Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 8049–8056

TETRAHEDRON

Highly stereoselective Friedel–Crafts type cyclization. Facile access to enantiopure 1,4-dihydro-4-phenyl isoquinolinones

Nicolas Philippe,[a] François Denivet,[a] Jean-Luc Vasse,[a] Jana Sopkova-de Olivera Santos,[b] Vincent Levacher[a,*] and Georges Dupas[a]

[a]*Laboratoire de Chimie Organique Fine et Hétérocyclique associé au CNRS, IRCOF-INSA, B.P. 08, F-76131 Mont Saint Aignan Cédex, France*
[b]*UFR des Sciences Pharmaceutiques (CERMN). 5 rue Vaubénard F-14032 Caen, France*

Received 2 May 2003; revised 1 July 2003; accepted 22 July 2003

Abstract—The present report describes a stereoselective synthesis of 1,4-dihydro-4-phenyl isoquinolinones **5** based on a stereoselective Friedel–Crafts type cyclization. Cyclization precursors **1** were prepared in two steps, from the readily available (*S*)-mandelic acid, in 60–80% overall yield. The stereoselective electrophilic cyclization was accomplished in 20–86% yield and with 20–97% ee. In the course of this work, the presence of the amide carbonyl was found to be particularly important to guarantee a stereospecific process during the electrophilic aromatic substitution.

1. Introduction

Among the diverse tetrahydroisoquinoline derivatives of pharmacological interests, 4-aryl-1,2,3,4-tetrahydroisoquinolines constitute an important class of biological active compounds which exhibit inhibitor properties with important neurotransmitters.[1] Despite their interesting neuropharmacological activity, stereoselective preparation of 4-aryl tetrahydroisoquinolines is rarely reported in literature. The stereocontrol of this motif, i.e. the gem-diaryl methane, still remains a challenge in stereoselective synthesis. To the best of our knowledge, aside from some resolution processes,[2] only two stereoselective methodologies have been developed to have access enantiopure 4-aryl-1,2,3,4-tetrahydroisoquinolines. The first one relies on a diastereoselective protonation of chiral lactam enolates.[3] The second strategy, based on a deracemisation process, was accomplished in the presence of (−)-sparteine as external chiral ligand.[4] In both cases, these methodologies produced satisfactory to high levels of stereoinduction. We wish to report herein, a complementary approach involving, as the key step of this work, a stereoselective Friedel–Crafts type cyclization of **1** (Fig. 1).

The stereochemical course of the Friedel–Crafts reaction usually proceeds with almost complete racemization attributed to the intermediate formation of a carbonium ion. Among the few examples of stereoselective Friedel–Crafts alkylations reported in the literature, one can quote the stereospecific alkylation of benzene by (+)-propylene oxide[5] and the stereospecific alkylation of benzene with (*S*)-alkyl 2-(sulfonyloxy)propionate.[6] Both examples make use of a Lewis acid ($AlCl_3$) providing modest to fair stereoselectivity. More recently, Branchaud reported an intramolecular stereoselective Friedel–Crafts alkylation of an episulfonium ion using $BF_3{\cdot}Et_2O$.[7] These isolated examples are encouraging and prompted us to undertake further investigations to assess the potential of Friedel–Crafts alkylations in the stereoselective preparation of 4-aryl tetrahydroisoquinolines (Fig. 2).

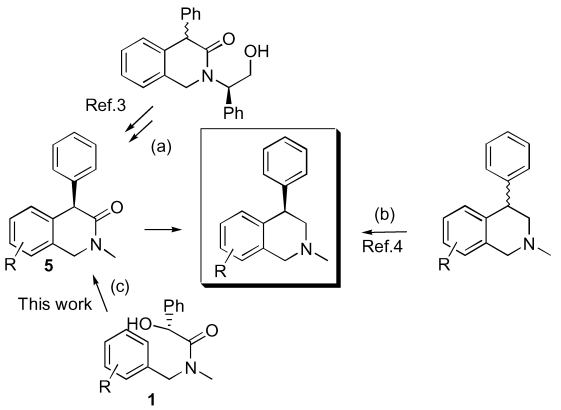


Figure 1. Previously reported routes to have access to enantiopure 4-aryl-1,2,3,4-tetrahydroisoquinolines: (a) diastereoselective protonation of lactam enolates; (b) deracemization processes; (c) stereoselective Friedel–Crafts type cyclization.

Keywords: Friedel–Crafts reaction; cyclization; isoquinolinone; stereoselective.
* Corresponding author. Tel.: +33-235-522-485; fax: +33-235-522-962; e-mail: vincent.levacher@insa-rouen.fr

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)01236-5

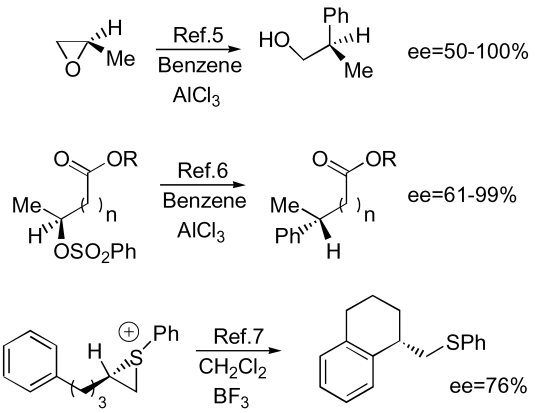


Figure 2. Literature data related to stereospecific Friedel–Crafts alkylation.

2. Results and discussion

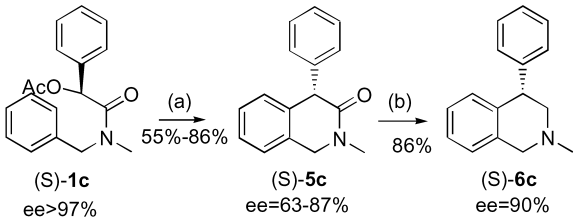
2.1. Preparation of the cyclization precursors 1

The required precursors **1** are prepared in a few steps from the readily available (*S*)-mandelic acid and aldehydes **2a**–**e**. Amines **3a**–**e** are obtained in 63–100% yields following a standard procedure of reductive amination. The commercially available (*S*)-mandelic acid was first protected as its *O*-acetyl mandelic acid **4** and then condensed, after activation into its acid chloride, with amines **3a**–**e** to give the desired cyclization precursors **1a**–**e** in 64–95% yields. It should be noticed that DIEA showed to be the only base tested in this condensation which provided **1a**–**e** without racemization. All other bases, such as triethylamine and DMAP led to partial racemization (Table 1).

2.2. Stereoselective cyclization of 1c to 1,4-dihydro-4-phenyl isoquinolinone 5c

The cylization was first conducted with **1c**, in CH_2Cl_2, in the presence of concentrated sulfuric acid as promoter of the cyclization (Table 2). Under these conditions, 1,4-dihydro-4-phenylisoquinolone **5c** is obtained in 30–86% yields. The stereoselectivity of the cyclization ranged from 63 to 87% ee, the best result in terms of yield and stereocontrol being obtained at −15°C (Table 2, entry 4). Attempts to improve the stereoselectivity by conducting the reaction at lower temperature resulted in low conversion to the cyclization product **5c** (Table 2, entry 5). At this stage it appeared important to make certain that the cyclized product **5c** did not racemize under the cyclization conditions. To this end, the enantiomerically enriched isoquinolone **5c** (ee=87%) was subjected to the cyclization conditions (H_2SO_4/CH_2Cl_2, rt, 12 h), after which chiral HPLC analysis of **5c** reveals no erosion of the optical purity. Subsequent reduction of **5c** into the known 4-phenyl-1,2,3,4-tetrahydroisoquinoline **6c** was accomplished in 86% yield (ee=90%). Absolute configuration of **6c** was assigned as (*S*) by comparison of optical rotation with the previously reported data in the literature.[8] Consequently, the cyclization proceeds with inversion of configuration at the reacting centre pointing out the S_N2 nature of this process.

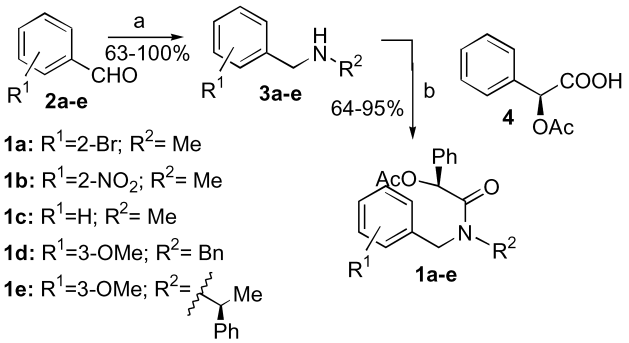
Table 2. Cyclization of **1c**. *Reagents and conditions*: (a) H_2SO_4/CH_2Cl_2, 4 h; (b) BH_3/THF, reflux, 12 h



Entry	Temperature (°C)	Yield (%)	ee[a] (%)
1	35	55	63
2	20	63	63
3	0	77	81
4	−15	86	87
5	−25	30	Not measured

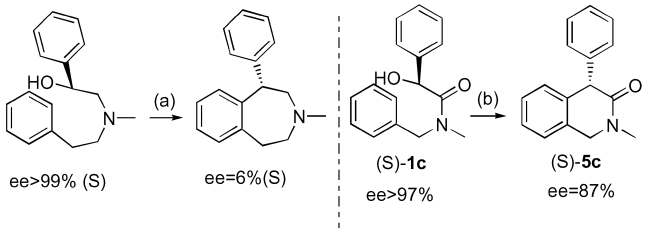
[a] Determined by chiral HPLC analysis.

Table 1. Preparation of the cyclization precursors. *Reagents and conditions*: (a) CH_3COCl, rt; (b) R^2NH_2/MeOH, rt, 2 h then $NaBH_4$, 0°C, 1 h; (c) $SOCl_2$, reflux, 4 h then CH_2Cl_2, 0°C→rt, $(i\text{-}Pr)_2EtN$/12 h



Entry	Aldehyde **2**/amine	Compound **3**, yield (%)	Compound **1**, yield (%)
1	**2a** (R^1=2-Br, R^2=Me)/$MeNH_2$	**3a**, 89	**1a**, 89 (ee>97%)[a]
2	**2b** (R^1=2-NO_2, R^2=Me)/$MeNH_2$	**3b**, 63	**1b**, 98%[b]
3	**2c** (R^1=H, R^2=Me)/$MeNH_2$	**3c**, 88	**1c**, 75 (ee>97%)[a]
4	**2d** (R^1=3-OMe, R^2=Bn)/$BnNH_2$	**3d**, 98	**1d**, 64 (ee>97%)[a]
5	**2e** [R^1=3-OMe, R^2=CH(Me)Ph]/(*S*)-$NH_2CH(Me)Ph$	**3e**, 93	**1e**, 64 (de>97%)[a]

[a] Determined by chiral HPLC analysis.
[b] The optical purity was not measured.

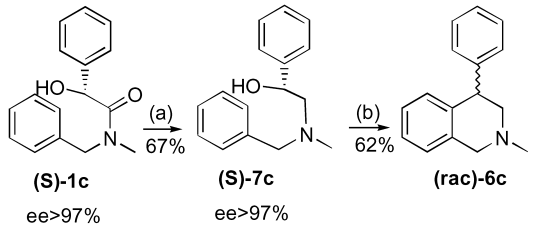


Scheme 1. Comparison of this work with previously reported similar Friedel–Crafts type cyclization. *Reagents and conditions*: (a) $HBF_4 \cdot OMe_2/CH_2Cl_2$, −20°C; (b) H_2SO_4/CH_2Cl_2, −15°C, 4 h.

2.3. Influence of the carbonyl group in the stereochemical outcome of the cyclization

The cyclization reaction of similar enantiopure substrates has been reported by Davies yielding 1-phenyl 1,2,3,4-tetrahydrobenzazepine with almost complete racemization.[9] These literature data suggest that, in our case, the carbonyl group is essential to ensure the stereoselectivity of the cyclization (Scheme 1).

To ascertain the influence of the carbonyl group in the stereocontrol of this cyclization, lactam **1c** (ee>97%) was reduced prior to treating the resulting alcohol **7c** (ee>97%) under the best cyclization conditions selected with **1c**. Treatment of enantiopure **7c** in CH_2Cl_2 with sulphuric acid at −15°C during 4 h, afforded **6a** in 62% yield in a racemic form (Scheme 2). The use of other acidic conditions such as *p*TsOH, TFA or $BF_3 \cdot Et_2O$ resulted in the recovery of the starting material. Only TfOH and $TiCl_4$ provided the cyclization product **6c**, however, with complete racemization. These results clearly demonstrate that the amide carbonyl constitutes a critical structural feature to give rise to a stereoselective process.

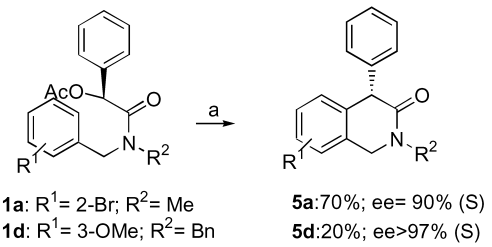


Scheme 2. *Reagents and conditions*: (a) $LiAlH_4$/THF, rt, 12 h; (b) H_2SO_4/CH_2Cl_2, −15°C, 4 h.

Although the role of the carbonyl group in the stereochemical outcome of the cyclization is not well established, one can presume that the electron withdrawing effect of the carbonyl amide would prevent the formation of the benzylic carbonium ion, allowing a S_N2 type process to take place.

2.4. Variation on the aromatic ring: cyclization of 1a,d,e,f

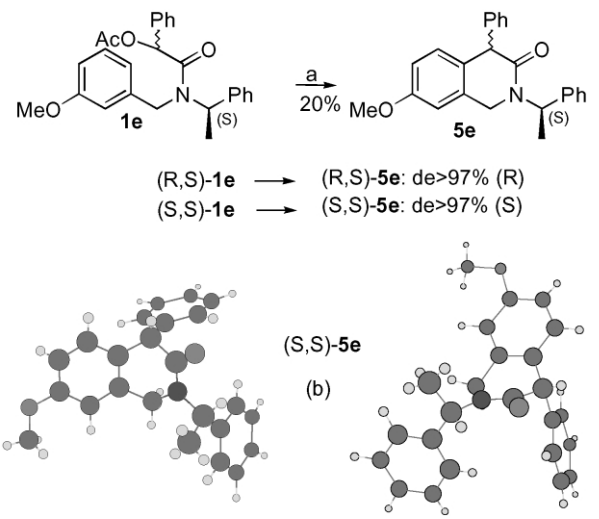
To study the scope and limitations of this electrophilic cyclization, we next investigated the reactivity of **1a**,**d**,**e**,**f** differently substituted at the benzene ring. Whereas **1a** cyclized in 70% yield with excellent stereoselectivity (ee=90%),[10] cyclization of **1d** provided **5d** in a poor yield (20%), however, in a somewhat higher enantioselectivity (ee>97%). It should be added that only **5d** arising from the cyclization at the *para* position with respect to the methoxy group was observed throughout this work. The modest yield observed in the cyclization of **1d** may be attributed to partial *O*-demethylation at the benzene ring,[11] which further may generate tarry materials. To circumvent this limitation, attempt to conduct the cyclization of **1d** at lower temperatures (−40°C) resulted in the recovery of the starting material (Scheme 3).



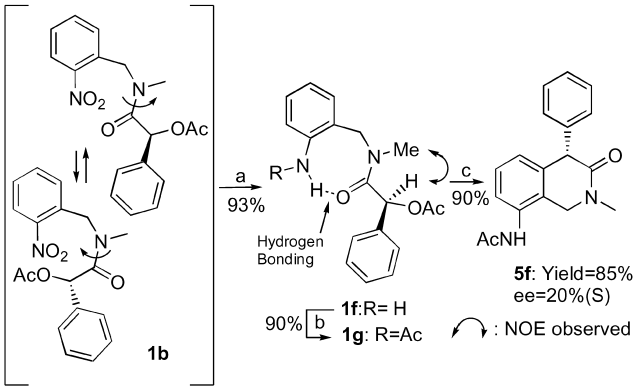
Scheme 3. *Reagents and conditions*: (a) H_2SO_4/CH_2Cl_2, −15°C, 4 h.

Substrate **1e** presents an additional chiral appendage at the nitrogen amide offering the opportunity to observe an eventual match/mismatch effect on the stereoselectivity of the cyclization. Both epimers (*R*,*S*)-**1e** and (*S*,*S*)-**1e** were prepared and subjected to cyclization. In both cases, the cyclized product **5e** was obtained in up to 97% ee with opposite absolute configuration at C-4. No evidence of a match/mismatch situation, which could have been promoted by the presence of the chiral appendage was observed. The absolute configuration at the *gem* diarylmethane position of **5e**, easily deduced from X-ray analysis,[12] confirmed the inversion of configuration during this stereoselective electrophilic cyclization process (Scheme 4).

We turned our attention to the cyclization of **1g**, precursor of (*S*)-Nomifensine.[13] Upon treatment with ammonium formate and Pd/C, **1b** afforded the corresponding amine **1f** (93%) which was acetylated to give **1g** in 90% yield. This protection of the amino group prevents the formation of benzadiazepines, as already reported in the cyclization of **1f** under similar conditions.[14] Cyclization of **1g** afforded **5f** in 85% yield and 22% ee (*S*). The modest stereoselectivity



Scheme 4. *Reagents and conditions*: (a) H_2SO_4/CH_2Cl_2, −15°C, 4 h; (b) X-ray structure of (*S*,*S*)-**5e** obtained by cyclization of (*S*,*S*)-**1e**.



Scheme 5. *Reagents and conditions*: (a) $HCOONH_4/Pd/C/CH_2Cl_2$, rt, 4 h; (b) $MeCOCl/NEt_3/CH_2Cl_2$, rt, 4 h; (c) H_2SO_4/CH_2Cl_2, −15°C, 4 h.

obtained with **1g** may be explained partly by conformational considerations. Interestingly, whereas cyclization precursors **1a**,**b**,**c**,**d**,**e** are obtained as a mixture of two amide rotamers, ^{1}H NMR spectra of **1f** and **1g** revealed the presence of a single rotamer. To account for this, one can assume that the conformational equilibrium would shift in favor of the conformation which contains an intramolecular hydrogen bond between the amide carbonyl and the NH group present in both compounds **1f** and **1g** as illustrated in Scheme 5. A NOESY experiment of **1g** furnished conformational information consistent with the presence of this intramolecular hydrogen bond. In such a conformation, the two reacting centers seemed too far to promote the ring closure. This unreactive conformation in conjunction with the electron withdrawing effect of the acetamido group, decrease the rate of the cyclization and may account for the poor stereoselectivity observed with **1g**.

3. Conclusion

This stereoselective Friedel–Crafts type cyclization provides a new and straightforward strategy, starting from commercially available (*S*)-mandelic acid, to control the benzylic stereochemistry of 1,4-dihydro-4-phenyl isoquinolinones **5**. Subsequent reduction furnish the corresponding enantio-enriched 1,2,3,4-dihydro-4-phenyl isoquinolines. In the course of this work, the presence of the amide carbonyl in precursors **1** appeared to be critical to ensure a high level of stereocontrol. This electrophilic cyclization, akin to a S_N2 process, was accomplished in acceptable yields and stereoselectivities ranging from 20 to 97% ee. Lastly, it should be noted that if this cyclization affords high degree of stereocontrol with aromatics sufficiently reactive toward electrophilic aromatic substitution, the main limitation of this method is the modest results observed with electron-poor aromatics.

4. Experimental

4.1. General methods

The infra-red spectra were recorded on a Beckmann IR 4250 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker apparatus (AVANCE 300). Spectra were recorded in deuteriochloroform or in hexadeuteriodimethylsulfoxide (DMSO-d_6). Chemical shift are given in ppm with TMS or HMDS as internal reference. Chemicals were purchased from Aldrich Co. and Janssen Co. and, unless otherwise stated, were used without further purification. Flash chromatography was performed with silica 60 (70–230 mesh from Merck) and monitored by thin layer chromatography with silica plates (Merck, Kieselgel 60 F_{254}). Benzylmethylamine was commercially available. The following compounds were prepared by literature methods.

4.2. Reductive amination of aldehydes 2

4.2.1. 2-(Bromobenzyl)-methylamine (3a). *Procedure* (A). To a solution of methanol (50 mL) and 2-bromobenzaldehyde (4.02 g, 22 mmol) was added a 40% aqueous solution of methylamine (2.44 mL, 28 mmol). After stirring at room temperature for 15 min, the solution was cooled to 0°C prior to adding sodium borohydride (0.41 g, 11 mmol) portion wise. The resulting solution was stirred at room temperature for 1 h. After addition of water (50 mL), methanol was evaporated under vacuum and the resulting aqueous phase extracted with CH_2Cl_2 (3×50 mL). The combined organic layers are dried ($MgSO_4$) and evaporated affording **3a** as a colorless oil (3.81 g, 89%). The product was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (1H, d, J=9.0 Hz), 7.10–6.79 (3H, m), 3.54 (2H, s), 2.16 (3H, s), 1.46 (1H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 138.76, 132.45, 129.94, 128.26, 127.08, 123.71, 55.39, 35.56. IR (neat) 3320, 2846, 1440, 1025, 750 cm^{-1}. Anal. calcd for $C_8H_{10}NBr$: C, 48.03; H, 5.04; N, 7.03. Found: C, 47.82; H, 5.06; N, 6.93.

4.2.2. 2-(Nitrobenzyl)methylamine (3b). According to the procedure (A) from 2-nitrobenzaldehyde (5.05 g, 33 mmol), a 40% aqueous solution of methylamine (3.74 mL, 43 mmol), methanol (40 mL), sodium borohydride (0.63 g, 17 mmol). Amine **3b** was obtained as an orange oil (3.60 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, d, J=9.0 Hz), 7.29–7.26 (2H, m), 7.12–7.06 (m, 1H), 3.66 (2H, s), 2.12 (3H, s), 1.83 (1H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 149.11, 135.20, 133.21, 130.62, 128.05, 124.79, 52.73, 36.06. IR (neat) 3334, 2851, 1530, 1345, 789, 730 cm^{-1}. Anal. calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.58; H, 6.08; N, 16.93.

4.2.3. 3-(Methoxybenzyl)benzylamine (3d). According to the procedure (A) from 3-methoxybenzaldehyde (6.05 g, 44.4 mmol), benzylamine (5.80 mL, 53.1 mmol), methanol (90 mL), sodium borohydride (4.0 g, 106 mmol). Amine **3d** was obtained as a yellow oil (10.00 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.25 (6H, m), 6.97 (2H, m), 6.83 (dd, 1H, J=8.0 Hz, J=2.5 Hz), 3.83 (5H, m), 3.82 (2H, s), 2.05 (1H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 159.83, 141.97, 140.26, 129.47, 128.53, 128.27, 127.06, 120.54, 113.68, 112.57, 55.27, 53.16, 53.13. IR (neat) 3342, 2834, 1601, 1585, 1489, 1454, 1264 cm^{-1}. Anal. calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.23; H, 7.49; N, 6.34.

4.2.4. (*S*)-*N*-(3-Methoxybenzyl)-1-phenylethylamine (3e). According to the procedure (A) from 3-methoxybenzaldehyde (8.0 g, 58.7 mmol), (*S*)-phenylethylamine (9.0 mL,

69.8 mmol), methanol (120 mL), sodium borohydride (4.40 g, 116 mmol). Amine **3d** was obtained as a yellow oil (13.0 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.21 (6H, m), 6.91–6.78 (3H, m), 3.89–3.82 (m, 4H), 3.88 (1H, d, J=13.3 Hz), 3.58 (1H, d, J=13.3 Hz), 1.65 (1H, s), 1.39 (3H, d, J=6.6 Hz). ^{13}C NMR (60 MHz, $CDCl_3$) δ 159.39, 145.27, 142.03, 128.97, 128.59, 128.37, 128.13, 120.04, 113.34, 111.90, 57.10, 54.63, 51.23, 24.20. IR (neat) 3025, 2961 cm^{-1}. Anal. calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.85; H, 8.10; N, 5.74.

4.2.5. (*S*)-Acetyl mandelic acid (4). A solution of acetyl chloride (4.8 mL, 68 mmol) and (*S*)-mandelic acid (4.09 g, 27 mmol) was stirred at room temperature for 12 h. After evaporation of the volatile material, (*S*)-acetyl mandelic acid **4** was obtained as a white solid (5.30 g, 100%) and used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.06 (1H, s), 7.36–7.24 (5H, m), 5.80 (1H, s), 3.88 (1H, d, J=13.3 Hz), 2.04 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 174.58, 170.64, 133.17, 129.58, 128.97, 127.78, 74.20, 20.69. IR (neat) 3013, 1753, 1688, 1205, 1046, 700 cm^{-1}. Anal. calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.93; H, 5.15. Mp (benzene) 98°C. $[\alpha]_D^{20}$=+151 (c 2.55, acetone). The optical purity was determined by HPLC analysis using a Chiracel OD column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **4** in 10 mL of hexane). Eluent: hexane/2-propanol/HCOOH: 98/2. Flow rate: 1 mL/min. Pressure: 300 psi. Temperature: 17°C. UV detection: λ=254 nm. Retention time: 28.7 min [(*S*)-enantiomer] and 31.3 min [(*R*)-enantiomer]. ee>98% (*S*).

4.3. Condensation of amines 3 with (*S*)-acetyl mandelic acid (4)

4.3.1. (*S*)-*N*-Methyl-*N*-(2-bromomethyl)-2-acetyloxy-2-phenylethanamide (1a). *Procedure* (B). To a solution of (*S*)-acetyl mandelic acid (1.01 g, 5.23 mmol) in CH_2Cl_2 (40 mL) and DMF (two drops), was slowly added oxalyl chloride (0.46 mL, 5.23 mmol). The solution was gently stirred for 1 h and the volatile materials were evaporated under vacuum to give (*S*)-2-acetoxy-2-phenylacetyl chloride. The residue was diluted in CH_2Cl_2 (40 mL) and the resulting solution was cooled to −20°C. A solution of 2-(bromobenzyl)-methylamine (0.872 g, 4.36 mmol) and *N*-ethyldiisopropylamine (2.22 mL, 13.1 mmol) in CH_2Cl_2 (40 mL) was slowly added over a period of 10 min at −20°C and then stirred at room temperature for 4 h. After washings with water (3×30 mL), the dichloromethane phase was dried ($MgSO_4$). Evaporation in vacuo afforded a thick oil which was purified over silica gel column chromatography (eluent: CH_2Cl_2) to give compound **1a** in 89% yield. Compound **1a** was obtained as a mixture of two rotamers which interconvert via rotation about the amide N–CO bond (ratio 7/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.00 (9H, m), 6.17 (0.7H, s), 5.96 (0.3H, s), 4.65 (1.4H, dd, J=16.2 Hz, J=15.9 Hz), 4.43 (0.6H, dd, J=17.4 Hz, J=18 Hz), 2.92 (1H, s), 2.86 (2H, s), 2.12 (2H, s), 2.04 (1H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 171.05, 168.68, 168.61, 135.60, 134.54, 133.53, 132.88, 129.68, 129.59, 129.21, 129.17, 128.91, 128.87, 128.68, 128.60, 127.95, 127.70, 123.51, 74.14, 73.66, 53.98, 51.57, 34.95, 34.85, 20.99, 20.88. IR (neat) 2960, 1729, 1661, 1238, 768 cm^{-1}. Anal. calcd for $C_{18}H_{18}NO_3Br$: C, 57.46; H, 4.82; N, 3.72. Found: C, 57.59; H, 4.61; N, 3.37. $[\alpha]_D^{20}$=+86.15 (c 0.325, $CHCl_3$). The optical purity was determined by HPLC analysis using a Chiracel OJ column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **1a** in 10 mL of hexane). Eluent: heptane/2-propanol: 92.5/7.5. Flow rate: 1 mL/min. Pressure: 300 psi. Temperature: 18°C. UV detection: λ=230 nm. Retention time: 18.4 min [(*S*)-enantiomer] and 24.0 min [(*R*)-enantiomer]. ee>97% (*S*).

4.3.2. (*S*)-*N*-Methyl-*N*-(2-nitrobenzyl)-2-acetyloxy-2-phenylethanamide (1b). According to the procedure (B) from (*S*)-acetyl mandelic acid (0.40 g, 2.06 mmol) in CH_2Cl_2 (15 mL) and DMF (two drops), oxalyl chloride (0.18 mL, 2.06 mmol), 2-(nitrobenzyl)-methylamine (0.285 g, 1.72 mmol) and *N*-ethyldiisopropylamine (0.98 mL, 5.15 mmol) in CH_2Cl_2 (15 mL). Compound **1b** was obtained as an orange oil in 98% yield. Compound **1b** was obtained as a mixture of two rotamers which interconvert via rotation about the amide N–CO bond (ratio 7/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (0.7H, d, J=8.4 Hz), 7.83 (0.3H, d, J=8.4 Hz), 7.42–7.07 (8H, m), 6.11 (0.7H, s), 5.85 (0.3H, s), 5.00 (0.7H, d, J=17.4 Hz), 4.81 (0.3H, d, J=19.2 Hz), 4.61 (0.3H, d, J=20.0 Hz), 4.55 (0.7H, d, J=17.4 Hz), 2.84 (3H, s), 1.99 (2H, s), 1.93 (1H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 170.79, 168.80, 148.12, 147.41, 133.99, 133.84, 132.95, 132.24, 129.54, 129.41, 128.99, 128.95, 128.57, 128.34, 127.89, 127.77, 125.18, 124.96, 73.93, 50.26, 49.33, 35.35, 34.62, 20.61, 20.54. IR (neat) 3456, 2938, 1667, 729 cm^{-1}. Anal. calcd for $C_{18}H_{18}NO_3Br$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.95; H, 5.28; N, 8.10.

4.3.3. (*S*)-*N*-Methyl-*N*-benzyl-2-acetyloxy-2-phenylethanamide (1c). According to the procedure (B) from (*S*)-acetyl mandelic acid (0.40 g, 2.06 mmol) in CH_2Cl_2 (15 mL) and DMF (two drops), oxalyl chloride (0.18 mL, 2.06 mmol), benzylmethylamine (0.208 g, 1.72 mmol) and *N*-ethyldiisopropylamine (0.88 mL, 5.16 mmol) in CH_2Cl_2 (20 mL). The crude product was purified by flash chromatography (SiO_2/eluent: cyclohexane/ethyl acetate 80/20) to give compound **1c** as a yellow oil in 75% yield. $[\alpha]_D^{20}$=+78.86 (c 0.875, $CHCl_3$). Compound **1c** was obtained as a mixture of two rotamers which interconvert via rotation about the amide N–CO bond (ratio 7/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.13 (10H, m), 6.22 (0.3H, s), 6.21 (0.7H, s), 4.68–4.53 (1.4H, d, J=14.4 Hz), 4.57–4.22 (0.6H, d, J=16.5 Hz), 2.89 (1H, s), 2.82 (2H, s), 2.19 (2H, s), 2.15 (1H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 170.95, 168.33, 136.69, 135.63, 134.15, 133.74, 129.55, 129.21, 129.16, 128.94, 128.82, 128.72, 127.92, 127.51, 126.93, 74.04, 73.68, 52.72, 51.49, 34.36, 33.96, 21.01, 20.93. IR (neat) 2934, 1659, 1237, 704 cm^{-1}. Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.85; H, 6.61; N, 4.55. The optical purity was determined by HPLC analysis using a Chiracel OD column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **1c** in 10 mL of hexane). Eluent: heptane/2-propanol: 90/10. Flow rate: 1 mL/min. Pressure: 400 psi. Temperature: 20°C. UV detection: λ=230 nm. Retention time: 14.5 min [(*S*)-enantiomer] and 10.8 min [(*R*)-enantiomer]. ee>97% (*S*).

4.3.4. (*S*)-*N*-Benzyl-*N*-(3-methoxybenzyl)-2-acetyloxy-2-phenylethanamide (1d). According to the procedure (B) from (*S*)-acetyl mandelic acid (0.20 g, 1.03 mmol) in CH_2Cl_2 (10 mL) and DMF (two drops), oxalyl chloride (0.09 mL, 1.03 mmol), 3-methoxybenzylmethylamine (0.195 g, 0.86 mmol) and *N*-ethyldiisopropylamine (0.44 mL, 2.58 mmol) in CH_2Cl_2 (20 mL). The crude product was purified by flash chromatography (SiO_2/eluent: cyclohexane/ethyl acetate: 80/20) to give compound **1d** as a yellow oil in 64% yield. $[\alpha]_D^{20}=+28.8$ (*c* 0.250, $CHCl_3$). Compound **1d** was obtained as a mixture of two rotamers which interconvert via rotation about the amide N–CO bond (ratio 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.09 (11H, m), 6.84–6.59 (3H, m), 6.21 (0.5H, s), 6.19 (0.5H, s), 5.09–4.84 (1H, m), 4.59–4.42 (1H, m), 4.25–4.09 (2H, m), 3.79 (1.5H, s), 3.74 (1.5H, s), 2.21 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 171.01, 170.94, 168.54, 168.48, 160.33, 160.02, 138.35, 137.15, 136.81, 135.46, 133.95, 133.91, 129.97, 129.67, 129.26, 129.19, 128.99, 128.93, 128.86, 128.69, 128.36, 127.95, 127.81, 127.56, 127.53, 127.16, 120.58, 119.39, 114.01, 113.80, 112.85, 111.98, 74.25, 55.46, 55.30, 49.31, 48.22, 48.05, 20.96. IR (neat) 3030, 1667, 1235, 1049, 752 cm^{-1}. Anal. calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.56. Found: C, 74.15; H, 6.31; N, 3.47. The optical purity was determined by HPLC analysis using a Chiracel OD column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **1d** in 10 mL of hexane). Eluent: heptane/2-propanol: 90/10. Flow rate: 1 mL/min. Pressure: 400 psi. Temperature: 20°C. UV detection: λ=230 nm. Retention time: 10.3 min [(*S*)-enantiomer] and 8.8 min [(*R*)-enantiomer]. ee>97% (*S*).

4.3.5. (*S*)-*N*-[(*S*)-1-Phenylethyl]-*N*-(3-methoxybenzyl)-2-acetyloxy-2-phenylethanamide (1e). According to the procedure (B) from (*S*)-acetyl mandelic acid (0.20 g, 1.03 mmol) in CH_2Cl_2 (10 mL) and DMF (two drops), oxalyl chloride (0.09 mL, 1.03 mmol), (*S*)-*N*-(3-methoxybenzylamine)-1-phenylethylamine (0.207 g, 0.86 mmol) and *N*-ethyldiisopropylamine (0.44 mL, 2.58 mmol) in CH_2Cl_2 (20 mL). The crude product was purified by flash chromatography (SiO_2/eluent: cyclohexane/ethyl acetate: 80/20) to give compound **1e** as a yellow oil in 64% yield. Compound **1e** was obtained as a mixture of two rotamers which interconvert via rotation about the amide N–CO bond (ratio 7/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–6.98 (10H, m), 6.80–6.40 (4H, m), 6.10 (1H, q, *J*=7.5 Hz), 5.84 (1H, s), 4.72 (0.3H, d, *J*=11.8 Hz), 4.14 (0.7H, d, *J*=18.2 Hz), 4.87 (0.7H, d, *J*=18.2 Hz), 3.75 (2H, s), 3.68–3.57 (1.3H, m), 2.13 (1H, s), 2.07 (2H, s), 1.34 (2H, d, *J*=8.6 Hz), 0.98 (1H, d, *J*=8.6 Hz). ^{13}C NMR (60 MHz, $CDCl_3$) δ 170.58, 170.08, 169.05, 168.15, 160.35, 159.55, 140.75, 140.20, 139.70, 139.20, 134.46, 133.66, 129.80, 129.70, 129.63, 129.31, 129.16, 129.09, 128.97, 128.91, 128.51, 127.99, 127.54, 127.48, 127.20, 119.37, 118.59, 113.67, 112.79, 112.11, 111.51, 75.32, 74.37, 55.43, 55.30, 54.98, 52.61, 46.51, 46.38, 20.93, 17.46, 17.18. Anal. calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.76; H, 6.30; N, 3.23.

4.3.6. (*S*)-*N*-Methyl-*N*-(2-aminobenzyl)-2-acetyloxy-2-phenylethanamide (1f). To a solution of **1b** (0.260 g, 0.76 mmol) in CH_2Cl_2 (15 mL) was added ammonium formate (0.480 g, 7.6 mmol) and 10% Pd/C (0.30 g). After stirring for 4 h at room temperature, the solution was filtered through a plug of celite and evaporated in vacuo affording **1f** as a yellow solid in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.62 (1H, m), 7.52–7.33 (4H, m), 7.08 (1H, t, *J*=7.5 Hz), 6.97 (1H, d, *J*=6.9 Hz), 6.63–6.57 (2H, m), 6.17(1H, s), 4.52 (2H, s), 2.80 (3H, s), 2.18 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 170.84, 168.56, 146.31, 133.62, 131.97, 131.03, 129.60, 129.23, 128.94, 118.83, 116.96, 115.52, 73.82, 49.25, 33.52, 21.01. Anal. calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.26; H, 6.36; N, 8.64.

4.3.7. (*S*)-*N*-Methyl-*N*-(2-acetamidobenzyl)-2-acetyloxy-2-phenylethanamide (1g). To a solution of **1f** (0.201 g, 0.64 mmol) and triethylamine (0.25 mL, 1.78 mmol) in CH_2Cl_2 (15 mL) was added acetyl chloride (0.13 mL, 1.83 mmol) at 0°C. The resulting solution was stirred at room temperature for 4 h. After addition of water (15 mL) and phases separation, the resulting aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by chromatography (SiO_2: cyclohexane/ethylacetate: 60:40) to afford **1g** in 90% yield. $[\alpha]_D^{20}=+0.73$ (*c* 2.89, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (1H, s), 8.40 (1H, d, *J*=9 Hz), 7.43–7.27 (6H, m), 7.12 (1H, d, *J*=9 Hz), 7.00 (1H, t, *J*=6 Hz), 6.13 (1H, s), 4.75 (1H, d, *J*=12 Hz), 4.30 (1H, d, *J*=12 Hz), 2.81 (3H, s), 2.21 (3H, s), 2.19 (2H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 170.64, 169.48, 169.35, 137.67, 132.93, 131.43, 129.64, 129.57, 129.18, 128.26, 123.74, 123.09, 121.71, 73.38, 49.34, 33.86, 24.49, 20.69. IR (neat) 3276, 1643, 1235, 759 cm^{-1}. Anal. calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.90; H, 6.31; N, 7.65. The optical purity was determined by HPLC analysis using a Chiracel OD column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **1g** in 10 mL of hexane). Eluent: heptane/2-propanol: 85/15. Flow rate: 1 mL/min. Pressure: 400 psi. Temperature: 20°C. UV detection: λ=230 nm. Retention time: 28.8 min [(*S*)-enantiomer] and 21.5 min [(*R*)-enantiomer]. ee>97% (*S*).

4.4. Friedel–Crafts type cyclization of 1

4.4.1. (*S*)-*N*-Methyl-8-bromo-4-phenyl-1,4-dihydroisoquinolin-3-one (5a). *Procedure* (C). To a solution of **1a** (276 mg, 0.73 mmol) in CH_2Cl_2 (1 mL) pre-cooled to −15°C was slowly added H_2SO_4 (1 mL). The solution was stirred at this temperature for 4 h. The reaction mixture was poured on ice–water and neutralized with sodium carbonate. The aqueous solution was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by flash chromatography (SiO_2/eluent: cyclohexane/ethyl acetate: 70:30) to give **5a** as a white solid in 70% yield and 90% ee (*S*). $[\alpha]_D^{20}=+61.49$ (*c* 1.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, *J*=7.5 Hz), 7.28–7.05 (7H, m), 4.84 (1H, s), 4.53 (2H, s), 3.11 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 169.26, 139.20, 137.91, 131.17, 130.95, 129.48, 128.9, 128.0, 127.97, 127.45, 121.22, 53.20, 52.33, 35.09. IR (neat) 3028, 2926, 1631, 1441, 1256, 716 cm^{-1}. Anal. calcd for $C_{16}H_{14}BrNO$: C, 60.78; H, 4.46; N, 4.43. Found: C, 59.72; H, 4.75; N, 4.43. The optical

purity was determined by HPLC analysis using a Chiracel OJ column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **5a** in 10 mL of heptane). Eluent: heptane/2-propanol: 80/20. Flow rate: 1 mL/min. Pressure: 400 psi. Temperature: 17°C. UV detection: λ=230 nm. Retention time: 14.2 min [(*S*)-enantiomer] and 18.7 min [(*R*)-enantiomer]. ee>90% (*S*). Recrystallization of the crude product in isopropanol afforded **5a** in 40% yield and 97% ee (*S*). Mp 148°C.

4.4.2. (*S*)-*N*-Methyl-4-phenyl-1,4-dihydroisoquinolin-3-one (5c). Compound **5c** was prepared according to the general procedure (C) from **1c** (0.214 mg, 0.72 mmol), CH_2Cl_2 (1 mL) and H_2SO_4 (1 mL). The crude product was purified by flash chromatography (SiO_2/eluent: cyclohexane/ethyl acetate: 70:30) to give **5c** as a white solid in 86% yield and 87% ee (*S*). $[\alpha]_D^{20}$=+22.04 (*c* 1.535, $CHCl_3$). Mp 133°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.11 (9H, m), 4.84 (1H, s), 4.62 (1H, d, *J*=15 Hz), 4.27 (1H, d, *J*=15 Hz), 3.08 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 169.76, 139.14, 135.67, 131.52, 128.61, 128.42, 127.94, 127.56, 127.08, 127.00, 125.28, 52.65, 52.47, 35.17. IR (neat) 2928, 1656, 1238, 761 cm^{-1}. Anal. calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.05; H, 6.55; N, 5.70. The optical purity was determined by HPLC analysis using a Chiracel OD column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **5c** in 10 mL of heptane). Eluent: heptane/2-propanol/formic acid: 90/9.5/0.5. Flow rate: 1 mL/min. Pressure: 360 psi. Temperature: 18°C. UV detection: λ=254 nm. Retention time: 12.7 min [(*S*)-enantiomer] and 15.9 min [(*R*)-enantiomer]. ee=87% (*S*).

4.4.3. (*S*)-*N*-Benzyl-7-methoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (5d). Compound **5d** was prepared according to the general procedure (C) from **1d** (0.236 mg, 0.585 mmol), CH_2Cl_2 (1 mL) and H_2SO_4 (1 mL). The crude product was purified by flash chromatography (SiO_2/eluent: cyclohexane/ethyl acetate: 80:20) to give **5d** as a yellow oil in 20% yield and 97% ee (*S*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–6.66 (13H, m), 4.92 (1H, s), 4.72 (2H, s), 4.40 (1H, d, *J*=16.0 Hz), 4.15 (1H, d, *J*=16.0 Hz), 3.77 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 170.54, 158.76, 139.19, 136.75, 132.99, 129.71, 129.15, 128.91, 128.80, 127.99, 127.92, 127.60, 127.27, 113.99, 110.59, 55.48, 52.38, 50.37, 50.07. IR (neat) 3382, 3007, 1651, 1274, 755 cm^{-1}. Anal. calcd for $C_{23}H_{21}NO_2$: C, 83.14; H, 6.16; N, 4.08. Found: C, 83.14; H, 6.25; N, 3.85. The optical purity was determined by HPLC analysis using a Chiracel OD column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **5d** in 10 mL of heptane). Eluent: heptane/2-propanol: 90/10. Flow rate: 1 mL/min. Pressure: 400 psi. Temperature: 15°C. UV detection: λ=230 nm. Retention time: 35.0 min [(*S*)-enantiomer] and 23.0 min [(*R*)-enantiomer]. ee>97% (*S*).

4.4.4. (*S*,*S*)-N-(1-Phenylethyl)-7-methoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (5e). Compound **5e** was prepared according to the general procedure (C) from **1e** (0.410 mg, 0.98 mmol), CH_2Cl_2 (1 mL) and H_2SO_4 (1 mL). The crude product was purified by flash chromatography (SiO_2/eluent: cyclohexane/ethyl acetate: 80:20) to give **5e** as a yellow oil in 20% yield and 97% de. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–6.67 (13H, m), 6.10 (1H, q, *J*=7.3 Hz), 4.90 (1H, s), 3.97 (1H, d, *J*=15 Hz), 3.83–8.78 (4H, m), 1.54 (3H, d, *J*=7.1 Hz).

4.4.5. (*S*,*S*)-*N*-Methyl-8-acetamido-4-phenyl-1,4-dihydroisoquinolin-3-one (5f). Compound **5f** was prepared according to the general procedure (C) from **1f** (0.101 mg, 0.286 mmol), CH_2Cl_2 (1 mL) and H_2SO_4 (1 mL). The crude product was purified by flash chromatography (SiO_2/eluent: CH_2Cl_2/EtOH: 95/5) to give **5f** as a white solid in 90% yield and 20% ee (*S*). Mp 182°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.16 (5H, m), 7.15 (d, 2H, *J*=6.4 Hz), 7.04 (d, 1H, *J*=7.2 Hz), 4.87 (s, 1H), 4.43 (1H, d, *J*=16 Hz), 4.14 (1H, d, *J*=16 Hz), 3.07 (3H, s), 2.24 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 170.02, 169.49, 138.58, 136.69, 133.04, 128.81, 128.42, 127.94, 127.34, 127.30, 126.45, 123.93, 52.91, 49.44, 35.03, 23.58. IR (neat) 3289, 1633, 1263, 698 cm^{-1}. Anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.15; H, 6.17; N, 9.22. The optical purity was determined by HPLC analysis using a Chiracel OD column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **5f** in 10 mL of heptane). Eluent: heptane/2-propanol: 85/15. Flow rate: 1 mL/min. Pressure: 320 psi. Temperature: 25°C. UV detection: λ=254 nm. Retention time: 30.1 min [(*S*)-enantiomer] and 18.9 min [(*R*)-enantiomer]. ee=20% (*S*).

4.5. Reduction procedure of 5c and 1c

4.5.1. (*S*)-*N*-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (6c). To a solution of sodium borohydride (540 mg, 14.6 mmol) in dry THF (30 mL) was added dropwise under argon a solution of iodine (740 mg, 5.8 mmol) in THF (20 mL) at 0°C. The mixture was kept for additional 5 min, compound (*S*)-**5c** (1.37 g, 5.8 mmol) was then added and the mixture was stirred under reflux overnight. After cooling the solution to 0°C, methanol (15 mL) was added dropwise and the resulting mixture was stirred at room temperature for a further 30 min. Solvents were evaporated to dryness and 20% aqueous NaOH (60 mL) was then added to the residue. The solution was stirred for 4 h at room temperature and then extracted with CH_2Cl_2 (3×40 mL). The organic layer was washed with 1N aqueous HCl (10 mL). The resulting acidic aqueous phase was washed with Et_2O (3×10 mL). After neutralization with 2 M NaOH (pH=6–7), the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated under vacuum to give **6c** in 86% yield as a thick colorless oil. $[\alpha]_D^{24}$=+15.6 (*c* 1.15, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.05 (8H, m), 6.90 (1H, d, *J*=7.5 Hz), 4.31 (1H, t, *J*=7.0 Hz), 3.80 (1H, d, *J*=15 Hz), 3.64 (1H, t, *J*=15 Hz), 3.08 (1H, dd, *J*=11.5, 5.0 Hz), 2.61 (1H, dd, *J*=11.5, 8.5 Hz), 2.46 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 144.85, 137.04, 135.12, 129.29, 129.02, 128.28, 126.39, 126.23, 126.11, 125.90, 61.79, 58.45, 45.96, 45.89. IR (neat) 3060, 3023, 2967, 2937, 2875, 2839, 2779 cm^{-1}. Anal. calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.11; H, 7.67; N, 6.34. The optical purity was determined by HPLC analysis using a Chiracel OD column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **6c** in 10 mL of hexane). Eluent: hexane/2-propanol: 90/10. Flow rate: 1 mL/min. Pressure: 400 psi. Temperature: 20°C. UV

detection: λ=230 nm. Retention time: 4.3 min [(*S*)-enantiomer] and 5.5 min [(*R*)-enantiomer]. ee=90% (*S*).

4.5.2. (*S*)-2-(*N*-Benzyl-*N*-methyl amino)-1-phenylethanol (7c). To a solution of **1c** (1.50 g, 5.06 mmol) in THF (50 mL) was added $LiAlH_4$ (0.76 g, 20 mmol) at −78°C. the solution was stirred at room temperature for 12 h. The solution was treated was water (0.5 ml), 10% aqueous NaOH (0.5 mL) and water (1 mL). The solution was filtered on a Buchner funnel and the THF evaporated under vacuum. The aqueous phase was extracted with $CHCl_3$ (3×20 mL). The combined organic layers were dried ($MgSO_4$) evaporated to afford **7c** in 67% yield. $[\alpha]_D^{20}$=+80.85 (*c* 10.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.22 (10H, m), 4.66 (1H, dd, *J*=10.2, 3.8 Hz), 3.65 (1H, d, *J*=13 Hz), 3.43 (1H, d, *J*=13 Hz), 2.55–2.40 (2H, m), 2.22 (3H, s). ^{13}C NMR (60 MHz, $CDCl_3$) δ 142.23, 138.18, 129.07, 128.5, 128.33, 127.46, 127.33, 125.91, 69.43, 65.49, 62.33, 41.74. IR (neat) 3340, 2795, 1453, 1024, 699 cm^{-1}. Anal. calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.44; H, 7.97; N, 5.76. The optical purity was determined by HPLC analysis using a Chiracel OJ column (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μL (0.5 mg of **7c** in 10 mL of hexane). Eluent: hexane/2-propanol: 90/10. Flow rate: 1 mL/min. Pressure: 400 psi. Temperature: 18°C. UV detection: λ=230 nm. Retention time: 9.2 min [(*S*)-enantiomer] and 11.2 min [(*R*)-enantiomer]. ee>97% (*S*).

Acknowledgements

We thank the CNRS, the région Haute Normandie and the CRIHAN for technical and financial support.

References

1. (a) Kihara, M.; Ikeuchi, M.; Adachi, S.; Nagao, Y.; Moritoki, H.; Yamaguchi, M.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543–1546. (b) Kihara, M.; Kashimoto, M.; Kobayashi, S.; Ishida, Y.; Moritoki, H.; Taira, Z. *J. Med. Chem.* **1990**, *33*, 2283–2286. (c) Riggs, R. M.; Nichols, D. E.; Foreman, M. M.; Truex, L. L.; Glock, D.; Kohli, J. D. *J. Med. Chem.* **1987**, *30*, 1454–1458.
2. Kunstmann, R.; Kruse, H.; Leven, M.; Paulus, E. F.; Schacht, U.; Schmitt, K.; Witte, P. U. *J. Med. Chem.* **1987**, *30*, 798–804.
3. Philippe, N.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Org. Lett.* **2000**, *2*, 2185–2187.
4. Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509–2516.
5. Nakajima, T.; Suga, S.; Sugita, T.; Ichikawa, K. *Tetrahedron* **1969**, 1807–1816.
6. Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* **1991**, *56*, 183–187.
7. Branchaud, B. P.; Blanchette, H. S. *Tetrahedron Lett.* **2002**, *43*, 351–353.
8. Kihara, M.; Ikeuchi, M.; Adachi, S.; Nagao, Y.; Moritoki, H.; Yamaguchi, M.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543–1546.
9. Coote, J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *Tetrahedron: Asymmetry* **1990**, *1*, 33–56.
10. Recrystallization of the crude product from isopropanol afforded **5a** in 40% yield and 97% ee (*S*).
11. During the preparation of benzazepines, *O*-demethylation is also observed in the course of similar electrophilic cyclization Gerritz, S. W.; Smith, J. S.; Nanthakumar, S. S.; Uehling, D. E.; Cobb, J. E. *Org. Lett.* **2000**, *25*, 4099–4102.
12. Crystallographic data for (*S*,*S*)-**5e** available from the Cambridge structural database (CSD).
13. (a) Zàra-Kacziàn, E.; György, L.; Deàk, G.; Seregi, A.; Dodà, M. *J. Med. Chem.* **1986**, *29*, 1189–1195. (b) Aboul-Enein, H. Y.; Islam, M. R.; Bakr, S. A. *J. Liq. Chromatogr.* **1988**, *11*, 1485–1493.
14. (a) Dandridge, P. A.; Kaiser, C.; Brenner, M.; Gaitonopoulos, D.; Sarau, H. M. *J. Med. Chem.* **1984**, *27*, 28–35. (b) Venkov, A. P.; Vodenicharov, D. M. *Synthesis* **1990**, 253–255.