Approaches to the synthesis of (+)- and (−)-epibatidine †

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Synthetic approaches to the powerful analgesic alkaloids (+)- and (−)-epibatidine are described. The starting material employed was natural (−)-quinic acid from which chiral enones and α-iodoenones were prepared. Stille coupling afforded suitable substrates for completion of the syntheses. A key step in this process was the diastereoselective reduction of a cyclohexanone with sodium borohydride and DMSO which sets up the stereochemistry necessary for the formation of the bicycloheptane system. The synthesis of a previously reported enone intermediate has also been improved.

Introduction

Epibatidine **1** is an alkaloid, first isolated from the skin of the Ecuadorian poisonous frog *Epipedobates tricolor* by Daly and co-workers in 1992.[1] Its low natural abundance (less than 1 mg obtained from about 750 frogs), and its strong non-opioid analgesic activity, greater than 200 times more potent than morphine and devoid of addictive effects has stimulated many synthetic efforts.[2–7,8] Epibatidine is an extremely potent nicotinic acetylcholine receptor agonist (Fig. 1),[9] and these receptors are involved in the mediation of several human disorders such as Alzheimer's and Parkinson's diseases. Interestingly, (+) and (−) enantiomers of epibatidine are nearly equipotent in analgesic tests. The effect of molecular chirality on other, perhaps undesirable, physiological activity is not known so non-racemic synthesis is still a valid target.

Here we report our approaches to the enantioselective synthesis of both enantiomers of epibatidine from (−)-quinic acid ‡ **2** (Fig. 1) which incorporates all the functionality of epibatidine before the formation of the azabicyclo[2.2.1]-heptane system.

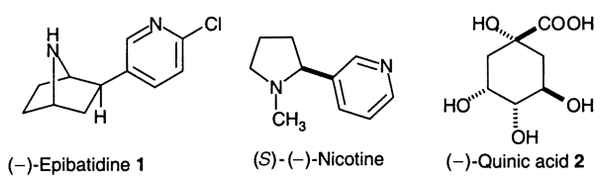
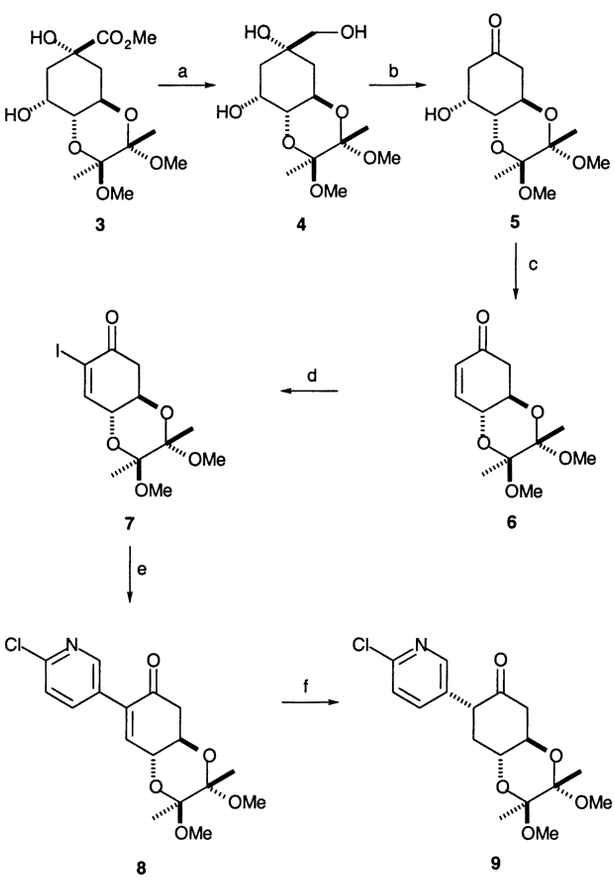


Fig. 1

Results and discussion

A retrosynthetic analysis for both enantiomers from known precursors derived from (−)-quinic acid indicated that introduction of the pyridine unit *via* a substrate controlled 1,4-addition to an α,β-unsaturated ketone could furnish both enantiomers. Trost and Cook [3] have already attempted some 1,4-addition strategies without success and we extended his study to a variety of organocopper derivatives also without success. We then turned our attention to the use of palladium catalysed coupling of the pyridine moiety to a suitable α-iodoenone which could also provide a route to both enantiomers depending upon the substrate **6** or **21**.

Our original strategy (Scheme 1) was based upon the 2,3-dimethoxybutane-2,3-diyldioxy acetal *trans* diol protecting group which created a rigid *trans*-decalin structure. The first two steps are already described in the literature.[8,10,11] Compound



Scheme 1 *Reagents and conditions*: (a) DIBAL-H, Et_2O, −78 °C/0 °C. (b) $NaIO_4$, H_2O, rt (97%, 2 steps). (c) Ac_2O, $(i\text{-Pr})_2NEt$, DMAP, CH_2Cl_2, 0 °C, 94%. (d) I_2, DMAP, pyridine–CCl_4 (1 : 1), 0 °C/rt, 96%. (e) $Bu_3SnC_5H_3NCl$, $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, CuI, THF, rt/60 °C, 85%. (f) K-Selectride®, THF, −78 °C, 99%.

† Experimental data for compounds **28a**, **29a**, **30a** and **31a** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b002980g/

‡ The IUPAC name for quinic acid is 1,3,4,5-tetrahydroxycyclohexanecarboxylic acid.

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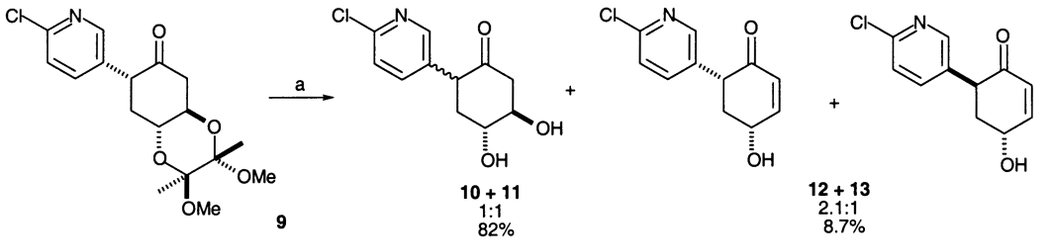
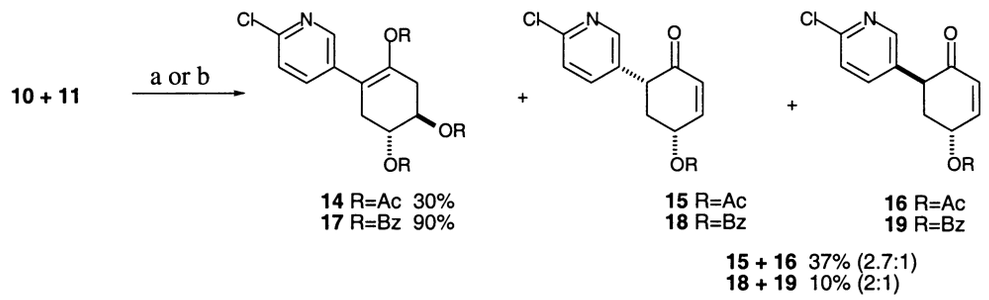


Scheme 2 *Reagents and conditions*: (a) CF_3COOH, CH_2Cl_2, H_2O, Δ, 90%.



Scheme 3 *Reagents and conditions*: (a) Ac_2O, $(i\text{-Pr})_2NEt$, DMAP, CH_2Cl_2, 0 °C, 67%. (b) BzCl, $(i\text{-Pr})_2NEt$, DMAP, CH_2Cl_2, 0 °C.

3 was obtained *via* a transacetalisation with 2,2,3,3-tetramethoxybutane,[24] in good yield. Reduction of the methyl ester with DIBAL-H afforded the very polar triol **4** (98%) which was not normally isolated but was oxidised directly to β-hydroxyketone **5** with $NaIO_4$. Enone **6** was obtained in 94% yield, by acetylation of **5** followed by elimination with diisopropylethylamine.[8,10,11] Finally, applying Johnson's method[14] but using DMAP to accelerate the elimination, iodoenone **7** was obtained in 96% yield.

A range of reaction conditions were tested to obtain **8** from **7**, using the Stille cross-coupling reaction with (2-chloro-5-pyridyl)tributyltin[15–17] to afford ketone **8** in 85% yield. A large rate enhancement was observed with triphenylarsine as the palladium ligand. The use of co-catalytic Cu(I) in this coupling reaction was also essential.[18] It has been reported[3,18] that with ligands, such as $AsPh_3$, the addition of CuI displayed little effect on the reaction rate, but with our system the presence of CuI was absolutely necessary, and Johnson[14,23] also used this combination in similar reactions.

Conjugate reduction of the enone **8** with K-Selectride®[19] afforded the epimer **9**, in quantitative yield. This high stereoselectivity is explained by the preference for the pyridine substituent to attain the equatorial position α to the enolisable ketone. Unfortunately, after cleavage of this acetal (Scheme 2) with trifluoroacetic acid, the rigidity of the molecule was lost, enolisation occurred and a mixture of the two epimers **10** and **11** (82%) was obtained in about a 1:1 ratio, along with a minor quantity (9%) of the two expected epimers of the eliminated products, **12** and **13** (2.1:1 respectively). The use of harsher conditions resulted in some decomposition but no increase in the amount of eliminated product.

Esterification of **10** and **11** gave the desired α,β-unsaturated ketones **16** and **19**, in low yields. Efforts to acetylate or benzoylate the hydroxy groups of **10** and **11** in the presence of Hunigs base (ethyldiisopropylamine) afforded, as the major products, the enol esters **14** and **17** respectively, indicating the ease with which this ketone enolises in the direction of the 2-(5-pyridyl) group (Scheme 3). Benzoylating conditions were particularly efficient at forming the enol ester **17**. Even in the presence of the less basic pyridine, esterification of the enolate also occurred. For all of these attempts the principal component of the small quantities of mixtures of eliminated epimers, was the *cis* isomer (**15** or **18**). Attempts to hydrolyse the enol acetate **15** with methanol, and to force the elimination with diisopropylethylamine were unrewarding. The use of sodium methoxide induced the elimination reaction but 1,4-addition of methanol to the enone occurred to give the mixture of epimers **20** (Fig. 2).

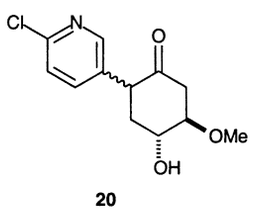


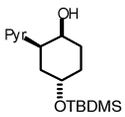
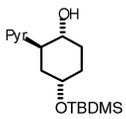
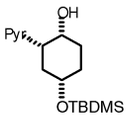
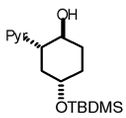
Fig. 2

After the failure of our initial approach we concentrated on one which depended upon a stereoselective carbonyl reduction reaction (Schemes 4 and 5). The first three steps are already described in the literature.[8,10,21] K-Selectride® was used to reduce the double bond of **21** chemoselectively, and the next two steps, as well as for enone **21**, were carried out using the published method.[8] Direct α-iodination of enone **23** afforded α-iodoenone **24**, in good yield (82%) and a Stille cross-coupling reaction introduced the chloropyridyl ring to form enone **25** (90%) (Scheme 4).

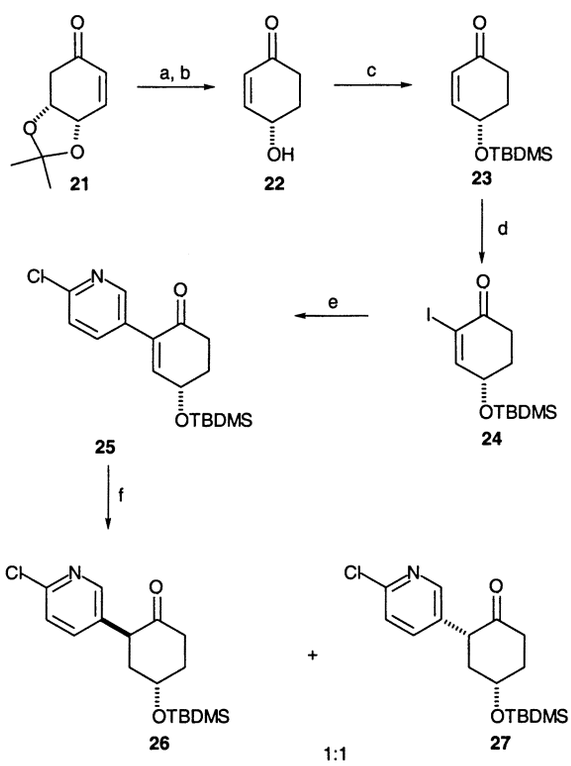
Conjugate reduction of enone **25** with K-Selectride®, gave the two epimers **26** and **27** in a 1:1 ratio. Trost and Cook[3] observed some selectivity with a similar system (NHBoc group instead of a OTBDMS group) and obtained the *cis* and *trans* products in a ratio of 4:1 respectively. The epimers **26** and **27** were very difficult to separate and since the pyridyl group was attached to an enolisable carbon atom, we reduced the carbonyl group of the compounds in the mixture (Table 1).

For the reduction of the mixture of **26** and **27** a variety of conditions were tested, and some interesting results obtained. L-Selectride® gave only the two *cis* diastereoisomers **28** and **29**, and both were the axial alcohols.[20] There were no significant differences between the ratios obtained with $NaBH_4$ and $NaBH_4$ with $CeCl_3{\cdot}7H_2O$, however, when the reduction was performed with $NaBH_4$ in the presence of DMSO the yield of the desired diastereoisomer **30** increased, and at −20 °C this improved further. However, simple borohydride reduction of this system at −20 °C afforded only slightly lower, selectivities. Since the yield of the required diastereoisomer is higher than expected from the ratio of the ketones **26** and **27**, we assume that **26** is being reduced more rapidly than **27** and that **27** is equilibrating with **26** *via* an enol under the reaction conditions.

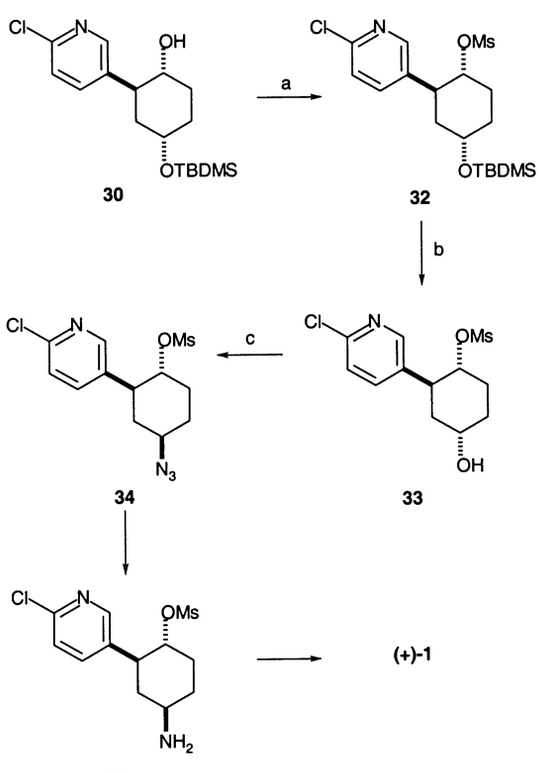
Table 1 Reduction of the carbonyl group of epimers **26** and **27**[a]

	Selectivity/%			
				
Conditions/yield	**28**	**30**	**29**	**31**
L-Selectride®, −78 °C/50%	32	0	68	0
DIBAL-H, −78 °C/67%	25	20	20	35
$NaBH_4$, 0 °C/99%	31	16	16	37
$NaBH_4$, $CeCl_3 \cdot 7H_2O$, 0 °C/97%	25	18	13	44
$NaBH_4$, DMSO (1 eq.), 0 °C/79%	17	49	13	21
$NaBH_4$, DMSO (2 eq.), 0 °C/95%	11	55	9	25
$NaBH_4$, −20 °C/98%	8	58	10	24
$NaBH_4$, DMSO (2 eq.), −20 °C/96%	8	62	4	26

[a] Pyr is 2-chloro-5-pyridyl.



Scheme 4 *Reagents and conditions*: (a) K-Selectride®, THF, −78 °C. (b) NaOH 0.5 M, THF, 0 °C. (c) TBDMSCl, $(i\text{-Pr})_2NEt$, DMAP, CH_2Cl_2, 0 °C/rt (51%, 3 steps). (d) I_2, DMAP, pyridine–CCl_4 (1 : 1), 0 °C/rt, 82%. (e) $Bu_3SnC_5H_3NCl$, $Pd_2(dba)_3 \cdot CHCl_3$, $AsPh_3$, CuI, THF, rt/60 °C, 90%. (f) K-Selectride®, THF, −78 °C, 88%.



Scheme 5 *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%. (b) Bu_4NF, THF, rt, 88%. (c) PPh_3, HN_3, DEAD, THF, 0 °C/rt, 94%.

Our assignment of the configurations to the various diastereoisomers produced was made by comparing the proton NMR spectra both of the reduction products and of their benzoates. The nature of this selectivity enhancement by DMSO is not understood although it must increase the rate of the equilibration reaction or the stereoselectivity of the reduction reaction.

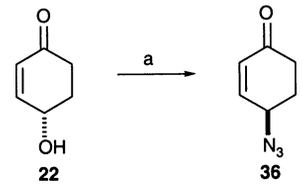
In our analysis the only way to explain the collected NMR data was by assuming that the pyridine moiety would control the conformation of the molecule by always adopting an equatorial position, in spite of the bulky OTBS group. Thus, on one hand, we could clearly see that compounds with *cis* H-1 and H-2, **28**, **29**, **28a** and **29a**, show a doublet for H-2, and the *trans* compounds **30**, **31**, **30a** and **31a** present a H-2 dt (Table 2). On the other hand, compounds **28**, **30**, **28a** and **30a**, all with the pyridine group above the plane of the molecule and the same chair conformation, have a lower field H-2 chemical shift than **29**, **31**, **29a** and **31a**, which have this group below the plane of the molecule. The H-1 and H-4 signals are singlets if the protons are in an equatorial position and multiplets if they are in an axial position, which correlates well with the expected values for the coupling constants between axial–equatorial, equatorial–equatorial and axial–axial protons in a chair conformation for cyclohexanes. Fortunately, the major diastereoisomer **30** obtained from the later attempts was that with the correct configuration for completion of the synthesis (Scheme 5).

Mesylation of **30** afforded **32** in quantitative yield, and removal of the TBDMS group was achieved with anhydrous TBAF.[10] By applying the Mitsunobu azide modification to compound **33**, azide **34** was obtained which presented a proton NMR spectrum identical to that previously reported.[5] The conversion of the racemic form of azide **34** to epibatidine has already been reported in two syntheses.[4,5]

Table 2 ^{1}H NMR and conformational assignments for the alcohols **28**–**31** and their benzoates **28a**–**31a**[a]

	δ(ppm), signal, J value							
Proton	**28**	**29**	**30**	**31**	**28a**	**29a**	**30a**	**31a**
H-1	4.21, s	3.89, s	3.70–3.62, m	3.77–3.72, m	5.37, s	5.28, s	5.18–5.09, m	5.11–5.04, m
H-2	3.27, d, J = 12.9 Hz	2.75, d, J = 13.2 Hz	3.04, dt, J = 11.7, 3.0 Hz	2.57, dt, J = 11.4, 3.0 Hz	3.49, d, J = 11.7 Hz	2.98, d, J = 12.9 Hz	3.43, dt, J = 12.4, 3.3 Hz	3.00, dt, J = 12.3, 3.0 Hz
H-4	4.01, s	3.71, m	4.09, s	3.67–3.60, m	4.32, s	3.84, m	4.15, s	3.86–3.79, m

[a] Pyr is 2-chloro-5-pyridyl.



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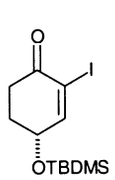
Scheme 6 *Reagents and conditions*: (a) DEAD, HN_3, PPh_3, THF, 0 °C/rt, 74%.

Another feasible route to (+)-epibatidine was tested (Scheme 6). Azide **36** was formed by a Mitsunobu azide reaction on enone **22**. After reduction of azide **36** and protection as the Boc amide, we expected to obtain the enantiomer of one of Trost's precursors in his epibatidine synthesis.[3] Attempted Staudinger reduction of azide **36** to the respective amine using standard conditions (triphenylphosphine TPP), resulted in severe destruction of the reagents. It is interesting to note that Trost, in a similar azide reduction, used a Staudinger reaction with the unusual trimethylphosphine.

The enone **39** has previously been reported[12] from the cyclohexane acetal **37**. As mentioned earlier the acid treatment of **9** afforded very low yields of unsaturated product **12**. Treatment of the readily available diacetal **38** with acid, however, afforded very good yields (85%) of the enone **39** which was immediately protected as its TBDMS ether **40** (Scheme 7). This method of preparing **40** is considerably easier than that described in the literature.[12] Tetramethoxybutane is readily obtained from inexpensive biacetyl. The protection of the *trans* diol using this reagent was high yielding and highly selective. The product resulting from the hydrolysis or acid elimination of the acetal was biacetyl which is yellow and acts as an indicator. Biacetyl is easily removed from the product either by washing or by evaporation. Cyclohexane-1,2-dione is expensive and the products formed by the hydrolysis or elimination from **37** are not volatile and not easily removed from the product. The rigidity of the acetal formed from biacetyl appears to be the same as that for the cyclohexanedione. The yield of product obtained from acetal **38** is very much higher than that reported for the cyclohexane acetal **37**. From enone **40** the iodoenone **41** could be prepared and provided an analoguous route to (−)-epibatidine.



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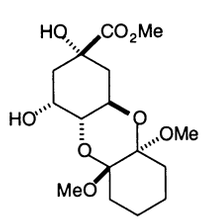

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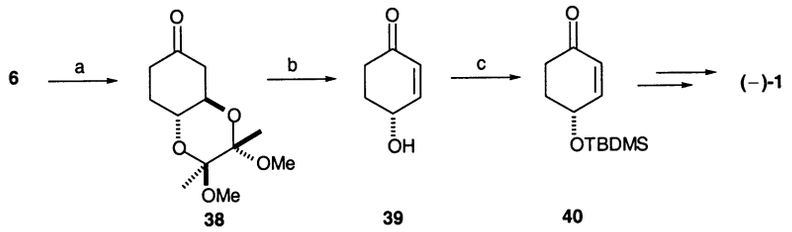
In summary, asymmetric routes have been developed for the synthesis of (+)- and (−)-epibatidine from readily available materials using mild reaction conditions. The other approaches to (−)-epibatidine reported here revealed important aspects of the reactivity of *trans* vicinal diols, and allowed us to prepare some potentially useful cyclohexane derivatives.

Experimental

General

Melting points were determined with a capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ with chemical shift values (δ) in ppm downfield from tetramethylsilane and at 300 K, and ^{13}C NMR spectra were obtained at 100.61 MHz in $CDCl_3$. DEPT, CH-COSY and



Scheme 7 *Reagents and conditions*: (a) Pearlman's catalyst, AcOEt, H_2 (50 psi), quantitative. (b) CF_3COOH, H_2O, CH_2Cl_2, reflux, 85%. (c) TBDMSCl, $(i\text{-Pr})_2NEt$, DMAP, CH_2Cl_2, 0 °C/rt, 98%.

HH-COSY were used as an aid to structure elucidation and carbon assignments but these data are not reported here. Microanalyses were performed by the ITQB analytical services using a combustion apparatus. IR (ν/cm^{-1}): measured on an FTIR spectrophotometer. Medium pressure preparative column chromatography: silica gel Merck 60 H. Preparative TLC: silica gel Merck 60 GF_{254}. Analytical TLC: Aluminium-backed silica gel Merck 60 F_{254}. Specific rotations ($[\alpha]_D^t$) were measured on an automatic polarimeter and values are given in 10^{-1} deg cm^2 g^{-1}. Reagents and solvents were purified and dried according to ref. 22. All the reactions were carried out in an inert atmosphere (argon or nitrogen), unless otherwise indicated.

(3*R*,4*R*,5*R*)-5-Hydroxy-3,4-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy]cyclohexan-1-one (5)

To a solution of **3**[24] (1.5 g, 4.68 mmol) in diethyl ether (40 mL) at −78 °C was slowly added DIBAL-H (diisobutylaluminium hydride 1.0 M solution in hexanes, 23.4 mL, 0.023 mmol). The reaction was stirred for 15 min at −78 °C and for a further 15 min at 0 °C. Water (30 mL) was added and the resulting gel was filtered and washed with water three times. To the aqueous filtrate containing triol **4**, was added $NaIO_4$ (1.71 g, 8.0 mmol) and the mixture was stirred at rt for 1 h, and then it was extracted with ethyl acetate (3 × 30 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to afford **5** (1.180 g, 97% from **3**) as white crystals. Compound **5**: mp 163–165 °C. $[\alpha]_D^{20}$ +159.8 (*c* 0.59 in CH_2Cl_2). Anal. calc. for $C_{12}H_{20}O_6$: C 55.37, H 7.74. Found: C 55.15, H 7.75%. ν_{max} (KBr)/cm^{-1}: 3481 (O–H), 3009, 2993, 2968, 2953, 2885 (all C–H), 1726 (C=O, sat. ketone). δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.25–4.23 (2H, m, H-3, H-5), 3.88 (1H, dd, J = 10.1, 2.4 Hz, H-4), 3.31 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 2.69–2.63 (3H, m, 2 × (H-2 and/or H-6) and/or OH), 2.54–2.46 (2H, m, 2 × (H-2 and/or H-6) and/or OH), 1.35 (3H, s, CH_3), 1.31 (3H, s, CH_3). δ_C (100.61 MHz; $CDCl_3$; Me_4Si) 205.4 (C-1), 100.2, 99.2 (2 × *C*(CH_3)OCH_3), 72.2, 67.6, 63.2 (C-3, C-4, C-5), 48.1, 47.9 (2 × OCH_3), 46.2, 44.7 (C-2, C-6), 17.6, 17.5 (2 × CH_3).

(4*R*,5*R*)-4,5-[(2*S*,3*S*)-2,3-Dimethoxybutane-2,3-diyldioxy]-cyclohex-2-en-1-one (6)

To a solution of **5** (1.180 g, 4.53 mmol) in CH_2Cl_2 (4.8 mL), at 0 °C, was added a catalytic amount of DMAP, diisopropylethylamine (1.59 mL, 9.5 mmol) and acetic anhydride (0.512 mL, 5.4 mmol). After stirring for 1 h at 0 °C all the starting material had been consumed. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by column chromatography (AcOEt–hexane 2:8) gave enone **6** (1.035 g, 94.2%) as white crystals. Mp 182–184 °C. $[\alpha]_D^{20}$ +64.4 (*c* 0.39 in CH_2Cl_2). Anal. calc. for $C_{12}H_{18}O_5$: C 59.49, H 7.49. Found: C 59.39, H 7.46%. ν_{max} (KBr)/cm^{-1}: 3003, 2966, 2955, 2930, 2856, 2839 (all C–H), 1680 (C=O, α,β-unsat. ketone). δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.85 (1H, dd, J = 10.1, 1.4 Hz, H-3), 6.00 (1H, d, J = 10.0 Hz, H-2), 4.49 (1H, dt, J = 9.0, 2.1 Hz, H-4), 4.09–4.00 (1H, m, H-5), 3.32 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 2.74 (1H, dd, J = 16.7, 5.2 Hz, H-6), 2.48 (1H, dd, J = 16.4, 13.4 Hz, H-6), 1.37 (3H, s, CH_3), 1.33 (3H, s, CH_3). δ_C (100.61 MHz; $CDCl_3$; Me_4Si) 196.8 (C-1), 148.5, 130.1 (C-2, C-3), 100.8, 99.7 (2 × *C*(CH_3)OCH_3), 69.2, 68.1 (C-4, C-5), 48.1, 48.0 (2 × OCH_3), 42.0 (C-6), 17.6 (2 × CH_3).

(4*R*,5*R*)-2-Iodo-4,5-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy]cyclohex-2-en-1-one (7)

To a solution of enone **6** (0.992 g, 4.09 mmol) in pyridine–CCl_4 (10 mL : 10 mL), at 0 °C, was added I_2 (2.604 g, 10.2 mmol) in pyridine–CCl_4 (6 mL : 6 mL) and a catalytic amount of DMAP. The reaction mixture was stirred at rt for 24 h, and then 20% aqueous $Na_2S_2O_3$ solution (15 mL) was added. The mixture was extracted with diethyl ether (3 × 10 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated to afford an orange solid which was purified by column chromatography. Elution with AcOEt–hexane 5:95 furnished **7** (1.448 g, 96%) as white crystals. Mp 190–192 °C. $[\alpha]_D^{20}$ +60.9 (*c* 0.63 in CH_2Cl_2). Anal. calc. for $C_{12}H_{17}O_5I$: C 39.15, H 4.65. Found: C 39.32, H 4.58%. ν_{max} (KBr)/cm^{-1}: 2958, 2947, 2918, 2860, 2833 (all C–H), 1682 (C=O, α,β-unsat. ketone). δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.63 (1H, d, J = 1.2 Hz, H-3), 4.49 (1H, d, J = 2.9 Hz, H-4), 4.08–4.01 (1H, m, H-5), 3.31 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 2.98 (1H, dd, J = 16.4, 4.7 Hz, H-6), 2.61 (1H, dd, J = 16.1, 13.4 Hz, H-6), 1.36 (3H, s, CH_3), 1.32 (3H, s, CH_3). δ_C (100.61 MHz; $CDCl_3$; Me_4Si) 189.9 (C-1), 156.8 (C-3), 103.7 (C-2), 101.0 and 99.8 (2 × *C*(CH_3)OCH_3), 71.2 and 67.6 (C-4, C-5), 48.2 and 48.1 (2 × OCH_3), 39.9 (C-6), 17.6, 17.5 (2 × CH_3).

(4*R*,5*R*)-2-(2-Chloro-5-pyridyl)-4,5-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy]cyclohex-2-en-1-one (8)

To a solution of **7** (0.800 g, 2.17 mmol) in THF (12 mL) was added $AsPh_3$ (0.068 g, 10 mol%), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.056 g, 2.5 mol%) and CuI (0.040 g, 10 mol%). The suspension was stirred for 10 min, and (2-chloro-5-pyridyl)tributyltin (1.138 g, 2.82 mmol) in THF (2 mL) was added. After stirring at 60 °C for 24 h, 10% aqueous Na_2SO_3 solution (5 mL) was added to the cooled (rt) suspension. The mixture was washed with 10% aqueous KF solution (10 mL) and extracted with diethyl ether (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and the solvent evaporated to give an orange solid residue. Purification by column chromatography (AcOEt–hexane 1:9) afforded **8** (0.653 g, 85%) as white crystals. Mp 147–149 °C. $[\alpha]_D^{20}$ +61.5 (*c* 0.66 in CH_2Cl_2). Anal. calc. for $C_{17}H_{20}O_5NCl$: C 57.71, H 5.70, N 3.96. Found: C 57.79, H 5.93, N 4.00%. ν_{max} (KBr)/cm^{-1}: 2991 and 2947 (C–H), 1678 (C=O, α,β-unsat. ketone). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.34 (1H, d, J = 3.0 Hz, pyr H-6), 7.66 (1H, dd, J = 9.0, 3.0 Hz, pyr H-4), 7.32 (1H, d, J = 9.0 Hz, pyr H-3), 7.00 (1H, s, H-3), 4.65 (1H, dd, J = 9.0, 3.0 Hz, H-4), 4.16 (1H, m, H-5), 3.36 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 2.93 (1H, dd, J = 15.0, 3.0 Hz, H-6), 2.66 (1H, dd, J = 15.0, 12.0 Hz, H-6), 1.40 (3H, s, CH_3), 1.36 (3H, s, CH_3).

(2*R*,4*R*,5*R*)-2-(2-Chloro-5-pyridyl)-4,5-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy]cyclohexan-1-one (9)

To a solution of **8** (0.682 g, 1.93 mmol) in THF (12 mL) at −78 °C was slowly added K-Selectride® (1.92 mL, 1.92 mmol). The reaction was stirred at this temperature for 1 h, and it was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 6 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated to yield a viscous residue which was purified by column chromatography (AcOEt–hexane 2.5:7.5). Compound **9** (0.679 g, 99%) was obtained as white crystals. Mp 156–158 °C. $[\alpha]_D^{20}$ +137.7 (*c* 0.48 in CH_2Cl_2). Anal. calc. for $C_{17}H_{22}O_5NCl$: C 57.39, H 6.23, N 3.94. Found: C 57.29, H 6.09, N 3.82%. ν_{max} (KBr)/cm^{-1}: 3013, 2993, 2951, 2883, 2835 (al C–H), 1720 (C=O, sat. ketone), 1591 (C=C). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.12 (1H, d, *J* = 3.0 Hz, pyr H-6), 7.38–7.31 (2H, m, pyr H-3 and H-4), 4.13–4.08 (1H, m, H-4 or H-5), 3.93–3.86 (1H, m, H-4 or H-5), 3.64 (1H, dd, *J* = 13.8, 5.7 Hz, H-2), 3.35 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 2.78–2.70 (2H, m, 2 × H-6), 2.31–2.24 (1H, m, H-3), 1.98 (1H, dt, *J* = 12.9 Hz, H-3), 1.53 (6H, s, 2 × CH_3). δ_C (100.61 MHz; $CDCl_3$; Me_4Si) 203.8 (C-1), 150.5 (pyr C-2), 149.6 (pyr C-6), 139.0 (pyr C-4), 131.5 (pyr C-5), 124.0 (pyr C-3), 99.8 and 99.5 (2 × *C*(CH_3)OCH_3), 69.3 and 68.0 (C-4, C-5), 51.6 (C-2), 48.2 and 48.1 (2 × OCH_3), 44.7 and 33.4 (C-3, C-6), 17.6 (2 × CH_3).

(2*R*/*S*,4*R*,5*R*)-2-(2-Chloro-5-pyridyl)-4,5-dihydroxycyclohexan-1-one (10 and 11) and (4*R*,6*R*)-6-(2-chloro-5-pyridyl)-4-hydroxycyclohex-2-en-1-one (12) and (4*R*,6*S*)-6-(2-chloro-5-pyridyl)-4-hydroxycyclohex-2-en-1-one (13)

To a solution of **9** (0.183 g, 0.51 mmol) in CH_2Cl_2 (5.6 mL) was added CF_3COOH (0.282 mL, 3.7 mmol) and water (0.056 mL). The reaction was refluxed for 5 h, and then it was cooled. The solvent was evaporated, the viscous residue was redissolved in AcOEt (5 mL) and solid $NaHCO_3$ was added. The suspension was filtered and the solvent evaporated again to afford a viscous residue. Purification by column chromatography (AcOEt–hexane 7:3) afforded a mixture of epimers **12** and **13** (0.010 g, 8.7%, 2.1:1 **12**–**13**) and a mixture of epimers **10** and **11** (0.102 g, 82%, in almost 1:1 ratio), both as colourless viscous oils. Epimers **10** and **11**: δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.18 (d, *J* = 3.0 Hz), 8.14 (d, *J* = 3.0 Hz), 7.50 (dd, *J* = 9.0, 3.0 Hz), 7.41 (m), 7.34–7.30 (m), 4.41 (br s), 4.19–4.05 (m), 3.80 (m), 3.68 (dd), 3.14 (dd, *J* = 15.0, 3.0 Hz), 2.90 (t, *J* = 6.0 Hz), 2.69–1.91 (m). *m*/*z* (EI): 241 ([M]$^+$, 5.12%), 207 (12.77), 205 (38.28), 170 (24.47), 168 (10.56), 152 (21.51), 142 (45.30), 140 (100), 127 (16.32), 115 (10.65), 104 (14.33), 84 (17.40), 77 (10). Compound **12**: δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.20 (1H, d, *J* = 2.4 Hz, pyr H-6), 7.57 (1H, dd, *J* = 8.4, 2.4 Hz, pyr H-4), 7.33 (1H, d, *J* = 8.1 Hz, pyr H-3), 7.03 (1H, d, *J* = 10.0 Hz, H-3), 6.13 (1H, dd, *J* = 10.5, 2.4 Hz, H-2), 4.83 (1H, m, H-4), 3.62 (1H, dd, *J* = 14.4, 3.9 Hz, H-6), 2.62–2.55 (1H, m, H-5), 2.36–2.28 (1H, m, H-5). Compounds **12** and **13**: *m*/*z* (EI): 223 ([M]$^+$, 4.90%), 219.90 (24.48), 140 (86.76), 104 (14.27), 84 (100), 77 (12.84), 55 (29.17).

(4*R*,5*R*)-1,4,5-Triacetoxy-2-(2-chloro-5-pyridyl)cyclohex-1-ene (14) and (4*R*,6*R*)-4-acetoxy-6-(2-chloro-5-pyridyl)cyclohex-2-en-1-one (15) and (4*R*,6*S*)-4-acetoxy-6-(2-chloro-5-pyridyl)cyclohex-2-en-1-one (16)

To a suspension of **10** and **11** (0.037 g, 0.15 mmol) in CH_2Cl_2 (1 mL), at 0 °C, was added a catalytic amount of DMAP, diisopropylethylamine (0.080 mL, 0.46 mmol) and acetic anhydride (0.029 mL, 0.030 mmol). After stirring for 3 h at 0 °C all the starting material had been consumed. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt–hexane 4:6) gave a mixture of epimers **15** and **16** (0.015 g, 37%, 2.7:1 **15**–**16**) and **14** (0.017 g, 30%), both fractions as colourless oils. Compound **14**: δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.30 (1H, d, *J* = 3.0 Hz, pyr H-6), 7.51 (1H, dd, *J* = 9.0, 3.0 Hz, pyr H-4), 7.30 (1H, d, *J* = 9.0 Hz, pyr H-3), 5.24–5.21 (2H, m, H-4, H-5), 2.86–2.81 (2H, m, 2 × (H-3 and/or H-6)), 2.57–2.50 (2H, m, 2 × (H-3 and/or H-6)), 2.09 (6H, s, 2 × $OC(O)CH_3$), 1.99 (3H, s, $OC(O)CH_3$). Compound **15**: δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.20 (1H, d, *J* = 3.0 Hz, pyr H-6), 7.45 (1H, dd, *J* = 5.7, 2.4 Hz, pyr H-4), 7.33 (1H, d, *J* = 8.1 Hz, pyr H-3), 6.92 (1H, dt, *J* = 10.5, 2.1 Hz, H-3), 5.86–5.81 (1H, m, H-4), 3.70 (1H, dd, *J* = 14.4, 4.2 Hz, H-6), 2.64–2.58 (1H, m, H-5), 2.42–2.34 (1H, m, H-5), 2.14 (3H, s, $OC(O)CH_3$). Compounds **15** and **16**: *m*/*z* (EI): 265 ([M]$^+$, 0.04%), 223 (10.24), 205 (23.16), 142 (37), 140 (100), 126 (9.44), 84 (44.34), 77 (5.83), 55 (5.33).

(4*R*,5*R*)-1,4,5-Tris(benzoyloxy)-2-(2-chloro-5-pyridyl)cyclohex-1-ene (17) and (4*R*,6*R*)-4-benzoyloxy-6-(2-chloro-5-pyridyl)-cyclohex-2-en-1-one (18) and (4*R*,6*S*)-4-benzoyloxy-6-(2-chloro-5-pyridyl)cyclohex-2-en-1-one (19)

To a suspension of **10** and **11** (0.032 g, 0.13 mmol) in CH_2Cl_2 (1 mL), at 0 °C, was added a catalytic amount of DMAP, diisopropylethylamine (0.069 mL, 0.40 mmol) and benzoyl chloride (0.031 mL, 0.026 mmol). After stirring for 3 h at 0 °C all the starting material had been consumed. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt–hexane 4:6) gave a mixture of epimers **18** and **19** (0.004 g, 10%, 2:1 **18**–**19**) as a colourless oil and **17** (0.066 g, 90%) as white crystals. Compound **17**: mp 52–54 °C. $[\alpha]_D^{20}$ −40.9 (*c* 0.94 in CH_2Cl_2). Anal. calc. for $C_{32}H_{24}O_6NCl$: C 69.38, H 4.37, N 2.53. Found: C 69.40, H 4.07, N 2.58%. ν_{max} (KBr)/cm^{-1}: 3063 (C–H), 1724 (C=O, ester). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.48 (1H, s, Ar or pyr H), 8.07–8.01 (5H, m, Ar and pyr H), 7.95–7.93 (2H, d, *J* = 6.0 Hz, Ar and/or pyr H), 7.59–7.28 (10H, 2m, Ar and pyr H), 5.73 (2H, s, H-4, H-5), 3.25–3.14 (2H, m, 2 × (H-3 and/or H-6)), 3.25–3.14 (2H, m, 2 × (H-3 and/or H-6)). Epimers **18** and **19**: δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.24 (d, *J* = 2.4 Hz, pyr H-6 **18**), 8.08–8.04 (m), 7.59 (m), 7.51–7.45 (m), 7.46 (d, *J* = 8.1 Hz), 7.06 (d, *J* = 10.5 Hz, H-3 **18**), 6.26 (dd, *J* = 10.2, 2.1 Hz, H-2 **18**), 6.09 (m, H-4 **18**), 5.78 (m, H-4 **19**), 4.10 (dd, *J* = 10.5, 5.1 Hz, H-6 **18**), 3.79 (dd, *J* = 14.4, 4.2 Hz, H-6 **18**), 2.80–2.49 (m). ν_{max} (KBr)/cm^{-1}: 1718 (C=O, ester), 1685 (C=O, α,β-unsat. ketone), 1564 (C=C). *m*/*z* (EI): 327 ([M]$^+$, 0.53%), 309 (2.25), 205 (6.85), 140 (2.70), 105 (100), 77 (17.72).

(4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-iodocyclohex-2-en-1-one (24)

To a solution of enone **23** (1.032 g, 4.56 mmol) in pyridine–CCl_4 (6 mL:6 mL), at 0 °C, was added I_2 (2.89 g, 11.4 mmol) in pyridine–CCl_4 (5 mL:5 mL) and a catalytic amount of DMAP. The reaction mixture was stirred at rt for 4 h, and then 20% aqueous $Na_2S_2O_3$ solution (15 mL) was added. The mixture was extracted with diethyl ether (3 × 10 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated to afford an orange residue which was purified by column chromatography. Elution with AcOEt–hexane 5:95 furnished **24** (1.317 g, 82%) as a colourless liquid. $[\alpha]_D^{20}$ −44.4 (*c* 1.68 in CH_2Cl_2). ν_{max} (film)/cm^{-1}: 2954, 2931, 2885, 2856 (all C–H), 1693 (C=O, α,β-unsat. ketone), 1589 (C=C). δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.61 (1H, s, H-3), 4.51 (1H, m, H-4), 2.83 (1H, dt, *J* = 16.8, 4.5 Hz, H-5 or H-6), 2.56–2.44 (1H, m, H-5 or H-6), 2.28–2.22 (1H, m, H-5 or H-6), 2.07–2.03 (1H, m, H-5 or H-6), 0.91 (9H, s, $SiC(CH_3)_3$), 0.13 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$).

(4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-chloro-5-pyridyl)cyclohex-2-en-1-one (25)

To a solution of **24** (0.883 g, 2.5 mmol) in THF (6 mL) was added $AsPh_3$ (0.076 g, 10 mol%), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.064 g, 2.5 mol%) and CuI (0.048 g, 10 mol%). The suspension was stirred for 10 min, and (2-chloro-5-pyridyl)tributyltin (1.304 g, 3.24 mmol) was added. After stirring at 60 °C for 24 h, 10% aqueous Na_2SO_3 solution (5 mL) was added to the cooled suspension. The mixture was washed with 10% aqueous KF solution (10 mL) and extracted with diethyl ether (3 × 10 mL), the combined organic layers dried ($MgSO_4$) and the solvent evaporated to give an orange liquid residue. Purification by column chromatography (AcOEt–hexane 0.5:9.5) afforded **25** (0.762 g, 90%) as a yellowish oil. $[\alpha]_D^{20}$ −50.8 (*c* 1.13 in CH_2Cl_2). ν_{max} (film)/cm^{-1}: 2955, 2930, 2885, 2858 (all C–H), 1685 (C=O, α,β-unsat. ketone), 1581 (C=C). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.34 (1H, d, *J* = 1.5 Hz, pyr H-6), 7.70 (1H, dd, *J* = 8.7, 2.4 Hz, pyr H-4), 7.33 (1H, d, *J* = 8.1 Hz, pyr H-3), 6.94 (1H, s, H-3), 4.69 (1H, m, H-4), 2.77 (1H, dt, *J* = 12.6, 4.2 Hz, H-5 or H-6), 2.52 (1H, dt, *J* = 12.9, 4.2 Hz, H-5 or H-6), 2.34–2.29 (1H, m, H-5 or H-6), 2.14–2.10 (1H, m, H-5 or H-6), 0.93 (9H, s, $SiC(CH_3)_3$), 0.16 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$).

(2*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-chloro-5-pyridyl)-cyclohexan-1-one (26) and (2*R*,4*S*)-4-[(*tert*-butyldimethylsilyl)-oxy]-2-(2-chloro-5-pyridyl)cyclohexan-1-one (27)

To a solution of **25** (0.200 g, 0.59 mmol) in THF (3 mL) at −78 °C was slowly added K-Selectride® (1 M in THF, 0.588 mL, 0.59 mmol). Saturated aqueous NH_4Cl solution (5 mL) was added and the temperature was allowed to rise to rt. The mixture was extracted with ethyl ether (3 × 5 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated to yield a residue that was purified by column chromatography (AcOEt–hexane 1:9). A mixture of the two epimers **26** and **27** was obtained (0.177 g, 88%, 1:1) as a colourless liquid. δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.13 (2H, d, *J* = 1.8 Hz, 2 × pyr H-6), 7.47–7.28 (4H, m, 2 × pyr H-4, 2 × pyr H-3), 4.30 (1H, s, H-4 **26**), 4.21 (1H, m, H-4 **27**), 3.68 (1H, dd, *J* = 13.5, 5.4 Hz, H-2 **26**), 2.95 (1H, dt, *J* = 13.5, 5.7 Hz, H-2 **27**), 2.56–1.80 (12H, m, 4 × H-3, 4 × H-5, 4 × H-6), 0.96 (9H, s, $SiC(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.14 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$). ν_{max} (film)/cm^{-1}: 2953, 2930, 2887 (all C–H), 1720 (C=O, sat. ketone), 1566 (C=C). *m*/*z* (EI): 339 ([M]$^+$, 1.93%), 282 (100), 240 (42.65), 226 (34.43), 190 (10.47), 140 (12.78), 115 (10.40), 75 (48.99).

(1*R*,2*R*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-chloro-5-pyridyl)cyclohexan-1-ol (30) and (1*S*,2*R*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-(2-chloro-5-pyridyl)cyclohexan-1-ol (28) and (1*R*,2*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-(2-chloro-5-pyridyl)cyclohexan-1-ol (29) and (1*S*,2*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-(2-chloro-5-pyridyl)cyclohexan-1-ol (31)

To a solution of **26** and **27** (0.293 g, 0.86 mmol) in methanol (6 mL) at −20 °C, was added DMSO (dimethyl sulfoxide, 0.161 mL, 1.72 mmol) and $NaBH_4$ (0.151 g, 3.44 mmol). The reaction was stirred until all the starting material had been consumed. Saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with diethyl ether (8 mL) and ethyl acetate (2 × 8 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to give a viscous residue, which was purified by column chromatography (AcOEt–hexane 1:9) and it afforded the four diastereoisomers **28**, **29**, **30** and **31** (0.283 g, 96%) 2:1:15.5:6.5, respectively. Compound **28**: $[\alpha]_D^{20}$ +32.0 (*c* 0.325 in CH_2Cl_2). ν_{max} (film)/cm^{-1}: 3353 (O–H), 2951, 2928, 2884, 2856 (C–H). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.29 (1H, s, pyr H-6), 7.61 (1H, dd, *J* = 8.4, 2.1 Hz, pyr H-4), 7.27 (1H, d, *J* = 7.8 Hz, pyr H-3), 4.21 (1H, s, H-1), 4.01 (1H, s, H-4), 3.27 (1H, d, *J* = 12.9 Hz, H-2), 2.18 (2H, dt, *J* = 11.4 Hz, 2 × H-3 or 2 × H-5 or 2 × H-6), 1.91–1.52 (4H, m, 2 × H-3 and/or 2 × H-5 and/or 2 × H-6), 0.90 (9H, s, $SiC(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$). Compound **29**: $[\alpha]_D^{20}$ −61.2 (*c* 0.25 in CH_2Cl_2). ν_{max} (film)/cm^{-1}: 3450 (O–H), 2891 and 2856 (C–H). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.27 (1H, d, *J* = 1.8 Hz, pyr H-6), 7.64 (1H, dd, *J* = 8.1, 2.4 Hz, pyr H-4), 7.28 (1H, d, *J* = 8.4 Hz, pyr H-3), 3.89 (1H, s, H-1), 3.71 (1H, m, H-4), 2.75 (1H, d, *J* = 13.2 Hz, H-2), 2.13–1.68 (6H, m, 2 × H-3, 2 × H-5, 2 × H-6), 0.90 (9H, s, $SiC(CH_3)_3$), 0.08 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$). Compound **30**: mp 79–80 °C. $[\alpha]_D^{20}$ −10.6 (*c* 0.32 in CH_2Cl_2). Anal. calc. for $C_{17}H_{28}O_2NSiCl$: C 59.71, H 8.25, N 4.10. Found: C 59.80, H 8.62, N 4.12%. ν_{max} (film)/cm^{-1}: 3375 (O–H), 2955, 2943, 2926, 2899, 2856 (all C–H). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.28 (1H, s, pyr H-6), 7.54 (1H, dd, *J* = 8.1, 2.1 Hz, pyr H-4), 7.29 (1H, d, *J* = 8.7 Hz, pyr H-3), 4.09 (1H, s, H-4), 3.70–3.62 (1H, m, H-1), 3.04 (1H, dt, *J* = 11.7, 3.0 Hz, H-2), 1.94–1.59 (6H, m, 2 × H-3, 2 × H-5, 2 × H-6), 0.92 (9H, s, $SiC(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$). Compound **31**: $[\alpha]_D^{20}$ −7.00 (*c* 0.74 in CH_2Cl_2). ν_{max} (film)/cm^{-1}: 3358 (O–H), 2933, 2885, 2857 (all C–H). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.25 (1H, s, pyr H-6), 7.56 (1H, dd, *J* = 8.4, 2.4 Hz, pyr H-4), 7.29 (1H, d, *J* = 8.4 Hz, pyr H-3), 3.77–3.72 (1H, m, H-1), 3.67–3.60 (1H, m, H-4), 2.57 (1H, dt, *J* = 11.4, 3.0 Hz, H-2), 2.15–1.97 (4H, m, 2 × H-3 and/or 2 × H-5 and/or 2 × H-6 or OH), 1.70–1.48 (3H, m, 2 × H-3 and/or 2 × H-5 and/or 2 × H-6), 0.87 (9H, s, $SiC(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$).

(1*R*,2*R*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-chloro-5-pyridyl)-1-[(methylsulfonyl)oxy]cyclohexane (32)

To a solution of **30** (0.085 g, 0.25 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added triethylamine (0.085 mL, 0.60 mmol) and mesyl chloride (0.030 mL, 0.38 mmol). When all the starting material had been consumed (10 min), saturated aqueous NH_4Cl solution (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). After drying ($MgSO_4$) the combined organic layers, the solvent was evaporated to afford **32** (0.103 g, 99%) as a viscous liquid. $[\alpha]_D^{20}$ −18.6 (*c* 0.42 in CH_2Cl_2). ν_{max} (KBr)/cm^{-1}: 2951, 2935, 2887, 2858 (C–H). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.28 (1H, d, *J* = 1.8 Hz, pyr H-6), 7.58 (1H, dd, *J* = 8.1, 2.4 Hz, pyr H-4), 7.32 (1H, d, *J* = 8.4 Hz, pyr H-3), 4.66 (1H, dt, *J* = 10.5, 5.4 Hz, H-1), 4.11 (1H, s, H-4), 3.32 (1H, m, H-2), 2.53 (3H, s, OSO_2CH_3), 2.24–2.17 (2H, m, H-3 and/or H-5 and/or H-6), 1.93–1.65 (4H, m, 2 × H-3 and/or 2 × H-5 and/or 2 × H-6). *m*/*z* (EI): 420.10 ([M + 1]$^+$, 0.22%), 362 (7.46), 192 (100), 153 (84.45), 126 (53), 117 (16.44). HRMS found: M$^+$ − Clpyr − TBDMS 192.045601, $C_7H_{12}O_4S$ requires 192.045631.

(1*S*,3*R*,4*R*)-3-(2-Chloro-5-pyridyl)-4-[(methylsulfonyl)oxy]-cyclohexan-1-ol (33)

To a solution of **32** (0.109 g, 0.26 mmol) in THF (2 mL) at rt was added Bu_4NF (0.085 mL, 0.60 mmol). The mixture was stirred at rt until all the starting material had been consumed (24 h). The reaction was diluted with ethyl acetate (2 mL) and water (2 mL) was added. After stirring for 5 min, the mixture was quenched with saturated NaCl (5 mL) and extracted with ethyl acetate (3 × 5 mL). Evaporation of the solvent afforded a viscous residue which was purified by preparative TLC (AcOEt–hexane 7:3) to yield **33** (0.070 g, 88%) as a white solid. Mp 108–109 °C. $[\alpha]_D^{20}$ −45.0 (*c* 0.28 in CH_2Cl_2). ν_{max} (KBr)/cm^{-1}: 3394 (O–H), 2957, 2935, 2895 (all C–H), 1587 (C=C). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.30 (1H, s, pyr H-6), 7.60 (1H, dd, *J* = 9.0, 3.0 Hz, pyr H-4), 7.32 (1H, d, *J* = 9.0 Hz, pyr H-3), 4.66 (1H, m, H-4), 4.20 (1H, s, H-1), 3.40–3.30 (1H, m, H-3), 2.54 (3H, s, OSO_2CH_3), 2.21–1.76 (6H, m, 2 × H-2, 2 × H-5, 2 × H-6). *m*/*z* (EI): 305 ([M]$^+$, 0.16%), 209 (7.38), 191 (100), 165 (21), 140 (15.47), 126 (16.15), 104 (10.81), 79 (9.72).

HRMS found: $M^+ - OMs - OH - 2H$ 191.049801, $C_{11}H_{10}NCl$ requires 191.050177.

(1*R*,2*R*,4*R*)-4-Azido-2-(2-chloro-5-pyridyl)-1-[(methylsulfonyl)-oxy]cyclohexane (34)

To a solution of **33** (0.074 g, 0.24 mmol) in THF (3 mL), at 0 °C, was added triphenylphosphine (0.093 g, 0.36 mmol), hydrazoic acid (0.84 M in benzene, 1.72 mL, 1.44 mmol) and DEAD (diethyl azodicarboxylate, 0.058 mL, 0.36 mmol) in THF dropwise. The reaction mixture was stirred at rt. When all the starting material had been consumed, the solvent was evaporated and the residue was purified by column chromatography (AcOEt–hexane 2:8) to afford a mixture of azide **34** and the eliminated by-product (19:1) as white crystals. Azide **34** was further purified by recrystallisation from ether (0.075 g, 94%). Mp 128–129 °C (lit.[5] racemic 119–120 °C). $[\alpha]_D^{20}$ −10.1 (*c* 0.345 in CH_2Cl_2). ν_{max} (KBr)/cm^{-1}: 2964, 2942 (both C–H), 2108 (N_3). δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.30 (1H, d, J = 1.8 Hz, pyr H-6), 7.61 (1H, dd, J = 8.4, 2.1 Hz, pyr H-4), 7.38 (1H, d, J = 8.4 Hz, pyr H-3), 4.61 (1H, dt, J = 10.8, 4.5 Hz, H-1), 4.52 (1H, m, H-4), 2.90 (1H, m, H-2), 2.53 (3H, s, OSO_2CH_3), 2.53–2.49 (1H, m, H-3 or H-5 or H-6), 2.25–2.20 (2H, m, 2 × H-2 and/or 2 × H-5 and/or 2 × H-6), 1.88–1.58 (2H, m, 2 × H-2 and/or 2 × H-5 and/or 2 × H-6). δ_C (100.61 MHz; $CDCl_3$; Me_4Si) 151.1 (pyr C-2), 149.7 (pyr C-6), 137.6 (pyr C-4), 134.8 (pyr C-5), 124.6 (pyr C-3), 82.1 (C-1), 57.9 (C-4), 44.6 (C-2), 38.1 (OSO_2CH_3), 37.3, 31.5 and 29.6 (C-3, C-5, C-6). *m*/*z* (EI): 205 (100%), 191 (18), 178 (92.53), 166 (30.27), 164 (41.41), 152 (24.24), 140 (35.89), 126 (40.43), 104 (54.22), 78.90 (47.71), 63 (15.17), 51 (21.45). HRMS found: $M^+ - OMs - N_3 - 2H$ 191.050765, $C_{11}H_{10}NCl$ requires 191.050177.

(4*R*,5*R*)-4,5-[(2*S*,3*S*)-2,3-Dimethoxybutane-2,3-diyldioxy]-cyclohexan-1-one (38)

A Parr hydrogenation flask was charged with enone **6** (0.080 g, 0.33 mmol), ethyl acetate (3 mL) and Pearlman's catalyst (palladium hydroxide on carbon, 0.0021 g). This mixture was hydrogenated (50 psi§) for 15 h. The suspension was filtered through a pad of Celite and the filtrate was concentrated to yield 0.080 g (quantitative yield) of the saturated product **38** as white crystals. $[\alpha]_D^{20}$ +152.6 (*c* 0.49 in CH_2Cl_2). ν_{max} (KBr)/cm^{-1}: 2955, 2889 (both C–H), 1721 (C=O, sat. ketone). δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.94–3.86 (1H, m, H-3 or H-4), 3.79–3.70 (1H, m, H-3 or H-4), 3.32 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 2.64–2.30 (4H, m, 2 × H-2 and/or 2 × H-5 and/or 2 × H-6), 2.11–1.99 (1H, m, H-2 or H-5 or H-6), 1.77–1.61 (1H, m, H-2 or H-5 or H-6), 1.33 (3H, s, CH_3), 1.32 (3H, s, CH_3).

(4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]cyclohex-2-en-1-one (40)

To a solution of **38** (0.080 g, 0.33 mmol) in CH_2Cl_2 (1.5 mL) was added CF_3COOH (0.179 mL, 2.34 mmol) and water (0.034 mL). The reaction was refluxed for 2 h and then it was cooled. The solvent was evaporated to afford a liquid residue. Purification by preparative TLC (AcOEt–hexane 7:3) afforded 0.032 g (85% yield) of the eliminated product **39** as a colourless liquid, which proton NMR spectrum was identical to that of its enantiomer.[21] This compound was dissolved in CH_2Cl_2 (1 mL) and, at 0 °C, diisopropylethylamine (0.132 mL, 0.76 mmol), a catalytic quantity of DMAP and *tert*-butyldimethylsilyl chloride (TBDMSCl, 0.092 g, 0.60 mmol) in CH_2Cl_2 (1 mL) were added. The reaction was stirred at rt for 18 h. Water (2 mL) was then added and the mixture was vigorously stirred for 15 min and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The liquid residue was purified by preparative TLC (AcOEt–hexane 2:8) to afford compound **40** (0.063 g, 98%) as a colourless oil. $[\alpha]_D^{20}$ +112.3 (*c* 0.98 in $CHCl_3$), (lit.[21] $[\alpha]_D$ −115.94 (*c* 1.06 in $CHCl_3$) for the enantiomer). ν_{max} (KBr)/cm^{-1}: 2954, 2930, 2857 (all C–H), 1690 (C=O). δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.83 (1H, dt, J = 10.2, 1.8 Hz, H-3), 5.92 (1H, dd, J = 10.2, 0.6 Hz, H-2), 4.53 (1H, m, H-4), 2.58 (1H, dt, J = 16.8, 4.5 Hz, H-6), 2.35 (1H, m, H-6), 2.22 (1H, m, H-5), 2.00 (1H, m, H-5), 0.92 (9H, s, $SiC(CH_3)_3$), 0.13 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$).

§ 1 psi = 6.89 kPa.

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