Palladium-catalysed enantiodivergent synthesis of *cis*- and *trans*-4-aminocyclohex-2-enols

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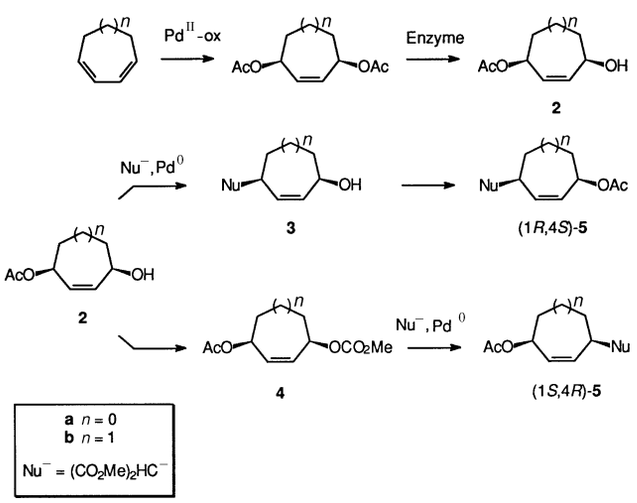
Enantiomerically pure *cis*- and *trans*-4-aminocyclohex-2-enols are prepared from cyclohexa-1,3-diene *via* (−)-*cis*-(1*R*,4*S*)-4-acetoxycyclohex-2-enol (−)-2a using palladium(0) chemistry. Benzylamine and diethylamine are tested in the Pd^0-catalysed allylic amination reactions. Since acetate is too slow as a leaving group and gave considerable amounts of side products, a number of leaving groups have been investigated. Of these phosphinate and 2,4-dichlorobenzoate are excellent leaving groups and result in efficient and highly stereoselective reactions; chloride as allylic leaving group also gives good results. By variation of the leaving group and proper choice of the protecting group it is possible to synthesise all four stereoisomers of 4-aminocyclohex-2-enol in good yield and high enantiomeric excess.

Introduction

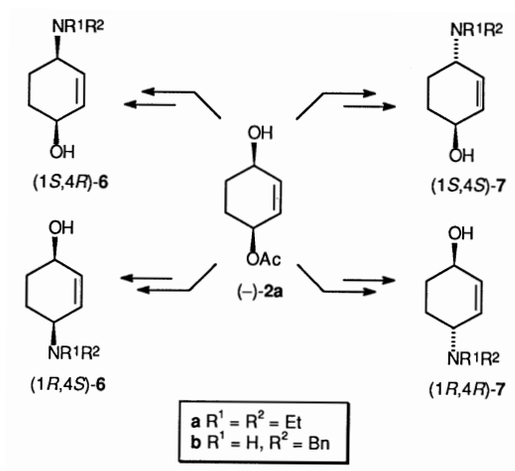
4-Aminocyclohex-2-enols are important structural elements in a number of biologically active compounds such as conduramines[1] and derivatives.[2] In connection with a project dealing with new substances for treatment of bronchitis complications, there was a need for a general synthesis of optically pure 4-aminocyclohex-2-enols.

We recently reported a method for an enantiodivergent synthesis of 4-substituted 2-cycloalkenols from cycloalka-1,3-dienes with a combination of palladium and enzyme chemistry (Scheme 1).[3] The method allows for preparation of both enantiomers with high selectivity.



Scheme 1

In the present paper we have used enantiomerically pure (−)-*cis*-(1*R*,4*S*)-4-acetoxycyclohex-2-enol (−)-**2a** as a key intermediate for further stereocontrolled palladium(0)-catalysed functionalisation and report on the enantiocontrolled synthesis of all four stereoisomers of 4-aminocyclohex-2-enol (Scheme 2). An interesting observation is that phosphinates are excellent leaving groups in the Pd^0-catalysed allylic substitution with primary and secondary amines.



Scheme 2

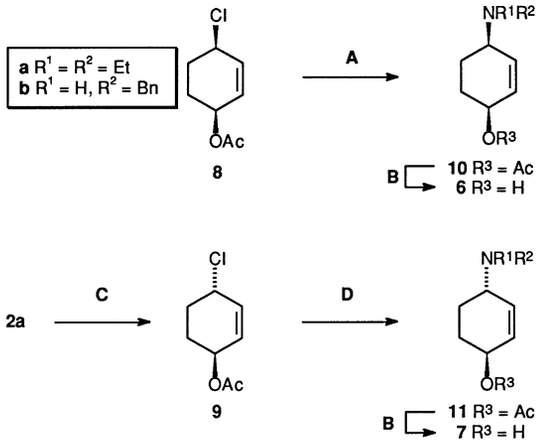
Results and discussion

(A) Racemates

The objective was to synthesise *cis*- and *trans*-4-aminocyclohex-2-enols in optically pure form starting from (−)-**2a**.[4] Diethylamine and benzylamine ($BnNH_2$) were employed as representative amines in the palladium(0)-catalysed allylic aminations. First, the allylic amination was performed to produce a racemic mixture of the amino alcohols (Scheme 3). Thus, *cis*-4-diethylaminocyclohex-2-enol **6a** and *cis*-4-benzylaminocyclohex-2-enol **6b** were prepared starting from *cis*-1-acetoxy-4-chlorocyclohex-2-ene **8**.[5]

The racemic *trans* stereoisomers were synthesised from (±)-**2a**.[6] Substitution of the OH by chloride with PPh_3 and *N*-chlorosuccinimide (NCS)[7] in THF afforded *trans*-1-acetoxy-4-chlorocyclohex-2-ene **9**. Pd^0-catalysed allylic amination of chloroacetate **9** with diethylamine or benzylamine gave after hydrolysis *trans*-4-diethylaminocyclohex-2-enol **7a** or *trans*-4-benzylaminocyclohex-2-enol **7b**, respectively. Amino alcohols **6** and **7** were used to set up a method for determination of the ee.

However, with **9** as the allylic substrate, a moderate regioselectivity was observed. Using conditions **A** in Scheme 3 and diethylamine as the nucleophile about 20% of the γ-substitution product (of *trans* stereochemistry) was obtained. Usually,



Scheme 3 *Reagents and conditions:* **A**, 5% $Pd(dba)_2$, 15% PPh_3, 1.2–3 equiv. NHR^1R^2, 3 equiv. Et_3N in THF, RT, N_2 or Ar atm: **10a** (77%), **10b** (81%); **B**, K_2CO_3 in MeOH–H_2O at RT: **6a** (95%), **6b** (98%), **7a** (96%), **7b** (98%); **C**, NCS, PPh_3, THF, RT (97%); **D**, reagents as for **A** but longer reaction times and 25% LiCl added to the reaction mixture: **11a** (71%), **11b** (76%)

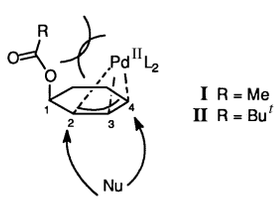


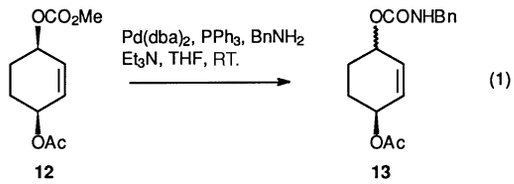
Fig. 1 Weaker bond in the 2-position because of steric interactions which increase the relative amount of γ-substitution product

attack at the 4-position relative to the acetate is strongly favoured in analogous 1,4-disubstituted alk-2-enes.[5] However, due to steric interaction between the acetate and the L_2Pd-group in π-allyl intermediate **I** (Fig. 1) palladium is forced away from the acetate which weakens the palladium–carbon bond in the 2-position.[8] This will increase the relative rate of attack at the 2-position in **I**. When R is *tert*-butyl **II** the relative amount of attack in the 2-position increased to 50–60% in the corresponding reaction (*vide infra*).

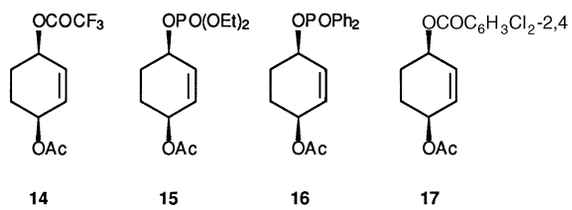
The reaction conditions were further investigated by variation of the solvent, amount of catalyst and ligand and by addition of salt (LiCl). The system with $Pd(dba)_2$ and PPh_3 in THF with an addition of 25 mol% LiCl decreased the amount of γ-product of **I** from 20 to 13% with Et_2NH and from 12 to 5% with $BnNH_2$.

(B) *cis* Enantiomers

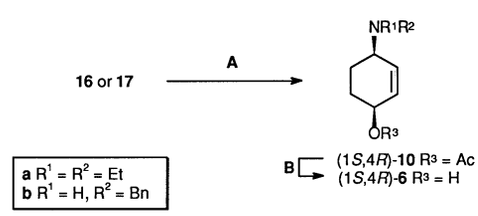
It has been shown that acetate can be used as a leaving group in Pd^0-catalysed allylic amination with both primary and secondary amines.[9] However, when (±)-**2a** was treated with benzylamine in the presence of $Pd(dba)_2$, PPh_3 and Et_3N in THF the conversion was low. In an attempt to improve the reaction, different catalysts, ligands and solvents were tried together with variation of the concentration and temperature. The best results were obtained with acetonitrile as the solvent at a reaction temperature of 40 °C. However, the yield of the desired product **6** was still unsatisfactory with considerable amounts of γ-product as well as inversion and elimination products.† Therefore better leaving groups were called for. To increase the reactivity in the Pd^0-catalysed nucleophilic displacement, the hydroxy group in **2a** was transformed into a reactive leaving group. It has been reported in the literature that ethyl and methyl carbonate can be used as a leaving group in Pd^0-catalysed allylic amination[10] but carbonate **12** gave the non-desired carbamate **13** on reaction with benzylamine [eqn. (1)].‡



The same results for similar substrates have been reported earlier in our laboratory[11] and elsewhere.[12] The use of trifluoroacetate **14** in the corresponding reaction gave **2a** and *N*-benzyltrifluoroacetamide, presumably because of faster nitrogen attack at the carbonyl carbon rather than formation of the π-allyl complex. Attempts to use a diethylphosphate ester[9d,e] as the leaving group, failed since **15** was very sensitive and hydrolysed quickly after preparation.



We next tried diphenylphosphinic and benzoate esters. Diphenylphosphinic ester **16** was prepared from enantiomerically pure (−)-**2a** (89%) according to Liebeskind *et al.*[13] and 2,4-dichlorobenzoate ester **17** was prepared (80% yield) by esterification of (−)-**2a** following the method of Hassner.[14] Both **16** and **17** were excellent substrates in the Pd^0-catalysed allylic amination with diethylamine and benzylamine and afforded the amino acetates (1*S*,4*R*)-**10a** and (1*S*,4*R*)-**10b**, which upon hydrolysis yielded the amino alcohols (1*S*,4*R*)-**6a** and (1*S*,4*R*)-**6b**, respectively (Scheme 4). In each case the allylic amination



Scheme 4 *Reagents and conditions:* **A**, 5% $Pd(dba)_2$, 15% PPh_3, 1.2–3 equiv. NHR^1R^2, 3 equiv. Et_3N in THF at RT, N_2 or Ar atm: **16** to **10a** (82%), **16** to **10b** (79%), **17** to **10a** (73%), **17** to **10b** (70%); **B**, K_2CO_3 in MeOH–H_2O at RT: yields as for step **B** shown in Scheme 3

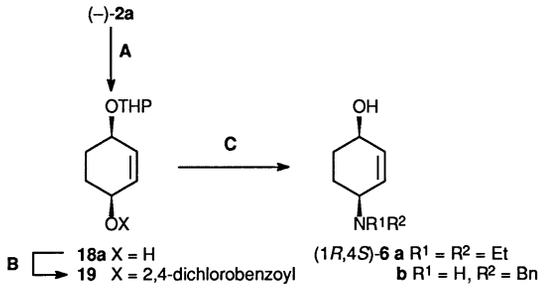
was highly stereoselective and the enantiomeric excess (ee) of the amino alcohols was ≥98% in both cases. For (1*S*,4*R*)-**6a** 2% of the *trans* isomer was observed. An explanation could be isomerisation of the π-allyl intermediate by nucleophilic attack by free Pd^0 on the allyl ligand.[15]

To form a carbon–nitrogen bond at the other allylic carbon in (−)-**2a**, it was necessary to protect the hydroxy group and then selectively hydrolyse the acetate before attachment of a leaving group (Scheme 5).

The hydroxy acetate (−)-**2a** was transformed into the alcohol **18a** with tetrahydropyran (THP) protection[16] and subsequent hydrolysis of the acetoxy group. The alcohol **18a** was transformed into its 2,4-dichlorobenzoate ester **19** (*vide supra*) which on Pd^0-catalysed amination and subsequent removal of the THP group afforded (1*R*,4*S*)-**6a** and (1*R*,4*S*)-**6b**.

† Loss of regio- and stereo-selectivity has previously been observed in Pd-catalysed reaction of allylic acetates with amines.[9b,g]

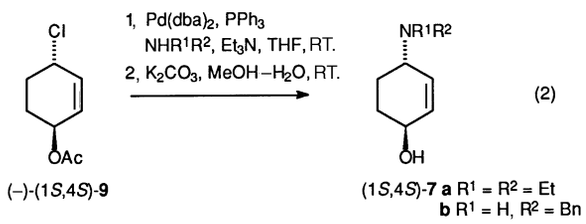
‡ The reaction proceeds *via* a (π-allyl)palladium intermediate.[11]



Scheme 5 *Reagents and conditions:* **A**, i, DHP, PPTS in CH_2Cl_2 at RT (98%); ii, 20% K_2CO_3 in MeOH–H_2O at RT (86%); **B**, 2,4-dichlorobenzoic acid, DCC, DMAP in CH_2Cl_2 at RT (87%); **C**, i, 5% $Pd(dba)_2$, 15% PPh_3, 1.2–3 equiv. NHR^1R^2, 3 equiv. Et_3N in THF at RT, N_2 or Ar atm; ii, *p*-TsOH, MeOH, RT, **6a** 55% yield in two steps, **6b** 65% yield in two steps

(C) *trans* Enantiomers

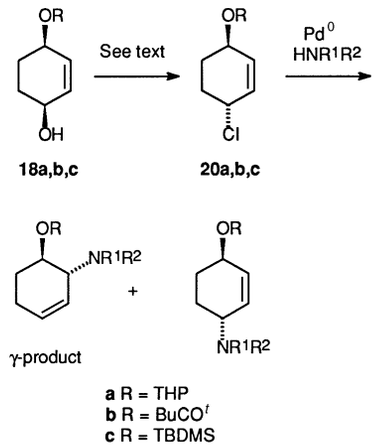
Reaction of the enantiomerically pure hydroxy acetate (−)-**2a** with NCS and PPh_3 in THF afforded optically active (1*S*,4*S*)-**9** with high stereospecificity (*cf*. racemic reaction, Scheme 3). Subsequent Pd^0-catalysed allylic amination employing Et_2NH and $BnNH_2$ followed by hydrolysis gave (1*S*,4*S*)-**7a** and (1*S*,4*S*)-**7b**, respectively [eqn. (2)]. The yields were the same



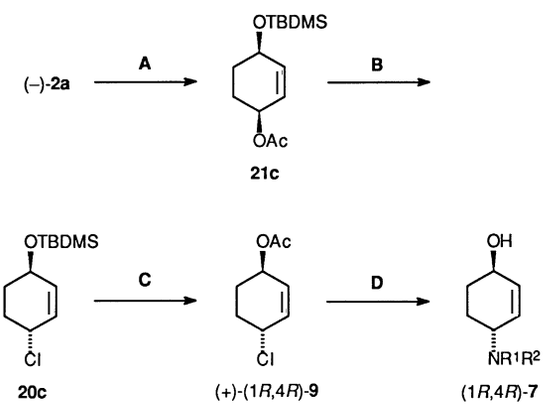
as for the racemates (Scheme 3) and the ee was in each case ≥ 98%.

When preparing the other *trans* enantiomer, the group at the other stereogenic carbon had to be substituted. Some difficulties were encountered when solving this problem. Substitution of the hydroxy group in **18a** by chloride with inversion using LiCl, methanesulfonyl chloride (MsCl), 2,4,6-trimethylpyridine in DMF and subsequent Pd^0-catalysed allylic amination of the allylic chloride **20a** should in analogy to the preparation of (1*S*,4*S*)-**7** from (1*S*,4*S*)-**9** give (1*R*,4*R*)-**7** after removal of the protecting group. Unfortunately, and to a much greater extent than what had been seen for **9**, the predominant product was the γ-substitution product (*vide supra*). Using pivalate§ as protecting group instead of THP led to the same discouraging result (Scheme 6). For example, with the pivalate **20b** the amount of γ-substitution product was 50–60% with diethylamine. This result supports the explanation suggested in Fig. 1 for the increased relative amount of γ-isomer. The use of *tert*-butyldimethylsilyl (TBDMS)¶ led to decomposition of the silyl ether bond in the amination. Another way to reach the other *trans* enantiomer (1*R*,4*R*)-**7** would be by a Mitsunobu reaction[18] of **6**. However, reaction of **6b** under Mitsunobu conditions failed, even when the amine was protected with *tert*-butoxycarbonyl (TBOC).‖

To solve the problem of obtaining the *trans*-(1*R*,4*R*)-enantiomer of the amino alcohol we prepared (1*R*,4*R*)-**9** as



Scheme 6



Scheme 7 *Reagents and conditions:* **A**, TBDMS-Cl, imidazole, CH_2Cl_2, 0 °C to RT (99%); **B**, i, 20% KOH in MeOH at RT (98%); ii, MsCl, LiCl, Et_3N in CH_2Cl_2, −20 °C to RT (91%); **C**, i, TBAF in THF at RT; ii, Ac_2O (83%); **D**, i, 5% $Pd(dba)_2$, 15% PPh_3, 25% LiCl, 1.2–3 equiv. NHR^1R^2, 0–3 equiv. Et_3N in THF at RT; ii, K_2CO_3 in MeOH–H_2O at RT: yields as in Scheme 3

described in Scheme 7. Silylation of (−)-**2a** with TBDMS-Cl gave *cis*-(1*S*,4*R*)-1-acetoxy-4-(*tert*-butyldimethylsilyloxy)cyclohex-2-ene **21c**. This compound was converted into (1*R*,4*R*)-**9** in the following way: hydrolysis of the acetate in **21c** and stereospecific substitution of the hydroxy group by chloride with inversion of configuration using MsCl, LiCl and Et_3N in methylene dichloride gave *trans*-(1*R*,4*R*)-1-chloro-4-(*tert*-butyldimethylsilyloxy)cyclohex-2-ene **20c**. Deprotection of TBDMS with tetrabutylammonium fluoride (TBAF) followed by quenching with acetic anhydride gave (1*R*,4*R*)-**9** (83%). Transformation of (1*R*,4*R*)-**9** into (1*R*,4*R*)-**7a** and (1*R*,4*R*)-**7b** was done as shown in eqn. (2) and the ee obtained was ≥98%.[19]

Conclusion

All four stereoisomers of biologically interesting 4-aminocyclohex-2-enols have been prepared in enantiomerically pure form by palladium(0)-catalysed reactions from the same starting material, (−)-*cis*-(1*R*,4*S*)-4-acetoxycyclohex-2-enol (−)-**2a**.

Experimental

^1H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at 300 or 400 and 75.4 or 100.6 MHz, respectively. ^{19}F NMR spectra were recorded for $CDCl_3$ solutions at 376.3 MHz. Chemical shifts are reported in ppm with $CDCl_3$ as internal standard (7.26 for ^1H and 77.00 ppm for ^{13}C) and coupling constants (*J*) are given in Hz. Assignment of ^{13}C was done with HETCOR and COSY experiments. Mass spectra were recorded on a

§ Prepared by selective hydrolysis of the acetate (Na_2CO_3, MeOH, RT)[17] in (±)-*cis*-1-acetoxy-4-pivaloyloxycyclohex-2-ene. The latter was obtained from esterification of (±)-**2a**.

¶ For an experimental procedure see preparation of **20c** in the Experimental section.

‖ The protection was done by mixing the aminoacetate with $(BOC)_2O$, Et_3N and catalytic amounts DMAP in methylene dichloride. Before the Mitsunobu reaction the acetate was hydrolysed.

Finnigan MAT INCOS 50 or a Hewlett Packard 5971 series instrument at 70 eV. Where indicated, mass spectra were recorded with pneumatically assisted electrospray mass spectrometry (ES-MS) on a Micromass VG Platform apparatus using direct inlet of a solution in acetonitrile or with an LC-column (Kromasil 100 × 4.6 mm, acetonitrile–water gradient with 5 mM formic acid). Optical rotations, recorded in units of 10^{-1} deg cm^2 g^{-1} measured at 25.0 °C on a Perkin–Elmer 241 polarimeter and concentrations are expressed as g 100 ml^{-1} in spectroscopically pure ethanol or methylene dichloride. Elemental analyses were performed by Analytische Laboratorien, Engelskirchen, Germany. Bis(dibenzylideneacetone)-palladium(0) [Pd(dba)$_2$] was prepared according to a literature procedure.[20] THF was distilled under nitrogen from sodium benzophenone ketyl. Pyridine and methylene dichloride were distilled under nitrogen from calcium hydride. Benzylamine, diethylamine and triethylamine were distilled from KOH and stored over KOH under nitrogen until used. Thin-layer chromatography (TLC) was run on Merck pre-coated 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 unless otherwise stated. Progress of reaction was followed by TLC until judged complete for all reactions. For flash chromatography Merck Kieselgel 60 (230–400 mesh) was used. Enantiomeric excess (ee) was checked with ^{1}H and ^{19}F NMR in $CDCl_3$ by Mosher esterification[21] for the diethylaminocyclohex-2-enols and by salt formation with optically pure (*S*)-mandelic acid,[22] for the 4-benzylaminocyclohex-2-enols.

General procedure for the Pd^0-catalysed aminations exemplified by the synthesis of (±)-*cis*-1-acetoxy-4-benzylaminocyclohex-2-ene 10b

To a solution that had been stirred at room temperature (RT) for 20 min containing Pd(dba)$_2$ (172 mg, 0.29 mmol), PPh_3 (225 mg, 0.86 mmol), $BnNH_2$ (737 mg, 6.87 mmol) and Et_3N (1.74 g, 17.18 mmol) in THF (30 ml) was added the *cis*-chloro acetate **8** (1.00 g, 5.73 mmol) in THF (10 ml). The reaction mixture was stirred at RT for 8 h and then evaporated. The residue was dissolved in diethyl ether (20 ml) and extracted with 1 M aq. HCl (3 × 50 ml). The aqueous phase was charged with fresh ether (80 ml) and the pH was adjusted to >10 with K_2CO_3 and KOH followed by two more extractions with ether (50 ml). The combined ether extracts were dried (K_2CO_3) and concentrated. The crude product was purified on silica (ethyl acetate–pentane gradient) to give **10b** (1.14 g, 81%). The silica was first conditioned with 2% Et_3N in pentane (Found for the HCl-salt: C, 63.9; H, 7.05. Calc. for $C_{15}H_{20}ClNO_2$: C, 63.9; H, 7.15%); δ_H(400 MHz; $CDCl_3$) 1.3–1.5 (1 H, br s, NH), 1.58–1.71 (1 H, m, CH_2), 1.73–1.84 (1 H, m, CH_2), 1.84–1.93 (2 H, m, CH_2), 2.04 (3 H, s, $COCH_3$), 3.14–3.21 (1 H, m, C*H*NHBn), 3.85, 3.88 (2 H, AB-system, J_{AB} 13.1, $PhCH_2$), 5.13–5.25 (1 H, m, CHOAc), 5.79 (1 H, ddd, *J* 10.0, 3.5 and 1.7, olefinic), 6.00 (1 H, dd, *J* 10.1 and 2.7, olefinic) and 7.21–7.37 (5 H, m, Ph); δ_C(100.6 MHz; $CDCl_3$, 13 peaks) 21.3 ($COCH_3$), 25.3 (CH_2CHOAc), 26.1 (CH_2CHN), 51.0 (CH_2Ph), 52.3 (CHN), 67.2 (*C*HOAc), 126.3 (CH, Ph), 126.9 (olefinic, *C*HCHOAc), 128.1 (CH, Ph), 128.4 (CH, Ph), 135.4 (olefinic, *C*HCHN), 140.3 (C, Ph) and 170.7 (C=O).

(A) Synthesis of the *cis*-4-aminocyclohex-2-enols

(±)-*cis*-1-Acetoxy-4-diethylaminocyclohex-2-ene 10a. The synthesis was carried out according to the general procedure above. Amounts used were allylic substrate **8** (300 mg, 1.718 mmol), Pd(dba)$_2$ (51 mg, 0.086 mmol), PPh_3 (68 mg, 0.258 mmol), Et_2NH (151 mg, 2.06 mmol), Et_3N (521 mg, 5.15 mmol) and THF (10 ml); reaction time 16 h; yield 280 mg, 77%; δ_H(300 MHz; $CDCl_3$) 1.04 (6 H, app t, *J* 7.2, CH_3), 1.41–1.61 (2 H, m, CH_2), 1.81–1.91 (1 H, m, CH_2), 2.04 (3 H, s, $COCH_3$), 2.11–2.20 (1 H, m, CH_2), 2.34–2.61 (4 H, m, NCH_2), 3.40–3.53 (1 H, m, $CHNEt_2$), 5.26–5.38 (1 H, m, CHOAc), 5.64–5.73 (1 H, m, olefinic) and 5.67–5.85 (1 H, m, olefinic); δ_C(100.6 MHz; $CDCl_3$, 10 peaks) 14.4 (NCH_2CH_3), 21.3 (CH_3CO_2), 22.3 (CH_2CHN), 28.3 (CH_2CHOAc), 44.1 (NCH_2), 56.4 (CHN), 70.2 (CHOAc), 129.2 (olefinic, *C*HCHN), 134.8 (olefinic, *C*HCHOAc) and 170.8 (C=O).

***cis*-(1*S*,4*R*)-1-Acetoxy-4-diethylaminocyclohex-2-ene (1*S*,4*R*)-10a.** The synthesis was carried out according to the general procedure. Amounts used were allylic substrate **16** (616 mg, 1.718 mmol), Pd(dba)$_2$ (51 mg, 0.086 mmol), PPh_3 (68 mg, 0.258 mmol), Et_2NH (151 mg, 2.06 mmol), Et_3N (521 mg, 5.15 mmol) and THF (20 ml); reaction time 2 h; yield 298 mg, 82%. Allylic substrate **17** (485 mg, 1.473 mmol), Pd(dba)$_2$ (44 mg, 0.074 mmol), PPh_3 (58 mg, 0.221 mmol), Et_2NH (183 mg, 2.50 mmol), Et_3N (447 mg, 4.42 mmol) and THF (20 ml); reaction time 6 h; yield 228 mg, 73%. Spectral data are in accordance with the racemate.

(±)-*cis*-4-Diethylaminocyclohex-2-enol 6a. The amino acetate **10a** (250 mg, 1.19 mmol) was dissolved in a stirred solution of K_2CO_3 (9 mg, 0.06 mmol) in MeOH–H_2O (4:1; 10 ml) at RT. After 5 h the mixture was evaporated, diluted with diethyl ether (100 ml), washed with water (10 ml) and brine (10 ml), dried (K_2CO_3) and evaporated. Purification of the residue on silica (gradient of diethyl ether–pentane 60:40 to ethyl acetate–MeOH 90:10) gave the title compound **6a** (191 mg, 95%) (Found for the HCl-salt: C, 58.3; H, 9.7. Calc. for $C_{10}H_{20}ClNO$: C, 58.4; H, 9.8%); δ_H(300 MHz; $CDCl_3$) 1.04 (6 H, app t, CH_3), 1.56–1.71 (3 H, m, 6-H and 5-H), 1.79–1.89 (1 H, m, 5-H), 1.96–2.14 (1 H, br s, OH), 2.38–2.65 (4 H, m, CH_2), 3.26–3.33 (1 H, m, 1-H), 4.07–4.12 (1 H, m, 4-H) and 5.79–5.91 (2 H, m, 5-H and 6-H); δ_C(75.4 MHz; $CDCl_3$, 8 peaks) 14.2 (CH_3), 17.9 (CH_2), 30.2 (CH_2), 44.2 (NCH_2), 56.7 (*C*HNEt$_2$), 63.4 (*C*HOAc), 130.2 (CH, olefinic), 135.4 (CH, olefinic); ν_{max}/cm^{-1} 3346 (OH, br), 2967, 2937, 2871, 1386 and 1066.

(−)-*cis*-(1*S*,4*R*)-4-Diethylaminocyclohex-2-enol (−)-(1*S*,4*R*)-6a. Starting from (1*S*,4*R*)-**10a** and applying the same conditions as for the preparation of (±)-**6a** yielded (−)-**6a**. Spectral data are in accordance with (±)-**6a**; $[\alpha]_D^{25}$ −70 (*c* 1.91 in EtOH); ee ≥98%.

(+)-*cis*-(1*R*,4*S*)-4-Diethylaminocyclohex-2-enol (+)-(1*R*,4*S*)-6a. See general procedure according to **10b**. Allylic substrate **19** (802 mg, 2.16 mmol), Pd(dba)$_2$ (64 mg, 0.108 mmol), PPh_3 (85 mg, 0.324 mmol), Et_2NH (174 mg, 2.38 mmol), Et_3N (656 mg, 6.48 mmol) and THF (25 ml) for 15 h yielded *cis*-(1*R*,4*S*)-4-diethylamino-1-(tetrahydropyran-2-yloxy)cyclohex-2-ene (373 mg, 68%). The THP group in the latter product (299 mg, 1.18 mmol) was removed with toluene-*p*-sulfonic acid (190 mg, 1.00 mmol) in MeOH (5 ml) at RT. After 12 h the mixture was evaporated and treated with diethyl ether (100 ml) and 1 M NaOH (10 ml). After extraction the organic phase was washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated. Purification of the residue on silica (gradient of diethyl ether–pentane, 60:40 to ethyl acetate–MeOH, 90:10) gave the title compound (+)-(1*R*,4*S*)-**6a** (161 mg, 81%; totally 55% in two steps). Same spectral data as for (±)-**6a**; $[\alpha]_D^{25}$ +66 (*c* 1.70 in EtOH); ee ≥98%.

(±)-*cis*-1-Acetoxy-4-benzylaminocyclohex-2-ene 10b. This compound is described above under the general procedure.

***cis*-(1*S*,4*R*)-1-Acetoxy-4-benzylaminocyclohex-2-ene (1*S*,4*R*)-10b.** See general procedure for (±)-**10b**. Pd(PPh$_3$)$_4$ (87 mg, 0.075 mmol) was used instead of Pd(dba)$_2$ for the allylic substrate **16** (539 mg, 1.504 mmol); amounts of reactants used were PPh_3 (20 mg, 0.076 mmol), $BnNH_2$ (161 mg, 1.503 mmol), Et_3N (340 mg, 3.36 mmol) and THF (17 ml); reaction time 2 h; yield 292 mg, 79%. For the allylic substrate **17** (311 mg, 0.95 mmol) the following amounts were used: Pd(dba)$_2$ (28 mg, 0.047 mmol), PPh_3 (38 mg, 0.142 mmol), $BnNH_2$ (311 mg, 2.83 mmol) and THF (17 ml); reaction time 2 h; yield 163 mg, 70%. Spectral data were in accordance with those of racemic **10b**.

(±)-*cis*-4-Benzylaminocyclohex-2-enol 6b. Prepared from amino acetate **10b** using the same hydrolysis conditions as for

the preparation of **6a** in 98% yield; δ_H(400 MHz; $CDCl_3$) 1.56–1.88 (6 H, m, 2 × CH_2, OH, NH), 3.09–3.21 (1 H, m, C*H*N-HBn), 3.83, 3.87 (2 H, AB-system, J_{AB} 13.0, PhCH_2NH), 4.09–4.18 (1 H, m, C*H*OH), 5.81–5.89 (2 H, m, olefinic) and 7.22–7.34 (5 H, m, Ph); δ_C(100.6 MHz; $CDCl_3$, 11 peaks) 24.9 (CH_2), 29.1 (CH_2), 51.1 (CH_2Ph), 52.3 (CHN), 64.7 (CHOH), 127.0 (CH, Ph), 128.1 (CH, Ph), 128.4 (CH, Ph), 130.7 (CH, olefinic), 133.1 (CH, olefinic) and 140.3 (C, Ph).

(−)-*cis*-(1*S*,4*R*)-4-Benzylaminocyclohex-2-enol (−)-(1*S*,4*R*)-6b. This compound was prepared as above for **6b** but starting with (1*S*,4*R*)-**10b**. Spectral data are as for (±)-**6b**; $[\alpha]_D^{25}$ −4.3 (*c* 0.845 in EtOH); ee ≥98%.

(+)-*cis*-(1*R*,4*S*)-4-Benzylaminocyclohex-2-enol (+)-(1*R*,4*S*)-6b. See general procedure for **10b**. Allylic substrate **19** (557 mg, 1.50 mmol), $Pd(dba)_2$ (45 mg, 0.075 mmol), PPh_3 (50 mg, 0.188 mmol), $BnNH_2$ (160 mg, 1.50 mmol), Et_3N (340 mg, 3.36 mmol) in THF (12 ml) for 20 h gave *cis*-(1*R*,4*S*)-4-benzylamino-1-(tetrahydropyran-2-yloxy)cyclohex-2-ene (426 mg, 94%). The THP group was removed according to the preparation of (+)-(1*R*,4*S*)-**6a** in 69% yield (65% in two steps); spectral data as for (±)-**6b**; $[\alpha]_D^{25}$ +4.2 (*c* 1.79 in EtOH); ee ≥98%.

(B) Synthesis of the *trans*-4-aminocyclohex-2-enols

(±)-*trans*-1-Acetoxy-4-diethylaminocyclohex-2-ene 11a. The general procedure described for **10b** was used but 25 mol% of LiCl was added to the reaction mixture together with the catalyst, phosphine and amine. Allylic substrate **9** (131 mg, 0.750 mmol), $Pd(dba)_2$ (22 mg, 0.037 mmol), PPh_3 (40 mg, 0.153 mmol), LiCl (8 mg, 0.189 mmol), $HNEt_2$ (165 mg, 2.26 mmol) in THF (7.5 ml) for 20 h yielded **11a** (113 mg, 71%); δ_H(300 MHz; $CDCl_3$) 1.04 (6 H, app t, *J* 7.2, CH_3), 1.41–1.61 (2 H, m, CH_2), 1.81–1.91 (1 H, m, CH_2), 2.04 (3 H, s, $COCH_3$), 2.11–2.20 (1 H, m, CH_2), 2.34–2.61 (4 H, m, NCH_2), 3.40–3.53 (1 H, m, $CHNEt_2$), 5.26–5.38 (1 H, m, CHOAc), 5.64–5.73 (1 H, m, olefinic) and 5.76–5.85 (1 H, m, olefinic); δ_C(100.6 MHz; $CDCl_3$, 10 peaks) 14.2 (NCH_2CH_3), 21.2 (CH_3CO_2), 22.3 (CH_2CHN), 28.2 (CH_2CHOAc), 44.1 (NCH_2), 56.4 (CHN), 70.1 (CHOAc), 129.2 (olefinic, *C*HCHN), 134.8 (olefinic, *C*HCHOAc) and 170.8 (C=O); *m*/*z* (LC prior to ES-MS) 212 ([M + H]$^+$, 82%), 139 (66%), 79 (7%), 61 (13%) and 60 (100%).

Spectroscopic data for the corresponding γ-product to **11a**. (±)-*trans*-4-Acetoxy-3-diethylaminocyclohexene; δ_H(400 MHz; $CDCl_3$) 1.01 (6 H, app t, *J* 7.1, CH_3), 1.56–1.75 (2 H, m, CH_2), 1.86–1.96 (1 H, m, CH_2), 2.04 (3 H, s, $COCH_3$), 2.07–2.20 (1 H, m, CH_2), 2.53 (4 H, app q, NCH_2), 3.36–3.43 (1 H, m, $CHNEt_2$), 5.00 (1 H, ddd, *J* 11.1, 7.7, 3.6, CHOAc), 5.53–5.60 (1 H, m, olefinic) and 5.74–5.82 (1 H, m, olefinic); δ_C(100.6 MHz; $CDCl_3$, 10 peaks) 14.5, 21.5, 24.0, 27.6, 44.4, 60.4, 70.9, 127.7, 128.9 and 170.6.

***trans*-(1*S*,4*S*)-1-Acetoxy-4-diethylaminocyclohex-2-ene (1*S*,4*S*)-11a.** The same procedure was used as for racemic **11a** but starting from (−)-**9**. Spectral data are in accordance with the racemate.

***trans*-(1*R*,4*R*)-1-Acetoxy-4-diethylaminocyclohex-2-ene (1*R*,4*R*)-11a.** The same procedure was used as for racemic **11a** but starting from (+)-**9**. Spectral data are in accordance with the racemate.

(±)-*trans*-4-Diethylaminocyclohex-2-enol 7a. This substance was prepared from amino acetate **11a** using the same hydrolysis conditions as for **6a** in 96% yield; δ_H(300 MHz; $CDCl_3$) 1.01 (6 H, app t, CH_3), 1.32–1.53 (2 H, m, 6-H), 1.76–1.89 (1 H, m, 5-H), 2.06–2.18 (1 H, m, 5-H), 2.31–2.59 (4 H, m, NCH_2), 2.60–2.80 (1 H, br s, OH), 3.37–3.47 (1 H, m, 1-H), 4.16–4.28 (1 H, m, 4-H) and 5.63–5.79 (2 H, m, 5-H and 6-H); δ_C(100.6 MHz; $CDCl_3$, 8 peaks) 14.1 (CH_3), 22.4 (CH_2), 32.5 (CH_2), 44.1 (NCH_2), 56.6 (*C*HNEt$_2$), 67.3 (*C*HOAc), 132.4 (CH, olefinic), 133.6 (CH, olefinic); *m*/*z* (LC prior to ES-MS) 170 ([M + H]$^+$, 100%); ν_{max}/cm^{-1} 3331 (OH, br), 2968, 2935, 2864, 1451, 1384 and 1065.

(−)-*trans*-(1*S*,4*S*)-4-Diethylaminocyclohex-2-enol (−)-(1*S*,4*S*)-7a. Preparation as for (±)-**7a** but with (1*S*,4*S*)-**11a** as the substrate. Same spectral data as for (±)-**7a**; $[\alpha]_D^{25}$ −102 (*c* 1.165 in EtOH); ee ≥98%.

(+)-*trans*-(1*R*,4*R*)-4-Diethylaminocyclohex-2-enol (+)-(1*R*,4*R*)-7a. Preparation as for (±)-**7a** but with (1*R*,4*R*)-**11a** as the substrate. Same spectral data as for (±)-**7a**; $[\alpha]_D^{25}$ +98 (*c* 0.600 in EtOH).

(±)-*trans*-1-Acetoxy-4-benzylaminocyclohex-2-ene 11b. The general procedure described for **10b** was used but 25 mol% of LiCl was added to the reaction mixture together with the catalyst, phosphine and amine. Amounts used were *trans*-chloro acetate **9** (720 mg, 4.13 mmol), $Pd(dba)_2$ (124 mg, 0.21 mmol), PPh_3 (162 mg, 0.62 mmol), LiCl (44 mg, 1.03 mmol), $BnNH_2$ (531 mg, 4.95 mmol) and Et_3N (1.25 g, 12.37 mmol) in THF (36 ml). The reaction mixture was stirred at RT for 20 h to give, on work-up, the amino acetate **11b** (770 mg, 76%); δ_H(400 MHz; $CDCl_3$) 1.45–1.64 (2 H, m, CH_2), 1.99–2.19 (2 H, m, CH_2), 2.04 (3 H, s, $COCH_3$), 2.58 (1 H, br s, NH), 3.27–3.33 (1 H, m, C*H*NHBn), 3.83, 3.86 (2 H, AB-system, J_{AB} 13.2, PhCH_2NH), 5.28–5.34 (1 H, m, CHOAc), 5.72 (1 H, dddd, *J* 10.4, 3.2, 2.0, 1.2, olefinic, C*H*CHOAc), 5.93 (1 H, dddd, *J* 10.4, 2.8, 1.6, 1.2, olefinic, C*H*CHN) and 7.20–7.45 (5 H, m, Ph); δ_C(100.6 MHz; $CDCl_3$, 13 peaks) 21.2 ($COCH_3$), 26.9 (CH_2CHOAc), 27.3 (CH_2CHN), 50.6 (CH_2Ph), 52.2 (CHN), 69.1 (*C*HOAc), 127.0 (CH, Ph), 127.9 (olefinic, *C*HCHOAc), 128.1 (CH, Ph), 128.4 (CH, Ph), 133.8 (olefinic, *C*HCHN), 139.8 (C, Ph) and 170.6 (C=O); *m*/*z* (LC prior to ES-MS) 246 ([M + H]$^+$, 100%), 139 (54%), 108 (3%), 79 (5%) and 61 (6%).

Spectroscopic data for the corresponding γ-product to **11b**: (±)-*trans*-4-acetoxy-3-benzylaminocyclohexene; δ_H(400 MHz; $CDCl_3$) 1.65–2.05 (3 H, br s and two m overlapping, CH_2, NH), 2.10–2.19 (2 H, m, CH_2), 3.25–3.33 (1 H, m, C*H*NH), 3.83, 3.88 (2 H, AB-system, J_{AB} 13.3, PhCH_2NH), 4.99 (1 H, ddd, *J* 8.9, 6.3 and 3.1, CHOAc), 5.62–5.69 (1 H, m, olefinic), 5.76–5.84 (1 H, m, olefinic) and 7.18–7.38 (5 H, m, aromatic); δ_C(100.6 MHz; $CDCl_3$, 13 peaks) 21.4, 23.2, 25.2, 50.5, 56.5, 72.6, 126.9, 127.1, 128.1, 128.3, 128.8, 140.6 and 170.8.

***trans*-(1*S*,4*S*)-1-Acetoxy-4-benzylaminocyclohex-2-ene (1*S*,4*S*)-11b.** The same procedure was used as for racemic **11b** but starting from (−)-**9**. Spectral data are in accordance with the racemate.

***trans*-(1*R*,4*R*)-1-Acetoxy-4-benzylaminocyclohex-2-ene (1*R*,4*R*)-11b.** The same procedure was used as for racemic **11b** but starting from (+)-**9**. Spectral data are in accordance with the racemate.

(±)-*trans*-4-Benzylaminocyclohex-2-enol 7b. The title compound was prepared from amino acetate **11b** using the same hydrolysis conditions as for **6a** in 98% yield; δ_H(400 MHz; $CDCl_3$) 1.36–1.51 (2 H, m, CH_2), 1.57–1.68 (2 H, br s, NH and OH), 2.03–2.15 (2 H, m, CH_2), 3.24–3.28 (1 H, m, C*H*NH), 3.82, 3.85 (2 H, AB-system, J_{AB} 13.0, PhCH_2NH), 4.23–4.26 (1 H, m, C*H*OH), 5.75–5.83 (2 H, m, olefinic) and 7.22–7.34 (5 H, m, Ph); δ_C(100.6 MHz; $CDCl_3$, 11 peaks) 27.9 (CH_2), 31.2 (CH_2), 50.8 (CH_2Ph), 52.7 (CHN), 66.8 (CHOH), 127.1 (CH, Ph), 128.2 (CH, Ph), 128.5 (CH, Ph), 132.0 (CH, olefinic), 132.1 (CH, olefinic) and 140.1 (C, Ph).

(−)-*trans*-(1*S*,4*S*)-4-Benzylaminocyclohex-2-enol (−)-(1*S*,4*S*)-7b. Preparation as for (±)-**7b** but with (1*S*,4*S*)-**11b** as the substrate. Same spectral data as for (±)-**7b**; $[\alpha]_D^{25}$ −122 (*c* 1.773 in EtOH); ee ≥98%.

(+)-*trans*-(1*R*,4*R*)-4-Benzylaminocyclohex-2-enol (+)-(1*R*,4*R*)-7b. Preparation as for (±)-**7b** but with (1*R*,4*R*)-**11b** as the substrate. Same spectral data as for (±)-**7b**; $[\alpha]_D^{25}$ +120 (*c* 1.394 in EtOH); ee ≥98%.

(C) Synthesis of the allylic substrates

(±)-*cis*-4-Acetoxycyclohex-2-enol (±)-2a. 1,4-Diacetoxycyclohex-2-ene[6] (17.39 g, 87.72 mmol) and K_2CO_3 (606 mg, 4.39 mmol) were dissolved in methanol–water (4:1; 150 ml) and the

solution stirred at RT for 40 min. It was then neutralised with 1 M aq. HCl and the methanol was removed *in vacuo*. The aqueous phase was saturated with NaCl and extracted with EtOAc and the extract was dried ($MgSO_4$) and concentrated. The residue was separated on silica (gradient EtOAc–pentane) to give **2a** (8.118 g, 59%). The spectral data were consistent with those previously reported.[4]

(−)-*cis*-(1*R*,4*S*)-4-Acetoxycyclohex-2-enol (−)-(1*R*,4*S*)-2a. Preparation according to ref. 4.

***cis*-1-Acetoxy-4-chlorocyclohex-2-ene 8.** The preparation was carried out as in ref. 5 and the spectral data were in accord with those reported therein.

(±)-*trans*-1-Acetoxy-4-chlorocyclohex-2-ene 9. To *N*-chlorosuccinimide (806 mg, 6.04 mmol) in THF (7 ml) under nitrogen was added a solution of PPh_3 (1.575 g, 6.01 mmol) in THF (7 ml). A slightly exothermic reaction ensued. After the reaction mixture had cooled to room temperature the alcohol **2a** (632 mg, 4.047 mmol) dissolved in THF (6 ml) was added to it; the mixture was then stirred at room temperature for 15 h. The solvent was removed and the residue was dissolved in a small amount of CH_2Cl_2 and purified on silica (diethyl ether–pentane, 5:95) to give the title compound **9** (684 mg, 97%). About 4% of the corresponding S_N2'-product was formed in the reaction. Spectral data for **9** were in accord with those reported in ref. 5.

(−)-*trans*-(1*S*,4*S*)-1-Acetoxy-4-chlorocyclohex-2-ene (−)-(1*S*,4*S*)-9. This compound was prepared in the same way as for the racemic compound **9** starting from (−)-**2a**. $[\alpha]_D^{25}$ −395 (*c* 1.01 in EtOH); 2.5% of the S_N2'-product contaminated the product.

(+)-*trans*-(1*R*,4*R*)-1-Acetoxy-4-chlorocyclohex-2-ene (+)-(1*R*,4*R*)-9. To a solution of compound **20c** (594 mg, 2.406 mmol) in THF (15 ml) was added tetrabutylammonium fluoride (TBAF) (1 M soln. in THF, 2.53 ml, 2.53 mmol) at room temperature. After 3 h, acetic anhydride (2.3 ml, 24.4 mmol) was added to the reaction mixture which was then stirred for an additional 12 h. It was then evaporated and the residue was separated on silica (gradient ether–pentane 5:95–15:85) to give the title compound (+)-**9** (347 mg, 83%). Spectral data were in accord with those reported in ref. 5; $[\alpha]_D^{25}$ +415 (*c* 0.89 in EtOH).

***cis*-(1*R*,4*S*)-4-Acetoxycyclohex-2-enyl diphenylphosphinate (1*R*,4*S*)-16.** The title compound was synthesized from the alcohol (−)-**2a** (1.00 g, 6.32 mmol) according to procedure A reported in ref. 14 (reaction time 30 h) except that in the aqueous work-up the organic extract was washed with saturated copper sulfate (3×), water (1×) and brine (1×) before being dried ($MgSO_4$). After evaporation of the extract the crude product was filtered through basic alumina eluting with diethyl ether. Removal of the ether afforded a colourless oil of the title compound **16** (2.02 g, 89%) which was sufficiently pure for the next step; δ_H(400 MHz; $CDCl_3$) 1.80–1.94 (3 H, m, CH_2), 2.01–2.06 (1 H, m, CH_2), 2.06 (3 H, s $COCH_3$), 4.84–4.91 [1 H, m, $CHOP(O)Ph_2$], 5.15–5.20 (1 H, m, CHOAc), 5.83–5.96 (2 H, m, olefinic), 7.44 (4 H, *o*-Ph), 7.51 (2 H, m, *p*-Ph), 7.82 (4 H, tdd, $^2J_{HP}$ 12.6, J_{HH} 8.2, 1.4, *o*-Ph); δ_C(100.6 MHz; $CDCl_3$, 13 peaks) 21.1 (CH_3CO_2), 24.6 (CH_2CHOAc), 26.9 (d, $^3J_{CP}$ 3.8, CH_2CHOP), 67.0 (*C*HOAc), 69.0 (d, $^2J_{CP}$ 6.0, CHOP), 128.4 (d, $^3J_{CP}$ 12.2, aromatic, CH), 129.9 (olefinic, *C*HCHOAc), 131.5 (d, $^2J_{CP}$ 17.5, aromatic, CH), 131.5 (d, $^3J_{CP}$ 3.0, olefinic, *C*HCHOP), 131.87 (d, $^1J_{CP}$ 136.6, aromatic, C), 131.92 (d, $^4J_{CP}$ 137.3, aromatic, C), 132.1 (d, $^4J_{CP}$ 1.5, aromatic, CH) and 170.2 (C=O); *m*/*z* (NH_4CO_2 added prior to ES-MS) 379 ([M + Na]$^+$, 5%), 374 ([M + NH_4]$^+$, 4%), 357 ([M + H]$^+$, 50%), 297 (3%), 219 (11%), 139 (100%) and 79 (6%).

***cis*-(1*R*,4*S*)-4-Acetoxycyclohex-2-enyl 2,4-dichlorobenzoate (1*R*,4*S*)-17.** A solution of *cis*-4-acetoxycyclohex-2-enol (−)-**2a** (953 mg, 6.10 mmol), 2,4-dichlorobenzoic acid (1.72 g, 9.00 mmol), dicyclohexylcarbodiimide (DCC) (1.86 g, 9.01 mmol) and *p*-dimethylaminopyridine (DMAP) (16 mg, 0.13 mmol) in methylene dichloride (50 ml) was stirred at RT for 3 h. Diethyl ether (50 ml) was added to the reaction mixture which was then washed with cold 5% aq. HCl (2 × 25 ml) and saturated aqueous $NaHCO_3$ (3 × 25 ml), dried ($MgSO_4$) and concentrated. The crude product was filtered through basic alumina and purified on silica using MPLC (EtOAc–CH_2Cl_2, 1:1, gradient in pentane) to give the title compound **17** (1.61 g, 80%); δ_H(300 MHz; $CDCl_3$) 1.90–2.06 (4 H, m, 2 × CH_2), 2.07 (3 H, s, $COCH_3$), 5.23–5.33 (1 H, m, CHOAc), 5.39–5.51 [1 H, m, CHOC(O)Ar], 5.94–6.05 (2 H, m, olefinic), 7.29 (1 H, dd, *J* 8.4 and 2.0, ArH), 7.47 (1 H, d, *J* 2.0, ArH) and 7.79 (1 H, d, *J* 8.4, ArH); δ_C(100.6 MHz; $CDCl_3$, 15 peaks) 21.1 (CH_3CO_2), 24.8 (CH_2), 25.0 (CH_2), 67.4 (CHOAc), 68.6 [*C*HOC(O)Ar], 126.9 (aromatic, CH*C*HCCl), 128.4 (aromatic, C), 129.3 [olefinic, *C*HCHOC(O)Ar], 130.9 (aromatic, CCl*C*HCCl), 131.2 (olefinic, *C*HCHOAc), 132.4 (aromatic, C*C*HCH), 134.8 (aromatic, C), 138.2 (aromatic, C), 164.2 (C=O) and 170.4 (C=O); *m*/*z* 273 (0.6%), 271 (5%), 269 (7%), 177 (12%), 175 (65%), 173 (100%), 149 (2%), 147 (8%), 145 (12%), 139 (12%), 96 (43%) and 79 (26%); $[\alpha]_D^{25}$ +56 (*c* 1.16 in EtOH).

(+)-*cis*-(1*S*,4*R*)-4-(Tetrahydropyran-2-yloxy)cyclohex-2-enol (+)-(1*S*,4*R*)-18a. To (−)-**2a** (535 mg, 3.38 mmol) dissolved in methylene dichloride (30 ml) was added dihydropyran (DHP) (425 mg, 5.05 mmol) and pyridinium toluene-*p*-sulfonate (PPTS) (85 mg, 0.338 mmol). The solution was stirred at RT for 4 h, after which it was diluted with diethyl ether (100 ml), washed with brine–water (1:1; 20 ml) and concentrated. The resulting crude product was dissolved in methanol (5 ml) and treated with K_2CO_3 (23 mg, 0.17 mmol) in water (1 ml). After being stirred at RT for 5 h the reaction mixture was diluted with water (10 ml) and then concentrated by evaporation of most of the methanol. The aqueous phase was extracted with diethyl ether (3 × 50 ml) and the combined organic fractions were then washed with brine (20 ml), dried ($MgSO_4$) and concentrated. Purification of the residue on silica (diethyl ether–pentane, 60:40) gave the title compound **18a** (650 mg, 98%) (Found: C, 65.9; H, 8.8. Calc. for $C_{11}H_{18}O_3$: C, 66.6; H, 9.15%); δ_H(400 MHz; $CDCl_3$) 1.48–1.94 (10 H, m, 5-H, 6-H, 8-H, 9-H and 10-H), 3.45–3.54 (1 H, m, 11-H), 3.86–3.97 (1 H, m, 11-H), 4.08–4.18 (2 H, m, 4-H and 7-H), 4.72–4.78 (1 H, m, 1-H) and 5.88–5.91 (2 H, m, 2-H and 3-H); δ_C(100.6 MHz; $CDCl_3$) 19.5 (C-9), 24.3 and 26.2 (C-5), 25.3 and 25.4 (C-10), 28.1 and 28.5 (C-6), 30.9 and 31.0 (C-8), 62.4 and 62.5 (C-11), 65.1 and 65.2 (C-1), 68.9 and 70.0 (C-4), 96.8 and 97.8 (C-7), 130.1 and 131.3 (olefinic), 132.5 and 132.6 (olefinic); *m*/*z* (M^+, >0.5%) 97 (51%), 85 (90%), 79 (63%), 67 (64%), 57 (65%) and 55 (100%); ν_{max}/cm^{-1} 3404 (OH, br), 2942, 2869, 1133, 1074, 1032 and 1000; $[\alpha]_D^{25}$ +38.1 (*c* 0.91 in CH_2Cl_2).

***cis*-4-Pivaloyloxycyclohex-2-enol 18b.** To a solution of the hydroxyacetate **2a** (1.00 g, 6.402 mmol), Et_3N (3.24 g, 32.01 mmol) and DMAP (22 mg, 0.180 mmol) in THF (25 ml) was added pivaloyl chloride (1.58 ml, 12.81 mmol). The reaction mixture was stirred at 50 °C for 24 h after which the solvent was removed and ether (60 ml) was added to the residue. The solution was washed with 1 M hydrochloric acid (× 3), sat'd aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Separation of the residue on silica (diethyl ether–pentane, 3:97 then 5:95) yielded *cis*-4-acetoxy-1-pivaloyloxycyclohex-2-ene (1.485 g, 95%); δ_H(400 MHz; $CDCl_3$) 1.19 (9 H, s, Bu^t), 1.77–1.96 (4 H, m, CH_2), 2.07 (3 H, s, $COCH_3$), 5.15–5.24 (2 H, m, CHOAc, CHOPiv) and 5.81–5.91 (2 H, m, olefinic); δ_C(100.6 MHz; $CDCl_3$, 11 peaks) 21.3, 24.8, 24.9, 27.1, 38.7, 66.9, 67.4, 130.0, 130.5, 170.5, 178.0. Selective hydrolysis of the acetate (1.112 g, 4.627 mmol) was performed with a 10% solution of $Na_2CO_3 \cdot 10\ H_2O$ (133 mg, 0.465 mmol) in MeOH–H_2O (4:1, 23 ml) at RT for 9 h. After removal of the methanol from the mixture it was extracted with ether and the extract dried (Na_2SO_4) and concentrated to give the title compound **18b** (839 mg, 92%); δ_H(400 MHz;

$CDCl_3$) 1.18 (9 H, s, Bu^t), 1.62–1.98 (5 H, m, CH_2, OH), 4.14–4.26 (1 H, m, C*H*OH), 5.10–5.24 (1 H, m, CHOPiv), 5.73–5.84 (1 H, m, olefinic) and 5.90–6.00 (1 H, m, olefinic); δ_C(100.6 MHz; $CDCl_3$, 9 peaks) 24.9 (C-5), 27.1 (C-9), 28.1 (C-6), 38.7 (C-8), 65.3 (C-1), 66.9 (C-4), 128.0 (C-3), 134.5 (C-2) and 178.1 (C-7); *m*/*z* 180 (2%), 113 (3%), 97 (23%), 96 (67%), 95 (14%), 85 (21%), 79 (21%) and 57 (100%).

***cis*-(1*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)cyclohex-2-enol (1*S*,4*R*)-18c.** To a stirred solution of **21c** (3.256 g, 12.039 mmol) was added KOH (135 mg, 2.408 mmol) in methanol (40 ml). The reaction mixture was stirred at RT for 4 h after which the solvent was removed and the residue was treated with water (30 ml) and diethyl ether (60 ml); the layers were separated and the pH of the aqueous layer was adjusted to 7 with 1 M hydrochloric acid; it was then further extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the product (2.698 g, 98%) which was pure enough for the next step; δ_H(400 MHz; $CDCl_3$) 0.073 (3 H, s, $SiCH_3$), 0.076 (3 H, s, $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 1.60–1.90 (5 H, m, 2 × CH_2, OH), 4.06–4.18 (2 H, two overlapping m, C*H*OH, CHOSi), 5.75 (1 H, dd, *J* 10.2 and 2.4, olefinic) and 5.79 (1 H, dd, *J* 10.2 and 3.1, olefinic); δ_C(100.6 MHz; $CDCl_3$, 10 peaks) −4.7 (C-7), −4.6 (C-7′), 18.1 (C-8), 25.8 (C-9), 28.2 (C-5), 28.4 (C-6), 64.8 (C-1), 66.3 (C-4), 130.7 (C-2) and 133.9 (C-3); $[\alpha]_D^{25}$ +34 (*c* 1.58 in EtOH).

***cis*-(1*S*,4*R*)-4-(Tetrahydropyran-2-yloxy)cyclohex-2-enyl 2,4-dichlorobenzoate (1*S*,4*R*)-19.** A solution of DCC (1.297 g, 6.285 mmol) and DMAP (13 mg, 0.105 mmol) in methylene dichloride (10 ml) was added to a stirred solution of **18a** (1.246 g, 6.285 mmol) and 2,4-dichlorobenzoic acid (1.200 g, 6.285 mmol) in methylene dichloride (25 ml) at RT. The solution was stirred at RT for 10 h, after which it was diluted with diethyl ether (300 ml). The organic phase was washed with 5% aqueous acetic acid (50 ml), water (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated. Purification of the residue on silica (diethyl ether–pentane, 60 : 40) gave the title compound **19** (2.20 g, 87%); δ_H(400 MHz; $CDCl_3$) 1.43–2.07 (10 H, m, 5-H, 6-H, 8-H, 9-H and 10-H), 3.47–3.54 (1 H, m, 11-H), 3.86–3.94 (1 H, m, 11-H), 4.15–4.27 (1 H, two overlapping m, 4-H), 4.73–4.78 (1 H, m, 7-H), 5.39–5.45 (1 H, m, 1-H), 5.89–5.95 (1 H, m, 3-H) and 6.01–6.09 (1 H, m, 2-H); δ_C(100.6 MHz; $CDCl_3$) 19.5 and 19.6 (CH_2), 24.4 and 26.3 (CH_2), 25.2 and 25.4 (CH_2), 25.5 and 26.1 (CH_2), 30.9 and 31.0 (CH_2), 62.5 and 62.6 (CH_2), 68.7 and 68.8 [allyl-*C*HOC(O)Ar], 69.3 and 70.4 (allyl-CHOTHP), 97.0 and 98.1 (THP-OCHO), 126.9 (aromatic, CH), 127.0 and 127.1 [olefinic, *C*HCHOC(O)Ar], 128.5 (aromatic, C), 130.9 (aromatic, CH), 132.5 (aromatic, CH), 133.8 and 134.9 (olefinic, *C*HCHOTHP), 135.8 (aromatic, C), 138.1 (aromatic, C) and 164.2 (C=O); *m*/*z* 273 (19%), 271 (29%), 194 (6%), 192 (61%), 190 (81%), 177 (12%), 175 (68%), 173 (100%), 147 (12%) and 145 (28%).

***trans*-1-Chloro-4-(tetrahydropyran-2-yloxy)cyclohex-2-ene 20a.** A solution of **18a** (100 mg, 0.504 mmol), LiCl (46 mg, 1.08 mmol) and 2,4,6-trimethylpyridine (504 μl, 3.78 mmol) in DMF (750 μl) was cooled to 0 °C and treated with MsCl (58 μl, 0.83 mmol) followed after 20 min by diethyl ether (40 ml). The solution was washed with water (5 ml) and brine (5 ml), dried ($MgSO_4$) and concentrated. The residue was purified on silica (diethyl ether–pentane, 40 : 60) to give the title compound **20a** (98 mg, 90%). Since the product is extremely unstable it should be prepared directly before further use; δ_H(400 MHz; $CDCl_3$) 1.40–2.40 (10 H, m, 5-H, 6-H, 8-H, 9-H, 10-H), 3.43–3.58 (1 H, m, 11-H), 3.83–3.98 (1 H, m, 11-H), 4.16–4.30 (1 H, m, 4-H), 4.54–4.65 (1 H, m, 7-H), 4.66–4.80 (1 H, m, 1-H) and 5.82–6.03 (2 H, m, olefinic); δ_C(100.6 MHz; $CDCl_3$) 19.7, 25.4, 25.4, 25.5, 27.5, 29.3, 29.7, 29.8, 31.1, 31.1, 54.6, 54.6, 62.6, 62.7, 68.3, 69.0, 97.3, 98.1, 130.4, 130.6, 131.1 and 131.7.

***trans*-1-Chloro-4-pivaloyloxycyclohex-2-ene 20b.** Triphenylphosphine (836 mg, 3.19 mmol) dissolved in THF (3 ml) was added to a solution of *N*-chlorosuccinimide (426 mg, 3.19 mmol) in THF (5 ml) to give slightly exothermic phosphonium salt formation. After cooling of the reaction mixture to RT (20 min), **18b** (416 mg, 2.098 mmol) in THF (3 ml) was added to it; it was then stored at RT for 24 h. After this, the solvent was evaporated from the mixture and pentane was added to the residue. The precipitated triphenylphosphine oxide and succinimide were filtered off and the pentane was removed *in vacuo* to give a residue which was purified on silica (EtOAc–pentane, 1 : 99). This afforded **20b** (305 mg, 67%) (8% of the reaction product was derived from the S_N2' substitution mechanism); δ_H(400 MHz; $CDCl_3$) 1.17 (9 H, s, Bu^t), 1.68–1.78 (1 H, m, CH_2), 1.94–2.04 (1 H, m, CH_2), 2.12–2.32 (2 H, m, CH_2), 4.57–4.64 (1 H, m, CHCl), 5.20–5.28 (1 H, m, CHOPiv), 5.82–5.89 (1 H, m, olefinic) and 5.98–6.04 (1 H, m, olefinic); δ_C(100.6 MHz; $CDCl_3$, 9 peaks) 24.8 (CH_2), 27.1 (CH_3), 28.7 (CH_2), 38.7 (C), 53.6 (CHCl), 65.7 (CHOPiv), 128.3 (olefinic, CH), 132.3 (olefinic, CH) and 177.8 (C=O).

***trans*-(1*R*,4*R*)-1-Chloro-4-(*tert*-butyldimethylsilyloxy)cyclohex-2-ene (1*R*,4*R*)-20c.** To compound **18c** (1.503 g, 6.58 mmol) was added LiCl (558 mg, 13.16 mmol) and Et_3N (2.75 ml, 19.74 mmol) in CH_2Cl_2 (25 ml). The solution was cooled to −20 °C and MsCl (610 μl, 7.881 mmol) was added to it *via* a syringe. The mixture was brought to RT over 3 h after which it was stirred for a further 17 h. It was then diluted with water–$NaHCO_3$ (sat'd) (1 : 1; 30 ml) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 70 ml). The combined organic phases were washed with brine (20 ml), dried ($MgSO_4$) and passed through a silica column packed with Et_3N–diethyl ether–pentane (4 : 2 : 94). Elution with diethyl ether–pentane (2 : 98 then 5 : 95) gave the title compound **20c** (1.484 g, 91%); δ_H(400 MHz; $CDCl_3$) 0.08 (6 H, s, $SiCH_3$ × 2), 0.89 [9 H, s, $SiC(CH_3)_3$], 1.60–1.67 (1 H, m, CH_2), 1.84–1.93 (1 H, m, CH_2), 2.02–2.11 (1 H, m, CH_2), 2.29–2.37 (1 H, m, CH_2), 4.23–4.27 (1 H, m, CHOSi), 4.56–4.60 (1 H, m, CHCl), 5.77 (1 H, dd, *J* 10.4 and 3.1, olefinic) and 5.82 (1 H, dd, *J* 10.4 and 3.2, olefinic); δ_C(100.6 MHz; $CDCl_3$, 10 peaks) −4.7 (C-7), −4.6 (C-7′), 18.2 (C-8), 25.8 (C-9), 29.7 (C-6), 29.9 (C-5), 54.9 (C-1), 64.9 (C-4), 129.5 (C-2) and 133.5 (C-3); *m*/*z* 248 (1%), 246 (2%), 191 (24%), 189 (64%), 93 (18%), 77 (15%) and 75 (100%); $[\alpha]_D^{25}$ +259 (*c* 1.75 in EtOH).

***cis*-(1*S*,4*R*)-1-Acetoxy-4-(*tert*-butyldimethylsilyloxy)cyclohex-2-ene (1*S*,4*R*)-21c.** A solution of TBDMS-Cl (2.665 g, 17.68 mmol) in methylene dichloride (40 ml) was cooled to 0 °C and imidazole (6.74 g, 99.0 mmol) was added to it. After 5 min (−)-**2a** (2.209 g, 14.14 mmol) dissolved in methylene dichloride (30 ml) was added to the mixture which was then stirred at 0 °C for *ca*. 30 min and then at RT for 20 h. After being quenched with water (10 ml), the reaction mixture was extracted with methylene dichloride (3 × 50 ml). The combined organic fractions were washed with brine (20 ml), dried (Na_2SO_4), concentrated and subjected to chromatography (diethyl ether–pentane 5 : 95) to give the title compound **21c** (3.79 g, 99%); δ_H(400 MHz; $CDCl_3$) 0.078 (3 H, s, $SiCH_3$), 0.082 (3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.65–1.95 (4 H, m, 2 × CH_2), 2.04 (3 H, s, $COCH_3$), 4.15–4.19 (1 H, m, CHOSi), 5.13–5.17 (1 H, m, CHOAc), 5.71–5.75 (1 H, m, olefinic) and 5.85–5.88 (1 H, m, olefinic); δ_C(100.6 MHz; $CDCl_3$) −4.7 ($SiCH_3$), −4.6 ($SiCH_3$), 18.1 (SiC), 21.2 ($COCH_3$), 25.3 (*C*H_2CHOAc), 25.8 [$SiC(CH_3)_3$], 28.4 (*C*H_2CHOSi), 66.3 (CHOSi), 67.0 (CHOAc), 126.2 (olefinic, *C*HCHOAc), 136.3 (olefinic, *C*HCHOSi) and 170.6 (C=O); *m*/*z* 210 (2%), 117 (100%), 79 (12%) and 75 (33%); $[\alpha]_D^{25}$ −40 (*c* 1.63 in EtOH).

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