Synthesis of chiral and achiral analogues of ambroxol *via* palladium-catalysed reactions

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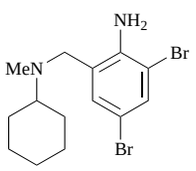
Chiral *cis*- and *trans*-4-aminocyclohex-2-enols and achiral 4-aminocyclohexanols, which all are analogues of ambroxol, are prepared *via* stereoselective allylic substitution of cyclohex-2-ene-1,4-diol derivatives or 1-acetoxy-4-chlorocyclohex-2-ene. The chiral target molecules are obtained in enantiomerically pure form by employing a previously described enantiodivergent synthesis of *cis*- and *trans*-4-aminocyclohex-2-enols. It has been found that bis(amine) nucleophiles 7a and 7b react only at the benzylic amino group under the conditions employed.

Introduction

Bromhexine **1** and its active metabolite ambroxol (*trans*-**2b**) have been used clinically for various respiratory problems.[1,2]



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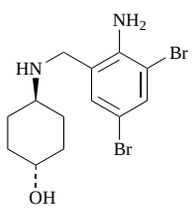


trans-**2b**

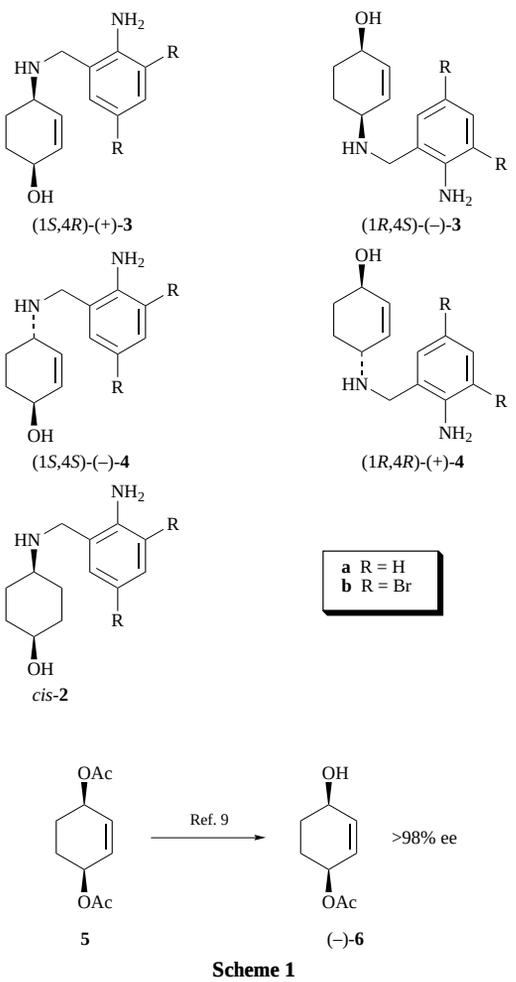
Ambroxol has been shown to be effective in ameliorating respiratory symptoms associated with cystic fibrosis, silicosis, chronic bronchitis and other pulmonary disorders.[1] It has also been shown to exhibit anti-inflammatory properties.[2] However, to the best of our knowledge, the mechanism of its pharmacological effect is still not known. For the purpose of some further investigation of this problem, some optically active, as well as achiral analogues of these compounds were prepared for further pharmacological evaluation.[3]

In general 1,4-amino alcohols are common structural elements in a number of biologically active compounds.[4,5] For example, some carbocyclic nucleosides[4] possess antiviral and antitumour activity. A group of antibacterial agents are valienamine and analogues.[5]

We recently reported methodology for the enantiodivergent synthesis of *cis*- and *trans*-4-aminocyclohex-2-enols using (1*R*,4*S*)-(−)-*cis*-4-acetoxycyclohex-2-enol (−)-**6** as the enantiopure precursor.[6,7] Herein we report on the application of this methodology to the synthesis of some analogues of ambroxol.

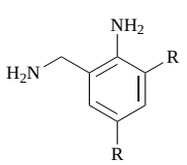
Results and discussion

Ambroxol (*trans*-**2b**) as well as its analogues *trans*-**2a**, *cis*-**2**, **3** and **4** were the target molecules for this study. The procedure is based upon the previously described desymmetrisation[6,8,9] of 1,4-diacetoxycyclohex-2-ene[10] **5** to (1*R*,4*S*)-(−)-*cis*-4-acetoxycyclohex-2-enol (−)-**6** (Scheme 1) followed by selective palladium-catalysed allylic nucleophilic substitution.[6,8] With its two differentiated allylic sites, (−)-**6** is a suitable precursor for further functionalisation. Manipulation of the relative reactivity of the two allylic oxygen moieties towards palladium(0)-catalysed allylic amination allows for the synthesis of all four possible stereoisomers of 4-aminocyclohex-2-enol.



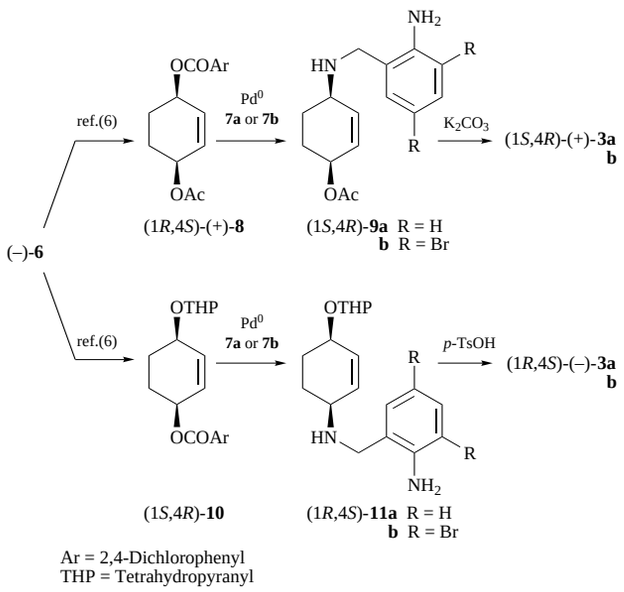
Scheme 1

The leaving groups employed in the allylic substrates were 2,4-dichlorobenzoate and chloride. The amines used for the preparation of the ambroxol analogues were 2-aminobenzylamine **7a** and 2-amino-3,5-dibromobenzylamine **7b**.

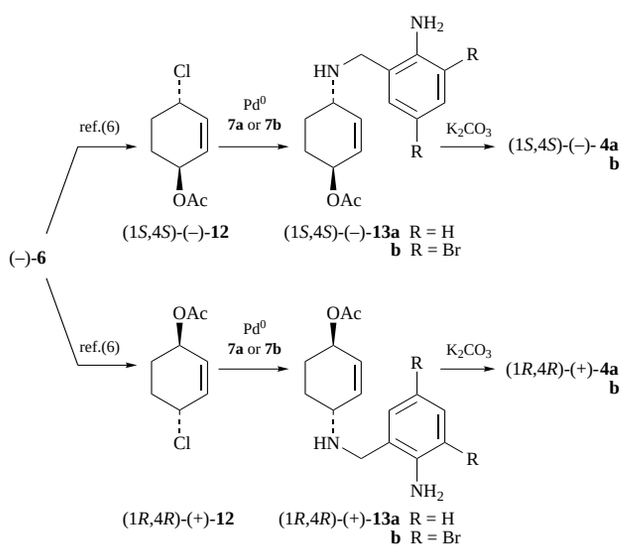


7a R = H
7b R = Br

These amine nucleophiles contain two amine functionalities, one benzylic and one aromatic primary amine. For an efficient synthesis a selective reaction of the benzylic amine site without prior protection of the aromatic amine was desirable. We found that with 1–3 equiv. of **7a** or **7b** and 5 mol% of Pd-catalyst the allylic substrates **8**, **10** and **12** afforded the desired amino alcohol derivatives with 99% selectivity. The synthesis of the target molecules (1*S*,4*R*)-**3**, (1*R*,4*S*)-**3**, (1*S*,4*S*)-**4** and (1*R*,4*R*)-**4** from (−)-**6** are summarised in Schemes 2 and 3.



Scheme 2 Synthesis of the *cis* enantiomers

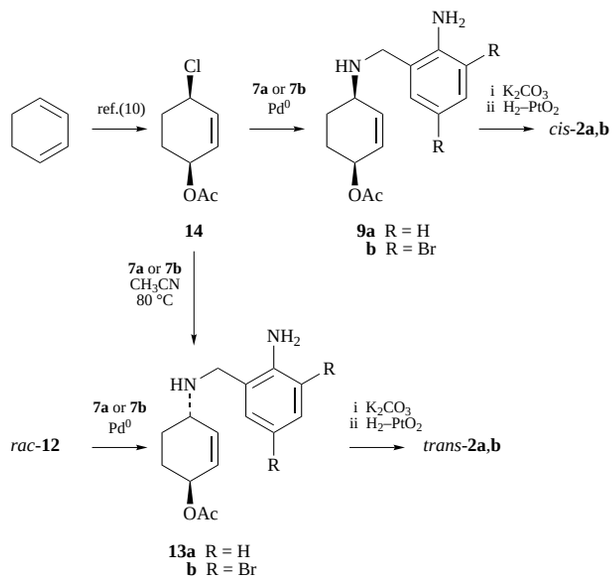


Scheme 3 Synthesis of the *trans* enantiomers

The allylic substrates **8** and **10** obtained according to reference 6 were allowed to react with the appropriate 2-aminobenzylamine (**7a** or **7b**) in the presence of the palladium catalyst [$Pd(dba)_2$ and PPh_3]. After hydrolysis or deprotection the target amines **3a** and **3b** were obtained in enantiomerically pure form (ee ⩾ 98%).

The corresponding *trans* isomers were prepared in an analogous palladium-catalysed amination of *trans*-chloroacetates (1*S*,4*S*)-**12** and (1*R*,4*R*)-**12** employing amines **7a** and **7b**. These chloroacetates were obtained in enantiomerically pure form as described earlier.[6] Subsequent hydrolysis of **13a** or **13b** gave in each case the enantiomerically pure target molecules **4a** and **4b**. The enantiomeric purity of the products was in each case determined by ^{1}H NMR spectroscopy utilising the magnetic non-equivalence in the diastereomeric salt formed with the amine and (*S*)-(+)-mandelic acid.

For the synthesis of achiral compounds *cis*-**2** and *trans*-**2** a more expedient route *via* the chloroacetate **14** was chosen. The latter compound is readily obtained from cyclohexa-1,3-diene.[11] A number of *cis*- and *trans*-1,4-disubstituted cyclohex-2-enes are accessible by stereoselective substitution of the allylic leaving groups in **14**.[11,12] A palladium catalysed reaction of **14** with amines **7a** or **7b** afforded the *cis* isomers **9a** and **9b**, respectively (Scheme 4). The corresponding non-catalysed substitution gave



Scheme 4 Synthesis of the achiral analogues *cis*-**2** and *trans*-**2**

the *trans* isomers **13a** and **13b**. The latter S_N2 reaction was slow and gave at best 37% of **13** (>96% *trans*) in CH_3CN at 80 °C. A prolonged reaction time gave a higher yield but with lower stereoselectivity. Compound **13** was therefore prepared from racemic **12** using the same pathway as in Scheme 3. Subsequent hydrolysis and hydrogenation of **9** and **13** afforded the target amino alcohols *cis*-**2** and *trans*-**2**, respectively.

Conclusion

Ambroxol analogues have been synthesised *via* palladium(0)-catalysed allylic amination. With this method unsaturated analogues **3** and **4** were obtained in enantiomerically pure form. Also saturated achiral analogues *trans*-**2a**, *cis*-**2** and ambroxol itself (*trans*-**2b**) were prepared employing this methodology.

Experimental

^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at 300 or 400 and 75.4 or 100.6 MHz, respectively. Chemical shifts are reported in ppm with $CDCl_3$ as the internal standard (7.26 for ^{1}H and 77.0 ppm for ^{13}C), and coupling constants (*J*) are given in Hz. Assignments of the NMR signals were done using ^{1}H-homodecoupling, COSY, NOESY, selective INEPT and HETCOR experiments. Mass spectra were recorded with pneumatically assisted electrospray mass spectrometry (ES–MS) on a Micromass VG Platform apparatus using a direct inlet of a solution in methanol or *via* separation on an LC-column (Kromasil C18 100 × 4.6 mm, acetonitrile–water gradient with 5 mM trifluoroacetic acid). Optical rotations (given in units of 10^{-1} deg cm^2 g^{-1}) were measured at 25.0 °C on a Perkin-Elmer 241 polarimeter and concentrations are expressed as g per 100 ml in spectroscopically pure ethanol or methylene chloride. Bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] was prepared according to literature procedures.[13] THF was

distilled under nitrogen from sodium benzophenone ketyl. Triethylamine was distilled from KOH and stored over KOH under nitrogen until used. Thin layer chromatography (TLC) was run on Merck precoated silica gel 60 F_{254} plates. All reactions were carried out in oven dried glassware and the Pd^0-catalysed reactions also under an argon or nitrogen atmosphere. The progress of reactions was followed by TLC until judged complete for all reactions. For flash chromatography Merck Kieselgel 60 (230–400 mesh) was used. Enantiomeric excess (ee) of the amines was checked with ^{1}H NMR spectroscopy in $CDCl_3$ by salt formation with optically pure (*S*)-(+)-mandelic acid. Normally about 10 mg of the amine was mixed with 1–2 equiv. of mandelic acid in 0.7 ml of solvent which gave excellent separation of the diastereomeric salts. (Using more material causes solubility problems which can be helped with a few drops of CD_3OD, as long as the same conditions are used for the sample as for the reference/racemate.)

(±)-*cis*-1-Acetoxy-4-(2-aminobenzylamino)cyclohex-2-ene 9a

To a solution that had been stirred at room temp. for 20 min containing $Pd(dba)_2$ (86 mg, 0.15 mmol), PPh_3 (113 mg, 0.43 mmol), 2-aminobenzylamine (420 mg, 3.43 mmol) and Et_3N (1.04 g, 10.3 mmol) in THF (15 ml) was added *cis*-chloroacetate **14** (500 mg, 2.86 mmol) in THF (10 ml). The reaction mixture was stirred at room temp. for 40 h. The solvent was evaporated and the residue was dissolved in diethyl ether (20 ml) and extracted with 1 M aq. HCl (3 × 50 ml). To the aqueous phase was added fresh diethyl ether (80 ml) and the pH was adjusted to >10 with K_2CO_3 and KOH under stirring. The organic phase was collected and the aqueous phase was further extracted with diethyl ether (50 ml). The combined ethereal extracts were dried (K_2CO_3) and concentrated. The crude product was purified on silica (ethyl acetate–pentane gradient) to give **9a** (540 mg, 73%). The silica was first conditioned with 2% Et_3N in pentane. δ_H(400 MHz; $CDCl_3$) 1.55–1.68 (1 H, m, CH_2), 1.74–1.95 (3 H, m, CH_2), 2.06 [3 H, s, C(O)CH_3], 3.10–3.19 (1 H, m, CHN), 3.88, 3.91 (2 H, AB-system, J_{AB} 12.5, ArCH_2N), 4.4–5.0 (1 H, br s, NH), 5.16–5.25 (1 H, m, C*H*OAc), 5.80 (1 H, dddd, *J* 10.1, 3.9, 1.9 and 0.7, olefinic CH-2), 6.01 (1 H, ddm, *J* 10.0 and 2.8, olefinic CH-3), 6.68 (1 H, ddm, *J* 7.8 and 1.2, ArH-3), 6.70 (1 H, ddd, *J* 7.4, 7.4 and 1.2, ArH-5), 7.04 (1 H, dm, *J* 7.4, ArH-6), 7.11 (1 H, ddd, *J* 7.8, 7.4 and 1.6, ArH-4); δ_C(75.4 MHz; $CDCl_3$, 15 peaks) 21.3 [C(O)*C*H_3], 25.1 (*C*H_2CHO), 26.0 (*C*H_2CHN), 50.2 (Ar*C*H_2N), 52.0 (CHN), 67.2 (CHO), 115.7 (Ar, CH-3), 117.6 (Ar, CH-5), 123.7 (Ar, C-1), 126.4 (olefinic CH-2), 128.3 (Ar, CH-4), 129.7 (Ar, CH-6), 135.2 (olefinic CH-3), 146.9 [Ar, C(NH_2)-2], 170.6 (C=O); *m/z* 283 ([M + Na]$^+$, 4%), 262 ([M + 2H]$^+$, 15), 261 ([M + H]$^+$, 81), 107 (8), 106 (100).

(1*S*,4*R*)-(−)-*cis*-1-Acetoxy-4-(2-aminobenzylamino)cyclohex-2-ene (1*S*,4*R*)-(−)-9a

This compound was synthesised as for the preparation of (±)-**9a** but with the use of allylic substrate (1*R*,4*S*)-(+)-**8** (251 mg, 0.76 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), PPh_3 (30 mg, 0.12 mmol), 2-aminobenzylamine (112 mg, 0.92 mmol) and Et_3N (303 mg, 3.0 mmol) in THF (6 ml) for 18 h to give 143 mg (72%) of the title compound. Spectral data were in accordance with those for (±)-**9a**; $[\alpha]_D^{25}$ −45 (*c* 2.10 in CH_2Cl_2).

(±)-*cis*-4-(2-Aminobenzylamino)cyclohex-2-enol 3a

Compound (±)-**9a** (400 mg, 1.54 mmol) was stirred with K_2CO_3 (220 mg, 1.60 mmol) in methanol (4 ml) and water (1 ml) at room temp. After 6 h the MeOH was evaporated and the mixture was diluted in diethyl ether (100 ml) and washed with water (10 ml) and brine (10 ml). Drying (K_2CO_3), evaporation and purification on silica (gradient of diethyl ether–pentane 60:40 to ethyl acetate–MeOH 90:10 with 2% Et_3N) gave the title compound (±)-**3a** (322 mg, 96%); δ_H(400 MHz; $CDCl_3$) 1.58–1.69 (1 H, m, CH_2), 1.70–1.88 (3 H, m, CH_2), 3.07–3.14 (1 H, m, CHN), 3.84, 3.89 (2 H, AB-system, J_{AB} 12.5, ArCH_2N), 4.12–4.19 (1 H, m, C*H*OH), 5.81 (1 H, ddd, *J* 10.1, 3.4 and 1.6, olefinic CH-2), 5.87 (1 H, ddm, *J* 10.1 and 2.8, olefinic CH-3), 6.65 (1 H, ddm, *J* 7.8 and 1.2, ArH-3), 6.68 (1 H, ddd, *J* 7.4, 7.4 and 1.2, ArH-5), 7.02 (1 H, ddm, *J* 7.4 and 1.6, ArH-6), 7.09 (1 H, ddd, *J* 7.8, 7.4 and 1.6, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 13 peaks) 24.8 (CH_2), 29.1 (CH_2), 50.2 (Ar*C*H_2N), 52.1 (CHN), 64.9 (CHOH), 115.8 (Ar, CH-3), 117.8 (Ar, CH-5), 123.7 (Ar, C-1), 128.5 (Ar, CH-4), 129.9 (Ar, CH-6), 130.9 (olefinic CH-2), 132.8 (olefinic CH-3), 146.9 [Ar, C(NH_2)-2]; *m/z* 241 ([M + Na]$^+$, 2%), 219 ([M + H]$^+$, 11), 107 (9), 106 (100).

(1*S*,4*R*)-(+)-*cis*-4-(2-Aminobenzylamino)cyclohex-2-enol (1*S*,4*R*)-(+)-3a

This compound was prepared in accordance with (±)-**3a** but with (1*S*,4*R*)-**9a** as the starting material. Yield and spectral data were in accordance with those for (±)-**3a**; $[\alpha]_D^{25}$ +0.9 (*c* 1.26 in EtOH); ee ⩾ 98%.

(1*R*,4*S*)-(−)-*cis*-4-(2-Aminobenzylamino)cyclohex-2-enol (1*R*,4*S*)-(−)-3a

The same procedure as for the preparation of (±)-**9a** was followed, but with the use of allylic substrate (1*S*,4*R*)-**10** (400 mg, 1.08 mmol), $Pd(dba)_2$ (33 mg, 0.05 mmol), PPh_3 (36 mg, 0.14 mmol), 2-aminobenzylamine (132 mg, 1.08 mmol) and Et_3N (244 mg, 2.4 mmol) in THF (10 ml) for 18 h to give (1*R*,4*S*)-**10a** (140 mg, 40%). The THP group in the latter product (140 mg, 0.43 mmol) was removed with toluene-*p*-sulfonic acid (95 mg, 0.50 mmol) in MeOH (5 ml) at room temp. After 12 h the MeOH was evaporated and diethyl ether (100 ml) and 1 M NaOH (10 ml) were added and after extraction the organic phase was washed with water (10 ml) and brine (10 ml). Drying ($MgSO_4$), evaporation and purification on silica (gradient of diethyl ether–pentane 60:40 to ethyl acetate–MeOH 90:10 with 2% Et_3N) gave the title compound (1*R*,4*S*)-**3a** (75 mg, 80%, 32% over two steps). Spectral data were in accordance with those for (±)-**3a**; $[\alpha]_D^{25}$ −1.0 (*c* 0.93 in EtOH); ee ⩾ 98%.

(±)-*cis*-1-Acetoxy-4-(2-amino-3,5-dibromobenzylamino)-cyclohex-2-ene 9b

The procedure for the preparation of (±)-**9a** was followed. Allylic substrate **14** (500 mg, 2.86 mmol) was reacted with $Pd(dba)_2$ (86 mg, 0.15 mmol), PPh_3 (113 mg, 0.43 mmol), 2-amino-3,5-dibromobenzylamine (960 mg, 3.43 mmol) and Et_3N (1.04 g, 10.3 mmol) in THF (25 ml). The reaction mixture was stirred at room temp. for 12 h. Yield: 729 mg (61%); δ_H(400 MHz; $CDCl_3$) 1.20 (1 H, br s, NH), 1.52–1.68 (1 H, m, CH_2), 1.74–1.98 (3 H, m, CH_2), 2.05 (3 H, s, $COCH_3$), 3.03–3.15 (1 H, m, CHN), 3.84, 3.87 (2 H, AB-system, J_{AB} 12.8, ArCH_2N), 5.14–5.27 (1 H, m, C*H*OAc), 5.35 (2 H, br s, ArNH_2), 5.79 (1 H, ddd, *J* 10.1, 3.8 and 1.8, olefinic CH-2), 5.95 (1 H, dd, *J* 10.1 and 2.6, olefinic CH-3), 7.09 (1 H, d, *J* 1.9, ArH-6), 7.48 (1 H, d, *J* 2.0, ArH-4); δ_C(75.4 MHz; $CDCl_3$, 15 peaks) 21.3 [C(O)CH_3], 25.0 (*C*H_2CHN), 25.9 (*C*H_2CHO), 50.1 (Ar*C*H_2N), 51.8 (CHN), 67.0 (CHO), 108.2 [Ar, C(Br)-5], 110.4 [Ar, C(Br)-3], 126.0 (Ar, C-1), 126.9 (olefinic CH-2), 131.4 (Ar, CH-6), 133.3 (Ar, CH-4), 134.6 (olefinic CH-3), 143.9 [Ar, C(NH_2)-2], 170.6 (C=O); *m/z* 422 ([M + 2H]$^+$, 7%), 421 ([M + H]$^+$, 43), 419 ([M + H]$^+$, 100), 417 ([M + H]$^+$, 45), 266 (4), 264 (8), 262 (4), 159 (18), 156 (54), 139 (24), 74 (60), 64 (40).

(1*S*,4*R*)-*cis*-1-Acetoxy-4-(2-amino-3,5-dibromobenzylamino)-cyclohex-2-ene (1*S*,4*R*)-9b

The procedure for the preparation of (±)-**9a** was followed. Allylic substrate (1*R*,4*S*)-**8** (235 mg, 0.71 mmol) was reacted with $Pd(dba)_2$ (21 mg, 0.035 mmol), PPh_3 (28 mg, 0.11 mmol), 2-amino-3,5-dibromobenzylamine·2HBr (376 mg, 0.85 mmol) and Et_3N (804 mg, 7.9 mmol) in THF (6 ml). The reaction mixture was stirred at room temp. for 18 h. Yield: 179 mg (60%). Spectral data were in accordance with those for (±)-**9b**; ee ⩾ 98%.

(±)-*cis*-4-(2-Amino-3,5-dibromobenzylamino)cyclohex-2-enol 3b
Compound (±)-**3b** was prepared in accordance with (±)-**3a** but with (±)-**9b** as the starting material; δ_H(400 MHz; $CDCl_3$) 1.39–1.84 (6 H, m, CH_2, OH, NH), 2.97–3.14 (1 H, m, CHN), 3.81, 3.85 (2 H, AB-system, J_{AB} 12.8, ArCH_2N), 4.08–4.23 (1 H, m, CHO), 5.34 (2 H, br s, ArNH_2), 5.78–5.85 (2 H, m, olefinic), 7.08 (1 H, d, *J* 2.2, ArH-6), 7.47 (1 H, d, *J* 2.2, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 13 peaks) 24.7 (CH_2), 29.0 (CH_2), 50.2 (ArCH_2N), 51.8 (CHN), 64.8 (CHO), 108.3 [Ar, C(Br)-5], 110.4 [Ar, C(Br)-3], 126.2 (Ar, C-1), 131.2 (Ar, CH-6), 131.4 (olefinic), 132.3 (olefinic), 133.3 (Ar, CH-4), 143.9 [Ar, C(NH_2)-2]; *m/z* 380 ([M + 2H]$^+$, 6%), 379 ([M + H]$^+$, 36), 377 ([M + H]$^+$, 70), 375 ([M + H]$^+$, 39), 266 (21), 264 (38), 262 (22), 114 (100).

(1*S*,4*R*)-(+)-*cis*-4-(2-Amino-3,5-dibromobenzylamino)cyclohex-2-enol (1*S*,4*R*)-(+)-3b
Compound (1*S*,4*R*)-(+)-**3b** was prepared in accordance with (±)-**3a** but with (1*S*,4*R*)-**9b** as the starting material. Spectral data were in accordance with those for (±)-**3b**; $[\alpha]_D^{25}$ +4.9 (*c* 1.34 in EtOH); ee ⩾ 98%.

(1*R*,4*S*)-(−)-*cis*-4-(2-Amino-3,5-dibromobenzylamino)cyclohex-2-enol (1*R*,4*S*)-(−)-3b
The same procedure was used as for the preparation of (1*R*,4*S*)-**3a**. Yield: 30% over two steps; $[\alpha]_D^{25}$ −4.6 (*c* 1.03 in EtOH); ee ⩾ 98%.

***cis*-4-(2-Aminobenzylamino)cyclohexanol *cis*-2a**
(±)-*cis*-4-(2-Aminobenzylamino)cyclohex-2-enol (±)-**3a** (200 mg, 0.916 mmol) and PtO_2 (7 mg, 0.031 mmol) were mixed in EtOH (20 ml) under nitrogen. The atmosphere was changed to hydrogen, 1 atm (balloon), and the reaction was stirred at room temp. for 25 min. The mixture was filtered on silica and Celite, the solvent was evaporated and the residue was separated on silica (EtOAc–Et_3N 98 : 2) to give the title compound (334 mg, 81%); δ_H(400 MHz; $CDCl_3$) 1.10–1.80 (10 H, m and br s, 4 × CH_2, OH, NH), 2.56–2.66 (1 H, m, CHN), 3.80 (2 H, s, NHCH_2Ar), 3.81–3.89 (1 H, m, C*H*OH), 6.65 (1 H, dd, *J* 7.8 and 1.2, ArH-3), 6.68 (1 H, ddd, *J* 7.4, 7.4 and 1.2, ArH-5), 7.03 (1 H, ddm, *J* 7.4 and 1.6, ArH-6), 7.08 (1 H, ddd, *J* 7.8, 7.4 and 1.6, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 11 peaks) 27.8 (CH_2-3), 31.1 (CH_2-2), 50.4 (ArCH_2N), 54.1 (CHN), 67.4 (*C*HOH), 115.7 (Ar, CH-3), 117.7 (Ar, CH-5), 124.6 (Ar, C-1), 128.2 (Ar, CH-4), 129.6 (Ar, CH-6), 146.8 [Ar, C(NH_2)-2]; *m/z* 222 ([M + 2H]$^+$, 21%), 221 ([M + H]$^+$, 100), 106 (70), 82 (45).

***cis*-4-(2-Amino-3,5-dibromobenzylamino)cyclohexanol *cis*-2b**
The same procedure as described for the preparation of *cis*-**2a** was used. Compound (±)-**3b** (64 mg, 0.170 mmol) and PtO_2 (1.4 mg, 0.006 mmol) in EtOH (10 ml) was stirred for 1.5 h under 1 atm of H_2 at room temp. to yield the title compound (52 mg, 81%); δ_H(400 MHz; $CDCl_3$) 1.24–1.94 (10 H, m, 4 × CH_2, OH, NH), 2.45–2.66 (1 H, m, CHN), 3.79 (2 H, br s, ArCH_2N), 3.84–3.94 (1 H, m, C*H*OH), 5.30 (2 H, br s, ArNH_2), 7.09 (1 H, d, *J* 2.3, ArH-6), 7.47 (1 H, d, *J* 2.3, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 11 peaks) 27.7 (CH_2-3), 31.1 (CH_2-2), 50.4 (ArCH_2N), 54.1 (CHN), 67.1 (*C*HOH), 108.2 [Ar, C(Br)-5], 110.3 [Ar, C(Br)-3], 126.8 (Ar, C-1), 131.3 (Ar, CH-6), 133.1 (Ar, CH-4), 144.0 [Ar, C(NH_2)-2]; *m/z* 381 ([M + H]$^+$, 40%), 379 ([M + H]$^+$, 80), 377 ([M + H]$^+$, 42), 266 (10), 264 (21), 262 (10), 116 (100).

(±)-*trans*-1-Acetoxy-4-(2-aminobenzylamino)cyclohex-2-ene 13a
The procedure for the preparation of (±)-**9a** was followed. Allylic substrate (±)-**12** (148 mg, 0.85 mmol), $Pd(dba)_2$ (25 mg, 0.04 mmol), PPh_3 (44 mg, 0.17 mmol), LiCl (8.5 mg, 0.20 mmol) and 2-aminobenzylamine (312 mg, 2.55 mmol) in THF (8 ml) were stirred at room temp. for 15 h. Yield: 258 mg (76%); δ_H(400 MHz; $CDCl_3$) 1.41–1.54 (1 H, m, CH_2CHN), 1.54–1.68 (1 H, m, CH_2CHO), 2.05 [3 H, s, C(O)CH_3], 2.02–2.17 (2 H, m, CH_2), 3.19–3.29 (1 H, m, CHN), 3.84, 3.87 (2 H, AB-system, J_{AB} 12.5, ArCH_2N), 5.26–5.35 (1 H, m, C*H*OAc), 5.71 (1 H, ddddm, *J* 10.2, 2.8, 2.1, and 1.0, olefinic CH-2), 5.94 (1 H, ddddm, *J* 10.2, 2.8, 1.7, and 1.0, olefinic CH-3), 6.66 (1 H, dm, *J* 7.8, ArH-3), 6.68 (1 H, ddd, *J* 7.4, 7.4 and 1.2, ArH-5), 7.02 (1 H, ddm, *J* 7.4 and 1.6, ArH-6), 7.09 (1 H, ddd, *J* 7.8, 7.4 and 1.6, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 15 peaks) 21.3 [C(O)*C*H_3], 26.9 (*C*H_2CHO), 27.4 (*C*H_2CHN), 50.0 (Ar*C*H_2N), 52.0 (CHN), 69.0 (CHOH), 115.7 (Ar, CH-3), 117.7 (Ar, CH-5), 123.8 (Ar, C-1), 127.6 (olefinic CH-2), 128.4 (Ar, CH-4), 129.7 (Ar, CH-6), 134.0 (olefinic CH-3), 146.9 [Ar, C(NH_2)-2], 170.6 (C=O); *m/z* 283 ([M + Na]$^+$, 4%), 262 ([M + 2H]$^+$, 9), 261 ([M + H]$^+$, 53), 107 (9), 106 (100).

(1*S*,4*S*)-(−)-*trans*-1-Acetoxy-4-(2-aminobenzylamino)cyclohex-2-ene (1*S*,4*S*)-(−)-13a
The same procedure as for the preparation of (±)-**13a** but with allylic substrate (1*S*,4*S*)-(−)-**12**. Spectral data were in accordance with those for (±)-**13a**; $[\alpha]_D^{25}$ −145 (*c* 1.59 in CH_2Cl_2); ee ⩾ 98%.

(1*R*,4*R*)-(+)-*trans*-1-Acetoxy-4-(2-aminobenzylamino)-cyclohex-2-ene (1*R*,4*R*)-(+)-13a
The same procedure as for the preparation of (±)-**13a** but with allylic substrate (1*R*,4*R*)-(+)-**12**. Spectral data were in accordance with those for (±)-**13a**; $[\alpha]_D^{25}$ +143 (*c* 0.98 in CH_2Cl_2); ee ⩾ 98%.

(±)-*trans*-4-(2-Aminobenzylamino)cyclohex-2-enol 4a
The hydrolysis of the acetate in **13a** was performed as described for **3a**; δ_H(400 MHz; $CDCl_3$) 1.31–1.54 (2 H, m, CH_2), 2.04–2.14 (2 H, m, CH_2), 3.16–3.25 (1 H, m, CHN), 3.83, 3.86 (2 H, AB-system, J_{AB} 12.4, ArCH_2N), 4.19–4.29 (1 H, m, C*H*OH), 5.75 (1 H, dddd, *J* 10.1, 2.4, 2.0 and 1.0, olefinic CH-2), 5.82 (1 H, dddd, *J* 10.1, 2.5, 1.6 and 1.0, olefinic CH-3), 6.65 (1 H, ddd, *J* 7.8, 1.2 and 0.4, ArH-3), 6.69 (1 H, ddd, *J* 7.4, 7.4 and 1.2, ArH-5), 7.02 (1 H, ddm, *J* 7.4 and 1.6, ArH-6), 7.09 (1 H, ddd, *J* 7.8, 7.4 and 1.6, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 13 peaks) 27.9 (CH_2), 31.1 (CH_2), 49.9 (Ar*C*H_2N), 52.5 (CHN), 66.6 (*C*HOH), 115.8 (Ar, CH-3), 117.8 (Ar, CH-5), 123.9 (Ar, C-1), 128.3 (Ar, CH-4), 129.7 (Ar, CH-6), 131.9 (olefinic CH-2), 132.0 (olefinic CH-3), 146.8 [Ar, C(NH_2)-2]; *m/z* 220 ([M + 2H]$^+$, 9%), 219 ([M + H]$^+$, 57), 107 (9), 106 (100).

(1*S*,4*S*)-(−)-*trans*-4-(2-Aminobenzylamino)cyclohex-2-enol (1*S*,4*S*)-(−)-4a
See preparation of (±)-**4a**. Spectral data were in accordance with those for (±)-**4a**; $[\alpha]_D^{25}$ −108 (*c* 1.34 in EtOH); ee ⩾ 98%.

(1*R*,4*R*)-(+)-*trans*-4-(2-Aminobenzylamino)cyclohex-2-enol (1*R*,4*R*)-(+)-4a
See preparation of (±)-**4a**. Spectral data were in accordance with those for (±)-**4a**; $[\alpha]_D^{25}$ +110 (*c* 1.83 in EtOH); ee ⩾ 98%.

(±)-*trans*-1-Acetoxy-4-(2-amino-3,5-dibromobenzylamino)-cyclohex-2-ene 13b
The procedure described for the preparation of (±)-**9a** was followed. Allylic substrate (±)-**12** (173 mg, 0.99 mmol) was reacted with $Pd(dba)_2$ (30 mg, 0.05 mmol), PPh_3 (53 mg, 0.20 mmol), LiCl (10 mg, 0.25 mmol) and 2-amino-3,5-dibromobenzylamine (786 mg, 2.81 mmol) in THF (10 ml). The reaction mixture was stirred at room temp. for 15 h. Yield: 284 mg (69%); δ_H(400 MHz; $CDCl_3$) 1.05 (1 H, br s, NH), 1.33–1.46 (1 H, m, CH_2CN), 1.47–1.63 (1 H, m, CH_2CO), 2.05 [3 H, s, C(O)CH_3], 2.00–2.20 (2 H, m, CH_2), 3.10–3.22 (1 H, m, CHN), 3.82, 3.85 (2 H, AB-system, J_{AB} 12.8, ArCH_2N), 5.22–5.42 (3 H, m and overlapping br s, C*H*OAc, ArNH_2), 5.68 (1 H, dddd, *J* 10.2, 2.8, 2.1 and 0.9, olefinic CHCO), 5.85 (1 H, dddd, *J* 10.2, 2.7, 1.7 and 0.9, olefinic CHCN), 7.04 (1 H, d, *J* 2.3, ArH-6), 7.42 (1 H, d, *J* 2.3, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 15 peaks) 21.3 [C(O)*C*H_3], 26.8 (*C*H_2CHO), 27.3 (*C*H_2CHN), 50.0 (Ar*C*H_2N),

51.8 (CHN), 68.8 (CHO), 108.2 [Ar, C(Br)-5], 110.4 [Ar, C(Br)-3], 126.0 (Ar, C-1), 128.2 (olefinic CH-2), 131.4 (Ar, CH-6), 133.3 (Ar, CH-4), 133.4 (olefinic CH-3), 143.9 [Ar, C(NH_2)-2], 170.6 (C=O); *m/z* 422 ([M + 2H]$^+$, 10%), 421 ([M + H]$^+$, 51), 419 ([M + H]$^+$, 100), 417 ([M + H]$^+$, 52), 266 (20), 264 (38), 262 (20), 156 (13), 139 (58), 96 (11), 64 (5).

(1*S*,4*S*)-(−)-*trans*-1-Acetoxy-4-(2-amino-3,5-dibromobenzylamino)cyclohex-2-ene (1*S*,4*S*)-(−)-13b

The same procedure was followed as for the preparation of (±)-**13b** but with allylic substrate (1*S*,4*S*)-(−)-**12**. Spectral data were in accordance with those for (±)-**13b**; $[a]_D^{25}$ −94 (*c* 1.71 in CH_2Cl_2); ee ⩾ 98%.

(1*R*,4*R*)-(+)-*trans*-1-Acetoxy-4-(2-amino-3,5-dibromobenzylamino)cyclohex-2-ene (1*R*,4*R*)-(+)-13b

The same procedure was followed as for the preparation of (±)-**13b** but with allylic substrate (1*R*,4*R*)-(+)-**12**. Spectral data were in accordance with those for (±)-**13b**; $[a]_D^{25}$ +95 (*c* 1.23 in CH_2Cl_2); ee ⩾ 98%.

(±)-*trans*-4-(2-Amino-3,5-dibromobenzylamino)cyclohex-2-enol 4b

The hydrolysis of the acetate in **13b** was performed as described for **3a**; δ_H(400 MHz; $CDCl_3$) 1.24–1.57 (4 H, m, CH_2, NH, OH), 2.02–2.18 (2 H, m, CH_2), 3.13–3.24 (1 H, m, CHN), 3.82, 3.84 (2 H, AB-system, J_{AB} 12.8, ArCH_2N), 4.20–4.30 (1 H, m, C*H*OH), 5.34 (2 H, br s, ArNH_2), 5.76–5.83 (2 H, m, olefinic), 7.09 (1 H, d, *J* 2.2, ArH-6), 7.48 (1 H, d, *J* 2.2, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 13 peaks) 27.8 (CH_2), 31.1 (CH_2), 50.0 (Ar*C*H_2N), 52.3 (CHN), 66.6 (*C*HOH), 108.3 [Ar, C(Br)-5], 110.4 [Ar, C(Br)-3], 126.2 (Ar, C-1), 131.4 (Ar, CH-6), 131.6 (olefinic), 132.4 (olefinic), 133.3 (Ar, CH-4), 143.9 [Ar, C(NH_2)-2]; *m/z* 380 ([M + 2H]$^+$, 8%), 379 ([M + H]$^+$, 51), 377 ([M + H]$^+$, 100), 375 ([M + H]$^+$, 50), 266 (12), 264 (25), 262 (13), 82 (30), 64 (30).

(1*S*,4*S*)-(−)-*trans*-4-(2-Amino-3,5-dibromobenzylamino)-cyclohex-2-enol (1*S*,4*S*)-(−)-4b

See preparation of (±)-**4b**; $[a]_D^{25}$ −65 (*c* 2.23 in EtOH); ee ⩾ 98%.

(1*R*,4*R*)-(+)-*trans*-4-(2-Amino-3,5-dibromobenzylamino)-cyclohex-2-enol (1*R*,4*R*)-(+)-4b

See preparation of (±)-**4b**; $[a]_D^{25}$ +66 (*c* 1.11 in EtOH); ee ⩾ 98%.

***trans*-4-(2-Aminobenzylamino)cyclohexanol *trans*-2a**

The synthesis of *trans*-**2a** was performed in accordance with the preparation of the the *cis*-analogue. (±)-**4a** (92 mg, 0.42 mmol), PtO_2 (7 mg, 0.031 mmol) and 1 atm of H_2, in EtOH (10 ml) at room temp. for 15 min gave the title compound (75 mg, 80%); δ_H(400 MHz; $CDCl_3$) 1.07–1.22 (2 H, m, CH_{2ax}CHN), 1.23–1.39 (3 H, m, CH_{2ax}CHO), 1.58–1.77 (1 H, m, CH_2), 1.91–2.09 (4 H, m, CH_2, OH, NH), 2.49 (1 H, tt, *J* 10.7 and 3.7, CHN), 3.61 (1 H, tt, *J* 10.5 and 4.1, C*H*OH), 3.80 (2 H, br s, ArCH_2N), 6.65 (1 H, dd, *J* 7.9 and 1.2, ArH-3), 6.68 (1 H, ddd, *J* 7.4, 7.4 and 1.2, ArH-5), 7.02 (1 H, ddm, *J* 7.4 and 1.6, ArH-6), 7.08 (1 H, ddd, *J* 7.8, 7.4 and 1.6, ArH-4), OH and NH as well as ArNH_2 give very broad signals in the regions 0.8–2.2 and 4.0–5.3 ppm respectively; δ_C(100.6 MHz; $CDCl_3$, 11 peaks) 31.2 (CH_2-3), 33.9 (CH_2-2), 50.5 (Ar*C*H_2N), 55.7 (CHN), 70.4 (CHOH), 115.7 (Ar, CH-3), 117.8 (Ar, CH-5), 124.5 (Ar, C-1), 128.2 (Ar, CH-4), 129.6 (Ar, CH-6), 146.7 [Ar, C(NH_2)-2]; *m/z* 222 ([M + 2H]$^+$, 14%), 221 ([M + H]$^+$, 100), 106 (39), 82 (53).

***trans*-4-(2-Amino-3,5-dibromobenzylamino)cyclohexanol *trans*-2b (ambroxol)**

The synthesis of *trans*-**2b** was performed in accordance with the preparation of *cis*-**2a**. (±)-**4b** (85 mg, 0.23 mmol), PtO_2 (2 mg, 0.009 mmol) and 1 atm of H_2 in EtOH (10 ml) at room temp. for 75 min gave the title compound (77 mg, 90%); δ_H(400 MHz; $CDCl_3$) 1.07–1.22 (2 H, m, CH_2), 1.23–1.53 (5 H, br s and m, OH, NH, CH_2), 1.54–1.74 (1 H, m, CH_2), 1.91–2.10 (4 H, m, CH_2), 2.46 (1 H, tt, *J* 10.6 and 3.5, CHN), 3.62 (1 H, tt, *J* 10.5 and 4.0, C*H*OH), 3.78 (2 H, br s, ArCH_2N), 5.34 (2 H, br s, ArNH_2), 7.08 (1 H, d, *J* 2.3, ArH-6), 7.47 (1 H, d, *J* 2.3, ArH-4); δ_C(100.6 MHz; $CDCl_3$, 11 peaks) 31.2 (CH_2), 33.9 (CH_2), 50.6 (Ar*C*H_2N), 55.4 (CHN), 70.3 (CHOH), 108.2 [Ar, C(Br)-5], 110.4 [Ar, C(Br)-3], 126.8 (Ar, C-1), 131.2 (Ar, CH-6), 133.2 (Ar, CH-4), 143.9 [Ar, C(NH_2)-2]; *m/z* 382 ([M + 2H]$^+$, 8%), 381 ([M + H]$^+$, 38), 379 ([M + H]$^+$, 75), 377 ([M + H]$^+$, 39), 266 (48), 264 (100), 262 (45), 116 (37).

Acknowledgements

Financial support from the Swedish Natural Science Research Council and the Swedish Research Council for Engineering Sciences are gratefully acknowledged. Ms Benita Hyllbrant is greatly acknowledged for assistance with the mass analyses.

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Paper 7/02141K
Received 27*th March* 1997
Accepted 10*th June* 1997