Synthetic Methods

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Domino Reactions of Donor–Acceptor-Substituted Cyclopropanes for the Synthesis of 3,3′-Linked Oligopyrroles and Pyrrolo[3,2-*e*]indoles**

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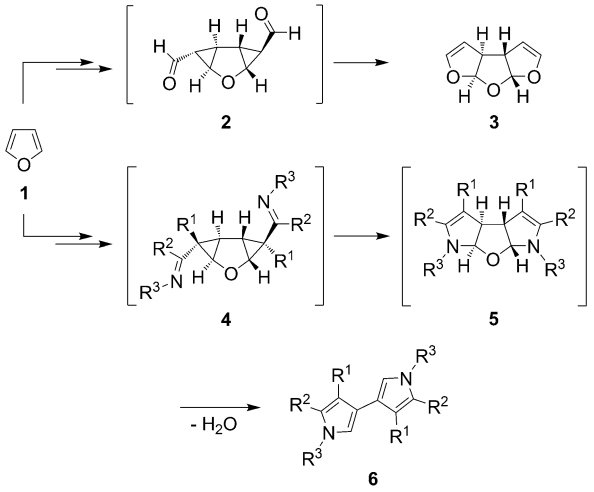
Pyrroles, oligopyrroles, and their derivatives are widespread in nature.[1] Furthermore, they play an important role in material science[2] and medicinal chemistry.[3] Among oligopyrroles, differentiation is made between the 2,2′-linked derivatives and those which are connected at the 3-position. Methods for the synthesis of 2,2′-linked oligopyrroles are multifarious, including Paal–Knorr cyclizations,[4] Vilsmeier condensations,[5] dipolar cycloadditions,[6] Ullmann couplings,[7] and other metal-mediated coupling reactions.[8] In contrast, the number of reports concerning the 3,3′-linkage of pyrrole moieties is much lower.[9,10] 3,3′-Linked dimers have been accessed, for instance, by Pd-catalyzed rearrangements of *N*-bridged diynes,[11] by Barton–Zard synthesis on pyrrole derivatives,[12] or by oxidative couplings.[13] Potential cross-coupling reactions suffer from the heavy accessibility of 3-substituted pyrroles. To the best of our knowledge, the only approach to 3,3′-linked oligopyrroles with more than two pyrrole units was performed by Magnus et al.[14] They applied a repetitive route using olefins and (*p*-toluenesulfonyl)methyl isocyanide as key reagent to build up the pyrrole moieties in a stepwise fashion, giving rise to electron-poor *N*-tosyl substituted oligomers.[14]

Herein we report the preparation of 3,3′-oligopyrroles, and even hitherto unknown electron-rich congeners, by making use of a domino sequence[15] initiated by the ring-enlargement of donor–acceptor-substituted (D-A) cyclopropanes.[16–18] This method allows a very fast and versatile access to bispyrroles, but also to ter- and quaterpyrroles.

Recently, we developed a method, starting from furan (**1**), to oligocyclic oligoacetals such as **3**. Key intermediates are D-A cyclopropanes with aldehyde acceptors of type **2** that rearrange immediately to **3** (Scheme 1, top).[19] On the basis of computational investigations regarding the ring enlargement of a variety of D-A cyclopropanes, we realized that imine acceptors as in **4** have a similar activation barrier for the cyclopropane–heterocyclopentene rearrangement compared to the respective aldehydes.[20] Thus, we thought of the formation of imines (from the corresponding stable ketones) leading to immediate ring enlargement (Scheme 1, bottom).[21] We anticipated that the annulated 2,3-dihydropyrrole moieties in **5** obtained in this transformation should eliminate water, affording bispyrroles of type **6**, as the tendency towards aromatization is much higher than in the case of the analogous 2,3-dihydrofuran derivative **3**.



Scheme 1. Previously reported oligoacetal synthesis (top) as well as envisioned bispyrrole synthesis (bottom) starting from furan (**1**).

To test our hypothesis, we prepared aliphatic and aromatic diketones **8** as starting materials (Table 1). Therefore, the diesters of type **7**, which are available in one step from furan,[22] were converted via the Weinreb amides into the respective tricyclic diketones **8**. Diketone **8a** ($R^1 = H$; $R^2 =$ Me) was selected as model substrate to explore optimized reaction conditions for the anticipated cascade consisting of imine formation, ring enlargement, and elimination of water. Aniline was chosen as the reaction partner. The best results were obtained using *p*-toluenesulfonic acid in benzene at 80 °C after a reaction time of 2 h (for details of the optimization, see the Supporting Information).[23]

The scope of this reaction was evaluated under these optimized conditions by changing both the diketone **8** as well as the amine. Six different diketones **8a**–**8f** were employed. As substituent R^1 on the three-membered ring, H, Me, and Ph

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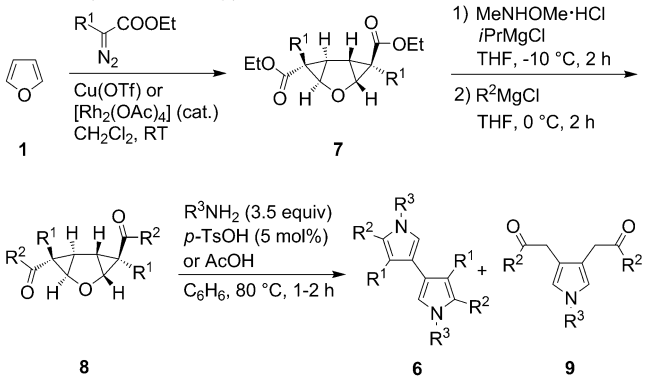
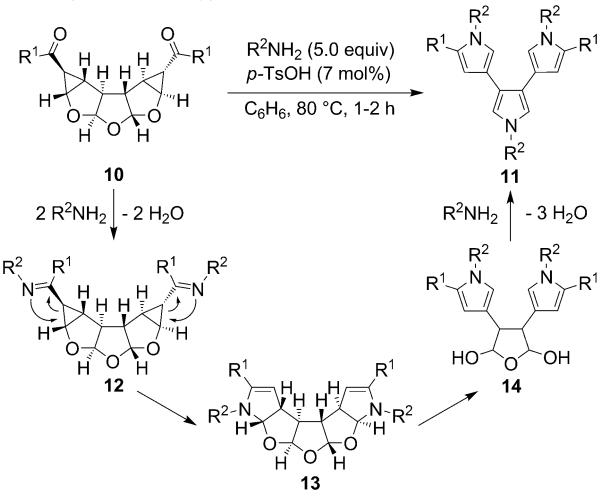
Table 1: Synthesis of bispyrroles **6**.



Entry	**8**	R^1	R^2	R^3		Yield [%] **6**	**9**
1[a]	**8a**	H	Me	Ph	**a**	81	–
2[b]	**8a**	H	Me	4-$MeOC_6H_4$	**b**	89	–
3[b]	**8a**	H	Me	4-HOC_6H_4	**c**	90	–
4[a]	**8a**	H	Me	4-BrC_6H_4	**d**	58	–
5[a,c]	**8a**	H	Me	Me	**e**	42	–
6[b]	**8b**	H	*n*Pr	4-$MeOC_6H_4$	**f**	77	17
7[a]	**8b**	H	*n*Pr	4-NCC_6H_4	**g**	19	74
8[a]	**8b**	H	*n*Pr	4-MeC_6H_4	**h**	70	13
9[a]	**8b**	H	*n*Pr	3-MeC_6H_4	**i**	72	20
10[a]	**8b**	H	*n*Pr	2-MeC_6H_4	**j**	47	37
11[b]	**8c**	H	*i*Pr	4-$MeOC_6H_4$	**k**	45	34
12[b]	**8d**	H	Ph	4-$MeOC_6H_4$	**l**	54	32
13[a]	**8d**	H	Ph	4-$MeC_6H_4SO_2$	**m**	–	89
14[b]	**8e**	Me	Me	4-$MeOC_6H_4$	**n**	67	–
15[a]	**8e**	Me	Me	4-$MeC_6H_4SO_2$	**o**	75	–
16[a]	**8e**	Me	Me	Ph	**p**	72	–
17[a]	**8e**	Me	Me	4-$F_3CC_6H_4$	**q**	69	–
18[a]	**8e**	Me	Me	Boc	**r**	39	–
19[a]	**8f**	Ph	Me	Ph	**s**	64	–
20[a]	**8f**	Ph	Me	4-$F_3CC_6H_4$	**t**	54	–

[a] *p*-TsOH was used as catalyst. [b] AcOH was used as catalyst. [c] The product is very air-sensitive.

Table 2: Synthesis of terpyrroles **11**.

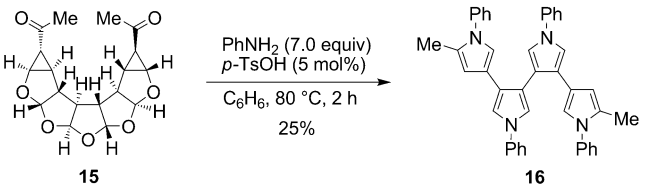


Entry	**10**	R^1	R^2		Yield [%]
1	**10a**	Me	Ph	**11a**	64
2	**10a**	Me	4-$MeOC_6H_4$	**11b**	38
3	**10a**	Me	4-BrC_6H_4	**11c**	58
4	**10a**	Me	4-MeC_6H_4	**11d**	53
5	**10b**	Ph	Ph	**11e**	32
6	**10b**	Ph	4-$NO_2C_6H_4$	**11f**	34

were chosen, whereas Me, *n*Pr, *i*Pr, and Ph served as residues at the ketone (see Table 1). Substituents of the amines were varied in anticipation of modulating the nucleophilicity from electron-donating to electron-withdrawing groups. Electron-rich anilines proved to be most suited for this transformation; therefore, the best results were obtained with 4-hydroxyaniline and 4-methoxyaniline. To assure solubility of these amines, acetic acid was used instead of *p*-TsOH. *N*-Alkyl-substituted reaction products proved to be very unstable; only the methyl-substituted congener **6e** could be isolated in moderate yield. As seen in Table 1, with anilines carrying an electron-withdrawing group (such as CF_3, CN) or with *p*-toluenesulfonamide as nitrogen source, a second product, a monopyrrole derivative **9**, was formed.[24] Interestingly, this product was only found in the case of $R^1 = H$. Carbamates such as $BocNH_2$ also delivered the respective bispyrrole **6r**, but only in fair yield.

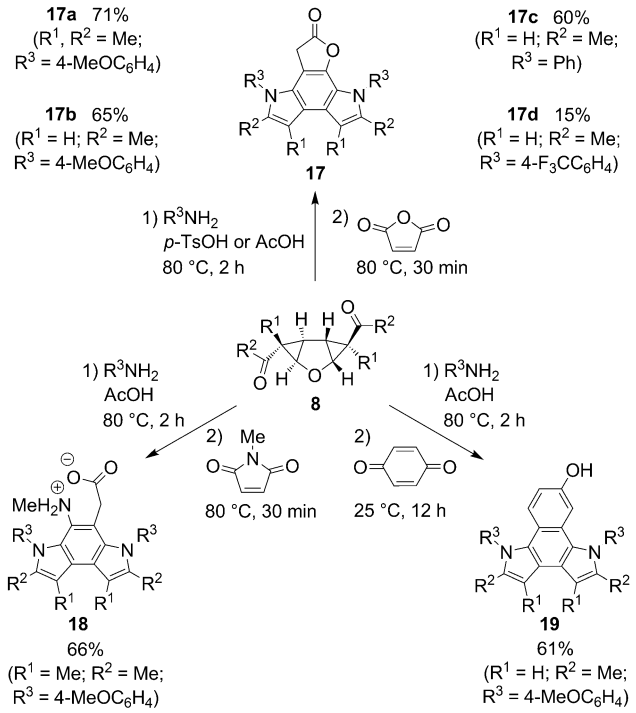
After the successful construction of 3,3′-linked bispyrroles, we tried to extend this sequence to access corresponding ter- and quarterpyrroles. Extended oligoacetalic diketones of type **10** served as starting materials.[23,25] Their treatment with aniline derivatives under the catalytic influence of *p*-TsOH furnished the desired trimers **11** in only one single step (Table 2). A plausible reaction mechanism to afford the domino product **11** is depicted in Table 2. The twofold imine formation to **12** is followed by the ring enlargement of both cyclopropane moieties. The resulting dihydropyrrole units in **13** are prone to aromatization. Twofold ring cleavage takes place, providing intermediate **14** with two aromatic pyrrole units and two hemiacetal moieties located at the central ring. As the final step, the inner pyrrole unit is formed in a Paal–Knorr-like course of action leading to the final compound **11**.

To demonstrate the potential of this domino sequence, we targeted the construction of quaterpyrrole **16** in a single reaction starting with the oligocyclic bisketone **15**.[23,25] After eight steps (similar to those presented in Table 2), quaterpyrrole **16** is formed in 25% yield (Scheme 2). To the best of our knowledge, electron-rich 3,3′-linked ter- and quaterpyrroles have never been reported to date. Their intrinsic instability is a major problem and might also explain the only moderate to low yields obtained in these transformations.



Scheme 2. Synthesis of quaterpyrrole **16**.

It has not escaped our notice that 3,3′-linked bispyrroles **6** would act as excellent nucleophiles that are comparable with enamines and ketene acetals.[26] This assumption was validated in the transformation of bispyrroles with maleic anhydride, maleimide, and *p*-benzoquinone into pyrrolo[3,2-*e*]indoles **17**–**19**. We observed that for bispyrrole formation, the intermolecular Michael addition of the in situ generated pyrrole nucleophile to α,β-unsaturated carbonyl compounds and the condensation can be combined in an one-pot process starting from **8** (Scheme 3). As anticipated, a strongly elec-



Scheme 3. One-pot procedure starting from biscyclopropanated furan **8** to pyrrolo[3,2-*e*]indoles **17**–**19**.

tron-withdrawing group such as 4-$F_3CC_6H_4$ decreases the nucleophilicity of the bispyrrole, resulting in a diminished yield of the respective pyrrolo[3,2-*e*]indole **17d**. The structures of **17a** and **19** were confirmed unambigiously by single-crystal X-ray analysis (Figure 1 and Supporting Information).[27,28]

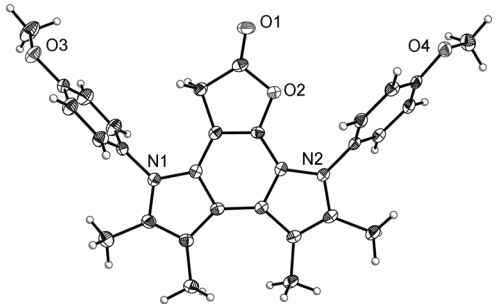


Figure 1. The molecular structure of **17a** in the solid state. Ellipsoids are set at 50% probability.

In conclusion, we have developed a novel strategy to build up 3,3′-linked oligopyrroles by using a domino approach. Ketone-substituted cyclopropanes were converted into the corresponding imines setting the stage for the domino cascade. Key for the success is the high tendency of donor–acceptor-substituted cyclopropanes to undergo ring enlargement combined with the bias for aromatization to pyrroles. In up to eight steps, bis-, ter-, and quaterpyrroles were obtained. The cascade can be further expanded by the addition of Michael acceptors reacting with the highly nucleophilic bispyrroles formed in situ to afford pyrrolo[3,2-*e*]indoles. These structural constituents are relevant subunits of duocarmycins, which are potent antitumor agents. Related studies directed to analogous reactions with thiocarbonyl acceptors are underway in our laboratory and will be reported in due course.

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[24] No optimization studies for the monopyrroles were performed. For their formation two scenarios can be envisioned: 1) A nucleophilic attack of the amine at the C2 position of the biscyclopropanated furan **8**. With electron-poor amines, such a Michael-like attack should be favored, resulting in the cleavage of the cyclopropane moieties. The generated bis(*N,O*-acetal) opens and re-cyclizes unter nitrogen inclusion into the five-membered ring. Elimination of water and amine affords the monopyrrole **9**. 2) Formation of the imine is too slow with electron-poor amines. The cyclopropane opens to form a highly electrophilic oxonium intermediate, which is able to react with the less-reactive electron-poor amine.
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[28] The crystal data and experimental details for the X-ray measurements are listed in the Supporting Information. CCDC 883456 (**17a**) and CCDC 883455 (**19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

