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Hybrid macrocycle formation and spiro annulation on *cis-syn-cis*-tricyclo[6.3.0.0^{2,6}]undeca-3,11-dione and its congeners via ring-closing metathesis

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Full Research Paper

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Abstract

We have developed a simple methodology to transform *cis-syn-cis*-triquinane derivative **2** into the diindole based macrocycle **6** involving Fischer indolization and ring-closing metathesis (RCM). Various spiro-polyquinane derivatives have been assembled via RCM as a key step.

Introduction

Design and synthesis of polyquinanes is an active area of research during the last three decades [1-10]. Various theoretically interesting as well as biologically active molecules such as dodecahedrane, [5.5.5.5]fenestrane and retigeranic acid A contain the quinane framework in their structures (Figure 1). A variety of quinane-based natural products isolated from terrestrial, microbial and marine sources have stimulated the growth of polyquinane chemistry. In this context, there is a continuous demand for the development of new methodologies to assemble cyclopentanoids (or quinanes) [11-21]. Several approaches are available for the synthesis of carbocyclic quinanes, however, only a limited number of methods is available for oxa- [22-25] and aza-polyquinanes [26-28]. The indole unit is present in a variety of plant alkaloids (e.g., reserpine, strychnine, physostigmine) and several important drugs contain indole as a key component [29-32]. Therefore, we are interested in designing new strategies to hybrid molecules containing both quinane and indole ring systems. On several occasions, the spirocyclic moiety seems to be a recurring motif in bioactive molecules. Consequently, assembling architecturally complex spirocycles is of great relevance to the diversity-oriented synthesis of biologically active spirocycles. In this context, new synthetic methods to generate multiple spirocenters in a simple manner remain a challenging task. Although, a variety of strategies have been investigated, a limited number of general methods are available [33-46] for the generation of multiple spirocenters in a

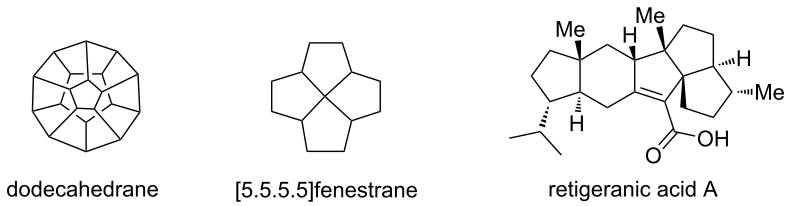


Figure 1: Natural and non-natural products containing quinane systems.

single step [43]. To expand the chemical space of aza-polyquinanes we conceived a new strategy based on Fischer indolization and ring-closing metathesis as the key steps.

To develop a simple synthetic methodology to aza-polycycles and spiropolycycles from readily available starting materials [47-52], bicyclic, tricyclic and pentacyclic diones (**1**–**3**) were identified as useful building blocks (Figure 2). The selection of these diones is based on their easy accessibility and also the symmetry involved with them. For example, with diones **1** and **2** one can apply a two-directional synthesis [53] to increase the brevity [54] of the overall synthesis. Earlier, we have shown that Weiss–Cook dione **1** [49-51] is a useful substrate for double Fischer indolization with a low melting mixture of L-(+)-tartaric acid and *N*,*N*′-dimethylurea (L-(+)-TA:DMU) [55] at 70 °C to generate an unusual C_s-symmetric diindole derivative along with the known C_2-symmetric diindole [56]. Also, based on Fischer indolization and ring-closing metathesis (RCM), we have developed a new strategy to indole-based propellane derivatives [57].

Here, the tricyclic dione **2** required was prepared starting with the Cookson's dione **4** in two steps involving flash vacuum pyrolysis (FVP) and hydrogenation steps (Scheme 1). A variety of synthetic transformations involving tricyclic diones **5** and **2** were reported in the literature [47].

To expand the utility of building block **2** in organic synthesis, we conceived a simple retrosynthetic approach to macrocylic aza-polyquinane **6** and spiro-polyquinane derivative **7** (Figure 3). The key steps involved here are: double Fischer indolization and RCM. To install the alkane chain connecting the two nitrogen atoms, we plan to use alkylation with allyl-bromide followed by RCM and hydrogenation protocols. It is known that a mono-indole derivative was obtained via Fischer indolization starting with dione **2** and two equivalents of phenylhydrazine hydrochloride, but the diindole derivative **8** [58] was not obtained under these conditions. Our experience with Fischer indolization of **1** using the low melting mixture protocol gave unusual results as compared with conventional Fischer indolization conditions. Therefore, the reactivity of **2**

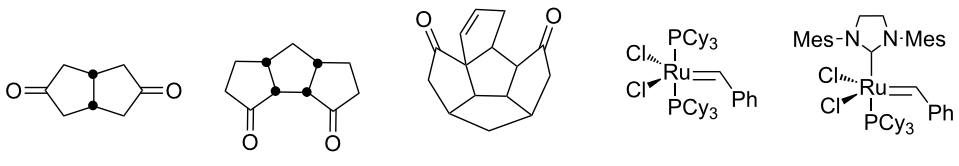
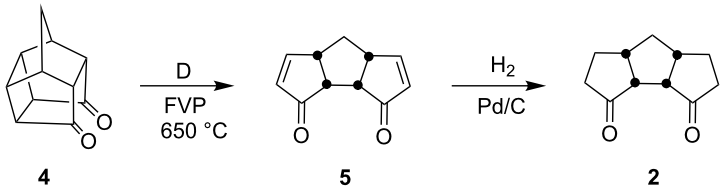


Figure 2: Quinane building blocks (**1**–**3**) and metathetic catalyst used in our strategy.



Scheme 1: Synthesis of tricyclic diones **5** and **2**.

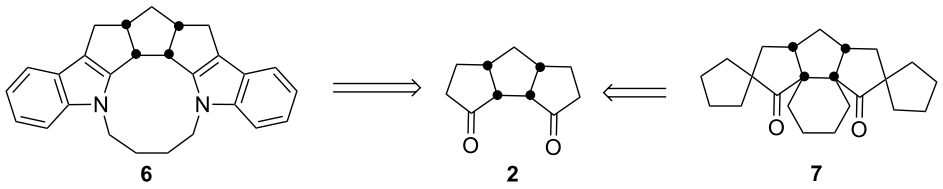


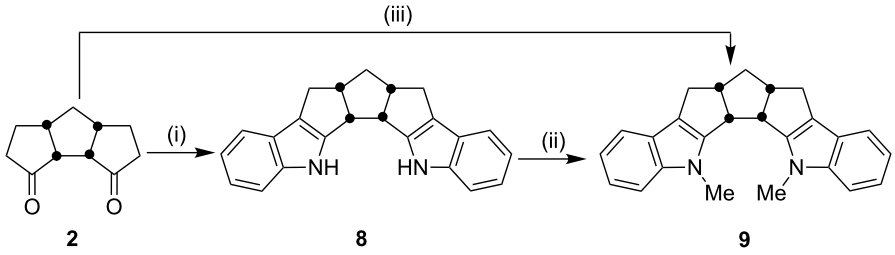
Figure 3: Retrosynthetic approach to aza-polyquinane **6** and spiro-polyquinane **7**.

under conditions of the low melting mixture is worthy of systematic investigation. Here, we are pleased to report our successful results in generating the diindole derivative **8** by utilizing a low melting mixture of L-(+)-TA:DMU and its subsequent utility in assembling the macrocyclic system **6** via RCM. During this venture, we also found that the tricyclic dione **2** is a useful substrate for the synthesis of spiro-polyquinane derivative **7** via a six fold allylation followed by a three-fold RCM and a hydrogenation sequence.

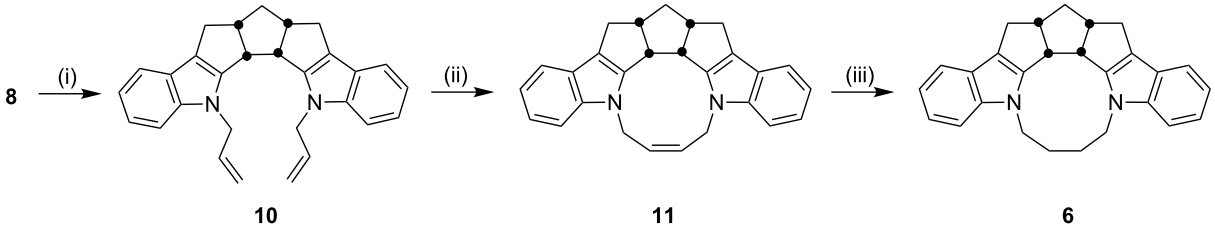
Results and Discussion

To realize the strategy shown in Figure 3, the tricyclic dione **2** was subjected to a two-fold Fischer indolization in the presence of two equivalents of phenylhydrazine hydrochloride with the aid of a low melting mixture of L-(+)-TA:DMU to generate the diindole derivative **8** (62%, Scheme 2). The structure of the diindole **8** has been established on the basis of ^{1}H NMR and ^{13}C NMR spectral data. The presence of 12 signals in the ^{13}C NMR spectrum clearly indicated that the C_s-symmetry is present in molecule **8**. Later, the diindole derivative was treated with methyl iodide in the presence of NaH/DMF at room temperature to deliver the dimethyl derivative **9**. Again, the C_s-symmetry present in **9** is evidenced by the appearance of 13 signals in the ^{13}C NMR spectrum. Alternatively, the diindole derivative **9** has been generated in a single step by reacting the dione **2** with *N*-methyl-*N*-phenyl-hydrazine under conditions using the described low melting mixture.

Next, the *N*-allylation of the diindole derivative **8** with allyl bromide in the presence of NaH/DMF gave diallyl derivative **10**, which was subjected to the RCM sequence in the presence of Grubbs' 2nd generation catalyst to produce the cyclized compound **11** (84%). Subsequently, the macrocyclic diindole derivative **11** was hydrogenated in the presence of H_2/Pd/C to afford the saturated compound **6** (Scheme 3).



Scheme 2: Synthesis of the diindole derivative **9** Reagents and conditions: (i) TA:DMU, $PhNHNH_3Cl$, 70 °C, 6 h, 62%; (ii) NaH, MeI, DMF, rt, 24 h, 87%; (iii) TA:DMU, 70 °C, $PhNMeNH_2$, 6 h, 76%.



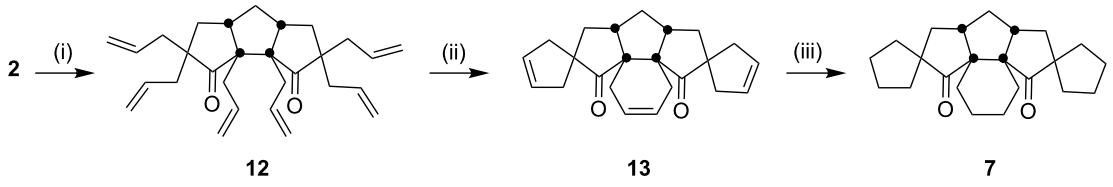
Scheme 3: Synthesis of the macrocyclic aza-polyquinane derivative **6**. Reagents and conditions: (i) NaH, allyl bromide, DMF, rt, 24 h, 65%; (ii) G-II, CH_2Cl_2, rt, 12 h, 84%; (iii) Pd/C, H_2, EtOAc, rt, 18 h, 95%.

To assemble the intricate spiro-polyquinane **7** via RCM as a key step [59-62], we started with the triquinane derivative **2**. To this end, the *cis-syn-cis*-triquinane dione **2** was treated with an excess amount of allyl bromide in the presence of NaH to generate the hexaallyl derivative **12** in 59% yield. Later, it was subjected to RCM with Grubbs' 1st generation catalyst to deliver the three-fold RCM product **13** in 80% yield. Furthermore, treatment of the hexacyclic dione **13** with Pd/C in EtOAc under hydrogen atmosphere (1 atm) gave the saturated spiro-polyquinane **7** in 90% yield (Scheme 4). Very few examples are known in the literature where multiple RCM was performed in a single operation to generate the molecules of medium molecular weight [63]. The present example involving the generation of triple spirocyclic compound **7** is unique and demonstrates the power and scope of the RCM approach. It is worth mentioning that previous attempts to functionalize **2** were unsuccessful [47].

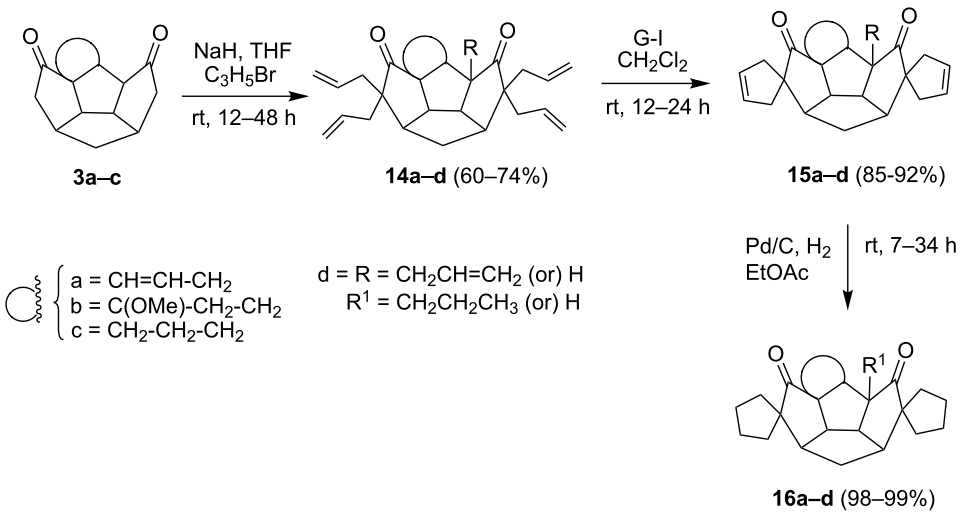
To generalize the spiroannulation sequence, allylation of pentacyclic diones **3a–c** [48] gave the tetraallyl diones **14a–c** in respectable yields. Next, treatment of these allylated derivatives **14a–c** with G-I catalyst gave the double RCM products **15a**, **15b** and **15c** in 92%, 92% and 91% yields, respectively (Scheme 5 and Table 1). Later, these double RCM products were subjected to the hydrogenation protocol in the presence of H_2/Pd/C to deliver the saturated bis-spiro-polyquinane derivatives **16a**, **16b** and **16a** in an excellent yield (Table 1). Similarly, the dione **3a** in the presence of an excess amount of NaH and allyl bromide gave the pentaallyl dione **14d** in 67% yield (Table 1). Next, the pentaallyl derivative **14d** was treated with G-I catalyst to produce the bis-spiro-polyquinane **15d**. ^{1}H NMR and ^{13}C NMR spectral data clearly indicated the presence of intact allyl residue along with the unsaturated double bonds. The bis-spiro-polyquinane **15d** was then subjected to hydrogenation sequence to deliver the saturated bis-spiro-polyquinane **16d** in good yield (Table 1).

Conclusion

In summary, we have developed a protocol for the synthesis of a diindole-based hybrid macrocycle through Fischer indoliza-

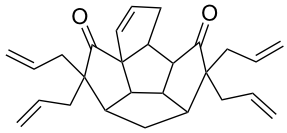
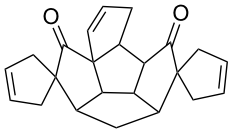
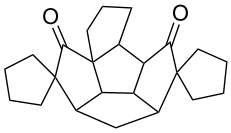
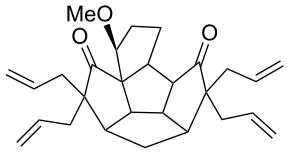
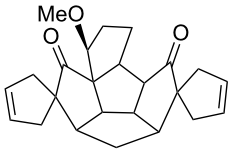
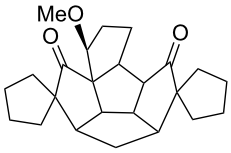
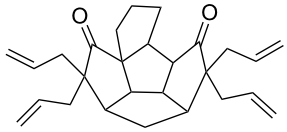
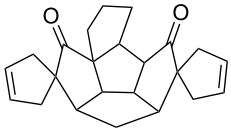
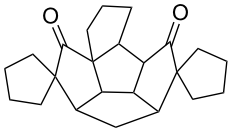
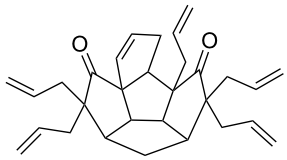
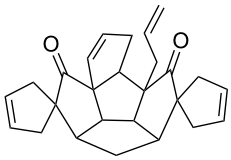
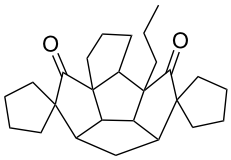


Scheme 4: Synthesis of the spiro-polyquinane **7**. Reagents and conditions: (i) NaH, allyl bromide, THF, rt, 24 h, 59%; (ii) G-I, CH_2Cl_2, rt, 15 h, 80%; (iii) Pd/C, H_2, EtOAc, rt, 24 h, 90%.



Scheme 5: General strategy to bis-spirocycles via RCM.

Table 1: List of bis-spirocycles assembled by RCM.

Allylation product (%)	Time	RCM product (%)	Time	Hydrogenation product (%)	Time
 **14a** (74%)	12 h	 **15a** (92%)	12 h	 **16a** (98%)	7 h
 **14b** (60%)	14 h	 **15b** (92%)	10 h	 **16b** (99%)	7 h
 **14c** (70%)	12 h	 **15c** (91%)	12 h	 **16a** (99%)	7 h
 **14d** (67%)	48 h	 **15d** (85%)	24 h	 **16d** (97%)	12 h

tion of the triquinane **2** followed by bis-*N*-allylation and RCM. The allylation-RCM sequence has also been extended to construct structurally intricate spiro-polyquinanes.

Supporting Information

Supporting Information File 1

Experimental and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-126-S1.pdf]

Supporting Information File 2

NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-126-S2.pdf]

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