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Diastereoselective synthesis of macrocycles incorporating the spiro-indolofurans and -indolodioxolanes

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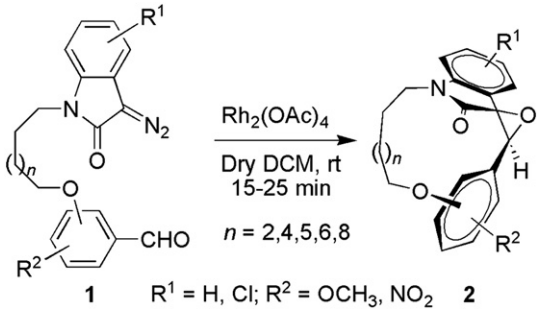
ABSTRACT

Generation of intramolecular macrocyclic carbonyl ylides from aldehyde group tethered to diazoamides in the presence of rhodium(II) acetate and their successful [3+2]-cycloaddition afforded the corresponding macrocycles incorporating spiro-indolofurans, -indolofuropyrroles, -indolofurofurans, and -indolodioxolanes in moderate to good yield with complete diastereoselectivity. The competition between the electrocyclization and [3+2]-cycloaddition reactions of macrocyclic carbonyl ylides was also demonstrated.

1. Introduction

Diazocarbonyl compounds find widespread applications in organic chemistry[1] especially in tandem processes and natural product synthesis.[2] The continual upsurge in molecular complexity and diversity in the natural product systems urges chemist to increase tools of their arsenal. The 1,3-dipolar cycloaddition reactions are appropriate potential tools for synthetic chemists to increase the efficacy, atom economy, selectivity, and complexity in a particular process. Metallocarbenoids can be generated from diazocarbonyl compounds that react with a series of functional groups,[3] whereby subsequent reactions can occur. The intramolecular generation of carbonyl ylides and their subsequent reactions are studied well, which constituted an important method for tetrahydrofuran systems and also applied for the synthesis of many natural products.[2a,4] Heterocyclic spiro compounds[5] occupy a key place among the various classes of organic molecules. Especially, the oxindole moiety constitutes a key structural element in several natural products,[6] including the antibiotic speradine[7] and the cytostatic welwistatin.[8] Consequently, the development of novel synthetic strategies leading to 3,3-disubstituted oxindole derivatives is of paramount importance. Synthesis of macrocycles via cyclopropanation[9] or insertion[10] reactions has been explained but there is no report[11] for the formation of macrocycles via carbonyl ylide as a dipole. Aromatic aldehyde tethered to diazoamides **1** in the presence of rhodium(II) acetate afforded the spiro-indolooxiranes **2** via generation of macrocyclic carbonyl ylide followed by a conrotatory electrocyclization[11] process (Scheme 1). As a part of our ongoing research on the carbonyl ylides[12] and supramolecular systems,[13] we herein demonstrate the new macrocycles incorporating spiro-indolofurans, -indolofuropyrroles, -indolofurofurans, and -indolodioxolanes by trapping the macrocyclic carbonyl ylides with alkyne, alkene or aldehyde as a dipolarophile.



Scheme 1. Synthesis of macrocyclic spiro-oxiranes **2**.

2. Results and discussion

Initially, the substrates having aldehyde functionality tethered to diazo functional group were planned. Toward this, O-alkylation

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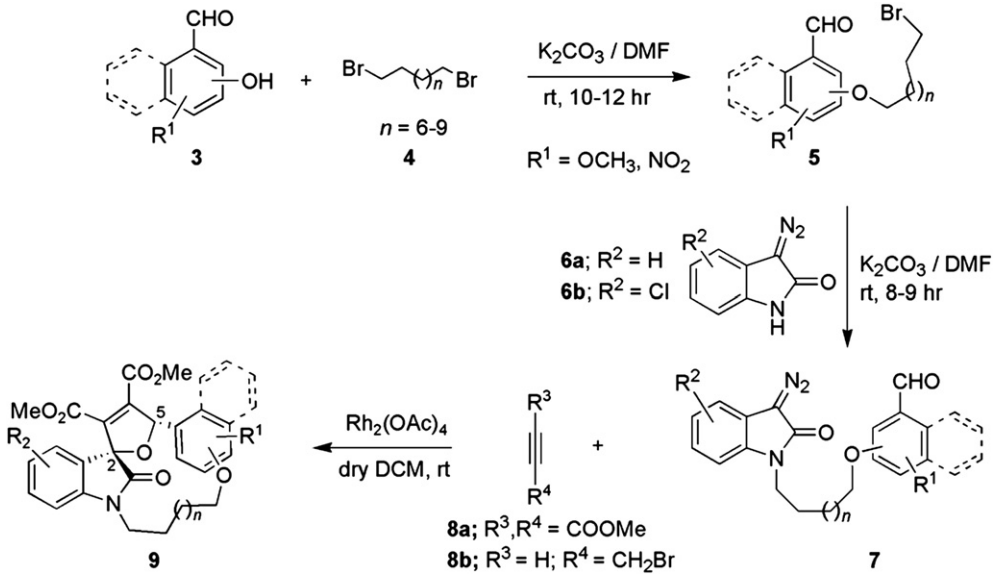
of 2-hydroxybenzaldehyde with 1,9-dibromononane was performed to furnish the corresponding bromobenzaldehyde **5a**. Subsequent N-alkylation of 3-diazooxindoles **6** with **5a** in the presence of potassium carbonate/DMF afforded the corresponding cyclic diazoamide **7a** in very good yield.

Reaction of diazoamide **7a** and dimethyl acetylenedicarboxylate (DMAD, **8a**) in the presence of 1.3 mol % of rhodium(II) acetate in dry DCM under argon atmosphere smoothly afforded the corresponding macrocycle **9a** in 60% yield as a single diastereomer (Scheme 2, entry a, Table 1). No other byproducts were observed. The ^{1}H NMR spectrum of **9a** revealed the presence of a singlet at δ 6.97 ppm for OCH proton. Furthermore, ^{13}C and DEPT-135 experiments disclosed the presence of a characteristic quaternary carbon (C2) at δ 89.29 ppm and a CH (C5) signal at 81.71 ppm, which unequivocally confirms the formation of the spiro-indolofuran unit. All other signals in ^{13}C spectrum are due to nine CH_2 carbons and eight CH carbons present (due to symmetry) with the assigned structure. The above reaction was carried out using different solvents, such as DCM, benzene or toluene at room temperature or reflux conditions and optimized using dry DCM at room temperature condition to afford the macrocycle **9a**.

diazoamide **7b** yielded the macrocycle **2** incorporating spiro-indolooxirane via electrocyclization[11] when propargyl bromide (**8b**) was used as the dipolarophile. Based on the above study, the electron-deficient dipolarophile favor the formation of spiro-indolofuran **9**.

After demonstrating the generation of macrocyclic carbonyl ylides and their successful trapping experiments with DMAD, the use of alkenes as a dipolarophile was planned. Toward this, a variety of alkenes, such as *N*-phenylmaleimide (NPM), maleic anhydride or cyclooctadiene were employed to afford the corresponding macrocyclic compounds incorporating the spiro-indole unit. Reaction of diazoamide **7b** (see the Table 2) and NPM in the presence of 1.3 mol % of rhodium(II) acetate in dry DCM under argon atmosphere furnished macrocycle **10a** incorporating the spiro-indolofuropyrrole in 65% as a single isomer (Scheme 3). ^{1}H, ^{13}C-Spectra confirm the formation of spiro-indolofuropyrrole ring system. A variety of spacers and substituents were made on diazoamides **7d**,**h**,**i** under similar conditions furnished the corresponding macrocycles **10b**–**d** in moderate yield (Table 2). The reaction of diazoamides **7** was planned with maleic anhydride to furnish the corresponding macrocycles **11** incorporating spiro-



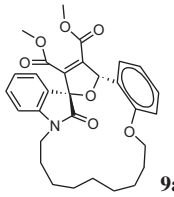
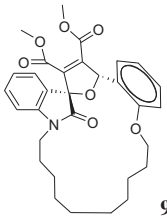
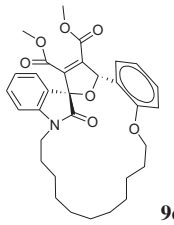
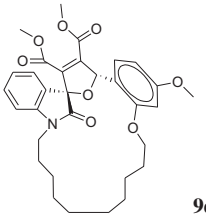
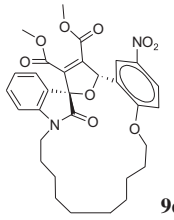
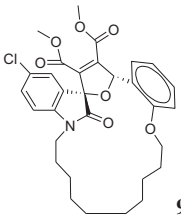
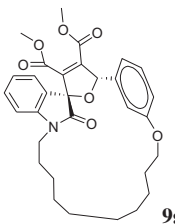
Scheme 2. Synthesis of macrocycles incorporating spiro-indolofurans **9**.

Stimulated by this result, spacer length modifications between diazo and aldehyde functionalities were planned. Thus, compounds **5b**,**c** having the respective spacer length (n=7,8) underwent N-alkylation to yield the corresponding diazoamides **7b**,**c**. Reaction of diazoamides **7b**,**c** and DMAD (**8a**) in the presence of rhodium(II) acetate catalyst as described above afforded the corresponding macrocycles **9b**,**c** in moderate yield as a single diastereomer. Next, reaction of diazoamides **7d**–**f** having electron-donating or -withdrawing substituent was performed under similar conditions to obtain the macrocycles **9d**–**f** in moderate yield. The presence of electron-donating substituent on diazoamide gave better yield than -withdrawing substituent and the results are illustrated in Table 1. Representatively, the structure of spiro-macrocyclic compound **9e** was confirmed by the single crystal X-ray analysis[14] (Fig. 1) and observed that the alkyl chain having C11–17 atoms have high thermal vibration. Based on the stereochemistry of **9e**, the similar stereochemistry was tentatively assigned for other products obtained in this reaction. Reaction of diazoamides having *meta*-substituted benzaldehyde **7g** or *ortho*-substituted naphthaldehyde **7h**,**i** furnished products in moderate yield. Reaction of indolofurofuran unit. Thus, reaction of diazoamides **7b**,**h** with maleic anhydride furnished the macrocycles **11a**,**b** (Table 2). However, reaction of **7b** and electron-rich cyclooctene as a dipolarophile afforded the spiro-indolooxirane **2**.

Next, our effort was invested to examine the trapping of macrocyclic carbonyl ylides with carbonyl group as a dipolarophile. Toward this, reaction of diazoamide **7b** (see the Table 1) and *p*-nitrobenzaldehyde in the presence of 1.3 mol % of $Rh_2(OAc)_4$ was carried out to give the corresponding macrocycle **13a** having spiro-indolodioxolane unit in moderate yield as a single isomer with complete diastereoselectivity (Scheme 4). The stereochemistry of the macrocyclic compound **13a** was confirmed by the single crystal X-ray analysis[14] (Fig. 2) and observed that the alkyl chain having C11–17 atoms have high thermal vibration. Similarly, other derivatives of macrocycles **13b**,**c** were also synthesized and the results are illustrated in Table 3. It is interesting to note that the opposite diasteroisomer[12a] of spiro-dioxolanes **13** was obtained via intramolecular carbonyl ylides.

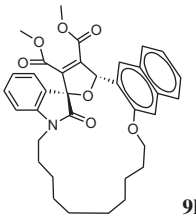
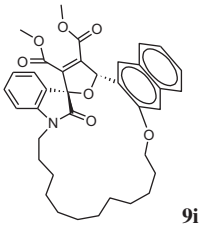
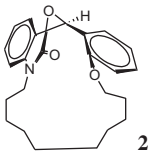
Mechanistically, it is proposed that the electron-deficient carbenoid carbon of rhodium(II) carbenoids **14** reacts with the

Table 1
Trapping of macrocyclic carbonyl ylides with DMAD

Entry	Aldehyde **3**	*n*	R^1	R^2	Diazoamide **7**	Product **9**	Yield[a] (%)
1	2-Hydroxybenzaldehyde	6	H	H	**7a**	 **9a**	60
2	2-Hydroxybenzaldehyde	7	H	H	**7b**	 **9b**	65
3	2-Hydroxybenzaldehyde	8	H	H	**7c**	 **9c**	63
4	2-Hydroxybenzaldehyde	7	4-OCH_3	H	**7d**	 **9d**	70
5	2-Hydroxybenzaldehyde	7	3-NO_2	H	**7e**	 **9e**	62
6	2-Hydroxybenzaldehyde	7	H	Cl	**7f**	 **9f**	63
7	3-Hydroxybenzaldehyde	7	H	H	**7g**	 **9g**	65

(*continued on next page*)

Table 1 (*continued*)

Entry	Aldehyde **3**	*n*	R^1	R^2	Diazoamide **7**	Product **9**	Yield[a] (%)
8	2-Hydroxynaphthaldehyde	7	H	H	**7h**	 **9h**	68
9	2-Hydroxynaphthaldehyde	9	H	H	**7i**	 **9i**	62
10[b]	2-Hydroxybenzaldehyde	7	H	H	**7b**	 **2**	70

[a] Isolated yield.
[b] Propargyl bromide was used as a dipolarophile; reactions were performed by addition of diazoamide **7** (1 equiv) and DMAD **8** (1.3 equiv) in the presence of 1.3 mol % of $Rh_2(OAc)_4$ in dry DCM (15 mL) at room temperature 15–20 min duration.

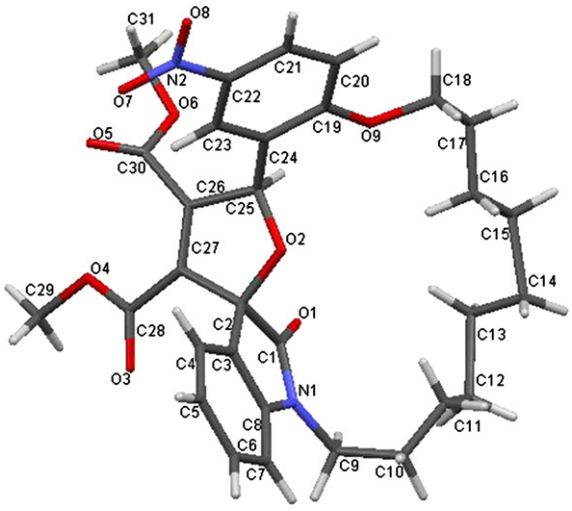
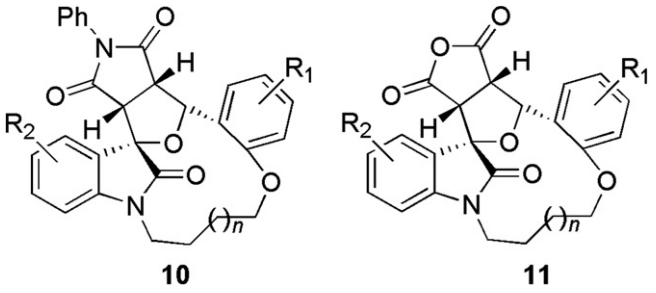


Fig. 1. Crystal structure of spiro-indolofuran **9e**.

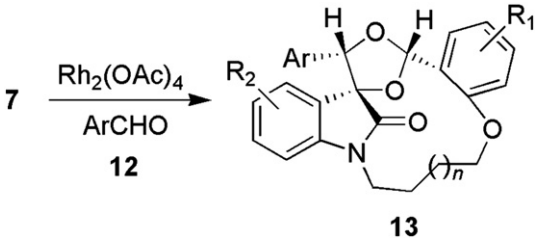
Table 2
Trapping of macrocyclic ylides with alkenes

Entry	Diazoamide **7**	Dipolarophile	Product (yield[a] %)
1	**7b**	NPM	**10a** (65%)
2	**7d**	NPM	**10b** (68%)
3	**7h**	NPM	**10c** (65%)
4	**7i**	NPM	**10d** (60%)
5	**7b**	Maleic anhydride	**11a** (59%)
6	**7h**	Maleic anhydride	**11b** (56%)
7	**7b**	Cyclooctene	**2** (70%)

[a] Isolated yield. Reactions were performed by addition of diazoamide **7** (1 equiv) and NPM/maleic anhydride (1.3 equiv) in the presence of 1.3 mol % of $Rh_2(OAc)_4$ in dry DCM (15 mL) at room temperature 15–25 min duration.



Scheme 3. Synthesis of spiro-indolofuropyrroles **10** and -indolofurofurans **11**.



Scheme 4. Synthesis of spiro-indolodioxolanes **13**.

remotely placed oxygen atom of the aromatic aldehyde functionality affording the interesting macrocyclic carbonyl ylides **15** (Scheme 5) in an intramolecular manner. From the observed stereochemistry of the products, the conformation of the most favorable carbonyl ylide intermediate **15** was proposed. Thus, the carbonyl ylide **15** might be stabilized by intramolecular hydrogen bonding interaction forming a six-membered[12a] transition state. Subsequently, 1,3-dipolar cycloaddition reaction of carbonyl ylides

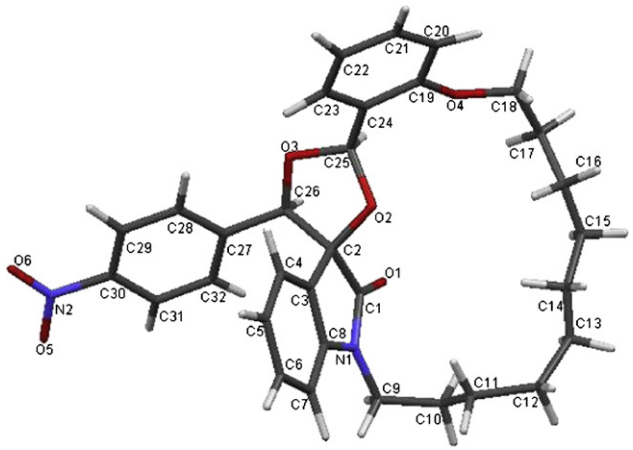


Fig. 2. Crystal structure of spiro-indolodioxolane **13a**.

Table 3
Trapping of macrocyclic ylides with aldehydes

Entry	Diazoamide	ArCHO	Product (yield[a] %)
1	**7b**	*p*-Nitrobenzaldehyde (**12a**)	**13a** (55%)
2	**7d**	*p*-Nitrobenzaldehyde (**12a**)	**13b** (59%)
3	**7b**	*m*-Bromobenzaldehyde (**12b**)	**13c** (50%)

[a] Isolated yield. Reactions were performed by addition of diazoamide **7** (1 equiv) and aromatic aldehyde **12** (1.3 equiv) in the presence of 1.4 mol % of $Rh_2(OAc)_4$ in dry DCM (15 mL) at room temperature 25–30 min duration.

15 with electron-deficient alkyne, alkene or aldehyde functional groups furnished the macrocycles **16** incorporating spiro-indoles with diasteroselectivity. It is noteworthy to mention that the absence[11] of dipolarophile or electron-rich dipolarophile resulted in the electrocyclization process.

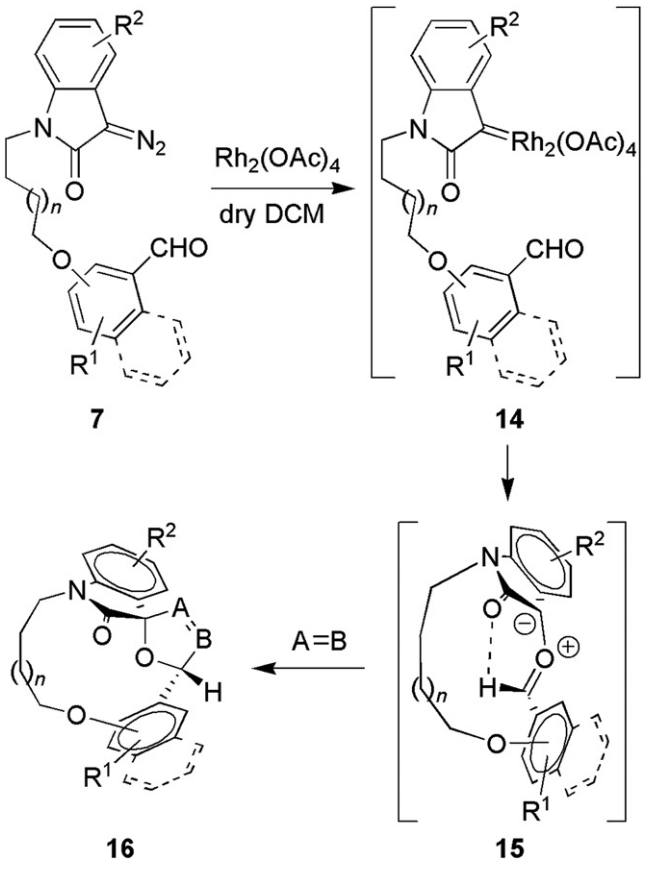
3. Conclusions

In conclusion, the generation of macrocyclic intramolecular carbonyl ylides and their subsequent intermolecular [3+2]-cycloaddition reactions in the presence of rhodium(II) acetate as a catalyst were demonstrated. Based on this concept, the successful synthesis of new macrocycles incorporating spiro-indolofurans, -indolofuropyrroles, -indolofurofurans, and -indolodioxolanes was established with complete diastereoselectivity. This research work represents the first paradigm for the trapping of macrocyclic carbonyl ylides.

4. Experimental section

4.1. General remarks

Melting points were determined on a capillary melting point apparatus and are uncorrected. IR spectra were recorded using ATR technique on a Bruker Alpha FTIR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 400 at 400 MHz using $CDCl_3$ in parts per million (δ) related to tetramethylsilane (δ=0.00) as an internal standard and are reported as follows; chemical shift (ppm), multiplicity (br=broad, s=singlet, d=doublet, m=multiplet), coupling constant (Hz) and integration. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz in $CDCl_3$. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center of the triplet at 77.7 ppm for $CDCl_3$. Carbon types were determined from ^{13}C NMR and DEPT experiments. High resolution mass analyses were performed using electrospray ionization technique on a Waters QTof-micro mass spectrometer. All solvents were purified by distillation following standard procedure. Thin layer chromatography was performed on silica or alumina plates and components visualized by observation under iodine/UV light at 254 nm. Column chromatography was performed on silica gel (100–200 mesh). All the reactions were conducted in oven-dried glassware under a positive pressure of argon with magnetic stirring. Reagents were added via syringes through septa.



Scheme 5. Plausible mechanism.

4.2. Synthesis of macrocycle 9a

A solution of aromatic aldehyde tethered to diazoamide **7a** (100 mg, 0.24 mmol) and dimethyl acetylenedicarboxylate (45 mg, 0.31 mmol), rhodium(II) acetate (1.42 mg, 1.3 mol %) in dichloromethane (15 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9a** (60%). Colorless solid; mp 210–212 °C; IR (neat): ν_{max} 2931, 2857, 1724, 1614, 1490, 1467, 1437, 1252, 1161, 1019, 991, 729 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ=1.22–1.25 (m, 7H, C*H*$_2$), 1.36–1.37 (m, 3H, C*H*$_2$), 1.66–1.73 (m, 4H, C*H*$_2$), 3.34 (dt, 1H, J_1=14 Hz, J_2=4 Hz, N–C*H*$_2$), 3.56 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.86 (td, 1H, J_1=9.4 Hz, J_2=2.4 Hz, N–C*H*$_2$), 4.00–4.05 (m, 1H, OCH_2), 4.09–4.17 (m, 1H, OCH_2), 6.71 (d, 1H, J=7.6 Hz, Ar*H*), 6.77 (d, 1H, J=7.6 Hz, Ar*H*), 6.88–6.92 (m, 2H, Ar*H*), 6.97 (s, 1H, CHO), 7.11 (dd, 1H, J_1=7.6 Hz, J_2=1.2 Hz, Ar*H*), 7.17–7.24 (m, 2H, Ar*H*), 7.36 (dd, 1H, J_1=7.6 Hz, J_2=1.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 26.40 (*C*H$_2$), 26.52 (*C*H$_2$), 27.87 (*C*H$_2$), 28.00 (*C*H$_2$), 28.39 (*C*H$_2$), 29.54 (*C*H$_2$), 30.82 (*C*H$_2$), 39.14 (*C*H$_2$), 52.50 (OCH_3), 52.66 (OCH_3), 69.16 (*C*H$_2$), 81.71 (CH, observed in DEPT-90 NMR), 89.29 (*quat-C*), 109.12 (=*C*H), 112.20 (=*C*H), 120.63 (=*C*H), 122.88 (=*C*H), 125.32 (=*C*H), 126.22 (*quat-C*), 127.27 (*quat-C*),

128.51 (=*C*H), 130.64 (=*C*H), 135.30 (*quat-C*), 144.64 (*quat-C*), 145.92 (*quat-C*), 157.35 (*quat-C*), 161.22 (*quat-C*), 163.19 (*quat-C*), 173.35 (*quat-C*); HRMS (ESI) calcd for $C_{30}H_{33}NO_7$ $[M+Na]^+$ 542.5758; found, 542.5766.

4.3. Synthesis of macrocycle 9b

A solution of diazoamide **7b** (100 mg, 0.23 mmol) and DMAD (44 mg, 0.30 mmol), rhodium(II) acetate (1.4 mg, 1.3 mol %) in dichloromethane (15 mL) was stirred at room temperature for 18 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9b** (65%). Colorless solid; mp 202–204 °C; IR (neat): ν_{max} 2927, 2856, 1715, 1652, 1610, 1599, 1488, 1433, 1246, 1122, 1016, 986, 760 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ=1.18–1.50 (m, 11H, CH_2), 1.69–1.73 (m, 5H, CH_2), 3.32 (dt, 1H, J_1=14.4 Hz, J_2=4.4 Hz, N–CH_2), 3.55 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.88 (td, 1H, J_1=9.4 Hz, J_2=2.4 Hz, N–CH_2), 4.02–4.10 (m, 2H, *OCH*$_2$), 6.70 (d, 2H, *J*=8.0 Hz, Ar*H*), 6.80 (d, 1H, *J*=8.4 Hz, Ar*H*), 6.89–6.95 (m, 2H, Ar*H*), 7.00 (s, 1H, CHO), 7.15–7.25 (m, 2H, Ar*H*), 7.38 (dd, 1H, J_1=7.6 Hz, J_2=1.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 24.89 (*C*H$_2$), 25.78 (*C*H$_2$), 26.09 (*C*H$_2$), 27.34 (*C*H$_2$), 27.94 (*C*H$_2$), 28.91 (*C*H$_2$), 28.30 (*C*H$_2$), 29.00 (*C*H$_2$), 39.07 (*C*H$_2$), 52.57 (O*C*H$_3$), 52.57 (O*C*H$_3$), 69.03 (*C*H$_2$), 89.48 (CH, observed in DEPT-90 NMR), 89.48 (*quat-C*), 108.75 (=*C*H), 113.12 (=*C*H), 120.84 (=*C*H), 122.78 (=*C*H), 125.39 (=*C*H), 126.60 (*quat-C*), 127.11 (*quat-C*), 128.67 (=*C*H), 130.64 (=*C*H), 130.67 (=*C*H), 135.48 (*quat-C*), 144.17 (*quat-C*), 145.38 (*quat-C*), 157.68 (*quat-C*), 161.22 (*quat-C*), 163.00 (*quat-C*), 173.57 (*quat-C*); HRMS (ESI) calcd for $C_{31}H_{35}NO_7$ $[M+Na]^+$ 556.6019; found, 556.6032.

4.4. Synthesis of macrocycle 9c

A solution of diazoamide **7c** (100 mg, 0.23 mmol) and DMAD (42 mg, 0.29 mmol), rhodium(II) acetate (1.32 mg, 1.3 mol %) in dichloromethane (15 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9c** (63%) Colorless solid; mp 210–212 °C; IR (neat): ν_{max} 2930, 2856, 1724, 1653, 1615, 1508, 1466, 1436, 1263, 1018, 992, 73 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ=1.16–1.49 (m, 12H, CH_2), 1.71–1.74 (m, 6H, CH_2), 3.24–3.30 (dt, 1H, J_1=14 Hz, J_2=4 Hz, N–CH_2), 3.51 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.85–3.89 (td, 1H, J_1=9 Hz, J_2=2.1 Hz, N–CH_2), 4.02–4.09 (m, 2H, *OCH*$_2$), 6.67 (d, 2H, *J*=8.0 Hz, Ar*H*), 6.76 (d, 1H, *J*=8.4 Hz, Ar*H*), 6.84–6.91 (m, 2H, Ar*H*), 6.99 (s, 1H, CHO), 7.11–7.22 (m, 2H, Ar*H*), 7.36 (dd, 1H, J_1=7.6 Hz, J_2=1.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 24.83 (*C*H$_2$), 25.75 (*C*H$_2$), 26.01 (*C*H$_2$), 27.30 (*C*H$_2$), 27.94 (*C*H$_2$), 28.05 (*C*H$_2$), 28.19 (CH$_2$), 28.79 (CH$_2$), 29.10 (CH$_2$), 39.01 (*C*H$_2$), 52.46 (O*C*H$_3$), 52.51 (O*C*H$_3$), 69.01 (*C*H$_2$), 89.41 (CH, observed in DEPT-90 NMR), 89.47 (*quat-C*), 108.70 (=*C*H), 112.67 (=*C*H), 119.81 (=*C*H), 121.58 (=*C*H), 124.89 (=*C*H), 125.90 (*quat-C*), 126.41 (*quat-C*), 127.57 (=*C*H), 130.14 (=*C*H), 130.37 (=*C*H), 134.58 (*quat-C*), 143.12 (*quat-C*), 145.28 (*quat-C*), 156.28 (*quat-C*), 161.12 (*quat-C*), 162.00 (*quat-C*), 171.57 (*quat-C*); HRMS (ESI) calcd for $C_{32}H_{37}NO_7$ $[M+Na]^+$ 570.6285; found, 570.6276.

4.5. Synthesis of macrocycles 9d

A solution of diazoamide **7d** (100 mg, 0.22 mmol) and DMAD (41 mg, 0.28 mmol), rhodium(II) acetate (1.3 mg, 1.32 mol %) in dichloromethane (15 mL) was stirred at room temperature for 15 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9d** (70%) Colorless solid; mp 201–203 °C; IR (neat): ν_{max} 2927, 2852, 1718, 1609, 1510, 1464, 1437, 1252, 1094, 1014, 984, 761 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ=1.16–1.87 (m, 8H, CH_2), 1.34–1.37 (m, 2H, CH_2), 1.44–1.48 (m, 1H, CH_2), 1.55–1.74 (m, 5H, CH_2), 3.31 (dt, 1H, J_1=14 Hz, J_2=4 Hz, N–CH_2), 3.54 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.78–3.82 (m, 1H, N–CH_2), 3.99–4.04 (m, 1H, OCH_2), 4.06–4.13 (m, 1H, OCH_2), 6.35 (d, 1H, *J*=2.4 Hz, Ar*H*), 6.45 (dd, 1H, J_1=8.4 Hz, J_2=2.4 Hz, Ar*H*), 6.70 (d, 1H, *J*=7.6 Hz, Ar*H*), 6.89–6.92 (m, 2H, Ar*H* & CHO), 7.14–7.21 (m, 2H, Ar*H*), 7.30 (d, 1H, *J*=8.4 Hz, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 24.90 (*C*H$_2$), 25.79 (*C*H$_2$), 26.09 (*C*H$_2$), 27.36 (*C*H$_2$), 27.99 (*C*H$_2$), 28.19 (*C*H$_2$), 28.28 (CH$_2$), 29.94 (CH$_2$), 39.07 (CH$_2$), 52.40 (OCH_3), 52.57 (OCH_3), 55.35 (OCH_3), 68.95 (*C*H$_2$), 81.54 (CH, observed in DEPT-90 NMR), 89.19 (*quat-C*), 100.13 (=*C*H), 105.31 (=*C*H), 108.70 (=*C*H), 119.20 (*quat-C*), 122.73 (=*C*H), 125.32 (=*C*H), 127.30 (*quat-C*), 129.57 (=*C*H), 130.58 (=*C*H), 134.89 (=*C*H), 144.17 (*quat-C*), 145.91 (*quat-C*), 158.86 (*quat-C*), 161.20 (*quat-C*), 161.70 (*quat-C*), 163.23 (*quat-C*), 173.69 (*quat-C*); HRMS (ESI) calcd for $C_{32}H_{37}NO_8$ $[M+Na]^+$ 586.6279; found, 586.6265.

4.6. Synthesis of macrocycles 9e

A solution of diazoamide **7e** (100 mg, 0.21 mmol) and DMAD (40 mg, 0.28 mmol), rhodium(II) acetate (1.26 mg, 1.32 mol %) in dichloromethane (15 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9e** (62%) Colorless solid; mp 182–185 °C; IR (neat): ν_{max} 2930, 2856, 1723, 1660, 1613, 1593, 1519, 1489, 1263, 1017, 992, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.09–1.23 (m, 8H, CH_2), 1.31–1.38 (m, 2H, CH_2), 1.47–1.49 (m, 1H, CH_2), 1.59–1.76 (m, 4H, CH_2), 1.77–1.81 (m, 1H, CH_2), 3.33 (dt, 1H, J_1=14 Hz, J_2=4.4 Hz, N–CH_2), 3.58 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.95 (td, 1H, J_1=10.8 Hz, J_2=3.2 Hz, N–CH_2), 4.06–4.13 (m, 1H, OCH_2), 4.13–4.20 (m, 1H, OCH_2), 6.73 (d, 1H, *J*=8.0 Hz, Ar*H*), 6.87 (d, 1H, *J*=9.2 Hz, Ar*H*), 6.93–6.97 (m, 2H, Ar*H*, CHO), 7.17 (d, 1H, *J*=8.0 Hz, Ar*H*), 7.21–7.25 (m, 1H, Ar*H*), 8.18 (dd, 1H, J_1=8.6 Hz, J_2=2.4 Hz, Ar*H*), 8.31 (d, 1H, *J*=2.4 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.87 (*C*H$_2$), 25.80 (*C*H$_2$), 25.94 (*C*H$_2$), 27.26 (*C*H$_2$), 28.06 (*C*H$_2$), 28.13 (*C*H$_2$), 28.14 (CH$_2$), 28.74 (CH$_2$), 39.14 (*C*H$_2$), 52.63 (OCH_3), 52.77 (OCH_3), 60.66 (*C*H$_2$), 80.60 (CH, observed in DEPT-90 NMR), 89.91 (*quat-C*), 108.98 (=*C*H), 112.19 (=*C*H), 123.09 (=*C*H), 124.83 (=*C*H), 125.46 (=*C*H), 126.16 (*quat-C*), 126.77 (=*C*H), 127.81 (*quat-C*), 131.07 (=*C*H), 137.46 (*quat-C*), 141.27 (*quat-C*), 142.62 (*quat-C*), 144.19 (*quat-C*), 161.09 (*quat-C*), 162.37 (*quat-C*), 162.51 (*quat-C*), 173.06 (*quat-C*); HRMS (ESI) calcd for $C_{31}H_{34}N_2O_9$ $[M+Na]^+$ 601.5994; found, 601.5979. Crystal data for the compound **9e**: (CCDC 851590) $C_{31}H_{34}N_2O_9$, *M*=578.60, 0.27×0.14×0.09 mm, Monoclinic, space group *P*–21 with *a*=14.0885(3) Å, *b*=10.6655(2) Å, *c*=20.5109(4) Å, α=90.00, β=98.6460(10), γ=90.00, *V*=3046.96(10) $Å^3$, *T*=293(2) K, R_1=0.0694, wR_2=0.1775 on observed data, *z*=4, D_{calcd}=1.261 mg cm^{-3}, *F*(000)=1224, Absorption coefficient=0.093 mm^{-1}, λ=0.71073 Å, 7283 reflections were collected on a smart apex CCD single crystal diffractometer 4087 observed reflections ($I \geq 2\sigma$ (*I*)). The largest difference peak and hole=0.733 and −0.366 e $Å^{-3}$, respectively. The structure was solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL-97 software.

4.7. Synthesis of macrocycles 9f

A solution of diazoamide **7f** (100 mg, 0.22 mmol) and DMAD (40 mg, 0.28 mmol), rhodium(II) acetate (1.3 mg, 1.3 mol %) in dichloromethane (15 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9f** (63%) Colorless solid; mp 205–207 °C; IR (neat): ν_{max} 2931, 2857, 1724, 1659, 1611, 1485, 1455, 1433, 1263, 1020, 990, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.19–1.318 (m, 8H, CH_2), 1.39–1.49 (m, 2H, CH_2), 1.51–1.58 (m, 1H, CH_2), 1.66–1.72 (m, 4H, CH_2), 1.76–1.86 (m, 1H, CH_2), 3.35–3.39 (m, 1H, N–CH_2), 3.66 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.91–3.92 (m, 1H, N–CH_2), 4.12–4.19 (m, 2H, OCH_2), 6.72 (d, 1H,

J=8.0 Hz, Ar*H*), 6.89 (d, 1H, J=8.4 Hz, Ar*H*), 7.03 (td, 1H, J_1=7.6 Hz, J_2=0.8 Hz, Ar*H*), 7.08 (s, 1H, CHO), 7.18 (d, 1H, J=2.0 Hz, Ar*H*), 7.25 (dd, 1H, J_1=8.0 Hz, J_2=2.4 Hz, Ar*H*), 7.32 (td, 1H, J_1=7.6 Hz, J_2=1.6 Hz, Ar*H*), 7.46 (dd, 1H, J_1=7.6 Hz, J_2=1.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.86 (*C*H$_2$), 25.75 (*C*H$_2$), 25.98 (*C*H$_2$), 27.30 (*C*H$_2$), 27.93 (*C*H$_2$), 28.09 (*C*H$_2$), 28.24 (*C*H$_2$), 28.96 (*C*H$_2$), 39.32 (*C*H$_2$), 52.58 (*C*H$_3$), 52.69 (*C*H$_3$), 68.89 (*C*H$_2$), 82.18 (CH, observed in DEPT-90 NMR), 89.14 (*quat-C*), 109.75 (=*C*H), 113.04 (=*C*H), 120.94 (=*C*H), 125.86 (=*C*H), 126.03 (*quat-C*), 128.07 (*quat-C*), 128.63 (=*C*H), 128.83 (*quat-C*), 130.56 (=*C*H), 130.91 (=*C*H), 134.35 (*quat-C*), 142.78 (*quat-C*), 146.30 (*quat-C*), 157.64 (*quat-C*), 160.89 (*quat-C*), 162.93 (*quat-C*), 173.28 (*quat-C*); HRMS (ESI) calcd for $C_{31}H_{34}ClNO_7$ $[M+Na]^+$ 591.0469; found, 519.0455.

4.8. Synthesis of macrocycles 9g

A solution of diazoamide **7g** (100 mg, 0.23 mmol) and DMAD (44 mg, 0.30 mmol), rhodium(II) acetate (1.4 mg, 1.3 mol %) in dichloromethane (15 mL) was stirred at room temperature for 17 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9g** (65%) Colorless solid; mp 218–220 °C; IR (neat): ν_{max} 2929, 2858, 1726, 1617, 1603, 1489, 1468, 1454, 1246, 1159, 995, 745 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ=1.17–1.53 (m, 12H, C*H*$_2$), 1.62–1.79 (m, 4H, C*H*$_2$), 3.29–3.36 (dt, 1H, J_1=14 Hz, J_2=4 Hz, N–C*H*$_2$), 3.59 (s, 3H, OCH$_3$), 3.64 (s, 3H, OCH$_3$), 3.93–3.97 (m, 1H, N–C*H*$_2$), 4.10–4.14 (m, 2H, *OCH*$_2$), 6.69–6.72 (m, 2H, Ar*H*), 6.81 (t, 1H, J=8.4 Hz, Ar*H*), 6.85–6.90 (m, 2H, Ar*H*), 7.05 (s, 1H, CHO), 7.11–7.20 (m, 2H, Ar*H*), 7.26 (dd, 1H, J_1=7.6 Hz, J_2=1.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 24.80 (*C*H$_2$), 25.73 (*C*H$_2$), 26.05 (*C*H$_2$), 27.29 (*C*H$_2$), 27.89 (*C*H$_2$), 28.85 (*C*H$_2$), 28.94 (*C*H$_2$), 29.02 (*C*H$_2$), 38.95 (*C*H$_2$), 52.17 (OCH$_3$), 52.37 (OCH$_3$), 68.85 (*C*H$_2$), 88.68 (CH, observed in DEPT-90 NMR), 89.18 (*quat-C*), 108.25 (=*C*H), 112.11 (=*C*H), 119.81 (=*C*H), 121.28 (=*C*H), 124.29 (=*C*H), 125.55 (*quat-C*), 126.51 (*quat-C*), 128.17 (=*C*H), 130.24 (=*C*H), 130.57 (=*C*H), 135.38 (*quat-C*), 144.07 (*quat-C*), 145.18 (*quat-C*), 157.38 (*quat-C*), 161.02 (*quat-C*), 162.59 (*quat-C*), 172.57 (*quat-C*); HRMS (ESI) calcd for $C_{31}H_{35}NO_7$ $[M+Na]^+$ 556.6019; found, 556.6036.

4.9. Synthesis of macrocycles 9h

A solution of diazoamide **7h** (100 mg, 0.21 mmol) and DMAD (39 mg, 0.27 mmol), rhodium(II) acetate (1.25 mg, 1.32 mol %) in dichloromethane (15 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9h** (68%) Yellow solid; mp 263–265 °C; IR (neat): ν_{max} 2926, 2855, 1718, 1613, 1512, 1488, 1465, 1246, 1013, 988, 733 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ=1.18 (br, 8H, C*H*$_2$), 1.43–1.52 (m, 4H, C*H*$_2$), 1.61–1.69 (m, 3H, C*H*$_2$), 1.76–1.81 (m, 1H, C*H*$_2$), 3.33 (dt, 1H, J_1=14 Hz, J_2=4.4 Hz, N–C*H*$_2$), 3.50 (s, 3H, OCH$_3$), 3.57 (s, 3H, OCH$_3$), 3.93–3.99 (m, 1H, N–CH$_2$), 4.10–4.17 (m, 1H, OCH$_2$), 4.21–4.26 (m, 1H, OCH$_2$), 6.95 (d, 1H, J=8.0 Hz, Ar*H*), 6.95 (td, 1H, J_1=7.6 Hz, J_2=0.8 Hz, Ar*H*), 7.22 (d, 1H, J=8.8 Hz, Ar*H*), 7.24 (td, 1H, J_1=8.0 Hz, J_2=1.2 Hz, Ar*H*), 7.28–7.32 (m, 1H, Ar*H*), 7.50–7.55 (m, 2H, Ar*H*), 7.69 (d, 2H, J=7.2 Hz, Ar*H*, CHO), 7.74 (d, 1H, J=8.8 Hz, Ar*H*), 8.51 (d, 1H, J=8.8 Hz, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 24.79 (*C*H$_2$), 24.28 (*C*H$_2$), 25.13 (*C*H$_2$), 26.14 (*C*H$_2$), 26.43 (*C*H$_2$), 26.82 (*C*H$_2$), 26.87 (*C*H$_2$), 27.78 (*C*H$_2$), 28.68 (*C*H$_2$), 37.83 (*C*H$_2$), 51.38 (OCH$_3$), 51.42 (OCH$_3$), 69.87 (*C*H$_2$), 79.42 (CH, observed in DEPT-90 NMR), 87.74 (*quat-C*), 107.88 (=*C*H), 115.55 (=*C*H), 115.84 (*quat-C*), 121.88 (=*C*H), 122.67 (=*C*H), 123.04 (=*C*H), 124.44 (=*C*H), 125.48 (=*C*H), 125.77 (*quat-C*), 127.83 (=*C*H), 128.77 (*quat-C*), 129.86 (*quat-C*), 131.03 (=*C*H), 132.43 (=*C*H), 133.66 (*quat-C*), 143.44 (*quat-C*), 147.92 (*quat-C*), 155.73 (*quat-C*), 160.61 (*quat-C*), 161.72 (*quat-C*), 172.35 (*quat-C*); HRMS (ESI) calcd for $C_{35}H_{37}NO_7$ $[M+Na]^+$ 606.6606; found, 606.6621.

4.10. Synthesis of macrocycles 9i

A solution of diazoamide **7i** (100 mg, 0.20 mmol) and DMAD (37 mg, 0.26 mmol), rhodium(II) acetate (1.2 mg, 1.34 mol %) in dichloromethane (15 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to give **9i** (62%) Colorless solid; mp 218–220 °C; IR (neat): ν_{max} 2923, 2853, 1714, 1611, 1595, 1514, 1464, 1293, 1014, 988, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.31 (br, s, 14H, C*H*$_2$), 1.44 (br, s, 2H, C*H*$_2$), 1.58–1.65 (m, 2H, C*H*$_2$), 1.68–1.74 (m, 1H, C*H*$_2$), 1.76–1.79 (m, 1H, C*H*$_2$), 3.28–3.35 (m, 1H, N–CH$_2$), 3.50 (s, 3H, OCH$_3$), 3.55 (s, 3H, OCH$_3$), 3.95–4.03 (m, 2H, N–CH$_2$,OCH$_2$), 4.12–4.15 (m, 1H, OCH$_2$), 6.76 (d, 1H, J=8.0 Hz, Ar*H*), 6.74 (td, 1H, J_1=7.8 Hz, J_2=0.8 Hz, Ar*H*), 7.17 (d, 1H, J=9.6 Hz, Ar*H*), 7.23–7.32 (m, 2H, Ar*H*), 7.50–7.57 (m, 2H, Ar*H*), 7.69–7.77 (m, 3H, Ar*H*, CHO), 8.51 (d, 1H, J=8.8 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.75 (*C*H$_2$), 25.88 (*C*H$_2$), 26.05 (*C*H$_2$), 26.79 (*C*H$_2$), 26.96 (*C*H$_2$), 27.27 (*C*H$_2$), 27.78 (*C*H$_2$), 28.24 (*C*H$_2$), 28.51 (*C*H$_2$), 29.49 (*C*H$_2$), 39.32 (*C*H$_2$), 52.36 (OCH$_3$), 52.39 (OCH$_3$), 70.72 (*C*H$_2$), 80.77 (CH, observed in DEPT-90 NMR), 88.77 (*quat-C*), 108.65 (=*C*H), 115.17 (=*C*H), 116.30 (*quat-C*), 122.80 (=*C*H), 123.62 (=*C*H), 124.18 (=*C*H), 125.47 (=*C*H), 126.40 (=*C*H), 126.74 (*quat-C*), 128.79 (=*C*H), 129.68 (*quat-C*), 130.87 (=*C*H), 131.97 (=*C*H), 133.44 (*quat-C*), 134.97 (*quat-C*), 144.52 (*quat-C*), 148.50 (*quat-C*), 156.71 (*quat-C*), 161.60 (*quat-C*), 162.75 (*quat-C*), 173.38 (*quat-C*); HRMS (ESI) calcd for $C_{37}H_{41}NO_7$ $[M+Na]^+$ 634.7137; found, 634.7127.

4.11. Synthesis of macrocycles 10a

A solution of diazoamide **7b** (100 mg, 0.23 mmol) and *N*-phenylmaleimide (53 mg, 0.30 mmol), in dry dichloromethane (15 mL) was allowed to react with rhodium(II) acetate (1.4 mg, 1.3 mol %) at room temperature for 18 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to furnish **10a** (65%). Colorless solid; mp 228–230 °C; IR (neat): ν_{max} 2931, 2857, 1715, 1614, 1491, 1468, 1374, 1264, 1192, 1042, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.03–1.05 (m, 3H, C*H*$_2$), 1.15–1.20 (m, 5H, C*H*$_2$), 1.27–1.38 (m, 4H, C*H*$_2$), 1.60–1.64 (m, 2H, C*H*$_2$), 1.76–1.85 (m, 2H, C*H*$_2$), 3.34 (dt, 1H, J_1=14 Hz, J_2=4 Hz, N–C*H*$_2$), 3.68 (d, 1H, J=8.0 Hz, CH), 3.96–4.07 (m, 1H, N–CH$_2$), 4.14–4.26 (m, 2H, OCH$_2$ & CH), 4.27–4.30 (m, 1H, OCH$_2$), 6.65 (d, 1H, J=8.4 Hz, Ar*H*), 6.81 (d, 1H, J=8.0 Hz, Ar*H*), 6.86–6.90 (m, 2H, Ar*H*), 7.02 (td, 1H, J_1=7.6 Hz, J_2=0.8 Hz, Ar*H*), 7.16–7.37 (m, 9H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.76 (*C*H$_2$), 25.71 (*C*H$_2$), 26.64 (*C*H$_2$), 26.90 (*C*H$_2$), 28.10 (*C*H$_2$), 28.60 (*C*H$_2$), 28.99 (*C*H$_2$), 29.31 (*C*H$_2$), 37.57 (*C*H$_2$), 49.90 (=*C*H), 50.98 (=*C*H), 69.43 (*C*H$_2$), 74.86 (CH, observed in DEPT-90 NMR), 83.42 (*quat-C*), 109.17 (=*C*H), 112.96 (=*C*H), 120.54 (=*C*H), 122.74 (=*C*H), 124.14 (*quat-C*), 125.85 (=*C*H), 126.20 (=*C*H), 127.38 (=*C*H), 128.34 (*quat-C*), 128.62 (=*C*H), 129.18 (=*C*H), 129.44 (=*C*H), 131.01 (=*C*H), 131.72 (*quat-C*), 143.88 (*quat-C*), 156.36 (*quat-C*), 173.43 (*quat-C*), 173.60 (*quat-C*), 174.74 (*quat-C*); HRMS (ESI) calcd for $C_{35}H_{36}N_2O_5$ $[M+Na]^+$ 587.6605; found, 587.6616.

4.12. Synthesis of macrocycles 10b

A solution of diazoamide **7d** (100 mg, 0.22 mmol) and NPM (50 mg, 0.28 mmol), in dry dichloromethane (15 mL) was allowed to react with rhodium(II) acetate (1.3 mg, 1.3 mol %) at room temperature for 15 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to furnish **10b** (68%). Colorless solid; mp 273–275 °C; IR (neat): ν_{max} 2920, 2853, 1715, 1612, 1504, 1495, 1468, 1380, 1198, 1025, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.17–1.20 (m, 6H, C*H*$_2$), 1.12–1.32 (m, 2H, C*H*$_2$), 1.35–1.39 (m, 3H, C*H*$_2$), 1.58–1.63 (m, 3H, C*H*$_2$), 1.74–1.84 (m, 2H, C*H*$_2$), 3.31–3.36 (dt, 1H, J_1=14 Hz, J_2=3.6 Hz, N–C*H*$_2$), 3.67–3.73 (m, 5H, CH$_2$ & OCH$_3$), 3.94 (td, 1H, J_1=9.6 Hz, J_2=2.4 Hz, N–CH$_2$),

4.12–4.18 (m, 2H, OCH_2 & CH), 4.20–4.24 (m, 1H, OCH_2), 6.39–6.43 (m, 1H, Ar*H*), 6.59 (d, 1H, *J*=8.4 Hz, Ar*H*), 6.80 (d, 2H, *J*=7.6 Hz, Ar*H*), 7.01 (t, 1H, *J*=7.6 Hz, Ar*H*), 7.16–7.23 (m, 3H, Ar*H*), 7.27–7.33 (m, 2H, Ar*H*), 7.37–7.41 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.77 (*C*H_2), 25.69 (*C*H_2), 26.57 (*C*H_2), 26.92 (*C*H_2), 28.05 (*C*H_2), 28.58 (*C*H_2), 28.90 (CH_2), 29.16 (CH_2), 37.64 (*C*H_2), 49.91 (=CH), 51.00 (=CH), 55.23 (OCH_3), 69.29 (*C*H_2), 74.77 (CH, observed in DEPT-90 NMR), 83.21 (*quat-C*), 99.99 (=*C*H), 105.13 (=*C*H), 109.15 (=*C*H), 117.34 (*quat-C*), 122.70 (=*C*H), 122.90 (*quat-C*), 126.21 (=*C*H), 126.74 (=*C*H), 126.97 (=*C*H), 127.31 (=*C*H), 128.64 (=*C*H), 129.10 (=*C*H), 130.96 (=*C*H), 131.75 (*quat-C*), 143.87 (*quat-C*), 157.45 (*quat-C*), 160.76 (*quat-C*), 173.51 (*quat-C*), 173.81 (*quat-C*), 174.78 (*quat-C*); HRMS (ESI) calcd for $C_{36}H_{38}N_2O_6$ $[M+Na]^+$ 617.6865; found, 617.6849.

4.13. Synthesis of macrocycles 10c

A solution of diazoamide **7h** (100 mg, 0.27 mmol) and NPM (48 mg, 0.27 mmol), in dry dichloromethane (20 mL) was allowed to react with rhodium(II) acetate (1.25 mg, 1.32 mol %) at room temperature for 20 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to furnish **10c** (65%). Colorless solid; mp 241–243 °C; IR (neat): ν_{max} 2926, 2854, 1716, 1614, 1596, 1499, 1468, 1375, 1187, 1066, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.07–1.10 (m, 3H, C*H*$_2$), 1.16–0.1.28 (m, 5H, C*H*$_2$), 1.37–1.41 (m, 2H, C*H*$_2$), 1.49–1.54 (m, 2H, C*H*$_2$), 1.68–1.73 (m, 2H, C*H*$_2$), 1.83–1.88 (m, 2H, C*H*$_2$), 3.36 (dt, 1H, J_1=14 Hz, J_2=4 Hz, N–C*H*$_2$), 3.82 (d, 1H, *J*=8.4 Hz, CH), 4.07 (td, 1H, J_1=11 Hz, J_2=3.2 Hz, N–CH$_2$), 4.15–4.24 (m, 2H, OCH_2 & CH), 4.36–4.41 (m, 1H, OCH_2), 6.82 (d, 1H, *J*=7.6 Hz, Ar*H*), 6.95–6.98 (m, 1H, Ar*H*), 7.07 (td, 2H, J_1=7.6 Hz, J_2=0.4 Hz, Ar*H*), 7.18–7.33 (m, 7H, Ar*H*), 7.35 (d, 2H, *J*=8.8 Hz, Ar*H*), 7.70 (d, 1H, *J*=8.0 Hz, Ar*H*), 7.75 (d, 1H, *J*=8.8 Hz, Ar*H*), 8.53 (d, 1H, *J*=8.4 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.80 (*C*H_2), 25.92 (*C*H_2), 26.45 (*C*H_2), 26.63 (*C*H_2), 27.78 (*C*H_2), 28.05 (*C*H_2), 28.19 (CH_2), 29.60 (CH_2), 37.92 (*C*H_2), 49.48 (=CH), 51.11 (=*C*H), 70.14 (*C*H_2), 76.68 (CH, observed in DEPT-90 NMR), 83.93 (*quat-C*), 109.23 (=*C*H), 114.27 (=*C*H), 115.42 (*quat-C*), 122.81 (=*C*H), 123.02 (*quat-C*), 123.16 (=*C*H), 124.30 (=*C*H), 125.90 (=*C*H), 126.25 (=*C*H), 127.36 (=*C*H), 128.35 (=*C*H), 128.89 (=*C*H), 129.25 (=*C*H), 129.49 (*quat-C*), 130.92 (=*C*H), 130.98 (=*C*H), 131.69 (*quat-C*), 133.08 (*quat-C*), 143.87 (*quat-C*), 155.11 (*quat-C*), 173.45 (*quat-C*), 173.49 (*quat-C*), 175.08 (*quat-C*); HRMS (ESI) calcd for $C_{39}H_{38}N_2O_5$ $[M+Na]^+$ 637.7192; found, 637.7179.

4.14. Synthesis of macrocycles 10d

A solution of diazoamide **7i** (100 mg, 0.20 mmol) and NPM (45 mg, 0.26 mmol), in dry dichloromethane (15 mL) was allowed to react with rhodium(II) acetate (1.2 mg, 1.34 mol %) at room temperature for 20 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to furnish **10d** (60%). Colorless solid; mp 220–222 °C; IR (neat): ν_{max} 2922, 2850, 1705, 1613, 1594, 1489, 1465, 1382, 1179, 1022, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.36–1.45 (m, 14H, C*H*$_2$), 1.70–0.1.86 (m, 5H, C*H*$_2$), 1.94–1.98 (m, 1H, C*H*$_2$), 3.70–3.78 (m, 1H, N–CH$_2$), 3.80–3.83 (m, 1H, N–CH$_2$), 3.86 (d, 1H, *J*=8.4 Hz, CH), 4.17 (td, 1H, J_1=8.8 Hz, J_2=3.6 Hz, OCH_2), 4.32 (t, 1H, *J*=8.8 Hz, CH), 4.35–4.39 (m, 1H, OCH_2), 6.91 (d, 1H, *J*=7.6 Hz, Ar*H*), 6.97–6.99 (m, 2H, Ar*H*), 7.15 (td, 1H, J_1=7.2 Hz, J_2=0.8 Hz, Ar*H*), 7.28–7.35 (m, 4H, Ar*H*), 7.37–7.44 (m, 3H, Ar*H*), 7.47 (d, 1H, *J*=8.8 Hz, Ar*H*), 7.79 (d, 1H, *J*=7.2 Hz, Ar*H*), 7.84 (d, 1H, *J*=9.2 Hz, Ar*H*), 8.74 (d, 2H, *J*=8.4 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.02 (*C*H_2), 25.68 (*C*H_2), 26.30 (*C*H_2), 26.59 (*C*H_2), 27.61 (*C*H_2), 27.96 (*C*H_2), 28.08 (CH_2), 28.85 (CH_2), 29.36 (*C*H_2), 29.98 (*C*H_2), 38.37 (*C*H_2), 49.14 (=CH), 51.68 (=*C*H), 69.24 (*C*H_2), 78.07 (CH, observed in DEPT-90 NMR), 84.07 (*quat-C*), 108.91 (=*C*H), 113.60 (=*C*H), 115.46 (*quat-C*), 122.69 (=*C*H), 123.06 (=*C*H), 123.11 (*quat-C*), 124.34 (=*C*H), 125.93 (=*C*H), 126.18 (=*C*H), 127.10 (=*C*H), 128.36 (=*C*H), 128.91 (=*C*H), 129.17 (=*C*H), 129.45 (*quat-C*), 130.78 (=*C*H), 130.90 (=*C*H), 131.65 (*quat-C*), 132.91 (*quat-C*), 143.77 (*quat-C*), 155.83 (*quat-C*), 173.26 (*quat-C*), 173.36 (*quat-C*), 175.32 (*quat-C*); HRMS (ESI) calcd for $C_{41}H_{42}N_2O_5$ $[M+Na]^+$ 665.7723; found, 665.7713.

4.15. Synthesis of macrocycles 11a

A solution of diazoamide **7b** (100 mg, 0.23 mmol) and maleic anhydride (30 mg, 0.30 mmol), in dry dichloromethane (20 mL) was allowed to react with rhodium(II) acetate (1.4 mg, 1.33 mol %) at room temperature for 25 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to furnish **11a** (59%). Colorless solid; mp 255–257 °C; IR (neat): ν_{max} 2920, 2851, 1715, 1614, 1491, 1467, 1246, 1184, 1039, 913, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.01–1.08 (m, 3H, C*H*$_2$), 1.20–1.24 (m, 5H, C*H*$_2$), 1.31–1.41 (m, 4H, C*H*$_2$), 1.59–1.71 (m, 2H, C*H*$_2$) 1.78–1.83 (m, 1H, C*H*$_2$), 1.87–1.94 (m, 1H, CH$_2$), 3.40 (dt, 1H, J_1=14.4 Hz, J_2=4 Hz, N–C*H*$_2$), 3.84 (d, 1H, *J*=8.8 Hz, CH), 4.08 (td, 1H, J_1=10 Hz, J_2=2.4 Hz, N–C*H*$_2$), 4.18–4.26 (m, 1H, OCH_2), 4.28–4.32 (m, 1H, OCH_2), 4.35 (t, 1H, *J*=8.4 Hz, CH), 6.68 (d, 1H, *J*=8.0 Hz, Ar*H*), 6.88 (d, 1H, *J*=7.6 Hz, Ar*H*), 6.94–6.97 (m, 2H, Ar*H*), 7.15 (td, 1H, J_1=7.6 Hz, J_2=0.8 Hz, Ar*H*), 7.27–7.32 (m, 2H, Ar*H*), 7.34 (d, 1H, *J*=6.8 Hz, Ar*H*), 7.39 (td, 1H, J_1=8.0 Hz, J_2=1.2 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.69 (*C*H_2), 25.64 (*C*H_2), 26.56 (*C*H_2), 26.78 (*C*H_2), 28.00 (*C*H_2), 28.52 (*C*H_2), 28.88 (CH_2), 29.29 (CH_2), 37.63 (*C*H_2), 51.01 (=CH), 51.47 (=*C*H), 69.41 (*C*H_2), 75.00 (CH, observed in DEPT-90 NMR), 83.50 (*quat-C*), 109.32 (=*C*H), 112.83 (=*C*H), 120.85 (=*C*H), 122.00 (*quat-C*), 123.09 (=*C*H), 123.75 (*quat-C*), 126.06 (=*C*H), 126.99 (=*C*H), 129.78 (=*C*H), 131.49 (=*C*H), 143.78 (*quat-C*), 156.05 (*quat-C*), 168.28 (*quat-C*), 168.94 (*quat-C*), 174.03 (*quat-C*); HRMS (ESI) calcd for $C_{29}H_{31}NO_6$ $[M+Na]^+$ 512.5493; found, 512.5479.

4.16. Synthesis of macrocycles 11b

A solution of diazoamide **7h** (100 mg, 0.21 mmol) and maleic anhydride (27 mg, 0.27 mmol), in dry dichloromethane (15 mL) was allowed to react with rhodium(II) acetate (1.25 mg, 1.32 mol %) at room temperature for 25 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to furnish **11b** (56%). Colorless solid; mp 230–232 °C; IR (neat): ν_{max} 2923, 2852, 1723, 1613, 1591, 1488, 1466, 1269, 1081, 818, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.10–1.19 (m, 4H, C*H*$_2$), 1.23–1.31 (m, 4H, C*H*$_2$), 1.38–1.47 (m, 4H, C*H*$_2$), 1.58–1.70 (m, 2H, C*H*$_2$), 1.81–1.93 (m, 2H, C*H*$_2$), 3.39 (dt, 1H, J_1=14 Hz, J_2=4 Hz, N–C*H*$_2$), 3.87 (d, 1H, *J*=8.2 Hz, CH), 4.10 (td, 1H, J_1=10.2 Hz, J_2=2.8 Hz, N–C*H*$_2$), 4.21–4.26 (m, 1H, OCH_2), 4.30–4.35 (m, 1H, OCH_2), 4.37 (t, 1H, *J*=8.4 Hz, CH), 6.39 (t, 1H, *J*=8.0 Hz, Ar*H*), 6.71 (d, 1H, *J*=7.6 Hz, Ar*H*), 6.83–6.95 (m, 2H, Ar*H*), 7.10–7.17 (m, 1H, Ar*H*), 7.27 (d, 2H, *J*=7.4 Hz, Ar*H*), 7.31–7.35 (m, 2H, Ar*H*), 7.39 (d, 2H, J_1=8.0 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.20 (*C*H_2), 25.10 (*C*H_2), 26.24 (*C*H_2), 26.36 (*C*H_2), 28.12 (*C*H_2), 28.80 (*C*H_2), 28.91 (CH_2), 29.32 (CH_2), 37.89 (*C*H_2), 51.15 (=CH), 51.53 (=*C*H), 69.75 (*C*H_2), 75.35 (CH, observed in DEPT-90 NMR), 85.50 (*quat-C*), 109.15 (=*C*H), 112.25 (=*C*H), 120.35 (=*C*H), 122.12 (*quat-C*), 123.19 (=*C*H), 124.15 (*quat-C*), 125.55 (=*C*H), 126.31 (=*C*H), 126.54 (=*C*H), 128.24 (=*C*H), 129.31 (=*C*H), 132.34 (=*C*H), 140.23 (*quat-C*), 143.78 (*quat-C*),152.35 (*quat-C*), 156.34 (*quat-C*), 167.65 (*quat-C*), 167.96 (*quat-C*), 175.12 (*quat-C*); HRMS (ESI) calcd for $C_{33}H_{33}NO_6$ $[M+Na]^+$ 562.6080; found, 562.6067.

4.17. Synthesis of macrocycles 13a

A solution of diazoamide **7b** (100 mg, 0.23 mmol) and *p*-nitrobenzaldehyde (47 mg, 0.31 mmol), in dry dichloromethane (15 mL)

was allowed to react with rhodium(II) acetate (1.5 mg, 1.4 mol %) at room temperature for 25 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to yield **13a** (55%). Colorless solid; mp 240–242 °C; IR (neat): ν_{max} 2923, 2852, 1712, 1605, 1522, 1492, 1454, 1247, 1062, 937, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.10–1.37 (m, 12H, CH_2), 1.59–1.82 (m, 4H, CH_2), 3.34 (dt, 1H, J_1=14 Hz, J_2=4.8 Hz, N–CH_2), 3.89 (td, 1H, J_1=11 Hz, J_2=4 Hz, N–CH_2), 4.02–4.07 (m, 1H, OCH_2), 4.18–4.24 (m, 1H, OCH_2), 5.71 (s, 1H, OCH), 6.60–6.68 (m, 2H, Ar*H*), 6.69 (dd, 2H, J_1=7.6 Hz, J_2=1.2 Hz Ar*H*), 6.86 (d, 1H, J=8.0 Hz, Ar*H*), 6.93 (s, 1H, OCH), 6.97–7.05 (m, 2H, Ar*H*), 7.30–7.35 (m, 2H, Ar*H*), 7.88 (dd, 1H, J_1=7.6 Hz, J_2=1.6 Hz, Ar*H*), 8.00 (d, 2H, J=7.2 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.66 (*C*H_2), 25.53 (*C*H_2), 25.96 (*C*H_2), 26.97 (*C*H_2), 27.57 (*C*H_2), 27.62 (*C*H_2), 27.91 (*C*H_2), 28.95 (*C*H_2), 39.10 (*C*H_2), 68.59 (*C*H_2), 83.29 (*quat-C*), 83.39 (OCH), 100.33 (OCH), 108.78 (=*C*H), 112.51 (=*C*H), 120.51 (=*C*H), 122.61 (=*C*H), 123.44 (=CH), 124.10 (*quat-C*), 125.57 (*quat-C*), 126.15 (=*C*H), 126.19 (=CH), 126.36 (=*C*H), 129.97 (=*C*H), 131.02 (=*C*H), 143.13 (*quat-C*), 143.79 (*quat-C*), 147.35 (*quat-C*), 157.83 (*quat-C*), 175.62 (*quat-C*); HRMS (ESI) calcd for $C_{32}H_{34}N_2O_6$ $[M+Na]^+$ 565.6119; found, 565.6132. Crystal data for the compound **13a**: (CCDC 851589) $C_{32}H_{34}N_2O_6$, M=542.61, 0.26×0.14×0.09 mm, Monoclinic, space group P–21 with a=14.5635(10) Å, b=10.8377(7) Å, c=18.1521(12) Å, α=90.00, β=97.7130(10), γ=90.00, V=2839.1(3) $Å^3$, T=293(2) K, R_1=0.0907, wR_2=0.2995 on observed data, z=4, D_{calcd}=1.270 mg cm^{-3}, F(000)=1152, Absorption coefficient=0.088 mm^{-1}, λ=0.71073 Å, 6151 reflections were collected on a smart apex CCD single crystal diffractometer 3812 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole=0.864 and −0.422 e $Å^{-3}$, respectively. The structure was solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL-97 software.

4.18. Synthesis of macrocycles 13b

A solution of diazoamide **7d** (100 mg, 0.22 mmol) and *p*-nitrobenzaldehyde (44 mg, 0.29 mmol), in dry dichloromethane (15 mL) was allowed to react with rhodium(II) acetate (1.4 mg, 1.42 mol %) at room temperature for 25 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to yield **13b** (59%). Colorless solid; mp 227–229 °C; IR (neat): ν_{max} 2926, 2853, 1725, 1675, 1596, 1522, 1467, 1259, 1031, 824, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.11–1.37 (m, 12H, CH_2), 1.59–1.80 (m, 4H, CH_2), 3.34 (dt, 1H, J_1=14.4 Hz, J_2=4.8 Hz, N–CH_2), 3.77 (s, 3H, OCH_3), 3.86 (td, 1H, J_1=11 Hz, J_2=4.0 Hz, N–CH_2), 4.00–4.05 (m, 1H, OCH_2), 4.17–4.24 (m, 1H, OCH_2), 5.69 (s, 1H, OCH), 6.41 (d, 1H, J=2.4 Hz, Ar*H*), 6.55 (dd, 1H, J_1=8.4 Hz, J_2=2.4 Hz, Ar*H*), 6.61 (d, 2H, J=8.0 Hz, Ar*H*), 6.66–6.68 (m, 1H, Ar*H*), 6.89 (s, 1H, OCH), 6.99 (td, 1H, J_1=7.6 Hz, J_2=1.6 Hz, Ar*H*), 7.33 (d, 2H, J=8.4 Hz, Ar*H*), 7.77 (d, 1H, J=8.4 Hz, Ar*H*), 7.97–8.01 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.18 (*C*H_2), 25.91 (*C*H_2), 26.75 (*C*H_2), 27.06 (*C*H_2), 28.91 (*C*H_2), 29.03 (*C*H_2), 29.13 (*C*H_2), 29.24 (*C*H_2), 40.04 (*C*H_2), 55.62 (OCH_3), 68.47 (*C*H_2), 77.26 (OCH), 78.61 (*quat-C*), 98.53 (OCH), 105.79 (=*C*H), 108.73 (=*C*H), 119.01 (*quat-C*), 122.60 (=*C*H), 122.88 (=*C*H), 125.77 (*quat-C*), 126.50 (=*C*H), 129.90 (=*C*H), 130.28 (=*C*H), 130.37 (=*C*H), 142.79 (*quat-C*), 143.47 (*quat-C*), 147.62 (*quat-C*), 163.43 (*quat-C*), 166.23 (*quat-C*), 175.92 (*quat-C*); HRMS (ESI) calcd for $C_{33}H_{36}N_2O_7$ $[M+Na]^+$ 595.6379; found, 595.6366.

4.19. Synthesis of macrocycles 13c

A solution of diazoamide **7b** (100 mg, 0.23 mmol) and *m*-bromobenzaldehyde (57 mg, 0.30 mmol), in dry dichloromethane (15 mL) was allowed to react with rhodium(II) acetate (1.5 mg, 1.4 mol %) at room temperature for 30 min. The reaction mixture was concentrated in vacuo and purified on silica (hexane/EtOAc, 65:35) to yield **13c** (50%). Colorless solid; mp 231–233 °C; IR (neat): ν_{max} 2929, 2857, 1719, 1606, 1522, 1493, 1467, 1251, 1066, 853, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.12–1.32 (m, 10H, CH_2), 1.61–1.79 (m, 6H, CH_2), 3.29 (dt, 1H, J_1=14 Hz, J_2=4 Hz, N–CH_2), 3.79–3.81 (m, 1H, N–CH_2), 3.98–4.03 (m, 1H, OCH_2), 4.09–4.20 (m, 1H, OCH_2), 5.64 (s, 1H, OCH), 6.36–6.3 (m, 1H, Ar*H*), 6.51 (dd, 1H, J_1=8.2 Hz, J_2=1.8 Hz, Ar*H*), 6.59 (d, 2H, J=7.8 Hz, Ar*H*), 6.61–6.65 (m, 2H, Ar*H*), 6.78 (s, 1H, OCH), 6.87 (td, 1H, J_1=7.8 Hz, J_2=1.8 Hz, Ar*H*), 7.21 (d, 2H, J=7.8 Hz, Ar*H*), 7.53 (d, 1H, J=8.0 Hz, Ar*H*), 7.72–7.86 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.59 (*C*H_2), 25.85 (*C*H_2), 26.45 (*C*H_2), 26.89 (*C*H_2), 27.91 (*C*H_2), 28.23 (*C*H_2), 29.05 (*C*H_2), 29.35 (*C*H_2), 39.45 (*C*H_2), 68.38 (*C*H_2), 80.24 (*quat-C*), 81.35 (OCH), 99.85 (OCH), 106.65 (=*C*H), 107.81 (=*C*H), 118.81 (*quat-C*), 120.21 (=*C*H), 121.41 (=*C*H), 122.13 (=*C*H), 124.10 (*quat-C*), 125.13 (*quat-C*), 126.02 (=*C*H), 126.11 (=*C*H), 126.26 (=*C*H), 128.87 (=*C*H), 132.42 (=*C*H), 142.23 (*quat-C*), 143.71 (*quat-C*), 147.21 (*quat-C*), 161.08 (*quat-C*), 175.72 (*quat-C*); HRMS (ESI) calcd for $C_{32}H_{34}BrNO_4$ $[M+Na]^+$ 599.5104; found, 599.5121.

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References and notes

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14. CCDC-851590 (for **9e**), 851589 (for **13a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.