Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1809–1816

TETRAHEDRON: *ASYMMETRY*

Stereochemical studies on the synthesis of 1,2,3,4-tetrahydroisoquinolin-4-ols

Luisa Carrillo, Dolores Badía,* Esther Domínguez,* Imanol Tellitu and José Luis Vicario

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

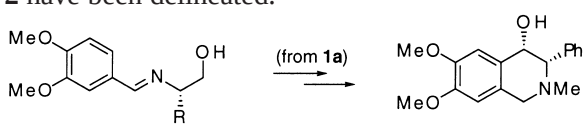
Received 6 April 1998; accepted 21 April 1998

Abstract

The stereoselectivity of the acid catalyzed promoted cyclization of adequately substituted α-aminoaldehydes to afford a series of tetrahydroisoquinolin-4-ols is studied. The results illustrate the effect of the substituents at C-1 and/or C-3 in the target heterocycle. The required precursors **5** and **10** were synthesized from the enantiomerically pure (−)-imines **1** by two different routes, and reacted with conc. HCl. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Despite the extensive results gathered over recent years on the synthesis of different isoquinolin-4-ols,[1] some aspects of the stereocontrolled access to their polysubstituted derivatives remain unexplored. In this context, pioneering work by Bates[2] on the Pictet–Spengler cyclization of (−)-norepinephrine and (−)-epinephrine revealed some deficiencies from regioselective and stereoselective points of view. Attracted also by their substantial biological and pharmacological activities,[3] we recently have been involved in a major effort to design and optimize different strategies conducive to the stereoselective preparation of the title compounds, and preliminary results have already been published. Thus, different sequences to obtain either (1*R*,3*S*,4*R*)- or (1*S*,3*S*,4*R*)-3-aryl-1-methyltetrahydroisoquinolin-4-ols from cyanohydrins[4] and, more recently, the transformation of enantiopure imines **1** into (3*S*,4*S*)-3-phenyltetrahydroisoquinolin-4-ol **2** have been delineated.[5]



1a, R=Ph
1b, R=^{i}Pr

(3*S*,4*S*)-**2**

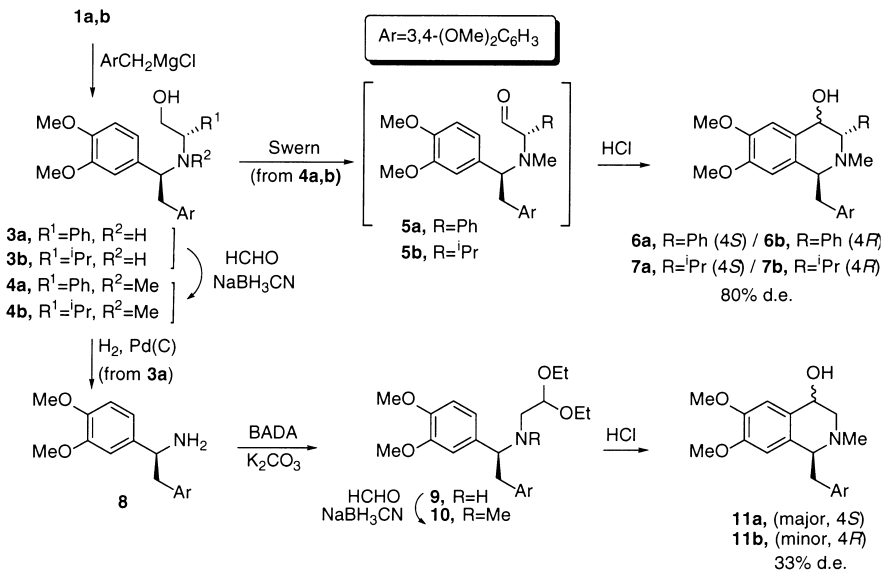
* Corresponding authors. Fax: +34-94-4648500; e-mail: qopdopee@lg.ehu.es

PII: S0957-4166(98)00164-5

Trying to improve our knowledge about the factors that govern the stereochemical outcome of our last strategy, and complementary to the observed 1,2-asymmetric induction due to the presence of an adjacent stereogenic center in imines **1**, the cyclization reaction of structurally related precursors was tested. Thus, the presence of a second stereogenic center (as in **5**), the steric and electronic nature of the α-substituent to the carbonyl function (**5a** vs **5b**), and the effect of a sole stereogenic center at a remote site (as in **10**) were investigated. The already mentioned precursors **5** and **10** were prepared starting from (−)-imines **1**, and then transformed into the corresponding tetrahydroisoquinolin-4-ols by electrophilic aromatic substitution with the results shown in this paper.

2. Results and discussion

First, imines **1** were alkylated with the appropriate Grignard reagent[6] to afford (1*S*,1′*S*)-aminoalcohols **3a** and **3b** which, in turn, were *N*-methylated and oxidized to α-aminoaldehydes **5a** and **5b** (Scheme 1). Due to their lability, aldehydes **5** were immediately reacted with an acetone solution of conc. HCl[7] yielding the corresponding (1*S*,3*S*,4*S*)-tetrahydroisoquinolin-4-ols **6a** and **7a** as the major (d.e.=80%) diastereoisomers. Alternatively, the hydrogenolytic removal of the chiral auxiliary in aminoalcohol **3a** afforded amine **8** which, after treatment with bromoacetaldehydediethylacetal (BADA) followed by formaldehyde, was transformed into aminoacetal **10**.†



Scheme 1.

The thus-formed derivative **10** was submitted to an acid-catalyzed heterocyclization process leading to (1*S*,4*S*)-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol **11a**, although with poor diastereoselectivity (d.e.=33%). It has to be pointed out that the use of non-protic solvents, such as acetone, in the heterocyclization step enables the target heterocycle to be obtained avoiding formation of undesired isopavine derivatives.[6]

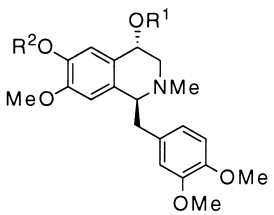
† The alternative *N*-alkylation sequence of **8** with formaldehyde followed by BADA was also evaluated and ruled out since it resulted in significant racemization of **10**.[6]

After separation of the pair of C-4 epimers, the enantiomeric excess was determined by chiral HPLC for all the stereoisomers prepared, and no racemization was detected in any of the described transformations (e.e.=95%).

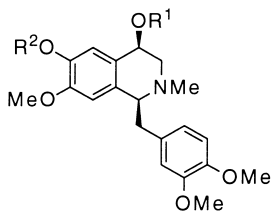
On the other hand, the stereochemical relationships of the stereogenic centers of heterocycles **6**, **7** and **11** were determined either by extensive NMR experiments or by comparison with spectroscopic data of structurally related compounds with well defined stereochemistry. In order to gain additional data, we have also studied the stereochemical behavior of isoquinoline (3*S*,4*S*)-**2** previously synthesized by our group.[5] Thus, the observation of an intense nuclear Overhauser effect between H-3 and H-4 in compound **2**, as well as the small value of their coupling constant (2.6 Hz), revealed a 3,4-*cis* relationship of the substituents at both stereogenic carbons. This stereochemical proposal could also be confirmed by comparison with spectroscopic data of the known stereoisomer (3*S*,4*R*)-**2**.[4] Thus, presumably, the isoquinoline (3*S*,4*S*)-**2** must be stabilized in a chair-like conformation with the phenyl substituent in an equatorial position, and the hydroxy group in a pseudoaxial orientation that enables the formation of a H-bond with the lone electron pair on the nitrogen.

Analogously, for both tetrahydroisoquinoline derivatives, **6** and **7**, the relative configuration of the major stereoisomers were assigned on the basis of NOE experiments. Thus, a 3,4-*cis* relationship between the substituents at C-3 and C-4 accounts for the observation of that effect between H-3 and H-4, as well as H-3 and the NMe group in compounds **6a** and **7a**, which is in good agreement with the absence of NOE in the corresponding minor epimers (1*S*,3*S*,4*R*)-**6b** and (1*S*,3*S*,4*R*)-**7b**.

However, because of the presence of several revealing masked signals in the ^{1}H-NMR spectra of isoquinolines **11**, their stereochemical relationships had to be assigned by comparison with similar compounds (roemecarine and epiroemecarine), whose stereostructures were established by Hoshino by X-ray crystallographic analysis of a roemecarine derivative.[8] The ^{1}H-NMR spectrum of the latter compound revealed a significant upfield-shifted absorption (1 ppm) for H-8 with respect to the same proton in its epimer epiroemecarine. A similar behavior was observed in the major stereoisomer of compound **11** which strongly suggests the same 1,4-*trans* relationship for the involved substituents. Other significant chemical shifts of compound **11**, which are also in good accordance with those reported for the natural alkaloid and its epimer, are shown in Scheme 2.



11a, R^1=H, R^2=Me, δ_{H8}=5.80 ppm, δ_{H4}=4.47 ppm
roemecarine, R^1=R^2=H, δ_{H8}=5.73 ppm, δ_{H4}=4.48 ppm
acetyl*roemecarine*, R^1=Ac, R^2=H, δ_{H8}=5.82, ppm

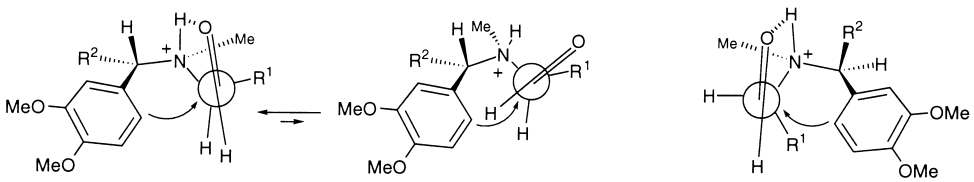


11b, R^1=H, R^2=Me, δ_{H8}=6.50 ppm, δ_{H4}=4.39 ppm
epiroemecarine, R^1=R^2=H, δ_{H8}=6.53 ppm, δ_{H4}=4.33 ppm
acetyl*epiroemecarine*, R^1=Ac, R^2=H, δ_{H8}=6.01

Scheme 2.

The observed stereoselectivity of the cyclization step could be rationalized in terms of the diastereoselective formation of the ammonium salt intermediate (epimer **I** vs **II** in Scheme 3) and thus, when R^1=Ph or i-Pr, the most stable epimer **I** (*S* configuration on the nitrogen) is the only stereoisomer formed. In this case, the electrophilic attack took place through an intramolecular H-bonded cyclic conformation (**IA**), and under these circumstances derivatives **2**, **6a** and **7a** were obtained diastereoselectively. On the other hand, an equilibrium between cyclic conformation **IA** and the open conformation **IB**, stabilized by a σ^*–π^* interaction,[9] could be proposed to explain the loss of stereoselectivity found in the cyclization of

aldehydes **5a** and **5b** to yield tetrahydroisoquinolines **6** and **7** respectively. Finally, such control was not observed for precursor **10** where the lack of substitution (R^1=H) in the adjacent position to the acetalic carbon led to epimers **I** and **II** with similar energetic contents. In this case, the poor stereoselectivity found in isoquinoline **11a** could be explained as a result of the slightly energetically preferred epimer **I** vs **II**, both stabilized by an intramolecular H-bond, where the steric interaction between the bulky substituent (R^2=CH_2Ar) and the carbonyl group is minimized.



Scheme 3.

To sum up, from our studies we can propose that, in order to get high diastereoselection in the cyclization reaction of α-aminoaldehydes to substituted tetrahydroisoquinolin-4-ols, a substituent (either aromatic or aliphatic) adjacent to the new stereogenic center is required. On the contrary, the presence of a bulky substituent at C-1 in the target heterocycle leads to losses of diastereoselectivity.

3. Experimental section

3.1. General procedures

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were measured on a Perkin–Elmer 1430 spectrophotometer as KBr plates or as neat liquid and peaks are reported in cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker ACE-250 apparatus at 250 MHz with $CHCl_3$ (7.26 ppm) as an internal reference in $CDCl_3$ solutions. ^{13}C-NMR spectra were recorded on the same spectrometer at 62.8 MHz with $CHCl_3$ (77.0 ppm) as an internal reference in $CDCl_3$ solutions. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), br s (broad singlet), br t (broad triplet), d (doublet), t (triplet), q (quadruplet), m (multiplet) or dd (doublet of doublets). Coupling constants, J, are reported in hertz. All solvents used were technical grade and purified according to standard procedures.[10] Thin layer chromatography was performed on silica gel 60 F_{254} plates and visualized by UV light or Dragendorf's reagent.[11] Flash column chromatography[12] was performed on Merck kieselgel 60 (70–230 mesh ASTM). All transfers of liquid solution and solvents were performed by syringe techniques or via cannula.[13] Combustion analyses were performed with a Perkin–Elmer 2400 CHN apparatus. Mass spectra were recorded under electron impact at 70 eV. GC–MS analyses were performed using a HP-5 column (5% phenylmethylpolysiloxane, 30 m×0.25 mm×0.25 μm). The HPLC separations were performed on a Hibar Lichrosorb Si 60 column (7 μm). Enantiomeric excess determinations were made by HPLC with a Chiralcel OD column, using a UV detector, and employing *n*-hexane:isopropanol 75:25 as eluent; flow rate 0.5 mL/min.

3.2. General procedure for the N-methylation of compounds **3**

Over a solution of the corresponding amino derivative **3** (1 mmol) and aqueous HCHO (35%, 5 mmol) in 8 mL of MeCN, $NaBH_3CN$ (5 mmol) was added in three portions at room temperature. When the starting material was completely consumed (TLC), water was added (5 mL) and the mixture was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was distilled at reduced pressure. The crude product obtained was purified as specified for each compound.

3.2.1. (+)-(2S,1′S)-2-[N-1,2-Bis(3,4-dimethoxyphenyl)ethyl-N-methyl]amino-2-phenylethanol **4a**

Following the general procedure, the reaction of (+)-aminoalcohol **3a** (0.52 g, 1.2 mmol), HCHO (0.5 mL, 6.0 mmol) and $NaBH_3CN$ (0.39, 6.0 mmol) yielded, after 20 h, the *N*-methylated aminoalcohol **4a** which was purified by flash column chromatography (CH_2Cl_2:EtOAc, 6:4) as a colorless oil (0.43 g, 0.96 mmol), yield 80%. $[\alpha]_D^{20}$ +31.5 (c=1.0, CH_2Cl_2); ^{1}H-NMR (δ, ppm): 2.20 (s, 3H, CH_3), 2.60–2.80 (br s, 1H, OH), 2.85 (dd, J=13.5, 9.0, 1H, ArCH_aH_b), 3.27 (dd, J=13.5, 5.6, 1H, ArCH$_a$$H_b$), 3.64–3.89 (m, 3H, ArC*H*, CH_2OH), 3.69 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.10 (dd, J=8.0, 5.2, 1H, PhC*H*), 6.34 (d, J=1.9, 1H, H_{arom}), 6.53 (dd, J=8.2, 1.9, 1H, H_{arom}), 6.66–6.71 (m, 4H, H_{arom}), 7.24–7.33 (m, 5H, H_{arom}); ^{13}C-NMR (δ, ppm): 32.6 (CH_3), 36.9 (Ar*C*H$_2$), 55.3, 55.4 (OCH_3), 61.5 (CH_2OH), 65.6, 65.7 (Ar*C*H, Ph*C*H), 110.1, 110.5, 111.6, 112.0, 120.4, 120.9, 127.4, 127.8, 128.5 (tC_{arom}), 133.5, 138.0, 146.8, 147.6, 147.8, 148.2 (qC_{arom}); IR (neat): 3600–3400; EI-MS *m/z*: 300 (100), 286 (8), 180 (71), 151 (15), 120 (13), 103 (13).

3.2.2. (+)-(2S,1′S)-2-[N-1,2-Bis(3,4-dimethoxyphenyl)ethyl-N-methyl]amino-2-isopropylethanol **4b**

Following the general procedure, the reaction of (+)-aminoalcohol **3b** (0.60 g, 1.5 mmol), HCHO (0.6 mL, 7.5 mmol) and $NaBH_3CN$ (0.47 g, 7.5 mmol) yielded after 15 h a crude product that was flash column chromatographed (hexanes:EtOAc, 8:2), and the resulting oil was crystallized from EtOH:hexanes to afford aminoethanol **4b** as a white solid (0.46 g, 1.1 mmol), yield 80%. $[\alpha]_D^{20}$ +73.0 (c=1.0, CH_2Cl_2); m.p.: 95–96°C; ^{1}H-NMR (δ, ppm): 0.80 (d, J=6.8, 3H, CH_3CH), 0.95 (d, J=6.8, 3H, CH_3CH), 1.66–1.77 (m, 1H, C*H*(CH_3)$_2$), 2.22 (s, 3H, NCH_3), 2.71 (dd, J=13.5, 9.0, 1H, ArCH_aH_b), 2.82–2.90 (m, 1H, C*H*CH(CH_3)$_2$), 3.27–3.35 (m, 2H, ArCH$_a$$H_b$, C$H_aH_b$OH), 3.52 (dd, J=10.4, 4.8, 1H, CH$_a$$H_b$OH), 3.69 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.88 (dd, J=8.9, 2.5, 1H, ArC*H*), 6.35 (d, J=2.0, 1H, H_{arom}), 6.52 (dd, J=8.2, 2.0 Hz, 1H, H_{arom}), 6.62–6.74 (m, 4H, H_{arom}); ^{13}C-NMR (δ, ppm): 19.3 (*C*H$_3$CH), 22.0 (*C*H(CH_3)$_2$), 27.4 (*C*HCH(CH_3)$_2$), 30.7 (NCH_3), 39.9 (Ar*C*H$_2$), 55.5, 55.6, 55.7 (OCH_3), 58.6 (CH_2OH), 66.1, 70.7 (Ar*C*H, Ph*C*H), 110.5, 110.7, 111.1, 112.5, 120.4, 121.0 (tC_{arom}), 131.5, 134.4, 147.1, 147.9, 148.2, 148.5 (qC_{arom}); IR (KBr): 3450; EI-MS *m/z*: 300 (100), 285 (49), 225 (9), 181 (5), 151 (14); anal. calcd for $C_{24}H_{35}NO_5$: C, 69.04; H, 8.45; N, 3.35. Found: C, 68.96; H, 8.45; N, 3.31.

3.3. One-pot general procedure for the transformation of aminoalcohols **4** into tetrahydroisoquinolines **6** and **7**

Over a cooled (−60°C) solution of oxalyl chloride (1.1 mmol) in 3 mL of CH_2Cl_2, a solution of DMSO (0.16 mL, 2.30 mmol) in 3 mL of the same solvent was added dropwise under argon, and the mixture was stirred for 15 min. Then, a solution of aminoalcohol **4** (1.1 mmol) in 10 mL of CH_2Cl_2 was added dropwise and the stirring was continued for 30 min. Working at the same low temperature, diisopropylethylamine (5.0 mmol) was added slowly and, after stirring for 15 min, the solution was

allowed to reach ambient temperature. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was distilled under reduced pressure to afford aldehydes **5** that were immediately submitted to acid catalyzed cyclization. Crude aldehydes **5** were dissolved in acetone (15 mL) and, after cooling with an ice bath, conc HCl (2 mL) was added and the mixture was stirred for 15 min at room temperature. Then, the crude product was basified with 1 M NaOH and extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was distilled under vacuum and the resulting oil was purified as specified for each compound.

3.3.1. (+)-(1S,3S,4S)-6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol ***6a*** *and (−)-(1S,3S,4R)-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol* ***6b***

Following the general procedure, (+)-aminoalcohol **4a** (0.43 g, 0.95 mmol) was transformed into a diastereomeric mixture (9:1) of tetrahydroisoquinolines (1*S*,3*S*,4*S*)-**6a** and (1*S*,3*S*,4*R*)-**6b** which were separated by flash column chromatography (CH_2Cl_2:EtOAc, 6:4), yield 75% (combined yield for the two steps).

6a: $[\alpha]_D^{20}$ +25.3 (c=1.0, CH_2Cl_2); ^{1}H-NMR (δ, ppm): 2.49 (s, 3H, NCH_3), 2.86 (dd, J=13.5, 7.0, 1H, ArCH_aH$_b$), 3.14 (dd, J=13.5, 3.9, 1H, ArCH$_a$$H_b$), 3.68 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.05 (dd, J=7.0, 3.9, 1H, H-1), 4.25 (d, J=4.6, 1H, H-3), 4.65 (d, J=4.6, 1H, H-4), 6.25 (s, 1H, H-8), 6.55 (d, J=1.8, 1H, H_{arom}-2′), 6.56 (dd, J=8.1, 1.8, 1H, H_{arom}-6′), 6.74 (d, J=8.1, 1H, H_{arom}-5′), 6.88 (s, 1H, H-5), 7.12–7.30 (m, 5H, H_{arom}); ^{13}C-NMR (δ, ppm): 39.6 (ArCH_2), 40.1 (NCH_3), 55.7, 55.8 (OCH_3), 64.4, 66.1, 68.6 (C-1, C-3, C-4), 109.1, 109.6, 110.7, 113.1, 122.2, 127.5, 128.2, 129.7 (tC_{arom}), 129.1, 129.6, 131.5, 137.6, 147.3, 147.6, 147.9, 148.3 (qC_{arom}); IR (neat): 3600–3300; EI-MS *m/z*: 447 (M^+−2, 2), 298 (100), 207 (27), 151 (52), 105 (26), 91 (25), 77 (20); anal. calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12. Found: C, 72.35; H, 6.78; N, 3.34.

6b: $[\alpha]_D^{20}$ −62.3 (c=0.5, CH_2Cl_2); ^{1}H-NMR (δ, ppm): 2.54 (s, 3H, NCH_3), 3.15 (d, J=4.5, 2H, ArCH_2), 3.65 (s, 3H, OCH_3), 3.81 (s, 9H, OCH_3), 4.07–4.10 (m, 2H, H-1, H-3), 4.40 (br s, 1H, H-4), 6.32 (d, J=1.8, 1H, H_{arom}-2′), 6.52 (dd, J=8.0, 1.9, 1H, H_{arom}-6′), 6.53 (s, 1H, H-8), 6.72 (d, J=8.0, 1H, H_{arom}-5′), 6.73 (s, 1H, H-5), 7.01–7.04 (m, 2H, H_{arom}), 7.20–7.24 (m, 3H, H_{arom}); ^{13}C-NMR (δ, ppm): 38.9 (ArCH_2), 39.7 (NCH_3), 55.6, 55.7, 55.8 (OCH_3), 62.6, 69.1, 70.9 (C-1, C-3, C-4), 109.1, 110.5, 111.3, 113.3, 122.1, 127.2, 128.2, 128.5 (tC_{arom}), 127.7, 129.7, 130.2, 138.8, 147.5, 147.8, 148.2, 148.3 (qC_{arom}); IR (neat): 3500–3300; EI-MS *m/z*: 447 (M^+−2, 1), 298 (100), 207 (21), 192 (11), 151 (27), 83 (24), 77 (16).

3.3.2. (+)-(1S,3S,4S)-6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-3-isopropyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol ***7a*** *and (−)-(1S,3S,4R)-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-3-isopropyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol* ***7b***

Following the general procedure, (+)-aminoalcohol **4b** (0.67 g, 1.60 mmol) was transformed into a diastereomeric mixture (9:1) of tetrahydroisoquinolines (1*S*,3*S*,4*S*)-**7a** and (1*S*,3*S*,4*R*)-**7b** which were separated by HPLC (hexanes:EtOAc, 4:6), yield 70% (combined yield for the two steps).

7a: $[\alpha]_D^{20}$ +32.1 (c=1.0, CH_2Cl_2); ^{1}H-NMR (δ, ppm): 1.06 (d, J=6.5, 3H, CH_3CH), 1.12 (d, J=6.5, 3H, CH_3CH), 2.20–2.30 (m, 1H, CH(CH_3)$_2$), 2.44 (s, 3H, NCH_3), 2.59–2.71 (m, 2H, H-3, ArCH_aH$_b$), 3.00 (dd, J=13.5, 7.0, 1H, ArCH$_a$$H_b$), 3.64 (s, 3H, OCH_3), 3.78–3.85 (m, 1H, H-1), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.56 (d, J=2.8, 1H, H-4), 6.14 (s, 1H, H-8), 6.67 (dd, J=8.1, 1.5, 1H, H_{arom}-6′), 6.75 (d, J=8.2, 1H, H_{arom}-5′), 6.80 (d, J=1.5, 1H, H_{arom}-2′), 6.89 (s, 1H, H-5); ^{13}C-NMR (δ, ppm): 20.2 (*C*H_3CH), 20.4 (*C*H_3CH), 25.5 (*C*H(CH_3)$_2$), 38.4 (NCH_3), 41.6 (ArCH_2), 55.5, 55.7,

55.8 (OCH_3), 60.8 (C-3), 65.0 (C-1), 66.7 (C-4), 110.5, 110.8, 111.8, 112.7, 121.5 (tC_{arom}), 128.4, 129.0, 133.0, 147.2, 147.8, 148.2, 148.5 (qC_{arom}); IR (neat): 3600–3400; EI-MS *m/z*: 414 (M^+-1, 1), 264 (100), 151 (19).

7b: $[\alpha]_D^{20}$ −20.2 (c=0.5, CH_2Cl_2); ^{1}H-NMR (δ, ppm): 0.68 (d, J=6.7, 3H, C*H*$_3$CH), 1.03 (d, J=6.7, 3H, C*H*$_3$CH), 1.51–1.72 (m, 1H, C*H*(CH_3)$_2$), 2.61 (dd, J=8.6, 3.1, 1H, H-3), 2.84 (s, 3H, NCH_3), 3.06 (dd, J=14.1, 2.7, 1H, ArC*H*$_a$H$_b$), 3.17 (dd, J=14.1, 4.9, 1H, ArCH$_a$*H*$_b$), 3.58 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.85 (s, 6H, 2×OCH_3), 4.08 (br t, 1H, H-1), 4.22 (d, J=3.1, 1H, H-4), 6.17 (d, J=1.4, 1H, H_{arom}-2′), 6.45 (dd, J=8.2, 1.4, 1H, H_{arom}-6′), 6.60–6.70 (m, 3H, H-5, H-8, H_{arom}-5′); ^{13}C-NMR (δ, ppm): 20.2 (*C*H$_3$CH), 20.5 (*C*H$_3$CH), 25.6 (*C*H(CH_3)$_2$), 38.4 (NCH_3), 40.6 (Ar*C*H$_2$), 55.5, 55.7, 55.9 (OCH_3), 60.8 (C-3), 65.1 (C-1), 66.8 (C-4), 110.6, 110.7, 111.8, 112.7, 121.4 (tC_{arom}), 128.3, 129.0, 133.0, 147.2, 147.8, 148.2, 148.4 (qC_{arom}); IR (neat): 3600–3400 (OH).

3.4. Synthesis of tetrahydroisoquinolin-4-ol ***11***

A solution of 1 mmol of aminoacetal **10**[6] in conc. HCl (15 ml) was stirred overnight at room temperature. The mixture was cooled in an ice bath, basified with 1 M NaOH and extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was distilled under vacuum to afford tetrahydroisoquinoline **11** as a mixture (66:34) of two diastereoisomers in a combined 85% yield. Both diastereoisomers were separated by flash column chromatography (CH_2Cl_2/MeOH 0–2%) to afford pure oily samples of tetrahydroisoquinolines (+)-(1*S*,4*S*)-**11a** and (−)-(1*S*,4*R*)-**11b**.

*3.4.1. (+)-(1*S*,4*S*)-6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol* ***11a***

$[\alpha]_D^{20}$ +25.0 (c=1.0, CH_2Cl_2); ^{1}H-NMR (δ, ppm): 1.70–1.90 (br s, 1H, OH), 2.55 (dd, J=13.1, 9.1, 1H, ArC*H*$_a$H$_b$), 2.66 (s, 3H, NCH_3), 2.77 (dd, J=12.5, 2.8, 1H, H-3$_a$), 3.13–3.22 (m, 2H, H-3$_b$, ArCH$_a$*H*$_b$), 3.48 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.77–3.81 (m, 1H, H-1), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.47 (br s, 1H, H-4), 5.80 (s, 1H, H-8), 6.48 (d, J=1.7, 1H, H_{arom}-2′), 6.54 (dd, J=8.2, 1.7, 1H, H_{arom}-6′), 6.76 (d, J=8.2, 1H, H_{arom}-5′), 6.89 (s, 1H, H-5); ^{13}C-NMR (δ, ppm): 34.7 (C-3), 42.8 (NCH_3), 54.3 (Ar*C*H$_2$), 55.2, 55.7, 55.8, 55.9 (OCH_3), 64.0, 65.9 (C-1, C-4), 110.1, 111.0, 111.2, 113.0, 122.0 (tC_{arom}), 127.5, 129.5, 131.1, 147.2, 147.5, 147.9, 148.6 (qC_{arom}); IR (neat): 3500–3300; EI-MS *m/z*: 371 (12), 222 (100), 208 (36), 190 (25), 151(61).

*3.4.2. (−)-(1*S*,4*R*)-6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol* ***11b***

$[\alpha]_D^{20}$ −70.4 (c=1.0, CH_2Cl_2); ^{1}H-NMR (δ, ppm): 2.66 (s, 3H, NCH_3), 2.84–2.98 (m, 1H, H-3$_a$), 3.02 (dd, J=11.6, 4.0, 1H, H-3$_b$), 3.13–3.15 (m, 2H, H-3$_b$, ArC*H*$_2$), 3.63 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.77–3.82 (m, 1H, H-3), 4.39 (br s, 1H, H-4), 6.32 (d, J=1.8, 1H, H_{arom}-2′), 6.50 (s, 1H, H-8), 6.49–6.54 (m, 1H, H_{arom}-6′), 6.68 (d, J=8.2, 1H, H_{arom}-5′), 6.77 (s, 1H, H-5); ^{13}C-NMR (δ, ppm): 39.3 (C-3), 43.1 (NCH_3), 55.6, 55.7, 55.8, 55.9 (OCH_3), 57.4 (Ar*C*H$_2$), 64.6, 65.9 (C-1, C-4), 109.5, 110.5, 110.9, 113.1, 122.1 (tC_{arom}), 128.3, 129.5, 129.9, 147.5, 147.7, 148.2, 148.4 (qC_{arom}); IR (neat): 3450–3200.

Acknowledgements

Financial support from the University of Basque Country (Project UPV 170.310-EA 154/96) and Basque Government (PI 96/53) is gratefully acknowledged. One of us (J.L.V.) thanks the Basque Government for a grant. The authors gratefully acknowledge PETRONOR, S. A. (Muskiz, Bizkaia) for the generous gift of hexane during the last few years.

References

1. (a) Ponzo, V. L.; Kaufman, T. S. *Can. J. Chem*. **1995**, *73*, 1348. (b) Tikk, I.; Deák, G.; Tóth, G.; Tamás, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 619 and references cited therein. (c) Blagg, J.; Coote, S. J.; Davies, S. G.; Mobbs, B. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2257. (d) Hoshino, O.; Tanahashi, R.; Okada, M.; Akita, H.; Oishi, T. *Tetrahedron: Asymmetry* **1993**, *4*, 933. (e) Simig, G.; Schlosser, M. *Synlett* **1990**, 50.
2. (a) Bates, H. A. *J. Org. Chem.* **1983**, *48*, 1932. (b) Bates, H. A. *J. Org. Chem.* **1981**, *46*, 4931.
3. (a) Ishida, Y.; Koga, N.; Nanbu, T.; Kihara, M.; Kobayashi, S. *Brit. J. Pharmacol.* **1988**, *94*, 19. (b) Kihara, M.; Ikeuchi, M.; Kobayashi, Y.; Nagao, Y.; Hashizume, M.; Moritoki, H. *Drug. Des. Discov.* **1994**, *11*, 175. (c) Kihara, M.; Kashimoto, M.; Kobayashi, Y.; Nagao, Y.; Moritoki, H. *Chem. Pharm. Bull.* **1994**, *42*, 67. (d) Kihara, M.; Ikeuchi, M.; Adachi, S.; Nagao, Y.; Moritoki, H.; Yamaguchi, M.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543. (e) Kihara, M.; Kashimoto, M.; Kobayashi, S.; Ishida, Y.; Moritoki, H.; Taira, Z. *J. Med. Chem.* **1990**, *33*, 2283. (f) Ohta, S.; Tachikawa, O.; Makino, Y.; Tasaki, Y.; Hirobe, M. *Life Sci*. **1990**, *46*, 599. (g) Kihara, M.; Ikeuchi, M.; Yamauchi, A.; Nukatsuka, M.; Matsumoto, H.; Toko, T. *Chem. Pharm. Bull.* **1997**, *45*, 939. (h) Kihara, M.; Ikeuchi, M.; Nagao, Y. *Drug. Des. Discov.* **1995**, *12*, 259.
4. (a) Tellitu, I.; Badía, D.; Domínguez, E.; García, F. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1567. (b) Badía, D.; Domínguez, E.; Tellitu, I. *Tetrahedron* **1992**, *48*, 4419.
5. Carrillo, L.; Badía, D.; Domínguez, E.; Ortega, F.; Tellitu, I. *Tetrahedron: Asymmetry* **1998**, *9*, 151.
6. Carrillo, L.; Badía, D.; Domínguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716.
7. See for example Hirsenkorn, R. *Tetrahedron Lett.* **1990**, *31*, 7591.
8. (a) Hoshino, O.; Itoh, K.; Tanahashi, R.; Umezawa, B.; Akita, H.; Takeshi, O. *Chem. Pharm. Bull.* **1990**, *38*, 3277. (b) Hoshino, O.; Ohtani, M.; Umezawa, B.; Itaka, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4873.
9. (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, 2199. (b) Cherest, M.; Felkin, H. *Tetrahedron Lett*. **1968**, 2205. (c) Ahn, N. T. N. *Top. Curr. Chem*. **1980**, 145. (d) Ponzo, V. L.; Kaufman, T. S. *Can. J. Chem*. **1995**, *73*, 1348.
10. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd Edition, Pergamon Press, Oxford, 1988.
11. Krebs, K. G.; Heusser, D.; Wimmer, H. *Thin-Layer Chromatography*; ed. Stahl, E.; Springer Verlag, Berlin, 1969; p. 873.
12. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
13. Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis Via Boranes*; John Wiley & Sons, New York, 1975.