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Asymmetric synthesis of (+)- and (−)-latifine

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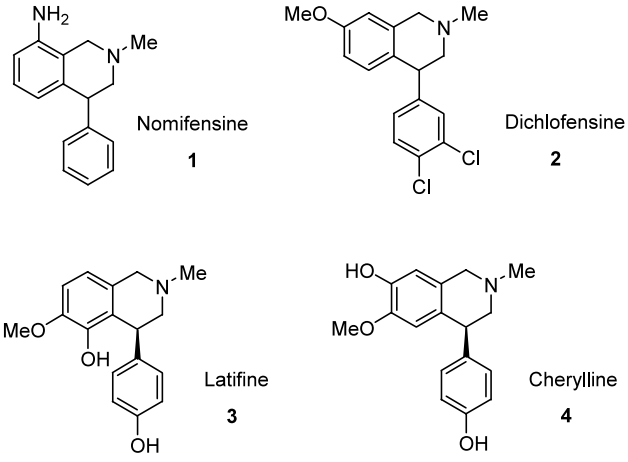
Abstract—A concise and novel synthesis of isoquinoline alkaloids (*S*)-latifine and of its antipode is reported. The key step relies on the stereoselective reduction of an appropriately substituted diarylenamine equipped with a chiral auxiliary followed by Pictet–Spengler cyclization to generate the tetrahydroisoquinoline unit.

1. Introduction

1,2,3,4-Tetrahydroisoquinolines of synthetic, plant and mammalian origin have been extensively studied because of their manifold pharmacological properties.[1] In particular, enantiomerically pure tetrahydroisoquinolines arylated at C(4) are of considerable interest because compounds possessing this heteroring unit display biological activities of medicinal interest[2] as witnessed by nomifensine[3] **1** and dichlofensine[4] **2** which exhibit central nervous activity and inhibit serotonin and dopamine uptake mechanisms. The 4-aryltetrahydroisoquinoline unit also represents the basic skeleton of the unique 5,6- and 6,7-dioxygenated naturally occurring alkaloids latifine **3** and cherylline **4** which have been isolated from *Amaryllidaceae* plants.[5]

Although this substitution pattern is found quite often in nature and in the biological domain, there are only a few efficient and general stereoselective methods available to control the stereochemistry at the C(4) position of the heterocyclic framework. Indeed compounds possessing the 4-aryltetrahydroisoquinoline unit are usually synthesized in their racemic form followed by a supplementary step of resolution.[6] Recently Levacher tackled this challenge and developed two complementary approaches to enantiopure compounds based upon the deracemization of racemic models via a metallation reprotonation sequence with the mediation of an enantiodiscriminating ligand.[6,7] Alternatively they are also accessible by chirality transfer upon diastereoselective protonation of chiral lactam enolates.[8] However applications of these elegant concepts have been mainly confined to structurally simple models, particularly devoid of competing metallation sites and/or phenolic hydroxy functions on the environmentally different aromatic moieties.



In continuation of our investigation into the asymmetric synthesis of alkaloids with a tetrahydroisoquinoline ring system as the main structural subunit,[9] we herein wish to disclose a novel and concise route to enantiomerically pure (+)- and (−)-latifine **3** which has been isolated from *Crinum latifolium*,[10] a plant used as rubefaciant and tonic.[11] This exemplary representative was chosen as a model since synthetic methods for the elaboration of this structurally challenging alkaloid in the racemic form are extremely rare.[12] Furthermore, extension to the enantioselective synthesis of the unnat-

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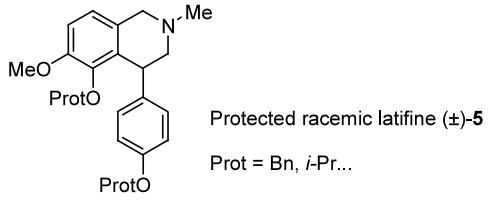
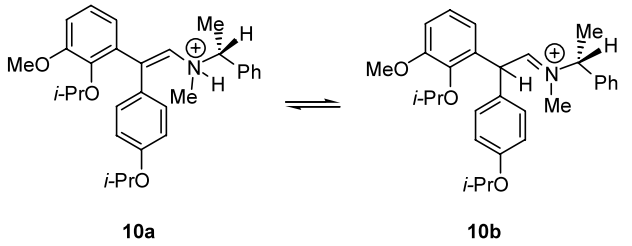
ural enantiomer was envisaged but the observed specific rotation of the synthetic material is still open to discussion.[12a] It is noteworthy that all prior attempts to deracemizate the protected precursor[12e] **5** by applying the asymmetric deprotronation protonation sequence were unrewarding even when varying the protections of the hydroxy phenolic groups (e.g. benzyl, isopropyl). This may tentatively be attributable to the sensitivity of the diverse functionalities with regard to the long reaction times and the harsh experimental conditions needed.



2. Results and discussion

Our strategy, which is depicted in the retrosynthetic Scheme 1, hinges upon our longstanding experience in the field of *N*-substituted enamine chemistry.[13]

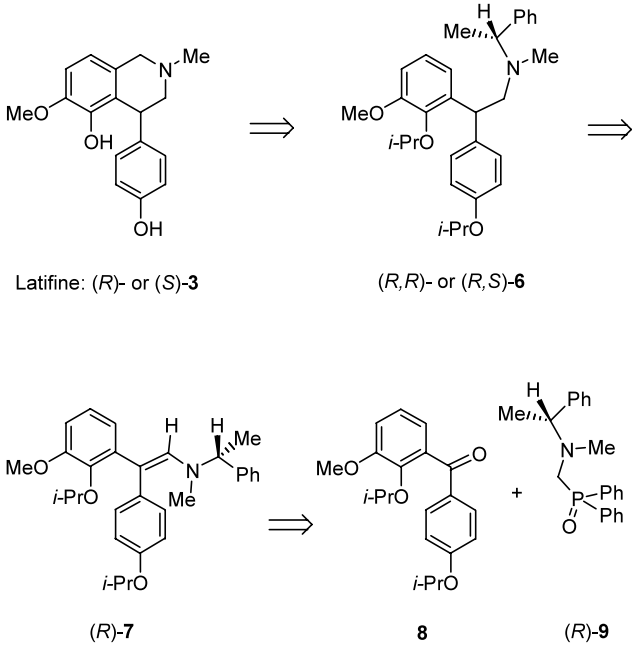
The key step of our conceptually new synthetic route was the diastereoselective hydrogenation of the appended diarylmethylene unit of the diarylenamine **7** derived from a tertiary amine bearing a removable stereocontrolling agent, i.e. the α-methylbenzyl group. We anticipated that the bulky α-methylbenzyl group might influence the sense and extent of diastereoselection associated with the formation of the transient iminium ion **10b** involved in the reduction of the enamine moiety and arising from the enammonium ion **10a** (Scheme 2).[14] This operation might then address the problem of stereocontrol at the stereogenic center adjacent to the differentially substituted aromatic units in **6** and consequently of the annulated model **3**.



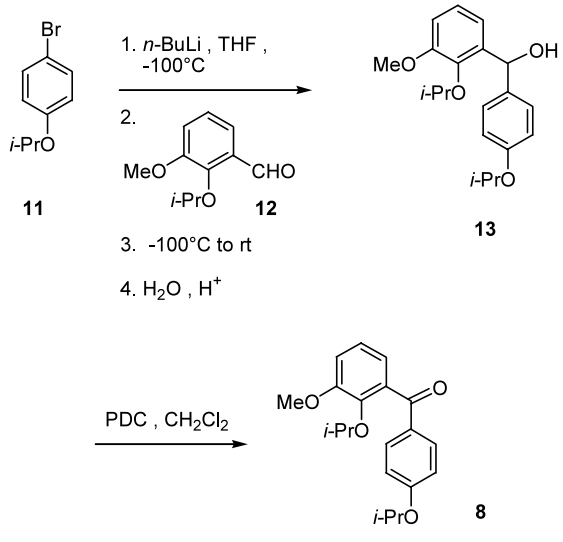
Scheme 2. Transient imminium ion.

The chiral appendage would be incorporated in the desired enamine **7** under the agency of the Horner process involving the benzophenone derivative **8** and the appropriate chiral phosphorylated amine **9**. Cleavage of the chiral auxiliary followed by Pictet–Spengler cyclization to generate the piperidine ring system and ultimate deprotection should complete the synthesis of the target product **3**.

The first facet of the synthesis was the elaboration of the rather congested benzophenone derivative **8**. This unsymmetrically trisubstituted diarylketone was constructed by reacting protected isovanillin **12** with the aryllithium species obtainable from the corresponding aryl bromide **11** by low temperature halogen metal exchange (Scheme 3). This coupling reaction delivered the dibenzylic alcohol **13** in an excellent yield. Oxidation with pyridinium dichromate generated the desired ketone linkage between the two aromatic components thus providing almost quantitatively the desired diarylketone **8**.



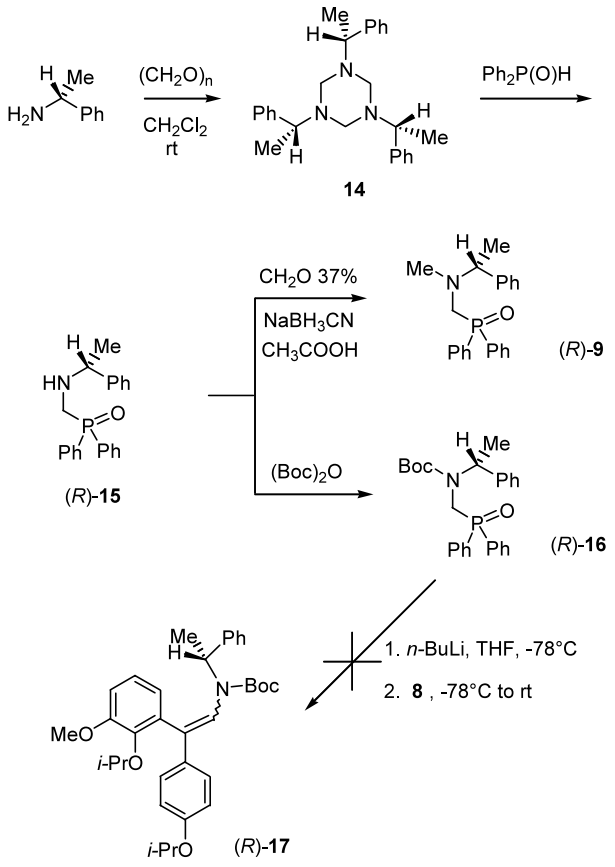
Scheme 1. Retrosynthetic scheme.



Scheme 3. Synthesis of the diarylketone **8**.

The synthetic route to the requisite diarylenamine **7** then necessitated the preliminary formation of the chiral phosphorylated amine **9**. We found that this amine

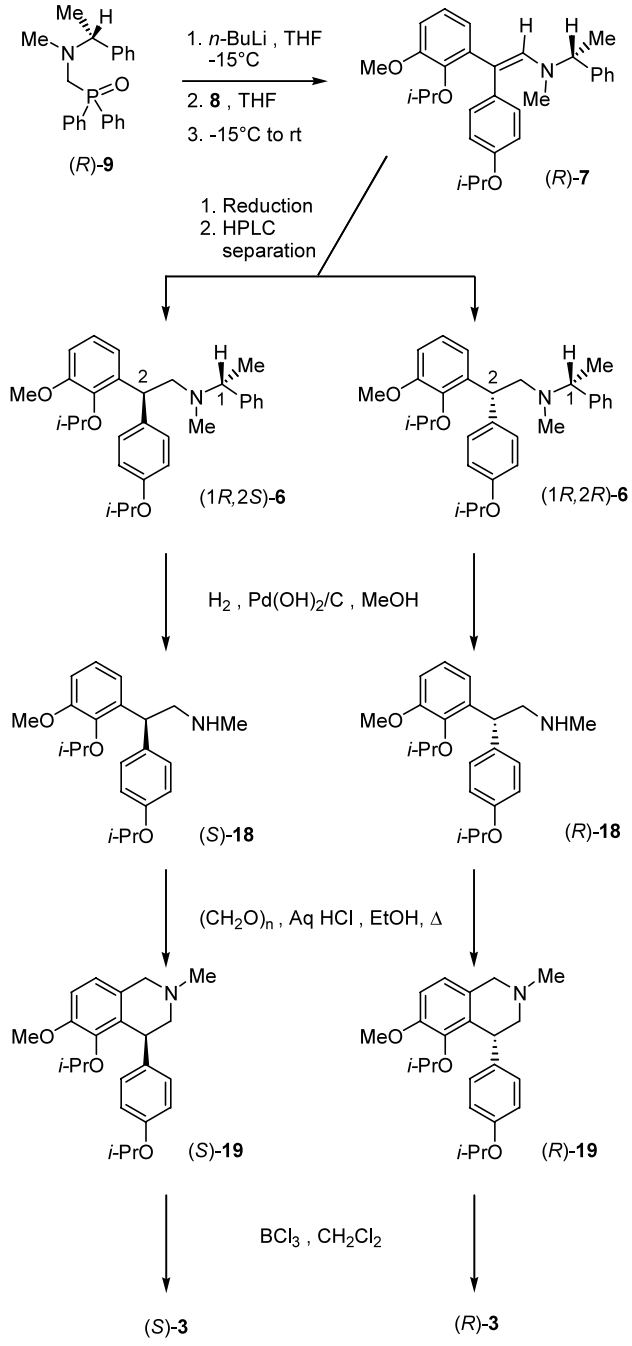
could be readily prepared via the three step sequence depicted in Scheme 4 involving the treatment with diphenylphosphine oxide of the appropriate hexahydrotriazine **14** product of the Mannich reaction of (*R*)-(+)-α-methylbenzylamine. Eischweiler–Clarke methylation of the resulting secondary amine **15** delivered the required phosphorylated amine **9** with an excellent yield (68% over the three steps).



Scheme 4. Synthesis of phosporylated amine derivatives.

Interestingly, at this stage we envisaged the alternative synthesis of the diarylated enecarbamate **17** assuming that the *N*-Boc group could be readily replaced by the mandatory *N*-methyl group and that catalytic asymmetric hydrogenation could be performed with a high degree of diastereoselectivity. Literature precedent, although scarce,[9a,15] indeed gave support to the feasibility of such an approach. For this purpose the phosphorylated *N*-Boc protected amine **16** was prepared but, unfortunately, all attempts to prepare the enecarbamate **17** by Horner reaction between the metalated carbamate **16** and the benzophenone derivative **8** were unrewarding, probably due to the steric congestion of both partners.

For the subsequent synthesis of the required enamine **7**, the Horner protocol, which has been mainly employed in related systems for homologation of a variety of carbonyl compounds[16] and for the generation of acyl anion equivalents,[17] was also applied. Deprotonation of **9** was conducted at −15°C using 1.1 equiv. of *n*-BuLi in THF and the so formed carbanion was reacted with the diarylketone **8** (Scheme 5). Warming to room temperature resulted in direct completion of the Horner reaction and almost exclusive formation of the prochiral enamine **7** (95%). Enamine **7** was obtained with a very high degree of stereoselectivity and the *E*-configuration of the exclusive stereomer was assigned from the ^{1}H NMR spectrum. The formation of the unique *E*-configured substrate may be tentatively explained by the presence of the bulky *O*-isopropyl group *ortho* to the styrylamine moiety. The driving force arising from the high degree of conjugation of this 1,1-diarylethylene model accounts for the high yield of the synthesis of



Scheme 5.

this enamine. Because the enamine partially hydrolyzed during chromatographic treatment, it was directly subjected to the reduction conditions.

A contentious issue in the formation of the diastereochemically enriched dibenzylamine derivative **6** was to determine the proper conditions to optimize the yield and the diastereoselective level of this simple process, namely by varying the nature of the reducing agent, the solvent and the temperature. $NaBH_4$, $NaBH_3CN$ and $NaBH(OAc)_3$ were used in this study and results are presented in Table 1. From Table 1 it can be seen that satisfactory diastereoselection was obtained with $NaBH(OAc)_3$ for reactions carried out in MeOH/HCl at low temperature (entry 6). The diastereomeric excess (de) was estimated by the integration of relevant signals in the ^1H NMR spectrum of the crude reaction mixture. An interesting observation emerging from this experiment is that the major diastereomer resulting from hydride reduction is the (1*R*,2*R*)-amine prone to give access to the unnatural compound. For all cases yields were quite acceptable. Separation of the pair of diastereomers proved more difficult than we anticipated and compounds (1*R*,2*S*)-**6** and (1*R*,2*R*)-**6** were finally separated by preparative HPLC.

The adoption of the isopropyl protecting group was rewarded here: hydrogenolysis of (1*R*,2*S*)-**6** with Pearlman's catalyst clipped the chiral appendage and delivered the enantiomerically pure diarylamine (*S*)-**18** while sparing the isopropyl protection. The diastereomeric amine (1*R*,2*R*)-**6** was transformed analogously into the enantiomeric (*R*)-configured diarylamine (*R*)-**18**. The cyclomethylenation of (*S*)-**18** by the Pictet–Spengler heterocyclization reaction proceeded uneventfully to furnish the initial annulated compound (*S*)-**19**. Analysis by chiral HPLC, under conditions optimized with use of racemic standard, showed that compound (*S*)-**19** was obtained as only one detectable enantiomer indicating that both processes, removal of chiral auxiliary and cyclization, proceeded without racemization of the previously formed stereogenic center. Finally the two phenolic hydroxy functions of the target natural product were easily retrieved by removal of the isopropyl protecting group of (*S*)-**19** and this simple operation delivered the natural enantiomer (*S*)-**3** with an excellent enantioselectivity (>95%) (Scheme 5).

Performing all these operations on the (*R*)-configured diarylethylamine (*R*)-**18** led to the unnatural antipode **3** with the (*R*)-configuration. The data obtained for both enantiomeric forms unequivocally proved that the configuration of the unnatural enantiomer was (*R*) with a specific rotation value matching that of the natural product, thus putting an end to the controversy.[12a]

3. Experimental

3.1. General

Mps were determined on a Reichert–Thermopan apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AM 300 spectrometer and were referenced against internal tetramethylsilane; ^{31}P NMR (121 MHz) spectra were referenced against H_3PO_4 as external standard. Coupling constants (*J*) are given in Hz and rounded to the nearest 0.1 Hz. Elemental analyses were determined by the CNRS microanalysis center. TLC was performed with plates coated with Kieselgel G (Merck). The plates were developed with petroleum ether (PE)–ethyl acetate (EA). The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Dry glassware was obtained by oven-drying and assembly under Ar. Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use. Methanol was distilled from magnesium turnings and acetonitrile from CaH_2 before storage over 4 Å molecular sieves.

3.2. (1*R*)-*N*-Diphenylphosphinoylmethyl-*N*-1-phenylethylamine, 15

A suspension of paraformaldehyde (1 g, 33.3 mmol) in a solution of (*R*)-(+)-α-methylbenzylamine (4 g, 33.1 mmol) in CH_2Cl_2 (20 ml) was stirred at rt for 3 h. After filtration, evaporation of the solvent left a colorless oil (12.5 g, 95%) corresponding to the hexahydrotriazine **14** which was used in the next step without further purification.

Table 1. Diastereoselectivity of the reduction[a] of the diarylenamine **7**

Entry	Reducing agent	Temp. (°C)	Time (h)	Yield (%)	De[b] (%)
1	$NaBH_4$	−25	1	80	10
2	$NaBH_4$	−78	2	62	30
3	$NaBH_3CN$	−25	1	75	24
4	$NaBH_3CN$	−78	3	70	40
5	$NaBH(OAc)_3$	−30	1	78	35
6	$NaBH(OAc)_3$	−78	4	60	85

[a] The reaction was conducted in a saturated solution of MeOH–HCl.

[b] The diastereomeric excess (de) was estimated by the integration of the N-CH_3 signal [(1*R*,2*S*)-**6**: δ 2.19 ppm; (1*R*,2*R*)-**6**: δ 2.30 ppm] in the ^1H NMR spectrum of the crude reaction mixture

A solution of hexahydrotriazine **14** (10 g, 25 mmol) and diphenylphosphine oxide (15.2 g, 75 mmol) was refluxed in toluene (100 ml) for 2 h under Ar. After evaporation of the solvent under vacuum, the crude product was chromatographed on SiO_2 column using acetone/PE (80:20) as eluent and the phosphorylated amine was finally purified by recrystallization from hexane–toluene to afford **15** as a pale yellow solid (20.2 g, 80%). Mp 190–191°C; $[\alpha]_D^{20}=+21.0$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{20}=+48.5$ (*c* 1.3, MeOH). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (d, $J=6.5$, 3H), 1.94 (brs, 1H, NH), 3.25 (dd, $J=8.0$, 3.6, 2H, NCH_2P), 3.76 (q, $J=6.5$, 1H), 7.12–7.31 (m, 5H, $H_{arom.}$), 7.34–7.56 (m, 6H, $H_{arom.}$), 7.58–7.75 (m, 4H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 24.5, 47.1 (d, $J=81$, NCH_2P), 60.0 (d, $J=14$, NCH), 126.8, 127.2, 128.4, 128.6, 130.9, 131.0, 131.2, 131.3, 131.5, 131.9, 132.2, 132.8. ^{31}P NMR ($CDCl_3$) δ (ppm): 30.1. Anal. calcd for $C_{21}H_{22}NOP$ (335) C, 75.12; H, 6.61; N, 4.17. Found C, 74.99; H, 6.54; N, 4.07.

3.3. (1*R*)-*N*-Diphenylphosphinoylmethyl-*N*-methyl-*N*-1-phenylethylamine, 9

To a solution of phosphorylated amine **15** (4 g, 12 mmol) in dry acetonitrile (40 ml) at 0°C was added formaldehyde (37%, 5.6 ml) with constant stirring. To this suspension was added sodium cyanoborohydride (1.2 g, 20 mmol). The pH of the mixture was adjusted to 3–4 using AcOH and then stirred for 2 h at rt. The mixture was basified with saturated sodium carbonate solution, extracted with CH_2Cl_2 (3×30 ml), dried over $MgSO_4$, filtered and the solvent evaporated. The product was purified by flash chromatography on silica gel using acetone/PE (75:25) as eluent followed by recrystallization from hexane/toluene to yield **9** as a white solid (3.54 g, 85%). Mp 113–114°C (lit.[18] 114–117°C); $[\alpha]_D^{20}=+10.5$ (*c* 1.6, $CHCl_3$); $[\alpha]_D^{20}=+49.3$ (*c* 1.0, MeOH) {lit.[18] $[\alpha]_D^{22}=+49.9$ (*c* 1.0, MeOH)}. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.28 (d, $J=6.8$, 3H), 2.44 (s, 3H, NCH_3), 3.22 (dd, $J=15.0$, 6.1, 1H, NCH_2P), 3.31 (dd, $J=15.0$, 6.5, 1H, NCH_2P), 3.69 (q, $J=6.8$, 1H), 7.09–7.25 (m, 5H, $H_{arom.}$), 7.34–7.56 (m, 6H, $H_{arom.}$), 7.58–7.73 (m, 4H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 24.5, 40.7 (NCH_3), 54.8 (d, $J=89$, NCH_2P), 64.9 (d, $J=12$, NCH), 127.0, 127.9, 128.1, 128.4, 128.5, 131.0, 131.2, 131.3, 131.5, 131.7, 132.3, 132.8. ^{31}P NMR ($CDCl_3$) δ (ppm): 29.6. Anal. calcd for $C_{22}H_{24}NOP$ (349) C, 75.62; H, 6.92; N, 4.01. Found C, 75.77; H, 7.11; N, 4.20.

3.4. 4-Isopropoxybromobenzene, 11

To a solution of 4-bromophenol (10 g, 58 mmol) and isopropyl bromide (7.87 g, 64 mmol) in DMF (100 ml) was added potassium carbonate (9.52 g, 69 mmol) and the mixture was heated overnight to reflux. After cooling, DMF was removed under reduced pressure and the residue was dissolved in Et_2O (100 ml) and washed with KOH (1N, 3×50 ml) and brine (50 ml). The organic layer was dried over $MgSO_4$, evaporated and purified by distillation under reduced pressure [bp 110°C (12 torr); lit.[19] 110–112°C (12 torr)] to afford **11** as a colorless oil (7.7 g, 52%). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.32 (d, $J=7.0$, 6H, $2CH_3$), 4.47 (sept., $J=7.0$, 1H), 6.77 (d, $J=9.0$, 2H, $H_{arom.}$), 7.36 (d, $J=9.0$, 2H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.9, 70.2, 112.5, 117.7, 132.3, 157.0.

3.5. 2-Isopropoxy-3-methoxybenzaldehyde, 12

To a solution of isovanillin (10 g, 65 mmol) and isopropyl bromide (8.85 g, 72 mmol) in DMF (100 ml) was added potassium carbonate (10.9 g, 79 mmol) and the mixture was refluxed overnight. After cooling, DMF was removed under reduced pressure and the residue was dissolved in Et_2O (200 ml) and washed with water (50 ml) and KOH (1N, 3×50 ml). The organic layer was dried over $MgSO_4$ and evaporation of the solvents left an oily residue which was purified by distillation under reduced pressure [bp 146°C (12 torr): lit.[20] 142°C (12 torr)] to give **12** as a colorless liquid (8.68 g, 68%). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22 (d, $J=6.2$, 6H, $2CH_3$), 3.77 (s, 3H, OCH_3), 4.54 (sept., $J=6.2$, 1H), 6.96–7.05 (m, 2H, $H_{arom.}$), 7.31 (dd, $J=7.3$, 2.1, 1H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.2, 55.9, 76.1, 117.8, 118.7, 123.6, 130.7, 150.5, 153.2, 190.7 (CHO).

3.6. (2-Isopropoxy-3-methoxy)-(4′-isopropoxyphenyl)-methanol, 13

4-Isopropoxybromobenzene **11** (2 g, 9.3 mmol) was dissolved in dry THF (50 ml) and cooled to −100°C under Ar. *n*-BuLi (1.6 M in hexanes, 10.24 mmol) was added dropwise. After 15 min, 2-isopropoxy-3-methoxybenzaldehyde **12** (1.62 g, 8.37 mmol) in THF (2 ml) was added dropwise. After being stirred at −100°C for 10 min, the reaction mixture was allowed to warm to rt over 1 h. Saturated aqueous NH_4Cl (40 ml) was added and the organic layer separated. The aqueous layer was extracted with Et_2O (2×40 ml) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent furnished an oily product which was purified by flash column chromatography using AE/PE (20:80) as eluent to yield **13** as a slightly yellow solid (2.34 g, 85%). Mp 64°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.17 (d, $J=6.2$, 3H, CH_3), 1.22 (d, $J=6.2$, 3H, CH_3), 1.31 (d, $J=6.1$, 6H, $2CH_3$), 3.01 (brd, 1H, OH), 3.82 (s, 3H, OCH_3), 4.51 (sept., $J=6.1$, 1H), 4.69 (sept., $J=6.2$, 1H), 6.09 (brd, 1H), 6.80–6.86 (m, 4H, $H_{arom.}$), 6.99 (t, $J=7.9$, 1H, $H_{arom.}$), 7.25–7.30 (m, 2H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.1, 22.4, 22.6, 55.7, 69.9, 71.4, 74.5, 115.6, 116.6, 119.8, 123.3, 127.8, 135.6, 138.2, 143.9, 152.4, 157.0. Anal. calcd for $C_{20}H_{26}O_4$ (330) C, 72.70; H, 7.93. Found C, 72.87; H, 8.07.

3.7. 2-Isopropoxy-3-methoxy-4′-isopropoxybenzophenone, 8

To a solution of alcohol **13** (2 g, 6.1 mmol) in CH_2Cl_2 (100 ml) was added portionwise pyridinium dichromate (PDC, 4.6 g, 12.2 mmol). The reaction mixture was stirred at rt for 10 h. After dilution with Et_2O (100 ml), filtration through a plug of Celite and evaporation of the solvents, the crude product was purified by flash column chromatography using AE/PE (20:80) as eluent to afford **8** as a colorless solid (1.79 g, 90%). Mp 34°C.

^{1}H NMR ($CDCl_3$) δ (ppm): 1.01 (d, $J=6.2$, 6H, 2 CH_3), 1.33 (d, $J=6.1$, 6H, $2CH_3$), 3.86 (s, 3H, OCH_3), 4.21 (sept., $J=6.2$, 1H), 4.61 (sept., $J=6.1$, 1H), 6.85 (d, $J=8.8$, 2H, $H_{arom.}$), 6.94 (dd, $J=7.5$, 1.6, 1H, $H_{arom.}$), 7.00 (dd, $J=8.2$, 1.6, 1H, $H_{arom.}$), 7.08–7.11 (m, 1H, $H_{arom.}$), 7.78 (d, $J=8.8$, 2H $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.9, 22.1, 55.8, 70.0, 76.7, 113.6, 114.8, 120.8, 123.9, 129.9, 132.5, 135.4, 144.3, 153.0, 162.1, 195.3 (CO). Anal. calcd for $C_{20}H_{24}O_4$ (328) C, 73.15; H, 7.37. Found C, 73.39; H, 7.55.

3.8. General procedure for synthesis of (1*R*)-*N*-[(2-(2-isopropoxy-3-methoxy)phenyl)-4′-isopropoxyphenyl]vinyl-*N*-methyl-*N*-1-phenylethylamine, 7

n-BuLi (1.6 M in hexanes, 2.1 ml, 3.3 mmol) was added dropwise to a solution of **9** (1.06 g, 3.04 mmol) in THF (50 ml) at −15°C for 20 min. A solution of the ketone **8** (0.5 g, 1.52 mmol) in THF (5 ml) was then added. After being stirred at −15°C for 10 min, the reaction mixture was allowed to come to rt over 1 h. Water (30 ml) was added and the organic layer separated. The aqueous layer was extracted with Et_2O (2×50 ml) and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvents, a yellow oily product **7** (0.66 g, 95%) was obtained and was directly used without further purification.

3.9. Typical procedure for the reduction of the enamine 7

To a solution of enamine **7** (0.56 g, 1.22 mmol) in a saturated solution of MeOH–HCl (30 ml) at −78°C was added sodium triacetoxyborohydride (1.3 g, 5 equiv., 6.1 mmol). The mixture was stirred at −78°C for 4 h. Water (20 ml) and saturated sodium hydrogenocarbonate solution (30 ml) were successively added and the aqueous layer was extracted with $CHCl_3$ (3×30 ml). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent furnished an oily product which was purified by flash column chromatography using AE/PE (40:60) as eluent (yield 60%; de 85%; Table 1, entry 6). The mixture of diastereomers was separated by chiral HPLC using a Chiralcel OD column. The eluent was hexane/isopropanol (HPLC grade 80:20) at 1 ml per min flow rate and monitored at a wavelength of 254 nm.

3.9.1. (1*R*,2*S*)-*N*-[2-((2-Isopropoxy-3-methoxy)phenyl)-4′-isopropoxyphenyl]ethyl-*N*-methyl-*N*-1-phenylethylamine, 6. First product $t_1=4.74$ min. Oil; $[\alpha]_D^{20}=+77.6$ (c 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.18 (d, $J=6.2$, 3H, CH_3), 1.30–1.33 (m, 12H, 4 CH_3), 2.19 (s, 3H, NCH_3), 2.77–2.92 (m, 2H), 3.72 (q, $J=6.2$, 1H), 3.81 (s, 3H, OCH_3), 4.48 (sept., $J=6.2$, 1H), 4.57 (sept., $J=6.2$, 1H), 4.75 (t, $J=7.6$, 1H), 6.67 (dd, $J=7.8$, 1.2, 1H, $H_{arom.}$), 6.71–6.79 (m, 3H, $H_{arom.}$), 6.92 (t, $J=7.8$, 1H, $H_{arom.}$), 7.08 (d, $J=8.6$, 2H, $H_{arom.}$), 7.15–7.25 (m, 5H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.4, 22.1, 22.6, 22.9, 38.1, 40.6, 55.5, 58.8, 62.3, 69.8, 74.2, 109.8, 115.4, 120.8, 122.9, 126.4, 127.8, 127.9, 129.5, 135.4, 138.4, 144.1, 144.4, 152.7, 155.9. Anal. calcd for $C_{30}H_{39}NO_3$ (461) C, 78.05; H, 8.52; N, 3.03. Found C, 78.22; H, 8.37; N, 2.79.

3.9.2. (1*R*,2*R*)-*N*-[2-((2-Isopropoxy-3-methoxy)phenyl)-4′-isopropoxyphenyl]ethyl-*N*-methyl-*N*-1-phenylethylamine, 6. Second product separated by HPLC column $t_2=5.84$ min. Oil; $[\alpha]_D^{20}=-74.8$ (c 1.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22 (d, $J=6.2$, 3H, CH_3), 1.28–1.36 (m, 12H, 4 CH_3), 2.30 (s, 3H, NCH_3), 2.70 (dd, $J=12.5$, 5.9, 1H), 3.02 (dd, $J=12.5$, 9.6, 1H), 3.65 (q, $J=6.2$, 1H), 3.82 (s, 3H, OCH_3), 4.53 (sept., $J=6.1$, 1H), 4.62 (sept., $J=6.1$, 1H), 4.76 (dd, $J=9.6$, 5.9, 1H), 6.68 (dd, $J=7.8$, 1.3, 1H, $H_{arom.}$), 6.75 (dd, $J=8.2$, 1.3, 1H, $H_{arom.}$), 6.81 (d, $J=8.6$, 2H, $H_{arom.}$), 6.93 (t, $J=7.8$, 1H, $H_{arom.}$), 7.14 (d, $J=8.6$, 2H, $H_{arom.}$), 7.19–7.27 (m, 5H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 16.7, 22.2, 22.6, 22.9, 37.7, 40.9, 55.6, 59.8, 63.6, 69.8, 74.2, 109.9, 115.5, 120.6, 122.9, 126.5, 127.8, 127.9, 129.7, 135.5, 138.4, 144.2, 144.3, 152.7, 156.0. Anal. calcd for $C_{30}H_{39}NO_3$ (461) C, 78.05; H, 8.52; N, 3.03. Found C, 77.98; H, 8.43; N, 2.97.

3.10. (2*S*)-*N*-[(2-(2-Isopropoxy-3-methoxy)phenyl)-4′-isopropoxyphenyl]ethyl-*N*-methylamine, 18

To a solution of diastereopure amine (1*R*,2*S*)-**6** (300 mg, 0.65 mmol) in MeOH (15 ml) was added $Pd(OH)_2$ on C (100 mg). Hydrogen was introduced and the reaction mixture was magnetically stirred at rt during 12 h. The solution was then filtered through Celite and after evaporation of the solvents, the residue was purified by flash column chromatography with $CHCl_3$/MeOH (94:6) as eluent and by recrystallization from hexane–toluene to yield (*S*)-**18** as a colorless solid (221 mg, 95%). Mp 121–123°C; $[\alpha]_D^{20}=+55.4$ (c 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.18 (d, $J=6.1$, 3H, CH_3), 1.27 (d, $J=6.0$, 6H, 2 CH_3), 1.31 (d, $J=6.1$, 3H, CH_3), 2.45 (brs, 3H, NCH_3), 3.33–3.40 (m, 2H), 3.78 (s, 3H, OCH_3), 4.47 (sept., $J=6.0$, 1H), 4.66 (sept., $J=6.1$, 1H), 4.93–4.99 (m, 1H), 6.67 (d, $J=7.6$, 1H, $H_{arom.}$), 6.77–6.82 (m, 3H, $H_{arom.}$), 6.96 (t, $J=7.9$, 1H, $H_{arom.}$), 7.21 (d, $J=8.5$, 2H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.0, 22.3, 22.8, 33.2, 40.0, 52.5, 55.6, 69.8, 74.7, 111.5, 116.2, 119.8, 123.8, 129.5, 130.7, 134.3, 144.0, 152.9, 157.1. Anal. calcd for $C_{22}H_{31}NO_3$ (357) C, 73.92; H, 8.74; N, 3.92. Found C, 74.16; H, 8.57; N, 4.03.

3.11. (2*R*)-*N*-[(2-(2-Isopropoxy-3-methoxy)phenyl)-4′-isopropoxyphenyl]ethyl-*N*-methylamine, 18

Prepared as previously in Section 3.10 starting from (1*R*,2*R*)-**6** (400 mg, 0.87 mmol). (*R*)-**18** was obtained as a colorless solid (300 mg, 97%). Mp 122–123°C. $[\alpha]_D^{20}=-55.3$ (c 0.94, $CHCl_3$). Anal. calcd for $C_{22}H_{31}NO_3$ (357) C, 73.92; H, 8.74; N, 3.92. Found C, 74.07; H, 8.88; N, 3.78. The spectroscopic data were similar to those for (*S*)-**18**.

3.12. (4*S*)-4-Isopropoxyphenyl-5-isopropoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 19

A solution of amine (*S*)-**18** (300 mg, 0.84 mmol) and formaldehyde (37%, 2.17 ml) in EtOH (15 ml) was acidified with 0.7 ml of concentrated aqueous HCl. The mixture was refluxed for 6 h. The solvent and excess reagent were removed by rotary evaporation and the residue was dissolved in $CHCl_3$ (20 ml) and treated successively with a solution of aqueous ammoniac 10% (20 ml), water (20 ml) and brine (20 ml). The dried solution (Na_2SO_4) was subjected to rotary evaporation and the residual solid was purified by flash column chromatography with $CHCl_3$/MeOH (93:7) as eluent to afford (*S*)-**19** as a pale yellow oil (232 mg, 75%). $[\alpha]_D^{20} = -3.4$ (*c* 0.76, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.81 (d, $J = 6.1$, 3H, CH_3), 1.09 (d, $J = 6.1$, 3H, CH_3), 1.29 (d, $J = 6.0$, 6H, $2CH_3$), 2.32 (s, 3H, NCH_3), 2.60–2.71 (m, 2H), 3.35 (d, $J = 14.3$, 1H), 3.75 (s, 3H, OCH_3), 3.80 (d, $J = 14.3$, 1H), 4.49 (sept., $J = 6.0$, 1H), 4.60 (sept., $J = 6.1$, 1H), 6.74 (d, $J = 8.6$, 1H, $H_{arom.}$), 6.78 (s, 4H, $H_{arom.}$), 7.05 (d, $J = 8.6$, 1H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.9, 22.2, 22.5, 41.1, 46.3, 55.6, 58.1, 61.7, 69.7, 73.1, 111.0, 115.2, 120.3, 128.9, 129.4, 131.2, 138.6, 144.4, 150.8, 155.8. Anal. calcd for $C_{23}H_{31}NO_3$ (369) C, 74.76; H, 8.46; N, 3.79. Found C, 74.66; H, 8.79; N, 3.98.

3.13. (4*R*)-4-Isopropoxyphenyl-5-isopropoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 19

Prepared as already described in Section 3.12 starting from (*R*)-**18** (250 mg, 0.7 mmol), (*R*)-**19** was obtained as a colorless oil (207 mg, 80%); $[\alpha]_D^{20} = +3.4$ (*c* 0.80, $CHCl_3$). Anal. calcd for $C_{23}H_{31}NO_3$ (369) C, 74.76; H, 8.46; N, 3.79. Found C, 74.87; H, 8.54; N, 4.05. The spectroscopic data were similar to those for (*S*)-**19**.

3.14. (4*S*)-4-Hydroxyphenyl-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-ol, 3

To a solution of compound (*S*)-**19** (114 mg, 0.31 mmol) in dried CH_2Cl_2 (5 ml) was added at −10°C and under Ar, a solution of boron trichloride (1 M in CH_2Cl_2, 3 equiv., 0.93 ml). The reaction mixture was stirred at 0°C for 2 h. The solution was then washed with water (20 ml) and the aqueous layer was extracted with AcOEt (3×30 ml). The combined organic layers were dried over $MgSO_4$. After filtration and evaporation of the solvents, the solid obtained was recrystallized from MeOH to afford (*S*)-latifine **3** as a white solid (81 mg, 92%). Mp 215–216°C; $[\alpha]_D^{20} = -25.6$ (*c* 0.5, MeOH). The spectroscopic data were similar to those reported for the natural product.[10]

3.15. (4*R*)-4-Hydroxyphenyl-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-ol, 3

Starting from (*R*)-**19** (150 mg, 0.41 mmol) to give (*R*)-latifine **3** as a white solid (104 mg, 90%). Mp 214–215°C. $[\alpha]_D^{20} = +25.5$ (*c* 0.5, MeOH). Anal. calcd for $C_{17}H_{19}NO_3$ (285) C, 71.56; H, 6.71; N, 4.91. Found C, 71.38; H, 6.86; N, 5.07.

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