Chemoenzymatic synthesis of chiral 2,2′-bipyridine ligands and their *N*-oxide derivatives: applications in the asymmetric aminolysis of epoxides and asymmetric allylation of aldehydes†‡

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A series of enantiopure 2,2′-bipyridines have been synthesised from the corresponding *cis*-dihydrodiol metabolites of 2-chloroquinolines. Several of the resulting hydroxylated 2,2′-bipyridines were found to be useful chiral ligands for the asymmetric aminolysis of *meso*-epoxides leading to the formation of enantioenriched amino alcohols (→84% *ee*). *N*-oxide and *N*,*N*′-dioxide derivatives of these 2,2′-bipyridines, including separable atropisomers, have been synthesised and used as enantioselective organocatalysts in the asymmetric allylation of aldehydes to give allylic alcohols (→86% *ee*).

Introduction

Dioxygenase-catalysed oxidation of arene substrates provides a direct route to a wide range of enantiopure mono- and poly-hydroxylated bioproducts. To date, these readily available chiral metabolites have been mainly used as synthetic precursors of a wide range of natural products.[1a–i] In order to find alternative applications in our laboratories, several of these hydroxylated arene products have also been evaluated as synthetic precursors of chiral ligands,[2a,b] chiral resolving agents,[2c] chiral scaffolds[2d] and chiral auxiliaries.[2e] Recent studies have centred on chiral 2,2′-bipyridines derived from *cis*-dihydrodiol metabolites of quinolines, which have shown considerable potential as chiral ligands.[2b] Anticipation that other types of 2,2′-bipyridines, including hydroxylated derivatives and *N*-oxides, could also be of value as both chiral ligands and chiral organocatalysts in other types of asymmetric synthesis, provided the main focus of the current study.

The dioxygenase-catalysed asymmetric dihydroxylation of quinoline substrates **1A–3A** to yield the corresponding enantiopure *cis*-dihydrodiol metabolites, **1B–3B** and **1C–3C** (Scheme 1) was achieved using whole cells of mutant bacterial strains including *Pseudomonas putida* (UV4) and *Sphingomonas yanoikuyae* (B8/36).[2b,3,4] The two *cis*-dihydroxylating biocatalysts used were toluene dioxygenase (TDO, present in *P. putida* UV4) and biphenyl dioxygenase (BPDO, present in *S. yanoikuyae* B8/36). TDO, having a smaller active site, was only able to accommodate the less bulky substrates (*e.g.* **1A** and **2A**), while BPDO, with a larger active site, was able to accept a substrate having greater steric requirements (*e.g.* **3A**). The isomeric *cis*-dihydrodiols **1B–3B** and **1C–3C** were readily separated by chromatography. Catalytic hydrogenation of the major *cis*-dihydrodiols **2B** and **3B** (PtO_2/H_2) yielded the corresponding *cis*-tetrahydrodiols (**2D** and **3D**) without hydrogenolysis of the chlorine atom.[2b,3,4] These stable *cis*-tetrahydrodiols were protected as their dioxolane derivatives (**2E–7E**) and homocoupled to give a series of chiral 2,2′-bipyridines (**2F–7F**, Scheme 1) using the previously reported method.[2b]

The potential of the protected 2,2′-bipyridines as chiral ligands was initially evaluated using Cu(I)-catalysed asymmetric allylic oxidations, the Kharasch–Sosnosky reaction and asymmetric cyclopropanations of the corresponding alkenes as model reactions.[2b] The encouraging results obtained, for both the asymmetric allylic oxidations (→97% *ee*) and cyclopropanations (→95% *ee*), during these preliminary studies, prompted this more extensive investigation of our chemoenzymatically-derived hydroxylated chiral 2,2′-bipyridines and their *N*-oxide derivatives on other types of asymmetric synthesis.

In this study, the potential of the quinoline *cis*-dihydrodiols (**2B** and **3B**) as synthetic precursors of an extended range of chiral 2,2′-bipyridines having (i) fully protected (**7F**, Scheme 1), (ii) partially protected (**9**, Scheme 2) or unprotected hydroxyl groups (**8**, Scheme 2) and (iii) a new range of *N*-oxides (**2I–7I**, Scheme 2) and *N*,*N*′-dioxides (**2J–7J**, Scheme 2) has been demonstrated. A comparison of the enantioselectivity values obtained using 2,2′-bipyridines **7F**, **8** and **9**, with established chiral ligands used earlier for the Sc-catalysed asymmetric aminolysis of *meso*-epoxides, has been carried out. The *ee* values obtained during the asymmetric allylation of benzaldehydes using *N*-oxides **2I–7I** and *N*,*N*′-dioxides **2J–7J** have also been compared with known asymmetric *N*-oxide and *N*,*N*′-dioxide organocatalysts.

Results and discussion

A preliminary study from these laboratories[2b] indicated that, in the context of an asymmetric allylic oxidation of cyclohexene **10**

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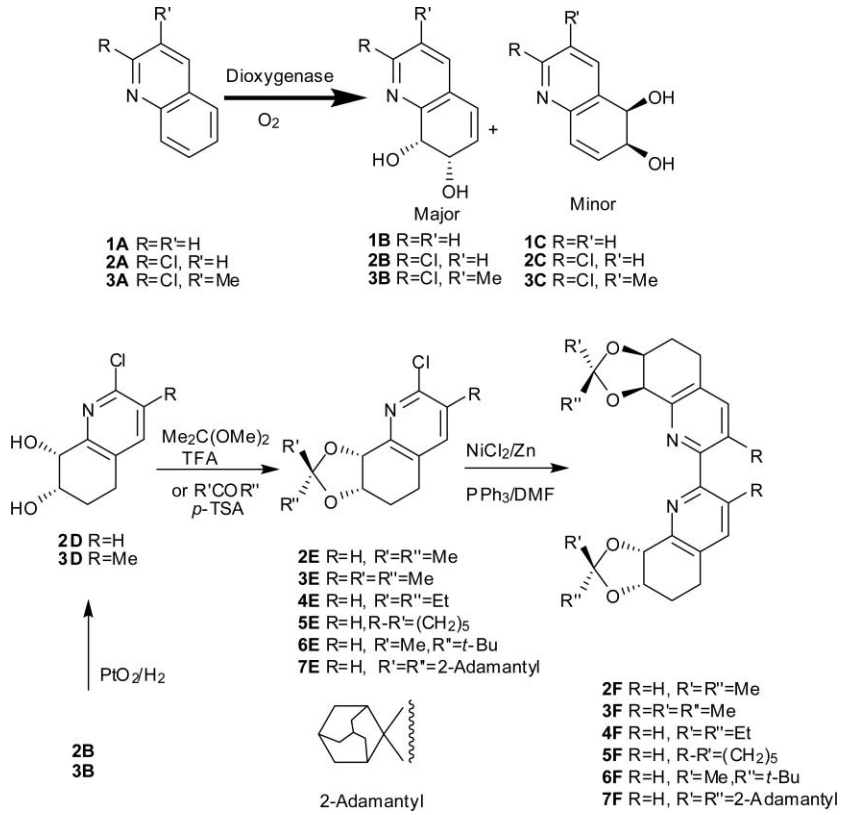


Scheme 1 Synthesis of *cis*-dihydrodiols (**1B–3B**, **1C–3C**) and 2,2′-bipyridines (**2F–7F**).

and cycloheptene **12** (Scheme 3), the most efficient of the 2,2′-bipyridine ligands **2F–6F** (Scheme 1) appeared to be compound **6F** (→97% *ee*). However, when these ligands were evaluated using the allylic oxidation of cyclopentene, although comparable yields were obtained (*ca.* 50% yield), the enantioselectivity values were less promising, with the best result (38% *ee*) again being obtained using compound **6F**. As this ligand also appeared to have the most bulky dioxolane substituents (R′ = Me and R″ = *tert*-Bu), a further 2,2′-bipyridine **7F**, containing the adamantylidine group (considered to be more sterically demanding than the cyclohexylidine group present in compound **5F**), was synthesised from the corresponding *cis*-tetrahydrodiol **2D**. Condensation of diol **2D** with 2-adamantanone in the presence of an acid catalyst yielded the protected diol **7E**. Following the standard coupling procedure ($NiCl_2/Zn/Ph_3P/DMF$) yielded the 2,2′-bipyridine **7F**. A comparison of the results obtained during asymmetric oxidation of both cyclohexene **10** and cycloheptene **12** using the reported 2,2′-bipyridine ligands (**5F** and **6F**),[2b] and the new ligand (**7F**), is shown in Table 1.

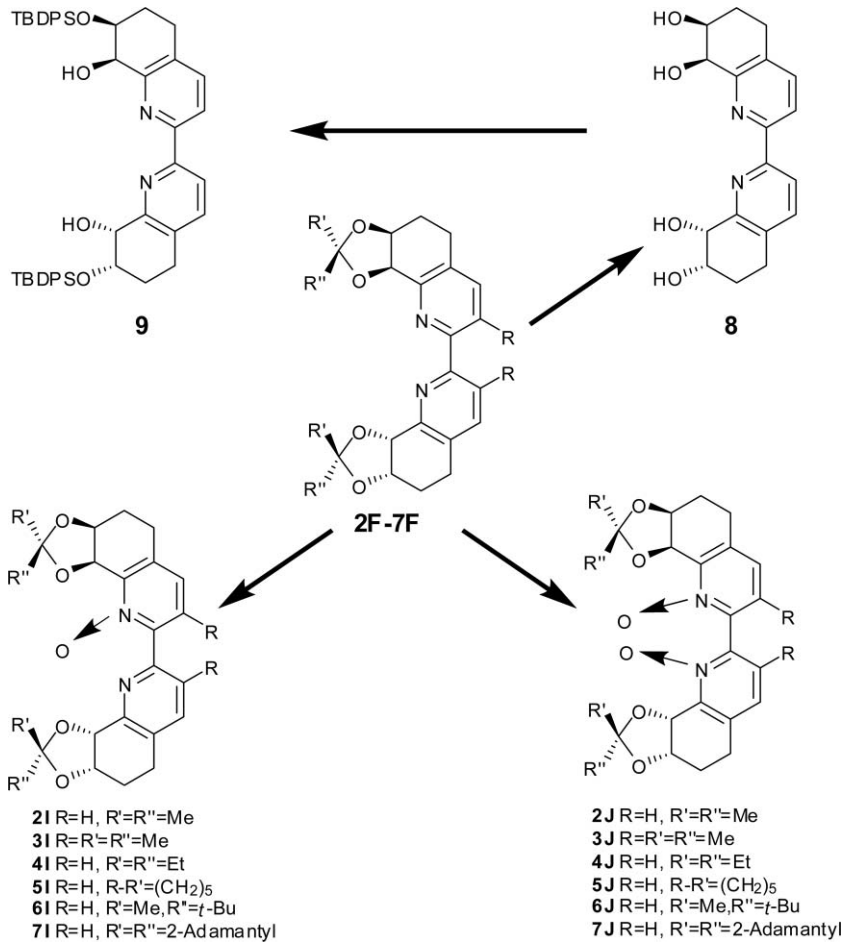
Despite the replacement of the cyclohexylidene group in the 2,2′-bipyridine **5F** by a more bulky adamantylidene group in ligand **7F**, the stereoselectivity observed in the synthesis of benzoate **11** using this ligand was either slightly less (79% *vs.* 85% *ee* using ligand **5F**) or similar (91% *vs.* 92% *ee* using ligand **5F**). Following this unsuccessful attempt to improve enantioselectivity over that found using ligands **5F** or **6F**, the effect on enantioselectivity of increasing the ligand's polarity was then examined. This was achieved by deprotection of the *bis*-acetonide **2F** (HCl/MeOH) to form the C_2-symmetric 2,2′-bipyridine tetraol **8** in acceptable yield (80%) (Scheme 2). The new polyhydroxylated compound **8** was not found to be a suitable ligand for the allylic oxidation procedure shown in Scheme 3. Preliminary studies have, however, shown that the minor *cis*-dihydrodiol isomers (*e.g.* **2C**) can also be chemically converted into the corresponding *cis*- or *trans*-tetrahydrotetraols, protected as *bis*-acetonides and coupled. This extended the range of chemoenzymatically-derived enantiopure 2,2′-bipyridines as chiral ligands in the Kharasch–Sosnosky reaction.

Table 1 Absolute configuration (Ab. config.) and enantiopurity values (% *ee*) of the benzoates (**11** and **13**) obtained by asymmetric allylic oxidation of alkenes (**10** and **12**)

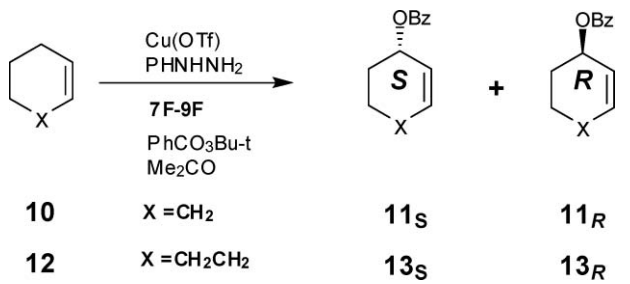
Alkene	Benzoate	Ligand	Ab. config.	*ee* (%)
10	**11**	**5F**	1*S* (**11**$_S$)	85[a]
12	**13**	**5F**	1*S* (**13**$_S$)	92[a]
10	**11**	**6F**	1*S* (**11**$_S$)	90[a]
12	**13**	**6F**	1*S* (**13**$_S$)	97[a]
10	**11**	**7F**	1*S* (**11**$_S$)	79
12	**13**	**7F**	1*S* (**13**$_S$)	91

[a] Ref. 3.

Reaction of the tetraol **8** with *tert*-butyldiphenylsilyl chloride in the presence imidazole as catalyst resulted in preferential protection of the less hindered OH groups on C-7, to give 2,2′-bipyridine diol **9** as the major product (45% yield) after preparative layer chromatography (PLC) purification. Earlier reports of 2,2′-bipyridines bearing two OH groups adjacent to the pyridine rings, *e.g.* **14**[5] and **15**,[6] showed them to be excellent chiral ligands for a range of asymmetric synthesis reactions. The 2,2′-bipyridine



Scheme 2 Synthesis of 2,2′-bipyridines (**8** and **9**), *N*-oxides (**2I–7I**) and *N*,*N*′-oxides (**2J–7J**).

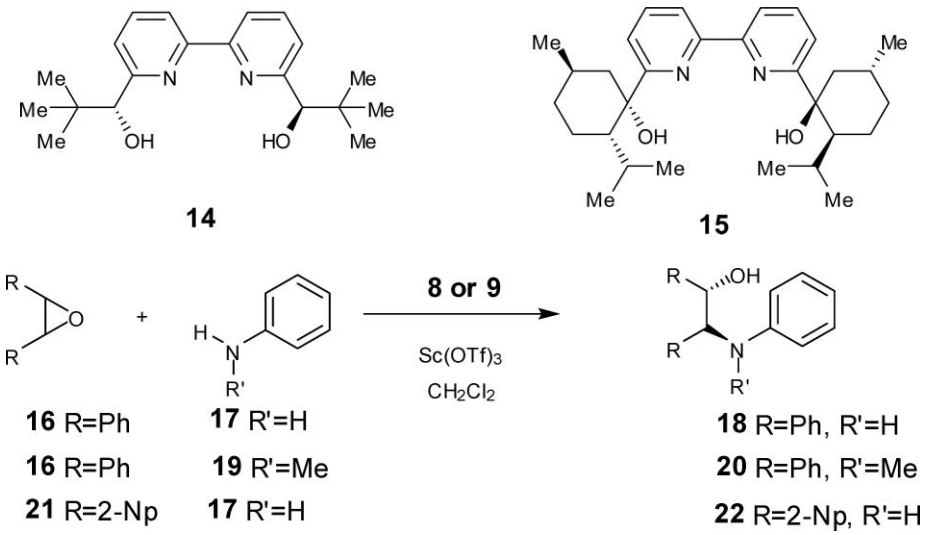


Scheme 3 Asymmetric allylic oxidation of alkenes **10** or **12** to benzoates **11** or **13**.

diol **15** was found to be a particularly enantioselective ligand for aminolysis of epoxides yielding aminoalcohols with high *ee* values (→97% *ee*).[6] The proximate OH groups appeared to be essential for the formation of the scandium–bipyridine complex, since their protection as MeO groups resulted in total loss of enantioselectivity.[6] As each of the new chiral 2,2′-bipyridines **8** and **9** had OH groups in comparable positions to those in compounds **14** and **15**, they were examined as potential ligands for the scandium-catalysed asymmetric aminolysis of *meso*-epoxides bearing phenyl (*e.g.* **16**) and 2-naphthyl substituents (*e.g.* **21**, Scheme 4).

The aminolysis of *cis*-stilbene oxide **16** was studied using aniline **17** or *N*-methylaniline **19**, with $Sc(OTf)_3$ (10 mol%) as Lewis acid and the enantiopure 2,2′-bipyridines **8** or **9** (12 mol%) as ligands, in CH_2Cl_2 solvent (Scheme 4). The enantioselectivity values for the resulting aminoalcohols found using *cis*-stilbene oxide **16** and ligand **9** with aniline **17** (aminoalcohol **18**, 61% *ee*) or *N*-methylaniline **19** (aminoalcohol **20**, 68% *ee*) were encouraging (Table 2), and prompted further studies using the more sterically hindered *meso*-epoxide, *cis*-1,2-bis-(2-naphthyl)ethane oxide **21**. Thus, using aniline **17** and ligand **9** with this epoxide (**21**) under similar conditions [$Sc(OTf)_3$, CH_2Cl_2], the resulting aminoalcohol product **22** was obtained with a higher *ee* value (84%) compared with that obtained earlier (82% *ee*) using ligand **14**.[6] The optimal enantioselectivity obtained by Schneider *et al.* was found in the synthesis of aminoalcohols **20** (→97% *ee*) using ligand **14**.[6]

The presence of hydroxyl groups in ligand **8**, while necessary for complexation with the scandium atom and the resulting enantioselectivity, also increased its water-solubility, a property which was further utilised. A recent literature report[7] showed that ligand **14** and a 1.2 mol% loading of scandium–bipyridine complex with dodecyl sulfate counterion $Sc(OSO_3C_{12}H_{25})_3$ in water, was sufficient to catalyse the asymmetric aminolysis of epoxide **16** (using amine **17**) yielding aminoalcohol **18** (91% *ee*). This was used as a precedent for a preliminary study of ligands **8** and **9** under



Scheme 4 Asymmetric aminolysis of *meso*-epoxides **16** and **21**.

Table 2 Asymmetric aminolysis of epoxides **16** and **21** using amines **17** and **19**, ligands **8** and **9**, and $Sc(OTf)_3$ in CH_2Cl_2 solvent

Epoxide	Amine	Ligand	Product (% yield)	Absolute configuration	*ee* (%)
16	**17**	**9**	**18** (64)	1*S*,2*S*	61
16	**19**	**9**	**20** (48)	1*S*,2*S*	68
16	**17**	**8**	**18** (50)[a]	1*S*,2*S*	57[a]
21	**17**	**9**	**22** (77)	1*S*,2*S*	84
21	**17**	**8**	**22** (43)[a]	1*S*,2*S*	62[a]

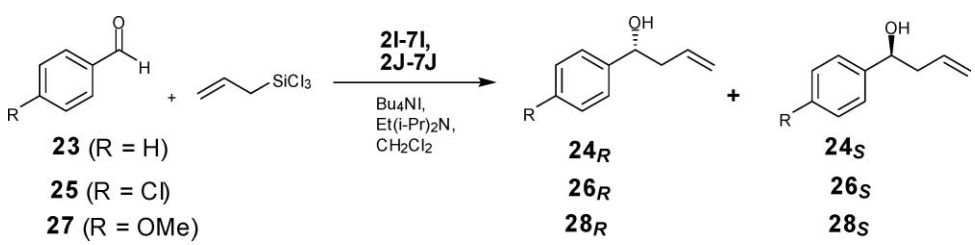
[a] Using ligand **8** (1.2 mol%), $Sc(OSO_3C_{12}H_{25})_3$ and water as solvent.

similar conditions (Table 2). The enantioselectivity values found during the formation of aminoalcohols **18** (57% *ee*) and **22** (62% *ee*) under aqueous conditions were only moderate in comparison to those reported earlier (→96% ee).[7] The unoptimised results shown in Table 2 in either CH_2Cl_2 (→84% *ee*) or water (→62% *ee*) do, however, indicate the potential of these new polyhydroxylated chiral 2,2′-bipyridines, **8** and **9**, as chiral ligands for the asymmetric aminolysis of *meso*-epoxides.

The second part of this study involved the peroxyacid oxidation of the chiral 2,2′-bipyridines **2F–7F** to give the corresponding *N*-oxides **2I–7I** and *N*,*N*′-dioxides **2J–7J** (Scheme 2), and an evaluation of the potential of these new 2,2′-bipyridine *N*-oxide derivatives as Lewis bases and enantioselective organocatalysts for the asymmetric allylation of aldehydes **23**, **25**, and **27** (the Sakuri–Hosomi reaction,[8a–d] Scheme 5). Mono-*N*-oxidation of the 2,2′-bipyridines **2F–7F** to yield the corresponding 2,2′-bipyridine *N*-oxides **2I–7I** was mainly observed using one equivalent of MCPBA in CH_2Cl_2 at 0 °C (54–72% yield). A lower yield of *N*-oxide **3I** (40%) was found when using the most hindered 2,2′-bipyridine **3F**. In all cases, the major *N*-oxide products (**2I–7I**) were readily separated from the minor amounts of *N*,*N*′-dioxides (**2J–7J**) and unreacted 2,2′-bipyridine by column chromatography. Using an excess of MCPBA, the 2,2′-bipyridine *N*,*N*′-dioxides **2J–7J** were generally isolated as the major products in higher yields (70–80%), with the exception of the more hindered *N*,*N*′-dioxide **3J** (52%), where the reaction again proved to be much slower.

^{1}H-NMR analysis indicated that all of the *N*-oxides and *N*,*N*′-dioxides were single compounds, except for those bearing Me groups at C-7 and C-7′, *i.e.* *N*-oxide **3I** and the *N*,*N*′-dioxide **3J**, which were found to exist as mixtures of atropisomers, *i.e.* $\mathbf{3I}_P : \mathbf{3I}_M$ (3 : 1) and $\mathbf{3J}_P : \mathbf{3J}_M$ (8 : 1). While these atropisomeric pairs were each found to be separable by multi-elution PLC, they also appeared to be configurationally unstable, with total equilibration occurring spontaneously at room temperature in $CDCl_3$ solution over a period of three weeks ($t_{1/2}$ > 2 d). However, the major isomer in each case ($\mathbf{3I}_P$ and $\mathbf{3J}_P$) could be isolated in pure form by recrystallisation. In order to confirm their structures, and preferred conformations/configurations, X-ray crystallographic analysis was carried out on the 2,2′-bipyridine *N*-oxide $\mathbf{3I}_P$ (Fig. 1) and *N*,*N*′-dioxides **2J** (Fig. 2), and $\mathbf{3J}_P$ (Fig. 3).

In the crystalline state, the parent 2,2′-bipyridine **2F** was earlier shown to have the two pyridine rings almost co-planar



Scheme 5 Asymmetric allylation of aldehydes **23**, **25**, and **27** using *N*-oxides **2I–7I** and *N*, *N*′-dioxides **2J–7J** as organocatalysts.

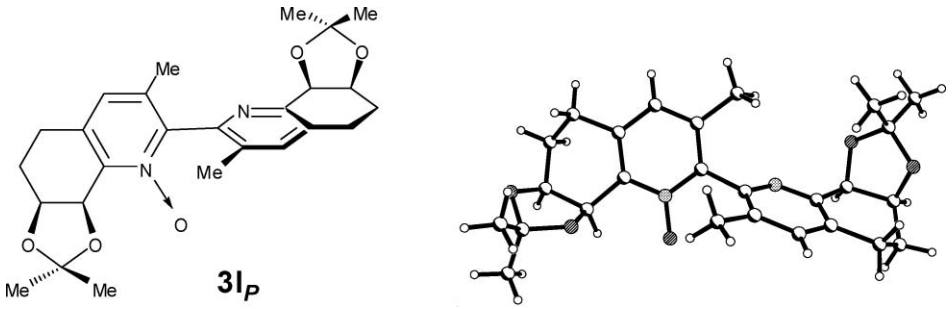


Fig. 1 X-Ray crystal structure of compound **3I$_P$**.

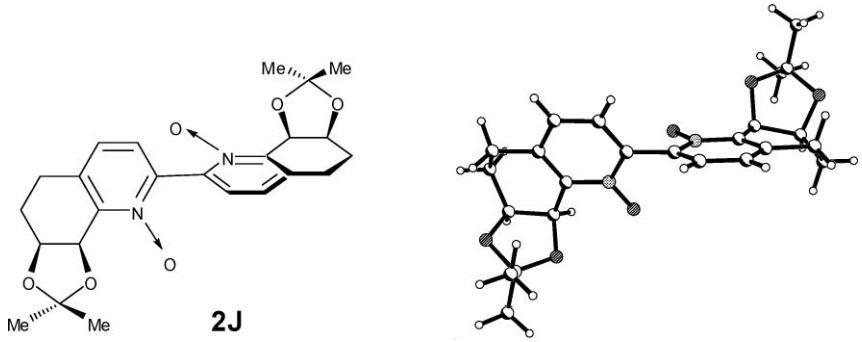


Fig. 2 X-Ray crystal structure of compound **2J**.

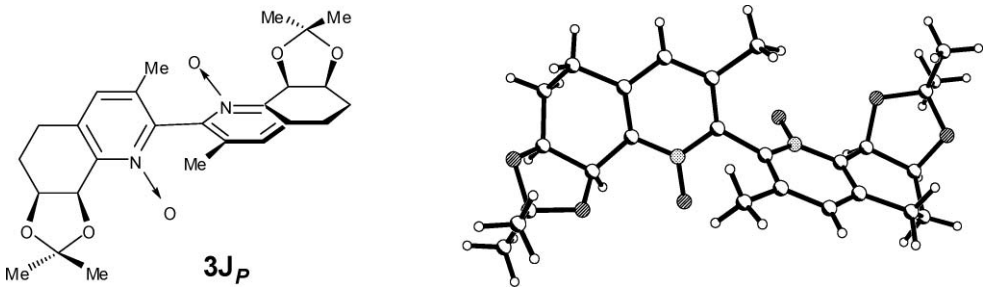


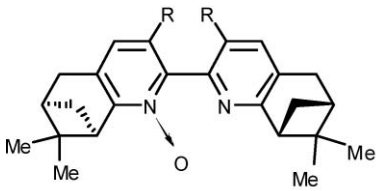
Fig. 3 X-Ray crystal structure of compound **3J$_P$**.

(N–C–C′–N′ torsional angle of 173°), with the two N atoms adopting a conjugated *transoid* conformation.[2b] Conversely, the preferred conformation within the 2,2′-bipyridine-*N*,*N*′-dioxide **2J** crystal structure was found to have the pyridine rings approaching the orthogonal (N–C–C′–N′ torsional angles of +67° and +68° for two independent molecules, Fig. 2); *i.e.* all molecules have helicity *P*. The major *N*-oxide atropisomer **3I$_P$**, crystallised from the mixture of atropisomers (**3I$_P$**/**3I$_M$**), consisted of two crystallographically independent molecules that did not differ significantly in preferred conformation (Fig. 1). Thus the pyridine rings were again almost orthogonal (N–C–C′–N′ torsional angles of +117° and +108°), *i.e.* all molecules have helicity *P* but, unlike compound **2J**, are closer to *transoid* than *cisoid*.

The crystal structure of the *N*,*N*′-dioxide **3J$_P$** was isomorphous with the *N*-oxide **3I$_P$**, *i.e.* it showed two crystallographically independent molecules with N–C–C′–N′ torsion angles of +112° and +107°, and helicity *P* (Fig. 3). It was evident from the formation and separation of the atropisomers **3I$_P$**/**3I$_M$** and **3J$_P$**/**3J$_M$** (and the absence of atropisomers from compound **2J**), and possibly also from the preferred conformations in the crystalline state, that the major steric interactions are found between the two Me groups on C-3 with the O atoms on each of the *N*-oxide groups playing a relatively minor role.

Earlier literature reports have shown that both *N*-oxide (*e.g.* **29** or **30**)[9a–c] and *N*,*N*′-dioxide derivatives (*e.g.* **31**)[10a–d,11,12] of chiral 2,2′-bipyridines are efficient chiral organocatalysts for the asymmetric allylation of some aldehydes (→97% *ee*).

The potential of *N*-oxides **2I**, **3I$_P$** and **4I–7I**, and *N*,*N*′-dioxides **2J**, **3J$_P$** and **4J–7J** as catalysts for asymmetric allylation was evaluated using similar conditions, *i.e.* allyltrichlorosilane, tetrabutylammonium iodide, diisopropylethylamine and benzaldehyde **23**, 4-chlorobenzaldehyde **25** and 4-methoxybenzaldehyde **27** (Tables 3 and 4). As found in the earlier studies with ligands **29–31**,[9–12] the rate of the allylation reaction was slower when using the *N*-oxides, and thus, these reactions were carried out at higher temperatures (0 °C or −40 °C) compared with the corresponding *N*,*N*′-dioxides (−78 °C). When the *N*-oxides **2I**, **3I$_P$** and **4I–7I** were



29 (R = H)
30 (R = Me)

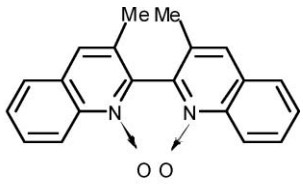


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Table 3 Asymmetric allylation of aldehydes **23**, **25** and **27** to yield allylic alcohols **24**, **26** and **28**, using allyltrichlorosilane and the *N*-oxide ligands **2I–7I** in CH_2Cl_2 after 24 h

Aldehyde	Catalyst	Product (% yield)	Temp./°C	Absolute configuration	*ee* (%)
23	**2I**	**24** (60)	0	*R*	35
25	**2I**	**26** (65)	0	*R*	46
27	**2I**	**28** (72)	0	*R*	63
27	**3I$_P$**	**28**(41)[a]	–40	*R*	86
23	**4I**	**24** (42)[a]	–40	*R*	24
27	**4I**	**28** (35)[a]	–40	*R*	67
23	**5I**	**24** (28)[a]	–40	*R*	30
27	**5I**	**28** (39)[a]	–40	*R*	81
27	**6I**	**28** (21)[a]	–40	*R*	56
27	**7I**	**28** (46)[a]	–40	*R*	60

[a] Incomplete reaction after 24 h.

Table 4 Asymmetric allylation of aldehydes **23**, **25** and **27** to yield allylic alcohols **24**, **26** and **28**, using allyltrichlorosilane and the *N*,*N*′-dioxide ligands **2J–7J** in CH_2Cl_2 after 12 h

Aldehyde	Catalyst	Product (% yield)	Temp./°C	Absolute configuration	*ee* (%)
23	**2J**	**24** (64)	–78	*R*	26
25	**2J**	**26** (61)	–78	*R*	31
27	**2J**	**28** (75)	–78	*R*	80
27	**3J$_P$**	**28** (68)[a]	–78	*R*	59
23	**4J**	**24** (62)	–78	*R*	16
27	**5J**	**28** (71)	–78	*R*	73
23	**5J**	**24** (28)	–78	*R*	14
27	**6J**	**28** (45)	–78	*S*	71
27	**6J**	**28** (63)	–78	*R*	72
27	**7J**	**28** (44)	–78	*R*	73

[a] Complete reaction after 18 h.

used, the reactions were incomplete after 24 h at –40 °C, and thus, yields were lower (21–46%, Table 3).

However, with *N*,*N*′-dioxides **2J**, **3J$_P$** and **4J–7J**, the reactions went to completion (28–75% yields, Table 4) when the allylation reactions were conducted at –78 °C. Similarly, as found earlier, the optimal results were obtained using 4-methoxybenzaldehyde **27** with either the *N*-oxides **2I**, **3I$_P$**, **4I–7I** (56–86% *ee*) or the *N*,*N*′-dioxides **2J**, **3J$_P$**, **5J–7J** (59–80% *ee*), compared to those obtained using benzaldehyde **23** (24–35% *ee* and 14–26% *ee*). It is noteworthy that the highest degree of enantioselectivity (86% *ee*) was observed using aldehyde **27** and the *N*-oxide atropisomer **3I$_P$** (Table 3). This observation is similar to that found using the *N*,*N*′-dioxide **31** during allylation of 4-methoxybenzaldehyde **27** where the product alcohol **28** was also found to have the highest *ee* value (92%) compared with other substituted aldehydes (R = H, CF_3).[12] Unfortunately, the additional presence of stereogenic chirality of the *N*,*N*′-dioxide atropisomer **3J$_P$** did not assist during allylation of aldehyde **27**, when lower enantioselectivity was found (59% *ee*, Table 4). In view of the recent proposal that two plausible reaction mechanisms could be used in the context of asymmetric allylation reactions using different *N*,*N*′-dioxide ligands and 4-substituted aldehydes,[10b] we have not attempted to further rationalise the range of *ee* values obtained herein. Since the reactions in CH_2Cl_2 with compounds **3I$_P$** and **3J$_P$** were carried out at low temperature (–40 or –78 °C respectively), and as the atropisomers were only found to interconvert very slowly at room temperature ($t_{1/2}$ > 2 d in $CDCl_3$), it is unlikely that any significant degree of atropisomerization had occurred during the asymmetric allylation reactions.

The allylic alcohol products were generally found to have a marked preference for the (*R*) absolute configuration (**24$_R$**, **26$_R$** and **28$_R$**) regardless of the nature of the aldehyde or ligand substituents. The only exception being aldehyde **27** and *N*-oxide ligand **6J** where the product **28** had an excess of the (*S*) enantiomer (71% *ee*). A recent study[10c] has shown that a change in solvent can have a dramatic effect on the preferred absolute configurations of the alcohol products obtained using atropisomeric 2,2′-bipyridine-*N*-oxides as organocatalysts for the asymmetric allylation of benzaldehydes. Although the optimal *ee* values of products obtained using the sixteen new chiral 2,2′-bipyridines, 2,2′-bipyridine *N*-oxides or *N*,*N*′-dioxides during the present study were found to be in the range 80–91% (Tables 1–4), it should be emphasised that optimisation studies have yet to be carried out. Having demonstrated the value of *cis*-dihydrodiols **2B** and **3B** as synthetic precursors of chiral ligands,[2b] chiral scaffolds[2d] and now chiral organocatalysts, efforts to find and develop more efficient dioxygenase biocatalysts to produce these compounds, without the formation of other *cis*-dihydrodiol isomers, are currently in progress.

Conclusions

In conclusion, the current report has shown that:

(i) the major enantiopure *cis*-dihydrodiol metabolites from 2-chloroquinoline (**2B**) and 3-methyl-2-chloroquinoline (**3B**) can be used as precursors in the synthesis of a new range of 2,2′-bipyridine ligands. These include ligands with: (a) fully protected hydroxyl groups (**2F–7F**), (b) free hydroxyl groups (**8** and **9**), and the corresponding *N*-oxides (**2I–7I**) and *N*,*N*′-dioxides (**2J–7J**).

(ii) the hydroxylated 2,2′-bipyridine ligands (**8** and **9**) can be applied as chiral ligands in the asymmetric aminolysis of *meso*-epoxides (**16** and **21**), leading to the formation of enantioenriched amino alcohols (**18**, **20** and **22** →84% *ee*).

(iii) the preferred conformations and configurations of 2,2′-bipyridine *N*-oxide (**2I–7I**) and *N*,*N*′-dioxide (**2J–7J**) derivatives (including the separable atropisomeric pairs **3I$_P$**/**3I$_M$** and

$3J_P/3J_M$) have been assigned by X-ray crystallography and NMR spectroscopy.

(iv) the *N*-oxide and *N*,*N*′-dioxide derivatives (**2I–7I**, **2J–7J**), can be utilised as enantioselective organocatalysts in the asymmetric allylation of aldehydes to give allylic alcohols (**24**, **26** and **28**, →86% *ee*).

(v) the remarkable enantioselectivity initially introduced through biocatalysis can now be transferred (*via* chemoenzymatic synthesis) to homogeneous catalysis and organocatalysis.

Experimental

NMR (^{1}H and ^{13}C) spectra were recorded on Bruker Avance DPX-300 and DPX-500 instruments and mass spectra were run at 70 eV, on a VG Autospec Mass Spectrometer, using a heated inlet system. Accurate molecular weights were determined by the peak matching method, with perfluorokerosene as the standard. Elemental microanalyses were carried out on a PerkinElmer 2400 CHN microanalyser. For optical rotation ($[\alpha]_D$) measurements (*ca.* 20 °C, 10^{-1} deg cm^2 g^{-1}), a PerkinElmer 341 polarimeter was used.

Flash column chromatography and PLC were performed on Merck Kieselgel type 60 (250-400 mesh) and $PF_{254/366}$ respectively. Merck Kieselgel type $60F_{254}$ analytical plates were used for TLC.

The 2,2′-bipyridine ligands **2F–6F** were obtained using the reported method[2c] and were supplemented by samples available from earlier studies in these laboratories.

Biotransformations of 2-chloroquinoline 2A and 2-chloro-3-methyl-quinoline 3A

Biotransformation of 2-chloroquinoline **2A** (100 g, 0.61 mol) was carried out using *P. putida* UV4 in a New Brunswick Scientific Bioflo 5000, 120 l fermentor and the previously reported method.[4] The crude bioproduct mixture was obtained by concentration of the aqueous culture medium under reduced pressure followed by repeated EtOAc extraction. The required (less polar) *cis*-dihydrodiol **2B** (24.5 g, 21%, R_f 0.3 in 7% MeOH in $CHCl_3$); $[\alpha]_D$ +146, MeOH) was separated from the minor *cis*-dihydrodiol **2C** (10.1 g, 8.5%, R_f 0.45); $[\alpha]_D$ +136, MeOH) by flash column chromatography of the crude mixture on silica gel (5% EtOAc in hexane → 10% MeOH in EtOAc). Biotransformation of 2-chloro-3-methylquinoline **3A** (0.2 g, 1.13 mmol) using *P. putida* UV4 under similar conditions resulted in >90% of the substrate being recovered and the production of several unidentified metabolites in very low yields.

The biotransformation of 2-chloro-3-methylquinoline **3A** (10.0 g, 0.056 mol) was repeated using *S. yanoikuyae* B8/36 and the conditions reported earlier.[2b,d] The major and less polar dihydrodiol **3B** (4.2 g, 35%, R_f 0.31 in 7% MeOH in $CHCl_3$); $[\alpha]_D$ +184, MeOH) was separated from the minor isomer **3C** (3.0 g, 25%, R_f 0.46); $[\alpha]_D$ +172, MeOH by a combination of flash column chromatography and PLC. Dihydrodiols **2B**, **2C**, **3B** and **3C** were found to be identical to authentic samples.[2d,3]

(3a*S*,9b*R*)-8-Chloro-3a,4,5,9b-tetrahydrospiro[1,3]dioxolo[4,5-*h*]quinoline-2,2-adamantane 7E

A mixture of *cis*-diol **2D** (1.5 g, 7.5 mmol), *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) and 2-adamantanone (2.8 g, 18.75 mol) in benzene (50 ml) was heated at reflux using a Dean–Stark trap for 20 h. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (50 ml), then washed with a saturated aqueous solution of $NaHCO_3$ (10 ml). The organic solution was dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude acetal **7E** obtained was purified by column chromatography (50% EtOAc–hexane) to yield a white crystalline compound (1.9 g, 76%); mp 98 °C (from EtOAc–hexane); $[\alpha]_D$ +78 (*c* 0.55, $CHCl_3$); HRMS (EI) Found: M^+ 331.1311, $C_{19}H_{22}ClNO_2$ requires 331.1339; δ_H (300 MHz, $CDCl_3$) 1.26-2.12 (16 H, m, adamantyl protons, H-4, H-4′), 2.53 (1H, ddd, $J_{5,4'}$ 4.2, $J_{5,4}$ 4.2, $J_{5,5'}$ 15.9, H-5), 2.98 (1H, ddd, $J_{5',4}$ 3.9, $J_{5',4'}$ 12.0, $J_{5',5}$ 15.6, H-5′), 4.67 (1 H, m, H-3a), 5.14 (1 H, d, $J_{9b,3a}$ 6.3, H-9b), 7.20 (1 H, d, $J_{7,6}$ 8.0, H-7), 7.42 (1 H, d, $J_{6,7}$ 8.0, H-6); δ_C (125 MHz, $CDCl_3$) 23.66, 27.33, 27.42, 28.45, 34.71, 35.25, 35.34, 35.61, 35.78, 37.56, 38.59, 73.33, 75.64, 112.05, 123.92, 133.52, 139.31, 149.47, 155.42; MS *m*/*z* (EI) 331 (M^+, ^{35}Cl, 84%), 333 (M^+, ^{37}Cl, 23%), 165 (100), 181 (97), 150 (66), 128 (38), 79 (63), 67 (21).

(3a*S*,9b*R*,3a′*S*,9b′*R*)-8,8′-bis{Spiro[[1,3]dioxolo[4,5*h*]quinoline-2,2′ adamantane]} 7F

To a stirred solution of nickel(II) chloride hexahydrate (1 g, 4.2 mmol) and triphenylphosphine (PPh_3) (3.64 g, 13.8 mmol) in dry, degassed dimethylformamide (10 ml) was added zinc powder (0.68 g, 10.2 mmol). The reaction mixture was heated at 60 °C for 1 h; the colour of the solution changed to red. A solution of acetal **7E** (1 g, 3 mmol), in dry degassed dimethylformamide (10 ml), was then added and the mixture was heated at 60 °C for 5 h; it was allowed to cool to room temperature and then poured into an aqueous solution of NH_4OH (10% w/w, 20 ml). The resultant mixture was extracted with dichloromethane (3 × 20 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford the crude product. Purification by column chromatography (50% EtOAc–hexane) gave bipyridine **7F** as a white crystalline solid (0.51 g, 58%); mp 289-290 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +210 (*c* 0.98, $CHCl_3$); Found: C, 76.8; H, 7.7; N, 4.7; $C_{38}H_{44}N_2O_4$ requires C, 77.0; H, 7.5; N, 4.7; δ_H (300 MHz, $CDCl_3$) 1.26-1.69 (30H, m, 2 × adamantyl protons, H-4, H-4′), 2.17 (2H, m, H-4″, H-4‴), 2.63 (2H, ddd, $J_{5,4''}$ 3.9, $J_{5,4}$ 3.9, $J_{5,5''}$ 15.6, H-5, H-5′), 3.04 (2H, ddd, $J_{5'',4}$ 3.6, $J_{5'',4''}$ 11.7, $J_{5'',5}$ 15.6, H-5″, H-5‴), 4.69 (2H, m, H-3a, H-3a′), 5.24 (2H, d, $J_{9b,3a}$ 6.6, H-9b, H-9b′), 7.53 (2H, d, $J_{6,7}$ 8.1, H-6, H-6′), 8.32 (2H, d, $J_{7,6}$ 8.1, H-7, H-7′); δ_C (125 MHz, $CDCl_3$) 24.40, 27.39, 27.49, 28.92, 34.93, 35.32, 35.41, 35.62, 35.96, 37.62, 38.56, 73.91, 76.54, 111.74, 121.09, 134.70, 137.13, 153.98, 155.15; MS *m*/*z* (ES) 593 (M^+ + H, 100%).

(7*S*,8*R*,7′*S*,8′*R*)-5,6,7,8,5′,6′,7′,8′-Octahydro-[2,2′]biquinolinyl-7,8,7′,8′-tetrol 8

A solution of acetonide **2F** (0.5 g, 1.22 mmol) in MeOH (6 ml) was treated with HCl solution (1.5 M, 2 ml) and the reaction mixture heated at 50 °C. When the starting material had reacted completely (3–4 h), the mixture was made alkaline by the addition of NH_4OH solution. The solvents were removed under reduced pressure and the crude product kept *in vacuo* at 50–60 °C until all the NH_4Cl salt sublimed off. Tetraol **8** was obtained as a white crystalline solid (0.3 g, 80%); mp 170–172 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +67 (*c* 0.5, MeOH); HRMS (ES) (Found: M^++H, 329.1417. $C_{18}H_{21}N_2O_4$

requires 329.1423); δ_H (500 MHz, CD_3OD) 1.98 (2H, m, H-6, H-6′), 2.28 (2H, m, H-6″, H-6‴), 2.78 (2H, ddd, $J_{5,6}$ 2.5, $J_{5,6''}$ 6.4, $J_{5,5''}$ 17.0, H-5, H-5′), 3.12 (2H, ddd, $J_{5'',6}$ 6.4, $J_{5'',6''}$ 10.9, $J_{5'',5}$ 17.0, H-5″, H-5‴), 4.42 (2H, m, H-7, H-7′), 4.68 (2H, d, $J_{8,7}$ 3.0, H-8, H-8′), 7.58 (2H, d, $J_{4,3}$ 8.0, H-4, H-4′), 8.23 (2H, d, $J_{3,4}$ 8.0, H-3, H-3′); δ_C (125 MHz, $CDCl_3$) 23.73, 25.66, 66.93, 71.02, 120.131, 131.81, 137.79, 153.29, 154.69; MS *m*/*z* (ES) 329 (M^++H, 100%), M^+ 328 (12).

(7*S*,8*R*,7′*S*,8′*R*)-7,7′-Di(1-(*tert*-butyl)-1,1-diphenylsilyloxy)-5,6,7,8,5′,6′,7′,8′-octahydro[2,2′]biquinolinyl-8,8′-diol 9

To a stirred solution of tetrol **8** (0.3 g, 0.9 mmol) and imidazole (0.34 g, 5 mmol), in dry DMF (5 ml) maintained at 0 °C under nitrogen, was added, dropwise over 20 min, *tert*-butyldiphenylsilyl chloride (0.3 ml, 1.09 mmol). The reaction mixture was stirred for 4 h at room temperature, diluted with dichloromethane (75 ml) and the solution washed with water. The organic layer was dried (Na_2SO_4), the solvent evaporated, and the crude product purified by PLC (20% EtOAc in hexane). The disilyl derivative **9** was obtained as a white solid (0.33 g, 45%); mp 74 °C (from EtOAc–hexane); $[\alpha]_D$ −38 (*c* 0.72, $CHCl_3$); HRMS (ES) (Found: M^++H, 807.3960. $C_{50}H_{57}N_2O_4Si_2$ requires 807.4014); δ_H (500 MHz, $CDCl_3$, D_2O exchange) 1.01 [18H, s, 2 × C(Me)$_3$], 1.75 (2H, m, H-6, H-6′), 1.99 (2H, m, H-6″, H-6‴), 2.68 (2H, ddd, $J_{5,6}$ 6.1, $J_{5,6''}$ 6.1, $J_{5,5''}$ 17.2, H-5, H-5′), 3.02 (2H, ddd, $J_{5'',6}$ 7.2, $J_{5'',6''}$ 7.2, $J_{5'',5}$ 17.2, H-5″, H-5‴), 4.40 (2H, m, H-7, H-7′), 4.68 (2H, d, $J_{8,7}$ 3.0, H-8, H-8′), 7.18-7.34 (12H, m, Ar*H*), 7.46 (2H, d, *J* 8.0, Ar*H*); 7.62 (4H, m, Ar*H*), 7.71 (4H, m, Ar*H*), 8.25 (2H, d, *J* 8.0, Ar*H*); δ_C (125 MHz, $CDCl_3$) 19.41, 24.74, 26.20, 26.57, 26.98, 70.57, 72.13, 119.92, 127.45, 127.61, 127.76, 129.53, 129.60, 129.68, 131.52, 133.90, 134.31, 134.80, 135.93, 137.02, 153.19, 154.62; MS *m*/*z* (ES) 807 (M^++H, 30%), 806 (M^+, 68%).

General procedure for the synthesis of *N*-oxides

m-Chloroperoxybenzoic acid (MCPBA, 50–55%, 1.1 equiv.) was added, in small portions, to a stirred solution of bipyridine (1 mmol) in dichloromethane (20 ml) at 0 °C, and the stirring continued at 0 °C for a further 4 h. The reaction mixture was washed, successively, with a saturated Na_2SO_3 solution, Na_2CO_3 solution and finally with water. The organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by column chromatography (10% MeOH in $CHCl_3$) to give the corresponding *N*-oxide as a white crystalline solid. This purification method was followed for all the *N*-oxides.

(3a*S*,9b*R*,3a′*S*,9b′*R*)-2,2,2′,2′-Tetramethyl-3a,4,5,9b,3a′,4′,5′,9b′-octahydro-[8,8′]bi[[1,3]-dioxolo[4,5*h*]quinolinyl] *N*-oxide 2I

Bipyridine **2F** (0.5 g, 1.22 mmol) gave *N*-oxide **2I** (0.3 g, 60%); mp 201–202 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +215 (*c* 1.0, $CHCl_3$); HRMS (EI) (Found: M^+, 424.2011. $C_{24}H_{28}N_2O_5$ requires 424.1998); δ_H (300 MHz, $CDCl_3$) 1.37 (3H, s, Me), 1.39 (3H, s, Me), 1.49 (3H, s, Me), 1.52 (3H, s, Me), 1.75 (2H, m, H-4, H-4′), 2.23 (2H, m, H-4″, H-4‴), 2.61 (2H, m, H-5, H-5′), 3.04 (2H, m, H-5″, H-5‴), 4.74 (2H, m, H-3a, H-3a′), 5.23 (1H, d, $J_{9'b,3a}$ 7.0, H-9b′), 5.75 (1H, d, $J_{9b,3a}$ 7.0, H-9b), 7.10 (1H, d, *J* 8.1, Ar), 7.55 (1H, d, *J* 8.1, Ar), 8.21 (1H, d, *J* 8.4, Ar), 8.91 (1H, d, *J* 8.1, Ar); δ_C (125 MHz, $CDCl_3$) 23.42, 23.73, 24.73, 25.23, 26.81, 26.84, 27.14, 28.14, 69.87, 72.77, 73.78, 76.31, 108,37, 108.85, 125.27 (2C), 126.75, 134.87, 136.09, 137.16, 145.65, 145.70, 148.38, 153.24; MS *m*/*z* (EI) 424 (M^+, 45%), 408 (34).

(3a*S*,9b*R*,3a′*S*,9b′*R*)-2,2,7,2′,2′,7′-Hexamethyl-3a,4,5,9b,3a′,4′,5′,9b′-octahydro-[8,8′]bi[[1,3]-dioxolo[4,5*h*]quinolinyl]*N*-oxide 3I$_P$

The oxidation of bipyridine **3F** (0.3 g, 0.7 mmol) with MCPBA yielded *N*-oxide **3I** as a mixture of atropisomers **3I**$_P$: **3I**$_M$ (3 : 1). These were separated by multi-elution PLC (EtOAc) to afford the major *N*-oxide (+)-**3I**$_P$ (0.09 g, 30%); mp 266–268 °C (from EtOAc–MeOH); $[\alpha]_D$ +104 (*c* 0.66, $CHCl_3$); HRMS (EI) (Found: M^+, 452.2313. $C_{26}H_{32}N_2O_5$ requires 452.2311); δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, Me), 1.36 (3H, s, Me), 1.42 (3H, s, Me), 1.46 (3H, s, Me), 1.82 (2H, m, H-4, H-4′), 2.05 (3H, s, Ar*Me*), 2.21 (5H, m, Ar*Me*, H-4″, H-4‴), 2.58 (2H, m, H-5, H-5′), 3.00 (2H, m, H-5″, H-5‴), 4.66 (2H, m, H-3a, H-3a′), 5.19 (1H, d, $J_{9'b,3a}$ 6.5, H-9b′), 5.63 (1H, d, $J_{9b,3a}$ 6.9, H-9b), 6.98 (1H, s, H-6′), 7.39 (1H, s, H-6); δ_C (125 MHz, $CDCl_3$) 17.89, 19.06, 23.60, 24.02, 25.36, 25.47, 27.34, 27.40, 27.63, 28.07, 108.60, 109.13, 127.47, 133.53, 134.59, 135.31, 136.91, 138.51, 143.14, 147.06, 150.08, 152.40; MS *m*/*z* (EI) 452 (M^+, 18%), 436 (100), 424 (13). Minor atropisomer **3I**$_M$. δ_H (300 MHz, $CDCl_3$) 1.25 (3H, s, Me), 1.29 (3H, s, Me), 1.33 (3H, s, Me), 1.38 (3H, s, Me), 1.75 (2H, m, H-4, H-4′), 1.82 (3H, s, Ar*Me*), 1.95 (3H, m, Ar*Me*), 2.05(2H, m, H-4″, H-4‴), 2.48 (2H, m, H-5, H-5′), 2.91 (2H, m, H-5″, H-5‴), 4.60 (2H, m, H-3a, H-3a′), 5.07 (1H, d, $J_{9'b,3a}$ 6.6, H-9b′), 5.573 (1H, d, $J_{9b,3a}$ 6.6, H-9b), 6.86 (1H, s, H-6′), 7.30 (1H, s, H-6).

(3a*S*,9b*R*,3a′*S*,9b′*R*)-2,2,2′,2′-Tetraethyl-3a,4,5,9b,3a′,4′,5′,9b′-octahydro-[8,8′]bi[[1,3]-dioxolo[4,5*h*]quinolinyl] *N*-oxide 4I

Bipyridine **4F** (1 g, 2.15 mmol) gave *N*-oxide **4I** (0.74 g, 72%); mp 139 °C (from EtOAc–MeOH); $[\alpha]_D$ +276 (*c* 1.08, $CHCl_3$); (Found: C, 69.8; H, 7.5; N, 5.7. $C_{28}H_{36}N_2O_5$ requires C, 70.0; H, 7.55; N, 5.8%); δ_H (500 MHz, $CDCl_3$) 0.73 (6H, m, 2 × CH_2Me), 1.02 (6H, m, 2 × CH_2Me) 1.62 (4H, m, 2 × CH_2Me), 1.58-1.83 (6H, m, 2 × CH_2Me, H-4, H-4′), 2.34 (2H, m, H-4″, H-4‴), 2.59 (2H, m, H-5, H-5′), 3.13 (2H, m, H-5″, H-5‴), 4.73 (2H, m, H-3a, H-3a′), 5.23 (1H, d, $J_{9'b,3a}$ 6.8, H-9b′), 5.75 (1H, d, $J_{9b,3a}$ 6.8, H-9b), 7.13 (1H, d, *J* 8.2, Ar*H*), 7.54 (1H, d, *J* 8.2, Ar*H*), 8.19 (1H, d, *J* 8.2, Ar*H*), 8.86 (1H, d, *J* 8.2, Ar*H*); δ_C (125 MHz, $CDCl_3$) 7.74, 7.94, 9.18, 23.45, 23.74, 27.15, 27.94, 29.25, 29.53, 29.91, 30.04, 50.90, 70.45, 72.94, 73.86, 76.61, 112.82, 113.01, 125.16, 125.81, 127.25, 134.86, 136.44, 137.49, 146.02, 146.54, 148.77, 154.15; MS *m*/*z* (EI) 480 (M^+, 5%), 435 (20), 379 (24), 293 (35), 277 (100), 199 (25), 85 (53), 71 (62).

(3a*S*,9b*R*,3a′*S*,9b′*R*)-8,8′-bis{Spiro[[1,3]dioxolo[4,5*h*]quinoline-2,1′-cyclohexane]} *N*-oxide 5I

Bipyridine **5F** (1 g, 2 mmol) yielded *N*-oxide **5I** (0.67 g, 65%); mp 246 °C (from $CHCl_3$–MeOH); $[\alpha]_D$ +226 (*c* 1.09, $CHCl_3$); (Found: C, 71.1; H, 7.0; N, 5.5. $C_{30}H_{36}N_2O_5$ requires C, 71.4; H, 7.2; N, 5.6%); δ_H (300 MHz, $CDCl_3$) 1.54-1.75 (22H, m, 2 × $(CH_2)_5$, H-4, H-4′), 2.25 (2H, m, H-4″, H-4″), 2.59 (2H, m, H-5, H-5′), 3.04 (2H, m, H-5″, H-5‴), 4.73 (2H, m, H-3a, H-3a′), 5.22 (1H, d, $J_{9'b,3a}$ 6.6, H-9b′), 5.75 (1H, d, $J_{9b,3a}$ 6.6, H-9b), 7.16 (1H, d, *J* 8.4, Ar*H*), 7.54 (1H, d, *J* 7.8, Ar*H*), 8.16 (1H, d, *J* 8.1, Ar*H*), 8.85

(1H, d, *J* 8.1, Ar*H*); δ_C (125 MHz; $CDCl_3$) 22.96, 24.30, 24.67, 25.01, 25.34, 25.72, 27.25, 28.64, 34.66, 35.23, 36.79, 37.49, 69.77, 72.72, 73.59, 75.85, 109.87, 110.32, 125.49, 125.87, 126.88, 135.39, 136.43, 137.64, 146.15, 146.45, 148.92, 154.13; MS *m*/*z* (EI) 504 (M^+, 2%), 256 (38), 375 (28), 293 (23), 488 (10).

(2*S*,3a*S*,9b*R*,2′*S*,3a′*S*,9b′*R*)-2,2′-di-*tert*-Butyl-3a,4,5,9b,3a′,4′,5′,9b′-octahydro-2,2′-dimethyl-[8,8′]bi[[1,3]-dioxolo[4,5*h*]quinolinyl]*N*-oxide 6I

Bipyridine **6F** (1 g, 1.96 mmol) formed *N*-oxide **6I** (0.7 g, 68%); mp 236 °C (from EtOAc–hexane); $[\alpha]_D$ +262 (*c* 1.16, $CHCl_3$); HRMS (ES) (Found: M^++H, 509.3022. $C_{30}H_{41}N_2O_5$ requires 509.3015); δ_H (300 MHz, $CDCl_3$) 0.87 [9H, s, C(Me)$_3$], 0.88 [9H, s, C(Me)$_3$], 1.43 (3H, s, Me), 1.46 (3H, s, Me), 1.78 (2H, m, H-4, H-4′), 2.34 (2H, m, H-4″, H-4‴), 2.56 (2H, m, H-5, H-5′), 3.09 (2H, m, H-5″, H-5‴), 4.78 (2H, m, H-3a, H-3a′), 5.24 (1H, d, $J_{9'b,3a}$ 7.1, H-9b′), 5.75 (1H, d, $J_{9b,3a}$ 6.9, H-9b), 7.06 (1H, d, *J* 8.4, Ar*H*), 7.51 (1H, d, *J* 8.1, Ar*H*), 8.21 (1H, d, *J* 8.2, Ar*H*), 8.90 (1H, d, *J* 8.1, Ar*H*); δ_C (125 MHz, $CDCl_3$) 17.83, 18.14, 23.46, 23.63, 25.26, 25.31, 26.69, 27.65, 38.14, 38.19, 69.65, 72.07, 73.02, 75.85, 113.25, 113.51, 124.56, 125.00, 126.73, 134.36, 136.10, 136.98, 145.60, 145.81, 148.58, 153.61; MS *m*/*z* (ES) 509 (M^+ + H, 75%).

(3a*S*,9b*R*,3a′*S*,9b′*R*)-8,8′-bis{Spiro[[1,3]dioxolo[4,5*h*]quinoline-2,2′adamantane]} *N*-oxide 7I

Bipyridine **7F** (0.5 g, 0.8 mmol) yielded *N*-oxide **7I** (0.28 g, 54%); mp 295 °C (decomp.; from $CHCl_3$–EtOAc); $[\alpha]_D$ +237 (*c* 0.74, $CHCl_3$); HRMS (ES) (Found: M^++ H, 609.3356. $C_{38}H_{45}N_2O_5$ requires 609.3328); δ_H (300 MHz, $CDCl_3$) 1.51-2.04 (30H, m, 2 × adamantyl protons, H-4, H-4′), 2.23 (2H, m, H-4″, H-4‴), 2.58 (2H, m, H-5, H-5′), 3.04 (2H, m, H-5″, H-5‴), 4.69 (2H, m, H-3a, H-3a′), 5.20 (1H, d, $J_{9'b,3a}$ 6.5, H-9b′), 5.75 (1H, d, $J_{9b,3a}$ 6.5, H-9b), 7.08 (1H, d, *J* 8.2, Ar*H*), 7.53 (1H, d, *J* 8.1, Ar*H*), 8.07 (1H, d, *J* 8.2, Ar*H*), 8.71 (1H, d, *J* 8.1, Ar*H*); δ_C (125 MHz, $CDCl_3$) 24.14, 24.28, 26.88, 27.28, 27.39, 27.45, 27.75, 28.58, 34.90, 35.36, 35,55, 35.81, 36.02, 36.31, 37.21, 37.54, 38.59, 38.99, 69.67, 72.91, 73.73, 76.36, 111.85, 112.02, 125.10, 125.34, 127.01, 135.28, 136.33, 138.03, 146.18, 146.37, 148.94, 154.35; MS *m*/*z* (ES) 609 (M^+ + H, 100%), 593 (10).

General procedure for the synthesis of *N*,*N*′-dioxides

m-Chloroperoxybenzoic acid (50–55%, 2.5 equiv.) was added, in small portions, to a stirred solution of bipyridine (1 mmol) in dichloromethane (20 ml) at 0 °C, and the stirring continued at room temperature overnight. The reaction mixture was washed, successively, with saturated Na_2SO_3 solution (10 ml), Na_2CO_3 solution (2 × 5 ml) and water. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and the residue obtained purified by column chromatography (10% MeOH in $CHCl_3$) to furnish the corresponding *N*,*N*′-dioxide as a white crystalline solid.

(3a*S*,9b*R*,3a′*S*,9b′*R*)-2,2,2′,2′-Tetramethyl-3a,4,5,9b,3a′,4′,5′,9b′-octahydro-[8,8′] bi[[1,3]-dioxolo[4,5*h*]quinolinyl] *N*,*N*′-dioxide 2J

Bipyridine **2F** (0.5 g, 1.13 mmol) gave *N*,*N*′-dioxide **2J** (0.38 g, 72%); mp 249 °C (from $CHCl_3$); $[\alpha]_D$ +256 (*c* 0.9, $CHCl_3$); (Found: C, 64.9; H, 6.6; N, 6.5. $C_{24}H_{28}N_2O_6$ requires C, 65.4; H, 6.4; N, 6.4%); δ_H (300 MHz, $CDCl_3$) 1.40 (6H, s, 2 × Me), 1.48 (6H, s, 2 × Me), 1.79 (2H, m, H-4, H-4′), 2.21 (2H, m, H-4″, H-4‴), 2.60 (2H, m, H-5, H-5′), 3.02 (2H, m, H-5″, H-5‴), 4.69 (2H, m, H-3a, H-3a′), 5.72 (2H, d, $J_{9b,3a}$ 6.8, H-9b, H-9b′), 7.09 (2H, d, $J_{6,7}$ 8.1 H-6, H-6′), 7.66 (2H, d, $J_{7,6}$ 8.1, H-7, H-7′); δ_C (125 MHz, $CDCl_3$) 23.55, 24.80, 26.92, 27.07, 69.17, 72.64, 108.73, 124.13, 127.48, 138.73, 140.33, 145.46; *m*/*z* (LSIMS) 441 (M^+ + H, 100%), 440 (M^+, 14%).

(3a*S*,9b*R*,3a′*S*,9b′*R*)-2,2,7,2′,2′,7′-Hexamethyl-3a,4,5,9b,3a′,4′,5′,9b′-octahydro-[8,8′]bi[[1,3]-dioxolo[4,5*h*]quinolinyl] *N*,*N*′-dioxide 3J$_P$

Bipyridine **3F** (0.2 g, 0.45 mmol) yielded *N*,*N*′-dioxide **3J** as a mixture (8 : 1) of atropisomers (**3J**$_P$: **3J**$_M$). These were separated by multi-elution PLC (EtOAc) to afford the major dioxide (+)-**3J**$_P$ (0.096 g, 45%); mp 289 °C (from EtOAc–MeOH); $[\alpha]_D$ +119 (*c* 0.63, $CHCl_3$); HRMS (EI) (Found: M^+ – 2 × O, 436.2343. $C_{26}H_{32}N_2O_6$ requires 436.2363); δ_H (300 MHz, $CDCl_3$) 1.34 (6H, s, 2 × Me), 1.45 (6H, s, 2 × Me), 1.80 (2H, m, H-4, H-4′), 2.10 (6H, m, 2 × Ar*Me*), 2.19 (2H, m, H-4″, H-4‴), 2.58 (2H, ddd, $J_{5,4''}$ 3.8, $J_{5,4}$ 3.8, $J_{5,5''}$ 15.4, H-5, H-5′), 3.00 (2H, ddd, $J_{5'',4}$ 3.9, $J_{5'',4''}$ 12.5, $J_{5'',5}$ 15.4, H-5″, H-5‴), 4.66 (2H, m, H-3a, H-3a′), 5.68 (2H, d, $J_{9b,3a}$ 6.6, H-9b, H-9b′), 6.97 (2H, s, H-6, H-6′); δ_C (125 MHz, $CDCl_3$) 18.19, 23.71, 25.44, 27.22, 27.41, 69.86, 73.12, 109.05, 126.80, 136.46, 137.73, 141.28, 143.27; MS *m*/*z* (EI) 436 ($M^+ - 2\times$ O, 3%), 451 (5), 368 (3), 284 (10), 256 (20), 213 (15), 129 (35), 97 (70), 83 (78), 71 (100). The atropisomer **3J**$_M$ was only identified as a minor component of the mixture, ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.38 (6H, s, 2 × Me), 1.44 (6H, s, 2 × Me), 1.74 (2H, m, H-4, H-4′), 2.04 (6H, m, 2 × Ar*Me*), 2.23 (2H, m, H-4″, H-4‴), 2.57 (2H, ddd, $J_{5,4''}$ 3.8, $J_{5,4}$ 3.8, $J_{5,5''}$ 15.4, H-5, H-5′), 3.04 (2H, ddd, $J_{5'',4}$ 3.9, $J_{5'',4''}$ 12.5, $J_{5'',5}$ 15.4, H-5″, H-5‴), 4.59 (2H, m, H-3a, H-3a′), 5.64 (2H, d, $J_{9b,3a}$ 6.6, H-9b, H-9b′), 6.94 (2H, s, H-6, H-6′).

(3a*S*,9b*R*,3a′*S*,9b′*R*)-2,2,2′,2′-Tetraethyl-3a,4,5,9b,3a′,4′,5′,9b′-octahydro-[8,8′] bi[[1,3]-dioxolo[4,5*h*]quinolinyl] *N*,*N*′-dioxide 4J

Bipyridine **4F** (0.5 g, 1 mmol) afforded *N*,*N*′-dioxide **4J** (0.42 g, 80%); mp 267–268 °C (from MeOH); $[\alpha]_D$ +347 (*c* 1.19, $CHCl_3$); (Found: C, 67.6; H, 7.1; N, 5.5. $C_{28}H_{36}N_2O_6$ requires C, 67.7; H, 7.3; N, 5.6%); δ_H (300 MHz, $CDCl_3$) 0.75 (6H, t, *J* 7.5, 2 × CH_2Me), 0.95 (6H, t, *J* 7.5, 2 × CH_2Me), 1.57-1.78 (10H, m, 4 × CH_2Me, H-4, H-4′), 2.30 (2H, m, H-4″, H-4‴), 2.59 (2H, ddd, $J_{5,4''}$ 3.7, $J_{5,4}$ 3.7, $J_{5,5''}$ 15.1, H-5, H-5′), 3.05 (2H, ddd, $J_{5'',4}$ 3.9, $J_{5'',4''}$ 11.4, $J_{5'',5}$ 15.1, H-5″, H-5‴), 4.67 (2H, m, H-3a, H-3a′), 5.72 (2H, d, $J_{9b,3a}$ 6.9, H-9b, H-9b′), 7.07 (2H, d, $J_{6,7}$ 8.1 H-6, H-6′), 7.61 (2H, d, $J_{7,6}$ 8.1, H-7, H-7′); δ_C (125 MHz, $CDCl_3$) 7.36, 8.36, 9.55, 23.69, 27.68, 29.67, 69.69, 73.28, 112.71, 124.46, 127.64, 139.19, 141.38, 146.16; MS *m*/*z* (EI) 496 (M^+, 6%), 435 (52), 379 (57), 293 (61), 256 (60), 213 (28), 185 (38), 171 (26), 129 (65), 83 (100); IR ν_{max} 1053.0, 1079.8, 1173.5, 1267.0,1280.5, 1343.8, 1456.8.

(3a*S*,9b*R*,3a′*S*,9b′*R*)-8,8′-bis{Spiro[[1,3]dioxolo[4,5*h*]quinoline-2,1′-cyclohexane]} *N*,*N*′-dioxide 5J

Bipyridine **5F** (0.6 g, 1.15 mmol) yielded *N*,*N*′-dioxide **5J** (0.48 g, 76%); mp 326 °C with decomposition (from $CHCl_3$–MeOH); $[\alpha]_D$ +340 (*c* 0.75, $CHCl_3$); (Found: C, 69.2; H, 6.8; N, 5.2. $C_{30}H_{36}N_2O_6$

requires C, 69.2; H, 7.0; N, 5.4%); δ_H (300 MHz, $CDCl_3$) 1.27-1.59 (22H, m, 2 × $(CH_2)_5$, H-4, H-4′), 2.23 (2H, m, H-4″, H-4‴), 2.59 (2H, ddd, $J_{5,4''}$ 4.0, $J_{5,4}$ 4.0, $J_{5,5''}$ 15.6, H-5, H-5′), 3.05 (2H, ddd, $J_{5'',4}$ 3.6, $J_{5'',4''}$ 12.0, $J_{5'',5}$ 15.6, H-5″, H-5‴), 4.74 (2H, m, H-3a, H-3a′), 5.75 (2H, d, $J_{9b,3a}$ 6.6, H-9b, H-9b′), 7.07 (2H, d, $J_{6,7}$ 8.1, H-6, H-6′), 7.59 (2H, d, $J_{7,6}$ 8.1, H-7, H-7′); δ_C (125 MHz, $CDCl_3$) 24.47, 24.92, 25.51, 27.59, 34.36, 37.14, 69.08, 72.90, 109.70, 124.45, 127.92, 139.55, 141.29, 145.97; MS *m*/*z* (EI) 520 (M^+, 3%), 368 (20), 353 (5), 256 (25), 185 (22), 129 (35), 111 (48), 97 (86), 83 (100).

(2*S*,3a*S*,9b*R*,2′*S*,3a′*S*,9b′*R*)-2,2′-di-*tert*-Butyl-3a,4,5,9b,3a′,4′,5′,9b′-octahydro-2,2′-dimethyl-[8,8′]bi[[1,3]-dioxolo[4,5*h*]quinolinyl] *N*,*N*′-dioxide 6J

Bipyridine **6F** (0.4 g, 0.79 mmol) gave *N*,*N*′-dioxide **6J** (0.29 g, 70%); mp 267 °C (from EtOAc–hexane); $[\alpha]_D$ +254 (*c* 0.47, $CHCl_3$); HRMS (ES) (Found: M^++H, 525.2943. $C_{30}H_{41}N_2O_6$ requires 525.2965); δ_H (500 MHz, $CDCl_3$) 0.90 [18H, s, 2 × $C(Me)_3$], 1.41 (6H, s, 2 × Me), 1.76 (2H, m, H-4, H-4′), 2.32 (2H, m, H-4″, H-4‴), 2.55 (2H, ddd, $J_{5,4''}$ 3.7, $J_{5,4}$ 3.7, $J_{5,5''}$ 15.5, H-5, H-5′), 3.08 (2H, ddd, $J_{5'',4}$ 3.9, $J_{5'',4''}$ 12.6, $J_{5'',5}$ 15.5, H-5″, H-5‴), 4.72 (2H, m, H-3a, H-3a′), 5.76 (2H, d, $J_{9b,3a}$ 7.0, H-9b, H-9b′), 7.04 (2H, d, $J_{6,7}$ 8.1, H-6, H-6′), 7.73 (2H, d, $J_{7,6}$ 8.1, H-7, H-7′); δ_C (125 MHz, $CDCl_3$) 17.97, 23.61, 25.31, 27.04, 38.16, 68.97, 71.99, 113.32, 123.82, 127.25, 138.55, 140.29, 145.67; MS *m*/*z* (ES) 525 (M^++H, 58%), 510 (6).

(3a*S*,9b*R*,3a′*S*,9b′*R*)-8,8′-bis{Spiro[[1,3]dioxolo[4,5*h*]quinoline-2,2′-adamantane]} *N*,*N*′-dioxide 7J

Bipyridine **7F** (0.5 g, 0.8 mmol) gave *N*,*N*′-dioxide **7J** (0.35 g, 66%); mp 308 °C (decomp.; from EtOAc–MeOH); $[\alpha]_D$ +435 (*c* 1.01, $CHCl_3$); HRMS (ES) (Found: M^+ + H, 625.3269. $C_{38}H_{45}N_2O_6$ requires 625.3278); δ_H (300 MHz, $CDCl_3$) 1.46-1.74 (28H, m, 2 × adamantyl protons), 1.96 (2H, m, H-4, H-4′), 2.17 (2H, m, H-4″, H-4‴), 2.58 (2H, ddd, $J_{5,4''}$ 3.9, $J_{5,4}$ 3.9, $J_{5,5''}$ 15.6, H-5, H-5′), 2.98 (2H, ddd, $J_{5'',4}$ 3.6, $J_{5'',4''}$ 11.7, $J_{5'',5}$ 15.6, H-5″, H-5‴), 4.63 (2H, m, H-3a, H-3a′), 5.81 (2H, d, $J_{9b,3a}$ 6.6, H-9b, H-9b′), 7.08 (2H, d, $J_{6,7}$ 8.0, H-6, H-6′), 7.46 (2H, d, $J_{7,6}$ 8.0, H-7, H-7′); δ_C (125 MHz, $CDCl_3$) 24.36, 27.34, 27.48, 28.35, 34.69, 35.07, 35.32, 35.67, 37.53, 38.63, 68.53, 72.72, 111.87, 124.30, 127.17, 139.74, 140.19, 141.66, 146.02; MS *m*/*z* (ES) 625 (M^++H, 100%), 609 (5), 483 (30), 224 (30), 211 (84), 196 (92), 181 (30).

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