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Synthesis of planar-chiral bridged bipyridines and terpyridines by metal-mediated coupling reactions of pyridinophanes

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Dedicated to Professor Philip E. Eaton on the occasion of his 72nd birthday

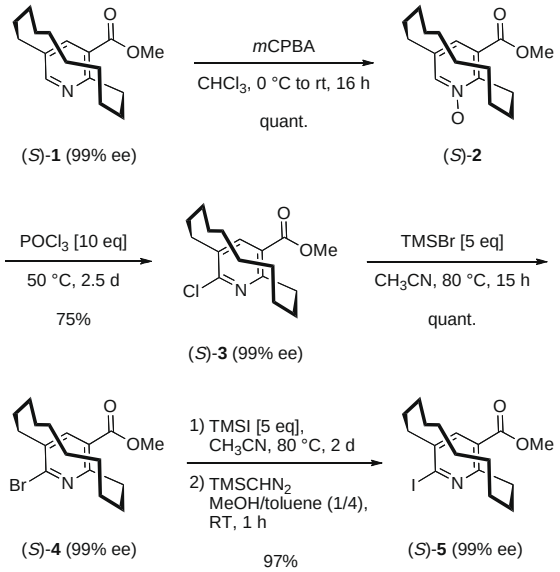
ABSTRACT

We have accomplished efficient synthesis of planar-chiral bridged 2,2′-bipyridine (*S*)-**6**, C_2-symmetric bipyridinophane (*S*,*S*)-**7**, bridged 2,2′:6′,2″-terpyridines (*S*)-**11**, and C_2-symmetric terpyridine (*S*,*S*)-**12** by metal-mediated biaryl cross-coupling or homo-coupling reactions of the corresponding 6-halo[10](2,5)pyridinophanes. Stille-type and Negishi cross-coupling reactions are particularly useful for the syntheses of **6**, **11**, and **12**. On the other hand, nickel-mediated homo-coupling reaction worked best for achieving the synthesis of structurally unique bipyridinophane **7.**

Many different types of chiral ligands have been developed for catalytic asymmetric reactions and, of these, optically active 2,2′-bipyridines and 2,2′:6′,2″-terpyridines have received considerable attention.[1–5] Most of these bipyridines are based on central- or axial-chirality and only limited examples are known of planar-chiral bipyridines. Although Vögtle and co-workers synthesized 13-pyridyl[2](1,4)benzeno[2](2,5)pyridinophane and 2-pyridyl[2]-(1,4)benzeno[2](5,8)quinolinophane, planar-chiral bipyridine and pyridylquinoline incorporating [2,2]parapyridinophane and quinolinophane skeletons,[6,7] yields of those racemic molecules are not satisfactory (23% and 36%, respectively) in the final pyridine-forming steps. Recently, Fu et al. reported the reductive coupling of ferrocene-type pyridine derivative for synthesizing racemic planar-chiral bipyridine with C_2-symmetry and also demonstrated effectiveness of the ligand in Cu(I)-catalyzed asymmetric cyclopropanation.[8] However, both Vögtle's and Fu's methods require resolution of their racemic bipyridines by chiral HPLC and efficiency of the resolution has not been described in literature.

We have previously reported new synthetic routes to bridged nicotinates and benzoates, [*n*]parapyridinophane (*n* = 8–14)[9] and [*n*]paracyclophane (*n* = 8–12)[10] derivatives, and we have also verified that crystallization-induced asymmetric transformation is practically useful for supplying an enantiomerically pure form of planar-chiral nicotinate (*S*)-**1**.[11,12] We have also demonstrated that the bridged ester is a promising planar-chiral building block and that bridged NADH analogs derived from (*S*)-**1** effected highly enantioselective reduction in biomimetic systems.[9a] In recent years, there have been developed palladium-catalyzed biaryl cross-coupling reactions and organic chlorides and more reactive bromides/iodides are now important synthetic intermediates for target biaryls.[13] Here we describe efficient synthesis of planar-chiral bridged 2,2′-bipyridines and unknown bridged 2,2′:6′,2″-terpyridines of cyclophane type by metal-mediated cross- and homo-coupling reactions of halogen-substituted bridged nicotinates having a parapyridinophane skeleton with several metal pyridine reagents.

Bridged halonicotinates (*S*)-**3**–**5** were obtained from (*S*)-**1** via N-oxide (*S*)-**2** (Scheme 1). The reaction with excess $POCl_3$ effected highly regioselective chlorination of (*S*)-**2** to give 6-chloropyridine,



Scheme 1. Synthesis of 6-halo[10](2,5)pyridinophanes, (*S*)-**3**–**5**.

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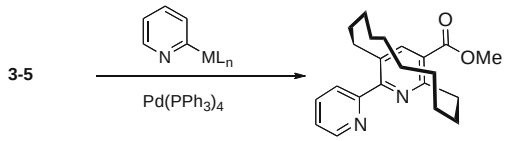
Table 1
Biaryl-coupling reactions for synthesis of (*S*)-**6**



6

Entry	**3–5**	ML$_n$	Pd(PPh$_3$)$_4$	Conditions			Yield/%
				Solvent	T	Time	
1	(±)-**3**	Sn(*n*-Bu)$_3$	10 mol %	Pyridine	Reflux	2 d	20
2	(*S*)-**4**	Sn(*n*-Bu)$_3$	14 mol %	Pyridine	Reflux	2 d	29 (28% ee)
3	(±)-**5**	Sn(*n*-Bu)$_3$	10 mol %	Pyridine	Reflux	2 d	40
4[a]	(*S*)-**5**	Sn(*n*-Bu)$_3$	10 mol %	DMF[b]	50 °C	6 h	60 (99% ee)
5	(±)-**3**	ZnBr	10 mol %	THF	50 °C	4 d	Trace
6	(±)-**4**	ZnBr	10 mol %	THF	50 °C	2 d	65
7	(±)-**5**	ZnBr	10 mol %	THF	rt	2 d	68
8	(±)-**5**	ZnBr	2 mol %	THF	rt	2 d	66
9	(*S*)-**5**	ZnBr	2 mol %	THF	50 °C	2 d	68 (99% ee)

[a] In the presence of CuI (0.2 equiv) and CsF (2 equiv).
[b] 0.3 M solution.

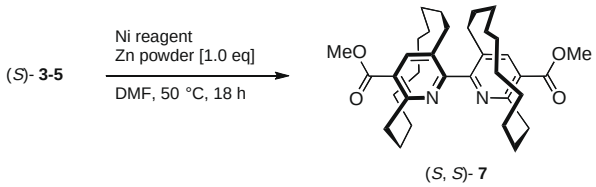
(*S*)-**3**, in 75% yield.[14] Further transhalogenation with TMSBr and TMSI resulted in the desired bromide (*S*)-**4** and iodide (*S*)-**5**[15] in excellent yields. The halogen/halogen displacement from (*S*)-**3** to (*S*)-**5** exhibited outstanding efficiency as compared to the similar conversion from 2-chloropyridine to 2-iodopyridine (49–72% yields)[16] according to an electron-withdrawing group at C-3 accelerating the substitutions at C-6. It is important to note here that these transhalogenations took place without losing their planar chirality.

Table 1 summarizes biaryl-coupling reactions for synthesis of (*S*)-**6**. We have initially examined Stille cross-coupling of **3-5** with 2-(tri-*n*-butylstannyl)pyridine. Though these reactions afforded bridged 2,2′-bipyridine **6** in poor to moderate yields (20–40%) (entries 1–3), enantiomeric excess of the optically active bipyridine dropped down remarkably from 99% ee to 28% ee during the course of reaction at high temperature in refluxing pyridine (entry 2). On the other hand, Baldwin's method[17] allows us to carry out the similar reactions at lower temperatures: Pd(0)- and CuI-catalyzed cross-coupling of the iodide (*S*)-**5** proceeded much efficiently in the presence of CsF at 50 °C to give the desired bipyridine (*S*)-**6**[18] in 60% yield with 99% ee (entry 4). Similarly, Negishi coupling with 2-pyridylzinc bromide worked even better to provide the compound **6** in up to 68% yield (entries 6–9). The milder conditions are compatible with the transformation of such planar-chiral molecules.

More exciting results were obtained by Ni(0)-mediated homo-coupling reactions[19] of (*S*)-**3–5**, giving C_2-symmetric bridged bipyridine (*S,S*)-**7**[20] (Table 2). Despite the fact that chloride (*S*)-**3** achieved moderate yield (entry 1), both bromide (*S*)-**4** and iodide (*S*)-**5** were good precursors and the maximum yield reached 78% (entry 2). Readily accessible $NiCl_2/PPh_3$ works well rather than air sensitive Ni(PPh$_3$)$_4$. The compound (*S,S*)-**7** was identified by ^{1}H NMR, ^{13}C NMR, and mass spectral data, all of which agree with the proposed structure of the bipyridinophane with C_2-symmetry.

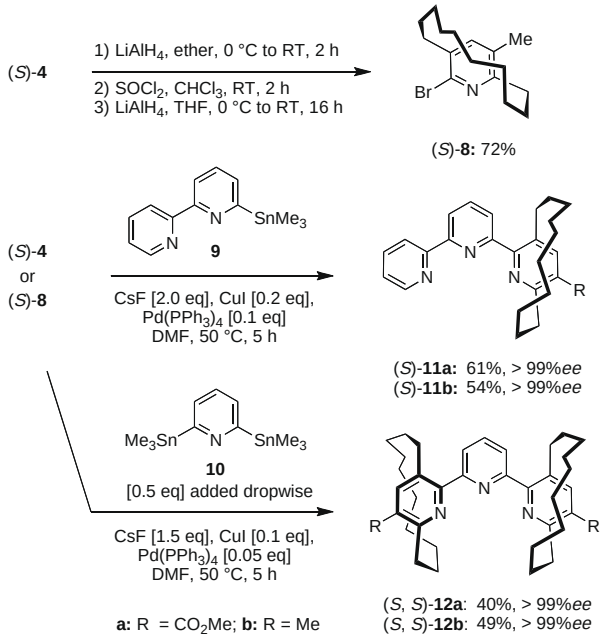
Finally, we synthesized bridged terpyridines, (*S*)-**11** and (*S,S*)-**12**, from (*S*)-**4** and (*S*)-**8**, the latter of which was derived from **4** in a few steps as illustrated in Scheme 2. The modified Stille cross-coupling with 2-(pyridin-2-yl)-6-(trimethylstannyl)pyridine (**9**)[21] resulted in the formation of the desired 2,2′:6′,2″-terpyridine derivative (*S*)-**11a,b**[22] in 61% and 54% yields, respectively. To obtain C_2-symmetric 2,2′:6′,2″-terpyridine**,** we initially carried out the reaction of (*S*)-**4** with 2,6-bis(trimethylstannyl)pyridine (**10**)[23] in such a way that bromide **4** was added dropwise to a heated solution of **10** to give 20% yield of the desired product (*S,S*)-**12a**[24] without a loss of planar-chirality (>99% ee). Since 2,6-bis(trimethylstannyl)pyridine is decomposed slowly under the

Table 2
Ni-mediated homo-coupling reactions for synthesis of (*S,S*)-**7**



(*S, S*)- **7**

Entry	**3–5**	Ni reagent	Yield (%)
1	(*S*)-**3**	$NiCl_2{\cdot}6H_2O$ [1.0 equiv], PPh_3 [4.0 equiv]	46
2	(*S*)-**4**	Ni(PPh$_3$)$_4$ [1.0 equiv]	63
3	(*S*)-**4**	$NiCl_2{\cdot}6H_2O$ [1.0 equiv], PPh_3 [4.0 equiv]	78
4	(*S*)-**5**	Ni(PPh$_3$)$_4$ [1.0 equiv]	63
5	(*S*)-**5**	$NiCl_2{\cdot}6H_2O$ [1.0 equiv], PPh_3 [4.0 equiv]	70



Scheme 2. Synthesis of planar-chiral terpyridines, **11a,b** and **12a,b**.

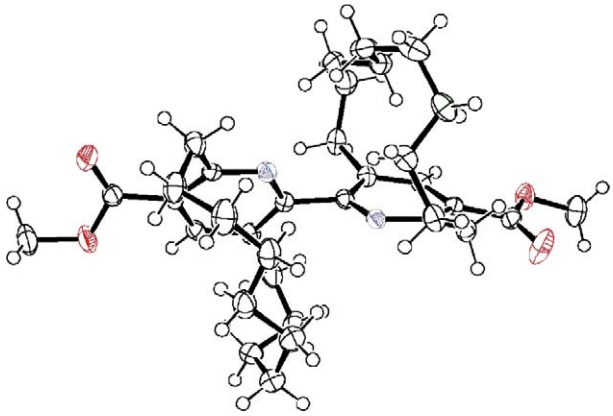


Figure 1. X-ray crystallographic structure of (*S,S*)-**7**.

reaction conditions, we employed a modified experimental protocol: bisstannylpyridine **10** was added dropwise to a solution of (*S*)-**4** instead and the yield of (*S,S*)-**12a** significantly increased to 40%. Similarly, double Stille-coupling of (*S*)-**8** also proceeded well to afford (*S,S*)-**12b**[24] in 49% yield.

X-ray crystallographic structure of unique (*S,S*)-**7** is shown in Figure 1.[25] The two pyridine rings of bipyridinophane moieties were found to have a dihedral angle of N–C–C–N with ca. +60 degrees, which is in good contrast to simple 2,2′-bipyridyl aligned in the same plane. This is ascribed to the characteristic bipyridinophane skeletons whose ansa-bridges are sterically demanding at C-5 and C-5′ vicinity to have the two pyridine rings twisted around the C–C bond of the bipyridyl unit. Although some distorted bipyridines are not suitable as metal ligands, zinc complexes (*S*)-**13** and (*S*)-**14**[26] were obtained when the planar-chiral bipyridines (*S*)-**6** and (*S,S*)-**7** reacted with zinc chloride. The formation of the complexes was determined by the ^{1}H NMR spectra and some selective data are listed in Figure 2. The data exhibited (1) characteristic down-field shifts were observed in their aromatic region and also in terminal oligomethylene protons ($\Delta\delta_{arom}$ = ca. 0.3 and $\Delta\delta_{CH2}$ = ca. 0.4–0.6 ppm, respectively); (2) the $\Delta\delta$ values are similar to each other and, therefore, the two complexes are at a comparable level of thermodynamic stability; and (3) more sterically demanding (*S,S*)-**14** is apparently C_2-symmetric.

It is noteworthy that (*S,S*)-**14** is quite stable complex to be stored in solid state and is also stable enough in chloroform solution. However, the complex seems to be kinetically less stable and decomplexation was observed during chromatography on

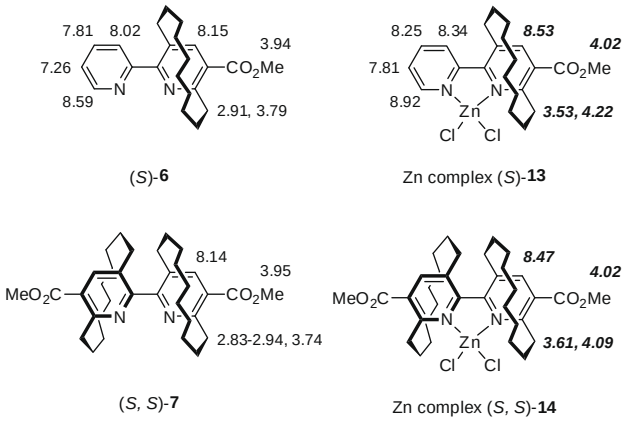


Figure 2. Representative chemical shifts in ^{1}H NMR spectra of (*S*)-**6**, (*S,S*)-**7** and their zinc complexes **13**,**14**.

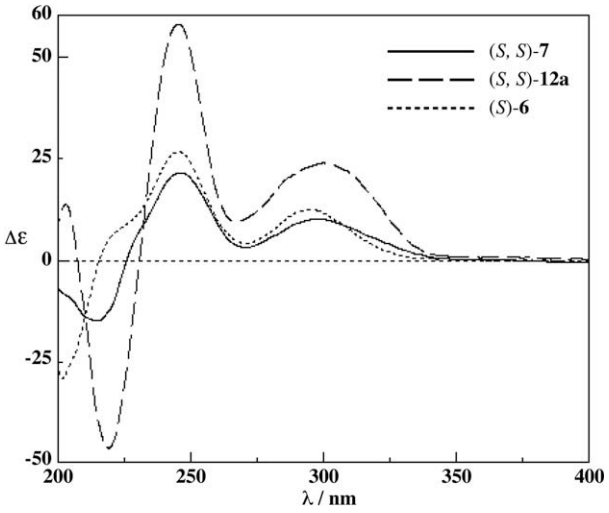


Figure 3. CD spectra of (*S*)-**6**, (*S,S*)-**7**, and (*S,S*)-**12a**.

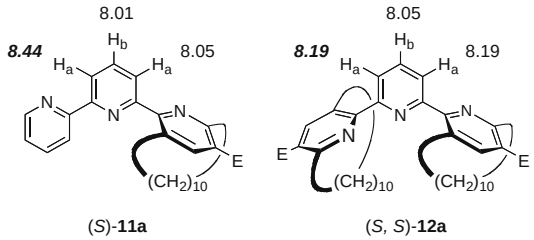


Figure 4. ^{1}H NMR chemical shifts for central pyridine rings of (*S*)-**11a** and (*S,S*)-**12a** (E = CO_2Me).

silica gel, filtration through Celite, extraction with water, or even stirring in acetonitrile.

Figure 3 illustrates CD spectra of bipyridines (*S*)-**6** and (*S,S*)-**7** and terpyridine (*S,S*)-**12a**; the two bipyridines showed nearly overlapping line shapes in terms of Cotton effects and their intensities, and the terpyridine exhibited an amplified but still similar shape as compared to the bipyridines. This observation suggests that their pyridine cores are aligned with similar non-planar orientation. A typical up-field shift of a central aromatic proton for (*S,S*)-**12a** (δ 8.19 ppm) also supports the non-planar structure where its H_a protons are located in a shielding region of the neighboring pyridine (Fig. 4). One of the corresponding protons for (*S*)-**11a** exhibits a standard chemical shift as well as that for simple terpyridine (δ 8.45 ppm).

Acknowledgment

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18. (*S*)-**6**: white solid; mp 70.1–72.1 °C; ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 0.49 (m, 1H), 0.57–1.00 (m, 9H), 1.16 (m, 1H), 1.20–1.32 (m, 2H), 1.41 (m, 1H), 1.61 (m, 1H), 1.91 (m, 1H), 2.64 (ddd, *J* = 12.8, 9.2, 4.0 Hz, 1H), 2.91 (ddd, *J* = 12.8, 9.2, 4.0 Hz, 1H), 3.64 (ddd, *J* = 12.0, 5.8, 4.0 Hz, 1H), 3.84 (ddd, *J* = 12.0, 5.8, 4.0 Hz, 1H), 3.95 (s, 3H), 7.33 (ddd, *J* = 7.6, 4.0, 1.2 Hz, 1H), 7.88 (td, *J* = 7.6, 1.6 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 8.15 (s, 1H), 8.66 (dd, *J* = 4.0, 1.2 Hz, 1H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 24.6, 26.0, 26.41, 26.47, 27.34, 27.37, 27.5, 27.8, 31.1, 35.7, 53.4, 123.24, 124.5, 124.7, 133.66, 136.9, 142.0, 148.5, 157.8, 158.3, 160.3, 167.1; CD (CH_3CN) λ_{ext} = 296 ($\delta\varepsilon$ = +12.5), 270 (+4.1), 246 (+26.7). HRMS (FAB+) *m/z*: calcd for $C_{22}H_{29}N_2O_2$ [M+H$^+$] 353.2229, found 353.2228.
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20. (*S,S*)-**7**: white solid; mp 149.9–151.1 °C (from MeOH); ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 0.38–0.52 (m, 4H), 0.60 (m, 2H), 0.74–1.13 (m, 16H), 1.30 (m, 2H), 1.45–1.68 (m, 6H), 1.83 (m, 2H), 2.77 (m, 2H), 2.83–2.94 (m, 4H), 3.74 (ddd, *J* = 12.8, 8.2, 4.1 Hz, 2H), 3.95 (s, 6H), 8.14 (s, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 24.4, 26.0, 26.5, 26.7, 27.4, 27.7, 27.9, 30.7, 35.6, 52.3, 124.2, 133.3, 140.6, 158.5, 159.9, 167.4; CD (CH_3CN) λ_{ext} = 297 ($\Delta\varepsilon$ = +10.3), 271 (+3.2), 247 (+21.5); $[\alpha]_D^{27}$ +288 (*c* = 0.21 in $CHCl_3$). HRMS (FAB+) *m/z*: calcd for $C_{34}H_{49}N_2O_4$ [M+H$^+$] 549.3692, found 549.3661.
21. Prepared from 2-bromopyridine with 2,6-bisstannylpyridine **10**[23] in the presence of 10 mol % of $Pd(PPh_3)_4$ in refluxing toluene for 20 h. For **9**: 60% yield; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (s, 9H), 7.27–7.29 (m, 1H), 7.44–7.46 (m, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.79–7.81 (m, 1H), 8.25–8.27 (m, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.66 (m, 1H).
22. For (*S*)-**11a**: solid; mp 102.7–103.9 °C; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 0.47–0.51 (m, 1H), 0.66 (m, 1H), 0.73–0.78 (m, 3H), 0.80–0.85 (m, 2H), 1.01–1.19 (m, 3H), 1.22 (m, 1H), 1.39–1.54 (m, 3H), 1.70 (m, 1H), 1.82 (m, 1H), 2.60 (ddd, *J* = 13.1, 9.2, 4.4 Hz, 1H), 2.80 (ddd, *J* = 13.1, 9.2, 4.4 Hz, 1H), 3.83–3.91 (m, 2H), 3.97 (s, 3H), 7.32 (m, 1H), 7.82 (dd, *J* = 7.5, 2.6 Hz, 1H), 8.01 (t, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.18 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.70 (m, 1H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 24.8, 26.2, 26.57, 26.61, 27.3, 27.4, 27.7, 27.9, 31.6, 35.9, 52.3, 120.4, 121.3, 123.7, 124.4, 124,5, 133.6, 136.8, 137.8, 142.1, 149.0, 154.8, 156.0, 157.37, 157.45, 160.2, 167.0. HRMS (FAB+) *m/z*: calcd for $C_{27}H_{32}N_3O_2$ [M+H$^+$] 430.2489, found 430.2490. For (*S*)-**11b**: oil; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 0.49–0.61 (m, 2H), 0.61–0.1.06 (m, 6H), 1.13–1.45 (m, 6H), 1.69 (m 1H), 1.89 (m, 1H), 2.40 (s, 3H), 2.57 (ddd, *J* = 12.1, 9.2, 4.4 Hz, 1H), 2.86 (ddd, *J* = 12.1, 9.2, 4.4 Hz, 1H), 3.09 (ddd, *J* = 12.1, 9.2, 4.4 Hz, 1H), 3.79 (ddd, *J* = 12.1, 9.2, 4.4 Hz, 1H), 7.30 (m, 1H), 7.39 (s, 1H), 7.80 (dd, *J* = 7.5, 2.6 Hz, 1H), 7.96 (t, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.69 (m, 1H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 18.4, 24.8, 25.7, 26.50, 26.55, 26.6, 27.5, 27.6, 27.9, 31.5, 34.0, 119.6, 121.2, 123.6, 124.4, 130.6, 133.7, 136.8, 137.8, 141.3, 149.0, 153.3, 154.6, 156.4, 157.3, 158.8. HRMS (FAB+) *m/z*: calcd for $C_{26}H_{32}N_3$ [M+H$^+$] 386.2591, found 386.2598.
23. Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull. Jpn.* **1982**, *30*, 1731–1737.
24. For (*S,S*)-**12a**: white solid; mp 168.6–169.1 °C (from MeOH); ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 0.49 (m, 2H), 0.61 (m, 2H), 0.63–0.78 (m, 8H), 0.80–0.85 (m, 4H), 1.23–1.32 (m, 5H), 1.23–1.46 (m, 5H), 1.58–1.72 (m, 4H), 1.92 (m, 2H), 2.48 (ddd, *J* = 13.7, 9.8, 4.4 Hz, 2H), 2.92 (ddd, *J* = 13.7, 9.8, 4.4 Hz, 2H), 3.66 (ddd, *J* = 14.6, 10.2, 4.4 Hz, 2H), 3.86 (ddd, *J* = 10.2, 6.4, 3.9 Hz, 2H), 3.95 (s, 6H), 8.05 (t, *J* = 8.0 Hz, 1H), 8.12 (s, 2H), 8.19 (d, *J* = 8.0 Hz, 2H) ; ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 24.7, 26.2, 26.5, 26.6, 27.2, 27.4, 27.7, 27.9, 31.3, 35.9, 52.3, 124.1, 124.3, 134.0, 137.8, 142.0, 157.0, 157.4, 160.0, 167.0 ; CD (CH_3CN) λ_{ext} = 300.1 ($\Delta\varepsilon$ = +23.5), 266.9 (+9.7), 245.4 (+58.0), 219.0 (−46.3); $[\alpha]_D$ = +405.8 (*c* = 0.535 in $CHCl_3$). HRMS (FAB+) *m/z*: calcd for $C_{39}H_{52}N_3O_4$ [M+H$^+$] 626.3958, found 626.3981. For (*S,S*)-**12b**: white solid; mp 183.1–183.6 °C (from MeOH); ^{1}H NMR (500.16 MHz, $CDCl_3$) δ 0.48–0.91 (m, 20H), 1.10–1.31 (m, 6H), 1.37 (m, 2H), 1.70 (m, 2H), 1.92 (m, 2H), 2.30–2.42 (m, 8H), 2.87 (ddd, *J* = 13.7, 9.8, 4.4 Hz, 2H), 3.11 (ddd, *J* = 14.6, 10.2, 4.4 Hz, 2H), 3.60 (ddd, *J* = 10.2, 6.4, 3.9 Hz, 2H), 7.32 (s, 2H),7.93 (t, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 18.5, 24.6, 25.8, 26.53, 26.57, 26.61, 27.59, 27.63, 27.9, 31.2, 34.0, 123.1, 130.3, 134.1, 137.6, 141.3, 153.8, 157.0, 158.1; CD (CH_3CN) λ_{ext} = 283.1 ($\Delta\varepsilon$ = +21.4), 260.7 (−2.2), 239.4 (+29.9), 209.7 (−27.8); $[\alpha]_D$ = +140.9 (*c* = 0.565 in $CHCl_3$). HRMS (FAB+) *m/z*: calcd for $C_{37}H_{51}N_3$ [M+H$^+$] 538.4161, found 538.4161.
25. X-ray crystal data for (*S,S*)-**7**: $C_{34}H_{48}O_4N_2$, M_w = 548.76, orthorhombic, space group $P2_12_12_1$ (No. 19), colorless, prism, dimensions 0.44 × 0.41 × 0.26 mm^3, μ(Mo$k\alpha$) = 0.784 cm^{-1}, *a* = 8.4349(3) Å, *b* = 18.5330(5) Å, *c* = 19.2294(6) Å, *V* = 3006.02(16) Å^3, *T* = −100 ± 1 °C, *Z* = 4, D_c = 1.212 g/cm^3. Of the 29566 reflections that were collected, 6857 were unique (R_{int} = 0.050). R_1 and wR_2 are 0.0358 and 0.0675, respectively [$I > 2.00s(I)$]. Crystallographic data (excluding structure factors) for the structure of (S, S)-**7** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 722776. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
26. For (*S*)-**13**: white solid; mp 289.2–291.0 °C; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 0.28–0.33 (m, 2H), 0.58–0.66 (m, 1H), 0.74–0.91 (m, 4H), 0.91–1.01 (m, 1H), 1.01–1.19 (m, 3H), 1.34–1.47 (m, 1H), 1.62–1.76 (m, 2H), 1.83–1.91 (m, 1H), 2.04–2.16 (m, 1H), 2.58 (ddd, *J* = 13.7, 8.2, 3.2 Hz, 1H), 3.16 (ddd, *J* = 13.3, 8.7, 4.1 Hz, 1H), 3.53 (ddd, *J* = 13.7, 8.2, 3.2 Hz, 1H), 4.02 (s, 3H), 4.22 (ddd, *J* = 13.7, 8.2, 3.2 Hz, 1H), 7.81 (td, *J* = 8.2, 2.0 Hz, 1H), 8.25 (td, *J* = 8.2, 2.0 Hz, 1H), 8.34 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.53 (s, 1H), 8.92 (dd, *J* = 8.2, 2.0 Hz, 1H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 24.65, 25.9, 26.1, 26.25, 26.3, 27.8, 30.2, 32.94, 37.25, 53.2, 126.7, 127.5, 128.5, 136.1, 141.4, 146.25, 148.66, 149.5, 149.6, 162.2, 164.86. HRMS (FAB+) *m/z*: calcd for $C_{22}H_{28}ClN_2O_2Zn$ [M−Cl$^-$] 451.1125, found 451.1135. For (*S,S*)-**14**: white solid; mp 266.1–267.3 °C; ^{1}H NMR (399.65 MHz, $CDCl_3$) δ 0.23–0.42 (m, 4H), 0.62–0.89 (m, 12H), 0.91–1.06 (m, 4H), 1.11 (m, 2H), 1.31 (m, 2H), 1.41–1.52 (m, 4H), 1.64 (m, 2H), 2.17 (m, 2H), 2.66 (ddd, *J* = 13.8, 10.7, 3.2 Hz, 2H), 3.05 (ddd, *J* = 13.8, 6.3, 3.4 Hz, 2H), 3.61 (ddd, *J* = 14.1, 9.3, 3.7 Hz, 2H), 4.02 (s, 6H), 4.09 (ddd, *J* = 14.1, 7.6, 3.9 Hz, 2H), 8.47 (s, 2H); ^{13}C NMR (125.40 MHz, $CDCl_3$) δ 24.3 (2C), 25.6 (2C), 25.9 (2C), 26.8 (2C), 27.5 (2C), 28.2 (2C), 29.2 (2C), 29.7 (2C), 32.8 (2C), 36.4 (2C), 53.2 (2C), 129.3 (2C), 138.1 (2C), 143.4 (2C), 149.6 (2C), 162.5 (2C), 165.3 (2C); CD ($CHCl_3$); λ_{ext} = 304 ($\Delta\varepsilon$ = +1.6), 282 (8.6), 246 (+35.4); $[\alpha]_D^{27}$ +303 (*c* = 0.24 in $CHCl_3$); MS (FAB+) *m/z* (%) 549 (100) [M−$ZnCl_2$+H$^+$]; MS (ESI+) *m/z* (%) 549 (100) [M−$ZnCl_2$+H$^+$] and peaks at 683 [M+H$^+$] or 647 [M−Cl$^-$] was absent. Anal. calcd for $C_{34}H_{48}Cl_2N_2O_4Zn$: C, 59.61; H, 7.06; N, 4.09. found: C, 58.22; H, 7.18; N, 3.91.