. H.; Jaworski, R. J.; Hartman, F. C. *Proc. Natl. Acad. Sci. USA*, **1979**, *76*, 673.

[38] For the synthesis of rac-**4**, see: (a) Kiparissides, Z.; Fichtner, R. H.; Poplawski, J.; Nalliah, B. C.; MacLean, D. B. *Can. J. Chem.* **1980**, *58*, 2770. (b) Shono, T.; Yoshida, K.; Ando, K.; Usui, Y.; Hamaguchi, H. *Tetrahedron Lett.* **1978**, *48*, 4819.

[39] For recent synthesis of salsolidine, see : Asymmetric transfer hydrogenantion: (a) Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, 1766. (b) Haraguchi, N.; Tsuru, K.; Arakawa, Y.; Itsuno, S. *Org. Biomol. Chem*. **2009**, *7*, 69. (c) Martins, J. E. D.; Contreras Redondo, M. A.; Wills, M. *Tetrahedron: Asymmetry*, **2010**, *21*, 2258. (d) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 4916. Imine reductase: (e) Leipold, F.; Hussain, S.; Ghislieri, D.; Turner, N. J. *Chem. Cat. Chem*. **2013**, *5*, 3505. (f) Genz, M.; Köhler, V.; Krauss, M.; Singer, D.; Hoffman, R.; Ward, T. R.; Sträter, N. *Chem. Cat. Chem*. **2014**, *6*, 736. (g) Muñoz Robles, V.; Dürrenberger, M.; Heinisch, T.; Lledós, A.; Schirmer, T.; Ward, T. R.; Maréchal, J.-D. *J. Am. Chem. Soc.* **2014**, *136*, 15676. Diastereoselective reduction: (h) Grajewska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry*, **2007**, *18*, 557.

[40] For recent synthesis of norlaudanosine, see for Asymmetric Pictet-Spengler cyclization: (a) Ruiz-Olalla, A.; Würdemann, M. A.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2015**, *80*, 5125. For asymmetric transfer hydrogenantion: (b) Werner, F.; Blank, N.; Opatz, T. *Eur. J. Org. Chem*. **2007**, 3911.

[41] Späth, E.; Dengel, F. *Chem. Ber*. **1938**, *71*, 113.

[42] Corrodi, H.; Hardegger, E. *Helv. Chim. Acta*, **1956**, *39*, 889.

[43] Borch, R. F.; Hassid, A. I. *J. Org. Chem*. **1972**, *37*, 1673

[44] Pyne, S. G.; Bloerm, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem*. **1990**, *55*, 1086.

[45] For the isolation of (–)-xylopinine, see: (a) Schmutz, J. *Helv. Chim. Acta*. **1959**, *29*, 335. For the synthesis of (–)-xylopinine, see: (b) Kametani, T.; Takagi, N.; Toyota, M.; Honda, T.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1*, **1981**, 2830. (c) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron*, **1987**, *43*, 5095. (d) Davis, F. A.; Mohanty, P. K. *J. Org. Chem*. **2002**, *67*, 1290. (e) Mujahidin, D.; Doye, S. *Eur. J. Org. Chem.* **2005**, 2689. For the synthesis of (+)-xylopinine, see: (f) Naito, T.; Tada, Y.; Ninomiya, I. *Heterocycles*, **1981**, *16*, 1141. (g) Czarnocki, Araźny, Z. *Heterocycles*, **1999**, 12, 2871.

[46] Louafi, F.; Hurvois, J.-P.; Chibani, A.; Roisnel, T. *J. Org. Chem*. **2010**, *75*, 5721.

[47] Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.***1996**, *61*, 9596.

[48] Shinohara, T.; Takeda, A.; Toda, J.; Sano, T. *Chem. Pharm. Bull*. **1998**, *46*, 430.

[49] Gawley, R. E.; Hart, G. C.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem*. **1986**, *51*, 3078.

[50] Ding, Z.-Y.; Wang, T.; He, Y.-M.; Chen, F.; Zhou, H.-F. Fan, Q.-H.; Guo, Q.; Chan, A. S. C. *Adv. Synth. Catal.* **2013**, *355*, 3727. $[\alpha]^{22}_{D}$ = –43 (*c* = 0.6, EtOH, 99:1 er).

[51] For the synthesis of *rac*-**10a**, see: Li, X.; Leonori, D.; Sheikh, N. S.; Coldham, I. *Chem. Eur. J.* **2013**, *19*, 7724.

[52] Itoh, T.; Nagata, K.; Yokoya, M.; Miyazaki, M.; Kameoka, K.; Nakamura, S.; Ohsawa, A. *Chem. Pharm. Bull.* **2003**, *51*, 951.

[53] Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem*. **1995**, *60*, 7149.

[54] For the synthesis of *rac*-**4**, see: (a) Memetzidis, G.; Stambach, J. F.; Jung, L.; Schott, C.; Heitz, C.; Stoclet, J. C. *Eur. J. Med. Chem.* **1991**, *26*, 605. (b) Kiparissides, Z.; Fichtner, R. H.; Poplawski, J.; Nalliah, B. C.; MacLean, D. B. *Can. J. Chem.* **1980**, *58*, 2770.

[55] Polniaszek, R. P.; McKee, J. A. *Tetrahedron Lett*. **1987**, *28*, 4511. No spectral data were reported in this reference for compound (+)-**1l**.

[56] Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Militerni, A. G. G.; Polidori, G.; Spagna, R.; *J. Appl. Cryst.* **1999**, *32*, 115.

[57] Sheldrick, G. M.; *Acta Cryst*. **2008**, A64 112.

[58] Farrugia, L. J.; *J. Appl. Cryst*. **1999**, *32*, 837.

[59] Farrugia, L. J.; *J. Appl. Cryst*. **1998**, *30*, 565.