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A new synthesis of (+)- and (−)-cherylline

Stéphane Lebrun, Axel Couture,* Eric Deniau and Pierre Grandclaudon
Laboratoire de Chimie Organique Physique, associé à l'ENSCL, UMR 8009, Université des Sciences et Technologies de Lille 1, F-59655 Villeneuve d'Ascq Cedex, France

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A new and concise synthesis of enantiopure antipodes of alkaloid cherylline has been devised. The synthetic strategy relies upon the reduction of a diversely and polyprotected diarylenamine bearing a chiral auxiliary. Separation of diastereopure intermediates, concomitant deprotections and intramolecular reductive amination complete the synthesis of the natural (*S*)-enantiomer and of the unnatural (*R*)-configured antipode.

Introduction

During the past few years much effort has been devoted to the stereoselective synthesis of isoquinoline alkaloids owing to increasing interest in their synthetic organic chemistry.[1] In particular, many strategies have been designed for the highly stereoselective synthesis of 1-substituted tetrahydroisoquinolines[2] that have proved to be valuable intermediates for the elaboration of a wide array of enantiopure alkaloids.[3] Paradoxically, although chiral non racemic 4-substituted derivatives are of considerable interest, due to their biological activities and as naturally occurring alkaloids,[4] research towards their stereoselective syntheses is not as widely extended as in the case of their 1-substituted congeners. In particular, very little work has been done on the asymmetric synthesis of arylated or heteroarylated C-4 tetrahydroquinolines[5] despite the remarkable biological properties of this class of compounds as exemplified by nomifensine[6] and dichlofensine,[7] which inhibit dopamine and noradrenaline (re)uptake mechanisms.

In this context, the synthesis of cherylline **1**, a unique representative of rare phenolic *Amaryllidaceae* alkaloids, which has been isolated from several *Crinum* species[8] and assigned the (*S*)-configured structure **1**, has proved to be exemplary. Several racemic syntheses of this structurally challenging alkaloid have indeed appeared in print and can be cursorily classified into three main categories which differ in the nature of the carbon–carbon bond formed in the ultimate step (Fig. 1). In most cases regioselective regeneration of the phenolic hydroxy functions and/or reduction of intermediately formed 1- or 3-oxo compounds complete the synthesis of the racemic product. Thus generation of the (a) carbon–carbon bond has been achieved by cyclization of suitably substituted β-phenethylisocyanates[9] and by Bischler–Napieralski reaction of *N*-formyl derivatives of polyalkoxyphenethylamines.[10] (d) Carbon–carbon bond formation has been secured by intramolecular Horner reaction followed by two reduction processes[11] but the most popular methods involve the creation of the (e) carbon–carbon bond by (i) photoinduced cyclization of *ortho*-halogenated *N*-acylbenzylamines,[12] (ii) acid catalyzed cyclization of suitably substituted norbelladine derivatives,[13] (iii) intramolecular coupling of quinonoid intermediates[14] or (iv) palladium-catalyzed intramolecular cyclization of amide-enolates.[15] Unfortunately, none of these methods could be extended to the synthesis of either the natural (*S*)-configured compound or the unnatural antipode. To the best of our knowledge only one asymmetric synthesis of (−)-cherylline relying upon a regiocontrolled Polonovski-type reaction on dibenzazocine *N*-oxides has appeared in print,[16] whereas otherwise the two antipodes have been obtained from the racemic parent compound by a resolution process.[17]

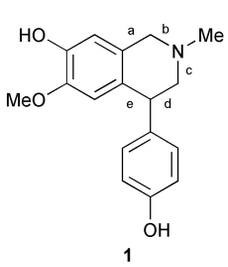

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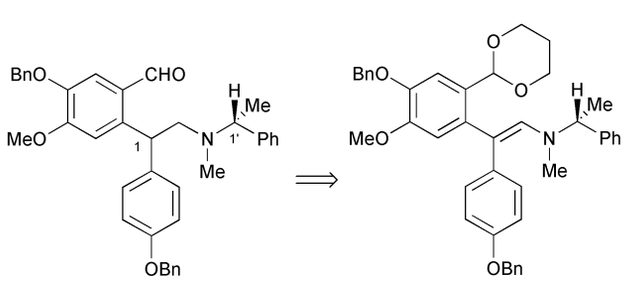
Fig. 1

Results and discussion

We wish therefore to disclose in this paper a new and concise synthetic approach that gives indiscriminately access to either (+) or (−)-cherylline and that involves for the first time the formation of the (b) carbon–carbon bond of the heterocyclic unit in the final step. Our synthetic route hinges upon the formation of the diastereomerically pure diarylethylamines (1*R*,1′*R*)- and (1*S*,1′*R*)-**2** obtained in the key step by reduction of the poly and diversely protected diarylenamine **3** equipped with a stereocontrolling appendage, *i.e.* the α-methylbenzylamine group (retrosynthetic Scheme 1). When formulating this synthetic plan we envisioned that the presence of this chiral auxiliary could significantly act on the level of diastereoselection at the tertiary carbon centre of **2** and consequently at the dibenzylic carbon centre embedded in the skeleton of the target natural product **1**. Subsequent deprotection of (1*R*,1′*R*)- or (1*S*,1′*R*)-**2** followed by regeneration of the hydroxy phenolic functions on the environmentally different aromatic moieties and cyclization indeed should not affect the stereochemistry of the dibenzylic chiral centre and therefore should complete the synthesis of the target natural product in both pure enantiomeric forms.



2 **3**

Scheme 1

The synthesis started with the assemblage of one of the major partners involved in the elaboration of **3**, *i.e.* the rather congested benzophenone derivative **4** (Scheme 2). Initially,

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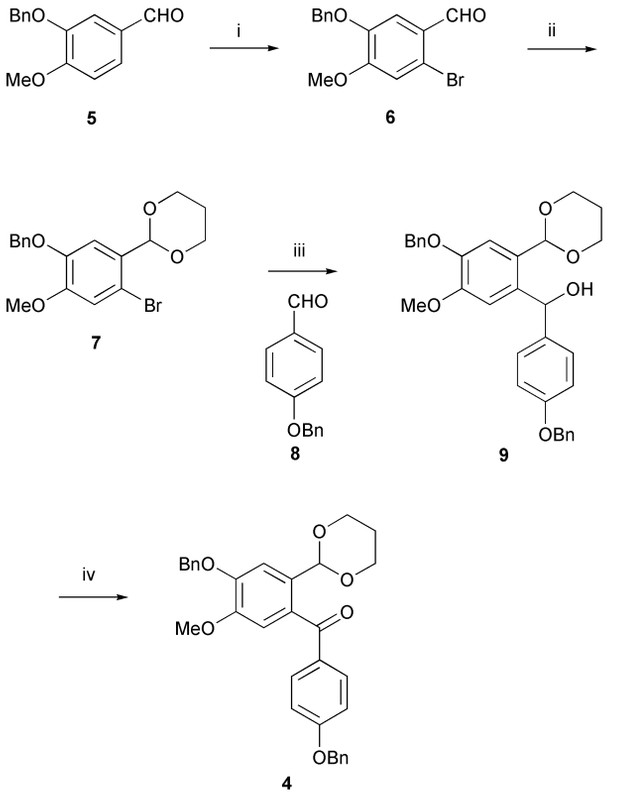
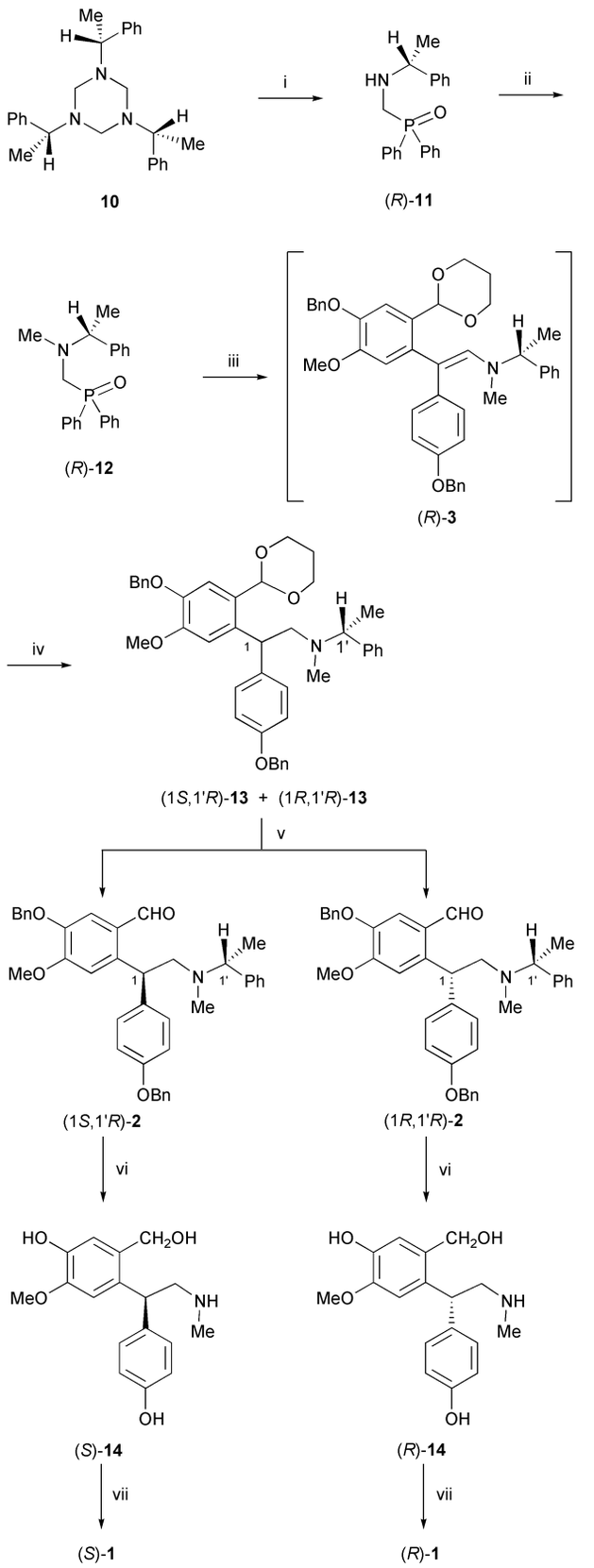


Scheme 2 *Reagents and conditions*: (i) Br_2, AcONa, AcOH, rt, 70 h; (ii) 1,3-propanediol, *p*-TsOH, toluene, reflux, 3 h; (iii) t-BuLi, THF, −85 °C, then **8**, −85 °C to rt, 1 h, then H_2O; (iv) PDC, CH_2Cl_2, 3 h.

benzyl protected isovanillin **5** was regioselectively brominated to furnish the bromobenzaldehyde **6** which was converted into the acetal **7** in order to save the formyl functionality for subsequent manipulations. Bromine–lithium exchange was performed with t-BuLi at low temperature and quenching with 4-benzyloxybenzaldehyde **8** delivered the unsymmetrically substituted dibenzylalcohol **9** in an excellent yield (60% over three steps). Oxidation under classical conditions furnished the desired diarylketone derivative **4** with a very satisfactory yield (81%).

For the synthesis of the diarylenamine **3** equipped with the chiral auxiliary we opted to adopt a synthetic method that has been mainly used for homologation of carbonyl compounds and for the generation of acyl anion equivalents.[18] This method relies upon Horner reaction between the diarylketone **4** and the anion derived from the phosphorylated methylamine **12** bearing the stereocontrolling agent (Scheme 3). Beforehand the mandatory chiral amine **12** was prepared by *N*-methylation of the secondary phosphorylated amine **11** obtained by treatment of the triazine **10**[19] with diphenylphosphine oxide.[20]

With the rather unstable diarylenamine **3** in hand we anticipated that the bulky stereocontrolling agent, *i.e.* the α-methylbenzyl group, could influence the degree of asymmetric induction upon hydrogenation of the diarylmethylene unit namely through chirality transfer *via* the transient species involved in the chemical process, *i.e.* enammonium and immonium ions.[21] Rather disappointingly, modest diastereoselectivity of this process was observed even by varying the nature of the reducing agent and the temperature. Table 1 summarizes results obtained with $NaBH_4$, $NaBH_3CN$ and $NaBH(OAc)_3$ in MeOH–HCl and it can be seen that the best diastereoselection [major diastereomer (1*R*,1′*R*)-**13**] was obtained with $NaBH_3CN$ for reactions carried out at −35 °C (entry 3) or with $NaBH(OAc)_3$ for reactions carried out at −20 °C (entry 4). Interestingly, catalytic hydrogenation of the parent diarylenamine decreased the diastereoselectivity to some



Scheme 3 *Reagents and conditions*: (i) $Ph_2P(O)H$, toluene, reflux, 2 h; (ii) CH_2=O (37%), $NaBH_3CN$, CH_3CN, pH 3–4, rt, 2 h; (iii) n-BuLi, THF, −15 °C; then **4**, −15 °C to rt, 2 h, NH_4Cl (10%); (iv) $NaBH_3CN$, sat. MeOH–HCl, −35 °C, 2 h or $NaBH(OAc)_3$, sat. MeOH–HCl, −20 °C, 2 h; (v) *p*-TsOH, toluene, H_2O, reflux, 4 h; then HPLC, chiralcel OD, ethanol–heptane (35 : 65); (vi) Pd/C, H_2, MeOH, rt, 24 h; (vii) *p*-TsOH, MeOH–toluene, reflux, 9 h.

extent as under these conditions the de was notably lowered to <10% (entry 7).

Regeneration of the formyl functionality delivered quanti-

Table 1 Diastereoselectivity of the reduction of the diarylenamine **3**

Entry	Reducing agent	Temp/°C	Time/h	Yield (%)	De[c] (%)
1	$NaBH_4$[a]	−35	2	72	<10
2	$NaBH_3CN$[a]	0	2	80	10
3	$NaBH_3CN$[a]	−35	2	75	25
4	$NaBH(OAc)_3$[a]	−20	2	78	25
5	$NaBH(OAc)_3$[a]	−35	2	70	18
6	$NaBH(OAc)_3$[a]	−78	4	No reaction	—
7	H_2, PtO_2[b]	20	2	85	<10

[a] The reduction was conducted in a saturated solution of MeOH–HCl. [b] The hydrogenation was conducted in MeOH under H_2 (3 atm). [c] The diastereomeric excess (de) was estimated by the integration of the N–CH_3 signal [(1*R*,1′*R*)-**13**, major isomer: δ 2.26 ppm; (1*S*,1′*R*)-**13**: δ 2.23 ppm] in the ^{1}H NMR spectrum of the crude reaction mixture.

tatively the benzaldehyde derivatives **2** and preparative HPLC separation of this pair of enriched diastereomers furnished the diastereopure isomers (1*R*,1′*R*)-**2** and (1*S*,1′*R*)-**2**. Catalytic hydrogenation of each of the diastereochemically pure (1*R*,1′*R*)-**2** and (1*S*,1′*R*)-**2** separately with Pd on C offered a triple advantage in effecting simultaneously the reduction of the carboxaldehyde function with concomitant removal of the chiral appendage and retrieval of the hydroxy phenolic functions. This efficient process gave straightforward access to (*R*)-**14** and (*S*)-**14**, direct candidates for the annulation reaction. The creation of the hetero-ring unit of the natural product proceeded uneventfully under acid conditions to afford the target alkaloids (*R*)-**1** and (*S*)-**1**. Chiral HPLC analysis by comparison with racemic standard unambiguously indicated that compound (*R*)-**1** and (*S*)-**1** were obtained with excellent enantioselectivity thus indicating that the stereogenic centre in (1*R*,1′*R*)-**13** and (1*S*,1′*R*)-**13** was spared and resisted the different chemical transformations on the pathway to the annulation reaction.

In conclusion, we have devised a new and concise method for the preparation of enantiopure (+) and (−)-cherylline. We succeeded in accomplishing the synthesis of the two antipodes of this alkaloid through reduction of a diarylenamine equipped with a chiral auxiliary, concomitant and differentiated deprotections followed by ultimate cyclization. Additionally this strategy is undoubtedly adaptable to the preparation of a range of substituted analogues and could be applied to other 4-(hetero)arylated models.

Experimental

General methods

Mps were determined on a Reichert-Thermopan apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR Bruker Vector 22 spectrometer. ^{1}H (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 centre. TLC was performed with plates coated with Kieselgel G (Merck). The plates were developed with petroleum ether (PE)–ethyl acetate (EA). Optical rotations are measured in 10^{-1} deg cm^2 g^{-1}. 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 a 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 on 4 Å molecular sieves.

Starting materials

Aldehydes **5**,[22] **6**[23] and **8**[22] were prepared according to standard procedures.

(1*R*)-*N*-Diphenylphosphinoylmethyl-*N*-phenylethylamine 11

A suspension of paraformaldehyde (1 g, 33.33 mmol) in a solution of (*R*)-(+)-α-methylbenzylamine (4 g, 33 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 3 h. Filtration and evaporation of the solvent left a colourless oil (12.5 g, 95%) corresponding to the hexahydrotriazine **10** which was used in the next step without further purification.

A solution of hexahydrotriazine **10** (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 **11** as white crystals (20.2 g, 80%). Mp 190–191 °C (Found: C, 75.4; H, 6.8; N, 4.3. $C_{21}H_{22}NOP$ requires C, 75.1; H, 6.6; N, 4.2%); $[\alpha]_D^{20} = +21$ (*c* 1.0, $CHCl_3$). IR ν_{max} (KBr)/cm^{-1} 3426 (NH), 1185 (P=O); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (3 H, d, *J* = 6.5), 1.94 (1 H, brs, NH), 3.25 (2 H, dd, *J* = 8.0, 3.6, NCH_2P), 3.76 (1 H, q, *J* = 6.5), 7.12–7.31 (5 H, m, H_{ar}), 7.34–7.56 (6 H, m, H_{ar}), 7.58–7.75 (4 H, m, H_{ar}). ^{13}C NMR ($CDCl_3$) δ (ppm): 24.5 (CH_3), 47.1 (d, J_{CP} = 81, NCH_2P), 60.0 (d, *J* = 14, NCH), 126.7 (CH_{ar}), 126.8 (CH_{ar}), 127.2 (CH_{ar}), 128.5 (d, J_{CP} = 11.5, CH_{ar}), 128.6 (d, J_{CP} = 11.5, CH_{ar}), 131.0 (d, J_{CP} = 9.5, CH_{ar}), 131.3 (d, J_{CP} = 9, CH_{ar}), 131.6 (d, J_{CP} = 98, C_{ar}), 131.9 (d, J_{CP} = 3, CH_{ar}), 132.2 (d, J_{CP} = 98, C_{ar}), 144.4. ^{31}P NMR ($CDCl_3$) δ (ppm): 30.1.

(1*R*)-*N*-Diphenylphosphinoylmethyl-*N*-methyl-*N*-phenylethylamine 12

To a solution of the phosphorylated amine **11** (4 g, 12 mmol) in 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 room temperature. 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 crude product was purified by flash chromatography on silica gel using acetone–PE (75 : 25) as eluent to yield amine **12** which was finally purified by recrystallization from hexane–toluene, white crystals (3.54 g, 85%). Mp 113–114 °C (lit.[24] 114–117 °C); $[\alpha]_D^{20}$ = +10.5 (*c* 1.6, $CHCl_3$), $[\alpha]_D^{20}$ = +49.3 (*c* 1.0, MeOH) {lit.[24] $[\alpha]_D^{22}$ = +49.9 (*c* 1.0, MeOH)}. IR ν_{max} (KBr)/cm^{-1} 1174 (P=O); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.28 (3 H, d, *J* = 6.8), 2.44 (3 H, s, NCH_3), 3.22 (1 H, dd, *J* = 15.0, 6.1, NCH_2P), 3.31 (1 H, dd, *J* = 15.0, 6.5, NCH_2P), 3.69 (1 H, q, *J* = 6.8), 7.09–7.25 (5 H, m, H_{ar}), 7.34–7.56 (6 H, m, H_{ar}), 7.58–7.73 (4 H, m, H_{ar}). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.9 (CH_3), 40.5 (d, J_{CP} = 2, NCH_3), 54.1 (d, *J* = 89, NCH_2P), 64.7 (d, *J* = 12, NCH), 127.3 (CH_{ar}), 127.6 (CH_{ar}), 128.4 (CH_{ar}), 128.7 (d, J_{CP} = 11.5, CH_{ar}),

128.8 (d, J_{CP} = 11.5, CH_{ar}), 131.4 (d, J_{CP} = 9, CH_{ar}), 131.5 (d, J_{CP} = 8.5, CH_{ar}), 132.0 (d, J_{CP} = 3, CH_{ar}), 132.3 (d, J_{CP} = 97, C_{ar}), 132.4 (d, J_{CP} = 98, C_{ar}), 142.9 (C_{ar}). ^{31}P NMR ($CDCl_3$) δ (ppm): 29.6.

2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)-1,3-dioxane 7

To a solution of bromoaldehyde **6** (14.5 g, 45 mmol) in toluene (100 mL) was added 1,3-propanediol (7.6 g, 100 mL) and *p*-TsOH (135 mg). The mixture was refluxed for 3 h and the water formed removed by azeotropic distillation using a Dean–Stark apparatus. The solvent was removed and the crude product was dissolved in CH_2Cl_2 (50 mL). The organic layer was washed successively with a saturated sodium hydrogen carbonate solution (40 mL) and brine (30 mL) and finally dried over $MgSO_4$. Evaporation of the solvent afforded **7** as a white solid which was recrystallized from hexane–toluene (14.5 g, 85%). Mp 115–116 °C (Found: C, 57.2; H, 5.2. $C_{18}H_{19}BrO_4$ requires C, 57.0; H, 5.05%). IR ν_{max} (KBr)/cm^{-1} 2854 (O*CH*O); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.43 (1 H, m, H_{acetal}), 2.31–2.50 (1 H, m, H_{acetal}), 3.83 (3 H, s, OCH_3), 4.00 (2 H, m, H_{acetal}), 4.25 (2 H, m, H_{acetal}), 5.11 (2 H, s, OCH_2Ph), 5.68 (1 H, s, OCHO), 7.00 (1 H, s, H_{ar}), 7.25–7.47 (6 H, m, H_{ar}). ^{13}C NMR ($CDCl_3$) δ (ppm): 25.7 (CH_2), 56.2 (OCH_3), 67.6 (OCH_2), 71.1 (OCH_2Ph), 100.9 (OCHO), 112.6 (CH_{ar}), 113.0 (C_{ar}), 115.6 (CH_{ar}), 127.8 (CH_{ar}), 128.0 (CH_{ar}), 128.5 (CH_{ar}), 129.8 (C_{ar}), 136.6 (C_{ar}), 147.9 (OC_{ar}), 150.5 (OC_{ar}).

2-[5-Benzyloxy-2-(4-benzyloxyphenylhydroxymethyl)-4-methoxy]-1,3-dioxane 9

A solution of t-BuLi (1.7 M in hexanes, 2.3 mL, 3.96 mmol) was added dropwise over a period of 10 min to a stirred solution of acetal **7** (1 g, 2.64 mmol) in anhydrous THF (25 mL) at −85 °C under Ar. The solution was stirred for 15 min at this temperature after which a solution of 4-benzyloxybenzaldehyde **8** (0.56 g, 2.12 mmol) in THF (5 mL) was added. The solution was stirred for 5 min at −85 °C and was allowed to warm to rt within 1 h. After this, water (10 mL), AcOEt (30 mL) were subsequently added. The organic layer was separated, rinsed with brine, dried ($MgSO_4$) and concentrated to dryness. Purification by flash column chromatography on silica gel using AE–PE (50 : 50) as eluent afforded alcohol **9**, oil (1.08 g, 80%) (Found: C, 74.8; H, 6.6. $C_{32}H_{32}O_6$ requires C, 75.0; H, 6.3%). IR ν_{max} (KBr)/cm^{-1} 3474 (OH), 2853 (O*CH*O); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.40 (1 H, m, H_{acetal}), 2.16–2.25 (1 H, m, H_{acetal}), 3.42 (1 H, d, J = 3.9, OH), 3.73 (3 H, s, OCH_3), 3.81–3.93 (2 H, m, H_{acetal}), 4.22 (2 H, m, H_{acetal}), 5.03 (2 H, s, OCH_2Ph), 5.08 (2 H, s, OCH_2Ph), 5.49 (1 H, s, OCHO), 6.16 (1 H, d, J = 3.9, ArCHAr), 6.74 (1 H, s, H_{ar}), 6.92 (2 H, d, J = 8.7, H_{ar}), 7.31–7.47 (13 H, m, H_{ar}). ^{13}C NMR ($CDCl_3$) δ (ppm): 25.5 (CH_2), 56.0 (OCH_3), 67.4 (OCH_2), 70.0 (ArCHAr), 71.1 (OCH_2Ph), 71.7 (OCH_2Ph), 100.3 (OCHO), 112.2 (CH_{ar}), 112.5 (CH_{ar}), 114.6 (CH_{ar}), 127.5 (CH_{ar}), 127.6 (CH_{ar}), 127.7 (C_{ar}), 127.9 (CH_{ar}), 127.95 (CH_{ar}), 128.5 (CH_{ar}), 128.6 (CH_{ar}), 135.4 (C_{ar}), 135.6 (C_{ar}), 137.1 (C_{ar}), 147.4 (OC_{ar}), 149.7 (OC_{ar}), 157.8 (OC_{ar}).

4,4′-Dibenzyloxy-6-(1,3-dioxanyl)-3-methoxybenzophenone 4

To a solution of alcohol **9** (1.27 g, 2.5 mmol) in CH_2Cl_2 (25 mL) was added pyridinium dichromate (PDC, 1.41 g, 3.75 mmol) and the reaction mixture was stirred under Ar for 3 h. Anhydrous Et_2O (50 mL) was added, the mixture was filtered on Celite and the filtrate washed with saturated aqueous sodium hydrogen carbonate solution (20 mL). The organic layer was dried (Na_2SO_4) and the residue obtained after removal of the solvent was purified by flash column chromatography using AE–PE (40 : 60) as eluent to afford ketone **4** which was recrystallized from hexane–toluene, white crystals (1.02 g, 81%). Mp 106–107 °C (Found: C, 75.3; H, 5.7. $C_{32}H_{30}O_6$ requires C, 75.3; H, 5.9%). IR ν_{max} (KBr)/cm^{-1} 2850 (O*CH*O), 1646 (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.31 (1 H, m, H_{acetal}), 2.02–2.13 (1 H, m, H_{acetal}), 3.71 (2 H, m, H_{acetal}), 3.82 (3 H, s, OCH_3), 4.07 (2 H, m, H_{acetal}), 5.13 (2 H, s, OCH_2Ph), 5.20 (2 H, s, OCH_2Ph), 5.59 (1 H, s, OCHO), 6.87 (1 H, s, H_{ar}), 7.01 (2 H, d, J = 8.6, H_{ar}), 7.33–7.49 (11 H, m, H_{ar}), 7.78 (2 H, d, J = 8.6, H_{ar}). ^{13}C NMR ($CDCl_3$) δ (ppm): 25.6 (CH_2), 56.2 (OCH_3), 67.3 (OCH_2), 70.2 (OCH_2Ph), 70.9 (OCH_2Ph), 98.7 (OCHO), 111.1 (CH_{ar}), 112.2 (CH_{ar}), 114.4 (2 CH_{ar}), 127.6 (CH_{ar}), 127.8 (CH_{ar}), 128.1 (CH_{ar}), 128.3 (CH_{ar}), 128.6 (CH_{ar}), 128.7 (CH_{ar}), 130.9 (C_{ar}), 131.0 (C_{ar}), 131.3 (C_{ar}), 132.4 (CH_{ar}), 136.2 (C_{ar}), 136.6 (C_{ar}), 148.7 (OC_{ar}), 149.8 (OC_{ar}), 162.6 (OC_{ar}), 195.7 (CO).

Synthesis of the diarylenamine 3

In an atmosphere of dry Ar, a solution of n-BuLi (1.6 M in hexanes, 1.35 mL, 2.16 mmol) was added dropwise to a solution of the phosphorylated amine **12** (0.68 g, 1.96 mmol) in THF (50 mL) at −15 °C with stirring. The orange solution was stirred for an additional 15 min and a solution of ketone **4** (0.5 g, 0.98 mmol) in THF (5 mL) was then slowly added. After stirring at −15 °C for 5 min, the reaction mixture was allowed to come to rt over 30 min and further stirred for 2 h. Aqueous 10% NH_4Cl (10 mL) and Et_2O (50 mL) were added and the organic layer separated, rinsed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness. The crude product was analysed by ^{1}H NMR spectroscopy in order to determine the stereochemistry of the exclusively formed isomer. (*E*)-Diarylenamine **3** obtained almost quantitatively was used directly in the following reduction step.

General procedure for reduction of diarylenamine 3 to amines (1*R*,1′*R*)-2 and (1*S*,1′*R*)-2

To a solution of diarylenamine **3** (0.63 g, 0.98 mmol) in a saturated solution of MeOH–HCl (20 mL) at −35 °C was added sodium cyanoborohydride (5 equiv., 308 mg, 4.9 mmol). The mixture was stirred at −35 °C for 2 h. Water (20 mL) and saturated sodium hydrogen carbonate solution (20 mL) were successively added and the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent furnished an oily product corresponding to a mixture of two diastereomers (1*R*,1′*R*)-**13** and (1*S*,1′*R*)-**13** (yield 75%, de 25%, Table 1, entry 3) which were purified by flash column chromatography using AE–PE (50 : 50) as eluent.

The mixture of (1*R*,1′*R*)-**13** and (1*S*,1′*R*)-**13** (1 g, 1.5 mmol) was dissolved in toluene (100 mL) and *p*-TsOH (10 mg) and water (3 mL) were added. The reaction mixture was refluxed for 4 h. After evaporation of the solvent, the crude product was purified by flash column chromatography using AE–PE (50 : 50) as eluent to yield (1*R*,1′*R*)-**2** and (1*S*,1′*R*)-**2** as a colourless oil. The mixture of diastereomers was finally separated by chiral HPLC using a preparative Chiralcel OD column (internal diameter: 50 mm; column length: 350 mm) with ethanol–heptane (HPLC grade, 35 : 65) as eluent. In a representative run 200 mg of material was separated and this protocol was repeated 5 times.

(1*R*,1′*R*)-5-Benzyloxy-2-{1-(4-benzyloxyphenyl)-2-[methyl-(1′-phenylethyl)amino]ethyl}-4-methoxybenzaldehyde 2

First product separated by HPLC, t_1 = 8.32 min. Oil (Found: C, 79.9; H, 6.8; N, 2.7. $C_{39}H_{39}NO_4$ requires C, 80.0; H, 6.7; N 2.4%); $[a]_D^{22}$ = +53.1 (*c* 1.05, $CHCl_3$). IR ν_{max} (KBr)/cm^{-1} 2862 (*CH*O), 1670 (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.42 (3 H, d, J = 6.6, CH_3), 2.24 (3 H, s, NCH_3), 2.80 (1 H, dd, J = 12.6, 5.5), 3.32 (1 H, dd, J = 12.6, 9.7), 3.56 (1 H, q, J = 6.6), 3.70 (3 H, s, OCH_3), 5.06 (2 H, s, OCH_2Ph), 5.11–5.19 (3 H, m, OCH_2Ph + CH), 6.52 (1 H, s, H_{ar}), 6.89 (2 H, d, J = 8.7, H_{ar}), 7.23–7.47

(18 H, m, H_{ar}), 10.22 (1 H, s, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 17.7 (CH_3), 38.7 (NCH_3), 40.7 (ArCHAr), 55.8 (OCH_3), 60.0 (NCH_2), 64.0 (NCH), 70.0 (OCH_2Ph), 70.9 (OCH_2Ph), 111.4 (CH_{ar}), 113.4 (CH_{ar}), 114.8 (CH_{ar}), 126.7 (CH_{ar}), 127.3 (C_{ar}), 127.5 (CH_{ar}), 127.6 (CH_{ar}), 127.7 (CH_{ar}), 127.9 (CH_{ar}), 128.0 (CH_{ar}), 128.5 (CH_{ar}), 128.6 (CH_{ar}), 129.3 (CH_{ar}), 135.3 (C_{ar}), 136.6 (C_{ar}), 137.0 (C_{ar}), 142.1 (C_{ar}), 143.7 (C_{ar}), 146.6 (OC_{ar}), 154.1 (OC_{ar}), 157.3 (OC_{ar}), 190.0 (CHO).

(1*S*,1′*R*)-5-Benzyloxy-2-{1-(4-benzyloxyphenyl)-2-[methyl-(1′-phenylethyl)amino]ethyl}-4-methoxybenzaldehyde 2

Second product separated by HPLC, t_2 = 16.35 min. Oil (Found: C, 80.2; H, 6.8; N, 2.6. $C_{39}H_{39}NO_4$ requires C, 80.0; H, 6.7; N 2.4%); $[\alpha]_D^{22} = -25.4$ (*c* 1.18, $CHCl_3$). IR ν_{max} (KBr)/cm^{-1} 2857 (*CH*O), 1675 (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm): 1.43 (3 H, d, *J* = 6.7, CH_3), 2.24 (3 H, s, NCH_3), 2.90–2.99 (2 H, m), 3.64 (1 H, q, *J* = 6.7), 3.77 (3 H, s, OCH_3), 5.04 (2 H, s, OCH_2Ph), 5.10–5.17 (3 H, m, OCH_2Ph + CH), 6.65 (1 H, d, H_{ar}), 6.92 (2 H, d, *J* = 8.7, H_{ar}), 7.08–7.52 (18 H, m, H_{ar}), 10.24 (1 H, s, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 16.1 (CH_3), 38.7 (NCH_3), 41.1 (ArCHAr), 55.9 (OCH_3), 59.4 (NCH_2), 63.4 (NCH), 70.0 (OCH_2Ph), 70.9 (OCH_2Ph), 111.5 (CH_{ar}), 113.8 (CH_{ar}), 114.8 (CH_{ar}), 126.5 (CH_{ar}), 127.3 (C_{ar}), 127.4 (CH_{ar}), 127.5 (CH_{ar}), 127.6 (CH_{ar}), 127.8 (CH_{ar}), 128.1 (CH_{ar}), 128.6 (CH_{ar}), 128.7 (CH_{ar}), 128.8 (CH_{ar}), 129.4 (CH_{ar}), 135.4 (CH_{ar}), 136.6 (CH_{ar}), 137.0 (CH_{ar}), 141.8 (CH_{ar}), 143.5 (CH_{ar}), 146.7 (OC_{ar}), 154.1 (OC_{ar}), 157.1 (OC_{ar}), 190.0 (CHO).

General procedure for the synthesis of amino alcohols (*R*)-14 and (*S*)-14

To a solution of diastereopure amine (1*R*,1′*R*)-**2** (300 mg, 0.51 mmol) or (1*S*,1′*R*)-**2** (400 mg, 0.68 mmol) in MeOH (10 mL) was added activated Pd/C (10%, 5 mg). Hydrogen was introduced and the reaction mixture was stirred for 24 h at room temperature, filtered through Celite and the solvent removed under reduced pressure. The crude product was purified by recrystallization from methanol.

(4*R*)-5-Hydroxymethyl-4-[1-(4-hydroxyphenyl)-2-methylamino-ethyl]-2-methoxyphenol 14

White crystals (130 mg, 84%). Mp 165–166 °C (Found: C, 67.3; H, 6.9; N, 4.5. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N 4.6%); $[\alpha]_D^{22}$ = +43.6 (*c* 0.25, MeOH). IR ν_{max} (KBr)/cm^{-1} 3250 (br, OH, NH); ^{1}H NMR (DMSO) δ (ppm): 2.24 (3 H, s, NCH_3), 2.38 (1 H, dd, *J* = 11.2, 7.3), 2.75 (1 H, dd, *J* = 11.2, 5.3), 3.39 (2 H, m, CH_2OH), 3.51 (3 H, s, OCH_3), 3.92–3.96 (1 H, m, ArCHAr), 6.24 (1 H, s, H_{ar}), 6.48 (1 H, s, H_{ar}), 6.65 (2 H, d, *J* = 8.5, H_{ar}), 6.95 (2 H, d, *J* = 8.5, H_{ar}). ^{13}C NMR (DMSO) δ (ppm): 43.7 (NCH_3), 45.6 (ArCHAr), 55.5 (OCH_3), 57.3 (OCH_2), 61.6 (NCH_2), 112.5 (CH_{ar}), 112.6 (CH_{ar}), 114.8 (CH_{ar}), 127.5 (C_{ar}), 127.7 (C_{ar}), 129.5 (CH_{ar}), 135.6 (C_{ar}), 144.8 (OC_{ar}), 146.1 (OC_{ar}), 155.6 (OC_{ar}).

(4*S*)-5-Hydroxymethyl-4-[1-(4-hydroxyphenyl)-2-methylamino-ethyl]-2-methoxyphenol 14

White crystals (166 mg, 80%). Mp 164–165 °C (Found: C, 67.4; H, 7.1; N, 4.5. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N 4.6%); $[\alpha]_D^{20} = -43.1$ (*c* 0.22, MeOH).

General procedure for the synthesis of the target (*R*)-cherylline and (*S*)-cherylline 1

To a solution of amino alcohol (4*R*)-**14** (100 mg, 0.33 mmol) or (4*S*)-**14** (150 mg, 0.49 mmol) in a mixture of MeOH–toluene (1 : 9, 10 mL) was added *p*-TsOH (10 mg). The reaction mixture was refluxed over a period of 9 h and the water formed removed by azeotropic distillation using a Dean–Stark apparatus. The end of the reaction was controlled by TLC and the solvent was removed under reduced pressure. The crude product was finally purified by recrystallization from EtOH.

(4*R*)-4-(4-Hydroxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol 1

White crystals (80 mg, 85%). Mp 213–214 °C (Found: C, 71.4; H, 6.9; N, 5.0. $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.7; N 4.9%); $[\alpha]_D^{22} = +70.2$ (*c* 0.2, MeOH). IR ν_{max} (KBr)/cm^{-1} 3331 (OH); ^{1}H NMR (CD_3OD) δ (ppm): 2.40 (3 H, s, NCH_3), 2.40 (1 H, m), 3.04 (1 H, m), 3.42 (1 H, d, *J* = 14.0), 3.58 (3 H, s, OCH_3), 3.68 (1 H, d, *J* = 14.0), 4.12 (1 H, m, ArCHAr), 6.32 (1 H, s, H_{ar}), 6.56 (1 H, s, H_{ar}), 6.74 (2 H, m, H_{ar}), 7.01 (2 H, m, H_{ar}). ^{13}C NMR (CD_3OD) δ (ppm): 45.5 (NCH_3), 45.6 (ArCHAr), 56.3 (OCH_3), 58.4 (NCH_2), 63.0 (NCH_2), 113.0 (CH_{ar}), 113.5 (CH_{ar}), 116.3 (CH_{ar}), 127.5 (C_{ar}), 129.4 (C_{ar}), 131.0 (CH_{ar}), 135.8 (C_{ar}), 146.3 (OC_{ar}), 148.2 (OC_{ar}), 157.3 (OC_{ar}).

(4*S*)-4-(4-Hydroxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol 1

White crystals (127 mg, 90%). Mp 214–215 °C (lit.,[16] 217–218 °C; lit.,[25] 210–213 °C); $[\alpha]_D^{22} = -70.3$ (*c* 0.2, MeOH) {lit.,[16] $[\alpha]_D^{21} = -70$ (*c* 0.1, MeOH); lit.,[25] $[\alpha]_D^{20} = -70.6$ (*c* 0.24, MeOH)}.

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