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SYNTHESIS OF C_2 SYMMETRIC 2,2′-BIPYRIDYL IMIDAZOLIDINONE AND OXAZABOROLIDINE DERIVATIVES[†]

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Abstract - 4,4′-*Bis*(bromomethyl)-2,2′-bipyridine reacts with *(4R,5R)*-1-propanoyl-4,5-diphenylimidazolidinone to form a C_2 symmetric chiral bipyridine derivative. Similarly reaction of 4,4′-*bis*(bromomethyl)-2,2′-bipyridine with an amino alcohol prepared from *L*-tyrosine affords a C_2 symmetric diaminodiol. Treatment of the latter product with either borane or trimethylboroxine forms oxazaborolidines that have been used as catalysts in the asymmetric reduction of acetophenone. High enantiomeric excesses are obtained.

INTRODUCTION

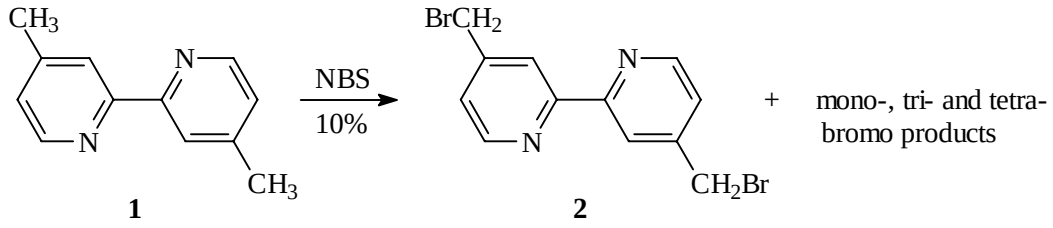
The advantage of solid-phase synthesis, in which a substrate, a reagent or a catalyst is attached to an insoluble support, is that the bound component can be isolated and purified simply by filtration.[1-3] However difficulties are often encountered in adapting previously optimised solution-phase procedures to solid-phase methods. The heterogeneous reaction conditions lead to different kinetic behavior, differences of reactivity and solvation, and other problems not encountered in solution-phase reactions. Methods for combining solution-phase reactions with solid-phase separation have been developed involving selective precipitation and selective solubility.[4-7] As part of a programme aimed at combining the advantages of solution-phase chemistry with solid-phase separation in asymmetric synthesis, [8,9] we have synthesised two C_2 symmetric bipyridine derivatives suitable for use in asymmetric

[†] This paper is dedicated to Professor Jim Kutney on the occasion of his 70th birthday.

alkylation and reduction reactions.

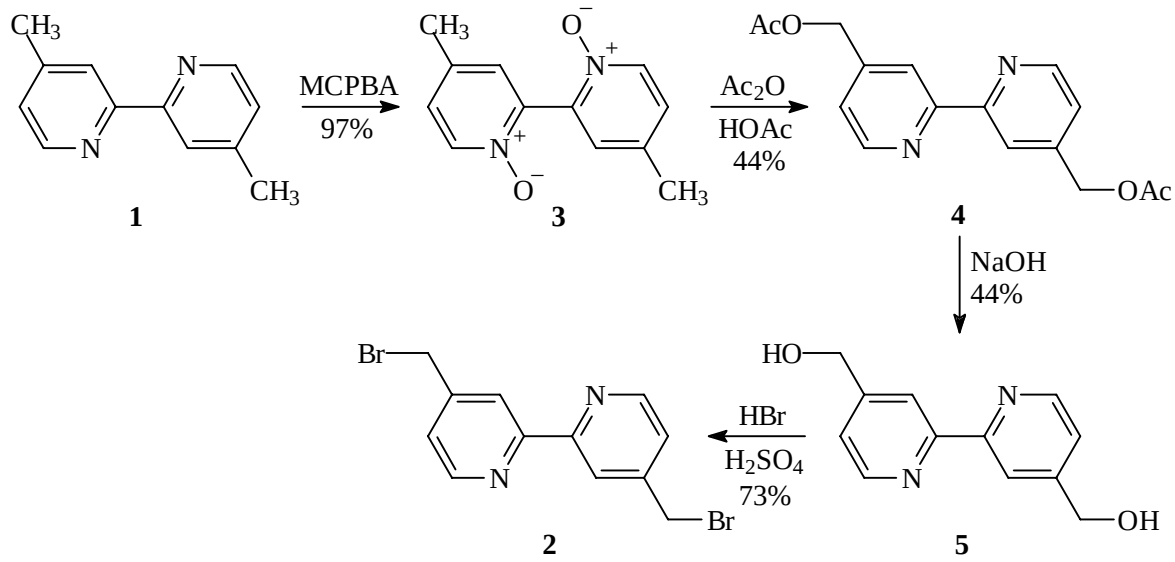
RESULTS AND DISCUSSION

Direct bromination of 4,4′-dimethyl-2,2′-bipyridine **(1)** using NBS gave a mixture of brominated products (Scheme 1), and after purification gave only a 10% yield of the desired 4,4′-*bis*(bromomethyl)-2,2′-bipyridine **(2)**.[10] Increasing the amount of NBS and the reaction time increased the amounts of the tri- and tetrabromo products but did not significantly alter the yield of **2**. This compound could also be prepared by a four-step sequence *via* the corresponding *N,N′*-dioxide **(3)** in 13.5% overall yield (Scheme 2).[9-11] However the most efficient synthesis of **2** was *via* the corresponding 4,4′-*bis*(trimethylsilyl) derivative **(6)** which afforded **2** in two steps in 94% overall yield (Scheme 3).[12]



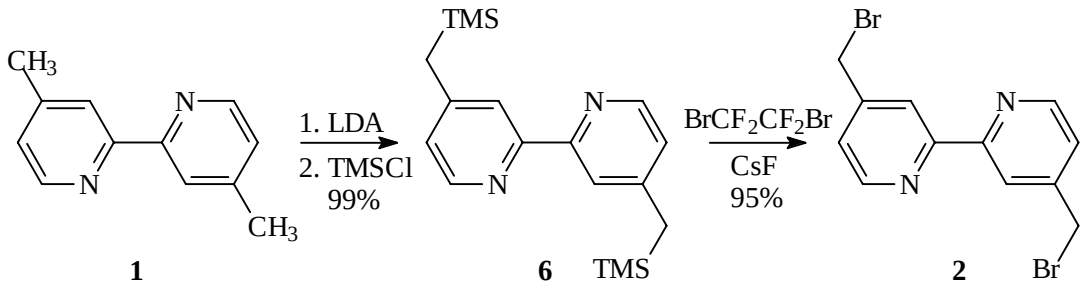
1 **2**

Scheme 1



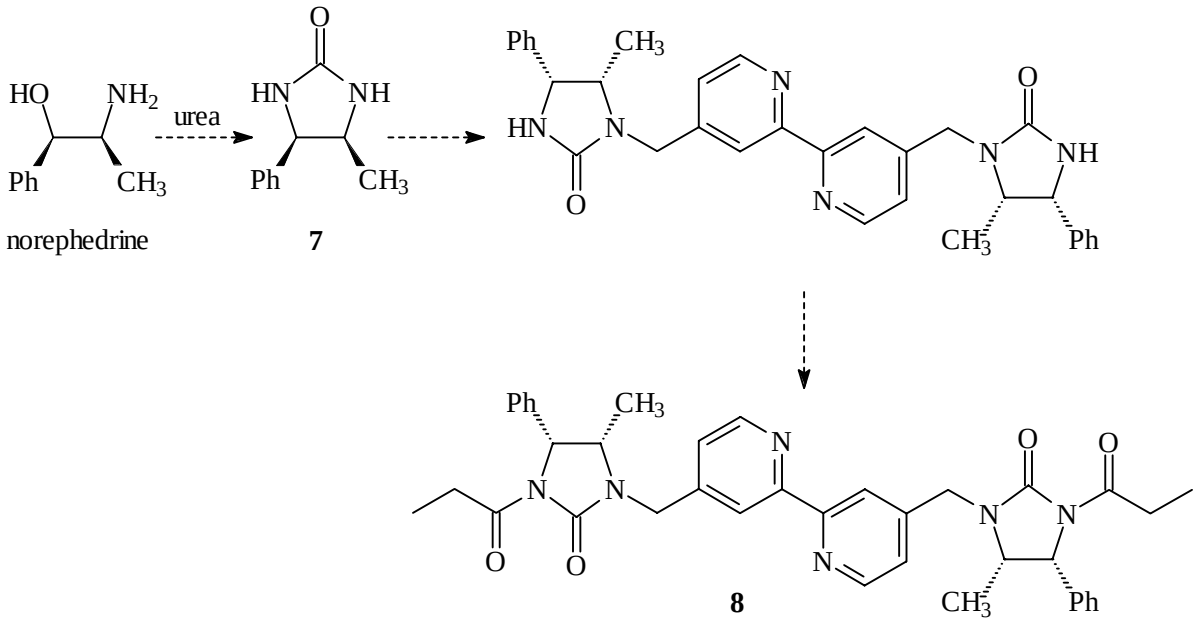
1 **3** **4** **5** **2**

Scheme 2



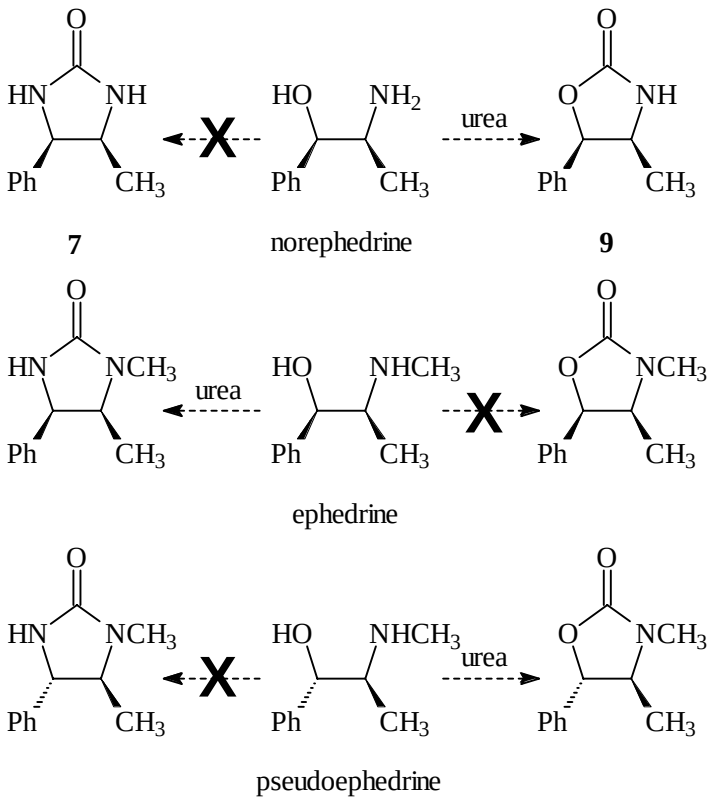
Scheme 3

Our original intention was to prepare the C_2 symmetric chiral bipyridine derivative **(8)** by reacting the dibromide **(2)** with the imidazolidinone **(7),** prepared from norephedrine (Scheme 4). However the attempted preparation of **7** was unsuccessful yielding instead the oxazolidinone **(9)**, as previously reported.[13,14] In this respect norephedrine differs from ephedrine itself, but resembles pseudoephedrine (Scheme 5).[13,14]

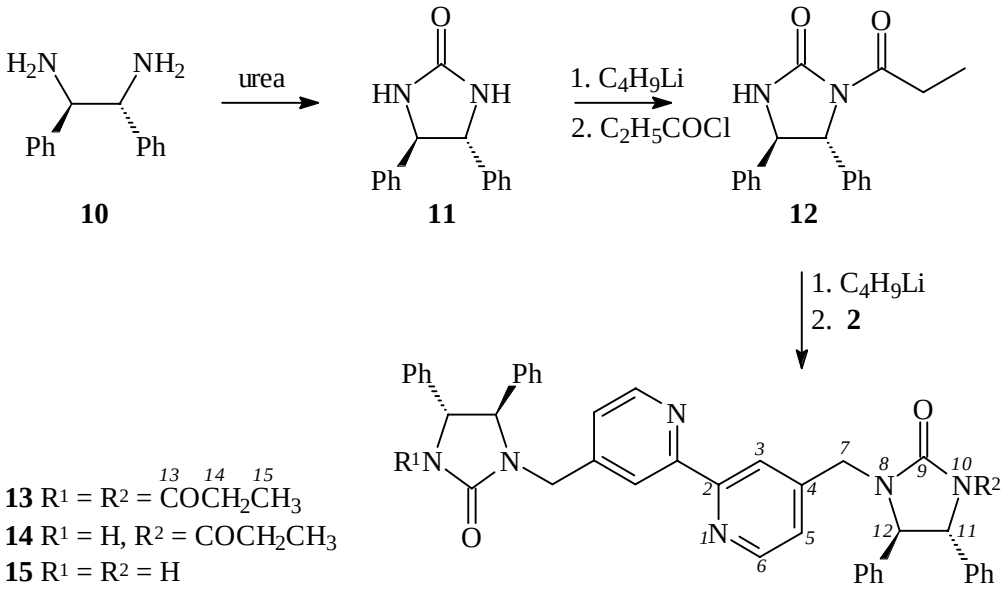


Scheme 4

We therefore chose to react 4,4′-*bis*(bromomethyl)-2,2′-bipyridine **(2)** with *(4R,5R)*-1-propanoyl-4,5-diphenylimidazolidinone **(12)**,[15] prepared from *(1R,2R)*-1,2-diphenylethane-1,2-diamine **(10)**, which yielded the C_2 symmetric chiral bipyridine derivative **(13)** (Scheme 6). When longer reaction times were employed increasing amounts of the de-acylated products **(14)** and **(15)** were also obtained.



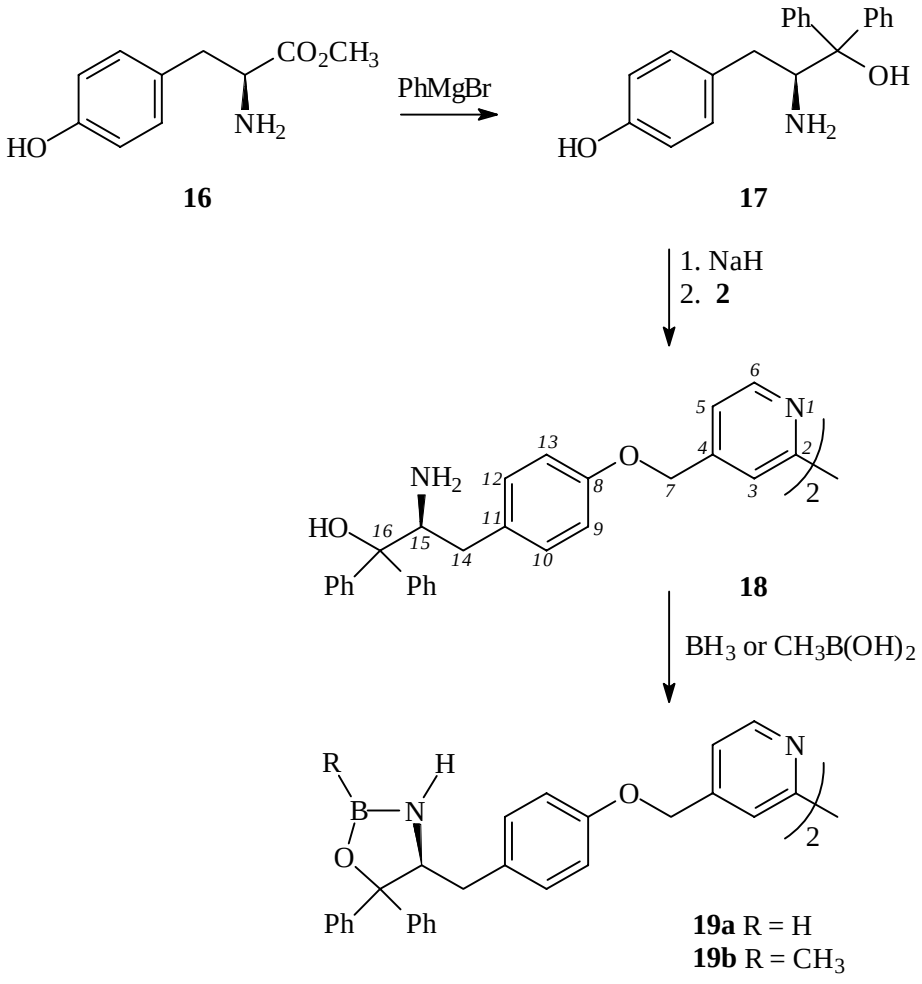
Scheme 5



Scheme 6

Our second objective was to prepare the C_2 symmetric diaminodiol **(18)** to use as a precursor for the generation of the C_2 symmetric oxazaborolidines **(19)** (Scheme 7). To this end the dibromide **(2)** was reacted with the amino alcohol **(17)**,[16] prepared by treating *L*-tyrosine methyl ester **(16)** with phenyl

magnesium bromide, affording **18** in 73% yield. BH_3.THF or $BH_3.(CH_3)_2S$ and trimethylboroxine were then used to convert **18** into **19a** and **19b** respectively. Typically BH_3.THF (4.4 equiv.) was added dropwise to **18** in THF at -78°C and the mixture stirred overnight at 30°C under nitrogen. Alternatively, $BH_3.(CH_3)_2S$ (8 equiv.) was added dropwise to **18** in THF at 30°C and the mixture stirred overnight under nitrogen.[17] The oxazaborolidine **(19a)** was not isolated but was stored in THF under nitrogen until required. To prepare **19b**, trimethylboroxine (1.34 equiv.) was added to **18** in toluene at room temperature and the solution stirred for 2 h before being heated to reflux overnight.[18] Removal of the toluene at atmospheric pressure followed by azeotropic removal of three further portions of toluene to remove water and excess methylboronic acid (as trimethylboroxine), and drying *in vacuo*, gave **19b**. The ^1H and ^{13}C NMR spectra of **19b** showed singlets at 0.0 ppm and 1.0 ppm respectively, due to the B-CH_3 group. However, other singlets were also present in this region suggesting that the product reacts with moisture during isolation or on solution in $CDCl_3$. Hence both **19a** and **19b** were stored in THF under nitrogen until required.



Scheme 7

The oxazaborolidines **(19a)** and **(19b)** were used in the asymmetric reduction of acetophenone with either BH_3.THF or $BH_3.(CH_3)_2S$. In each case the reducing agent used for the reduction was the same as that used for formation of the oxazaborolidine. Enantiomeric excesses (ees) were determined by chiral HPLC. The results which are summarised in the Table 1 show that high ees are obtained with both catalysts. While in most cases the reductions were complete after 1 h and gave an essentially quantitative yield, the one with **19b** using BH_3.THF (Entry 3) was incomplete after 20 h and gave only 78% ee. When the reaction was repeated and allowed to run for 72 h the reaction was still incomplete and the ee was still only 75%. When $BH_3.(CH_3)_2S$ was used (Entry 4) instead of BH_3.THF a precipitate appeared after 20 min but the reaction was complete in 1 h and gave 91% ee. With 0.05 equiv. of **19b** no precipitate was observed (Entry 5). However, the lower number of equivalents of the catalyst leads to a decrease in ee. At low catalyst concentrations non-catalysed reduction presumably takes place.

Table 1. Asymmetric reduction of acetophenone

Entry	**Catalyst**	**Equivalents**	**Boron Source**	**ee%**
1	**19a**	0.63	BH_3.THF	87
2	**19a**	0.50	$BH_3.(CH_3)_2S$	87
3	**19b**	0.50	BH_3.THF	78
4	**19b**	0.50	$BH_3.(CH_3)_2S$	91
5	**19b**	0.05	$BH_3.(CH_3)_2S$	84

A molecular modelling investigation was carried out to compare the energy profiles of **13** and **18** with bipyridine. It was expected that **13** and **18** would be less stable in the *cisoid* conformation than bipyridine due to the presence of the large substituent groups. This would be an important consideration in any investigation of the metal-binding properties of these compounds. The structures were constructed using Sybyl software and energetically optimised using Tripos Force Field. A systematic search procedure was applied in order to obtain the energy profile for each molecule. Rotation around the relevant bond was performed with 10° increments over a range of 0° (*cisoid*) to 180° (*transoid*). The energy at each step was calculated to produce an energy profile for each compound (Figure 1). The difference in energy between the *cisoid* conformation and the global minimum energy conformation was determined for each compound (Table 2). The low energy difference for bipyridine shows that it can readily adopt the *cisoid* conformation. In the case of **13** and **18** the higher energy difference between the *cisoid* conformation and the global energy minimum indicates that as expected these compounds will find it harder to adopt a *cisoid* conformation.

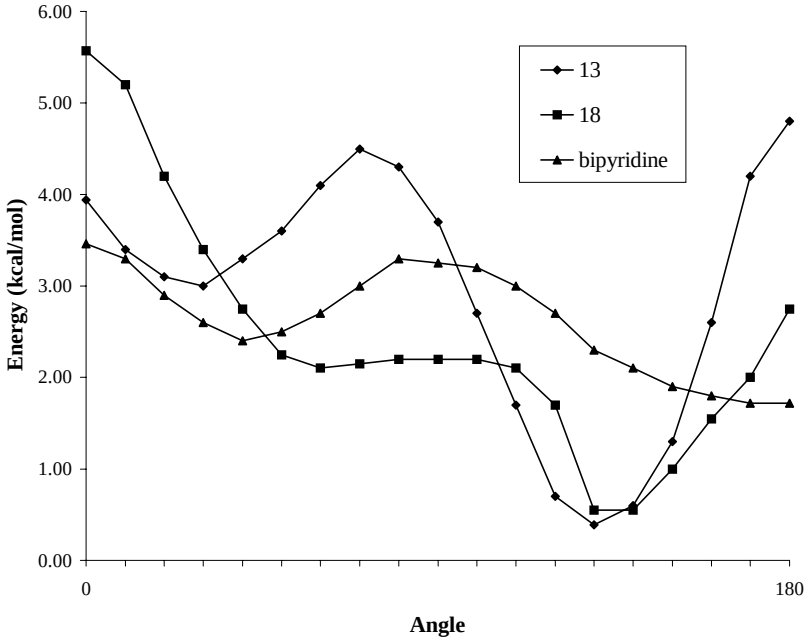


Figure 1. Energy profiles for bipyridine, 13, and 18

Table 2. Energy values (kcal/mol)

	Bipyridine	**13**	**18**
E_{min}	1.72	0.39	0.55
E_{cisoid}	3.46	3.94	5.57
$\Delta E_{cisoid-min}$	1.74	3.55	5.02

EXPERIMENTAL

^{1}H NMR spectra were recorded at 400 MHz on a Bruker AC spectrometer. ^{13}C NMR spectra were recorded on a Bruker AC spectrometer at 100 MHz. All spectra were run in $CDCl_3$ unless otherwise indicated. The MS spectra were recorded on a VG Analytical Quattro II triple quadrupole mass spectrometer, whilst accurate MS measurements were obtained on a Finnigan MAT 900 XL instrument. Melting points were recorded on an Electrothermal IA9100 digital melting point apparatus and are uncorrected. Chiral HPLC was carried out on a Daicel Chiralcel OJ column, eluent 95% hexane/5% isopropanol, using a Milton Roy instrument comprising 3100 SpectroMonitor, 3000 ConstaMetric pump, and CI-4100 computing integrator. Thin layer chromatography was carried out on Whatman Al Sil G/UV fluorescent plates and revealed by UV at 254 nm. Flash chromatography was performed with silica gel (Fisher, Matrex Silica 60, 35-70 μ).

Solvents were purified and dried when necessary using standard methods.[19] Reactions were carried out under an inert atmosphere using argon or nitrogen from the cylinder passed through H_2SO_4 and $CaCl_2$. Dry solids were obtained by drying *in vacuo* over P_2O_5 in a pistol. Low temperature baths were prepared by making a slurry of solid CO_2 in acetone (-78°C) or of ice in acetone (-10°C). Solutions of *n*-butyllithium in hexane were purchased from Aldrich Chemical Co. Ltd. and were estimated before use following the standard procedure.[19] NBS was purified by literature methods.[19] Diisopropylamine was dried by distilling from KOH.

Preparation of 4,4′-*bis*(bromomethyl)-2,2′-bipyridine (2) : Method A

To a mixture of 4,4′-dimethyl-2,2′-bipyridine **(1)** (4.0 g, 21.7 mmol) and NBS (8.0 g, 44.9 mmol) in refluxing dry CCl_4 was added AIBN (0.25 g, 1.58 mmol). The resulting solution was stirred for 3 h under nitrogen. The reaction was monitored by TLC, eluent : 98% DCM/2% acetone, the silica plates were deactivated in 10% triethylamine/90% hexane prior to use, R_f **(2)** = 0.47. Then the solution was cooled in an ice bath and filtered to remove precipitated succinimide. The yellow solution was evaporated to dryness and the residue was dissolved in a minimum of DCM and purified by flash chromatography, eluent : 98% DCM/2% acetone. A double recrystallisation from DCM/hexane of the appropriate fractions afforded **2** as a pale brown solid (0.76 g, 10.1%), mp 119-121°C (lit.,[12] 116-118°C).

Preparation of 4,4′-*bis*(bromomethyl)-2,2′-bipyridine (2) : Method B

a) Preparation of 4,4′-dimethyl-2,2′-bipyridinyl-1,1′-dioxide (3)

m-CPBA (43%, 56.3 g, 136.0 mmol) was added to a solution of **1** (10.0 g, 54.3 mmol) in DCM (250 mL), followed by anhydrous Na_2SO_4 (15.0 g, 105.6 mmol). After stirring at rt for 4 h, the mixture was filtered. The reaction was monitored by TLC, eluent : 90% DCM/10% methanol, R_f **(3)** = 0.35. The solvent was removed *in vacuo* and the crude product purified by flash chromatography, eluent : 90% DCM/10% methanol, to afford **3** as a pale yellow solid (11.4 g, 97.1%), mp 235-237°C (lit.,[9] 240°C).

b) Preparation of 4,4′-*bis*(acetoxymethyl)-2,2′-bipyridine (4)

Acetic anhydride (5.2 g, 51.0 mmol) was added to a solution of **3** (5.0 g, 23.1 mmol) in acetic acid (40 mL) and the resulting mixture heated to reflux for 4 h. The reaction was monitored by TLC, eluent 90% DCM/10% methanol, R_f **(4)** = 0.44. The solvents were removed *in vacuo*, the residue taken up in ethyl acetate, washed with 15% aq. K_2CO_3 and brine, and dried ($MgSO_4$). The product was purified by flash chromatography, eluent 60% DCM/40% ethyl acetate, to give **4** as a pale yellow solid (3.0 g, 43.5%),

mp 102-104°C (lit.,[9] 99°C).

c) Preparation of 4,4′-*bis*(hydroxymethyl)-2,2′-bipyridine (5)

A solution of **4** (7.0 g, 23.3 mmol) and NaOH (2.8 g, 70.0 mmol) in methanol (60 mL)/water (15 mL) was heated to reflux for 3 h. The reaction was monitored by TLC, eluent 90% DCM/10% methanol, R_f **(5)** = 0.09. Then the solvent was removed and the residue dissolved in a mixture of water and ethyl acetate. The aqueous layer was washed with ethyl acetate and the combined organic fractions were washed with brine and then dried ($MgSO_4$). The crude product was recrystallised from ethyl acetate to afford **5** as a pale yellow powder (2.22 g, 44.0%), mp 160-162°C (lit.,[9] 159°C).

d) Preparation of 4,4′-*bis*(bromomethyl)-2,2′-bipyridine (2)

A solution of **5** (0.9 g, 4.2 mmol) in 48% hydrobromic acid (16.2 mL, 136 mmol) was heated at reflux for 5 h. The reaction was monitored by TLC, eluent : 90% DCM/10% methanol, R_f **(2)** = 0.68. The reaction mixture was then cooled to 0°C and 6N NaOH solution added until pH = 7. The precipitate was filtered and dried *in vacuo* to afford **2** as pale brown crystals (1.03 g, 72.3%), mp 119-121°C, identical to the sample prepared by Method A.

Preparation of 4,4′-*bis*(bromomethyl)-2,2′-bipyridine (2) : Method C

a) Preparation of 4,4′-*bis*(trimethylsilyl)-2,2′-bipyridine (6)

To diisopropylamine (3.8 mL, 27.1 mmol) in dry THF (30 mL) at -78°C was added *n*-C_4H_9Li (1.45 M in hexane, 16.5 mL, 23.9 mmol). The solution was stirred at -78°C for 20 min. Then **1** (2.0 g, 10.9 mmol) was dissolved in dry THF (40 mL) and transferred dropwise *via* a cannula to the LDA solution. The flask and cannula were rinsed with THF (2 x 3 mL). The dark-brown solution was stirred at -78°C for 20 min, warmed to -10°C for 25 min and then cooled to -78°C before addition of TMSCl (3.6 mL, 28.4 mmol). After 5-10 sec the reaction was quenched with ethanol (5 mL). Saturated aq. $NaHCO_3$ was added to the cold reaction mixture. The solution was then allowed to warm to rt. The product was extracted into ethyl acetate and the combined organic fractions were washed with brine and then dried (Na_2SO_4). Filtration and concentration afforded **6** as a slightly off-white powder (3.55 g, 99.0%), mp 93-95°C (lit.,[12] 90-92°C).

b) Preparation of 4,4′-*bis*(bromomethyl)-2,2′-bipyridine (2)

To a dry DMF solution (40 mL) of **6** (4.98 g, 15.2 mmol) and $BrCF_2CF_2Br$ (5.4 mL, 45.4 mmol) was added anhydrous CsF (6.8 g, 45.5 mmol). The reaction was stirred at rt for 3 h. The reaction was

monitored by TLC, the silica plates being deactivated in 10% triethylamine/90% hexane prior to use and dried under high vacuum for at least 10 min prior to developing, eluent : 80% hexane/20% ethyl acetate, R_f **(2)** = 0.14. The reaction mixture was poured into a mixture of ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic fractions were washed with water and brine, and then dried (Na_2SO_4). Filtration and concentration *in vacuo* gave **2** as pale brown crystals (4.92 g, 94.8%), mp 117-119°C, identical to the sample prepared by Method A.

Preparation of *(4R,5R)*-4,5-diphenylimidazolidinone (11)

(1R,2R)-1,2-Diphenylethane-1,2-diamine **(10)** (3.02 g, 14.2 mmol), urea (0.91 g, 15.1 mmol), and water (10 drops) were heated at 200°C until no starting material could be detected by TLC (approx. 1 h). Flash chromatography of the residue, eluting with ethyl acetate, gave **11** as a white solid (2.56 g, 75%), mp 197-198°C (lit.,[15] 196-197.5°C).

Preparation of *(4R,5R)*-4,5-diphenyl-1-propionylimidazolidinone (12)

To a solution of **11** (1.87 g, 6.31 mmol) in THF (30 mL) was added *n*-C_4H_9Li (1.3 M, 12.0 mL, 12.6 mmol) dropwise at -10°C and stirred for 30 min before propionyl chloride (0.73 g, 7.89 mmol) was added. The reaction temperature was allowed to reach rt and stirring was continued overnight. The reaction mixture was quenched with satd. NH_4Cl (5 mL), diluted with DCM (20 mL) and the organic layer separated. The aqueous layer was extracted with DCM (2 x 50 mL) and the combined organic fractions were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue, eluting with 80% hexane/20% ethyl acetate, gave **12** as a white solid (1.875 g, 81%), mp 118-119°C (lit.,[15] 120-121°C).

Preparation of 4,4′-*bis*[1-(4,5-diphenyl-3-propionylimidazolidinonyl)methyl]-2,2′-bipyridine (13)

NaH (60% suspension, 0.027g, 0.675mmol) was washed 3 times with dry petroleum spirit (bp 40-60°C) under a nitrogen atmosphere. Dry DMF (10 mL) was added and the solution was cooled to -10°C before the addition of a solution of **12** (0.201 g, 0.676 mmol) in DMF (5 mL). The reaction mixture was stirred at -10°C for 20 min when a solution of **2** (0.120 g, 0.351 mmol) in DMF (5 mL) was added. The reaction mixture was stirred at -10°C for 1 h and then quenched with methanol and the DMF was removed *in vacuo*. The residue was extracted into DCM (3 x 40 mL), and the combined extracts were washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Separation by reverse phase flash chromatography afforded **13** as a pink gum (0.132 g, 51%). ^{1}H NMR ($CDCl_3$) : 8.57 (2H, d, *J* = 4.4 Hz, H-6), 8.15 (2H, s, H-3), 7.15-7.40 (22H, m, phenyl and H-5), 5.15 (2H, d, *J* = 2.9 Hz, H-12), 5.04 (2H, d, *J* = 15.9 Hz, H-7a), 4.24 (2H, d, *J* = 2.9 Hz, H-11), 3.84 (2H, d, *J* = 15.9 Hz, H-7b),

3.11 (4H, q, J = 7.3 Hz, COCH_2CH$_3$), 1.17 (6H, t, J = 7.3 Hz, COCH$_2$CH_3) . ^{13}C NMR ($CDCl_3$) : 173.9 (COCH$_2$CH$_3$), 155.1 (C-9), 149.2 (C-6), 145.3 (C-2), 140.5 (C-4), 137.9, 129.6, 129.2, 129.1, 128.2, 126.4, 125.2, (phenyl), 123.0 (C-5), 120.4 (C-3), 64.9 (C-12), 63.6 (C-11), 44.6 (C-7), 29.5 and 29.7 (COCH$_2$CH$_3$), 8.5 (COCH$_2$$CH_3$). *m/z* (FAB) : 791 (M+Na, 17%), 769 (M+H, 80). Acc. FAB (M+H) = 769.3501. $C_{48}H_{45}N_6O_4$ requires 769.3502.

Preparation of *L*-tyrosine methyl ester hydrochloride (16)

Thionyl chloride (6.7 mL, 91.1 mmol) was added dropwise to a solution of *L*-tyrosine (15.0 g, 82.8 mmol) in methanol (50 mL) at 0°C. The mixture was heated to reflux for 3 h then cooled to rt and the solvent removed *in vacuo* to afford **16** as an off-white powder (19.15 g, 99.8%), mp 194-196°C (lit.,[20] 190°C).

Preparation of *(2S)*-2-amino-3-(4-hydroxyphenyl)-1,1-diphenylpropan-1-ol (17)

A dry three-necked flask was charged with magnesium turnings (7.4 g, 304.4 mmol) under nitrogen and dry THF (30 mL) was added. One crystal of iodine was then added and the mixture stirred until the brown colour disappeared. Neat bromobenzene (1 mL, 9.2 mmol) was added and the flask heated with a hot air gun until the reaction started. Then a solution of bromobenzene (31 mL, 295 mmol) in THF (60 mL) was added at such a rate that the mixture boiled gently without external heating. The mixture was then stirred for 3 h at rt when **16** was added in small portions. The brown suspension was stirred overnight at rt and was then slowly poured onto ice. 6N HCl was added until pH = 1. The solution was stirred for 1 h and then made alkaline by adding ammonia. The solution was stirred for a further 1 h. The organic layer was separated, the aqueous layer was extracted with ethyl acetate, and the combined organic fractions were washed with brine and water, then dried ($MgSO_4$) and evaporated. The crude product was recrystallised from ethanol to afford **17** as off-white crystals (6.27 g, 65.0%), mp 213-215°C (lit.,[16] 215-217°C).

Preparation of *(S,S)*-4,4′-*bis*[4-(2-amino-3-hydroxy-3,3-diphenylpropyl)phenoxymethyl]-2,2′-bi-pyridine (18)

A solution of **17** (3.74 g, 11.7 mmol) in dry DMF (20 mL) was added dropwise at rt to NaH (60%, 0.71 g, 17.7 mmol). After the evolution of hydrogen was complete **2** (2.0 g, 5.8 mmol) was added dropwise. The resulting mixture was stirred at rt under nitrogen for 3 h. The solution was then poured into a mixture of water and DCM. The aqueous layer was extracted with DCM and the combined organic fractions were dried ($MgSO_4$). The solvent was removed and the crude product was recrystallised from

ethanol/ethyl acetate to afford **18** as pale brown crystals (3.45 g, 72.8%), mp 97-99°C. ^{1}H NMR : 2.32 (2H, dd, *J* = 14.0, 10.8 Hz, H-14a), 2.50 (2H, dd, *J* = 14.0, 2.4 Hz, H-14b), 4.05 (2H, dd, *J* = 10.8, 2.4 Hz, H-15), 5.08 (4H, s, H-7), 6.84 (4H, d, *J* = 8.6 Hz, H-9,13), 7.03 (4H, d, *J* = 8.6 Hz, H-10,12), 7.11 (4H, m, H-4′,4″), 7.24 (8H, m, H-2′,6′,2″,6″), 7.35 (2H, dd, *J* = 1.4, 5.0 Hz, H-5), 7.54 (8H, m, H-3′,5′,3″,5″), 8.38 (2H, d, *J* = 1.4 Hz, H-3), 8.60 (2H, d, *J* = 5.0 Hz, H-6). ^{13}C NMR ($CDCl_3$) : 35.8 (C-14), 58.2 (C-15), 68.4 (C-7), 78.5 (C-16), 115.1 (C-9,13), 119.0 (C-5), 121.8 (C-3), 125.4, 125.8, 126.5, 126.8, 128.2, 128.5, 144.3, 146.8 (2 x phenyl), 130.2 (C-10,12), 132.4 (C-11), 147.5 (C-4), 149.5 (C-6), 156.1 (C-8), 156.9 (C-2). *m/z* (CI) : 819 (M+H, 16%), 635 (13), 413 (16), 391 (20), 259 (18), 183 (29), 152 (36), 135 (50). *m/z* (FAB) : 841 (M+Na, 44%), 819 (M+H, 100), 796 (8). Acc. FAB (M+H) = 819.3893. $C_{54}H_{51}N_4O_4$ requires 819.3910.

Reduction of acetophenone by 19a with BH_3.THF

To a solution of **18** (0.51 g, 0.63 mmol) in dry THF (10 mL) BH_3.THF (1M, 2.75 mL, 2.75 mmol) was added slowly at -78°C under nitrogen. The mixture was then warmed to 30°C and stirred overnight. A solution of acetophenone (0.11 mL, 1.0 mmol) in dry THF (2 mL) was added dropwise simultaneously with BH_3.THF (1 M, 1.2 mL, 1.2 mmol). The reaction was monitored by TLC, eluent 95% DCM/5% ethyl acetate, R_f of acetophenone = 0.74, R_f of 1-phenylethanol = 0.48. After the addition the mixture was stirred for 1 h at 30°C and was then quenched with 2N HCl (1 mL). The solvent was removed and the residue was taken up in ether and **17** precipitated as its hydrochloride salt. The precipitate was then collected on a glass filter and washed with ether. The ether extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 1-phenylethanol as a colourless oil which was analysed by HPLC (see Table 1, Entry 1).

Reduction of acetophenone by 19a with BH_3.DMS

To a solution of **18** (0.41 g, 0.5 mmol) in dry THF (10 mL) BH_3.DMS (0.38 mL, 4.0 mmol) was added slowly at 30°C under nitrogen. The mixture was stirred overnight at 30°C. BH_3.DMS (0.11 mL, 1.2 mmol) was added slowly and the solution stirred for 1 h. A solution of acetophenone (0.11 mL, 1.0 mmol) in dry THF (2 mL) was then added dropwise. After the addition the mixture was stirred for 1 h at 30°C and was then quenched with 2N HCl (1 mL). The product was isolated as described above and analysed by HPLC (see Table 1, Entry 2).

Reduction of acetophenone by 19b with BH_3.THF

To a solution of **18** (0.41 g, 0.5 mmol) in dry toluene (20 mL) trimethylboroxine (0.095 mL, 0.68 mmol)

was added under nitrogen. The solution was heated to reflux overnight. The solution was concentrated (1 atm) to *ca.* 5 mL. Toluene (20 mL) was added and the solution was again concentrated at 1 atm. The process was repeated twice more. Finally the solvent was removed *in vacuo* and the residue was dissolved in dry THF (10 mL). A solution of acetophenone (0.11 mL, 1.0 mmol) in dry THF (2 mL) was added dropwise simultaneously with BH_3.THF (1.M, 1.2 mL, 1.2 mmol) at 30°C. The reaction was incomplete after 72 h but was nevertheless quenched with 2N HCl (1 mL). The product was isolated as described above and analysed by HPLC (see Table 1, Entry 3).

Reduction of acetophenone by 19b with BH_3.DMS

To a solution of **18** (0.41 g, 0.5 mmol) in dry toluene (20 mL) trimethylboroxine (0.095 mL, 0.68 mmol) was added under nitrogen. The solution was heated to reflux overnight. The solution was concentrated (1 atm) to *ca.* 5 mL. Toluene (20 mL) was added and the solution was again concentrated at 1 atm. The process was repeated twice more. Finally the solvent was removed *in vacuo* and the residue was dissolved in dry THF (10 mL). BH_3.DMS (0.11 mL, 1.2 mmol) was added slowly at 30°C and the solution was stirred for 1 h. A solution of acetophenone (0.11 mL, 1.0 mmol) in dry THF (2 mL) was added dropwise. The reaction was stirred for 1 h at 30°C before being quenched with 2N HCl (1 mL). The product was isolated as described above and analysed by HPLC (see Table 1, Entry 4).

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REFERENCES

1. P. H. H. Hermkens, H. C. J. Ottenheijm, and D. C. Rees, *Tetrahedron*, 1996, **52**, 4527.
2. J. S. Fruchtel and G. Jung, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 17.
3. F. Balkenhohl, C. von dem Bussche-Hunnefeld, A. Lansky, and C. Zechel, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2288.
4. P. Wentworth and K. D. Janda, *Chem. Commun.*, 1999, 1917.
5. C. G. Blettner, W. A. Konig, W. Stenzel, and T. Schotten, *Synlett*, 1998, 295.
6. A. Studer, S. Hadida, R. Ferritto, S.-Y. Kim, P. Jeger, P. Wipf, and D. P. Curran, *Science*, 1997, **275**, 823.
7. H. Perrier and M. Labelle, *J. Org. Chem.*, 1999, **64**, 2110.
8. S. V. Ley, A. Massi, F. Rodrigez, D. C. Horwell, R. A. Lewthwaite, M. C. Pritchard, and A. M. Reid,

Angew. Chem., Int. Ed. Engl., 2001, **40**, 1053.

9. D. C. Horwell, R. A. Lewthwaite, M. C. Pritchard, and A. M. Reid, private communication.
10. C. Kaes, M. W. Hosseini, A. De Cian, and J. Fischer, *Tetrahedron Lett.,* 1997, **38**, 4389.
11. G. R. Newkome, G. E. Kiefer, D. K. Kohli, Y.-J. Xia, F. R. Fronczek, and G. R. Baker, *J. Org. Chem.,* 1989, **54**, 5105.
12. C. L. Fraser, N. R. Anastasi, and J. J. S. Lamba, *J. Org. Chem.,* 1997, **62**, 9314.
13. W. J. Close, *J. Org. Chem.,* 1950, **15**, 1131.
14. A. Cruz, E. Geniz, and R. Contreras, *Tetrahedron Asymmetry,* 1998, **9**, 3991.
15. W. Sankhavasi, M. Yamamoto, S. Kohmoto, and K. Yamada, *Bull. Chem. Soc. Jpn.,* 1991, **64**, 1425.
16. S. Itsuno, M. Nakano, K. Ito, A. Hirao, M. Owa, N. Kanda, and S. Nakahama, *J. Chem. Soc., Perkin Trans. 1,* 1985, 2615.
17. M. P. Sibi, G. R. Cook, and P. Liu, *Tetrahedron Lett.,* 1999, **40**, 2477.
18. D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. T. Jones, K. Hoogsteen, M. W. Baum, and E. J. J. Grabowski, *J. Org. Chem.,* 1991, **56**, 751.
19. D. D. Perrin and W. L. F. Amarego, *Purification of Laboratory Chemicals,* Pergamon Press.
20. *Dictionary of Organic Compounds,* fifth edition, Vol. 5, p. 5653.