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A general procedure for the asymmetric synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolines

Jose L. Vicario, Dolores Badía,* Luisa Carrillo and Eneritz Anakabe

Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco-Euskal Herriko Unibertsitatea, PO Box 644, 48080 Bilbao, Spain

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Abstract—A general procedure for the asymmetric synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolines with any desired substitution pattern at both aromatic rings is reported. The methodology relies on the deoxygenation of 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols **1a**–**e**, which can be easily prepared from chiral non-racemic arylglycines under ionic hydrogenation conditions The target heterocycles are obtained as almost enantiomerically pure compounds. Further experiments allow establishing that this transformation occurs via S_N1 mechanism in which a carbocationic intermediate species is firstly formed and afterwards it undergoes rapid reaction with a nucleophilic hydride carrier to afford the reduction product.

1. Introduction

The isoquinoline core is a structural motif common to a large and diverse family of natural products, which have shown a remarkable array of biological activities.[1] Among the members of this family, those in which the nitrogen-containing ring is partially hydrogenated, the 1,2,3,4-tetrahydroisoquinolines, constitute a major group in this class of interesting alkaloids. In this particular case, several stereogenic centres can be incorporated in the heterocyclic skeleton. Taking into account the significant variation in the biological activity profile between enantiomers observed in some cases,[2] the development of efficient methodologies for the stereoselective synthesis of these compounds has became a challenging task for the organic chemist.[2,3]

Many reports can be found in the literature that describe several procedures for the stereoselective synthesis of differently substituted tetrahydroisoquinolines, most of them are focused on 1-substituted derivatives.[4] Some papers have been published that account for the stereoselective synthesis of 3-substituted tetrahydroisoquinolines, mainly introducing a carboxy- or an alkyl chain at this position.[5] However, the number of references describing the asymmetric synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolines is even more limited.[6] These are known as a relevant class of compounds among the isoquinoline alkaloids, both as important synthetic intermediates for the elaboration of other related alkaloids[7] like protoberberines, pavines or benzo[*c*]phenanthridines as well as enjoying considerable attention as potential therapeutic agents.[8]

Among the different strategies described for the construction of the isoquinoline core, the classical Pictet–Spengler[9] or Bischler–Napieralsky/reduction[10] procedures occupy a prominent position and indeed, we have reported the asymmetric synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolines starting from chiral nonracemic 1,2-diarylethylamines.[11] Unfortunately, the use of these heterocyclization procedures as key steps in the construction of the heterocyclic system has a strong limitation, which is that the substitution pattern at the aromatic ring of the isoquinoline skeleton becomes imposed by the electronic requirements of the cyclization step. Several approaches have been used to overcome these difficulties, but normally complex modifications have to be performed that result in complicated protecting group strategies.[12] This makes these heterocyclization methods unsuitable for the synthesis of 7,8-disubstituted derivatives, which are very commonly found in nature, as illustrated by the cases of the alkaloids *chelidonine* and *caseadanine* (Fig. 1).

Recently, we developed a procedure for the asymmetric synthesis of 6,7-disubstituted 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols using arylglycines as chiral tem-

* Corresponding author. Tel.: +34-94-6012633; fax: +34-94-4648500; e-mail: qopbaurm@lg.ehu.es

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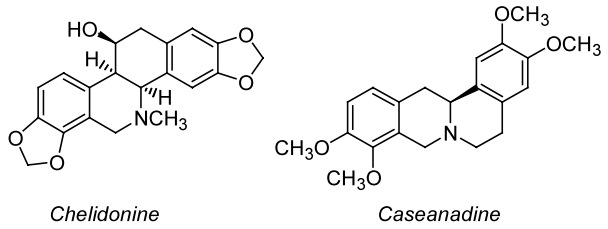
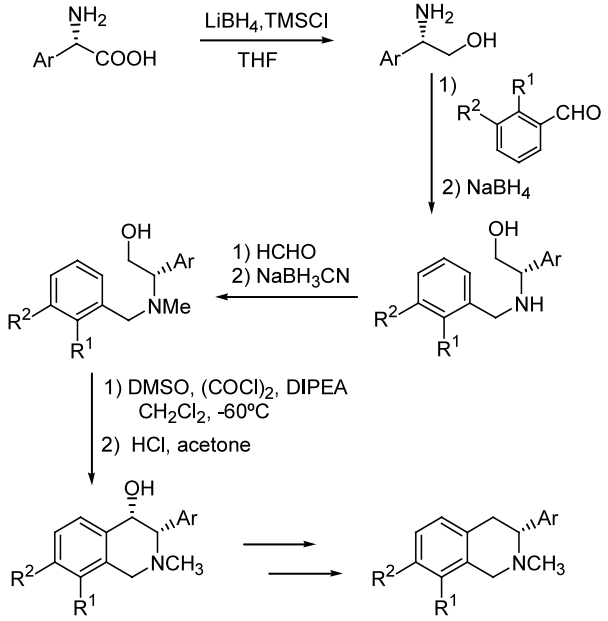


Figure 1.

plates (see Scheme 1).[13] This strategy, which is actually a chiral modification of the original Pomeranz–Fristch heterocyclization, allowed us the access to any kind of substitution pattern both at the isoquinoline aromatic ring and at the 3-aryl substituent and therefore, it can be an exceptionally useful approach to the target 3-aryl-1,2,3,4-tetrahydroisoquinolines, provided that a procedure is found for the conversion of the obtained 4-hydroxy substituted derivatives into simple 3-aryl heterocycles.



Scheme 1.

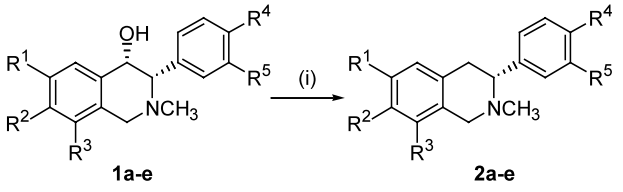
In this context, the so-called ionic hydrogenation reaction is a widely employed reductive transformation that allows the deoxygenation of alcohols into the corresponding alkanes,[14] as is required in our case. A wide variety of Brönsted or Lewis acid/hydride donor reagent combinations have been developed,[15] the carboxylic acid/$NaBH_4$ couple being a frequently employed system. The commonly postulated mechanism for this transformation involves conversion of the alcohol to an intermediate carbenium ion assisted by the carboxylic acid group, which is followed by reduction with a hydride carrier.[16] This is the main reason why this reaction has been limited to alcohols that form stable carbocations.[17] Other alcohols cannot be reduced cleanly, instead yielding oligomerization side products along with starting material.[17e]

Considering that the already mentioned 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols are benzylic alcohols, the formation of a resonance-stabilized carbocation can be foreseen, which should allow us to complete the deoxygenation reaction on these substrates. In this context, we wish to report here a simple and efficient procedure for converting these 4-hydroxy-substituted 3-aryl-1,2,3,4-tetrahydroisoquinolines into simple 3-aryl substituted heterocycles using the ionic hydrogenation reaction. The most remarkable feature of the methodology presented relies on its suitability for the preparation of the target compounds with any desired substitution pattern both at the aromatic ring of the tetrahydroisoquinoline core and at the 3-aryl substituent. This is of particular interest because different 6,7-disubstituted derivatives should be easily prepared in a simple and efficient way. These compounds are extremely useful precursors for the preparation of several other naturally occurring alkaloids.

2. Results and discussion

We started with the synthesis of the key 3-aryl-1,2,3,4-tetrahydroisoquinolin-4-ols **1a**–**e** using enantioenriched arylglycines as chiral precursors, according to a procedure developed in our group.[13] With these amino alcohols in hand, we proceeded to perform the ionic hydrogenation in order to convert them into the desired simple 3-aryl substituted heterocycles.

Among the different reported carboxylic acid/$NaBH_4$ combination of reagents we choose TFA as the proton source, due to its high ionising power together with its low nucleophilic character.[18] Consequently, the tetrahydroisoquinolin-4-ols **1a**–**e** were treated with a solution of $NaBH_4$ in TFA, affording, after a 2–3 h period, the reduced heterocycles **2a**–**e** in excellent yields after flash column chromatography purification (see Scheme 2). Remarkably, chiral HPLC analysis of the crude reaction mixture indicated that the reaction proceeded with no racemization at the remaining stereogenic centre in the 3-position, thus, 3-aryl-1,2,3,4-tetrahydroisoquinolines **2a**–**e** were obtained in near enantiomerically pure form (see Table 1).



Scheme 2. *Reagents and conditions*: (i) TFA, $NaBH_4$, CH_2Cl_2, rt.

Considering that very little is known about the mechanism of this reaction, especially concerning its application using chiral β-amino alcohol substrates, further experiments were performed to obtain a better understanding of this transformation. As already mentioned,

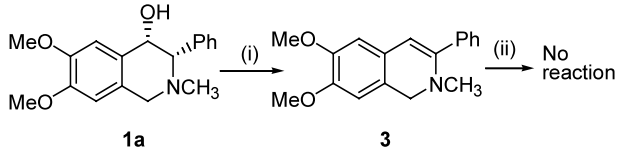
Table 1. Ionic hydrogenation of isoquinolin-4-ols **1a–d**

Prod.	R^1	R^2	R^3	R^4	R^5	Yield (%)[a]	ee (%)[b]
2a	OMe	OMe	H	H	H	75	95
2b	H	OMe	OMe	H	H	80	95
2c	H	OMe	OH[c]	H	H	85	95
2d	H	OMe	OMe	OMe	OMe	80	92
2e	H	OMe	OMe	OCH_2O		85	94

[a] Yield of pure product isolated after column chromatography.
[b] Determined by chiral HPLC analysis (Chiracel OD column; hexanes>/*iso*-Propanol 98/2; flow rate 0.90 mL/min).
[c] In the starting isoquinolin-4-ol R^3=OBn, therefore, deoxygenation occurred together with debenzylation.

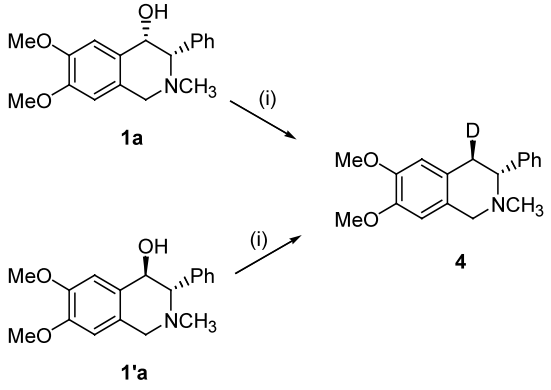
the mechanism commonly postulated in the literature involves the formation of a carbocationic intermediate species followed by quenching with a hydride carrier in a typical S_N1-type mechanism.[16] However, other authors[19] have suggested the possibility of a dehydration/elimination sequence leading to an intermediate alkene which, upon electrophilic addition of H^+ followed by reduction by the hydride species could also explain the formation of the final product and also account for the formation of oligomerization products in many cases. Finally, even the possibility of S_N2 displacement of OH by a hydride nucleophile, favoured by protonation of the hydroxy group should not be discarded.

In our case, the corresponding dehydration product **3** was obtained after treating isoquinolin-4-ol **1a** with TFA, which could be isolated and characterized. However, this alkene failed to react with a TFA/$NaBH_4$ mixture, even after 3 days stirring at room temperature. This result allowed us to discard the possibility of the elimination/H^+ electrophilic addition/H^- addition mechanism and therefore, only the possibility of a nucleophilic displacement of OH by a hydride reagent had to be considered, either of S_N1 or S_N2 kind (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt. (ii) $NaBH_4$, TFA, CH_2Cl_2, rt.

Next, we performed the ionic hydrogenation reaction using deuterated reagents. Treatment of **1a** with either $NaBD_4$/TFA or $NaBD_4$/TFA-*d* afforded the monodeuterated reduction product **4** cleanly in which incorporation of the deuterium atom was found to occur exclusively at C-4 (Scheme 4). Besides, the reaction was found to be fully diastereoselective, obtaining the deuterated analogue **4** as a single 3,4-*trans* diastereoisomer, as could be checked by NMR analysis of the crude reaction mixture. The relative configuration of both stereogenic centres was determined by NOE experiments.



Scheme 4. *Reagents and conditions*: (i) $NaBD_4$, TFA, or $NaBD_4$, TFA-*d*, CH_2Cl_2, rt.

This result is consistent with the substitution mechanism and is further evidence that the reaction does not proceed through an alkene intermediate. However, two possible mechanisms are still available to explain these results: the exclusive formation of the 3,4-*trans* deuterated isomer can result from both S_N2 pathway or an S_N1 route, in which the attack of the hydride species to the intermediate carbocation becomes stereochemically controlled by the presence of the C-3 stereogenic centre, thus explaining the observed high diastereoselectivity of the reaction.

The final proof came from the ionic hydrogenation of tetrahydroisoquinolin-4-ol **1′a**, which the C-4 epimer of **1a**. This compound was prepared in enantiomerically pure form according to the reported procedure.[11a] In this case, reduction with any of the deuterated reagents afforded the deuterated heterocycle **4**, again with full regio- and diastereocontrol (Scheme 4). This result rules out the possibility of the bimolecular substitution pathway and definitely points towards the first formation of a configurationally stable chiral carbocationic intermediate, which reacts with the hydride carrier reagent with 1,2-asymmetric induction exerted by the stereogenic centre present at the adjacent carbon atom (Fig. 2).

It also has to be pointed out that the exclusive incorporation of deuterium at the 4-position also indicates that the carbocation intermediate is fairly stable and does not undergo transposition, even to the adjacent C-3 position, which is also a benzylic one. Additionally, the fact that isoquinolines **2a–e** are obtained in enantiomeric purities comparable to those of the alcohol precursors supports this postulation.

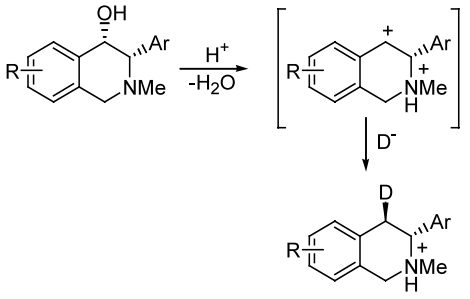
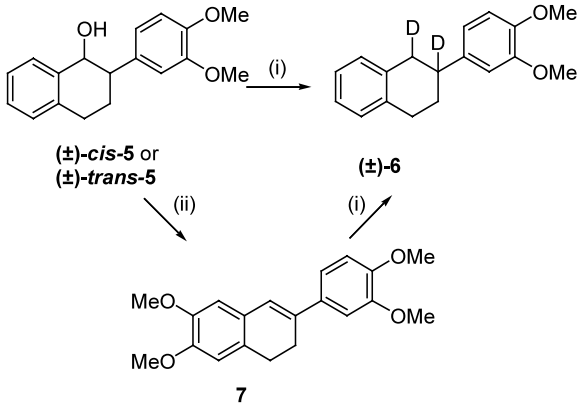


Figure 2. Proposed mechanism for the ionic hydrogenation of isoquinolines **1a**–**e**.

The presence of the nitrogen atom of the isoquinoline ring is a crucial element in this reaction. In fact, similar experiments performed during the ionic hydrogenation of the related 2-aryl-tetrahydro-1-naphthols **5** (Scheme 5) indicated that, in this case, the reaction proceeds by initial dehydration to yield an intermediate alkene **7**, followed by H^+ electrophillic attack/hydride quenching.



Scheme 5. *Reagents and conditions*: (i) $NaBD_4$, TFA-*d*, CH_2Cl_2, rt. (ii) TFA, CH_2Cl_2, rt.

This can be interpreted in terms of the formation of an ammonium salt by protonation of the tertiary amine functionality present in the tetrahydroisoquinoline skeleton prior to the dehydration step that leaves to the carbocationic intermediate (Fig. 2). Once this carbocation is formed, the transposition side reaction is very unlikely to occur because two adjacent positive charges would develop in the resulting intermediate.

3. Conclusions

A very efficient and straightforward procedure has been developed to prepare chiral nonracemic 3-aryl substituted 1,2,3,4-tetrahydroisoquinolines in a stereoselective way starting from the corresponding isoquinolin-4-ols, which can be easily prepared using arylglycines as chiral templates. The procedure involves the ionic hydrogenation of the precursors using the $NaBH_4$/TFA combination of reagents and affords the deoxygenated compounds in excellent yields and with no loss of enantiomeric purity compared to the starting materials. This methodology allows the preparation of these heterocycles with any desired substitution pattern at both aromatic rings, which is of outstanding importance because 7,8-disubstituted derivatives, which are not easily obtained using conventional heterocyclization routes like Pictet–Spengler or Bischler–Napieralsky cyclization, can be accessed readily in this way.

Additionally, mechanistic studies performed on the ionic hydrogenation of these particular substrates have allowed us to unambiguously establish that an S_N1 pathway is involved. Consequently, the reaction proceeds through formation of an intermediate carbocationic species, which is configurationally stable and undergoes rapid reaction with the nucleophilic hydride carrier species. The stereogenic centre at the C-3 position exerts very effective stereochemical control over the approach of the nucleophile and therefore stereodefined C-4 deuterated analogues can be prepared easily using this procedure. We have also demonstrated that the presence of an α-ammonium moiety is required in order to avoid competitive dehydration of the starting material that would eventually lead to racemization of the final products.

4. Experimental

4.1. General procedures

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20–25°C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solution and resonances are reported in ppm relative to tetramethylsilane unless otherwise stated. Assignment of individual ^{13}C resonances are supported by DEPT experiments. $^1H\{^1H\}$ NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[20] Mass spectra were recorded under electron impact at 70 eV. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}). Visualization was accomplished by UV light or by spraying with Dragendorff's reagent.[21] Flash column chromatography[22] on silica gel was performed with Merck Kiesegel 60 (230–400 mesh). Determination of enantiomeric excesses was performed by chiral HPLC analysis of non crystallized samples using a Chiracel OD® column with a UV detector with the eluents and flow rates as indicated in each case. All solvents used in reactions were dried and purified according to standard procedures.[23] All air- or moisture-sensitive reactions were performed under argon. The glassware was over dried (140°C) overnight and purged with argon.

4.2. General procedure for reductions using $NaBH_4$–TFA. Synthesis of tetrahydroisoquinolines, 2a–e

Over a cooled (0°C) suspension of $NaBH_4$ pellets (0.38 g, 10 mmol) in trifluoroacetic acid (4.6 mL, 60 mmol) was dropwise added a solution of the corresponding tetrahydroisoquinolin-4-ol **1** (1.0 mmol) in CH_2Cl_2. The

reaction mixture was stirred at room temperature until complete conversion (typically 2–3 h) and then the volatiles were removed under reduced pressure. The resulting slurry was basified with 1 M NaOH (10 mL) and extracted with CH_2Cl_2. The combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography to afford tetrahydroisoquinolines **2a**–**e**.

4.2.1. (3*R*)-6,7-Dimethoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline, 2a. The reaction of the tetrahydroisoquinolin-4-ol **1a** (100 mg, 0.33 mmol) with $NaBH_4$ (0.13 g, 3.34 mmol) following the general procedure afforded tetrahydroisoquinoline **2a** (70 mg, 0.25 mmol) as an oil. Yield: 75%. $[\alpha]_D^{20}$: +28.0 (*c* 0.5, CH_2Cl_2). IR ($CHCl_3$): 1530 cm^{-1}. ^1H NMR (δ, ppm): 2.16 (s, 3H); 2.89 (dd, $J=16.2$, 4.3 Hz, 1H); 3.07 (dd, $J=16.1$, 9.9 Hz, 1H); 3.37 (dd, $J=9.9$, 4.3 Hz, 1H); 3.83 (s, 3H); 3.86 (s, 3H); 3.92 (d, $J=14.7$ Hz, 1H); 6.56 (s, 1H); 6.57 (s, 1H); 7.24–7.36 (m, 5H). ^{13}C NMR (δ, ppm): 37.7; 43.3; 55.8; 55.9; 58.3; 66.5; 108.8; 110.6; 126.2; 127.4; 127.9; 128.5; 142.6; 147.2; 147.5. MS (EI) *m*/*z* (rel. int.): 283 (M^+, 14); 164 (100); 149 (12); 121 (10); 77 (10).

4.2.2. (3*R*)-7,8-Dimethoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline, 2b. The reaction of the tetrahydroisoquinolin-4-ol **1b** (150 mg, 0.50 mmol) with $NaBH_4$ (0.21 g, 5.55 mmol) following the general procedure afforded tetrahydroisoquinoline **2b** (110 mg, 0.40 mmol) as an oil. Yield: 80%. Mp: 95–98°C (diethyl ether), $[\alpha]_D^{20}$: +96.2 (*c* 0.1, CH_2Cl_2). IR ($CHCl_3$): 1550 cm^{-1}. ^1H NMR (δ, ppm): 2.20 (s, 3H); 2.91 (dd, $J=$ 16.2, 4.0 Hz, 1H); 3.10 (dd, $J=16.1$, 10.3 Hz, 1H); 3.34 (dd, $J=10.3$, 4.0 Hz, 1H); 3.45 (d, $J=16.2$ Hz, 1H); 3.86 (s, 6H); 4.21 (d, $J=16.2$ Hz, 1H); 6.78 (s, 2H); 7.26–7.36 (m, 5H). ^{13}C NMR (δ, ppm): 37.8; 43.5; 54.0; 55.8; 60.1; 66.2; 110.6; 123.1; 123.5; 127.3; 127.6; 127.8; 128.4; 142.7; 144.8; 150.1. MS (EI) *m*/*z* (rel. int.): 283 (M^+, 58); 206 (24); 164 (100); 149 (66).

4.2.3. [3*R*]-8-Hydroxy-2-methyl-7-methoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline, 2c. The reaction of the tetrahydroisoquinolin-4-ol **1c** (50 mg, 0.13 mmol) with $NaBH_4$ (0.05 g, 1.28 mmol) following the general procedure afforded tetrahydroisoquinoline **2c** (30 mg, 0.11 mmol) as an oil. Yield: 85%. $[\alpha]_D^{20}$: +77.6 (*c* 0.1, CH_2Cl_2). IR (neat): 1530 cm^{-1}. ^1H NMR (δ, ppm): 2.20 (s, 3H); 2.90 (dd, $J=16.0$, 4.0 Hz, 1H); 3.10 (dd, $J=16.0$, 10.3 Hz, 1H); 3.35 (dd, $J=10.3$, 4.0 Hz, 1H); 3.43 (d, $J=16.2$ Hz, 1H); 3.87 (s, 3H); 4.20 (d, $J=16.2$ Hz, 1H); 6.57 (d, $J=8.5$ Hz, 1H); 6.72 (d, $J=8.5$ Hz, 1H); 7.03–7.37 (m, 5H). ^{13}C NMR (δ, ppm): 37.7; 43.5; 53.4; 56.0; 66.2; 108.8; 118.5; 121.1; 127.3; 127.9; 128.3; 128.5; 128.7; 140.0; 141.4; 142.7; 143.9. MS (EI) *m*/*z* (rel. int.): 269 (M^+, 58); 192 (25); 150 (69); 135 (25); 120 (100), 91 (10), 77 (16).

4.2.4. (3*R*)-3-(3,4-Dimethoxyphenyl)-7,8-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 2d. The reaction of the tetrahydroisoquinolin-4-ol **1d** (58 mg, 0.13 mmol) with $NaBH_4$ (0.05 g, 1.28 mmol) following the general procedure afforded tetrahydroisoquinoline **2d** (30 mg, 0.11 mmol) as an oil. Yield: 80%. $[\alpha]_D^{20}$: +45.2 (*c* 0.1, CH_2Cl_2). IR (neat): 1560 cm^{-1}. ^1H NMR (δ, ppm): 2.20 (s, 3H); 2.89 (dd, $J=16.2$, 3.6 Hz, 1H); 3.10 (dd, $J=16.2$, 10.3 Hz, 1H); 3.28 (dd, $J=10.3$, 3.6Hz, 1H); 3.43 (d, $J=16.6$ Hz, 1H); 3.88 (s, 6H); 3.89 (s, 6H); 4.24 (d, $J=16.6$ Hz, 1H); 6.78–6.93 (m, 5H). ^{13}C NMR (δ, ppm): 37.8; 43.2; 54.2; 55.8; 55.9; 60.2; 66.1; 110.6; 110.8; 120.2; 123.2; 127.4; 128.8; 130.9; 135.4; 144.9; 148.2; 149.2; 150.2. MS (EI) *m*/*z* (rel. int.): 343 (M^+, 53); 312 (31); 164 (100), 149 (60).

4.2.5. (3*R*)-7,8-Dimethoxy-2-methyl-3-(3,4-methylendioxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 2e. The reaction of the tetrahydroisoquinolin-4-ol **1e** (56 mg, 0.13 mmol) with $NaBH_4$ (0.05 g, 1.28 mmol) following the general procedure afforded tetrahydroisoquinoline **2e** (30 mg, 0.11 mmol) as an oil. Yield: 85%. $[\alpha]_D^{20}$: +50.1 (*c* 0.1, CH_2Cl_2). IR (neat): 1600 cm^{-1}. ^1H NMR (δ, ppm): 2.24 (s, 3H); 2.88–3.13 (m, 2H); 3.32 (m, 1H); 3.48 (d, $J=16.4$ Hz, 1H); 3.87 (s, 6H); 4.21 (d, $J=16.4$ Hz, 1H); 5.97 (s, 2H); 6.78–6.89 (m, 5H). ^{13}C NMR (δ, ppm): 37.5; 43.2; 53.7; 55.8; 60.2; 65.8; 101.0; 107.9; 108.1; 110.9; 121.4; 123.2; 127.3; 130.6; 138.6; 144.9; 146.9; 147.9; 150.3. MS (EI) *m*/*z* (Rel. Int.): 327 (M^+, 64); 296 (17); 164 (100), 149 (58).

4.3. General procedure for reductions using tandem $NaBD_4$–TFA

To a cooled (0°C) suspension of $NaBD_4$ (0.38 g, 10 mmol) in trifuoroacetic acid (4.6 mL, 60 mmol) was added dropwise a solution of the corresponding alcohol (1 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature until complete conversion (typically 2–3 h). The volatiles were removed in vacuo and the resulting slurry was basified with 1 M aqueous NaOH (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removes in vacuo. The resulting residue was purificated by flash column chromatography.

4.3.1. (3*R*,4*R*)-3-Phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-d_1, 4. The reaction of the tetrahydroisoquinolin-4-ol **1e** (100 mg, 0.33 mmol) with $NaBD_4$ (0.11 g, 3.28 mmol) following the general procedure afforded deuterated tetrahydroisoquinoline **4** (70 mg, 0.25 mmol) as an oil. Yield: 75%; $[\alpha]_D^{20}$: +27.1 (*c* 0.1, CH_2Cl_2); ^1H NMR (δ, ppm): 2.16 (s, 3H), 3.05 (d, $J=10.3$, 1H), 3.38 (d, $J=10.3$, 1H), 3.54 (d, $J=14.9$, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 3.92 (d, $J=14.9$, 1H), 6.56 (s, 1H), 6.57 (s, 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (δ, ppm): 37.4 (t, $J=20.7$), 43.3, 55.8, 55.9, 58.2, 66.4, 108.8, 110.5, 126.1, 126.2, 127.3, 127.9, 128.5, 142.6, 147.2, 147.5; EI-MS *m*/*z*: 284 (M^+, 22), 165 (100), 150 (11).

4.3.2. 2-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydronaphtalene-1,2-d_2, 6. The reaction of the alcohol (±)-*cis*-**5** (100 mg, 0.35 mmol) with $NaBH_4$ (0.13 g, 3.50 mmol) following the general procedure afforded naphthalene **6** (75 mg, 0.28 mmol) as a white solid. Yield:

80%. Mp (Et_2O) 65–67°C. ^1H NMR (δ, ppm): 1.91–1.97 (m, 1H); 2.11–2.16 (m, 1H); 2.93–2.97 (m, 3H); 3.89 (s, 3H); 3.90 (s, 3H); 6.82–6.89 (m, 3H); 7.11–7.15 (m, 4H); ^{13}C NMR (δ, ppm): 29.7; 30.4; 37.8 (t, $J=$ 8.0); 40.2; 55.7; 55.8; 110.1; 111.0; 118.4; 125.5; 125.7; 128.8; 128.9; 136.2; 136.6; 139.2; 147.3; 148.7. MS (EI) m/z (rel. int.): 270 (M^+, 100); 165 (98); 138 (76).

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References

1. (a) Shamma, M. *Isoquinoline Alkaloids*, *Chemistry and Pharmacology*; Academic Press: New York, 1972; (b) Scott, J. D.; Williams, R. M. *Chem. Rev*. **2002**, *102*, 1669; (c) Bentley, K. B. *Nat. Prod. Rep*. **2001**, *18*, 148.
2. (a) Tatton, W. G.; Ju, W. Y. L.; Holland, D. P.; Tai, C.; Kwan, M. *J. Neurochem*. **1994**, *63*, 1572; (b) Maruyama, W.; Naoi, M.; Kasamatsu, T.; Hashizume, Y.; Takahashi, T.; Kohda, K.; Dostert, P. *J. Neurochem*. **1997**, *69*, 322.
3. For a review, see: Rodzwadowska, M. D. *Heterocycles* **1994**, *39*, 903.
4. (a) Chan, W.; Lee, A. W. M.; Jiang, L. *Tetrahedron Lett*. **1995**, *36*, 715; (b) Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2661; (c) Chan, W.; Lee, A. W. M.; Jiang, L. *Tetrahedron Lett*. **1995**, *36*, 715; (d) Munchoff, M. J.; Meyers, A. I. *J. Org. Chem*. **1996**, *61*, 4607; (e) Chau, P.; Czuba, I. R.; Rizzacasa, M. A.; Bringmann, G.; Gulden, K.-P.; Schäffer, M. *J. Org. Chem*. **1996**, *61*, 7101; (f) Yamazaki, N.; Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett*. **1996**, *37*, 6161; (g) Commins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327; (h) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res*. **1997**, *30*, 90; (i) Kang, J.; Kim, J. B.; Cho, K. H.; Cho, B. T. *Tetrahedron: Asymmetry* **1997**, *8*, 657; (j) Takaba, K.; Haginaka, J.; Kunitomo, J.; Shingu, T. *Heterocycles* **1997**, *45*, 1111; (k) Wanner, K. H.; Beer, H.; Höfner, G.; Ludwig, M. *Eur. J. Org. Chem*. **1998**, 2019; (l) Bravo, P.; Crucianelly, M.; Farina, A.; Meille, S. V.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem*. **1998**, 435; (m) Itoh, T.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1154; (n) Wünsch, B.; Nerdinger, S. *Eur. J. Org. Chem*. **1999**, 503; (o) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron Lett*. **2000**, *41*, 5533; (p) Tietze, L. F.; Zhou, Y.; Töpken, E. *Eur. J. Org. Chem*. **2000**, 2247; (q) Ukaji, Y.; Yoshida, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2000**, *11*, 733; (r) Gluszynska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2359; (s) Jensen, K. B.; Roberson, M.; Jorgensen, K. A. *J. Org. Chem*. **2000**, *65*, 9080; (t) Pedrosa, R.; Andrés, C.; Iglesias, J. M. *J. Org. Chem*. **2001**, *66*, 243; (u) Herberich, B.; Kinugawa, M.; Vazquez, A.; Williams, R. M. *Tetrahedron. Lett*. **2001**, *42*, 543; (v) Zawadzka, A.; Leniewski, A.; Maurin, J. K.; Wojtasiewicz, K.; Czarnocki, Z. *Org. Lett*. **2001**, *3*, 997; (w) Adam, S.; Pannecoucke, X.; Combret, J.-C.; Quirion, J.-C. *J. Org. Chem*. **2001**, *66*, 8744.
5. (a) Gosmann, G.; Guillaume, D.; Husson, J.-P. *Tetrahedron Lett*. **1996**, *37*, 4369; (b) Corey, E. J.; Gin, D. Y. *Tetrahedron Lett*. **1996**, *37*, 7163; (c) Monsees, A.; Laschat, S.; Dix, I.; Jones, P. G. *J. Org. Chem*. **1998**, *63*, 10018; (d) Barbier, D.; Marazano, C.; Riche, C.; Das, B. C.; Potier, P. *J. Org. Chem*. **1998**, *63*, 1767; (e) Ohba, M.; Nishimura, Y.; Kato, M.; Fujii, T. *Tetrahedron* **1999**, *55*, 4999; (f) Katritzky, A. R.; Cobo-Domingo, J.; Yang, B.; Steel, P. J. *Tetrahedron: Asymmetry* **1999**, *10*, 255; (g) Brozda, D.; Koroniak, L.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017; (h) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett*. **2000**, *2*, 3901.
6. (a) Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *J. Org. Chem*. **1999**, *64*, 4610; (b) Davis, F. A.; Andemichael, Y. W. *J. Org. Chem*. **1999**, *64*, 8627; (c) Derdau, V.; Snieckus, V. *J. Org. Chem*. **2001**, *66*, 1992. See also Ref. 11.
7. (a) Dyke, S. F.; Kinsman, R. G.; Kametami, T. G.; Fukumato, K.; McDonald, E. In *Isoquinolines*, *Heterocyclic Compounds*; Grethe, G., Ed.; Wiley: New York, 1981; Vol. 38, p. 1; (b) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589; (c) Carrillo, L.; Badía, D.; Domínguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem*. **1997**, *62*, 6716; (d) Vicario, J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1947; (e) Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *Tetrahedron: Asymmetry* **2000**, *11*, 1227.
8. (a) Kametani, T.; Hirata, S.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1466; (b) Ito, K.; Furukawa, H.; Iida, Y.; Lee, K. H.; Soine, T. O. *J. Chem. Soc., Chem. Commun*. **1974**, 1037; (c) Shamma, M.; Tomlinson, H. H. *J. Org. Chem*. **1978**, *43*, 2852; (d) Cushman, M.; Choong, T. C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem*. **1980**, *45*, 5067; (e) Valenta, V.; Holubek, J.; Svatek, E.; Dlabac, A.; Bartosova, M.; Protiva, M. *Collect. Czech. Chem. Commun*. **1983**, *48*, 1447; (f) Clark, R. D.; Jahangir, J. *J. Org. Chem*. **1989**, *54*, 1174.
9. For a review on Pictet–Spengler cyclization, see: Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, *95*, 1797.
10. See for example: (a) Larsen, R. D.; Reamer, R. A.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem*. **1991**, *56*, 6034; (b) Venkov, A. P.; Ivanov, I. I. *Tetrahedron* **1996**, *52*, 12299.
11. (a) Tellitu, I.; Badía, D.; Domínguez, E.; García, F. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1567; (b) Carrillo, L.; Badía, D.; Domínguez, E.; Anakabe, E.; Osante, I.; Tellitu, I.; Vicario, J. L. *J. Org. Chem*. **1999**, *64*, 1115.
12. (a) Kametani, T.; Nakano, K.; Shishido, K.; Fukumoto, K. *J. Chem. Soc. (C)* **1971**, 3350; (b) Badía, D.; Domínguez, E.; Iriondo, C. *Bull. Soc. Chim. Belg*. **1986**, *95*, 207; (c) Cutter, P. S.; Miller, R. B.; Schore, N. E. *Tetrahedron* **2002**, *58*, 1471.
13. Anakabe, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem*. **2001**, 4343.
14. (a) Kursanov, D. N.; Parnes, Z. N.; Kalinkin, M. I.; Loim, N. M. *Ionic Hydrogenation and Related Reactions*; Harwood Academic Publishers: New York, 1985; (b) Gribble, G. W. *Reductions in Organic Synthesis*, Abdel-Magid, A.F., Ed.; ACS Symposium Series 641. Washing-

ton, 1996, pp. 167–200; (c) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Wiley-VCH: New York, 1997.
15. See for example: (a) Nordlander, E.; Payne, M. J.; Njoroge, F. G.; Vishwanath, V. M.; Han, G. R.; Laikes, G. D.; Balk, M. A. *J. Org. Chem.* **1985**, *50*, 3619; (b) Olah, G. A.; Arvanaghi, M.; Ohannesian, L. *Synthesis* **1986**, 770; (c) McComsey, D. F.; Reitz, A. B.; Maryanoff, C. A.; Maryanoff, B. E. *Synth. Commun.* **1986**, *16*, 1535; (d) Lomas, J. S.; Bru-Capdeville, V. *J. Chem. Soc., Perkin Trans 2* **1997**, 2589; (e) Yato, M.; Homma, K.; Ishida, A. *Heterocycles* **1998**, 233; (f) Li, C.; Rehman, A.; Dalley, N. K.; Savage, P. B. *Tetrahedron Lett.* **1999**, *40*, 1861.
16. Gribble, G. W. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley&Sons: New York, 1995; Vol. 7, p. 4649.
17. (a) Gribble, G. W.; Leese, R. M.; Evans, B. E. *Synthesis* **1977**, 172; (b) Ogata, F.; Takagi, M.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1981**, *103*, 1145; (c) Briody, J. M.; Marshall, G. L. *Synthesis* **1982**, 939; (d) Mitchell, R. H.; Lai, Y. H. *J. Org. Chem.* **1984**, *49*, 2534; (e) Nutaitis, C. F.; Bernando, J. E. *Synth. Commun.* **1990**, *20*, 487; (f) Nutaitis, C. F.; Obaza-Nutaitis, J. *Org. Prep. Proc. Int.* **1997**, *29*, 315.
18. Gribble, G. W. *Chem. Soc. Rev.* **1998**, 295.
19. Greenhouse, R.; Ramirez, C.; Muchowski, J. M. *J. Org. Chem.* **1985**, *50*, 2961. See also Ref. 17e.
20. Kinss, M.; Sanders, J. K. M. *J. Magn. Reson.* **1984**, *56*, 518.
21. Stahl, E. *Thin Layer Chromatography*; 2nd ed.; Berlin: Springer Verlag, 1969.
22. Still, W. C.; Kann, H.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
23. Armarego, W. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th ed.; Butterworth-Heinmann Newton: MA, 1997.