Concave 1,10-Phenanthrolines by Ring-Closing Metathesis[‡]

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Keywords: Metathesis / Macrocycles / Cyclophanes / Cleavage reactions

Ring-closing metathesis using Grubbs' catalyst has been applied to the synthesis of the concave 1,10-phenanthrolines **5**. Instead of a kinetically controlled double macrocyclization of the tetraphenol precursor **2** by two equivalents of ditosylates or diiodides, the new three step synthesis separates the alkylation of **2** from the macrocyclization. After the tetraalkylation of **2**, the resulting tetraalkene **3** is cyclized by metathesis under thermodynamic control to give the bimacrocycles **4** in up to 92% yield. Hydrogenation of the alkene double bonds gave the bimacrocycles **5** in considerably improved overall yields (for instance for **5b** from 19 to 79%).

The high selectivity of enzymes is largely caused by their concave geometry. Concave reagents have copied their lamp-shape geometry and numerous classes of concave acids, concave bases and concave ligands have been synthesized.[1] Among these, the concave 1,10-phenanthrolines have proven to be very useful. They are concave bases[2] but they are also good ligands due to the two nitrogen atoms of the 1,10-phenanthroline moiety that can strongly bind metal ions by chelation.[2,3] Besides using them as carriers,[4] these complexes have been used to enhance selectivities in transition-metal-catalyzed Diels−Alder reactions,[5] allylations[6] and cyclopropanations.[7]

The skeleton of the concave 1,10-phenanthrolines **5** is bimacrocyclic with two aryl rings as bridgeheads i.e. they are dibenzena-1,10-phenanthrolinabicyclophanes.[8] The aryl bridgeheads were introduced by addition of 2-lithium-1,3-dimethoxybenzene to the 1,2- and 9,10-double bonds of 1,10-phenanthroline giving 2,9-bis(2,6-dimethoxyphenyl)-1,10-phenanthroline (**1**) after hydrolysis and rearomatization.[2b] In the past, the methyl ethers have been cleaved by reaction with boron tribromide; however, this reaction is sometimes not reproducible. Therefore a new demethylation has now been worked out: the tetramethyl ether **1** is reacted with molten pyridinium chloride at 200 °C giving the tetraphenol **2** as its hydrochloride in 83% yield.

In the past, this tetraphenol **2** has been doubly bridged by α,ω-diiodides or α,ω-ditosylates to give the bimacrocyclic concave 1,10-phenanthrolines **5** in yields of up to ca. 30% (Scheme 1). When substituted side chains were used, however, the yields dropped considerably.[2c] In this publication, we would like to present an alternative route to concave 1,10-phenanthrolines **2** which exploits the ring-closing metathesis reaction and improves the yields from the tetraphenol **2** to the bimacrocycles **5** to 57−79%.

This new route first alkylates the four phenol functions of **2** with ω-bromo-1-alkenes thus separating the alkylation reaction from the macrocyclization. In the next step of the reaction sequence, the alkene units are coupled using Grubbs' catalyst[9] to yield the unsaturated bimacrocycles **4**, before final hydrogenation gives the concave 1,10-phenanthrolines **5**. The yields of this new approach are compared with the yields of the original synthesis in Table 1.

Although the new approach uses three steps instead of one, the *overall* yields are much better. Therefore it can be expected that concave 1,10-phenanthrolines **5** containing substituents in the side chains may be synthesized in good yields as well. The main difference between the two reaction pathways is a thermodynamic instead of a kinetic control during the bimacrocyclization.[10] In the original approach, the macrocyclization is kinetically controlled. If the alkylation occurs at a different phenol group to that intended, oligomers and polymers are formed.[11] In contrast, in the new approach, the macrocyclization step is not the alkylation but the ring-closing metathesis. This reaction is thermodynamically controlled[10] thus leading to the most stable products. Entropic reasons call for the formation of the bimacrocycles if they are not too strained.[12]

In a ring-closing metathesis, *cis*- or *trans*-double bonds may be formed. In the crude reaction mixtures of **4a** and **4b**, NMR signals for different vinylic protons of **4** are observed. Interestingly, however, the ratios are very different for **4a** and **4b**. The larger bimacrocycle **4b** exists mainly as one symmetrical isomer while the smaller bimacrocycle **4a** shows two different sets of NMR signals for the vinylic protons in a 55:45 ratio. Unfortunately, an unambiguous assignment of the stereochemistry was not successful. For the synthesis of the final concave 1,10-phenanthrolines **5** this stereochemical problem is of no importance because both, *cis*- and *trans*-double bonds, will be hydrogenated to the same alkane chain in **5**.

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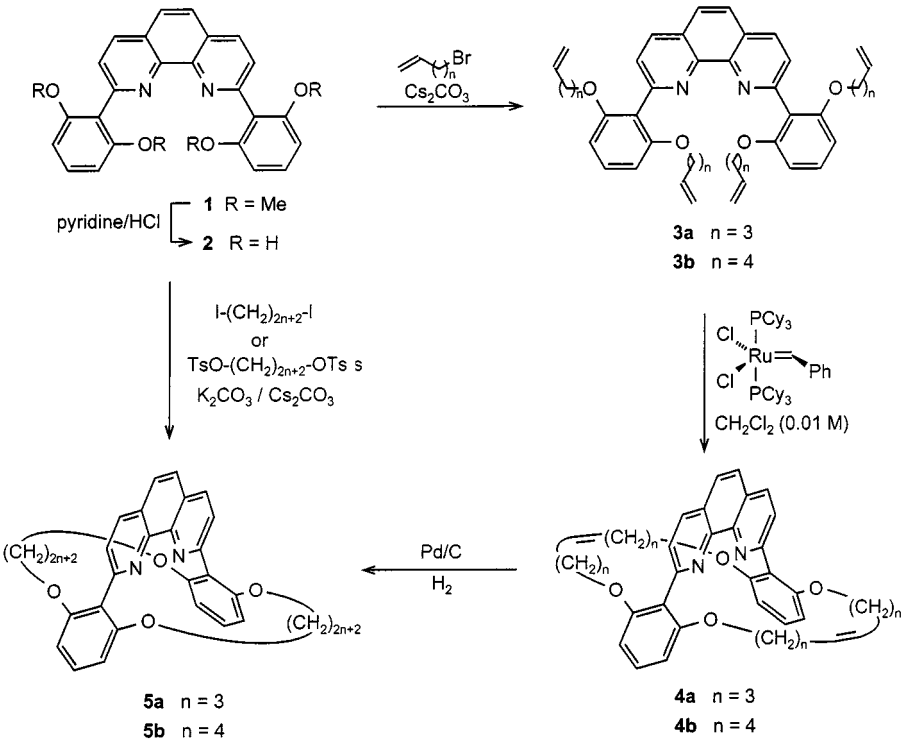

Scheme 1

Table 1. Comparison of the yields of the one-step bimacrocyclization with the three-step synthesis using ring-closing metathesis to give concave 1,10-phenanthrolines **5**

	Alkylation of **2**·HCl Yield [%]	Ring-closing metathesis Yield [%]	Hydrogenation Yield [%]	*Overall* yield of the three-step synthesis [%]	One-step bimacrocyclization Yield [%][2b]
a	79	73	99	57	28
b	90	92	95	79	19

Experimental Section

General: The following chemicals were obtained commercially and were used without further purification: benzylidenebis(tricyclohexylphosphane)dichlororuthenium(II) (Fluka), 6-bromo-1-hexene (Fluka), 5-bromo-1-pentene (Fluka), dimethyl sulfoxide (Merck), palladium (10%) on activated carbon (Merck). 2,9-Bis(2,6-dimethoxyphenyl)-1,10-phenanthroline (**1**) was prepared according to the literature procedure.[2b] Dry solvents were obtained with suitable desiccants: dichloromethane and pyridine were distilled from calcium hydride, and ethyl acetate was distilled from calcium chloride. Column chromatography was carried out on basic alumina (Macherey−Nagel, activity I). The ^{1}H NMR spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer, with TMS as internal standard. IR spectra were recorded on a Perkin−Elmer 1600 Series. MS spectra were recorded on a Finnigan MAT 8230. Elemental analyses were carried out on VarioEl, Elementaranalysensysteme GmbH.

2,9-Bis(2,6-dihydroxyphenyl)-1,10-phenanthroline Hydrochloride (2·HCl): While stirring, pyridine (7.90 mL, 97.0 mmol) was added to 9.00 mL of concentrated hydrochloric acid. Water was removed by distillation until the temperature of the pyridinium chloride melt reached 200 °C. After cooling to 140 °C, 2,9-bis(2,6-dimethoxyphenyl)-1,10-phenanthroline (**1**) (770 mg, 1.70 mmol) was added and the mixture was heated to 200 °C for 3 h in an argon flow to remove the produced chloromethane. After cooling below 100 °C, 10 mL of water was added and the mixture was poured into 75 mL of warm water. The orange precipitate was filtered, washed with 100 mL of dilute hydrochloric acid and 100 mL of water and dried in vacuo to obtain 610 mg (83%) of **2**·HCl. The ^{1}H NMR spectrum was in accordance with the literature.[2b]

2,9-Bis[2,6-di(pent-4-enoxy)phenyl]-1,10-phenanthroline (3a): Under argon, 2,9-bis(2,6-dihydroxyphenyl)-1,10-phenanthroline hydrochloride (**2**·HCl) (198 mg, 457 μmol) and cesium carbonate (1.96 g, 6.02 mmol) were suspended in 10 mL of dimethyl sulfoxide. After the addition of 5-bromo-1-pentene (710 μL, 6.01 mmol), the mixture was stirred for 3 days at room temperature. The solvent was removed in vacuo and the residue was dissolved in 10 mL of water and 10 mL of dichloromethane. The layers were separated and the water layer was extracted three times with 20 mL of dichloromethane. The combined organic layer was washed with dilute aqueous sodium hydroxide and dried with magnesium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography (eluent: dichloromethane), to give 241 mg (79%) of **3a**, m.p. 111 °C. − IR (KBr): $\tilde{\nu}$ = 3072 cm^{-1} (arom. C−H), 2936, 2871 (aliph. C−H), 1639 (aliph. C=C), 1596 (arom. C=C), 1459, 1102 (C−O−C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 (m_c, 8 H, OCH_2CH_2), 1.87 (m_c, 8 H, CH_2CH=), 3.92 (t, J = 6.4 Hz, 8 H, OCH_2), 4.73−4.82 (m, 8 H, CH=CH_2), 5.57 (ddt, J_t = 6.7 Hz, J_d = 10.3 Hz, J_d = 17.0 Hz, 4 H, CH=CH_2), 6.61 (d,

J = 8.4 Hz, 4 H, 3′,3′′,5′,5′′-H), 7.23 (t, J = 8.4 Hz, 2 H, 4′,4′′-H), 7.61 (d, J = 8.2 Hz, 2 H, 3,8-H), 7.80 (s, 2 H, 5,6-H), 8.21 (d, J = 8.2 Hz, 2 H, 4,7-H). − EI-MS (70 eV): m/z (%) = 669 (100) [M^+], 628 (97) [$M^+ - C_3H_5$], 614 (74) [$M^+ - C_4H_7$], 600 (20) [$M^+ - C_5H_9$]. − HRMS ($C_{44}H_{48}N_2O_4$): calcd. 668.36139; found 668.36120; ($C_{43}{}^{13}CH_{48}N_2O_4$): calcd. 669.36475; found 669.36475. − $C_{44}H_{48}N_2O_4$ (668.36): calcd. C 79.01, H 7.23, N 4.19; found C 78.88, H 7.06, N 4.09.

2,9-Bis[2,6-di(hex-5-enoxy)phenyl]-1,10-phenanthroline (3b): Analogously to the synthesis of **3a**, compound **3b** was prepared from **2**·HCl and 6-bromo-1-hexene in a yield of 90%, m.p. 108−109 °C. − IR (KBr): $\tilde{\nu}$ = 3072 cm^{-1} (arom. C−H), 2934 (aliph. C−H), 1639 (aliph. C=C) 1596 (arom. C=C), 1458, 1104 (C−O−C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (m_c, 8 H, CH_2CH$_2$CH=), 1.49 (m_c, 8 H, OCH$_2$CH_2), 1.80 (m_c, 8 H, CH_2CH=), 3.91 (t, J = 6.4 Hz, 8 H, OCH_2), 4.72−4.81 (m, 8 H, CH=CH_2), 5.30 (s, 0.1 H, CH_2Cl$_2$), 5.53 (ddt, J_t = 6.6 Hz, J_d = 10.4 Hz, J_d = 16.9 Hz, 4 H, CH=CH$_2$), 6.61 (d, J = 8.4 Hz, 4 H, 3′,3′′,5′,5′′-H), 7.24 (t, J = 8.4 Hz, 2 H, 4′,4′′-H), 7.60 (d, J = 8.2 Hz, 2 H, 3,8-H), 7.80 (s, 2 H, 5,6-H), 8.19 (d, J = 8.2 Hz, 2 H, 4,7-H). − EI-MS (70 eV): m/z (%) = 725 (100) [M^+], 670 (18) [$M^+ - C_4H_7$], 656 (65) [$M^+ - C_5H_9$], 642 (98) [$M^+ - C_6H_{11}$]. − HRMS ($C_{48}H_{56}N_2O_4$): calcd. 724.42401; found 724.42390; ($C_{47}{}^{13}CH_{56}N_2O_4$): calcd. 725.42737; found 725.42690. − $C_{48}H_{56}N_2O_4$ (724.99): calcd. C 79.52, H 7.79, N 3.86; $C_{48}H_{56}N_2O_4$·0.1CH_2Cl_2: calcd. C 78.77, H 7.72, N 3.82; found C 78.68, H 7.72, N 3.70.

General Procedure for the Synthesis of 4: Under argon, 5 mol % of benzylidenebis(tricyclohexylphosphane)dichlororuthenium(II) was added to a 0.01 M solution of tetraalkene **3** in dichloromethane. After stirring for 6 h another 5 mol % of benzylidenebis(tricyclohexylphosphane)dichlororuthenium(II) was added and the solution was stirred for another 16 h. The solvent was then evaporated and the residue was purified by column chromatography (eluent: dichloromethane) to give the product as a mixture of the three possible isomeric compounds.

2,11,13,22-Tetraoxa-1,12(1,3,2)-dibenzena-23(2,9)-1,10-phenanthrolinabicyclo[10.10.1]tricosaphan-6,17-diene (4a):[8] Yield: 73%. − Ratio of isomeric double bonds: 55:45. − IR (KBr): $\tilde{\nu}$ = 2922 cm^{-1} (aliph. C−H), 1596, 1581 (arom. C=C), 1457, 1246, 1091 (C−O−C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3−1.8 (m, 16 H, CH_2), 3.8−4.2, 4.15 (m, m_c, 8 H, OCH_2), 4.66 (m_c, 2.2 H, CH=), 4.99 (m_c, 1.8 H, CH=), 5.30 (s, 0.1 H, CH_2Cl$_2$), 6.6−6.7 (m, 4 H, 3′,3′′,5′,5′′-H), 7.2−7.3 (m with t at 7.25, J = 8.3 Hz and t at 7.24, J = 8.3 Hz, 2 H, 4′,4′′-H), 7.60, 7.65 (2 × d, J = 8.2 Hz, 2 H, 3,8-H), 7.82, 7.83 (2 × s, 2 H, 5,6-H), 8.22, 8.33 (2 × d, J = 8.2 Hz, 2 H, 4,7-H). − EI-MS (70 eV): m/z (%) = 612 (100) [M^+], 584 (8) [$M^+ - C_2H_4$]. − HRMS ($C_{40}H_{40}N_2O_4$): calcd. 612.29883; found 612.29900; ($C_{39}{}^{13}CH_{40}N_2O_4$): calcd. 613.30219; found 613.30200. − $C_{40}H_{40}N_2O_4$ (612.77): calcd. C 78.41, H 6.58, N 4.57; $C_{40}H_{40}N_2O_4$·0.1CH_2Cl_2: calcd. C 77.53, H 6.52, N 4.51; found C 77.55, H 6.83, N 4.57.

2,13,15,26-Tetraoxa-1,14(1,3,2)-dibenzena-27(2,9)-1,10-phenanthrolinabicyclo[12.12.1]heptacosaphan-7,20-diene (4b):[8] Yield: 92%. − Ratio of isomeric double bonds: 92:8. − IR (KBr): $\tilde{\nu}$ = 2925 cm^{-1} (aliph. C−H), 1595 (arom. C=C), 1457, 1247, 1103 (C−O−C). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.9−1.7, 1.05, 1.35, 1.55 (m, m_c, m_c, m_c, 24 H, CH_2), 3.84 (m_c, 8 H, OCH_2), 4.44 (m_c, 0.3 H, CH=), 4.73 (tt, J = ca. 1.6 Hz, J = 3.5 Hz, 3.7 H, CH=), 5.30 (s, CH_2Cl$_2$), 6.5−6.7 (m with d at 6.57, J = 8.3 Hz, 4 H, 3′,3′′,5′,5′′-H), 7.1−7.3 (m with t at 7.22, J = 8.3 Hz, 2 H, 4′,4′′-H), 7.5−7.7 (m with d at 7.56, J = 8.2 Hz, 2 H, 3,8-H), 7.8−7.9 (m with s at 7.83, 2 H, 5,6-H), 8.2−8.3 (m with d at 8.23, J = 8.2 Hz, 2 H, 4,7-H). − EI-MS (70 eV): m/z (%) = 669 (51) [M^+], 641 (100) [$M^+ - C_2H_4$], 627 (25) [$M^+ - C_3H_6$], 598 (62) [$M^+ - C_5H_{11}$]. − HRMS ($C_{44}H_{48}N_2O_4$): calcd. 668.36139; found 668.36120; ($C_{43}{}^{13}CH_{48}N_2O_4$): calcd. 669.36475; found 669.36440. − $C_{44}H_{48}N_2O_4$ (668.87): calcd. C 79.01, H 7.23, N 4.19; $C_{44}H_{48}N_2O_4$·0.4CH_2Cl_2: calcd. C 75.88, H 7.00, N 3.99; found C 75.74, H 7.17, N 3.69.

General Procedure for the Synthesis of 5: Bimacrocycle **4** (200 mg) was dissolved in 10 mL of ethyl acetate by heating. After the addition of 50 mg of palladium (10%) on activated carbon the suspension was stirred for 6 h under a hydrogen atmosphere at room temperature. After filtration and evaporation of the solvent, the crude product was recrystallized from petroleum ether (b.p. 60−90 °C). The ^{1}H NMR spectra were in accordance with the literature.[2c]

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[10] A very impressive proof for the thermodynamic control of the metathesis reaction has been published by: M. S. Wendland, S. C. Zimmerman, *J. Am. Chem. Soc.* **1999**, *121*, 1389−1390. If enough catalyst is used (4 mol % per allyl group) *all* allyl groups on the outer perimeter of the dendrimer are coupled. In the case of kinetic control, untouched allyl groups should remain at the remote positions on the surface of the dendrimer. All allyl groups, however, are coupled. See also ref.[12]

[11] In principle, the macrocyclization could also connect two oxygen atoms attached to the same aryl bridgehead to give a metacyclophane. However, even in the kinetically controlled bismacrocyclizations, this bridging pattern has never been observed. The resulting metacyclophane would be strained. For a discussion of this alternative see ref.[2b]

[12] In an equilibrium, the Gibbs free enthalpies ΔG of the different products determine the major product. In the case of the metathesis, the enthalpy of formation of an alkene should contribute with comparable ΔH for a bimacrocycle and a polymer if the macrocycle is not too strained. However, in solution, the formation of *one* polymer molecule is entropically less favoured than the formation of *many* bimacrocycles. Thus ΔG is mainly determined by $-T\Delta S$ in solution. In our macrocyclizations, undesired polymers formed from the bimacrocyclic metathesis products only if, after completion of the metathesis, the reaction mixture was concentrated and was allowed to stand overnight with the catalyst still present.

Received December 4, 2000
[O00615]