# Preparation of chiral enantiopure 2-(hydroxyalkyl)pyridine derivatives. Use of the chiral pool

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Enantiomerically pure 2-(1-hydroxyalkyl)pyridines were prepared *via* reaction of 2-lithiopyridine with (*R*)-2,3-*O*-isopropylideneglyceraldehyde, methyl (*S*)-2-methoxypropionate and methyl (*S*)-2-methoxy-2-phenylacetate, obtained from D-mannitol, L-lactic acid and L-mandelic acid, respectively. 6,6′-Bis(1-hydroxyalkyl)-2,2′-bipyridines were obtained from the same naturally occurring chiral compounds and 2-bromo-6-lithiopyridine with subsequent Ni-catalysed coupling.

## Introduction

Chiral pyridyl alcohols have proven to be versatile reagents in asymmetric catalysis. Their use in catalytic applications includes the addition of diethylzinc to aldehydes,[1,2] nickel-catalysed conjugate addition of diethylzinc,[3] and epoxidation of olefins.[4] Pyridyl alcohols with an oxazoline unit have been used in the addition of diethylzinc to aldehydes[5] and in palladium-catalysed allylic substitutions.[6] Furthermore, ligands with interesting catalytic properties have been obtained by transformation of chiral pyridyl alcohols into pyridyl phosphines[7] and phosphites,[7b,c] and $C_3$-symmetric phosphorus esters have been prepared from the same family of compounds.[8]

Due to the numerous applications of chiral pyridyl alcohols, efficient methods for their preparation are highly desirable, and a variety of methods have indeed been presented. These include methods relying on (i) asymmetric synthesis, involving biological methods as well as synthetic reagents and catalysts, (ii) resolution of racemic alcohols, and (iii) the use of chiral compounds from the chiral pool.

The biological methodologies include lipase-catalysed resolutions, either *via* ester hydrolysis,[9] esterification and transesterification,[10] aldol condensation[11] or oxidation resulting in deracemization,[12] microbial hydrolysis and reduction[13] or baker's yeast reductions[14] or oxidations.[15] In addition, synthetic NADH models[16] and catalytic antibodies[10b] have been employed for the same purpose. The use of these methods is commonly limited to only a few substrates and often the two enantiomers are obtained in a maximum yield of 50% each; in the case where one single enantiomer is obtained, its antipode is not accessible. Recent studies involving ruthenium- and palladium-catalysed isomerisation of the starting material led to efficient dynamic kinetic resolution.[17]

Synthetic procedures which have been employed include electrochemical reduction in the presence of some chiral agent,[18] asymmetrically modified lithium and sodium borohydrides,[19] oxazaborolidine reductions,[20] proline–borane reductions,[21] *B*-chlorodiisopinocampheylborane (DIP-Cl) and analogues,[22,23] hydrosilylations and diethylzinc additions,[24] diastereoselective reductions,[25,26] and Baylis–Hillman reactions.[27] Some of the reagents, stoichiometric as well as catalytic, have shown rather poor results, and access to enantiomerically pure derivatives usually requires subsequent transformation into and separation of the diastereomeric derivatives.

Several of the reagents employed for the preparation of pyridyl alcohols owe their selectivity to size discrimination. Since the sterical demand of a *tert*-butyl group is similar to that of a pyridyl group, lower selectivity is usually observed in the preparation of 2-(1-hydroxy-2,2-dimethylpropyl)pyridine, both in kinetic resolution involving enzyme-catalysed hydrolysis/esterification, and in reduction employing chiral hydride reagents. In one method, advantage was taken of the higher selectivity obtained for the 6-bromo derivative, the desired compound being obtained by radical debromination using $Bu_3SnH$–AIBN.[22] In order to obtain the enantiomerically pure compound, separation of diastereomeric ester derivatives was necessary.

Separation of diastereomeric derivatives is in fact often required as a final step in synthetic procedures employing one of the asymmetric transformations above, since scalemic mixtures are commonly obtained. However, the method has occasionally also been employed for the preparation of (hydroxyalkyl)pyridine derivatives from racemic mixtures. Camphenic acid,[1e] tartrates[28] and isocyanates[29] prepared from chiral primary amines have been employed for the separation of monosubstituted (hydroxyalkyl)pyridines, but separation of the diastereomeric esters or carbamates has often proved to be difficult. Nevertheless, a tertiary alcohol, 1-(isoquinolin-1-yl)-1-(2-pyridyl)ethanol was conveniently separated in multigram quantities *via* derivatisation with enantiopure isocyanates.[30] (*R*,*R*)-2,6-Bis(1-hydroxy-2,2-dimethylpropyl)pyridine was prepared from the racemate (obtained by reaction of 2,6-dibromopyridine with pivalaldehyde and separation from the *meso* isomer) by multiple crystallisations of the dibenzoyl tartrate salt.[3c] Pyridyl alcohols containing an additional stereocenter of defined absolute configuration have also been separated by column chromatography,[5,6,3] and chiral HPLC has been employed to achieve the separation of 2,6-bis(1-hydroxyalkyl)-pyridines.[32]

Pyridyl alcohols attached to dendrimers[33] and polymers[34] have also been described.

Use of the chiral pool constitutes an often useful alternative procedure for the preparation of chiral compounds.[35–39] This procedure often requires several steps, generally resulting in poor overall yields, and usually only one enantiomer is readily available. The advantage is that the chiral sources often are cheap and that stereochemically pure compounds are easily obtained by normal separation procedures.

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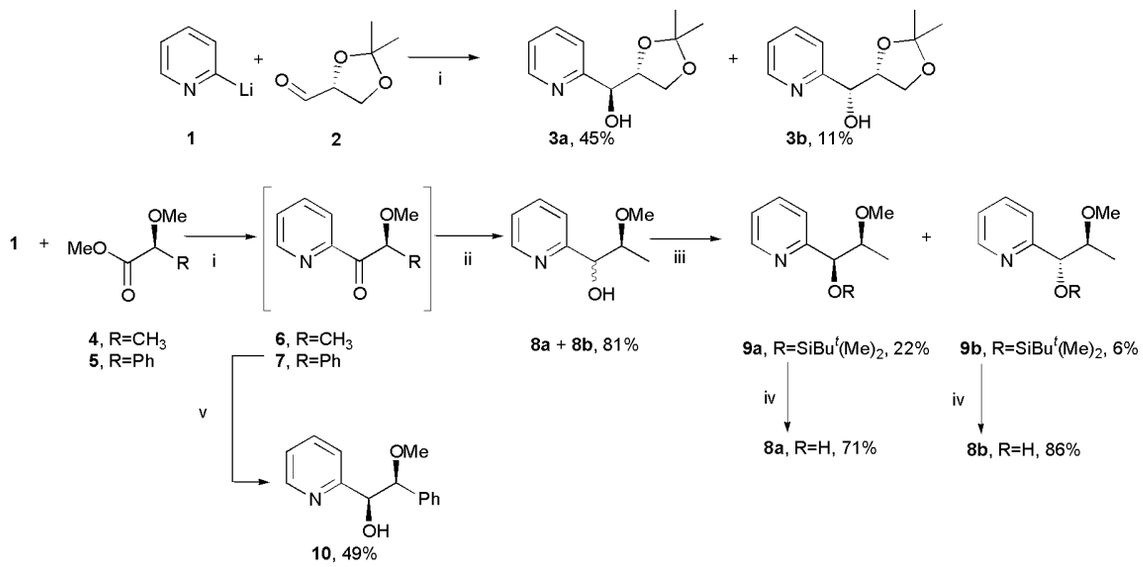



**Scheme 1** *Reagents and conditions*: i, $Et_2O$, −78 °C; ii, $NaBH_4$, MeOH, 0 °C to RT; iii, TBDMSCl, imidazole, DMF, RT; iv, TBAF, THF, 0 °C and RT; v, $NaBH_4$, $Et_2O$, MeOH, −78 °C to RT.

The convenience of the method has been demonstrated in a few cases. Reaction of 2-pyridyllithium with menthone, for example, takes place to yield in one step the desired tertiary alcohol as a single diastereomer.[35b] We have recently shown that the nitrile obtained by reacting (1*R*,2*S*,5*R*)-menthyl tosylate with sodium cyanide could be treated with 2-pyridyllithium to yield a ketone (41%).[8] Reduction of the ketone using $NaBH_4$ was shown to afford two isomeric alcohols (77 and 16% yield, respectively), which proved to be easy to separate by ordinary chromatography. Reaction of 2-pyridyllithium with 2,3 : 5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone and 2,3-*O*-isopropylidene-D-ribono-1,4-lactone gave pyridyl alcohols in 74 and 54% yields, respectively.[37a] Finally, nickel-catalysed coupling of (3*R*)-3-(2-bromo-6-pyridyl)-1,2 : 5,6-di-*O*-isopropylidene α-D-glucofuranose, obtained from 6-bromo-2-lithiopyridine and the appropriate glucose derivative, afforded a $C_2$-symmetric bipyridine.[37d] A variety of chiral pyridyl alcohols have also been obtained by cobalt(I)-catalysed cocyclotrimerization of acetylene with optically active nitriles, the nitrile being obtained from the chiral pool or from some other source.[39]

In this paper the use of other cheap chiral sources for the preparation of chiral enantiopure 2-(1-hydroxyalkyl)pyridines is presented.

## Results and discussion

### 2-(1-Hydroxyalkyl)pyridines

D-Mannitol, L-lactic acid and L-mandelic acid were selected as starting material for the preparation of chiral 2-(1-hydroxyalkyl)pyridines in enatiomerically pure form. Thus, reaction of 2-lithiopyridine (**1**) with (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**), obtained from D-mannitol,[40] gave in one step two epimeric alcohols **3a** and **3b** (Scheme 1), which could be separated by chromatography (45 and 11%, respectively).

Methyl (*S*)-2-methoxypropionate (**4**, obtained by esterification of lactic acid using methanol followed by *O*-methylation) was reacted with 2-lithiopyridine to yield ketone **6** (Scheme 1). *In situ* reduction using sodium borohydride gave a mixture of isomeric alcohols (**8a** and **8b**, 94% yield from methyl (*S*)-2-methoxypropionate). Unfortunately, the alcohols proved to be difficult to separate and had to be converted to silyl ethers (**9a** and **9b**) prior to chromatography, a procedure that decreased the yields substantially. Final hydrolysis afforded the desired alcohols **8a** and **8b** (71 and 86%, respectively).

The analogous reaction of 2-pyridyllithium with *O*-methylmandelate (**5**, obtained from L-mandelic acid), yielding **7** (Scheme 1), followed by *in situ* reduction at room temperature using sodium borohydride gave a mixture of isomeric alcohols (ratio 8 : 1, **10** being the major one). At lower temperature (−78 °C) **10** was obtained as a single isomer (49%), thus avoiding laborious separation procedures.

### 6,6′-Bis(1-hydroxyalkyl)-2,2′-bipyridines

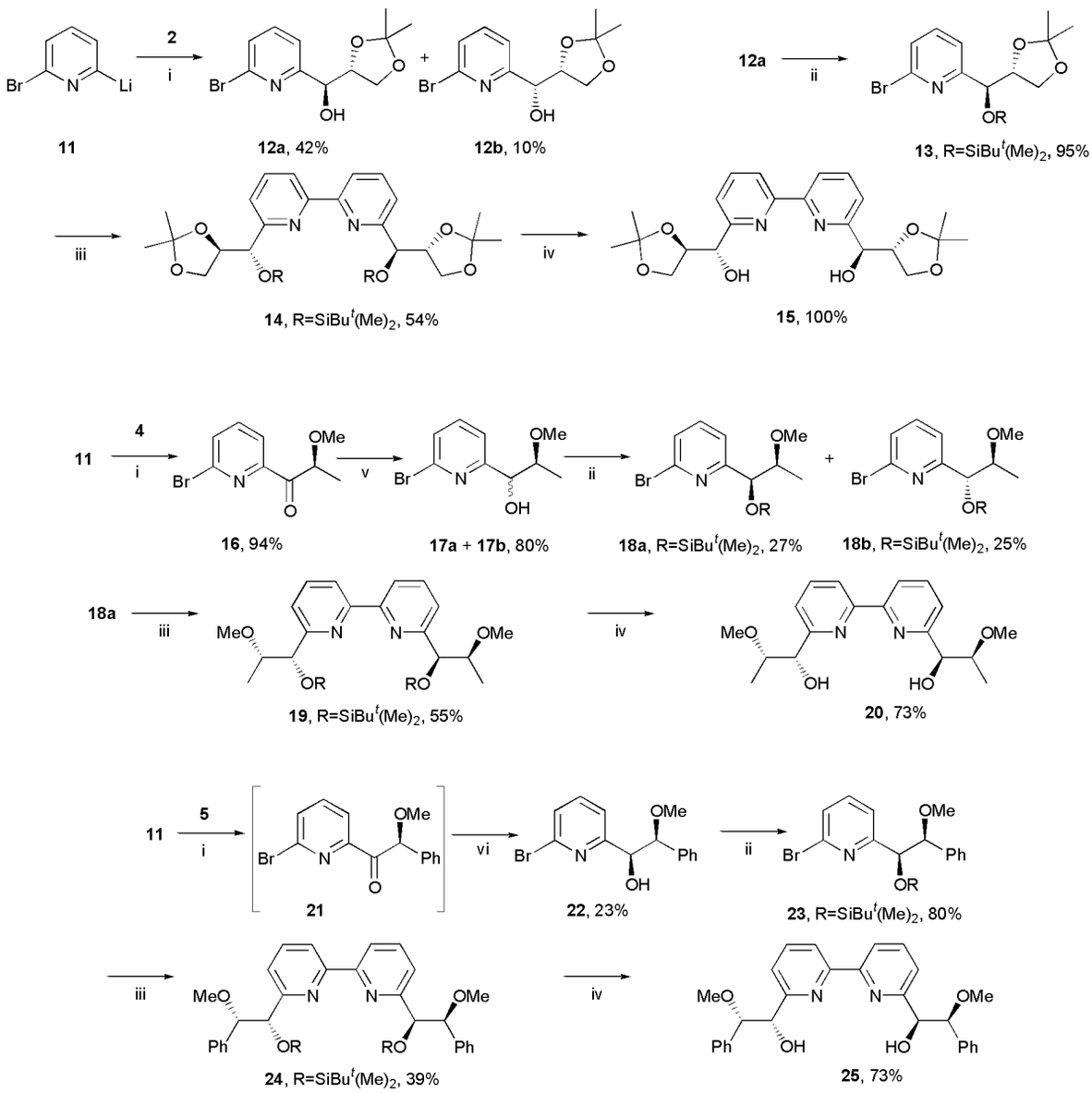
Reaction of 2-bromo-6-lithiopyridine (**11**, obtained from 2,6-dibromopyridine) with (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**) gave an epimeric mixture of alcohols (**12a** and **12b**, Scheme 2). The alcohols were separated by column chromatography to yield pure **12a** and **12b** (42 and 10% yield, respectively). The alcohol group of the major isomer **12a** (see below) was converted to a silyl ether (**13**) using *tert*-butyldimethylsilyl chloride (56%), and the product obtained was subjected to nickel-catalysed coupling to yield bipyridine **14** (60%), which was quantitatively desilylated to **15**.

The analogous reaction of 2-bromo-6-lithiopyridine (**11**) with methyl *O*-methyllactate (**4**) afforded the expected ketone **16** (94%, Scheme 2), which was reduced to an epimeric mixture of alcohols **17a** and **17b** (80%). The alcohols had to be converted to *tert*-butyldimethylsilyl ethers before separation (yielding **18a** and **18b** in 27 and 25% yield, respectively).

Reaction of 2-bromo-6-lithiopyridine (**11**) with *O*-methylmandalate (**5**) yielded the expected ketone **21** (Scheme 2). *In situ* reduction using sodium borohydride at −78 °C afforded **22** (23% yield from *O*-methylmandalate) as a single isomer which was converted to *tert*-butyldimethylsilyl ether **23** (80% yield). Silyl ethers **18a** and **23** were subjected to nickel-catalysed coupling to give bipyridines **19** and **24** (55 and 39%, respectively), which were desilylated to give **20** and **25** (73% for both compounds).

### Determination of absolute configurations

The configuration at the methanol carbon atoms of **12a** and **12b** was determined from the $^1$H NMR chemical shifts of the Mosher's esters prepared by reaction of **12a** and **12b** with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.[41] According to the model,[42] upfield shifts of the methyl and methylene protons and the methoxy protons of the ester derived from **12a** (compared to those of the ester derived from **12b**) indicated this compound to be (1*S*,2*R*)-2,3-*O*-isopropylidene-1-(6′-bromo-2′-pyridyl)-1,2,3-trihydroxypropane. In the nickel-catalysed coupling of **12a**, some debromination occurred yielding **3a**, which thus was shown to be (1*S*,2*R*)-2,3-*O*-isopropylidene-1-(2′-pyridyl)-1,2,3-trihydroxypropane.




**Scheme 2** *Reagents and conditions*: i, $Et_2O$, −78 °C to RT; ii, TBDMSCl, imidazole, DMF, RT; iii, $PPh_3$, $NiCl_2$, Zn, DMF, 70 °C; iv, TBAF, THF, RT; v, $NaBH_4$, MeOH, 0 °C to RT; vi, $NaBH_4$, $Et_2O$, MeOH, −78 °C to RT.

Conversion of the mixture of **8a** and **8b** to Mosher's esters showed in an analogous manner that the more abundant isomer from the reduction had *S* absolute configuration at the newly formed stereocenter, and thus was **8a**.

The Mosher's ester of **10** was prepared and its $^1$H NMR fully assigned with standard COSY and NOESY experiments. The NOESY spectra (−15 °C, mixing times 400, 600 and 800 ms) of this Mosher's ester showed **10** to be (1*S*,2*S*)-2-methoxy-1-(2′-pyridyl)phenylethan-1-ol.

Debromination of **22** (lithiation using *n*-BuLi followed by quenching with water) yielded **10** (of known absolute configuration) which thus showed **22** to have *S* configuration at the methanol carbon.

Comparison of chemical shifts and coupling constants of the diastereomeric pairs **9a**,**b** (derived from **8a**,**b** of known absolute configuration) and **18a**,**b** suggested **18a** to have *S* configuration at the silyl ether carbon. The validity of this comparison was corroborated by similar differences in chemical shifts and coupling constants of **8a**, **10** and **22** and their respective diastereomers.†

† Compounds **10** and **22** were obtained along with their corresponding diasteromers when ketones **7** and **21**, respectively, were reduced at higher temperatures.

## Conclusions

Cheap, readily available, naturally occurring chiral compounds were employed for the preparation of enantiopure 2-(1-hydroxyalkyl)pyridines and $C_2$-symmetric 6,6′-bis(1-hydroxyalkyl)-2,2′-bipyridines. These types of ligands have wide applications in asymmetric catalysis. The 2-bromo-substituted pyridyl alcohols are useful synthons for further functionalisations and derivatives are currently being synthesised for future use in asymmetric catalysis.

## Experimental

### General

$^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ at 400 and 100.6 MHz, respectively, with TMS as internal standard, unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium–benzophenone ketyl. (2*R*)-2,3-*O*-Isopropylideneglyceraldehyde (**2**) was prepared according to a known procedure.[40] As the aldehyde polymerises on standing, it had to be distilled immediately before use (the distillate preferably cooled to −78 °C during distillation). *O*-Methylation to obtain methyl (*S*)-2-methoxypropionate (**4**) was performed using a known procedure.[43] Optical rotations were measured on

a Perkin-Elmer 241 Polarimeter and are reported in units of $10^{-1}$ deg cm$^2$ g$^{-1}$.

**(1*S*,2*R*)-2,3-*O*-Isopropylidene-1-(2′-pyridyl)-1,2,3-trihydroxypropane (3a) and (1*R*,2*R*)-2,3-*O*-isopropylidene-1-(2′-pyridyl)-1,2,3-trihydroxypropane (3b).** Butyllithium (5.0 mL, 1.6 M, 8.0 mmol) was added dropwise during 30 min to 2-bromopyridine (1.149 g, 7.27 mmol) in dry diethyl ether (45 mL) at −78 °C under nitrogen. The reaction mixture was stirred for 15 min and then aldehyde **2** (0.947 g, 7.27 mmol) in diethyl ether (10 mL), cooled to −78 °C, was added dropwise during 15 min. The temperature was allowed to rise slowly to room temperature and stirring continued overnight (15 h). The reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (40 mL). The phases were separated, the aqueous layer extracted with $CH_2Cl_2$ (3 × 30 mL), and the combined organic phases were dried over $MgSO_4$. Evaporation *in vacuo* gave a yellow oil which was purified by MPLC on silica gel (5 × 3 cm column, hexane–EtOAc continuous gradient, 0.375–80% EtOAc) to give colourless oils: 0.69 g of **3a** (45%) eluting first and then 0.17 g of **3b** (11%; the order was reversed using a less polar gradient). **3a**: (Found: C, 62.95; H, 7.4; N, 6.6. $C_{11}H_{15}O_3N$ requires C, 63.1; H, 7.2; N, 6.7%); $[\alpha]_D^{22}$ −22 (*c* 1.03 in $CHCl_3$); $\delta_H$ 8.51 (1H, ddd, *J* 4.9, 1.7 and 1.1 Hz, 6-pyridyl), 7.67 (1H, dt, *J* 7.8 and 1.7 Hz, 4-pyridyl), 7.43 (1H, ddd, *J* 7.8, 1.5 and 1.1 Hz, 3-pyridyl), 7.21 (1H, ddd, *J* 7.8, 4.9 and 1.5 Hz, 5-pyridyl), 4.67 (1H, t, *J* 5.6 Hz, 1-H), 4.42 (1H, d, *J* 5.6, OH), 4.12 (2H, m, 2-H and 3-H), 4.01 (1H, dd, *J* 8.2 and 6.2 Hz, 3-H), 1.48 (3H, s, Me), 1.32 (3H, s, Me); $\delta_C$ 158.65, 148.25, 136.60, 122.93, 122.15, 109.71, 79.03, 72.95, 66.56, 26.81, 25.30. **3b**: $\delta_H$ 8.55 (1H, ddd, *J* 4.9, 1.8 and 1.0 Hz, 6-pyridyl), 7.70 (1H, dt, *J* 7.7 and 1.8 Hz, 4-pyridyl), 7.44 (1H, ddd, *J* 7.7, 1.5 and 1.0 Hz, 3-pyridyl), 7.23 (1H, ddd, *J* 7.7, 4.9 and 1.5 Hz, 5-pyridyl), 4.76 (1H, t, *J* 5.3 Hz, 1-H), 4.44 (1H, td, *J* 6.4 and 5.3 Hz, 2-H), 4.00 (1H, dd, *J* 8.6 and 6.4 Hz, 3-H), 3.94 (1H, br d, *J* 5.3 Hz, OH), 3.91 (1H, dd, *J* 8.6 and 6.4 Hz, 3-H), 1.41 (3H, s, Me), 1.34 (3H, s, Me); $\delta_C$ 158.59, 148.49, 136.57, 122.90, 121.63, 109.70, 78.82, 73.46, 65.81, 26.42, 25.22.

**(1*S*,2*S*)-2-Methoxy-1-(2-pyridyl)propan-1-ol and (1*R*,2*S*)-2-methoxy-1-(2-pyridyl)propan-1-ol (8a and 8b).** Methyl (*S*)-2-methoxypropionate (**4**, 2.36 g, 20 mmol) in diethyl ether (45 mL) was added to 2-pyridyllithium, prepared *in situ* from 2-bromopyridine (3.16 g, 20 mmol) and butyllithium (14 mL, 1.6 M, 22 mmol) in diethyl ether (70 mL, stirring at −78 °C under $N_2$ for 30 min). After stirring at −78 °C for 2 h, the reaction mixture was stirred for an additional hour at room temperature before quenching the reaction with saturated aqueous $NH_4Cl$ (60 mL). The aqueous phase was extracted three times with diethyl ether (60 mL each). The combined organic phases were washed with water and brine, dried ($Na_2SO_4$) and evaporated, leaving 3.29 g of crude pyridyl ketone which was dissolved in MeOH (50 mL). $NaBH_4$ (1.51 g, 40 mmol) was added portionwise to the reaction mixture at 0 °C. The reaction was allowed to reach room temperature and was stirred overnight. Aqueous NaOH (40 mL, 2.0 M) was added and most of the MeOH evaporated. The remaining water phase was extracted three times with $CH_2Cl_2$. Drying ($Na_2SO_4$) and evaporation of the solvent left 2.68 g (81%) of crude **8a** and **8b** (ratio 4 : 1) as a brown liquid, which was used without further purification.

**(1*S*,2*S*)-2-Methoxy-1-(2-pyridyl)-1-(*tert*-butyldimethylsilyloxy)propane and (1*R*,2*S*)-2-methoxy-1-(2-pyridyl)-1-(*tert*-butyldimethylsilyloxy)propane (9a and 9b).** Alcohols **8a** and **8b** (2.67 g, 16 mmol), *tert*-butyldimethylsilyl chloride (2.89 g, 19 mmol) and imidazole (2.72 g, 40 mmol) were dissolved in DMF (5 mL). The reaction mixture was stirred overnight at room temperature. A dilute solution of $Na_2CO_3$ was added and the resulting water phase extracted three times with hexane. The combined organic phases were washed with brine and dried ($Na_2SO_4$), and the solvent evaporated to give a brown liquid. The liquid was dissolved in hexane (100 mL) and pumped onto a MPLC column (7 × 3 cm). Chromatography (continuous gradient from hexane to hexane–EtOAc 98 : 2) gave 981 mg of pure **9a** (22%) and 281 mg of pure **9b** (6%). **9a**: $[\alpha]_D^{20}$ −4 (*c* 2.3 in MeOH); $\delta_H$ 8.52 (1H, d, *J* 4.5 Hz, 6-pyridyl), 7.67 (1H, t, *J* 7.7 Hz, 4-pyridyl), 7.51 (1H, d, *J* 7.7 Hz, 3-pyridyl), 7.14 (1H, dd, *J* 7.7 and 4.5 Hz, 5-pyridyl), 4.91 (1H, d, *J* 3.4 Hz, *H*COSi), 3.62 (1H, qd, *J* 6.3 and 3.4 Hz, *H*COMe), 3.38 (3H, s, OMe), 1.01 (3H, d, *J* 6.3 Hz, Me), 0.92 (9H, s, Bu$^t$), 0.10 (3H, s, SiMe), −0.06 (3H, s, SiMe). **9b**: $[\alpha]_D^{20}$ 6 (*c* 1.6 in MeOH); $\delta_H$ 8.52 (1H, d, *J* 4.5 Hz, 6-pyridyl), 7.67 (1H, t, *J* 7.7 Hz, 4-pyridyl), 7.48 (1H, d, *J* 7.9 Hz, 3-pyridyl), 7.16 (1H, dd, *J* 7.7 and 4.5 Hz, 5-pyridyl), 4.73 (1H, d, *J* 4.9 Hz, *H*COSi), 3.55 (1H, qd, *J* 6.4 and 4.9 Hz, *H*COMe), 3.29 (3H, s, OMe), 1.05 (3H, d, *J* 6.4 Hz, Me), 0.88 (9H, s, Bu$^t$), 0.07 (3H, s, SiMe), −0.08 (3H, s, SiMe).

**(1*S*,2*S*)-2-Methoxy-1-(2-pyridyl)propan-1-ol (8a).** Tetrabutylammonium fluoride (378 mg, 1.2 mmol) was added to a solution of **9a** (281 mg, 1 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 5 h. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (0.7 mL) and water (5 mL) and the resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with brine (5 mL), dried ($Na_2SO_4$) and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel (1.5 × 7 cm column, hexane–diethyl ether continuous gradient: 50–100% diethyl ether) yielding 118 mg (71%) of **8a** as a white solid, mp 71.5–72.5 °C (Found: C, 64.75; H, 7.92; N, 8.33. $C_9H_{13}NO_2$ requires C, 64.65; H, 7.84; N, 8.38%); $[\alpha]_D^{20}$ −28 (*c* 1.0 in $CHCl_3$); $\delta_H$ 8.55 (1H, ddd, *J* 4.9, 1.8 and 1.0 Hz, 6-pyridyl), 7.69 (1H, td, *J* 7.7 and 1.8 Hz, 4-pyridyl), 7.41 (1H, ddd, *J* 7.7, 1.5 and 1.0 Hz, 3-pyridyl), 7.20 (1H, ddd, *J* 7.7, 4.9 and 1.5 Hz, 5-pyridyl), 4.85 (1H, t, *J* 4.6 Hz, C*H*OH), 3.88 (1H, d, *J* 4.6 Hz, OH), 3.59 (1H, qd, *J* 6.3 and 4.6 Hz, C*H*OMe), 3.38 (3H, s, OMe), 1.05 (3H, d, *J* 6.3 Hz, Me); $\delta_C$ 160.01, 148.23, 136.40, 122.25, 121.48, 80.41, 74.31, 56.55, 13.38.

**(1*R*,2*S*)-2-Methoxy-1-(2-pyridyl)propan-1-ol (8b).** Tetrabutylammonium fluoride (250 mg, 0.79 mmol) was added to a solution of **9b** (185 mg, 0.66 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 5 h. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (0.5 mL) and water (5 mL) and the resulting mixture was extracted with diethyl ether (4 × 30 mL). The combined organic phases were washed with brine (5 mL), dried ($Na_2SO_4$) and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel (1.5 × 7 cm column, eluent: diethyl ether) yielding 94 mg (86%) of **8b** as an oil (Found: C, 64.46; H, 7.88; N, 8.34. $C_9H_{14}NO_2$ requires C, 64.65; H, 7.84; N, 8.38%); $[\alpha]_D^{20}$ 180 (*c* 1.0 in $CHCl_3$); $\delta_H$ 8.56 (1H, ddd, *J* 5.0, 1.9 and 1.1 Hz, 6-pyridyl), 7.67 (1H, td, *J* 7.7 and 1.9 Hz, 4-pyridyl), 7.41 (1H, ddd, *J* 7.7, 1.5 and 1.1 Hz, 3-pyridyl), 7.22 (1H, ddd, *J* 7.7, 5.0 and 1.5 Hz, 5-pyridyl), 4.69 (1H, t, *J* 4.9 Hz, C*H*OH), 4.27 (1H, d, *J* 4.9 Hz, OH), 3.69 (1H, qd, *J* 6.3 and 4.9 Hz, C*H*OMe), 3.37 (3H, s, OMe), 1.04 (3H, d, *J* 6.3 Hz, Me); $\delta_C$ 159.20, 148.14, 136.38, 122.56, 121.77, 80.03, 75.29, 56.94, 14.52.

**(1*S*,2*S*)-2-Methoxy-1-(2′-pyridyl)-2-phenylethan-1-ol (10).** Methyl (*S*)-2-methoxy-2-phenylacetate (**5**, 570 mg, 3.5 mmol) was added during 20 min to 2-pyridyllithium, prepared *in situ* from 2-bromopyridine (500 mg, 3.2 mmol) and butyllithium (1.52 mL, 2.5 M, 3.8 mmol) in a mixture of diethyl ether (4.4 mL), THF (2.2 mL) and hexane (2.2 mL, BuLi was added dropwise over 1.5 h followed by stirring at −78 °C under $N_2$ for 75 min). After stirring at −78 °C for 70 min, MeOH (4.4 mL) was added followed by $NaBH_4$ (239 mg, 6.3 mmol), and the

stirring was continued for another 22 h in the thawing ice-bath. The reaction mixture was diluted with diethyl ether (25 mL) and water (5 mL), the phases were separated and the water phase was extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried ($Na_2SO_4$) and evaporated. The remaining solid was recrystallised from hexanes–EtOAc, yielding 351 mg (49%) of **10** (Found: C, 73.19; H, 6.72; N, 6.06. $C_{14}H_{14}NO_2Br$ requires C, 73.34; H, 6.59; N, 6.11%); $[a]_D^{20}$ 10 (*c* 0.9 in $CHCl_3$); $\delta_H$ 8.54 (1H, ddd, *J* 4.9, 1.8 and 1.2 Hz, 6-pyridyl), 7.58 (1H, td, *J* 7.8 and 1.8 Hz, 4-pyridyl), 7.25–7.33 (3H, m, phenyl), 7.16–7.21 (3H, m, phenyl and 5-pyridyl), 7.09 (1H, dt, *J* 7.8 and 1.2 Hz, 3-pyridyl), 4.95 (1H, t, *J* 5.9 Hz, C*H*OH), 4.41 (1H, d, *J* 5.9 Hz, C*H*OMe), 4.05 (1H, d, *J* 5.9 Hz, OH), 3.25 (3H, s, OMe); $\delta_C$ 159.16, 148.52, 138.18, 136.40, 128.44, 128.27, 128.20, 122.98, 122.75, 87.47, 76.27, 57.58.

**(1*S*,2*R*)-2,3-*O*-Isopropylidene-1-(6′-bromo-2′-pyridyl)-1,2,3-trihydroxypropane (12a) and (1*R*,2*R*)-2,3-*O*-isopropylidene-1-(6′-bromo-2′-pyridyl)-1,2,3-trihydroxypropane (12b).** 2,6-Dibromopyridine (3.00 g, 12.7 mmol) was suspended in dry diethyl ether (150 mL) under nitrogen. After cooling to −78 °C, butyllithium (8.70 mL, 1.6 M, 13.9 mmol) was added within 30 seconds. The solution was stirred at −78 °C for 45 min, whereafter a solution of aldehyde **2** (3.30 g, 25.4 mmol) in diethyl ether (20 mL), cooled to –78 °C, was added dropwise during 20 min. The temperature was allowed to rise over several hours to room temperature, and stirring was continued overnight (15 h). The reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (100 mL). The phases were separated, the aqueous layer extracted with $CH_2Cl_2$ (3 × 70 mL) and the combined organic phases were dried over $MgSO_4$. Evaporation *in vacuo* gave a yellow oil which was purified by MPLC on silica gel (8 × 3 cm column, hexane–EtOAc continuous gradient: 0.375–80% EtOAc) to give 1.54 g of **12a** (42%, eluting first) and 0.40 g of **12b** (10%) as colourless oils. **12a**: (Found: C, 45.68; H, 4.76; N, 4.79. $C_{11}H_{14}NO_3Br$ requires C, 45.85; H, 4.90; N, 4.86%); $[a]_D^{20}$ −23 (*c* 1.00 in $CHCl_3$); $\delta_H$ 7.56 (1H, t, *J* 7.7 Hz, 4-pyridyl), 7.42 (1H, d, *J* 7.7 Hz, 3- or 5-pyridyl), 7.41 (1H, d, *J* 7.7 Hz, 3- or 5-pyridyl), 4.69 (1H, dd, *J* 6.6 and 5.2 Hz, 1-H), 4.23 (1H, dt, *J* 6.6 and 5.6 Hz, 2-H), 4.07 (1H, dd, *J* 8.6 and 5.6 Hz, 3-H), 4.01 (1H, dd, *J* 8.6 and 6.6 Hz, 3-H), 3.60 (1H, d, *J* 5.2 Hz, OH), 1.49 (3H, s, Me), 1.34 (3H, s, Me); $\delta_C$ 160.56, 141.10, 138.98, 127.29, 120.84, 109.82, 78.54, 72.87, 66.15, 26.77, 25.16. **12b**: crystallised slowly, mp 62–64 °C; $[a]_D^{20}$ −46 (*c* 0.89 in $CHCl_3$); $\delta_H$ 7.56 (1H, t, *J* 7.7 Hz, 4-pyridyl), 7.46 (1H, d, *J* 7.7 Hz, 3- or 5-pyridyl), 7.40 (1H, d, *J* 7.7 Hz, 3- or 5-pyridyl), 4.71 (1H, dd, *J* 5.9 and 4.9 Hz, 1-H), 4.43 (1H, dt, *J* 6.4 and 4.9 Hz, 2-H), 4.06 (1H, dd, *J* 8.6 and 6.4 Hz, 3-H), 3.99 (1H, dd, *J* 8.6 and 6.4 Hz, 3-H), 3.34 (1H, d, *J* 5.9 Hz, OH), 1.43 (3H, s, Me), 1.34 (3H, s, Me); $\delta_C$ 161.08, 141.15, 138.98, 127.14, 120.10, 109.82, 78.47, 73.52, 66.03, 26.47, 25.12.

**(1*S*,2*R*)-1-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-(6′-bromo-2′-pyridyl)-1,2,3-trihydroxypropane (13).** Pyridyl alcohol **12a** (278 mg, 0.965 mmol) was added to a solution of *tert*-butyldimethylsilyl chloride (195 mg, 1.26 mmol) and imidazole (165 mg, 2.41 mmol) in dry DMF (5 mL). The solution was stirred under nitrogen at room temperature for 72 h and then quenched with 5% aqueous $Na_2CO_3$ (5 mL). The aqueous phase was extracted with 5 × 10 mL hexane and the combined organic phases were dried ($MgSO_4$). Evaporation of the solvent yielded 371 mg (95%) of the silylated alcohol **13**, which was used without further purification. $\delta_H$ 7.54 (1H, t, *J* 7.8 Hz, 4-pyridyl), 7.42 (1H, d, *J* 7.8 Hz, 3- or 5-pyridyl), 7.37 (1H, d, *J* 7.8 Hz, 3- or 5- pyridyl), 4.90 (1H, d, *J* 4.3 Hz, 1-H), 4.39 (1H, ddd, *J* 7.0, 6.5 and 4.3 Hz, 2-H), 3.95 (1H, dd, *J* 7.9 and 7.0 Hz, 3-H), 3.76 (1H, dd, *J* 7.9 and 6.5 Hz, 3-H), 1.40 (3H, s, Me), 1.32 (3H, s, Me), 0.90 (9H, s, Bu′), 0.10 (3H, s, SiMe), −0.08 (3H, s, SiMe).

**6,6′-Bis[(1*S*,2*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-1,2,3-trihydroxypropyl]-2,2′-bipyridine (14).** Dry DMF (5 mL) was degassed *via* three consecutive freeze-thaw cycles at −78 °C under vacuum. $NiCl_2$ hexahydrate (274 mg, 1.15 mmol) and triphenylphosphine (1185 mg, 4.52 mmol) were added, followed by degassing. The solution was stirred at 70 °C under $N_2$ until all material had dissolved. After cooling to room temperature, zinc (78 mg, 1.19 mmol) was added and the mixture was stirred for 1 h at 70 °C under $N_2$. The bromopyridine **13** (371 mg, 0.922 mmol) in degassed dry DMF (3 mL) was added and the mixture was stirred for 2 h at 70 °C under $N_2$. After cooling to room temperature, 5% aqueous $NH_3$ (15 mL) was added to quench the reaction. The mixture was extracted with diethyl ether (4 × 20 mL), the combined organic phases were washed with water (2 × 20 mL) and brine (20 mL), the organic phase was dried ($MgSO_4$) and the solvent evaporated to give orange crystals, which were purified by MPLC on silica gel (6 × 3 cm column, hexane–EtOAc continuous gradient: 0.375–20% EtOAc) to give 184 mg (54%) of bipyridine **14** as white crystals, mp 107.5–109.5 °C; $\delta_H$ 8.34 (2H, dd, *J* 7.8 and 1.1 Hz, 3- or 5-pyridyl), 7.80 (2H, t, *J* 7.8 Hz, 4-pyridyl), 7.45 (2H, dd, *J* 7.8 and 1.1 Hz, 3- or 5-pyridyl), 5.03 (2H, d, *J* 4.3 Hz, 1-H), 4.51 (2H, dt, *J* 6.6 and 4.2 Hz, 2-H), 4.09 (2H, dd, *J* 7.9 and 6.6 Hz, 3-H), 3.80 (2H, dd, *J* 7.9 and 6.6 Hz, 3-H), 1.44 (6H, s, Me), 1.34 (6H, s, Me), 0.92 (18H, s, SiBu′), 0.13 (6H, s, SiMe), −0.07 (6H, s, SiMe).

**6,6′-Bis[(1*S*,2*R*)-2,3-*O*-isopropylidene-1,2,3-trihydroxypropyl]-2,2′-bipyridine (15).** Silylated bipyridine **14** (157 mg, 0.214 mmol) was dissolved in dry THF (8 mL) and treated with tetrabutylammonium fluoride trihydrate (151 mg, 0.479 mmol) under $N_2$ and stirred overnight. The reaction was quenched with saturated aqueous $NH_4Cl$ (8 mL), the THF evaporated and the aqueous phase extracted with diethyl ether (3 × 15 mL). The combined ether phases were dried ($MgSO_4$) and the solvent evaporated to give the desilylated pyridyl alcohol **15** as white crystals in essentially quantitative yield. An analytically pure sample was obtained by recrystallisation from ethyl acetate–hexane 1:4 (Found: C, 63.6; H, 9.6; N, 6.6. $C_{22}H_{28}O_6N_2$ requires C, 63.45; H, 6.8; N, 6.7%); mp 92.5–93.5 °C; $[a]_D^{20}$ −71 (*c* 0.91 in $CHCl_3$); $\delta_H$ 8.34 (2H, d, *J* 8.0 Hz, 3- or 5-pyridyl), 7.86 (2H, t, *J* 7.8 Hz, 4-pyridyl), 7.49 (2H, d, *J* 7.6 Hz, 3- or 5-pyridyl), 4.78 (2H, t, *J* 5.9 Hz, 1-H), 4.41 (2H, d, *J* 5.5 Hz, OH), 4.20 (4H, m, 2-H and 3-H), 4.08 (2H, m, 3-H), 1.54 (6H, s, Me), 1.37 (6H, s, Me); $\delta_C$ 158.15, 154.04, 137.69, 122.46, 120.20, 109.80, 79.12, 72.99, 66.55, 26.84, 25.33.

**(*S*)-1-Methoxyethyl 6-bromo-2-pyridylketone (16).** Methyl (*S*)-2-methoxypropionate (1.36 g, 11.5 mmol) in diethyl ether (30 mL) was added to 2-bromo-6-lithiopyridine (**11**), prepared *in situ* from 2,6-dibromopyridine (2.72 g, 11.5 mmol) and butyllithium (7.9 mL, 1.6 M, 12.7 mmol) in diethyl ether (90 mL, stirring at −78 °C under $N_2$ for 1 h). After stirring at −78 °C for 90 min, the reaction mixture was allowed to reach room temperature and then stirred at this temperature overnight. A saturated aqueous solution of $NH_4Cl$ (20 mL) was added followed by water (20 mL). The phases were separated and the aqueous phase extracted twice with diethyl ether. The combined organic phases were washed with brine and dried ($MgSO_4$). Evaporation left 2.66 g (94%) of crude **16** as a brown liquid, $[a]_D^{20}$ −34 (*c* 5.8 in MeOH); $\delta_H$ 8.03 (1H, dd, *J* 7.2 and 1.4 Hz, 3-pyridyl), 7.72 (1H, dd, *J* 7.9 and 7.0 Hz, 4-pyridyl), 7.68 (1H, dd, *J* 7.9 and 1.2 Hz, 5-pyridyl), 5.23 (1H, q, *J* 7.0 Hz, C*H*OMe), 3.43 (3H, s, OMe), 1.47 (3H, d, *J* 7.0 Hz, Me); $\delta_C$ 199.28, 152.96, 141.24, 139.27, 132.05, 121.37, 77.71, 57.54, 17.94.

**(1*S*,2*S*)-2-Methoxy-1-(6-bromo-2-pyridyl)-1-(*tert*-butyldimethylsilyloxy)propane and (1*R*,2*S*)-2-methoxy-1-(6-bromo-2-pyridyl)-1-(*tert*-butyldimethylsilyloxy)propane (18a and 18b).** $NaBH_4$ (3.27 g, 86 mmol) was added portionwise to an ice-cold

solution of ketone **16** (2.64 g, 10.8 mmol) in methanol (50 mL). The reaction mixture was stirred overnight and then quenched by the addition of 0.1 M HCl (20 mL) and water (50 mL). The aqueous phase was extracted three times with $CH_2Cl_2$. The combined organic phases were dried ($MgSO_4$), and the solvent evaporated leaving 2.14 g (80%) of a mixture of **17a** and **17b** as a brown liquid which was used without further purification. Imidazole (1.48 g, 21.8 mmol) and *tert*-butyldimethylsilyl chloride were added to the mixture of alcohols **17a** and **17b** (2.14 g, 8.7 mmol) in dry DMF (10 mL). The reaction mixture was stirred overnight at room temperature, and then a dilute aqueous solution of $NH_4Cl$ (50 mL) was added. The aqueous phase was extracted three times with diethyl ether. The combined organic phases were washed with brine and dried ($MgSO_4$), and the solvent was evaporated. Purification of the residue by MPLC (8 × 3 cm silica gel, continuous gradient from hexane to hexane–EtOAc 80 : 20) yielded 857 mg (27%) of **18a** and 775 mg (25%) of **18b** as clear liquids. **18a**: $[\alpha]_D^{20}$ −38 (*c* 2.0 in $CHCl_3$); $\delta_H$ 7.53 (1H, t, *J* 7.6 Hz, 4-pyridyl), 7.48 (1H, ddd, *J* 7.6, 1.2 and 0.6 Hz, 3-pyridyl), 7.33 (1H, dd, *J* 7.6 and 1.2 Hz, 5-pyridyl), 4.90 (1H, d, *J* 3.1 Hz, C*H*OSi), 3.62 (1H, dq, *J* 6.3 and 3.1 Hz, C*H*OMe), 3.39 (3H, s, OMe), 0.97 (3H, d, *J* 6.3 Hz, Me), 0.92 (9H, s, Bu$^t$), 0.11 (3H, s, SiMe), −0.04 (3H, s, SiMe); $\delta_C$ 164.19, 140.74, 138.56, 126.15, 120.13, 80.67, 76.53, 56.89, 25.86, 18.26, 13.12, −4.71, −5.05. **18b**: $[\alpha]_D^{20}$ 51 (*c* 4.1 in $CHCl_3$); $\delta_H$ 7.53 (1H, t, *J* 7.9 Hz, 4-pyridyl), 7.47 (1H, dd, *J* 7.9 and 1.2 Hz, 3-pyridyl), 7.34 (1H, dd, *J* 7.9 and 1.2 Hz, 5-pyridyl), 4.69 (1H, d, *J* 4.3 Hz, C*H*OSi), 3.56 (1H, dq, *J* 6.4 and 4.3 Hz, C*H*OMe), 3.20 (3H, s, OMe), 1.13 (3H, d, *J* 6.4 Hz, Me), 0.89 (9H, s, Bu$^t$), 0.07 (3H, s, SiMe), −0.08 (3H, s, SiMe); $\delta_C$ 164.13, 140.45, 138.31, 126.29, 120.78, 80.23, 78.53, 57.57, 25.81, 18.23, 15.53, −4.80, −4.97.

**6,6′-Bis[(1*S*,2*S*)-2-methoxy-1-(*tert*-butyldimethylsilyloxy)-propyl]-2,2′-bipyridine (19).** $NiCl_2 \cdot 6H_2O$ (297 mg, 1.25 mmol) and $PPh_3$ (1.29 g, 4.9 mmol) were added to degassed DMF (9 mL), and the solution was warmed to 70 °C. Zinc powder (85 mg, 1.3 mmol) was added and heating was continued for 1 h. Pyridyl bromide **18a** (360 mg, 1 mmol) in degassed DMF (2 mL) was added to the resulting suspension, and heating was continued for another 2 h. The reaction was quenched by the addition of 5% $NH_3$ solution (25 mL). The water phase was extracted three times with diethyl ether. The combined organic phases were washed twice with water and once with brine and dried ($Na_2SO_4$), and the solvent was evaporated. Purification of the residue by MPLC (6 × 3 cm silica gel, continuous gradient from hexane to EtOAc) yielded 154 mg (55%) of **19** as a white solid, $[\alpha]_D^{20}$ −58 (*c* 1.0 in MeOH); $\delta_H$(500 MHz, $CDCl_3$) 8.29 (2H, d, *J* 7.7 Hz, 3-pyridyl), 7.80 (2H, t, *J* 7.7 Hz, 4-pyridyl), 7.54 (2H, d, *J* 7.7 Hz, 5-pyridyl), 5.04 (2H, d, *J* 3.0 Hz, C*H*OSi), 3.77 (2H, dq, *J* 6.4 and 3.0 Hz, C*H*OMe), 3.44 (6H, s, OMe), 1.04 (6H, d, *J* 6.4 Hz, Me), 0.95 (18H, s, Bu$^t$), 0.14 (6H, s, SiMe), −0.02 (6H, s, SiMe); $\delta_C$(125.8 MHz, $CDCl_3$) 161.71, 154.84, 137.01, 120.97, 119.14, 81.37, 76.94, 56.81, 25.90, 18.30, 13.34, −4.70, −4.97.

**6,6′-Bis[(1*S*,2*S*)-1-hydroxy-2-methoxypropyl]-2,2′-bipyridine (20).** Tetrabutylammonium fluoride (338 mg, 1.07 mmol) was added to **19** (272 mg, 0.48 mmol) in THF (10 mL), and the resulting solution was stirred at room temperature overnight. The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (10 mL). The mixture was diluted with diethyl ether, the phases separated and the aqueous phase extracted twice with diethyl ether. The combined organic phases were washed with brine and dried ($Na_2SO_4$), and the solvent evaporated leaving a slightly yellow semisolid. The crude product was purified by flash chromatography (6 × 1.5 cm silica gel, eluent: 50 mL of hexane–EtOAc 80 : 20, 50 mL of hexane–EtOAc 50 : 50, 100 mL EtOAc), yielding 116 mg (73%) of **20** as a white semisolid, $[\alpha]_D^{20}$ −50 (*c* 1.1 in MeOH); $\delta_H$ 8.32 (2H, dd, *J* 7.8 and 0.8 Hz, 3-pyridyl), 7.83 (2H, t, *J* 7.8 Hz, 4-pyridyl), 7.42 (2H, dd, *J* 7.8 and 0.8 Hz, 5-pyridyl), 4.89 (2H, t, *J* 4.7 Hz, C*H*OH), 4.17 (2H, br d, *J* 4.7 Hz, OH), 3.62 (2H, dq, *J* 6.2 and 4.7 Hz, C*H*OMe), 3.39 (6H, s, OMe), 1.11 (6H, d, *J* 6.2 Hz, Me); $\delta_C$ 158.88, 154.09, 137.36, 121.71, 119.68, 80.62, 74.16, 56.65, 13.59.

**(1*S*,2*S*)-2-Methoxy-1-(6′-bromo-2′-pyridyl)-2-phenylethan-1-ol (22).** Methyl (*S*)-2-methoxy-2-phenylacetate (2.82 g, 15.7 mmol) in diethyl ether (40 mL) was added to 2-bromo-6-lithiopyridine (**11**), prepared *in situ* from 2,6-dibromopyridine (2.64 g, 11.1 mmol) and butyllithium (8.5 mL, 1.6 M, 13.6 mmol) in diethyl ether (50 mL, BuLi was added in 8 min followed by stirring at −78 °C under $N_2$ for 40 min). After stirring at −78 °C for 90 min, methanol (20 mL) and $NaBH_4$ (0.45 g, 11.9 mmol) were added. The reaction mixture was allowed to slowly reach room temperature and stirring was continued overnight. The reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (4 mL) followed by stirring for 30 min. Water (10 mL) and diethyl ether (50 mL) were added and the layers separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL), the combined organic layers were dried ($Na_2SO_4$) and evaporated leaving a yellow oil. The crude product was purified by flash chromatography on silica gel using hexane–diethyl ether (80 : 20) as eluent. Recrystallisation from hexane yielded **22** (788 mg, 23%) as a white solid, mp 65 °C; $[\alpha]_D^{20}$ −52 (*c* 1.1 in $CHCl_3$); $\delta_H$ 7.41 (1H, t, *J* 7.6 Hz, 4-pyridyl), 7.35 (1H, dd, *J* 7.6 and 1.1 Hz, 3-pyridyl), 7.24–7.32 (3H, m, Ph), 7.14–7.19 (2H, m, Ph), 7.05 (1H, dd, *J* 7.6 and 1.1 Hz, 5-pyridyl), 4.96 (1H, t, *J* 5.7 Hz, C*H*OH), 4.46 (1H, d, *J* 5.7 Hz, C*H*OMe), 3.40 (1H, d, *J* 5.7 Hz, OH), 3.25 (3H, s, OMe); $\delta_C$ 160.96, 140.75, 138.43, 137.19, 128.11, 128.06, 127.86, 126.85, 121.05 86.29, 75.89, 57.12.

**(1*S*,2*S*)-2-Methoxy-1-(6′-bromo-2′-pyridyl)-1-(*tert*-butyldimethylsilyloxy)-2-phenylethane (23).** Imidazole (454 mg, 6.7 mmol) and *tert*-butyldimethylsilyl chloride (469 mg, 3.1 mmol) were added to **22** (788 mg, 2.6 mmol) in dry DMF (3 mL). The reaction mixture was stirred under nitrogen for 20 h at room temperature, then a saturated aqueous solution of NaCl (30 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 20 mL), the combined organic phases were dried ($Na_2SO_4$) and evaporated. Purification of the residue by flash chromatography on silica gel using hexane–EtOAc (70 : 30) as eluent yielded **23** (859 mg, 80%) as a white solid, mp 70 °C; $[\alpha]_D^{20}$ −97 (*c* 0.6 in $CHCl_3$); $\delta_H$ 7.38 (1H, t, *J* 7.7 Hz, 4-pyridyl), 7.32 (1H, dd, *J* 7.7 and 1.0 Hz, 3-pyridyl), 7.20–7.22 (3H, m, Ph), 7.09–7.12 (2H, m, Ph), 7.05 (1H, dd, *J* 7.7 and 1.0 Hz, 5-pyridyl), 5.01 (1H, d, *J* 4.9 Hz, C*H*OSi), 4.42 (1H, d, *J* 4.9 Hz, C*H*OMe), 3.19 (3H, s, OMe), 0.78 (9H, s, Bu$^t$), −0.07 (3H, s, SiMe), −0.16 (3H, s, SiMe); $\delta_C$ 163.87, 140.54, 138.40, 137.58, 128.57, 127.62, 127.45, 126.42, 120.58, 86.90, 78.07, 56.89, 25.73, 18.18, −4.99, −5.09.

**6,6′-Bis[(1*S*,2*S*)-2-Methoxy-1-(*tert*-butyldimethylsilyloxy)-2-phenylethyl]-2,2′-bipyridine (24).** $NiCl_2 \cdot 6H_2O$ (191 mg, 0.81 mmol) and $PPh_3$ (725 mg, 3.92 mmol) were added to degassed DMF (6 mL). The solution was warmed to 70 °C, zinc powder (48 mg, 0.73 mmol) was added and heating continued for 1 h. Pyridyl bromide **23** (236 mg, 0.56 mmol) in degassed DMF (2 mL) was added to the resulting suspension, and heating continued for another 2 h. The reaction was quenched by the addition of 5% $NH_3$ solution (25 mL). The water phase was extracted three times with diethyl ether. The combined organic phases were washed twice with water, once with brine, dried ($Na_2SO_4$) and evaporated. Purification of the residue by MPLC yielded 14 mg (8%) of **24** as a white solid and the partly deprotected compound (49 mg, 31%) which resulted in a total yield of 39%. **24**: $\delta_H$ 8.58 (2H, ddd, *J* 4.9, 1.7 and 0.9 Hz, 3-pyridyl), 7.58 (2H, dt, *J* 7.6 and 1.7 Hz, 4-pyridyl), 7.12–7.28 (12H, m, Ph and

5-pyridyl), 4.92 (2H, d, *J* 5.9 Hz, C*H*OSi), 4.39 (2H, d, *J* 5.9 Hz, C*H*OMe), 3.14 (6H, s, OMe), 0.73 (18H, s, Bu$^t$), −0.18 (6H, s, SiMe), −0.026 (6H, s, SiMe); $\delta_C$ 162.20, 148.38, 138.61, 136.10, 128.49, 127.56, 122.21, 121.84, 87.49, 78.92, 56.95, 25.72, 18.09, −5.02, −5.25; the signal from one aromatic carbon was not observed.

**6,6′-Bis[(1*S*,2*S*)-1-hydroxy-2-methoxy-2-phenylethyl]-2,2′-bipyridine (25).** Tetrabutylammonium fluoride (338 mg, 1.07 mmol) was added to a solution of **24** (272 mg, 0.48 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature overnight and it was quenched by the addition of saturated aqueous $NH_4Cl$ (10 mL). The mixture was diluted with diethyl ether, the phases separated and the aqueous phase extracted twice with diethyl ether. The combined organic phases were washed with brine, dried ($Na_2SO_4$) and the solvent evaporated leaving a slightly yellow semisolid. The crude product was purified by flash chromatography (6 × 1.5 cm silica gel, eluent: 50 mL of hexane–EtOAc 80:20, 50 mL of hexane: EtOAc 50:50, 100 mL EtOAc), yielding 116 mg (73%) of **25** as a white semisolid, $[a]_D^{20}$ −50 (*c* 1.1 in MeOH); $\delta_H$ 8.19 (2H, d, *J* 7.6 Hz, 3-pyridyl), 7.74 (2H, t, *J* 7.6 Hz, 4-pyridyl), 7.20–7.35 (10H, m, Ph), 7.19 (2H, d, *J* 7.6 Hz, 5-pyridyl), 5.02 (2H, d, *J* 5.7 Hz, C*H*OH), 4.44 (2H, d, *J* 5.7 Hz, C*H*OMe), 4.3 (2H, br d, *J* 5.7 Hz, OH), 3.26 (6H, s, OMe); $\delta_C$ 158.88, 154.09, 137.36, 121.71, 119.68, 80.62, 74.16, 56.65, 13.59; the signals from three carbons were not observed.

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