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Synthesis of hydroquinone-, biphenol-, and binaphthol-containing aza macroheterocycles via regioselective hydroformylation and reductive amination

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Abstract—Rhodium(I) catalyzed regioselective hydroformylation of diolefins and subsequent reductive amination of the dialdehydes in the presence of α,ω-diamines is applied to azamacroheterocyclic ring synthesis. Starting from aromatic diallyl ethers of hydroquinone, biphenol and binaphthol 20–28 membered macroheterocycles were obtained in up to 78% yield.

1. Introduction

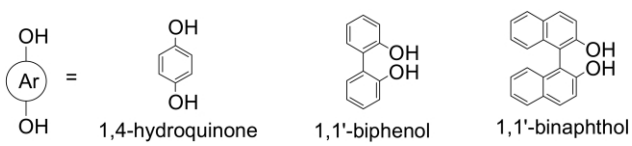
Macroheterocycles containing chiral subunits are desired synthetic targets due to their increasing use as tools in chiral recognition[1] and as ligands in asymmetric metal catalysis.[2,3] Nonnatural atropisomeric biaryl systems with axial chirality, e.g. 2,2′-substituted 1,1′-binaphthyls, are available in both enantiomeric forms and therefore frequently integrated into macroheterocyclic systems and used for various applications.[2]

There are several methods available for the synthesis of medium-and large-sized heterocyclic systems.[4] The most common access is provided by the Richman–Atkins approach,[5] which involves nucleophilic substitution of α,ω-dihalides, -ditosylates or -dimesylates with α,ω-ditosylamides or α,ω-diols in the presence of base. However, with this approach the starting materials are sometimes difficult to obtain and all nitrogen atoms in the final macrocycle generally have to be protected.

In one of the alternative approaches azamacroheterocyclic systems are synthesized starting from dialdehydes and diamines via diimine formation.[6] Frequently these diimines are reduced to saturated amines in a second step. This type of reductive amination of aldehydes can also be performed in a one step procedure and furthermore conveniently be combined with an in situ generation of the aldehydes via hydroformylation in a single reaction sequence starting from olefins and amines.[7] Thus the olefin components react under hydroformylation conditions (CO, H_2, rhodium catalyst) in the presence of amines in an overall 'hydroaminomethylation' addition reaction. We recently reported successful applications of this tandem reaction in the synthesis of macroheterocycles from diolefins and diamines in comparatively high yields.[8]

2. Results and discussion

In this work we report the application of this procedure in the synthesis of azamacroheterocycles containing hydroquionone, 1,1′-biphenol and finally the axially chiral (*R*)- or (*S*)-1,1′-binaphthol units (Scheme 1). The diolefinic building blocks were prepared as diallylic ethers of these phenolic diols.



Scheme 1.

With these substrates, however, possible Claisen rearrangements occuring at elevated temperatures had to be prevented by choosing appropriate conditions. Furthermore, in order to prevent the formation of regioisomeric aldehydes (*n*,*n*, *n*,*iso*, *iso*,*iso*) which are expected, when performing hydroformylation with unsubstituted diallyl systems, bismethylallyl systems of type **1a**-**c** were used. Here, according to 'Keuleman's rule'[9] hydroformylation is expected to occur only in the terminal position. On the other hand, however,

Keywords: macrocycles; hydroaminomethylation; regioselective hydroformylation; reductive amination; rhodium catalysis; chiral ligands; BINOL.

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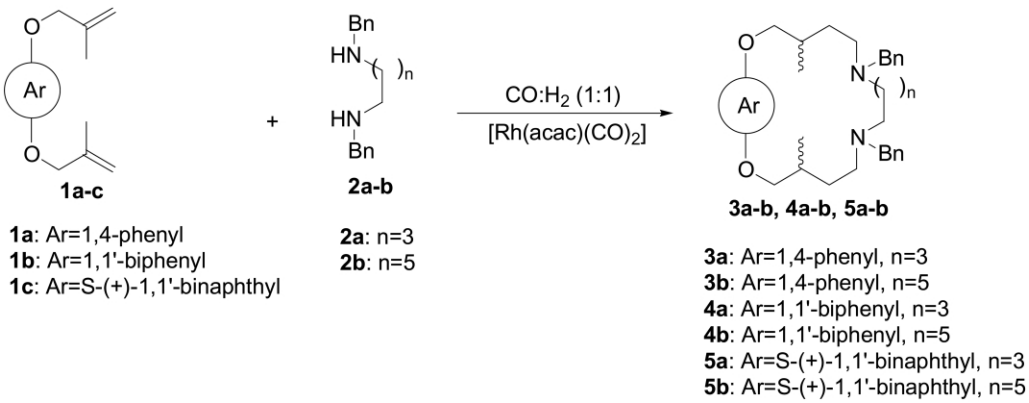


Scheme 2.

upon hydroformylation of the methallylic group two new stereogenic centers are generated, leading to a mixture of meso and D,L stereoisomers. Use of the chiral BINOL unit should reveal a possible stereocontrol.

As model compounds the diamine units **2a**,**b** were easily prepared from tetramethylene diamine and hexamethylene diamine.[10a,b] Monobenzyl protection of both amino groups prevents overalkylation and leaves the option to prepare cryptand type molecules after debenzylation followed by a second hydroaminomethylation of the resulting macrocyclic diamine with the same or a different diolefin as shown before.[8a] Furthermore, the resulting free NH groups can be used to attach side-chains (e.g. long hydrophobic chains), or polymer units.

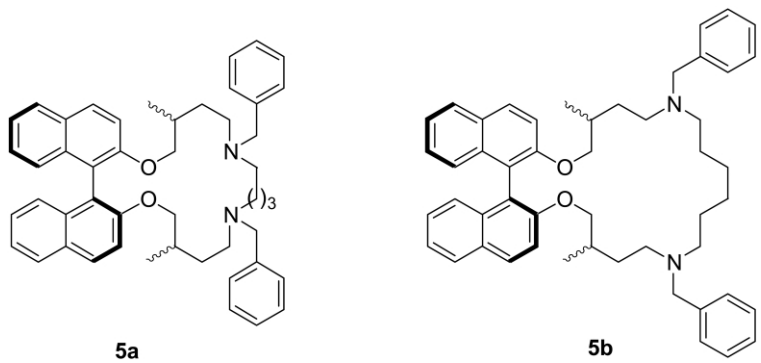
As compared to our previous work,[8a] for the hydroaminomethylation of bis-methylallyl phenyl ethers (**1a**-**c**, Scheme 2) in the presence of diamines **2a**,**b** milder conditions could be used. Lower temperatures were chosen (80°C instead of 120°C) in order to prevent possible Claisen rearragement of the aromatic allyl ethers at temperatures higher than 90–100°C. The rhodium catalyst was changed from $[Rh(cod)Cl]_2$ to $[Rh(acac)(CO)_2]$, since the former is more active at higher while the latter is more active at lower temperatures. As shown in Table 1 the yields of macrocycles **3a**,**b**, **4a**,**b**, and **5a**,**b** are comparetively high.

Table 1. Hydroaminomethylation reaction of bis-methylallyl phenyl ethers **1a**-**c** with **2a**,**b**

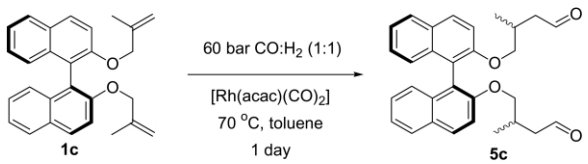
Entry	Ar	Diamine	Product	Yield (%)
1	Phenyl-	**2a**	**3a**	64
2	Phenyl-	**2b**	**3b**	59
3	1,1′-Biphenyl-	**2a**	**4a**	68
4	1,1′-Biphenyl-	**2b**	**4b**	75
5	*S*-(+)-binaphthyl-	**2a**	**5a**	78
6	*S*-(+)-binaphthyl-	**2b**	**5b**	78

The best yields (78%) were observed for the macrocyclic compounds **5a** and **5b** (Scheme 3) containing the S-BINOL unit. This findings are establishing the hitherto best results in synthesis of macroheterocycles via hydroaminomethylation.

According to this procedure, as expected, exclusively the *n*,*n*-dialdehydes and macrocycles thereof are formed, but with generation of two new stereocenters at both carbons bearing the methyl groups. Thus, the final products are obtained as a mixture of enantiomers resp. diastereoisomers (*R*,*S*,*R*,*R*,*S*,*S*), which could not be separated. According to the ^{1}H NMR spectra **3a**,**b** are obtained as a 1:1 mixture of the DL and *meso* isomers. **4a**,**b** and **5a**,**b** are also formed as a mixture of stereoisomers with approximately 1:1 ratio. For further clarification of the stereocontrol during the hydroformylation step aldehyde **5c** (Scheme 4) was prepared in the absence of the diamines **2a**,**b** in a control experiment. Here again according to ^{1}H NMR three stereoisomers are detectable in a statistical 1:2:1 ratio (S_{axial},*R*,*R*/S_{axial},*R*,*S*+$_{axial}$,*R*,*S*+S_{axial},*S*,*R*/S_{axial},*S*,*S*). Thus no stereocontrol of the BINOL unit is effective during hydroformylation under the chosen conditions.

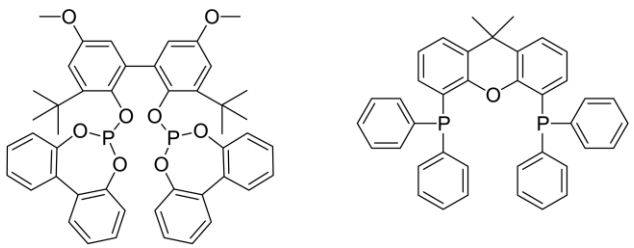


Scheme 3.



Scheme 4.

In order to avoid these complications with the newly generated stereogenic centers from the methallyl groups, the unsubstituted allyl ethers **6a-c** of hydroquinone, 1,1′-biphenol and (*R*)-1,1′-binaphthol were prepared and converted under hydroformylation conditions in the presence of BIPHEPHOS[11] and XANTPHOS[12a] (Scheme 5) to control the required regioselectivity towards the *n*,*n*-dialdehydes.



Scheme 5.

The first runs with BIPHEPHOS were unsuccessful, since this ligand is not sufficiently stable under the conditions required, therefore XANTPHOS (Scheme 5) was used as the ligand.

It is known that XANTPHOS can be used even under harsher conditions (up to 120°C) without decomposition and with good regioselectivities.[12b] Under the conditions used here (70°C, CO/H_2 20 bar), the desired *n*,*n*-dialdehydes were obtained in up to 80% yield (Table 2).

Table 2. Hydroformylation of **6a-c** in the presence of XANTPHOS

Entry	Ar	Aldehyde	Yield (%)
1	Phenyl-	**7a**	78
2	1,1′-Biphenyl-	**7b**	63
3	*R*-(−)-1,1′-binaphthyl-	**7c**	80

The regioselectivity with use of this ligand for allylic ethers in the best cases ranges in the area of 90–95% (*n*/*iso*). Therefore if using a diolefin, the yield of *n*,*n*-dialdehyde cannot be expected to be better than 80–85%. Heteroallyl compounds in the absence of any ligands usually prefer hydroformylation to form the *iso*-product (1:2 *n*/*iso*),[13] thus use of XANTPHOS in the present case gives satisfying results.

First control experiments of a tandem hydroaminomethylation conversion of the diolefins in the presence of diamines directly to the macrocycles revealed that XANTPHOS as an additional ligand controlling the regioselectivity under the conditions used is not efficient in the presence of the amines. Consequently macrocycles **8a**,**b**, **9a**,**b**, and **10a**,**b** were prepared in a stepwise manner, with first running the hydroformylation of the diolefins in the presence of the XANTPHOS ligand and the catalyst, isolation and characterization of the *n*,*n*-dialdehyde and then converting these in a second autoclave reaction in the presence of the diamine and the same rhodium catalyst with 40–50 bar of hydrogen. The yields are given in Table 3 and, with one exeption, range from 43 to 71%.

Table 3. Reductive amination of the aldehydes **7a-c** with diamines **2a**,**b**

Entry	Aldehyde	Diamine	Product	Yield (%)
1	**7a**	**2a**	**8a**	52
2	**7a**	**2b**	**8b**	48
3	**7b**	**2a**	**9a**	43
4	**7b**	**2b**	**9b**	29
5	**7c**	**2a**	**10a**	50
6	**7c**	**2b**	**10b**	71

The overall yields in the stepwise procedure (hydroformylation and reductive amination) varied from 18 to 57% for the macrocycles **8a**,**b**, **9a**,**b**, and **10a**,**b**, whereas yields using the tandem hydroformylation in the case of the methallyl ethers **1a-c** reaction to form macrocycles **3a**,**b**, **4a**,**b**, and **5a**,**b** were in the range of 59–76%. If, however, comparing these results with classical methods of reductive amination[14] using $NaBH_3CN$ or $Na(OAc)_3BH$ as reducing agents, for **9a** a yield of only 32% and for **9b** of only 19% was obtained. Interestingly, to our knowledge, there are only few examples for the synthesis of azamacroheterocycles via reductive amination starting from dialdehydes and secondary diamines. In the examples presented here the comparably high yields with the rhodium catalyzed reductive ammination may be due to a template effect of the rhodium during ring closure, which is even more effective in the tandem procedure with lower stationary concentrations of the dialdehydes.

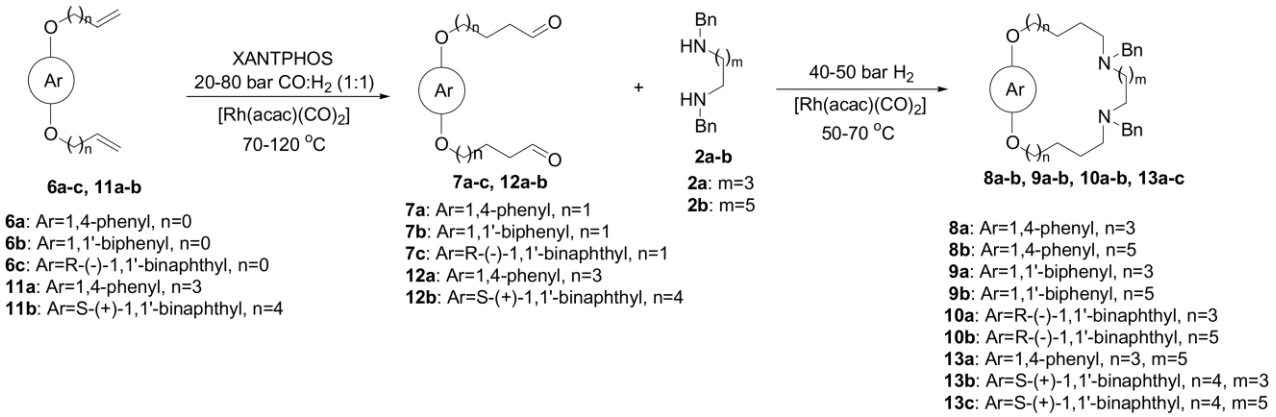
In contrast to the NMR spectra of **8b**, **9a**, **9b**, and **10b** those of the products **8a**, and **10a** showed splitted signals for the *N*-benzyl methylene and the oxygen neighbouring methylene protons. These splittings are changing towards single signals upon heating (**8a**). This is attributed to different rigid stereoisomeric conformations of the ring and/or different 'frozen' pyramidal geometries at the nitrogens with the benzyl groups either on the same side or on different sides of the ring. At room temperature this is not observed with macrocycles **8b**, **9b**, and **10b** containing the longer hexamethylene diamine chain. Thus the molecular dynamics of the products obtained appear to be very sensitive to the chain length of the subunits. These effects may also influence the tendency of ring closure and the corresponding yields for the individual macrocycles. The results presented here, however do not show a clear tendency in this direction.

For comparison selected examples of unsaturated ethers as diolefins other than allyl ethers were stepwise converted under slightly modified reaction conditions as described above to form macroheterocycles with up to 28 membered rings (Table 4, Scheme 6).

Harsher reaction conditions had to be used for the hydroformylation step in order to obtain the dialdehydes.

Table 4. Regioselective hydroformylation of **11a**,**b** and reductive amination of **12a**,**b** with diamines **2a**,**b**

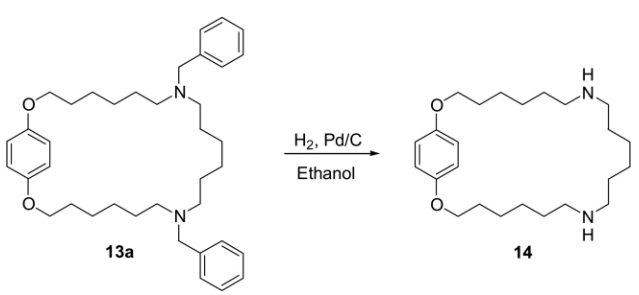
Entry	Ar	*n*	Aldehyde	Yield (%)	*m*	Product	Yield (%)
1	Phenyl	3	**12a**	74	5	**13a**	53
2	*S*-(+)-1,1′-binaphthyl	4	**12b**	58	3	**13b**	77
3	*S*-(+)-1,1′-binaphthyl	4	**12b**	58	5	**13c**	78



Scheme 6.

While typical hydroformylation conditions for *O*-allylic olefins were 20 bar of CO/H_2 pressure (1:1) and temperatures of 70°C, for aldehyde **11a** we had to use temperatures of 120 and 100°C for **11b**. In both cases the pressure had to be increased to 60–80 bar CO/H_2 (1:1). The conditions for the reductive amination step were maintained. The results compiled in Table 4 again show good yields and selectivities.

Unexpectedly with increasing ring size compound **13a** according to NMR showed the same rigidity characteristics as previously described for compounds **8a** and **10a** while this could not be observed for compounds **13b** or **13c**. After debenzylation of **13a** to the secondary diamine ring system **14** (Scheme 7) the observed signal splitting at the O-neighbouring methylene groups disappeared, thus clearly showing that the benzyl groups are responsible for this effect.



Scheme 7.

3. Conclusion

In conclusion, the procedure described here shows a high potential for a versatile synthesis of various macroheterocycles of different ring size containing rigid and axially chiral aromatic subunits in good yields and selectivities. The diamine unit as well as the diolefin unit can be varied in many different ways as already shown in our previous reports.[7,8] Continuing these investigations the method offers various options for fine-tuning the coordination properties and geometries of ligands for transition metal catalysts or hosts for molecular recognition.

4. Experimental

4.1. General remarks

All chemicals were purchased from commercial sources. ^1H and ^{13}C NMR spectra were recorded at room temperature with a Bruker DRX 400 and DRX 500 spectrometers using $CDCl_3$ as solvent and TMS as an internal standard. Infrared spectra were recorded with a Nicolet Impact 400 D spectrometer using neat compounds as films between NaCl plates or as disks with KBr and only the major bands are noted. Mass spectra were recorded with a JEOL JMS-SX 102A spectrometer. Elemental analyses were performed with a Leco CHNS-932 analyzer.

Pressure reactions were carried out in autoclaves (250 ml, PTFE insert) from Berghof, Eningen. After charging the autoclave with the starting material, the catalyst precursor, and the solvent (1,4-dioxane or toluene), the reactor was flushed with argon, pressurised with hydrogen and carbon monoxide, and heated to the required reaction temperature. Following the reaction, the solvent was removed by rotary evaporation and products were purified by column chromatography on silica gel 60 (70–230 mesh ASTM) from Macherey-Nagel GmbH & Co. KG.

4.1.1. Preparation of 7,12-dibenzyl-4,15-dimethyl-2,17-dioxa-7,12-diaza-bicyclo[16.2.2]docosa-1(21)18(22),19-triene (3a). 1,4-Bis-(2-methyl-allyloxy)-benzene (**1a**)[15a] (77 mg, 0.35 mmol), *N*,*N*′-dibenzyl-butane-1,4-diamine (**2a**)[10a] (81 mg, 0.30 mmol) and $[Rh(acac)(CO)_2]$ (4 mg, 16 μmol) were dissolved in 40 ml of 1,4-dioxane and placed in the autoclave. The autoclave was pressurised with 80 bar CO/H_2 (1:1) and heated at 80°C for 3 days. After cooling the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel,

CH_2Cl_2/MeOH 97:3) to give 99 mg (64%) of **3a** as a viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=7.21–7.17 (m, 8H), 7.16–7.13 (m, 2H), 6.82 (s, 2H), 6.81 (s, 2H), 4.06 (dd, J=11.0, 4.5 Hz, 1H), 3.90 (dd, J=11.0, 5.3 Hz, 1H), 3.78 (dd, J=10.8, 8.3 Hz, 1H), 3.66 (dd, J=10.8, 8.0 Hz, 1H), 3.56 (d, J=4.0 Hz, 1H), 3.42 (d, J=13.5 Hz, 1H), 3.21 (d, J=13.5 Hz, 1H), 3.11 (d. J=13.5 Hz, 1H), 2.39–2.24 (m, 2H), 2.20–2.09 (m, 4H), 2.03–1.97 (m, 2H), 1.87–1.80 (m, 1H), 1.76–1.72 (m, 2H), 1.62–1.54 (m, 1H), 1.22–1.16 (m, 1H), 1.12–0.94 (m, 4H), 0.90–0.84 (m, 1H), 0.67 & 0.64 (two d, 1:1, J=6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=152.22, 140.12, 128.95 & 128.88, 127.98, 126.62, 116.15 & 115.95, 72.86 & 72.74, 59.00 & 58.88, 53.38 & 53.08, 50.90 & 50.73, 29.12 & 29.04, 29.06 & 28.87, 25.84 & 25.69, 16.44 & 16.05. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2952, 2794, 1506, 1228, 1207. HRMS (FAB): for $C_{34}H_{46}N_2O_2$ calcd: 513.3481 $[M-H]^+$, 515.3638 $[M+H]^+$; found: 513.3469, 515.3612.

4.1.2. Preparation of 7,14-dibenzyl-4,17-dimethyl-2,19-dioxa-7,14-diaza-bicyclo[18.2.2]tetracosa-1(23), 20(24),21-triene (3b). 1,4-Bis-(2-methyl-allyloxy)-benzene (**1a**) (53 mg, 0.24 mmol), *N*,*N*′-dibenzyl-hexane-1,6-diamine (**2b**)[10b] (72 mg, 0.24 mmol) and [Rh(acac)$(CO)_2$] (3 mg, 12 μmol) were dissolved in 40 ml of 1,4-dioxane and placed in the autoclave. The autoclave was pressurised with 80 bar CO/H_2 (1:1) and heated at 80°C for 3 days. After cooling the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to give 78 mg (59%) of **3b** as a viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=7.20–7.18 (m, 8H), 7.15–7.11 (m, 2H), 6.79 (s, 4H), 3.87–3.77 (m, 4H), 3.46 (d, J=5.0 Hz, 1H), 3.43 (d, J=4.8 Hz, 1H), 3.31 (s, 1H), 3.28 (s, 1H), 2.40–2.25 (m, 4H), 2.23–2.16 (m, 2H), 2.12–2.05 (m, 2H), 2.03–1.96 (m, 2H), 1.64–1.57 (m, 2H), 1.31–1.25 (m, 2H), 1.20–1.11 (m, 4H), 0.88–0.86 (m, 4H), 0.78 (two d, 1:1, J=6.8 Hz, 6H) ^{13}C NMR (100 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=152.69, 152.62, 140.05, 128.91, 128.84, 127.99, 126.60, 115.63, 72.76, 72.70, 59.04, 58.98, 53.41, 53.34, 50.37, 29.90, 29.79, 29.52, 29.48, 27.82, 27.77, 26.87, 17.15, 17.09. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2931, 2794, 1506, 1228, 1028. HRMS (FAB): for $C_{36}H_{50}N_2O_2$ calcd: 543.3951 $[M+H]^+$; found: 543.3946.

4.1.3. Preparation of 2,2′-bis-(methyl-allyloxy)-biphenyl (1b). Biphenyl-2,2′diol (6.02 g, 32.3 mmol) was added to a stirred mixture of methylallyl chloride (7.6 g, 84.5 mmol) and potassium carbonate (11.1 g, 80.5 mmol) in 50 ml of acetone and heated under reflux for 2 days. After cooling K_2CO_3 was removed by filtration and the acetone was evaporated. The crude product was purified by column chromatography (silica gel, cyclohexane/MTBE 9:1) to give 4.97 g (52%) of **1b** as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22–7.17 (m, 4H), 6.90 (dt, J=6.8, 1.0 Hz, 2H), 6.83 (d, J=8.3 Hz, 2H), 4.77 (d, J=26.1 Hz, 4H), 4.26 (s, 4H), 1.57 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.11, 140.96, 131.44, 128.30, 128.24, 120.24, 112.08, 11.52, 71.63, 19.21. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=3072, 2911, 1442, 1228. EA: for $C_{20}H_{22}O_2$ (294.40 g/mol) calcd: C: 81.6%, H: 7.5%, found: C: 81.4%, H: 7.4%. MS (FAB): 294 $[M]^+$, 239, 154, 136.

4.1.4. Preparation of 10,15-dibenzyl-7,18-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-5,20-dioxa-10,15-diaza-dibenzo[*a*,*c*]cycloeicosene (4a). 2,2′-Bis-(2-methyl-allyloxy)-biphenyl (**1b**) (66 mg, 0.22 mmol), *N*,*N*′-dibenzyl-butane-1,4-diamine (**2a**) (65 mg, 0.24 mmol) and [Rh(acac)$(CO)_2$] (3 mg, 12 μmol) were dissolved in 40 ml of 1,4-dioxane and placed in the autoclave. The autoclave was pressurised with 80 bar CO/H_2 (1:1) and heated at 80°C for 3 days. After cooling solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to give 90 mg (68%) of **4a** as a viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=7.22–7.12 (m, 14H), 6.89–6.81 (m, 4H), 3.93–3.51 (m, 4H), 3.49–3.27 (m, 4H), 2.29–2.16 (m, 8H), 1.84–1.77 (m, 2H), 1.49–1.41 (m, 2H), 1.38–1.22 (m, 4H), 1.16–1.04 (m, 2H), 0.67–0.55 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=156.80 & 156.66, 140.10 & 140.04 & 140.01, 131.67 & 131.32 & 131.09, 128.93 & 128.88 & 128.82, 128.60 & 128.57, 128.22 & 128.16 & 128.07 & 128.02, 126.67 & 126.59, 120.15 & 120.00, 119.87 & 119.43, 112.99 & 112.93 & 112.12 & 111.94, 73.83 & 73.50 & 73.32, 59.16 & 58.93 & 58.87, 53.36 & 53.20, 51.36 & 51.13 & 51.10 & 50.81, 31.39 & 31.33 & 31.18, 30.68 & 30.11, 25.12 & 24.86 & 24.69, 17.31 & 17.05 & 16.92 & 16.82. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2929, 2796, 1444, 1259, 1236. HRMS (FAB): for $C_{40}H_{50}N_2O_2$ calcd: 591.3951 $[M+H]^+$, found: 591.3984.

4.1.5. Preparation of 10,17-dibenzyl-7,20-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21-hexadecahydro-5,22-dioxa-10,17-diaza-dibenzo[*a*,*c*]cyclodocosene (4b). 2,2′-Bis-(2-methyl-allyloxy)-biphenyl (**1b**) (162 mg, 0.55 mmol), *N*,*N*′-dibenzyl-hexane-1,6-diamine (**2b**) (151 mg, 0.51 mmol) and [Rh(acac)$(CO)_2$] (4 mg, 16 μmol) were dissolved in 40 ml of 1,4-dioxane and placed in the autoclave. The autoclave was pressurised with 80 bar CO/H_2 (1:1) and heated at 80°C for 3 days. After cooling solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to give 235 mg (75%) of **4b** as a viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=7.19–7.10 (m, 14H), 6.81 (t, J=7.2 Hz, 2H), 6.71 (t, J=8.2 Hz, 2H), 3.57–3.50 (m, 4H), 3.32 (dd, J=22.9, 13.7 Hz, 4H), 2.26–2.17 (m, 8H), 1.71–1.66 (m, 2H), 1.30–1.23 (m, 4H), 1.09–1.03 (m, 8H), 0.67 (d, J=6.7 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=156.75 & 156.61, 139.38 & 139.88, 131.55 & 131.46, 128.88, 128.64, 128.36, 128.13, 128.01 & 127.96, 126.62 & 126.57, 120.00 & 119.95 & 119.90, 112.64 & 112.36, 74.05 & 73.89 & 73.55 & 73.46, 58.94 & 58.85 & 58.76, 53.07 & 52.98 & 52.82, 51.13 &

50.96 & 50.90 & 50.87, 31.44 & 31.29 & 31.23 & 31.13, 30.95 & 30.91, 30.29, 26.69 & 26.65 & 26.51 & 26.45, 17.09 & 17.02 & 16.85. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2927, 2794, 1466, 1261. HRMS (FAB): for $C_{42}H_{54}N_2O_2$ calcd: 618.4185 $[M]^+$; found: 618.4172.

4.1.6. Preparation of 10,15-dibenzyl-7,18-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-5,20-dioxa-10,15-diaza-dinaphtho[*a*,*c*]cycloeicosene (5a). (*S*)-(−)-2,2′-Bis-(2-methyl-allyloxy)-[1,1′]binaphthalenyl (**3c**)[16] (153 mg, 0.39 mmol), *N*,*N*′-dibenzyl-butane-1,4-diamine (**2a**) (100 mg, 0.37 mmol) and [Rh(acac)$(CO)_2$] (4 mg, 16 μmol) were dissolved in 40 ml of 1,4-dioxane and placed in the autoclave. The autoclave was pressurised with 80 bar CO/H_2 (1:1) and heated at 80°C for 3 days. After cooling solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to give 200 mg (78%) of **5a** as a viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=7.85–7.71 (m, 4H), 7.35–7.07 (m, 18H), 3.94–3.85 (m, 2H), 3.64–3.51 (m, 2H), 3.48–3.15 (m, 4H), 2.23–2.13 (m, 4H), 2.07–1.95 (m, 4H), 1.71–1.59 (m, 2H), 1.37–1.01 (m, 8H), 0.39–0.27 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=154.75 & 154.63 & 154.40, 140.31 & 140.12, 134.25 & 134.21, 129.34 & 129.28, 129.10 & 129.06, 128.99 & 128.97 & 128.94, 128.87, 128.81 & 128.75, 128.01 & 127.97, 127.73 & 127.70, 126.60 & 126.59, 126.50, 125.96 & 125.93, 125.46 & 125.45 & 125.42, 123.38 & 123.24, 120.91 & 120.52 & 120.38, 116.24 & 116.17, 115.63 & 115.49, 74.88 & 74.69 & 74.62, 59.09 & 58.98 & 58.83 & 58.70, 53.44 & 53.16 & 53.13, 50.95 & 50.93 & 50.84 & 50.75, 31.19 & 31.11 & 31.09, 30.61 & 30.57, 29.98 & 29.89, 25.19 & 25.14 & 25.00 & 24.72, 16.78 & 16.69 & 16.48. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2951, 2796, 1508, 1456, 1265, 1244. HRMS (FAB): for $C_{48}H_{54}N_2O_2$ calcd: 691.4264 $[M+H]^+$, found: 691.4294.

4.1.7. Preparation of 10,17-dibenzyl-7,20-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21-hexadecahydro-5,22-dioxa-10,17-diaza-dinaphtho[*a*,*c*]cyclodocosene (5b). (*S*)-(−)-2,2′-Bis-(2-methyl-allyloxy)-[1,1′]-binaphthalenyl (**3c**) (150 mg, 0.38 mmol), *N*,*N*′-dibenzyl-hexane-1,6-diamine (**2b**) (113 mg, 0.38 mmol) and [Rh(acac)$(CO)_2$] (4 mg, 16 μmol) were dissolved in 40 ml of 1,4-dioxane and placed in the autoclave. The autoclave was pressurised with 80 bar CO/H_2 (1:1) and heated at 80°C for 3 days. After cooling solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to give 213 mg (78%) of **5b** as a viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=7.82–7.74 (m, 4H), 7.33–7.28 (m, 2H), 7.21–7.12 (m, 16H), 3.84–3.76 (m, 2H), 3.63–3.56 (m, 1H), 3.49–3.41 (m, 1H), 3.36–3.28 (m, 3H), 3.21–3.15 (m, 1H), 2.26–2.14 (m, 4H), 2.09–2.01 (m, 4H), 1.69–1.54 (m, 2H), 1.32–0.95 (m, 12H), 0.35 & 0.29 (two m, 1:1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereomers: δ=154.63, 154.55 & 154.52, 140.20, 139.95, 134.25 & 134.22, 129.29, & 129.24 & 129.92, 128.99 & 129.96, 128.89 & 128.86 & 128.82, 128.01 & 127.97, 127.73 & 127.70, 126.60 & 126.53, 125.94, 125.52 & 125.47, 123.34, 120.84 & 120.76 & 120.71, 116.02 & 115.92 & 115.85, 75.23 & 75.02 & 74.82 & 74.72, 58.87 & 58.75 & 58.66 & 58.61, 53.03 & 52.98 & 52.78, 50.99 & 50.88 & 50.74, 31.27 & 31.11 & 31.07 & 31.03, 30.63 & 30.50, 30.09, 26.88 & 26.76 & 26.64 & 26.48, 16.70 & 16.65 & 16.55. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2927, 2794, 1591, 1506, 1456, 1263, 1242. HRMS (FAB): for $C_{50}H_{58}N_2O_2$ calcd: 719.4577 $[M+H]^+$; found: 719.4567.

4.1.8. Preparation of 3-methyl-4-[2′-(2-methyl-4-oxo-butoxy)-[1,1′]binaphthalenyl-2-yloxy]-butyraldehyde (5c). (S)-(−)-2,2′-Bis-(2-methyl-allyloxy)-[1,1′]binaphthalenyl (**3c**) (135 mg, 0.34 mmol) and [Rh(acac)$(CO)_2$] (4 mg, 16 μmol) were dissolved in 15 ml of toluene and placed in the autoclave. Mixture was pressurised with 60 bar CO/H_2 (1:1) and heated at 80°C for 1 day. After cooling solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, CH_2Cl_2) to give 114 mg (73%) of **5c** as a colourless viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$), signals for a 1:1:2 mixture of 3 diastereomers: δ=9.04, 9.03 & 8.92 (three t, 1:1:2, *J*=1.7 Hz, 1H), 7.87 (d, *J*=2.7 Hz, 1H), 7.85 (d, *J*=2.7 Hz, 1H), 7.77 (d, *J*=8.2 Hz, 2H), 7.31–7.27 (m, 2H), 7.24 (t, *J*=7.2 Hz, 2H), 7.16–7.08 (m, 4H), 3.87 (dd, *J*=8.7, 4.7 Hz, 1H), 3.82–3.78 (m, 1H), 3.69–3.66 (m, 1H), 3.59–3.54 (m, 1H), 2.11–1.99 (m, 2H), 1.86–1.79 (m, 2H), 1.70–1.61 (m, 2H), 0.60, 0.59 & 0.56 (three d, 1:1:2, *J*=5.0, 5.0, 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): signals for a 1:1:2 mixture of 3 diastereomers: δ=201.99 & 201.96 & 201.87, 154.00 & 153.91, 133.99, 129.32, 129.29, 127.84, 126.28, 125.32 & 125.29, 123.72 & 123.69, 120.50 & 120.47 & 120.38, 115.52 & 115.43 & 115.34 & 115.28, 73.64 & 73.60 & 73.55 & 73.52, 47.30 & 47.16, 28.36 & 28.33, 16.62 & 16.47. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}] 2960, 1722, 1591, 1506, 1271, 1242. HRMS (FAB): for $C_{30}H_{30}O_4$ calcd: 454.2144 $[M]^+$; found: 454.2155.

4.1.9. Preparation of 4-[4-(4-oxo-butoxy)-phenoxy]-butyraldehyde (7a). 1,4-Bis-allyloxy-benzene (**6a**)[15b] (500 mg, 2.63 mmol), [Rh(acac)$(CO)_2$] (5 mg, 19 μmol), XANTPHOS (50 mg, 86 μmol) and toluene (15 ml) were dissolved in the autoclave. The solution was pressurised with 20 bar CO/H_2 (1:1) and heated at 70°C for 18 h. The solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, Et_2O/*n*-hexane 1:1) to give 515 mg (78%) of **7a** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ=9.77 (s, 2H), 6.73 (s, 4H), 3.88 (t, *J*=6.0 Hz, 4H), 2.59 (dt, *J*=5.7, 1.2 Hz, 4H), 2.04–2.01 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=201.95, 152.88, 115.32, 67.21, 40.60, 22.03. IR (disk, KBr), $\tilde{\nu}$ [cm^{-1}]=2951, 2833, 2727, 1714, 1512, 1238. EA: for $C_{14}H_{18}O_4$ (250.29 g/mol) calcd: C: 67.2%, H: 7.2%, found: C: 66.7%, H: 7.2%. HRMS (EI): calcd: 250.1205 $[M]^+$; found: 250.1196. Mp: 49°C.

4.1.10. Preparation of 4-[2′-(4-oxo-butoxy)-biphenyl-2-yloxy]-butyraldehyde (7b). 2,2′-Bis-allyloxy-biphenyl

(**6b**)[17] (586 mg, 2.20 mmol), [Rh(acac)(CO)$_2$] (4 mg, 16 μmol), XANTPHOS (41 mg, 71 μmol) and toluene (15 ml) were dissolved in the autoclave. The solution was pressurised with 20 bar CO/H$_2$ (1:1) and heated at 70°C for 18 h. The solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, Et$_2$O/*n*-hexane 1:1) to give 451 mg (63%) of **7b** as a colourless viscous oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ=9.46 (s, 2H), 7.23 (dt, *J*=6.5, 1.5 Hz, 2H), 7.14 (dd, *J*=5.8, 1.8 Hz, 2H), 6.94 (dt, *J*=6.3, 1.0 Hz, 2H), 6.87 (d, *J*=8.3 Hz, 2H), 3.87 (t, *J*=5.8 Hz, 4H), 2.29 (dt, *J*=5.8, 1.2 Hz, 4H), 1.88–1.82 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ=202.05, 156.14, 131.32, 128.52, 128.45, 120.62, 110.57, 67.39, 40.35, 22.00. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2937, 1722, 1441, 1234. EA: for C$_{20}$H$_{22}$O$_4$ (326.40 g/mol) calcd: C: 73.6%, H: 6.8%, found: C: 73.3%, H: 6.9%. MS (EI): 326 [M]$^+$, 256, 228, 212, 197.

4.1.11. Preparation of (*R*)-(+)-4-[2′-(4-oxo-butoxy)-[1,1′]binaphtalenyl-2-yloxy]-butyraldehyde (7c). (*R*)-(+)-2,2′-Bis-allyloxy-[1,1′]binaphthalenyl (**6c**)[16] (412 mg, 1.12 mmol), [Rh(acac)(CO)$_2$] (3 mg, 12 μmol), XANTPHOS (30 mg, 52 μmol) and toluene (15 ml) were dissolved in the autoclave. The solution was pressurised with 20 bar CO/H$_2$ (1:1) and heated on 70°C for 18 h. The solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, toluene/EtOAc 9:1) to give 384 mg (80%) of **7c** as a colourless viscous oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ=9.05 (s, 2H), 7.88 (t, *J*=9.0 Hz, 2H), 7.80 (d, *J*=8.2 Hz, 2H), 7.33 (d, *J*=9.0 Hz, 2H), 7.27 (t, *J*=8.0 Hz, 2H), 7.16 (dt, *J*=5.7, 1.0 Hz, 2H), 4.00–3.96 (m, 2H), 3.85–3.81 (m, 2H), 1.85–1.72 (m, 4H), 1.66–1.58 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ=201.78, 153.93, 131.89, 129.32, 129.26, 127.84, 126.27, 125.20, 123.71, 120.58, 115.75, 68.42, 39.70, 21.75. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2937, 1722, 1591, 1506, 1263. HRMS (EI): for C$_{28}$H$_{26}$O$_4$ calcd: 426.1831 [M]$^+$; found: 426.1816. $[\alpha]_D^{20}$=−92.9 (*c*=0.8, CH$_2$Cl$_2$).

4.1.12. Preparation of 7,12-dibenzyl-2,17-dioxa-7,12-diaza-bicyclo[16.2.2]docosa-1(21)18(22),19-triene (8a). 4-[4-(4-Oxo-butoxy)-phenoxy]-butyraldehyde (**7a**) (136 mg, 0.54 mmol), *N*,*N*′-dibenzyl-butane-1,4-diamine (**2a**) (160 mg, 0.60 mmol) and [Rh(acac)(CO)$_2$] (4 mg, 16 μmol) were mixed in 40 ml of toluene and stirred for 1 hour. The solution was placed in the autoclave, pressurised with 60 bar hydrogen and heated at 70°C for 2 days. The solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 97:3) to give 137 mg (52%) of **8a** as a colourless viscous oil.

^{1}H NMR (400 MHz, CDCl$_3$): signals for a 2:1 mixture of two stereoisomeric forms: δ=7.22–7.13 (m, 10H), 6.83 & 6.67 (two s, 1:2, 4H), 4.08 & 3.79–3.74 (t and m, 1:2, *J*=5.8 Hz, 4H), 3.45 & 3.35 (two s, 2:1, 4H), 2.38–2.35 & 2.33–2.30 & 2.22 (two m and t, *J*=6.5 Hz, 8H), 2.06–1.99 (m, 4H), 1.70–1.63 & 1.61–1.53 & 1.39–1.37 (three m, 8H). ^{13}C NMR (100 MHz, CDCl$_3$): signals for a 2:1 mixture of two stereoisomeric forms: δ=153.07 & 152.18, 140.05 & 139.95 & 139.91, 128.85 & 128.74, 128.08 & 128.02, 126.67 & 126.60, 116.58 & 115.42 & 115.30, 68.34 & 68.32 & 67.86, 58.92 & 58.85, 53.54 & 53.47, 53.23 & 53.12 & 53.05, 26.17, 25.67, 21.90. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2943, 2796, 1506, 1228. HRMS (FAB): for C$_{32}$H$_{42}$N$_2$O$_2$ calcd: 487.3325 [M+H]$^+$; found: 487.3341.

4.1.13. Preparation of 7,14-dibenzyl-2,19-dioxa-7,14-diaza-bicyclo[18.2.2]tetracosa-1(23),20(24),21-triene (8b). 4-[4-(4-Oxo-butoxy)-phenoxy]-butyraldehyde (**7a**) (104 mg, 0.42 mmol), *N*,*N*′-dibenzyl-hexane-1,6-diamine (**2b**) (126 mg, 0.42 mmol) and [Rh(acac)(CO)$_2$] (4 mg, 16 μmol) were mixed in 40 ml of toluene and stirred for 1 hour. The solution was placed in the autoclave, pressurised with 50 bar hydrogen and heated at 50°C for 2 days. The solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 97:3) to give 103 mg (48%) of **8b** as a white amorphous solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ=7.22–7.12 (m, 10H), 6.81 (s, 4H), 4.02 (t, *J*=6.0 Hz, 4H), 3.38 (s, 4H), 2.31 (t, *J*=6.3 Hz, 4H), 2.16 (t, *J*=7.3 Hz, 4H), 1.69–1.64 (m, 4H), 1.57–1.52 (m, 4H), 1.22–1.12 (m, 4H), 0.93–0.87 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ=152.61, 140.18, 128.80, 128.02, 126.59, 115.97, 67.85, 59.06, 53.42, 52.44, 27.85, 26.22, 22.06. IR (disk, KBr), $\tilde{\nu}$ [cm^{-1}]=2931, 2794, 1506, 1228. EA: for C$_{34}$H$_{46}$N$_2$O$_2$ (514.74 g/mol) calcd: C: 79.3%, H: 9.0%, N: 5.4%, found: C: 79.0%, H: 8.8%, N: 5.4%. HRMS (FAB): calcd: 515.3638 [M+H]$^+$; found: 515.3636.

4.1.14. Preparation of 10,15-dibenzyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-5,20-dioxa-10,15-diaza-dibenzo[*a*,*c*]cycloeicosene (9a). 4-[2′-(4-Oxo-butoxy)-biphenyl-2-yloxy]-butyraldehyde (**7b**) (42 mg, 0.13 mmol), *N*,*N*′-dibenzyl-butane-1,4-diamine (**2a**) (45 mg, 0.17 mmol) and [Rh(acac)(CO)$_2$] (3 mg, 12 μmol) were mixed in 40 ml of toluene and stirred for 1 hour. The solution was placed in the autoclave, pressurised with 60 bar hydrogen and heated at 70°C for 2 days. The solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 97:3) to give 31 mg (43%) of **9a** as a colourless viscous oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ=7.23–7.12 (m, 14H), 6.92–6.85 (m, 4H), 3.89–3.80 (m, 4H), 3.47–3.33 (dd, *J*=58.3, 13.7 Hz, 4H), 2.32–2.21 (m, 8H), 1.71–1.61 (m, 2H), 1.58–1.49 (m, 2H), 1.39–1.37 (m, 8H). ^{13}C NMR (125 MHz, CDCl$_3$): δ=156.81, 131.15, 128.96, 128.79, 128.31, 128.04, 126.62, 120.24, 112.27, 68.65, 59.25, 53.34, 27.27, 24.95, 23.53. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2960, 2796, 1593, 1261, 1026. HRMS (FAB): for C$_{38}$H$_{46}$N$_2$O$_2$ calcd: 563.3638 [M+H]$^+$; found: 563.3665.

4.1.15. Preparation of 10,17-dibenzyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21-hexadecahydro-5,22-dioxa-10,17-diaza-dibenzo[*a*,*c*]cyclododecosene (9b). 4-[2′-(4-Oxo-butoxy)-biphenyl-2-yloxy]-butyraldehyde (**7b**) (48 mg, 0.15 mmol), *N*,*N*′-dibenzyl-hexane-1,6-diamine (**2b**) (44 mg, 0.15 mmol) and [Rh(acac)(CO)$_2$] (3 mg, 12 μmol) were mixed in 40 ml of toluene and stirred for 1 h. The solution was placed in the autoclave, pressurised with 60 bar hydrogen and heated at 70°C for 2 days. The

solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to give 25 mg (29%) of **9b** as a colourless viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22–7.12 (m, 14H), 6.92–6.82 (m, 4H), 3.82 (t, J=6.5 Hz, 4H), 3.40 (s, 4H), 2.28–2.22 (m, 8H), 1.59–1.54 (m, 4H), 1.41–1.33 (m, 8H), 1.24–1.18 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.76, 140.18, 131.17, 128.84, 128.79, 128.28, 128.02, 126.59, 120.24, 112.37, 68.68, 59.08, 53.09, 27.33, 26.44, 26.29, 23.70. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2935, 2794, 1504, 1442, 1261. HRMS (FAB): for $C_{40}H_{50}N_2O_2$ calcd: 591.3951 $[M+H]^+$; found: 591.3922.

4.1.16. Preparation of 10,15-dibenzyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-5,20-dioxa-10,15-diaza-dinaphtho[*a*,*c*]cycloeicosene (10a). 4-[2′-(4-Oxo-butoxy)-[1,1′]binaphthalenyl-2-yloxy]-butyraldehyde (**7c**) (50 mg, 0.12 mmol), *N*,*N*′-dibenzyl-butane-1,4-diamine (**2a**) (33 mg, 0.12 mmol) and [Rh(acac)(CO)$_2$] (3 mg, 12 μmol) were mixed in 40 ml of toluene and stirred for 1 h. The solution was placed in the autoclave, pressurised with 50 bar hydrogen and heated at 60°C for 1 day. The solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to give 39 mg (50%) of **10a** as a colourless viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): signals for a 2:1 mixture of two stereoisomeric forms: δ=7.86 (dd, J=14.2, 9.0 Hz, 2H), 7.77 (d, J=8.0 Hz, 2H), 7.34 (dd, J=9.0, 1.7 Hz, 2H), 7.24–7.05 (m, 16H), 4.16–4.12 & 3.95–3.91 (two m, 1:2, 2H), 3.86–3.82 & 3.81–3.77 (two m, 1:2, 2H), 3.54–3.50 & 3.33 & 3.30–3.28 (two m and s, 1:2:1, 4H), 2.44–2.36 (m, 1H), 2.23–2.10 (m, 7H), 1.50–1.41 (m, 5H), 1.34–1.31 (m, 3H), 1.20–1.13 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): signals for a 2:1 mixture of two stereoisomeric forms: δ=154.63 & 154.02, 140.16, 134.21, 129.26, 129.05, 128.88 & 128.85, 128.76, 128.04 & 127.99, 127.77 & 127.73, 126.67 & 126.57, 126.07 & 126.03, 125.43 & 125.26, 123.38 & 123.03, 120.68, 116.13 & 113.83, 69.81 & 66.74, 59.02, 53.17 & 52.84, 51.31, 27.23 & 26.52, 24.89, 23.12. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2944, 2796, 1508, 1263. HRMS (FAB): for $C_{46}H_{50}N_2O_2$ calcd: 663.3951 $[M+H]^+$; found: 663.3981.

4.1.17. Preparation of (*R*)-(+)-10,17-dibenzyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21-hexadecahydro-5,22-dioxa-10,17-diaza-dinaphtho[*a*,*c*]cyclodocosene (10b). (R)-(−)-4-[2′-(4-Oxo-butoxy)-[1,1′]binaphthalenyl-2-yloxy]-butyraldehyde (**7c**) (115 mg, 0.27 mmol), *N*,*N*′-dibenzyl-hexane-1,6-diamine (**2b**) (83 mg, 0.28 mmol) and [Rh(acac)(CO)$_2$] (3 mg, 12 μmol) were mixed in 40 ml of toluene and stirred for 1 h. The solution was placed in the autoclave, pressurised with 50 bar hydrogen and heated at 65°C for 2 days. The solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) to give 132 mg (71%) of **10b** as a colourless viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.83 (d, J=9.0 Hz, 2H), 7.76 (d, J=8.3 Hz, 2H), 7.32 (d, J=9.0 Hz, 2H), 7.24–7.06 (m, 16H), 3.91–3.85 (m, 2H), 3.83–3.77 (m, 2H), 3.32 (dd, J=23.1, 13.8 Hz, 4H), 2.20 (t, J=6.5 Hz, 4H), 2.15–2.04 (m, 4H), 1.44–1.31 (m, 8H), 1.23–1.20 (m, 4H), 1.17–1.10 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.66, 140.19, 134.18, 129.29, 129.06, 128.77, 127.99, 127.77, 126.55, 126.03, 125.46, 123.40, 120.79, 116.25, 70.04, 58.84, 52.91, 52.78, 27.26, 26.58, 26.39, 23.20. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2929, 2794, 1508, 1454, 1263, 1085. HRMS (FAB): for $C_{48}H_{54}N_2O_2$ calcd: 691.4264 $[M+H]^+$, 713.4083 $[M+Na]^+$; found: 691.4250, 713.4091. $[\alpha]_D^{20}$=−65.4 (c=0.44, CH_2Cl_2).

4.1.18. Preparation of 1,4-bis-pent-4-enyloxy-benzene (11a). Potassium hydroxide (3.08 g, 54.9 mmol) was dissolved in absolute ethanol (200 ml) at room temperature. To this stirred solution were added hydroquinone (2.00 g, 18.2 mmol) and 5-bromo-pent-1-ene (8.12 g, 54.5 mmol). The solution was heated at 80°C and allowed to stir for 24 h. After being cooled to a room temperature, the mixture was diluted with water and CH_2Cl_2, and the layers were separated. The aqueous phase was further extracted with CH_2Cl_2, and combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give 3.81 g (85%) of **11a** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ=6.74 (s, 4H), 5.82–5.74 (m, 2H), 4.98 (dd, J=17.2, 1.7 Hz, 2H), 4.92 (d, J=9.5 Hz, 2H), 3.84 (t, J=6.5 Hz, 4H), 2.18–2.13 (m, 4H), 1.81–1.75 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=153.15, 137.90, 115.40, 115.07, 67.81, 30.11, 28.52. IR (disk, KBr), $\tilde{\nu}$ [cm^{-1}]=2939, 2868, 1510, 1057. EA: for $C_{16}H_{22}O_2$ (246.35 g/mol) calcd: C: 78.0%, H: 9.0%, found: C: 78.2%, H: 9.1%. MS (FAB): 246 $[M]^+$, 191, 178, 123, 110, 70. Mp: 34–36°C.

4.1.19. Preparation of *S*-(+)-2,2′-bis-hex-5-enyloxy-[1,1′]binaphthalenyl (11b). To a solution of *S*(+)-[1,1′]binaphthalenyl-2,2′-diol (3.03 g, 10.6 mmol) in THF (30 ml) were added 5-hexen-1-ol (3.47 g, 34.6 mmol) and triphenylphosphine (6.88 g, 26.2 mmol) at room temperature. Diisopropyl azodicarboxylate (5.30 g, 26.2 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 24 h. The solution was decanted, and solids were washed several times with hexanes. The organic solutions were combined and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/*n*-hexane 4:1) to give 4.14 g (87%) of **11b** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.87 (d, J=9.0 Hz, 2H), 7.80 (d, J=8.0 Hz, 2H), 7.35 (d, J=9.0 Hz, 2H), 7.35 (t, J=6.5 Hz, 2H), 7.17–7.11 (m, 4H), 5.53–5.45 (m, 2H), 4.79–4.73 (m, 2H), 3.94–3.84 (m, 4H), 1.71–1.67 (m, 4H), 1.40–1.33 (m, 4H), 1.00–0.94 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=154.45, 138.66, 134.19, 129.26, 129.05, 127.77, 126.04, 125.46, 123.40, 120.68, 115.78, 114.15, 69.48, 33.04, 28.74, 24.78. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2935, 1591, 1508, 1271, 1242. EA: for $C_{32}H_{34}O_2$ (246.35 g/mol) calcd: C: 85.3%, H: 7.6%, found: C: 85.5%, H: 7.4%. MS (FAB): 450 $[M]^+$, 368, 286, 269. $[\alpha]_D^{20}$=+75.3 (c=0.6, CH_2Cl_2).

4.1.20. Preparation of 6-[4-(6-oxo-hexyloxy)-phenoxy]-hexanal (12a). 1,4-Bis-pent-4-enyloxy-benzene (**11a**)

(200 mg, 0.81 mmol), [Rh(acac)(CO)$_2$] (3 mg, 12 μmol), XANTPHOS (29 mg, 50 μmol) and toluene (15 ml) were dissolved in the autoclave. The solution was pressurised with 80 bar CO/H$_2$ (1:1) and heated at 120°C for 18 h. Solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, Et$_2$O/*n*-hexane 3:2) to give 0.183 g (74%) of **12a** as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ=9.70 (s, 2H), 6.73 (s, 4H), 3.83 (t, *J*=6.3 Hz, 4H), 2.39 (dt, *J*=7.3, 1.5 Hz, 4H), 1.73–1.66 (m, 4H), 1.66–1.58 (m, 4H), 1.46–1.39 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ=202.47, 153.02, 115.28, 68.08, 43.71, 29.05, 25.62, 21.73. IR (disk, KBr), $\tilde{\nu}$ [cm^{-1}]=2943, 2729, 1712, 1510, 1227. EA: for $C_{18}H_{26}O_4$ (306.40 g/mol) calcd: C: 70.6%, H: 8.6%, found: C: 70.3%, H: 8.7%. HRMS (EI): calcd: 306.1831 [M]$^+$; found: 306.1825. Mp: 42–44°C.

4.1.21. Preparation of *S*-(+)-7-[2′-(7-oxo-heptyloxy)-[1,1′]binaphthalenyl-2-yloxy]-heptanal (12b). 2,2′-Bis-hex-5-enyloxy-[1,1′]binaphthalenyl (**11b**) (212 mg, 0.47 mmol), [Rh(acac)(CO)$_2$] (3 mg, 12 μmol), XANTPHOS (31 mg, 53 μmol) and toluene (15 ml) were dissolved in the autoclave. The solution was pressurised with 60 bar CO/H$_2$ (1:1) and heated at 100°C for 18 h. Solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, CH$_2$Cl$_2$) to give 0.139 g (58%) of **12b** as a yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ=9.56 (s, 2H), 7.83 (d, *J*=9.0 Hz, 2H), 7.75 (d, *J*=8.2 Hz, 2H), 7.31 (d, *J*=9.0 Hz, 2H), 7.21 (dt, *J*=7.7, 1.2 Hz, 2H), 7.12–7.05 (m, 4H), 3.91–3.87 (m, 2H), 3.81–3.77 (m, 2H), 2.05 (dt, *J*=7.5, 1.7 Hz, 4H), 1.33–1.26 (m, 4H), 1.23–1.16 (m, 4H), 0.91–0.86 (m, 4H), 0.80–0.74 (m, 4H). ^{13}C NMR (125 MHz, CDCl$_3$): δ=202.80, 154.41, 134.13, 129.23, 129.00, 127.72, 125.99, 125.41, 123.40, 120.68, 115.81, 69.51, 43.47, 29.01, 28.33, 25.20, 21.64. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2933, 1722, 1591, 1508, 1263. HRMS (EI): for $C_{34}H_{38}O_4$ calcd: 510.2770 [M]$^+$; found: 510.2767. $[\alpha]_D^{20}$=+48.4 (*c*=0.58, CH$_2$Cl$_2$).

4.1.22. Preparation of 9,16-dibenzyl-2,23-dioxa-9,16-diaza-bicyclo[22.2.2]octacosa-1(27),24(28),25-triene (13a). 6-[4-(6-Oxo-hexyloxy)-phenoxy]-hexanal (**12a**) (53 mg, 0.17 mmol), *N*,*N*′-dibenzyl-hexane-1,6-diamine (**2b**) (59 mg, 0.2 mmol) and [Rh(acac)(CO)$_2$] (3 mg, 12 μmol) were dissolved in 20 ml of toluene and stirred for 1 h. The solution was placed in the autoclave, pressurised with 40 bar hydrogen and heated at 50°C for 1 day. The solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 97:3) to give 52 mg (53%) of **13a** as a yellow viscous oil.

^{1}H NMR (400 MHz, CDCl$_3$): signals for a 2:1 mixture of two stereoisomeric forms: δ=7.25–7.18 (m, 10H), 6.78 & 6.72 (two s, 2:1, 4H), 3.94 & 3.79 (two t, 2:1, *J*=6.5 Hz, 4H), 3.45 & 3.40 (two s, 2:1, 4H), 2.33–2.25 & 2.20 (m and t, 2:1, *J*=7.0 Hz, 8H), 1.69–1.62 (m, 4H), 1.44–1.23 (m, 16H), 1.18–1.15 & 1.08–1.05 (two m, 1:2, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): signals for a 2:1 mixture of two stereoisomeric forms: δ=153.12 & 152.87, 140.27 & 140.23, 128.78, 128.02 & 128.01, 126.58 & 126.54, 116.05 & 115.33, 68.49 & 68.30, 58.76, 53.75, 53.31, 28.13, 27.53 & 27.48, 26.98, 26.56 & 26.14, 25.16. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2933, 2792, 1506, 1228. HRMS (FAB): for $C_{38}H_{54}N_2O_2$ calcd: 570.4185 [M]$^+$; found: 570.4186.

4.2. Preparation of *S*-(+)-13,18-dibenzyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25-eicosahydro-5,26-dioxa-13,18-diaza-dinaphtho[*a*,*c*]cyclohexacosene (13b)

S-(+)-7-[2′-(7-Oxo-heptyloxy)-[1,1′]binaphthalenyl-2-yloxy]-heptanal (**12b**) (55 mg, 0.11 mmol), *N*,*N*′-dibenzyl-butane-1,4-diamine (**2a**) (27 mg, 0.10 mmol) and [Rh(acac)(CO)$_2$] (4 mg, 16 μmol) were dissolved in 30 ml of toluene and stirred for 1 h. The solution was placed in the autoclave, pressurised with 40 bar hydrogen and heated at 50°C for 1 day. The solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 97:3) to give 58 mg (77%) of **13b** as a yellow viscous oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ=7.85–7.74 (m, 4H), 7.35–7.02 (m, 18H), 3.86–3.80 (m, 4H), 3.42–3.38 (m, 4H), 2.27–2.22 (m, 8H), 1.42–1.26 (m, 12H), 1.21–1.18 (m, 2H), 1.13–1.07 (m, 6H), 1.04–1.01 (m, 4H). ^{13}C NMR (125 MHz, CDCl$_3$): δ=154.57, 154.51, 140.34, 134.24, 129.17, 129.00, 128.79, 128.01, 127.75, 126.57, 126.04, 125.43 & 125.40, 123.31, 120.55, 120.47, 115.75, 69.77 & 69.63, 59.19 & 59.11, 53.69 & 53.46 & 53.42, 52.76, 29.35, 29.09, 28.55, 27.24 & 27.40, 26.72 & 26.56, 25.70, 25.41, 24.88. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2941, 1593, 1508, 1271, 1088. HRMS (FAB): for $C_{52}H_{62}N_2O_2$ calcd: 747.5290 [M+H]$^+$; found: 747.4899. $[\alpha]_D^{20}$=+82.1 (*c*=0.7, CH$_2$Cl$_2$).

4.3. Preparation of *S*-(+)-13,18-dibenzyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25-eicosahydro-5,26-dioxa-13,18-diaza-dinaphtho[*a*,*c*]cyclohexacosene (13c)

S-(+)-7-[2′-(7-Oxo-heptyloxy)-[1,1′]binaphthalenyl-2-yloxy]-heptanal (**12b**) (49 mg, 0.10 mmol), *N*,*N*′-dibenzyl-hexane-1,4-diamine (**2b**) (34 mg, 0.11 mmol) and [Rh(acac)(CO)$_2$] (3 mg, 12 μmol) were dissolved in 30 ml of toluene and stirred for 1 h. The solution was placed in the autoclave, pressurised with 50 bar hydrogen and heated at 60°C for 1 day. The solvent was removed in a rotary evaporator and the crude product was purified by column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 97:3) to give 58 mg (78%) of **13c** as a yellow viscous oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ=7.81 (d, *J*=9.0 Hz, 2H), 7.74 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=9.0 Hz, 2H), 7.24–7.18 (m, 10H), 7.14–7.08 (m, 4H), 7.06–7.03 (m, 2H), 3.88–3.80 (m, 4H), 3.43 (d, *J*=2.2 Hz, 4H), 2.30–2.24 (m, 8H), 1.38–1.34 (m, 8H), 1.32–1.26 (m, 4H), 1.23–1.21 (m, 4H), 1.09–1.07 (m, 4H), 0.99–0.97 (m, 8H). ^{13}C NMR (125 MHz, CDCl$_3$): δ=154.49, 140.33, 134.24, 129.18, 129.00, 128.79, 128.02, 127.75, 126.57, 126.03, 125.45, 123.31, 120.59, 115.74, 69.58, 59.07, 53.45, 53.34, 29.27, 28.95, 27.17, 27.04, 26.94, 26.88, 25.59. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2931, 2794, 1593, 1508, 1263. HRMS (FAB): for

$C_{54}H_{66}N_2O_2$ calcd: 774.5124 $[M]^+$; found: 774.5118. $[\alpha]_D^{20}=+54.3$ ($c=0.88$, CH_2Cl_2).

4.4. Preparation of 2,23-dioxa-9,16-diaza-bicyclo-[22.2.2]octacosa-1(27),24(28),25-triene (14)

9,16-Dibenzyl-2,23-dioxa-9,16-diaza-bicyclo[22.2.2]octacosa-1(27),24(28),25-triene (**13a**) (114 mg, 0.20 mmol), palladium on charcoal (150 mg, 10% Pd) and ethanol (100 ml) were stirred under hydrogen (1 bar) for 24 h. After removal of palladium by filtration, the solvent was removed in a rotary evaporator to give 75 mg (96%) of **14** as a yellow viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.77$ (s, 4H), 3.93 (t, $J=6.0$ Hz, 4H), 2.59–2.54 (m, 8H), 1.70–1.65 (m, 4H), 1.51–1.38 (m, 12H), 1.35–1.30 (m, 4H), 1.27–1.23 (m, 4H), 1.19 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=202.80$, 154.41, 134.13, 129.23, 129.00, 127.72, 125.99, 125.41, 123.40, 120.68, 115.81, 69.51, 43.47, 29.01, 28.33, 25.20, 21.64. IR (film, NaCl), $\tilde{\nu}$ [cm^{-1}]=2929, 1506, 1286. HRMS (FAB): for $C_{24}H_{42}N_2O_2$ calcd: 391.3325 $[M+H]^+$; found: 391.3319.

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