Nontemplated versus Templated Synthesis of a 56-Membered Macrocycle

Markus Albrecht,*[a] Yeni,[a] Roland Fröhlich[b]

[a] Institut für Organische Chemie, RWTH Aachen, Landoltweg 1, 52074 Aachen, Germany
Fax +49(241)8092385; E-mail: markus.albrecht@oc.rwth-aachen.de

[b] Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, 49148 Münster, Germany

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Abstract: The amine-substituted quinquephenylene **1** was prepared in a Suzuki coupling approach and by reaction with terephthalic dialdehyde (**7**) it was transformed into the phenyl-connected diimine **8**. Ring-closing metathesis with the Grubbs I or II catalyst led to the corresponding macrocycle **9**. Hydrogenation resulted in the reduction of the double bonds as well as the removal of the template to yield the 56-membered macrocycle **6** in an overall yield of 43% (from **1**). Direct metathesis reaction of **1** followed by hydrogenation afforded **6** in only 21% yield.

Key words: macrocycles, quinquephenylene, ring-closing metathesis, preorganization, template effect

Since Pedersens discovery of the crown ethers in 1967 macrocyclic compounds play an important role as receptors in supramolecular chemistry. The binding of guest species in the interior of the compounds depends on the size of the cavity, and also on appropriate functionalities, which are able to interact with the guests.[1]

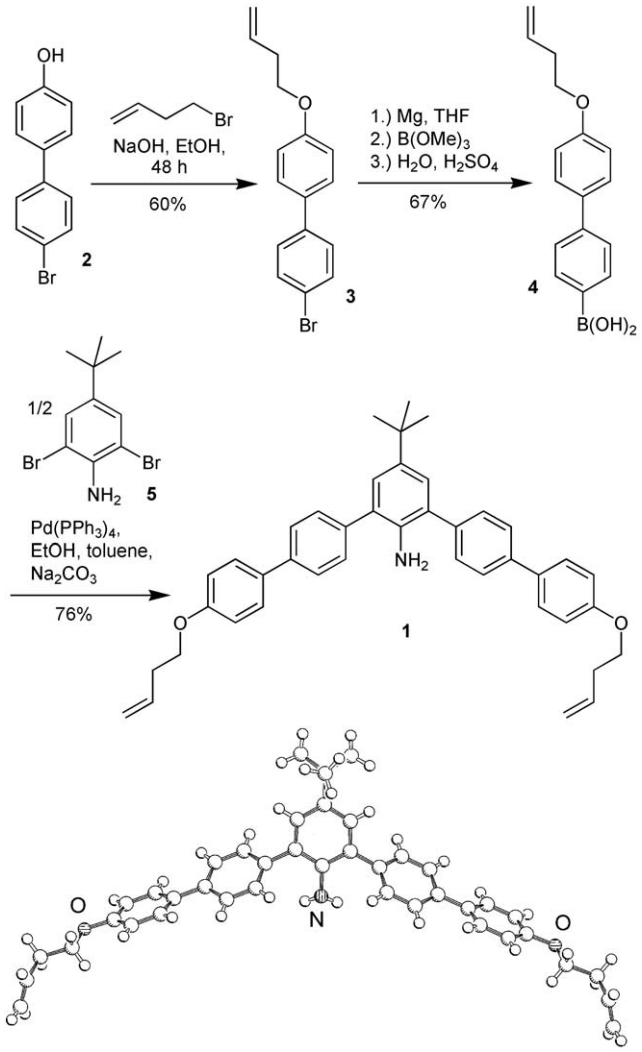
Today, the preparation of small and medium-sized macrocycles follows well-established procedures.[2] However, the specific high-yield synthesis of huge macrocycles, which preferably bear internal functional groups, is still a challenge. Investigations by Sanders,[3] Höger,[4] and many others show that such macrocycles can be obtained in template-directed syntheses.[5]

In 2004 Guan presented the synthesis of a 'medium-sized' 26-membered macrocycle by a double ring-closing-metathesis (RCM) approach using a bisimine as template. The reaction yields an internally functionalized rigid cyclophane with a rather small cavity.[6]

Now we describe the formation of a 56-membered macrocycle, which possesses two rigid quinquephenylene units and two flexible hexyl bridges. The synthesis is performed following a templated as well as nontemplated strategy.

As the key building block in our synthesis, the amine-substituted 1,1′:4′,1″:3″,1‴:4‴,1⁗-quinquephenyle **1** is initially prepared and structurally characterized as it is shown in Scheme 1. Williamson ether synthesis of 4-bromo-1-butene with 4-bromo-4′-hydroxy biphenyl (**2**) affords the ether **3** in 60%. Reaction of **3** with magnesium and quenching with $B(OMe)_3$ followed by sulfuric acid results in the formation of the boronic acid **4** (67%). The amine **1** is finally obtained in 76% yield in a double Suzuki coupling reaction[7] with half an equivalent of the dibromo aniline **5**[8] in the presence of tetrakis(triphenylphosphane) palladium(0) (see Scheme 1).

X-ray quality crystals of **1** are obtained from chloroform–methanol. The structure is shown in Scheme 1 (bottom). The curvature of the quinquephenylene with the amine group located on the concave side is well recognized. In addition, butenyloxy groups are located at the termini.[9]



Scheme 1 Synthesis and solid-phase structure of the quinquephenylene **1**

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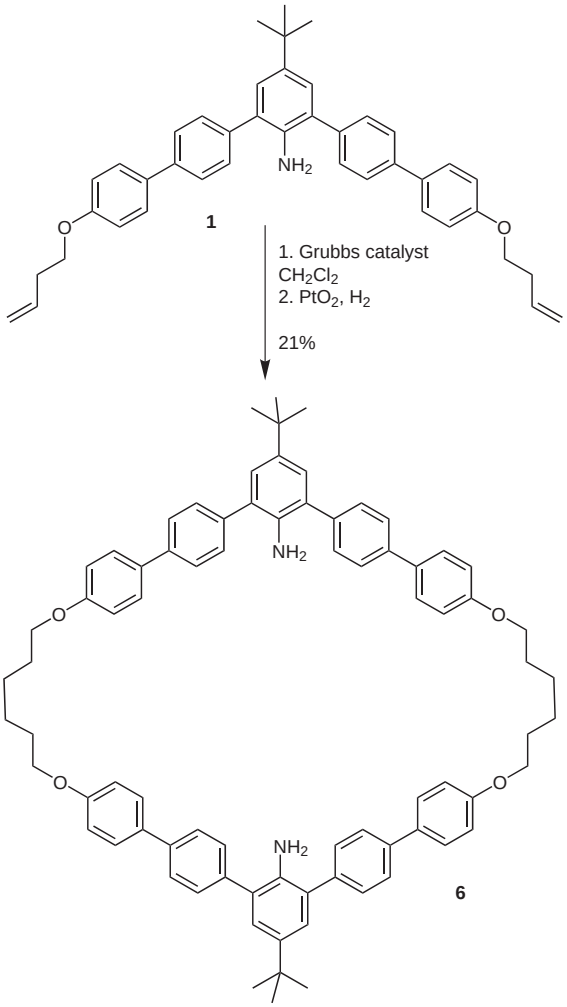
Derivative **1** represents a 'semicircle' and therefore seems to be appropriate to form macrocycles in a dimerizing RCM. The reaction cannot proceed intramolecularly; at least two molecules of **1** have to take part. However, reacting **1** with Grubbs I catalyst results in the formation of undefined, probably oligomeric material, which is still soluble, but does not afford resolved NMR spectra.[10]



Scheme 2 Nontemplated synthesis of macrocycle **6** using ring-closing metathesis

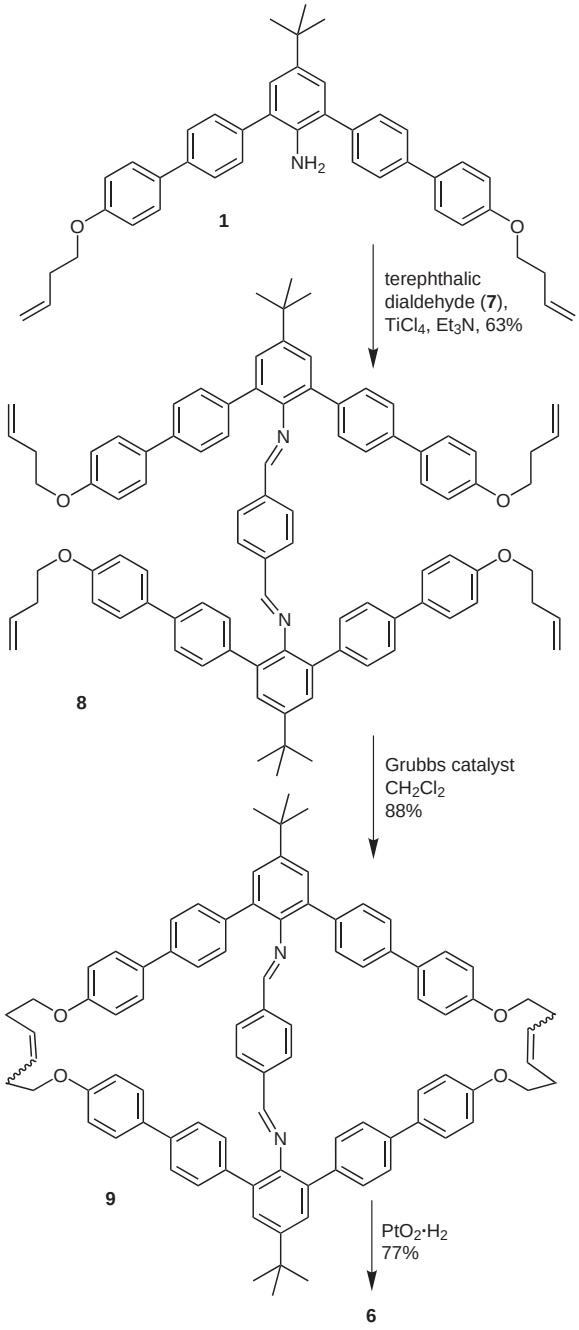
Reaction of **1** with the Grubbs catalyst of the second generation results in the formation of the desired 'unsaturated' macrocycle, which immediately is hydrogenated (PtO_2) to afford **6** in 21% yield (Scheme 2).

In order to improve the macrocyclization by RCM, the reaction is intramolecularized by using terephthalic dialdehyde as a template. Reaction of two equivalents of **1** with terephthalic dialdehyde **7** in dichloromethane in the presence of titanium tetrachloride and triethylamine[11] results in the formation of the diimine **8** in 63% yield (Scheme 3).

Ring-closing metathesis of **8** results in the formation of the macrocycle **9**. The Grubbs I as well as Grubbs II catalysts are appropriate for this reaction with the second-generation catalyst reacting faster. Compound **9** is isolated as mixture of the *E* and *Z* isomers (ratio 1:3). In the case of this templated reaction the ring closing occurs much faster as in the nontemplated case.

The derivatives **9** possess the structure of a moleculare turnstile, as it was described in 1995 by Moore. In contrast to his example, **9** possess flexible hexylidene bridges in the outer circle.[12]

Hydrogenation (H_2, PtO_2) of the bisimine **9** results in the reduction of the C=C double bonds and in the simultaneous reductive cleavage of the imines. The 56-membered macrocycle **6** is isolated in 77% yield.



Scheme 3 Templated synthesis of **6** by RCM utilizing terephthalic dialdehyde **7** as the template of choice

The macrocycle **6** obtained by either of the two protocols is characterized by its ^{1}H NMR and ^{13}C NMR, elemental analysis as well as positive ESI-MS spectrum. The latter shows the dominating peak at *m/z* = 1135.4 which is assigned to the protonated species [**6**·H]$^+$ (sprayed from chloroform–methanol).[13]

Our results show that the huge cyclophane **6** can be obtained in a ring-closing metathesis with subsequent reduction of the double bonds in 21% yield starting with the simple pre-organized building block **1**. On the other hand, the templated reaction is superior to this short-step protocol due to avoiding oligomeric/polymeric side products during the ring-closing metathesis. Imination of **1** (2 equiv) with terephthalic dialdehyde followed by RCM and subsequent hydrogenation of the double bond accompanied by removal of the template affords the macrocycle **6** in an overall yield of 43%.

The presented building block **1** and its macrocyclization will be further studied by us in order to get a deeper insight in the underlying templating process, and to apply the findings in the preparation of topologically interesting molecules. In addition, **6** will be tested as macrocyclic receptor for small organic molecules.

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References and Notes

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(9) (a) **Characterization of 1**
Mp 198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, ^3J = 8.5 Hz, 4 H, H_{ar}), 7.53 (d, ^3J = 8.5 Hz, 4 H, H_{ar}), 7.49 (d, ^3J = 8.8 Hz, 4 H, H_{ar}), 7.15 (s, 2 H, H_{ar}), 6.92 (d, ^3J = 8.8 Hz, 4 H, H_{ar}), 5.86 (ddt, $^3J_{trans}$ = 17.0 Hz, $^3J_{cis}$ = 10.4 Hz, ^3J = 6.7 Hz, 2 H, HC=), 5.12 (dm, $^3J_{trans}$ = 17.0 Hz, 2 H, =CH_{trans}), 5.05 (dm, $^3J_{cis}$ = 10.4 Hz, 2 H, =CH_{cis}), 4.00 (t, ^3J = 6.7, 4 H, CH_2), 2.51 (q, ^3J = 6.7, 4 H, CH_2), 1.28 (s, 9 H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (C), 141.7 (C), 139.7 (C), 138.3 (C), 137,5 (C), 134.4 (CH), 133.2 (C), 129.8 (CH), 128.0 (CH), 127.8 (C), 127.0 (CH), 126.9 (CH), 117.1 (CH_2), 114.9 (CH), 67.4 (CH_2), 34.2 (C), 33.8 (CH_2), 31.7 (CH_3). MS (EI, 70 eV): *m/z* (%) = 593.3 (100) [M^+, $C_{42}H_{43}NO_2^+$], 578.2 (97), 538.2 (3), 523.2 (12). Anal. Calcd for $C_{42}H_{43}NO_2$·0.5 H_2O: C, 83.68; H, 7.36; N, 2.32. Found: C, 83.76; H, 7.35; N, 2.11. X-ray crystal structure analysis for **1**: formula $C_{42}H_{43}NO_2$, *M* = 593.77, colorless crystal 0.30 × 0.10 × 0.10 mm, *a* = 9.656(1), *b* = 35.774(1), *c* = 9.666(1) Å, *V* = 3339.0(5) Å^3, ρ_{calc} = 1.181 g cm^{-3}, μ = 0.549 mm^{-1}, empirical absorption correction (0.853 ≤ T ≤ 0.947), *Z* = 4, orthorhombic, space group *P*nma (No. 62), λ = 1.54178 Å, *T* = 223 K, ω and φ scans, 13160 reflections collected (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.60 Å^{-1}, 2693 independent (R_{int} = 0.047) and 2683 observed reflections [I ≤ 2 σ(I)], 215 refined parameters, *R* = 0.081, wR^2 = 0.246, max. residual electron density 0.35 (–0.20) e Å^{-3}, hydrogen atoms are calculated and refined riding.
Data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN,[9b] absorption correction Denzo,[9c] structure solution SHELXS-97,[9d] structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, 1997), graphics SCHAKAL (E. Keller, Universität Freiburg, 1997).
CCDC 649216 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033, E-mail: deposit@ccdc.cam.ac.uk]. (b) Otwinowski, Z.; Minor, W. *Methods in Enzymology* **1997**, *276*, 307. (c) Otwinowski, Z.; Borek, D.; Majewski, W.; Minor, W. *Acta Crystallogr., Sect. A: Fundam. Crystallogr.* **2003**, *59*, 228. (d) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Fundam. Crystallogr.* **1990**, *46*, 467.

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(13) **Characterization of 6**
Mp >250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, ^3J = 8.4 Hz, 8 H, H_{ar}), 7.49–7.40 (m, 16 H, H_{ar}), 7.12 (s, 4 H, H_{ar}), 6.86 (d, ^3J = 8.7 Hz, 8 H, H_{ar}), 3.98 (t, ^3J = 6.2 Hz, 8 H, CH_2), 1.82 (m, 8 H, CH_2), 1.53 (m, 8 H, CH_2), 1.26 (s, 18 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7 (C), 141.0 (C), 139.6 (C), 138.5 (C), 138.4 (C), 133.1 (C), 129.8 (CH), 128.0 (CH), 127.3 (C), 127.0 (CH), 126.6 (CH), 115.0 (CH), 67.5 (CH_2), 34.1 (C), 31.6 (CH_3), 28.6 (CH_2), 25.0 (CH_2). ESI-MS (+): *m/z* = 1135.4 [MH^+, $C_{80}H_{82}N_2O_4$ + H^+]. Anal. Calcd for $C_{80}H_{82}N_2O_4$·H_2O: C, 83.30; H, 7.34; N, 2.43. Found: C, 83.47; H, 7.37; N, 1.99.