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Fluorescence screening of tartaric acid-derived azamacrocycles synthesized via sequential hydroformylation/reductive amination as potential ligands for asymmetric catalysis

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Abstract—Azamacrocycles containing a tartaric acid-derived unit and aryl units were synthesized via rhodium-catalyzed hydroformylation while the subsequent reductive amination was carried out in a tandem or stepwise fashion. Upon fluorescence emission experiments, some of the macrocycles showed chelating affinities toward transition metals such as zinc or rhodium.

1. Introduction

Chiral macrocycles serve a wide variety of functions in asymmetric reactions, from acting as reagents for the optical resolution of amino acids and their derivatives, substrates for ion complexation, ligands in asymmetric synthesis to act as carbohydrate mimics in building enzyme models.[1] One of the more widely-used chiral units in catalysis is derived from L-tartaric acid, a very inexpensive and easily available compound. Acyclic tartaric acid derivatives are used as phosphorus or nitrogen ligands in asymmetric hydrogenation,[2] allylboration,[3] epoxidation,[4] or in the stereoselective addition of organometallics to a carbonyl group as seen with TADDOL type ligands.[5] Furthermore, amides derived from tartaric acid are used as the resolving agent when absorbed on silica[6] in the resolution of both α-amino acid derivatives or complexes of platinum(II) with tartaric acid amine derivatives, some of which exhibit antitumor activity.[7] There are numerous reports of syntheses[8] and applications of L-tartaric acid-based crowns or azacrowns. They can be used in selective ion complexation,[9] ion transport,[10] chiral recognition,[11] molecular catalysis,[12] or as photoionophores.[13]

Macrocycles potentially have improved characteristics as chiral auxiliaries over their acyclic analogues, as the decrease in the number of diastereomeric transition states in many metal-catalyzed enantioselective processes can be even higher,[14] due to the presence of other groups on the macrocycle which can both contribute to the rigidity of the system and act as complexing/directing moieties able to influence the enantioselectivity of a process.

In previous reports,[15,16] we have demonstrated efficient syntheses of azamacrocycles containing aryl and piperazine units via tandem (hydroaminomethylation) or stepwise (regioselective hydroformylation followed by reductive amination) processes. This work applies these methods toward the synthesis of azamacrocycles containing tartaric acid-derived units and investigates their use as ligands in asymmetric synthesis by employing a rapid fluorescence spectroscopic assay. Fluorescence screening was chosen as the method of evaluation due to its high sensitivity toward detecting the interactions of fluorophores with metals.[17]

2. Results and discussion

The synthesis of azamacrocycles via sequential hydroformylation/reductive amination requires both a diolefin and diamine. Depending on the desired structure and recognition abilities, which we want to be present in

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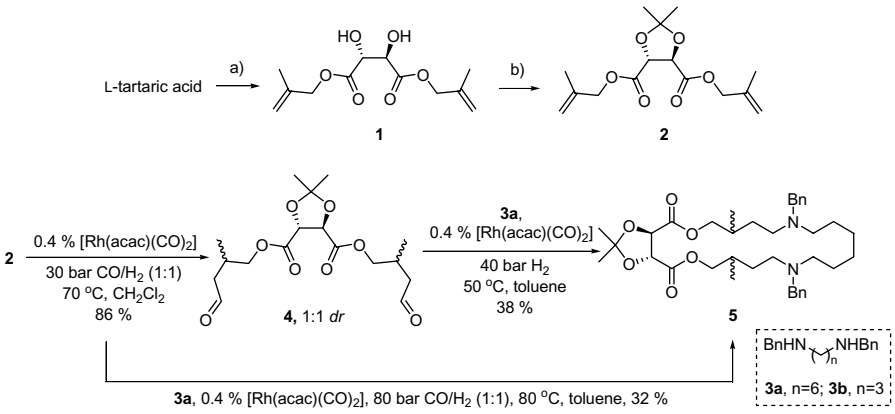
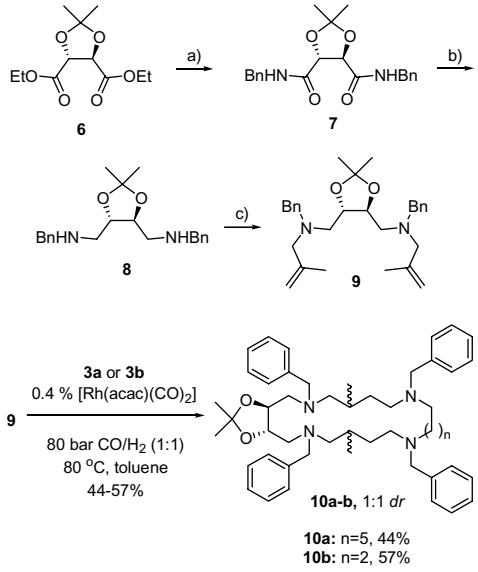


Scheme 1. Reagents and conditions: (a) methylallyl chloride, Et_3N, DMF, 63%; (b) 2,2-dimethoxypropane, p-$TsOH_{(cat.)}$, C_6H_6, 59%.

the final compound, various groups can be included in one or both precursors. Our plan was to synthesize chiral olefins containing ester or amine derivatives of tartaric acid. Furthermore, to prevent the formation of regioisomers, olefins bearing methylallyl groups were synthesized. Acetonide-protected tartaric acid methylallyl ester **2** was made starting from L-tartaric acid in two steps (Scheme 1). Subsequent esterification of the acid with methallyl chloride was performed according to a modified procedure,[18] giving ester **1** in 63% isolated yield. The second step was the protection of the diol as an acetonide with 2,2-dimethoxypropane.

The synthesis of azamacrocycle **5** using diamine **3a**[19a] was performed using two methods, first via the hydroaminomethylation and second via the stepwise hydroformylation/reductive amination sequence (Scheme 1). The isolated yield of **5** in the first case (tandem reaction) was 32%, while in the stepwise method, aldehyde **4** was isolated in 86% after the hydroformylation step. The purity of aldehyde **4** was sufficient enough for it to be used in the next step without further purification. The subsequent rhodium-catalyzed reductive amination/cyclization step was performed by adding amine **3a** to aldehyde **4**, stirring the mixture until imine/enamine formation was complete, and finally pressurizing the mixture with H_2.

After this encouraging result, attempts at the generation of a tetraazamacrocycle were made. For this purpose, an aminodiolefin derived from tartaric acid was synthesized. Protected diester **6** was prepared from commercially available (+)-diethyl L-tartrate and 2,2-dimethoxypropane according to a literature procedure.[20] Diamide **7** was synthesized in 94% yield after the amidation of **6** with benzylamine, using K_2CO_3 in methanol. This represents an improvement upon a previously reported synthesis[21] of **7** which gave the amide after four synthetic steps when starting from dimethyl L-tartrate. Amide **7** was sufficiently pure to be taken on to reduction with $LiAlH_4$ to give diamine **8** in 78% yield. Finally, methallylation of **8** proceeded to give bis-methallyl amine **9** in 37% yield. Ultimately, two hydroaminomethylation reactions were performed with diolefin **9**. When paired with amine **3a**, the final yield of azamacrocycle **10a** was 44%, while when using amine **3b**,[19b] the yield of azamacrocycle **10b** was 57% (Scheme 2).

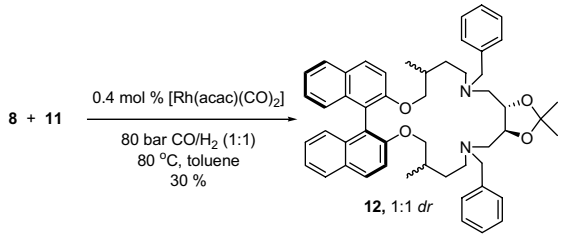


Scheme 2. Reagents and conditions: (a) $BnNH_2$, K_2CO_3, MeOH, 94%; (b) $LiAlH_4$, 1,4-dioxane, 78%; (c) methallylchloride, NaOH, *i*-PrOH, 37%.

NMR spectra of **10a** and **10b** showed that these were very rigid structures. There was signal splitting present in almost every resonance in the ^{13}C NMR spectrum of both compounds. This rigidity could in some way be expected, as both of the tetraazamacrocycles not only have benzyl groups on their nitrogens but also a 1,3-dioxolane ring within the macrocycle making the entire system prone to rigid conformations. A similar result was also observed in cases where only the two benzyl groups were present in the macrocycle.[15]

After the synthesis of chiral macrocycles containing a tartaric acid unit, our subsequent goal was the synthesis and incorporation of a second chiral unit into the macrocycle. Our previous experience in the synthesis

of macrocycles containing an (*S*)-BINOL unit[15] via hydroaminomethylation prompted us to carry out an analogous synthesis in this case. Amine **8**, a secondary amine, is appropriate for use in this methodology, while hydroaminomethylation was performed with olefin **11**[22] to give BINOL-macrocycle **12** in 30% isolated yield as a 1:1 mixture of diastereoisomers as determined by NMR (Scheme 3).



Scheme 3.

This result was better than expected for the coupling of two rigid units, and thus the stepwise method was also performed to see if further gains in product yields could be obtained. Starting from dialdehydes **13**[15] and **14**[16] and amine **8**, two macrocycles having aryl and chiral units were synthesized (Fig. 1). The isolated yield of azamacrocycle **15** containing a resorcinol unit was low after several attempts (15%), which indicates that the rigidity of the compound is quite high and that cyclization cannot be easily accomplished. The isolated yield of compound **16** was comparable to the tandem reaction −39%. Even though full rotation of the C1–C1′ bond of the BINOL unit is not possible, a small degree of naphthol movement is possible, making the whole system more flexible and allowing for the cyclization to proceed at a higher yield than in the case of the resorcinol derivative **15**.

One final synthetic transformation was performed by removing the acetonide from the diol in **15** (Scheme 4). Following mild acidic cleavage, macrocyclic diol **18** was obtained in 65% isolated yield. Alternatively **18** was synthesized via the stepwise reductive amination/cyclization reaction starting from aldehyde **14** and diamine **17**.[23] Although, this route should be easier as it required fewer synthetic steps, the compound obtained this way was more difficult to purify sufficiently since the macrocyclic amino alcohol is very polar and makes for difficult silica gel chromatography.

The macrocycles obtained via the previously described syntheses have very interesting structures, possessing both chiral and aryl units. Furthermore, macrocycle **16**

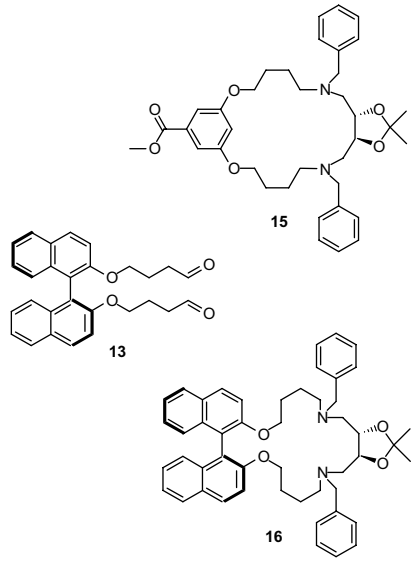


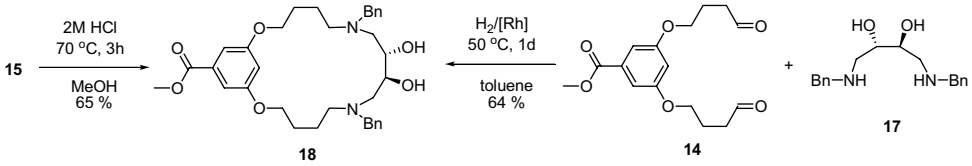
Figure 1.

has two chiral units, one of which (BINOL) is commonly employed in ligands used in catalytic asymmetric transformations.[24] As BINOL is also a suitable fluorophore, we used it to investigate the complexation of aryl-containing azamacrocycles with some transition metals commonly used in catalysis, such as rhodium, zinc, or titanium.

For this investigation, we dissolved macrocycles **15**, **16**, and **18** in acetonitrile and performed fluorescent spectroscopy measurements upon the addition of various amounts of metals. The first experiment was the titration of **15** with Zn^{2+} (Fig. 2). Enhancement of the emission signal was observed until addition of one equivalent of metal, where it remained constant upon the addition of more metal to the system. This likely indicates the formation of a 1:1 complex between the macrocycle and zinc.

Experiments using **15** with rhodium and titanium failed to show any noticeable interaction with the host. One can rapidly conclude, however, that chelation of **15** with zinc is effective, and that this ligand:metal pair would be worth further investigation in asymmetric reactions where zinc is used as the catalyst.

Fluorescence experiments with **16** showed somewhat different results. While effective complexation with zinc and titanium was not observed, quenching of the fluorescence was seen this time upon the addition of rhodium. Since this effect can be due either to complex



Scheme 4.

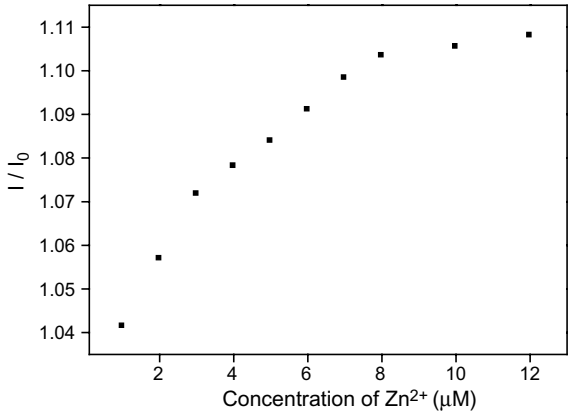


Figure 2. Enhancement of the fluorescence intensity of **15** (10 μM, λ_{ex} = 308 nm, CH_3CN, 25 °C) upon addition of $ZnCl_2$.

formation between the fluorophore and the quencher (static quenching) or due to collisions between the fluorophore and the quencher (dynamic quenching),[25] experiments were performed at two different temperatures (25 °C and 40 °C). With an increase of the temperature, static quenching was expected to be lower (complex formation is disfavored at higher temperatures), while the physical collisions involved in the dynamic quenching should be higher at higher temperatures. As shown in Figure 3, the quenching of the fluorescence emission was lower when increasing the temperature, clearly indicating that rhodium does indeed form a complex with macrocycle **16**.

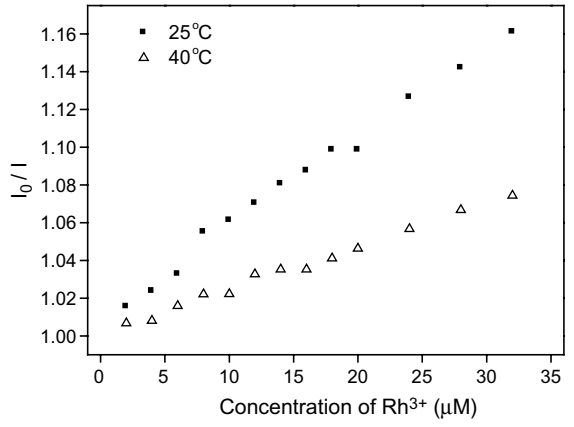


Figure 3. Quenching of the fluorescence intensity of **16** (20 μM, λ_{ex} = 337 nm, CH_3CN, 25 and 40 °C) upon addition of $RhCl_3$. Calculated values for 25 °C: $K_s = 4.89 \times 10^{-2}$ mol^{-1} (r = 0.9974), for 40 °C: $K_s = 2.28 \times 10^{-2}$ mol^{-1} (r = 0.9956).

The same results were observed with compound **18**. Upon addition of rhodium to its solution in acetonitrile, an analogous quenching of the fluorescence intensity is observed (Fig. 4). Temperature dependent experiments were performed again, confirming the formation of a ligand:metal complex which is more stable at lower temperatures.

Static quenching constants were calculated upon fitting of the curves according to the Stern–Volmer equation:

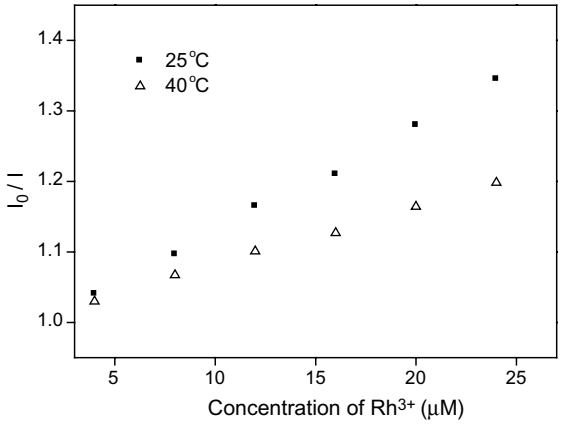


Figure 4. Quenching of the fluorescence intensity of **17** (20 μM, λ_{ex} = 308 nm, CH_3CN, 25 and 40 °C) upon addition of $RhCl_3$. Calculated values for 25 °C: $K_s = 15.13 \times 10^{-2}$ mol^{-1} (r = 0.9988), for 40 °C: $K_s = 8.29 \times 10^{-3}$ mol^{-1} (r = 0.9991).

$F_0/F = 1 + K_s[Q]$.[25] The calculated values were approximately halved in both cases when the temperature was increased from 25 to 40 °C.

An interesting relationship was noticed between the structure of the azamacrocycle and its affinity for chelating different metals. Although macrocyles **15** and **18** have similar structures and sizes of the macrocyclic cavity, they chelate drastically different metals (**15** chelates Zn, **18** chelates Rh). This property is potentially important since this difference in affinity results from a simple synthetic transformation, such as deprotection of the acetonide. Furthermore, the difference in affinities of **15** and **16** toward rhodium might be due to the distance of two ether oxygens from one another. In macrocycle **16** they are closer and can participate more in chelation, while in **15** they are further apart from one another.

3. Conclusion

In conclusion, we have reported a procedure for the efficient synthesis of azamacrocycles containing chiral (tartaric acid derivatives) and aryl units via hydroaminomethylation strategies. Depending on the choice of reactants, the chiral unit can be easily introduced either as part of the aldehyde or the amine required for the reductive amination/cyclization step. This is an additional example of tandem and stepwise hydroformylation/reductive amination reactions offering various options for the rapid synthesis of azamacrocycles bearing various functional groups.

In addition, the complexation of some macrocycles with zinc and rhodium was investigated. The selectivity of complexation for these metals differs, and complex stability seems to be greatly dependent on the structure of the macrocycle. Nonetheless, these results are both promising and encouraging, showing that these easily-synthesized compounds can be used as asymmetric ligands for zinc and rhodium.

4. Experimental

4.1. General remarks

All chemicals were purchased from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at room temperature with a Bruker DRX 400 and DRX 500 spectrometers. Unless otherwise specified, $CDCl_3$ was used as solvent with TMS (0.00 ppm) as the internal standard. The ^{13}C NMR spectra were referenced to $CDCl_3$ (77.00 ppm). FTIR spectra were performed on a Nicolet Impact 400 D spectrometer using neat compounds as films between NaCl plates or as KBr pellets. Mass spectra were recorded with a JEOL JMS-SX 102A spectrometer (FAB), on Finnigan MAT TSQ spectrometer (ESI) and Finnigan MS 8200 spectrometer (EI, 70 eV). GC–MS coupling was recorded on Finnigan ION-TRAP spectrometer (model 800, EI, 70 eV) with Aerograph 8521-a (CP-Sil-5CB 25 m) from Dani. Elemental analyses were performed with a Leco CHNS-932 analyzer. Optical rotations were performed on a Perkin Elmer 341 polarimeter. Fluorescence measurements were performed with a Perkin Elmer LS 50B spectrofluorometer at 25 and 40 °C. Column chromatography was carried out on silica gel 60 (70–230 mesh ASTM) from Macherey-Nagel GmbH & Co. KG, Düren, or Alumina N (Activity III) from ICN Biomedicals, Eschwege. Pressure reactions were carried out in autoclaves of type A (250 mL, PTFE insert) from Berghof, Eningen or similar housemade autoclaves (100 mL, stainless steel) with specially designed heating and stirring mantles.

General procedure for reactions in the autoclave: After charging the autoclave with the starting material, the catalyst precursor, and the solvent, the reactor was flushed with argon, pressurized with H_2 and CO, and heated to the required reaction temperature. Following the reaction, the solvent was removed by rotary evaporation and the products were purified by column chromatography.

General method A: hydroaminomethylation reaction: Diolefin, diamine, and catalyst were dissolved in toluene and placed in the autoclave. The autoclave was pressurized with CO and H_2 and heated. After cooling, the solvent was removed in a rotary evaporator and the crude mixture purified by column chromatography.

General method B: reductive amination reaction: Dialdehyde, diamine, and catalyst were dissolved in toluene, placed in the autoclave and stirred at room temperature for 1 h. The autoclave was pressurized with H_2 and heated. After cooling, the solvent was removed in a rotary evaporator and the crude mixture purified by column chromatography.

4.1.1. Preparation of (2*R*,3*R*)-2,3-dihydroxy-succinic acid bis-(2-methylallyl) ester 1. To a solution of (2*R*,3*R*)-tartaric acid (5.01 g, 33.4 mmol) in 15 mL of sieve-dried DMF at 0 °C under nitrogen, was added Et_3N (18.5 mL, 133.5 mmol). The reaction mixture was allowed to warm to room temperature and a solution of methylallyl chloride (13 mL, 132.8 mmol) in 10 mL of dry DMF added over a period of 3 h. The reaction mixture was stirred overnight at room temperature. The solvent was removed in vacuo at <35 °C. The residue was taken up in 40 mL of EtOAc and washed with 2×20 mL ice water, 2×20 mL ice cold saturated $NaHCO_3$ solution, and 2×10 mL of saturated NaCl solution. The organic layer was dried to give 5.43 g (63%) of crude **1** as a yellow oil. Compound **1** was used for the next reaction without further purification. An analytical sample was prepared after purification by column chromatography (silica gel, *n*-hexane:Et_2O 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.98$ (s, 2H), 4.92 (s, 2H), 4.66–4.58 (m, 6H), 3.46 (br s, 2H), 1.72 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.16$, 138.94, 113.87, 72.09, 69.27, 19.22. IR (film, NaCl), ν [cm^{-1}] = 3489, 2945, 1747, 1660, 1452, 1379, 1269, 1128, 1091, 908. EA for $C_{12}H_{18}O_6$ (258.27 g/mol) calcd: C, 55.8; H, 7.0. Found: C, 55.6; H, 7.0. MS (FAB): 281 $[M+Na]^+$, 259 $[M+H]^+$. $[\alpha]_D^{20} = +21.9$ (*c* 0.5, CH_2Cl_2).

4.1.2. Preparation of (4*R*,5*R*)-2,2-dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid bis-(2-methylallyl) ester 2. To a stirred solution of **1** (1.02 g, 3.95 mmol) and *p*-TsOH (13 mg, 68 μmol) in benzene (7 mL) at room temperature was added 2,2-dimethoxy propane (495 mg, 4.75 mmol). The reaction mixture was heated at 80 °C for 3 h while benzene–MeOH azeotrope was distilled. After cooling, the reaction mixture was neutralized with 20 mg of anhydrous Na_2CO_3. The resulting suspension was subjected to a short-path column chromatography (silica gel, *n*-hexane/EtOAc 10:1) and the combined fractions concentrated under reduced pressure to give an oil. The crude product was purified by column chromatography (silica gel, *n*-hexane/EtOAc 95:5) to give 692 mg (59%) of **2** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.96$ (s, 2H), 4.91 (s, 2H), 4.78 (s, 2H), 4.58 (s, 4H), 1.71 (s, 6H), 1.46 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.20$, 138.88, 113.80, 77.07, 68.84, 26.27, 19.33. IR (film, NaCl), ν [cm^{-1}] = 2989, 1766, 1660, 1454, 1383, 1375, 1205, 1113, 999, 908. EA for $C_{15}H_{22}O_6$ (298.34 g/mol) calcd: C, 60.4; H, 7.4. Found: C, 60.5, H, 7.5. MS (FAB): 321 $[M+Na]^+$, 299 $[M+H]^+$. $[\alpha]_D^{20} = -37.6$ (*c* 1.1, CH_2Cl_2).

4.1.3. Preparation of (4*R*,5*R*)-2,2-dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid bis-(2-methyl-4-oxo-butyl) ester 4. Compound **2** (195 mg, 0.65 mmol), [Rh(acac)-$(CO)_2$] (4 mg, 16 μmol) was dissolved in CH_2Cl_2 (10 mL) and placed in the autoclave. The autoclave was pressurized with 80 bar CO:H_2 (1:1) and heated at 80 °C for 18 h. After cooling the solvent was removed in a rotary evaporator and the crude mixture purified by column chromatography (silica gel, CH_2Cl_2) to give 200 mg (86%) of **4** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.70$ (s, 2H), 4.68 (s, 2H), 4.11–4.08 (m, 2H), 4.02–3.98 (m, 2H), 2.51–2.42 (m, 4H), 2.33–2.28 (m, 2H), 1.43 (s, 6H), 0.97 (d, $J = 6.5$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.76$, 169.40, 113.92, 7.05, 69.57, 47.51, 27.62, 26.31. IR (film, NaCl), ν [cm^{-1}] = 2964, 2939, 1755, 1724, 1464, 1377, 1259, 1207, 1165, 1109, 1016. GC–MS: 358.5 $[M]^+$, 252.1, 207.2, 178.2.

4.1.4. Preparation of 10,17-dibenzyl-2,2,7,20-tetramethyl-octadecahydro-1,3,5,22-tetraoxa-10,17-diaza-cyclopenta-cyclodocosene-4,23-dione 5. *General method A*: Compound **2** (181 mg, 0.61 mmol), **3a** (180 mg, 0.61 mmol) and [Rh(acac)(CO)$_2$] (7 mg, 27 μmol) were dissolved in toluene (40 mL), pressurized with 80 bar CO:H$_2$ (1:1), heated at 80 °C for 2 d and purified by column chromatography (silica gel, CH_2Cl_2:MeOH 97:3) to give 123 mg (32%) **5** as a colorless viscous oil.

General method B: Compound **4** (170 mg, 0.47 mmol), **3a** (141 mg, 0.48 mmol) and [Rh(acac)(CO)$_2$] (6 mg, 23 μmol) were dissolved in toluene (40 mL), pressurized with 40 bar H_2, heated at 50 °C for 1 d and purified by column chromatography (silica gel, CH_2Cl_2:MeOH 97:3) to give 110 mg (38%) **5** as a colorless viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereoisomers: δ = 7.25–7.20 (m, 8H), 7.17–7.13 (m, 2H), 4.72–4.69 (m, 2H), 4.03–3.91 (m, 4H), 3.52–3.46 (m, 2H), 3.41–3.34 (m, 2H), 2.38–2.26 (m, 8H), 1.94–1.88 (m, 2H), 1.57–1.48 (m, 2H), 1.45 (s, 6H), 1.43–1.35 (m, 4H), 1.28–1.18 (m, 6H), 0.77 (dd, J = 6.0, 3.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereoisomers: δ = 169.65 and 169.62, 139.99 and 139.96, 128.82, 128.06, 126.71, 113.83, 77.27, 70.59 and 70.54, 59.14, 53.37 and 53.31, 50.79 and 50.70, 30.66 and 30.63, 30.45 and 30.37, 27.14 and 27.00 and 26.95 and 26.91, 26.46, 16.74 and 16.68. IR (film, NaCl), ν [cm^{-1}] = 2931, 2856, 2796, 1761, 1454, 1373, 1254, 1205, 1111, 1078, 735, 698. HRMS (FAB) for $C_{37}H_{54}N_2O_6$ calcd: 622.3982 [M]$^+$, found: 622.3994.

4.1.5. Preparation of (4*R*,5*R*)-2,2-dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid bis-benzylamide (7). A mixture of **6** (5.01 g, 20.34 mmol), benzylamine (5.24 g, 48.90 mmol), K_2CO_3 (0.67 g, 4.85 mmol) and MeOH (50 mL) was refluxed for 18 h and then cooled. Excess benzylamine was removed by distillation under reduced pressure (0.2 mbar) to give 7.08 g (94%) of **7** as a reddish viscous oil, which was used for the next step without further purification. Spectroscopic data for **7** were the same as reported in the literature.[21]

4.1.6. Preparation of (4*S*,5*S*)-benzyl-[5-(benzylamino-methyl)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl]-amine 8. $LiAlH_4$ (1.90 g, 50.07 mmol) was suspended into 100 mL abs. dioxane. A solution of **7** (7.05 g, 19.1 mmol) in 50 mL of abs. dioxane was added dropwise and mixture refluxed for 18 h. After cooling, 3 mL of water were added slowly to the solution, followed by 3 mL of 10% NaOH and 5 mL water. The solution was filtered and solvent evaporated to give 5.07 g (78%) of crude **8** as a yellow viscous oil. An analytical sample was prepared by column chromatography purification (Al_2O_3N, Act III, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.21 (m, 8H), 7.18–7.15 (m, 2H), 3.90–3.85 (m, 2H), 3.73 (s, 4H), 2.73–2.67 (m, 4H), 1.62 (br s, 2H), 1.31 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.10, 128.33, 128.02, 126.90, 108.70, 78.74, 53.98, 51.16, 27.17. IR (film, NaCl), ν [cm^{-1}] = 2983, 2931, 2825, 1495, 1454, 1379, 1369, 1254, 1215, 1167, 1072, 1028, 737, 698. EA for $C_{21}H_{28}N_2O_2$ (340.47 g/mol) calcd: C, 74.1; H, 8.3; N, 8.2. Found: C, 73.9; H, 8.4; N, 8.0. HRMS (FAB): calcd: 341.2229 [M+H]$^+$, found: 341.2241. $[\alpha]_D^{20} = -14.6$ (c 0.7, CH_2Cl_2).

4.1.7. Preparation of (4*S*,5*S*)-benzyl-(5-{[benzyl-(2-methylallyl)-amino]-methyl}-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-(2-methylallyl)-amine 9. To a mixture of **8** (1.75 g, 5.14 mmol) in *i*-PrOH (15 mL), methylallyl chloride (1.40 g, 15.46 mmol) was added dropwise and kept for 2 h at 50–60 °C, after which the reaction mixture was neutralized with 40% NaOH (1 mL) and stirred for 30 min. Then, another 1.40 g of methylallyl chloride was added, and the mixture stirred for 2 h at 80 °C. The reaction was cooled and treated with 40% NaOH (1 mL). Isopropanol was removed in a rotary evaporator and water (20 mL) added to the mixture. The aqueous layer was extracted with Et_2O (3 × 30 mL), the organic phase washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2:EtOAc 9:1) to give 847 mg (37%) of **9** as a yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.12 (m, 10H), 4.81 (br s, 2H), 4.73 (br s, 2H), 3.76–3.74 (m, 2H), 3.52 (dd, J = 78.8, 13.8 Hz, 4H), 2.90 (dd, J = 56.2, 13.5 Hz, 4H), 2.47 (ddd, J = 52.2, 13.2, 2.0 Hz, 4H), 1.63 (s, 6H), 1.25 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.73, 139.57, 128.86, 128.07, 126.70, 112.88, 108.75, 48.76, 61.52, 58.73, 55.66, 27.23, 20.83. IR (film, NaCl), ν [cm^{-1}] = 2983, 2933, 2798, 1452, 1379, 1369, 1065, 897, 739, 698. EA for $C_{29}H_{40}N_2O_2$ (448.65 g/mol) calcd: C, 77.6; H, 9.0; N, 6.2. Found: C, 77.7; H, 9.2; N, 6.0. HRMS (FAB): calcd: 447.3012 [M+H]$^+$, found: 447.3015. $[\alpha]_D^{20} = +5.0$ (c 1.0, CH_2Cl_2).

4.1.8. Preparation of (4*S*,5*S*)-5,10,17,22-tetrabenzyl-2,2,7,20-tetramethyl-docosahydro-1,3-dioxa-5,10,17,22-tetraaza-cyclopentacyclodocosene (10a). *General method A*: Compound **9** (115 mg, 0.26 mmol), **3a** (79 mg, 0.27 mmol) and [Rh(acac)(CO)$_2$] (4 mg, 16 μmol) were dissolved in toluene (40 mL), pressurized with 80 bar CO:H$_2$ (1:1), heated at 80 °C for 3 d and purified by column chromatography (silica gel, CH_2Cl_2:MeOH 97:3) to give 89 mg (44%) **10a** as a yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): signals for a mixture of diastereoisomers: δ = 7.26–7.12 (m, 20H), 3.86–3.70 (m, 3H), 3.63–3.56 (m, 1H), 3.54–3.47 (m, 3H), 3.42–3.34 (m, 3H), 2.61–2.44 (m, 4H), 2.38–2.24 (m, 8H), 2.20–2.08 (m, 4H), 1.69–1.50 (m, 4H), 1.44–1.38 (m, 4H), 1.28–1.25 (m, 6H), 1.22–1.17 (m, 4H), 1.09–0.98 (m, 2H), 0.79–0.65 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): signals for a mixture of diastereoisomers: δ = 140.20 and 139.82 and 139.76 and 139.49, 129.20 and 129.09 and 128.97 and 128.83 and 128.71, 128.24 and 128.13 and 127.99 and 126.86, 126.79 and 126.67 and 126.64 and 126.57, 108.88 and 108.79 and 108.59, 79.43 and 79.29, 78.30 and 78.25, 62.73 and 62.33 and 61.79, 61.40 and 61.29, 60.09 and 59.98 and 59.84, 59.66 and 59.55, 59.22 and 59.13, 57.54 and 56.81 and 56.59 and 56.06, 54.79, 53.42 and 53.36 and 53.31, 51.19 and 51.11 and 50.93, 32.11 and 31.93, 29.46 and 29.33 and 29.13 and 28.83, 27.33 and 27.30, 27.26 and 27.15 and 27.06 and 26.98

and 26.86, 18.42 and 18.37 and 18.33 and 18.27. IR (film, NaCl), ν [cm^{-1}] = 3026, 2929, 2856, 2796, 1495, 1452, 1377, 1369, 1259, 1240, 1066, 1028, 804, 735, 698. HRMS (FAB) for $C_{51}H_{72}N_4O_2$ calcd: 772.5655 $[M]^+$; found: 772.5631.

4.1.9. Preparation of (4*S*,5*S*)-5,10,14,19-tetrabenzyl-2,2,7,17-tetramethyl-octadecahydro-1,3-dioxa-5, 10,14,19-tetraaza-cyclopentacyclononadecene 10b. *General method A*: Compound **9** (116 mg, 0.26 mmol), **3b** (74 mg, 0.29 mmol) and [Rh(acac)$(CO)_2$] (5 mg, 19 μmol) were dissolved in toluene (40 mL), pressurized with 80 bar CO:H_2 (1:1), heated at 80 °C for 3 d and purified by column chromatography (silica gel, CH_2Cl_2:MeOH 97:3) to give 109 mg (57%) **10b** as a yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereoisomers: δ = 7.27–7.12 (m, 20H), 3.94–3.78 (m, 2H), 3.75–3.72 (m, 1H), 3.56 (s, 1H), 3.53–3.32 (m, 6H), 2.78–2.65 (m, 2H), 2.54–2.44 (m, 2H), 2.42–2.26 (m, 8H), 2.22–2.00 (m, 4H), 1.72–1.50 (m, 6H), 1.32–1.23 (m, 6H), 1.11–0.98 (m, 2H), 0.81–0.73 (m, 2H), 0.69–0.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereoisomers: δ = 139.92 and 139.82 and 139.75 and 139.68, 129.12 and 129.03, 128.93 and 128.83, 128.05 and 128.02, 127.97, 126.64, 108.72 and 108.55, 79.48 and 79.10 and 78.36, 62.62 and 61.89 and 61.49 and 60.82, 60.49 and 60.24 and 59.95 and 59.84, 59.24 and 59.13 and 59.06 and 58.89, 57.55 and 56.71 and 56.62 and 55.91, 51.81 and 51.70 and 51.58 and 51.53 and 51.46, 51.28 and 51.19, 32.12, 31.66, 29.55 and 29.38 and 29.01 and 28.93, 27.41 and 27.28, 18.44 and 18.42 and 18.40 and 18.33. IR (film, NaCl), ν [cm^{-1}] = 3060, 3026, 2951, 2931, 2868, 2798, 1495, 1452, 1379, 1369, 1252, 1061, 1028, 910, 735, 698. HRMS (FAB) for $C_{48}H_{66}N_4O_2$ calcd: 731.5264 $[M+H]^+$, 753.5083 $[M+Na]^+$; found: 731.5290, 753.5081.

4.1.10. Preparation of (9*S*,13*S*)-7,15-dibenzyl-4,11,11,18-tetramethyl-2,10,12,20-tetraoxa-7,15-diaza-dinaphtho[*a*,*c*]-bicyclo[18.3.0.0^{9,13}]-cyclotriacosane 12. *General method A*: Compound **11** (147 mg, 0.37 mmol), **8** (126 mg, 0.37 mmol) and [Rh(acac)$(CO)_2$] (4 mg, 16 μmol) were dissolved in toluene (40 mL), pressurized with 80 bar CO:H_2 (1:1), heated at 80 °C for 3 d, and purified by column chromatography (silica gel, CH_2Cl_2:EtOAc 9:1) to give 86 mg (30%) **12** as a yellow viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereoisomers: δ = 7.93–7.86 (m, 4H), 7.42–7.37 (m, 2H), 7.34–7.14 (m, 16H), 4.06–4.04 (m, 0.5H), 3.99–3.98 (m, 0.5H), 3.92–3.90 (m, 1H), 3.84–3.70 (m, 4H), 3.68–3.58 (m, 2H), 3.52–3.41 (m, 2H), 2.76–2.71 (m, 1H), 2.67–2.65 (m, 0.5H), 2.54–2.49 (m, 3.5H), 2.41–2.37 (m, 0.5H), 2.28–2.10 (m, 2.5H), 1.60–1.52 (m, 2H), 1.41–1.39 (m, 3H), 1.37–1.35 (m, 3H), 1.34–1.29 (m, 4H), 0.59–0.57 (m, 3H), 0.34–0.32 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): signals for a 1:1 mixture of diastereoisomers: δ = 154.67 and 154.64 and 154.58 and 154.52, 139.46 and 139.41, 134.24, 129.43 and 129.23 and 129.14 and 129.11, 129.03 and 129.00 and 128.96 and 128.88, 128.06 and 128.02 and 127.99, 127.77 and 127.70, 126.71 and 126.68 and 126.64, 126.01 and 125.95, 125.45 and 125.41, 123.48 and 123.38 and 123.29 and 123.26, 121.39 and 120.79 and 120.73 and 120.29, 116.70 and 116.12 and 115.49 and 115.45, 108.76 and 108.73, 78.98 and 78.92 and 78.71 and 78.62, 75.02 and 74.89 and 74.27 and 73.67, 59.60 and 59.45 and 59.07, 57.39 and 56.99 and 56.81 and 56.62, 51.68 and 51.63 and 51.50 and 51.25, 31.36 and 31.29 and 30.86, 30.97 and 30.62 and 29.96 and 29.75, 27.29 and 27.26 and 27.18, 16.70 and 16.65 and 16.54 and 16.47. IR (film, NaCl), ν [cm^{-1}] = 2954, 2929, 2871, 2808, 1622, 1591, 1508, 1495, 1456, 1379, 1369, 1354, 1265, 1244, 1147, 1066, 1018, 908, 806, 735. HRMS (FAB) for $C_{51}H_{58}N_2O_4$ calcd: 763.4475 $[M+H]^+$, 785.4294 $[M+Na]^+$; found: 763.4510, 785.4258.

4.1.11. Preparation of (9*S*,13*S*)-7,15-dibenzyl-11,11-dimethyl-2,10,12,20-tetraoxa-7,15-diaza-tricyclo[19.3.1.0^{9,13}]-pentacosa-1(24),21(25),22-triene-23-carboxylic acid methyl ester 15. *General method B*: Compound **13** (191 mg, 0.62 mmol), **8** (229 mg, 0.67 mmol) and [Rh(acac)$(CO)_2$] (17 mg, 66 μmol) were dissolved in toluene (40 mL), pressurized with 40 bar H_2, heated at 50 °C for 1 d and purified twice by column chromatography (silica gel, CH_2Cl_2, then *n*-hexane:EtOAc 4:1) to give 57 mg (15%) **15** as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.12 (m, 10H), 7.11 (s, 1H), 7.10 (s, 1H), 6.75 (s, 1H), 4.13–4.09 (m, 2H), 4.07–4.02 (m, 2H), 3.81 (s, 3H), 3.68 (br s, 2H), 3.51 (dd, J = 112.5, 13.7 Hz, 4H), 2.57–2.42 (m, 6H), 2.37–2.32 (m, 2H), 1.72–1.66 (m, 4H), 1.58–1.45 (m, 4H), 1.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.82, 139.50, 132.18, 128.99, 128.12, 126.74, 109.02, 106.95, 78.88, 67.99, 58.88, 56.58, 53.59, 52.15, 27.23, 26.05, 23.09. IR (film, NaCl), ν [cm^{-1}] = 2933, 2871, 2806, 1724, 1593, 1452, 1348, 1300, 1236, 1163, 1061, 769, 737. HRMS (FAB): for $C_{37}H_{48}N_2O_6$ calcd: 616.3512 $[M]^+$; found: 616.3542. $[\alpha]_D^{21}$ = +13.0 (*c* 0.2, CH_2Cl_2).

4.1.12. Preparation of (9*S*,13*S*)-7,15-dibenzyl-11,11-dimethyl-2,10,12,20-tetraoxa-7,15-diaza-dinaphtho[*a*,*c*]-bicyclo[18.3.0.0^{9,13}]-cyclotriacosane 16. *General method B*: Compound **14** (221 mg, 0.45 mmol), **8** (176 mg, 0.52 mmol) and [Rh(acac)$(CO)_2$] (11 mg, 43 μmol) were dissolved in toluene (40 mL), pressurized with 40 bar H_2, heated at 50 °C for 1 d, purified twice by column chromatography (silica gel, CH_2Cl_2, then *n*-hexane:EtOAc 4:1) to give 130 mg (39%) **16** as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 7.24–7.10 (m, 14H), 7.05–7.03 (m, 2H), 3.94–3.89 (m, 2H), 3.80–3.76 (m, 2H), 3.73 (br s, 2H), 3.47 (dd, J = 108.7, 13.8 Hz, 4H), 2.48 (dd, J = 74.0, 12.3 Hz, 4H), 2.31–2.28 (m, 2H), 2.12–2.09 (m, 2H), 1.44–1.41 (m, 2H), 1.36–1.19 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.68, 139.46, 134.21, 129.26, 129.06, 128.93, 128.05, 127.79, 126.70, 126.11, 125.40, 123.42, 120.67, 116.08, 108.71, 78.79, 69.49, 59.39, 56.96, 53.27, 27.23, 27.03, 23.43. IR (film, NaCl), ν [cm^{-1}] = 3059, 2981, 2935, 2871, 2806, 1722, 1680, 1622, 1593, 1506, 1495, 1456, 1431, 1379, 1369, 1354, 1331, 1263, 1169, 1147, 1132, 1084, 1020, 808, 737. HRMS (FAB) for $C_{49}H_{54}N_2O_4$ calcd: 735.4162 $[M+H]^+$; found: 735.4136. $[\alpha]_D^{21}$ = −78.7 (*c* 0.8, CH_2Cl_2).

4.1.13. Preparation of (9*S*,10*S*)-7,12-dibenzyl-9,10-dihydroxy-2,17-dioxa-7,12-diaza-bicyclo[16.3.1]docosa-1(21),18(22),19-triene-20-carboxylic acid methyl ester 18

4.1.13.1. Procedure A. Compound **15** (33 mg, 0.054 mmol) was dissolved in CH_3OH (3 mL) and 2 M HCl (3 mL) added. The solution was heated at 70 °C for 5 h. After cooling, methanol was removed in a rotary evaporator, and the solution subjected to pH 12 with solid NaOH and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. The yield of crude **18** was 20 mg (65%) as a colorless viscous oil.

4.1.13.2. Procedure B. *General method B*: Compound **13** (200 mg, 0.65 mmol), **16** (195 mg, 0.65 mmol) and [Rh(acac)$(CO)_2$] (19 mg, 74 μmol) were dissolved in toluene (40 mL), pressurized with 40 bar H_2, heated at 50 °C for 1 d and purified twice by column chromatography (silica gel, CH_2Cl_2, then *n*-hexane:EtOAc 4:1) to give 240 mg (64%) **18** as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.15 (m, 10H), 7.10 (d, J = 2.3 Hz, 2H), 6.78 (s, J = 2.3 Hz, 1H), 4.02 (t, J = 5.3 Hz, 4H), 3.82 (s, 3H), 3.53 (dd, J = 117.7, 13.3 Hz, 4H), 3.49 (br s, 2H), 2.67–2.53 (m, 4H), 2.44–2.39 (m, 4H), 1.76–1.57 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.83, 159.77, 132.01, 129.15, 128.34, 127.23, 108.77, 107.55, 68.80, 67.93, 59.38, 56.36, 53.33, 52.18, 25.85, 22.71. IR (film, NaCl), ν [cm^{-1}] = 3427, 3311, 3028, 2949, 2871, 2852, 1732, 1606, 1495, 1454, 1300, 1238, 1157, 1053, 910, 768. HRMS (FAB): for $C_{34}H_{44}N_2O_6$ calcd: 577.3278 $[M+H]^+$; found: 577.3260 $[\alpha]_D^{21} = -24.0$ (*c* 0.06, CH_2Cl_2).

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