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New enantiopure C_2 symmetric bis(2-oxazolinyl)cage (Cage-Box) ligands from 4,5-dicyanopyridazine

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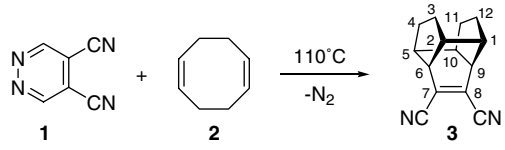
Abstract—7,8-Dicyanotetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene **3**, obtained from 4,5-dicyanopyridazine **1** and cycloocta-1,5-diene **2** through a three-step pericyclic homodomino process, was found to react with optically active β-amino alcohols **4a**–**d**, under zinc chloride catalysis, to afford a new class of enantiopure C_2 symmetric bis(oxazolinyl)cage (Cage-Box) ligands **6a**–**d**, along with the corresponding mono(oxazolinyl) derivatives **5a**–**d**.

1. Introduction

Since the example reported by Brunner et al. in 1986 concerning the use of optically active pyridine oxazoline ligands in asymmetric catalysis,[1] a great range of ligands containing one, two or three oxazoline rings, diverse structural features and various heteroatoms has been successfully developed and employed in many kinds of asymmetric reactions.[2] In particular, as the presence of a C_2 symmetry axis is able to reduce the number of possible catalyst–substrate arrangements and then the number of competing diastereomeric transition states,[3] the interest in enantiopure C_2 symmetric bis(oxazoline) (Box) ligands has enormously increased and in the last 15 years chiral Box ligands with a great deal of structural diversity have been applied in an impressive variety of metal-catalyzed processes, establishing them among the most versatile ligands in asymmetric catalysis.[4] Therefore, although chiral bis(oxazolines) have been introduced since 1989, synthetic efforts towards new enantiopure derivatives, with their ability to work efficiently in the preparation of optically active compounds, are still intensively pursued in organic synthesis.

Oxazoline systems have usually been synthesized from readily available precursors such as amino alcohols and nitrile or carboxylic acid derivatives.[5] In particular, Bolm et al. have described the preparation of chiral bis(oxazolines) by direct reaction of dinitriles with enantiomerically pure β-amino alcohols under zinc chloride catalysis.[6]

Recently, we have reported a facile access to cage systems through hetero Diels–Alder reactions of 4,5-dicyanopyridazine (DCP) **1** with different bis-dienophiles.[7] A three-step pericyclic homodomino process allowed the formation of cage derivatives containing a maleonitrile moiety, coming from **1**. In particular, treatment of DCP with an excess of cycloocta-1,5-diene **2** at 110 °C afforded the tetracyclic compound **3** in almost quantitative yield (Scheme 1).[7b]



Scheme 1.

From this basis, and in the light of the great interest still devoted to the synthesis of new and more efficient catalysts for asymmetric synthesis, we decided to investigate the possibility of exploiting dinitrile **3** for the construction of a new class of optically active C_2 symmetric bis(oxazoline) ligands, as well as the formation of the corresponding metal complexes.

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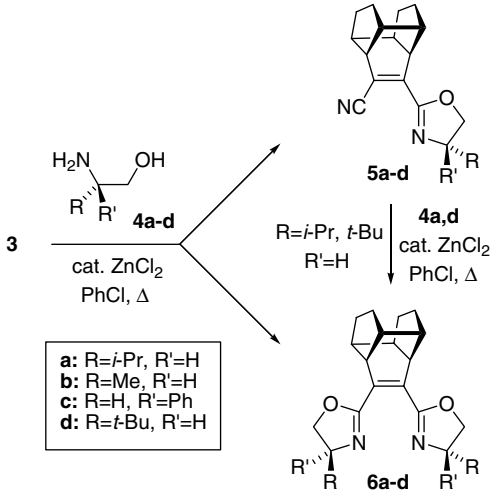
2. Results and discussion

According to Bolm's procedure, when a solution of **3** and (*S*)-(+)-2-amino-3-methyl-1-butanol **4a** (3 equiv) in anhydrous chlorobenzene was heated under reflux for 7 days in the presence of a catalytic amount of anhydrous zinc dichloride (10 mol %), mono(2-oxazoline) **5a** and bis(2-oxazoline) **6a** were isolated in 49% and 32% yields, respectively, after aqueous workup and flash column chromatography (Scheme 2; Table 1, entry 1).[8]



Scheme 2.

Table 1. Reactions of **3** with amino alcohols **4a–d**

Entry	Amino alcohol (equiv)	Time (days)	**5** Yield (%)[a]	**6** Yield (%)[a]
1	**4a** (3)	7	**5a** 49	**6a** 32
2	**4a** (5)	3	**5a** 35	**6a** 46
3	**4b** (2)	4	**5b** 30	**6b** 17
4	**4b** (5)	3	**5b** 14	**6b** 36
5	**4c** (5)	3	**5c** 24	**6c** 45
6	**4d** (3)	7	**5d** 63	**6d** 35
7	**4d** (5)	9	**5d** 48	**6d** 51

[a] Isolated yields.

Performing the above reaction with 5 equiv of **4a** for shorter reaction times (3 days), the bis(oxazoline) **6a** became the predominant product isolated in 46% yield, along with mono(oxazoline) **5a** (Table 1, entry 2). Attempts to improve the formation of **6a** employing larger amounts of $ZnCl_2$ (up to 30 mol %) or amino alcohol (up to 10 equiv) and/or prolonged reaction times (up to 11 days) were unsuccessful. Mono(oxazoline) **5a** was converted into the corresponding bis-derivative **6a** in 69% yield, by reaction with **4a** (5 equiv) in the previously reported conditions for 13 days (Scheme 2).

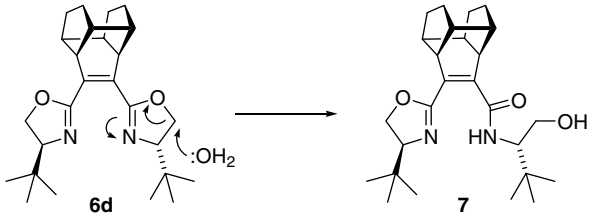
Treatment of **3** with (*S*)-(+)-2-amino-1-propanol **4b**, under the standard conditions, gave rise to a complex reaction mixture from which bis(oxazoline) **6b** and mono(oxazoline) **5b** were isolated in 36% and 14% yields, respectively (Table 1, entry 4). Operating for longer reaction times with minor amounts of **4b**, we achieved a partial conversion of compound **3** (81%) with **5b** as the predominant product (Table 1, entry 3).

When (*R*)-(−)-2-amino-2-phenylethanol **4c** was allowed to react with **3**, we isolated from a complex crude reaction mixture derivatives **5c** and **6c** in 24% and 45% yields, respectively (Table 1, entry 5).[9]

(*S*)-(+)-2-Amino-3,3-dimethyl-1-butanol **4d** gave better results. Treatment of **3** with 3 equiv of the above reagent afforded compounds **5d** and **6d** in 63% and 35% yields, respectively (Table 1, entry 6). The formation of **6d** was notably improved operating with larger amounts of **4d** (5 equiv) for longer reaction times (Table 1, entry 7). As reported for **5a**, treatment of mono(oxazoline) **5d** with amino alcohol **4d** (5 equiv) for 12 days gave the bis-derivative **6d** in 49% yield, along with unreacted starting material (50%) (Scheme 2).

In all cases, efforts to achieve better results in terms of both overall yields and bis(oxazoline) formation by using larger amounts of amino alcohol and/or longer reaction times failed, due to increasing decomposition processes probably due to the poor thermal stability of the employed amino alcohols. In fact, complex reaction mixtures were obtained when **4a–d** were heated alone in refluxing PhCl for prolonged times.

Moreover, while mono(oxazolines) are very stable species, the corresponding bis(oxazolines) **6a–d**, and especially the encumbered *tert*-butyl derivative **6d**, appeared quite unstable on prolonged storage at room temperature. As reported for other oxazoline ligands,[10] ring-opening processes, favoured by released steric strain, probably take place affording β-hydroxyamides through nucleophilic attack by water on the C-5 carbon of the oxazoline ring. This trend was observed for all systems **6a–d**, but in the case of bis(oxazoline) **6d**, after some weeks at room temperature in the solid state or in $CDCl_3$ solution, a complete conversion into β-hydroxyamide **7** was observed (Scheme 3). Nevertheless, compounds **6a–d** can be stored under nitrogen at low temperature (−10 °C) without significant change, even for long periods.

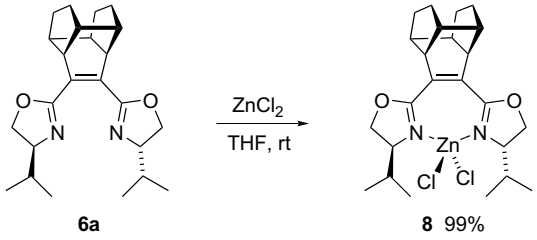


Scheme 3.

In the light of the interest associated with the study of coordination chemistry of oxazolines,[11] and with the aim of investigating the complexation of the above (Cage-Box) ligands with transition metals, bis(oxazoline) **6a** was allowed to react with a stoichiometric

amount of $ZnCl_2$ in anhydrous tetrahydrofuran, at room temperature, leading to the 1:1 Zn(II) complex **8**, isolated in almost quantitative yield (Scheme 4). The molecular structure of **8** was determined by single-crystal X-ray diffraction analysis (Fig. 1).[12] The zinc atom appears tetrahedrally surrounded by two nitrogen atoms of the chelate bis(oxazoline) and two chlorine atoms, with a bite angle (N–Zn–N) of 92.6(3)°. The rigid seven-membered cycle is not planar, with dihedral angles between the oxazoline moieties and the alkene bridge of 45.1°. One of the isopropyl groups points into the cavity of the metal cycle, whereas the other one points out, leading to a non-equivalence of the two substituents. As reported for similar complexes,[6] the ^1H and ^{13}C NMR spectra in $CDCl_3$ solution at room temperature are consistent with a C_2 symmetric structure. In fact, in the former spectrum a single set of signals was detected for the two isopropyl groups (two doublets at δ 0.70 and 0.83 for the diastereotopic methyl groups and a heptuplet of doublets at δ 2.53 for the methine protons) as well as for the bridgehead protons H-6 and H-9 of the cage system that gave only one triplet at δ 2.59. Moreover, the corresponding carbon pattern presents just 12 resonances. Such behaviour could presumably be ascribed to rapid interconversion on the NMR time scale between conformations obtained through metal atom displacement from above to below with respect to the alkene plane.

Similar observations in the ^1H and ^{13}C NMR patterns of compounds **6a–d** confirmed their C_2 symmetry, while the same spectra of mono(oxazolines) **5a–d** clearly showed well separated signals for the bridgehead protons and the corresponding carbon atoms of the tetracyclic skeleton in the range 2.57–2.60 and 3.08–3.11 ppm, and 44.1–44.3 and 47.5–47.8 ppm, respectively.



6a **8** 99%

Scheme 4.

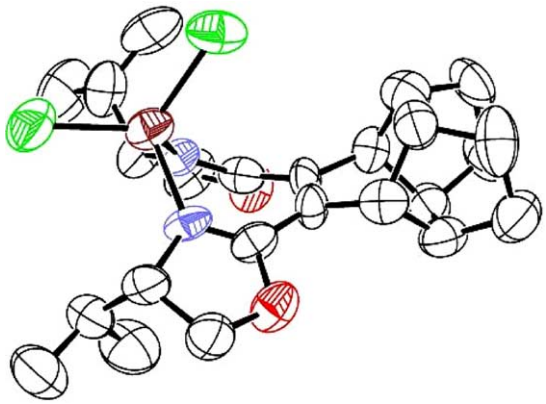


Figure 1. ORTEP drawing of complex **8** with hydrogens omitted for clarity.

3. Conclusions

In summary, these findings clearly evidenced the possibility of obtaining a new class of enantiopure C_2 symmetric bis(oxazolinyl)cage (Cage-Box) ligands, as well as mono(oxazolinyl) derivatives, from the tetracyclic cage system **3** and commercially available in enantiomerically pure form β-amino alcohols **4a–d**, in satisfactory yields. For compounds **5a**,**d** and **6a**,**d**, a careful choice of reaction conditions (equivalents of amino alcohol and reaction times) allowed to some extent modulation of the preference towards the former or the latter species. Moreover, the isolation of mono(oxazolines), at first sight disappointing due to their resistance to complete conversion into the corresponding bis-derivatives, could be promising for the synthesis of new mono(oxazoline) ligands of different types, through suitable elaborations of the still present nitrile function. Beside such transformations, the synthetic applications of new bis(oxazolines) **6a–d** as chiral ligands in different kinds of metal catalyzed asymmetric reactions are under investigation in our laboratory and progress will be reported in due course.

4. Experimental

4.1. General

All commercially available reagents were used as received. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230–400 mesh) were used for TLC and flash chromatographies, respectively; petroleum ether employed for crystallizations and chromatographic workup refers to the fractions of bp 30–50 and 40–70 °C, respectively. IR spectra were measured as KBr pellets with a Perkin–Elmer Spectrum BX FT-IR System spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions with a Varian Mercuryplus 400 instrument, operating at 400 and 100.58 MHz, respectively. Mass spectra were recorded on a QMD 1000 Carlo Erba instrument by GC or direct inlet; relative percentages are shown in brackets. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer.

4.2. Reactions of 3 with amino alcohols 4a–d. General procedure

To a solution of anhydrous $ZnCl_2$ (0.007 g, 0.05 mmol), melted under high vacuum and cooled under nitrogen, in dry chlorobenzene (2.5 mL) were added compound **3** (0.105 g, 0.5 mmol) and the appropriate amount of amino alcohol at room temperature. The resulting mixture was heated under reflux for the reported time. The residue coming from evaporation under reduced pressure was dissolved in dichloromethane, washed with water and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried,

evaporated to dryness and separated by flash column chromatography, through gradient elution.

4.2.1. Reactions of 3 with (*S*)-(+)-2-amino-3-methyl-1-butanol 4a. (A) Chromatography (petroleum ether/ethyl acetate 5:1 v/v) of the residue obtained by heating of **3** and amino alcohol **4a** (0.155 g, 1.5 mmol) for 7 days gave 7-cyano-8-[(4*S*)-4-isopropyl-2-oxazolin-2-yl]-tetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene **5a** ($R_f = 0.38$, 0.073 g, 49%) as white crystals: mp 116–117 °C (from petroleum ether/ether); $[\alpha]_D^{25} = -80.9$ (*c* 1.0, $CHCl_3$); IR 2957, 2883, 2868, 2212, 1652, 1599 cm^{-1}; ^{1}H NMR δ 0.90 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.54–1.67 (m, 4H), 1.72–1.88 (m, 5H), 1.89–2.00 (m, 4H), 2.58 (t, $J = 3.0$ Hz, 1H), 3.08 (t, $J = 2.9$ Hz, 1H), 4.00–4.06 (m, 1H), 4.14 (t, $J = 8.3$ Hz, 1H), 4.41 (dd, $J = 9.8$ and 8.5 Hz, 1H); ^{13}C NMR δ 18.0 (q), 18.9 (q), 25.5 (t, 2×), 25.6 (t), 25.7 (t), 32.65 (d), 40.6 (d, 2×), 40.7 (d), 40.9 (d), 44.2 (d), 47.6 (d), 70.6 (t), 72.4 (d), 116.4 (s), 117.4 (s), 143.4 (s), 160.2 (s). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.97; H, 8.06; N, 9.49.

The slowest moving band, recovered with ethyl acetate as eluent, afforded 7,8-bis[(4*S*)-4-isopropyl-2-oxazolin-2-yl]tetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene **6a** ($R_f = 0.40$, 0.062 g, 32%) as ivory crystals: mp 89–90 °C (from petroleum ether); $[\alpha]_D^{24} = -89.6$ (*c* 1.0, $CHCl_3$); IR 2955, 2872, 1694, 1642 cm^{-1}; ^{1}H NMR δ 0.86 (d, $J = 6.9$ Hz, 6H), 0.96 (d, $J = 6.7$ Hz, 6H), 1.52–1.60 (m, 4H), 1.67–1.86 (m, 6H), 1.94 (m, 4H), 2.70 (br s, 2H), 3.93–3.99 (m, 4H), 4.18–4.27 (m, 2H); ^{13}C NMR δ 18.0 (q), 19.1 (q), 25.5 (t), 25.55 (t), 32.45 (d), 40.4 (d), 40.5 (d), 45.7 (d), 69.7 (t), 72.5 (d), 133.4 (s), 162.6 (s). Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.66; H, 9.25; N, 7.58.

(B) When the above reaction was carried out with 5 equiv of amino alcohol **4a** (0.258 g, 2.5 mmol) for 3 days, chromatographic workup of the crude product afforded compounds **5a** (0.052 g, 35%) and **6a** (0.088 g, 46%), identical with the species previously obtained.

4.2.2. Reactions of 3 with (*S*)-(+)-2-amino-1-propanol 4b. (A) The residue obtained by reaction of **3** and **4b** (0.075 g, 0.078 mL, 1.0 mmol) for 4 days was resolved into three components by chromatographic workup. When petroleum ether/ethyl acetate 3:1 v/v was employed as eluent, the first band afforded unreacted **3** ($R_f =$ 0.75, 0.020 g, 19%) while the second one gave 7-cyano-8-[(4*S*)-4-methyl-2-oxazolin-2-yl]tetracyclo[7.3.0.0^{2,6}0^{5,10}]-dodec-7-ene (**5b**) ($R_f = 0.33$, 0.040 g, 30%) as white crystals: mp 164–165 °C (from petroleum ether/ether); $[\alpha]_D^{25} = -99.5$ (*c* 0.5, $CHCl_3$); IR 2990, 2956, 2932, 2884, 2216, 1647, 1595 cm^{-1}; ^{1}H NMR δ 1.35 (d, $J = 6.6$ Hz, 3H), 1.56–1.65 (m, 4H), 1.8 (m, 4H), 1.93–2.04 (m, 4H), 2.60 (t, $J = 2.8$ Hz, 1H), 3.08 (t, $J = 2.8$ Hz, 1H), 3.98 (t, $J = 8.2$ Hz, 1H), 4.32 (m, 4H), 4.55 (dd, $J = 9.2$ and 8.3 Hz, 1H); ^{13}C NMR δ 21.1 (q), 25.5 (t), 25.55 (t), 25.6 (t), 25.7 (t), 40.6 (d), 40.7 (d), 40.8 (d), 40.85 (d), 44.3 (d), 47.6 (d), 61.8 (d), 74.6 (t), 116.6 (s), 117.4 (s), 143.3 (s), 160.4 (s). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.72; H, 7.54; N, 10.39.

The slowest moving fractions (ethyl acetate/methanol 10:1 v/v) yielded 7,8-bis[(4*S*)-4-methyl-2-oxazolin-2-yl]tetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene **6b** ($R_f = 0.46$, 0.028 g, 17%) as ivory needles: mp 142–143 °C (petroleum ether/ether); $[\alpha]_D^{23} = -104.3$ (*c* 0.5, $CHCl_3$); IR 2952, 2887, 1682, 1631 cm^{-1}; ^{1}H NMR δ 1.27 (d, $J = 6.6$ Hz, 6H), 1.52–1.56 (m, 4H), 1.67–1.78 (m, 4H), 1.95 (m, 4H), 2.69 (br s, 2H), 3.80 (t, $J = 7.8$ Hz, 2H), 4.22 (m, 2H), 4.36 (dd, $J = 9.4$ and 7.8 Hz, 2H); ^{13}C NMR δ 21.1 (q), 25.55 (t), 25.6 (t), 40.5 (d), 40.6 (d), 45.6 (d), 61.8 (d), 73.9 (t), 133.6 (s), 162.7 (s). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.63; H, 8.24; N, 8.47.

(B) Operating as above, chromatography of the residue obtained by heating of **3** and **4b** (0.188 g, 0.195 mL, 2.5 mmol) for 3 days afforded derivatives **5b** (0.019 g, 14%) and **6b** (0.059 g, 36%).

4.2.3. Reactions of 3 with (*R*)-(−)-2-amino-2-phenylethanol 4c. Chromatographic workup (petroleum ether/ethyl acetate 3:1 v/v) of the crude product coming from the reaction of **3** and **4c** (0.343 g, 2.5 mmol) for 3 days gave 7-cyano-8-[(4*R*)-4-phenyl-2-oxazolin-2-yl]-tetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene **5c** ($R_f = 0.44$, 0.040 g, 24%) as white crystals: mp 129–130 °C (petroleum ether/ether); $[\alpha]_D^{25} = +107.5$ (*c* 0.1, $CHCl_3$); IR 3020, 2948, 2883, 2212, 1649, 1598 cm^{-1}; ^{1}H NMR δ 1.52–1.57 (m, 4H), 1.70–1.77 (m, 4H), 1.89–1.97 (m, 4H), 2.57 (t, $J = 2.9$ Hz, 1H), 3.11 (t, $J = 2.9$ Hz, 1H), 4.24 (t, $J = 8.6$ Hz, 1H), 4.76 (dd, $J = 10.2$ and 8.6 Hz, 1H), 5.25 (dd, $J = 10.1$ and 8.7 Hz, 1H), 7.19–7.25 (m, 3H), 7.27–7.32 (m, 2H); ^{13}C NMR δ 25.5 (t), 25.6 (t), 25.65 (t), 25.7 (t), 40.6 (d), 40.8 (d), 40.9 (d), 40.95 (d), 44.3 (d), 47.8 (d), 69.9 (d), 75.4 (t), 117.3 (s, 2×), 126.8 (d), 127.8 (d), 128.8 (d), 141.4 (s), 143.1 (s), 161.5 (s). Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.98; H, 7.01; N, 8.71.

The subsequent fractions (ethyl acetate) yielded 7,8-bis-[(4*R*)-4-phenyl-2-oxazolin-2-yl]tetracyclo[7.3.0.0^{2,6}0^{5,10}]-dodec-7-ene **6c** ($R_f = 0.61$, 0.102 g, 45 %) as pale yellow crystals: mp 149–150 °C (pentane/ether); $[\alpha]_D^{24} =$ +200.3 (*c* 0.25, $CHCl_3$); IR 3057, 3026, 2943, 2924, 2896, 2877, 1684, 1639, 1600 cm^{-1}; ^{1}H NMR δ 1.63–1.66 (m, 4H), 1.83–1.85 (m, 4H), 2.09 (br s, 4H), 2.91 (br s, 2H), 4.21 (t, $J = 8.3$ Hz, 2H), 4.70 (dd, $J = 10.2$ and 8.3 Hz, 2H), 5.29 (dd, $J = 10.1$ and 8.4 Hz, 2H), 7.29–7.39 (m, 10H); ^{13}C NMR δ 25.5 (t), 25.55 (t), 40.5 (d), 40.6 (d), 45.8 (d), 70.0 (d), 74.6 (t), 126.8 (d), 127.4 (d), 128.5 (d), 133.7 (s), 142.0 (s), 163.9 (s). Anal. Calcd for $C_{30}H_{30}N_2O_2$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.60; H, 6.90; N, 5.98.

4.2.4. Reactions of 3 with (*S*)-(+)-2-amino-3,3-dimethyl-1-butanol 4d. (A) Chromatography (petroleum ether/ethyl acetate 7:1 v/v) of the residue obtained by heating of **3** and amino alcohol **4d** (0.176 g, 1.5 mmol) for 7 days gave 7-cyano-8-[(4*S*)-4-*tert*-butyl-2-oxazolin-2-yl]tetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene **5d** ($R_f = 0.41$, 0.098 g,

63%) as white crystals: mp 141–142 °C (from petroleum ether); $[\alpha]_D^{23} = -87.7$ (*c* 0.25, $CHCl_3$); IR 2956, 2869, 2215, 1652, 1599 cm^{-1}; ^1H NMR δ 0.92 (s, 9H), 1.56–1.64 (m, 4H), 1.77–1.83 (m, 4H), 1.89–1.99 (m, 4H), 2.58 (t, $J = 3.0$ Hz, 1H), 3.08 (t, $J = 2.9$ Hz, 1H), 3.98 (dd, $J = 10.2$ and 7.9 Hz, 1H), 4.23 (dd, $J = 8.8$ and 8.0 Hz, 1H), 4.34 (dd, $J = 10.2$ and 8.9 Hz, 1H); ^{13}C NMR δ 25.45 (t), 25.5 (t), 25.6 (t), 25.7 (t), 25.8 (q), 34.0 (s), 40.55 (d), 40.6 (d), 40.65 (d), 40.9 (d), 44.1 (d), 47.5 (d), 69.2 (t), 75.9 (d), 116.3 (s), 117.4 (s), 143.5 (s), 160.05 (s). Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.70; H, 8.63; N, 9.00.

The slowest moving band (petroleum ether/ethyl acetate 2:1 v/v) yielded 7,8-bis[(4*S*)-4-*tert*-butyl-2-oxazolin-2-yl]tetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene **6d** ($R_f = 0.37$, 0.072 g, 35%) as a white solid; an analytical sample, obtained by dissolution in ether, filtration on silica gel, evaporation to dryness and evacuation at room temperature (10^{-2} Torr), melted at 120–121 °C; $[\alpha]_D^{25} = -76.8$ (*c* 0.5, $CHCl_3$); IR 2952, 2900, 2862, 1684, 1643, 1607 cm^{-1}; ^1H NMR δ 0.92 (s, 18H), 1.55–1.60 (m, 4H), 1.74–1.80 (m, 4H), 1.97 (br s, 4H), 2.76 (br s, 2H), 3.97 (m, 2H), 4.10 (m, 2H), 4.25 (m, 2H); ^{13}C NMR δ 25.55 (t), 25.6 (t), 26.0 (q), 33.8 (s), 40.3 (d), 40.6 (d), 45.8 (d), 68.5 (t), 76.0 (d), 133.4 (s), 162.6 (s). MS: *m*/*z* (%) 410 [M^+], 353 (100), 326, 253, 57. Anal. Calcd for $C_{26}H_{38}N_2O_2$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.68; H, 9.65; N, 6.53.

(B) When the above reaction was performed with amino alcohol **4d** (0.293 g, 2.5 mmol) for 9 days, chromatographic workup of the crude product afforded compounds **5d** (0.075 g, 48%) and **6d** (0.105 g, 51%), identical with the species previously obtained.

4.3. Conversion of mono(oxazolines) 5a and 5d into bis(oxazolines) 6a and 6d

(A) Following the standard procedure, when a mixture of **5a** (0.148 g, 0.5 mmol), $ZnCl_2$ (0.007 g, 0.05 mmol) and amino alcohol **4a** (0.258 g, 2.5 mmol) in anhydrous PhCl (2.5 mL) was heated under reflux for 13 days, we succeeded in the isolation, by chromatographic workup (ethyl acetate), of compound **6a** ($R_f = 0.40$, 0.132 g, 69%).

(B) Operating as above, the crude product coming from reaction of **5d** (0.155 g, 0.5 mmol) with amino alcohol **4d** (0.293 g, 2.5 mmol) for 12 days was subjected to chromatographic resolution (petroleum ether/ethyl acetate 7:1 v/v → 2:1 v/v) affording, beside unreacted **5d** ($R_f = 0.41$, 0.078 g, 50%), bis(oxazoline) **6d** ($R_f = 0.37$, 0.101 g, 49%).

4.4. Transformation of 6d into 7

A solution of **6d** (0.042 g, 0.1 mmol) in $CDCl_3$ (0.5 mL) was allowed to stay at room temperature for 14 days to give 7-[(4*S*)-4-*tert*-butyl-2-oxazolin-2-yl]-8-[(1*S*)-1-hydroxymethyl-2,2-dimethylpropylcarbamoyl]-tetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene **7** (0.042 g, 98%), isolated by evaporation to dryness as a pale yellow sticky product. An analytical sample was obtained by washing with pentane and prolonged evacuation at room temperature (10^{-2} Torr). $[\alpha]_D^{23} = -68.2$ (*c* 0.25, $CHCl_3$); IR 3420, 3288, 2954, 2874, 1638, 1614 cm^{-1}; ^1H NMR δ 0.92 (s, 9H), 1.00 (s, 9H), 1.52–1.68 (m, 4H), 1.73–1.83 (m, 4H), 1.91–2.00 (m, 4H), 2.73 (br s, 1H), 2.96 (br s, 1H), 3.56 (dd, $J = 11.2$ and 8.8 Hz, 1H), 3.88 (dd, $J = 11.2$ and 3.2 Hz, 1H), 3.94–4.01 (m, 2H), 4.16–4.21 (m, 3H), 8.65 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR δ 25.5 (t), 25.6 (t), 25.65 (t), 25.7 (q), 26.0 (t), 27.0 (q), 33.5 (s), 33.9 (s), 39.7 (d), 40.1 (d), 40.6 (d), 40.9 (d), 44.8 (d), 45.25 (d), 60.8 (d), 63.2 (t), 68.3 (t), 75.45 (d), 128.6 (s), 142.8 (s), 163.2 (s), 168.1 (s). MS: *m*/*z* (%) 428 [M^+], 397, 371, 353, 312 (100), 254. Anal. Calcd for $C_{26}H_{40}N_2O_3$: C, 72.86; H, 9.41; N, 6.54. Found: C, 73.18; H, 9.65; N, 6.32.

4.5. {7,8-Bis[(4*S*)-4-isopropyl-2-oxazolin-2-yl]tetracyclo[7.3.0.0^{2,6}0^{5,10}]dodec-7-ene}zinc(II)chloride 8

A solution of bis-oxazoline **6a** (0.096 g, 0.25 mmol) in dry tetrahydrofuran (1.5 mL) was added to a solution of anhydrous $ZnCl_2$ (0.034 g, 0.25 mmol) in the same solvent (2.5 mL) and the resulting mixture was stirred at room temperature overnight. Evaporation to dryness of the pale yellow solution gave Zn(II) complex **8** (0.129 g, 99%) as white solid that was crystallized from diisopropyl ether/ethanol as colourless crystals: mp 259–260 °C; $[\alpha]_D^{23} = +58.2$ (*c* 0.25, $CHCl_3$); IR 2958, 2929, 2872, 1663, 1624 cm^{-1}; ^1H NMR δ 0.70 (d, $J = 6.9$ Hz, 6H), 0.83 (d, $J = 7.1$ Hz, 6H), 1.47–1.51 (m, 4H), 1.64–1.74 (m, 4H), 1.94–2.02 (m, 4H), 2.53 (heptd, $J = 7.0$ and 3.1 Hz, 2H), 2.59 (t, $J = 2.6$ Hz, 2H), 4.31–4.40 (m, 6H); ^{13}C NMR δ 14.4 (q), 18.6 (q), 25.55 (t), 25.6 (t), 29.6 (d), 40.3 (d), 40.5 (d), 45.6 (d), 69.3 (d), 69.5 (t), 135.2 (s), 166.1 (s). Anal. Calcd for $C_{24}H_{34}Cl_2N_2O_2Zn$: C, 55.56; H, 6.61; N, 5.40. Found: C, 55.18; H, 6.99; N, 5.02.

4.6. X-ray crystal structure determination for 8

Compound **8**: $C_{24}H_{34}Cl_2N_2O_2Zn$, $M = 518.8$, Orthorhombic, space group $P212121$, $a = 11.193(1)$, $b = 12.614(1)$, $c = 22.262(1)$ Å, $V = 3143.1(5)$ Å^3, $Z = 4$, $D_c = 1.096$, $\mu = 0.969$ mm^{-1}, $F(000) = 1088$. 9751 Reflections were collected with a $4.14 < \theta < 23.27$ range with a completeness to theta 98.5%; 4307 were independent, the parameters were 280 and the final *R* index was 0.0495 for reflections having $I > 2\sigma I$, and 0.1291 for all data. X-ray analysis was carried out with a Goniometer Oxford Diffraction KM4 Xcalibur2 at room temperature. Graphite-monochromated Mo/Kα radiation (40 mA/−40 kV) and a KM4 CCD/SAPPHIRE detector were used for cell parameter determination and data collection. The integrated intensities, measured using the ω scan mode, were corrected for Lorentz and polarization effects.[13] The substantial redundancy in data allows empirical absorption corrections (SADABS)[14] to be applied using multiple measurements of symmetry-equivalent reflections. The structure was solved by direct methods of SIR97[15] and refined using the full-matrix least squares on F^2 provided by SHELXL97.[16] The non-hydrogen atoms were refined anisotropically whereas

hydrogen atoms were assigned in calculated positions and refined as isotropic.

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