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Reactions of macrocyclic rhodium carbenoids: regioselective synthesis of indol-3-yl macrocyclic lactones and cryptands

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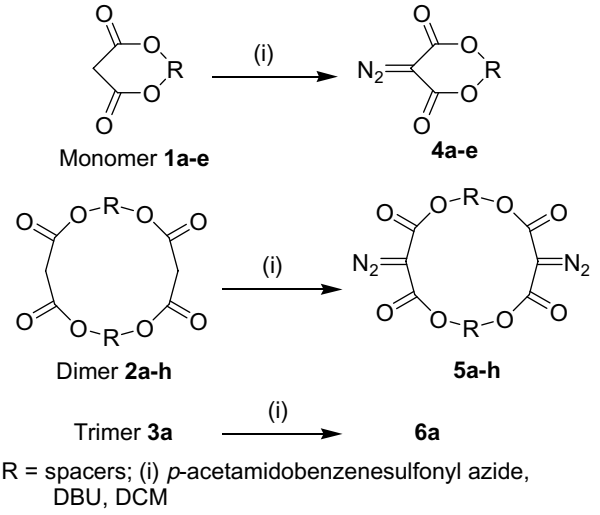
Abstract

A wide variety of new macrocyclic diazocarbonyl compounds with various spacers was synthesized. Macrocyclic rhodium(II) carbenoid insertion with various substituted indoles was performed to afford regioselectively, indol-3-yl macrocyclic di- or tetralactones (C3-alkylation). Double carbenoid insertion was also performed to afford indolyl cryptand molecules.

Keywords: Carbenoids; Cryptands; Diazo ketones; Macrocyclic lactones; Indoles; Rhodium(II) acetate

The reaction of α-diazocarbonyl compounds with rhodium(II) carboxylates is a well described method to generate rhodium carbenoids, which can undergo an array of reactions such as cyclopropanation, C–H or heteroatom–H insertion and ylide formation.[1] Carbenoid insertion reactions are important tools for C–C bond formation.[2] Generation of carbenoids and their insertion reactions with heterocyclic compounds, either intramolecularly[3] or intermolecularly,[4] has been described in the literature. However, the intermolecular carbenoid insertion is known to provide a mixture[4a–d] of products. Recently, the synthesis and the reactions of macrocyclic compounds has received a great deal of attention due to their large number of applications.[5] Some macrocyclic diazocarbonyl compounds have been used for the study of molecular mousetraps[6] and host–guest complexations.[7] In continuation of our research on macrocyclic lactones[8] and cryptands,[9] herein we report the regioselective intermolecular alkylation/insertion of macrocyclic metallo-carbenoids furnishing a range of indolyl macrocyclic di- or tetralactones and cryptands.

We began our efforts with the synthesis of macrocyclic mono-, bis- or tris-diazocarbonyl compounds. Initially, the reaction of malonyl chloride with tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), hexa(ethylene glycol) or 1,8-octanediol was carried out to furnish[5c] the respective monomers **1a–e**, dimers **2a–e** and trimers **3a–e** (Scheme 1). Similar methods were followed to synthesize macrocycles **2f–h** using ethylene glycol, diethylene glycol



Scheme 1. Synthesis of macrocyclic diazocarbonyl compounds.

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or 1,6-hexanediol, respectively. Further, active methylene compounds **1a**, **2a** and **3a** were treated with 4-acetamidobenzenesulfonyl azide in the presence of DBU to afford the corresponding mono-,[10] bis-[11] and tris-diazocarbonyl compounds **4a**, **5a** and **6a**, respectively (Scheme 1). The mono-diazocarbonyl compounds **4b–d**, 3-diazo-1,5-dioxacyclotridecane-2,4-dione **4e** and bis-diazocarbonyl compounds **5b–h** (Fig. 1) were synthesized successfully using the method described above. These macrocyclic diazocarbonyl compounds **4–6** were fully characterized based on the spectral data.

Next, carbenoid insertion reactions of mono-diazocarbonyl compounds with N-substituted or unsubstituted indoles were performed.[12] The macrocyclic diazo compound **4b** was reacted with indole using 2 mol % of rhodium(II) acetate as catalyst in dry DCM at reflux to afford the respective indol-3-yl macrocyclic dilactone **7a** in 66% yield (Scheme 2 and Table 1). Further, the C-alkylation of indole occurred regioselectively.[4e,f]

Subsequently, the macrocyclic diazo compound **4b** was reacted with 5-bromoindole and 5-nitroindole to afford the respective indol-3-yl macrocyclic dilactones **7b** and **7c** in 80% and 61% yields. This interesting result led us to synthesize libraries of indol-3-yl macrocyclic dilactones. Thus, the diazocarbonyl compounds **4a**,**b**,**e** were treated with *N*-methylindole to furnish the corresponding 1-methylindol-3-yl macrocyclic dilactones **7d–f** in good yields. The reaction of **4b** with *N*-benzylindole afforded the respective

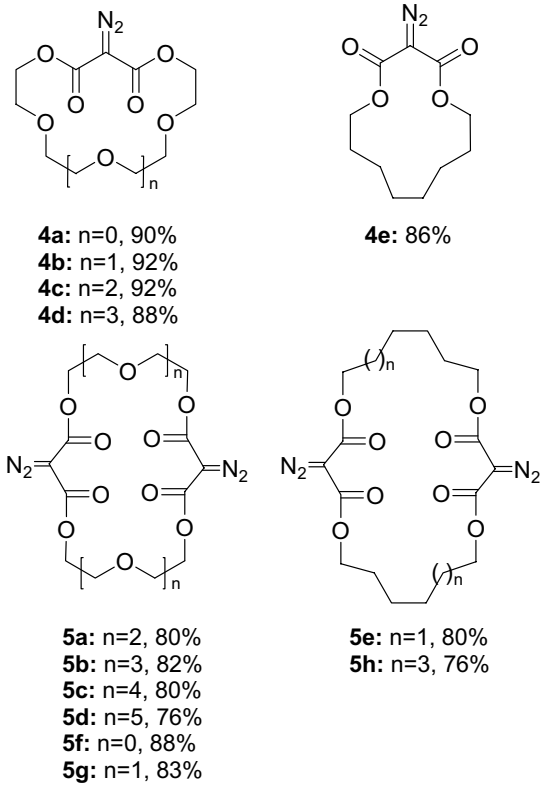
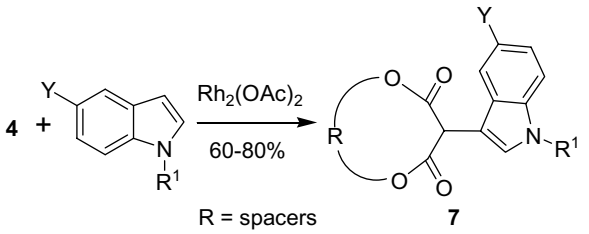


Fig. 1. Synthesized macrocyclic diazocarbonyl compounds.



Scheme 2. Reaction of macrocyclic carbenoids with substituted indoles.

Table 1
Synthesis of indol-3-yl macrocyclic dilactones via Scheme 2

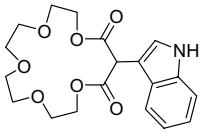
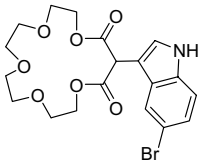
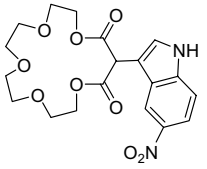
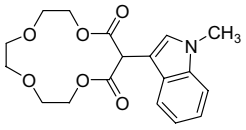
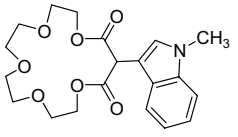
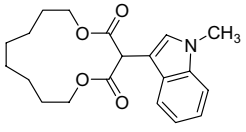
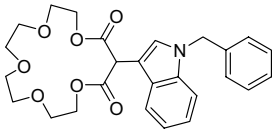
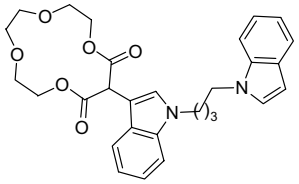
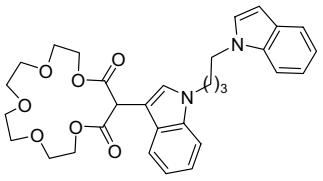
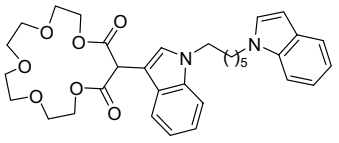
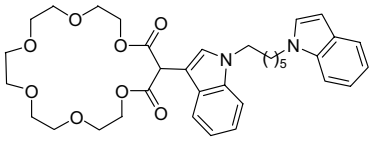
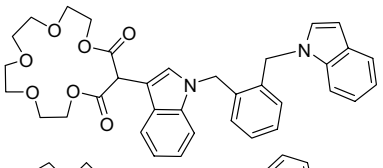
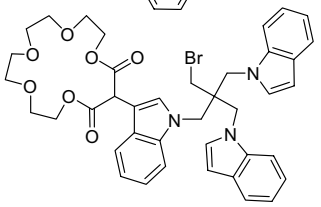
Entry	Diazocarbonyl compound	Indol-3-yl macrocyclic dilactone **7**	Yield[a] (%)
1	**4b**		66 (**7a**)
2	**4b**		80 (**7b**)
3	**4b**		61 (**7c**)
4	**4a**		70 (**7d**)
5	**4b**		72 (**7e**)
6	**4e**		76 (**7f**)
7	**4b**		74 (**7g**)
8	**4a**		75 (**7h**)

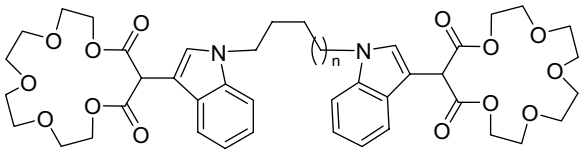
Table 1 (*continued*)

Entry	Diazocarbonyl compound	Indol-3-yl macrocyclic dilactone **7**	Yield[a] (%)
9	**4b**		73 (**7i**)
10	**4b**		78 (**7j**)
11	**4c**		82 (**7k**)
12	**4b**		66 (**7l**)
13	**4b**		60 (**7m**)

[a] Yields are unoptimized and refer to isolated pure compound.

1-benzylindol-3-yl macrocyclic dilactone **7g**. Reaction of an equimolar quantity of 13-membered macrocyclic diazocarbonyl compound **4a** and 1,1′-butane-1,4-diylbis(1*H*-indole) afforded the corresponding C3-alkylation product **7h** in 75% yield. Similar reactions of **4b** or **4c** with 1,1′-butane-1,4-diylbis(1*H*-indole), 1,1′-hexane-1,6-diylbis(1*H*-indole) or 1,1′-[1,2-phenylenbis(methylene)]-bis(1*H*-indole) furnished the respective indol-3-yl macrocyclic dilactones **7i**–**l**. Further, the tris-indole product **7m** was obtained from the reaction of **4b** and the corresponding tris-indole. All the products showed a characteristic singlet around δ 5 ppm and the absence of the indole 3-CH proton which confirmed the C3-alkylation reaction of the macrocyclic diazocarbonyl compounds.

Encouraged by the above results, we envisaged the formation of two C–C bonds via a double carbenoid insertion reaction.[13] To this end, 1 equiv of 1,1′-butane-1,4-diylbis(1*H*-indole) or 1,1′-hexane-1,6-diylbis(1*H*-indole) was reacted with 2.5 equiv of macrocyclic diazocarbonyl compound **4b** in the presence of 2 mol % of $Rh_2(OAc)_4$ as catalyst under reflux to furnish the respective bis-crown compounds **8a**,**b**, (Fig. 2) and a minor amount (20–25%) of mono alkylated products **7i**,**j**. The structures of products **8** were confirmed from spectral data.



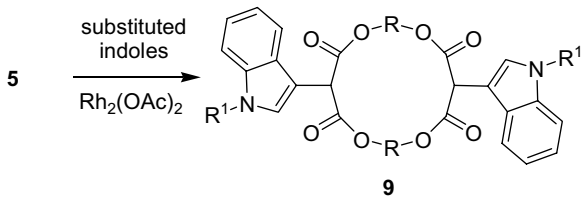
8a: n=1, 42%
8b: n=3, 40%

Fig. 2. Synthesis of bis-crown ethers **8** via double-carbenoid insertion.

Next, the double C-alkylation of bis-diazocarbonyl compounds with substituted indoles was investigated.[14] Thus, the reaction of macrocyclic bis-diazo compound **5a** with excess *N*-methylindole or *N*-benzylindole was performed at reflux to afford the corresponding bis-indol-3-yl macrocyclic tetralactones **9a**,**b** in moderate yields (Scheme 3 and Table 2). The macrocyclic bis-diazocarbonyl compounds **5f**,**g** were reacted with excess *N*-benzylindole or *N*-methylindole to afford the bis-indol-3-yl macrocyclic tetralactones **9c**–**e** in moderate yields. Similarly, the bis-diazocarbonyl compounds **5e**,**h** were reacted with excess *N*-methylindole to afford the corresponding double C3-alkylation products **9f**,**g**.

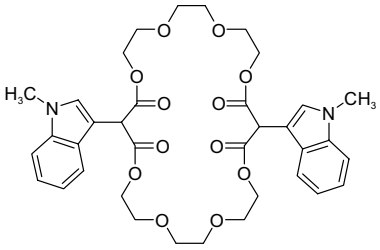
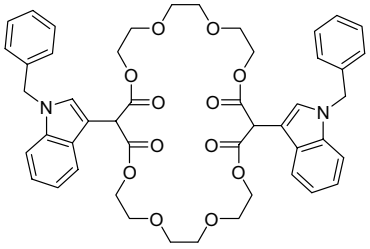
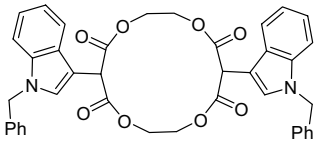
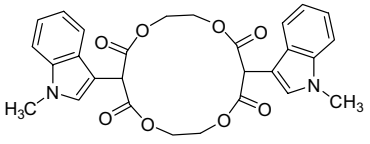
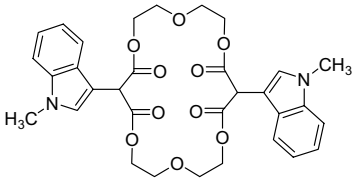
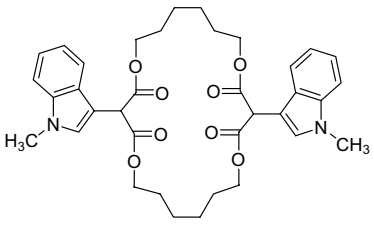
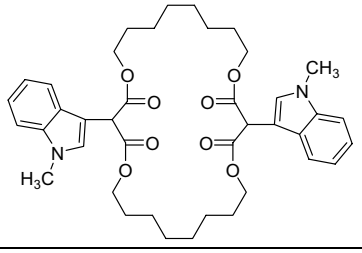
Finally, we envisaged the synthesis of cryptands based on the above intermolecular carbenoid insertion strategy.[15] Towards this, an equimolar amount of the bis-diazocarbonyl compound **5e** and 1,1′-butane-1,4-diylbis(1*H*-indole) were refluxed in dry benzene and then column chromatographic purification furnished cryptand **10** in 30% yield (Fig. 3) via intermolecular double carbenoid insertion. Similarly, the reaction of the bis-diazocarbonyl compound **5g** with 1,1′-(1,2-phenylenbis(methylene))-bis(1*H*-indole) afforded the respective cryptand **11** in 32% yield. Mechanistically, all the above reactions might proceed via a zwitterionic intermediate[4a,b,e] to afford the C3-alkylation product regioselectively.

In conclusion, we have synthesized several mono- and bis-diazo macrocyclic compounds and demonstrated their regioselective intermolecular carbenoid insertion reactions affording a range of indol-3-yl macrocyclic dilactones. Intermolecular double carbenoid insertion was performed with either mono- or bis-diazocarbonyl compounds. The advantage of the intermolecular double alkylation methodology was demonstrated by achieving the synthesis of indolyl cryptands for the first time. A supramolecular study of the above synthesized macrocycles is under progress in our laboratory.



Scheme 3. Reaction of bis-diazocarbonyl compounds with indoles.

Table 2
Synthesis of indol-3-yl macrocyclic tetralactones via Scheme 3

Entry	Diazocarbonyl compound	Indol-3-yl macrocyclic dilactone **9**	Yield[a] (%)
1	**5a**		42 (**9a**)
2	**5a**		40 (**9b**)
3	**5f**		50 (**9c**)
4	**5f**		52 (**9d**)
5	**5g**		44 (**9e**)
6	**5e**		53 (**9f**)
7	**5h**		56 (**9g**)

[a] Yields are unoptimized and refer to isolated pure compound.

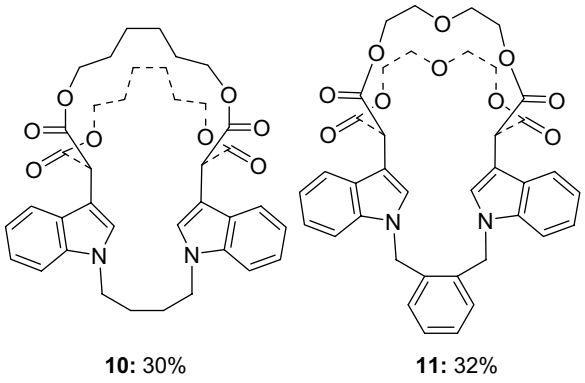


Fig. 3. Synthesis of indolyl cryptands via double carbenoid insertion.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.102.

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Synlett **2005**, 2611–2614; (g) Bradshaw, J. S.; Maas, G. E.; Izatt, R. M.; Christensen, J. J. *Chem. Rev.* **1979**, *79*, 37–52; (h) Masamune, S.; Bates, S. G.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585–607. and references cited therein.

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9. Muthusamy, S.; Gnanaprakasam, B. *Tetrahedron Lett.* **2007**, *48*, 6821–6824.
10. *General procedure for the synthesis of macrocyclic diazocarbonyl compounds* **4**: To a solution containing macrocyclic dilactone **1** (1 mmol) and 4-acetamidobenzenesulfonyl azide (1.2 mmol) in dry dichloromethane (50 mL) was added DBU (1.5 mmol) under an argon atmosphere and the reaction stirred at room temperature overnight. To the reaction mixture, water (150 mL) was added and the aqueous extracted with DCM (3×100 mL). The organic layers were combined, washed with water (2×200 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure at room temperature and the residue subjected to short silica gel column chromatography to obtain the respective pure diazo ketones **4**.
11. *General procedure for the synthesis of macrocyclic diazocarbonyl compounds* **5**: To a solution containing macrocyclic tetralactone **2** (0.5 mmol) and 4-acetamidobenzenesulfonyl azide (1.25 mmol) in dry dichloromethane (100 mL) was added DBU (1.5 mmol) under an argon atmosphere and the reaction stirred at room temperature overnight. Water (150 mL) was added and the aqueous extracted with DCM (3×100 mL). The combined organic layers were washed with water (2×200 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure at room temperature and the residue subjected to short silica gel column chromatography to afford the respective pure macrocyclic diazocarbonyl compounds **5**.
12. *General procedure for the synthesis of indol-3-yl macrocyclic dilactones* **7**: To an oven-dried flask, macrocyclic diazocarbonyl compound **4** (0.5 mmol) and substituted indole (0.6 mmol) in dry benzene or DCM (50 mL) were added under an inert atmosphere. To the above reaction mixture, 2 mol % of rhodium(II) acetate was added and the mixture refluxed for 4 h. Progress of the reaction was monitored by TLC. On completion, the solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective indol-3-yl macrocyclic dilactones **7**. Selected spectral data. *15-(1H-Indol-3-yl)-1,4,7,10,13-pentaoxacyclohexadecane-14,16-dione* **7a**: White solid; mp 105–108 °C; ν_{max} (KBr)/cm^{-1} 3383, 3264, 2873, 1748, 1458, 1289, 1251, 1132, 1106, 741. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.75 (s, 1H, N*H*), 7.64 (d, 1H, Arom-*H*, $J = 2$ Hz), 7.59–7.07 (m, 4H, Arom-*H*), 5.01 (s, 1H, C*H*), 4.52–4.03 (m, 4H, OCH_2), 3.76–3.69 (m, 12H, OCH_2). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 168.5 (*C*=O), 135.9 (quat-*C*), 124.7 (=*C*H), 122.0 (=*C*H), 119.8 (=*C*H), 119.1 (=*C*H), 111.4 (=*C*H), 106.7 (quat-*C*), 103.4 (quat-*C*), 70.5 (O*C*H$_2$), 70.3 (O*C*H$_2$), 68.7 (O*C*H$_2$), 64.6 (O*C*H$_2$), 49.6 (*C*H). HRMS (ESI$^+$) calcd for $C_{19}H_{23}NO_7Na$ (M+Na)$^+$: 400.1372, found 400.1381. *15-(1-Methyl-1H-indol-3-yl)-1,4,7,10,13-pentaoxacyclohexadecane-14,16-dione* **7e**: White solid; mp 91–93 °C; ν_{max} (KBr)/cm^{-1} 3053, 2910, 2875, 1724, 1475, 1277, 1255, 1221, 1142, 1117, 1107, 749. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.66 (d, 1H, Arom-*H*, $J = 4$ Hz), 7.30–7.12 (m, 4H, Arom-*H*), 5.03 (s, 1H, C*H*), 4.53–4.42 (m, 2H, OCH_2), 4.21–4.12 (m, 2H, OCH_2), 3.76–3.59 (m, 15H, OCH_2 and NCH_3). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 168.3 (*C*=O), 136.6 (quat-*C*), 128.7 (=*C*H), 126.9 (quat-*C*), 121.7 (=*C*H), 119.4 (=C*H*), 119.1 (=*C*H), 109.2 (=*C*H), 105.4 (quat-*C*), 70.6 (O*C*H$_2$), 70.3 (O*C*H$_2$), 68.6 (O*C*H$_2$), 64.6 (O*C*H$_2$), 49.4 (N*C*H$_3$), 32.7 (*C*H). HRMS (ESI$^+$) calcd for $C_{20}H_{25}NO_7Na$ (M+Na)$^+$: 414.1529, found 414.1513.
13. *General procedure for the synthesis of bis-indol-3-yl crown compounds* **8**: To an oven-dried flask, 1,1′-butane-1,4-diylbis(1*H*-indole) or 1,1′-hexane-1,6-diylbis(1*H*-indole) (0.3 mmol) and 2 mol % of rhodium(II) acetate in dry benzene or DCM (100 mL) were charged under an inert atmosphere and refluxed. To the above refluxing mixture, macrocyclic diazocarbonyl compound **4** (0.75 mmol) in dry benzene or DCM was added slowly over 1 h using a syringe pump and the mixture refluxed for 6 h. Progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue was purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective bis C–H insertion products **8**. *Bis-indol-3-yl macrocyclic dilactones* **8a**: White solid; mp 128–132 °C; ν_{max} (KBr)/cm^{-1} 2928, 2879, 1739, 1468, 1353, 1291, 1220, 1140, 754. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.68–7.64 (d, 2H, Arom-*H*, $J = 4$ Hz), 7.30–7.12 (m, 8H, Arom-*H*), 5.02 (s, 2H, C*H*), 4.51–4.41 (m, 4H, OCH_2), 4.20–4.03 (m, 8H, OCH_2 and NCH_2), 3.76–3.69 (m, 24H, OCH_2), 1.84 (t, 4H, CH_2). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 168.3 (*C*=O), 135.8 (quat-*C*), 127.8 (=*C*H), 127.1 (quat-*C*), 121.8 (=*C*H), 119.6 (=*C*H), 119.4 (=C*H*), 109.4 (=*C*H), 105.8 (quat-*C*), 70.6 (O*C*H$_2$), 70.3 (O*C*H$_2$), 68.7 (O*C*H$_2$), 64.6 (O*C*H$_2$), 49.5 (*C*H), 45.9 (N*C*H$_2$), 27.5 (*C*H$_2$). HRMS (ESI$^+$) calcd for $C_{42}H_{53}N_2O_{14}Na$ (M + H + Na)$^+$: 832.3395, found 832.3331. *Bis-indol-3-yl macrocyclic dilactones* **8b**: White solid; mp 168–170 °C; ν_{max} (KBr)/cm^{-1} 3050, 2930, 2876, 1734, 1466, 1274, 1248, 1222, 1132, 743. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.66–7.61 (m, 2H, Arom-*H*), 7.58–7.00 (m, 8H, Arom-*H*), 5.03 (s, 2H, C*H*), 4.53–3.98 (m, 12H, OCH_2 and NCH_2), 3.78–3.61 (m, 24H, OCH_2), 1.80–1.74 (m, 4H, CH_2), 1.31–1.25 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 168.4 (*C*=O), 135.8 (quat-*C*), 127.8 (=*C*H), 127.2 (quat-*C*), 121.7 (=*C*H), 119.5 (=*C*H), 119.4 (=C*H*), 109.2 (=*C*H), 105.7 (quat-*C*), 70.6 (O*C*H$_2$), 70.4 (O*C*H$_2$), 68.7 (O*C*H$_2$), 64.6 (O*C*H$_2$), 49.4 (*C*H), 46.0 (N*C*H$_2$), 29.8 (*C*H$_2$), 26.3 (*C*H$_2$). HRMS (ESI$^+$) calcd for $C_{44}H_{56}N_2O_{14}Na$ (M+Na)$^+$: 859.3629, found 859.3588.
14. *General procedure for the synthesis of bis(indol-3-yl) macrocyclic tetralactones* **9**: To an oven-dried flask, bis-diazocarbonyl compound **5** (0.3 mmol) and substituted indole (0.7 mmol) in dry benzene or DCM (100 mL) were charged under an inert atmosphere. To the above reaction mixture, 2 mol % of rhodium(II) acetate was added and the mixture refluxed for 6 h. Progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective bis(indol-3-yl) macrocyclic tetralactones **9**. *12,25-Bis-(1-methyl-1H-indol-3-yl)-1,4,7,10,14,17,20,23-octaoxacyclohexacosane-11,13,24,26-tetraone* **9a**: Brown thick oil; ν_{max} (neat)/cm^{-1} 3057, 2946, 2874, 1746, 1471, 1333, 1142, 735. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.61 (d, 2H, Arom-*H*, $J =$ 8 Hz), 7.25–7.10 (m, 8H, Arom-*H*), 5.00 (s, 2H, C*H*), 4.28 (m, 8H, OCH_2), 3.71–3.62 (m, 16H, OCH_2), 3.52 (s, 6H, NCH_3). ^{13}C NMR (CD_3OD, 50.3 MHz) δ 169.0 (*C*=O), 137.3 (quat-*C*), 129.3 (quat-*C*), 127.5 (=*C*H), 122.4 (=CH), 120.1 (=*C*H), 119.7 (=CH), 109.9 (quat-*C*), 70.9 (O*C*H$_2$), 69.3 (O*C*H$_2$), 65.3 (OCH$_2$), 49.9 (*C*H), 33.3 (N*C*H$_3$). HRMS (ESI$^+$) calcd for $C_{36}H_{42}N_2O_{12}Na$ (M+Na)$^+$: 717.2635, found 717.2702.
15. *General procedure for the synthesis of indolyl cryptands* **10**, **11**: To an oven dried flask, bis-diazocarbonyl compound **5e**, **g** (0.3 mmol) and 1,1′-(1,2-phenylenbis(methylene))-bis(1*H*-indole) or 1,1′-butane-1,4-diylbis(1*H*-indole) (0.3 mmol) in dry benzene (100 mL) were charged under an inert atmosphere. To the above reaction mixture, 2 mol % of rhodium(II) acetate was added and the mixture refluxed for 6 h. Progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective cryptands **10** or **11**. *Bis-indol-3-yl cryptand* **10**: Brown thick oil; ν_{max} (neat)/cm^{-1} 2930, 1730, 1465, 1144, 911, 731. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.58 (d, 2H, Arom-*H*), 7.36–7.01 (m, 8H, Arom-*H*), 5.00 (s, 2H, C*H*), 4.22–4.09 (m, 12H, OCH_2, NCH_2), 1.95–1.35 (m, 20H, CH_2). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 168.3 (*C*=O), 135.5 (quat-*C*), 127.6 (=*C*H), 127.3 (quat-*C*), 126.7

(=*C*H), 121.9 (=*C*H), 121.4 (=*C*H), 120.9 (=*C*H), 119.6 (=*C*H), 119.2 (=C*H*), 118.4 (=*C*H), 109.4 (=*C*H), 109.2 (=*C*H), 106.5 (quat-*C*), 65.1 (O*C*H_2), 50.3 (*C*H), 45.7 (N*C*H_2), 28.5 (*C*H_2), 28.3 (*C*H_2), 27.9 (*C*H_2), 27.6 (*C*H_2), 27.1 (*C*H_2), 25.6 (*C*H_2), 24.9 (*C*H_2), 24.6 (*C*H_2). HRMS (ESI^+) calcd for $C_{38}H_{44}N_2O_8Na$ $(M+Na)^+$: 679.2995, found 679. 2901. *Bis-indol-3-yl cryptand* **11**: Brown solid; mp 218–220 °C (decomposition); ν_{max} (neat)/cm^{-1} 3055, 2932, 1734, 1464, 1305, 1282, 1144, 910, 730. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.67–6.91 (m, 14H, Arom-*H*), 5.19 (s, 4H, NCH_2), 5.06 (s, 2H, C*H*), 4.44–4.12 (m, 8H, OCH_2), 3.67–3.46 (m, 8H, OCH_2). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 168.0, 135.1, 134.7, 129.4, 128.7, 127.8, 127.0, 122.4, 120.2, 118.3, 109.8, 106.9, 68.8, 64.8, 50.5, 48.1. HRMS (ESI^+) calcd for $C_{38}H_{36}N_2O_{10}Na$ $(M+Na)^+$: 703.2268, found 703.2283.