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First example of an atropselective dehydro-Diels–Alder (ADDA) reaction

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ABSTRACT

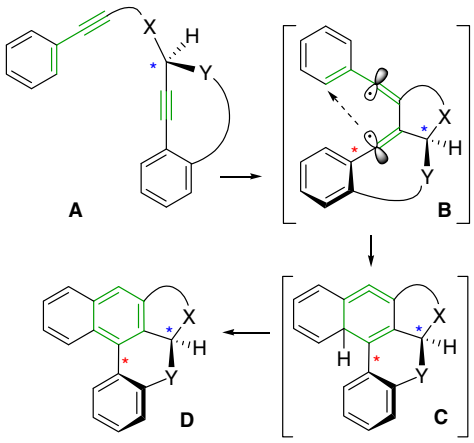
A new concept of a stereoselective synthesis of axially chiral biaryls, formed in the course of the dehydro-Diels–Alder (DDA) reaction, has been disclosed. It is based on asymmetric induction of the newly formed chirality axis by a chirality center, which is present in the two synthesized DDA reactants. Depending on the different length of the linkers joining the alkyne moieties the DDA reaction may be triggered photochemically or thermally, where only the thermal variant was stereoselective.

Biaryls are widespread structural elements in natural products as well as in synthetic drugs and the development of synthetic routes is, therefore, an important topic of organic chemistry.[1] Due to the often hindered rotation around the bond joining the two aryl moieties many biaryls exhibit a chirality axis and two atropisomers occur. Similarly to compounds bearing a chirality center stereoselective syntheses of biaryls with respect to the chirality axis (atropselective syntheses[2]) are highly desirable because the physiological activity of the atropisomers is a priori not identical.

Most of the synthetic routes to biaryls are based on coupling reactions between two preexisting aryl derivatives whereas only few methods are known which rest upon a complete assembly of one of the aryl moieties. One of the most efficient of these methods is the dehydro-Diels–Alder (DDA) reaction.[3] Despite bearing analogy to the classical concerted Diels–Alder (DA) reaction (it is also a [4+2] cycloaddition) the DDA reaction differs from the DA reaction in two important aspects: (1) the DDA normally proceeds according to a multi-step mechanism and (2) the DDA may be initiated both thermally and photochemically (the latter is called photo-dehydro-Diels–Alder (PDDA) reaction).[4]

In the past years we demonstrated that the PDDA reaction is a powerful tool for the synthesis of biaryls.[5] The self-evident approach to conceive an asymmetric (thermal or photochemical) DDA reaction is to achieve an asymmetric induction from a chirality center present in the reactant onto the new chirality axis, which is formed in the DDA reaction.[6] Recently we found that an efficient transfer of the stereochemical information which is based solely on weak non-covalent interactions is hardly feasible.[5e] Herein we wish to describe the first successful asymmetric DDA reaction (ADDA reaction) which results from a doubly bridged DDA reactant.

Our concept for an ADDA reaction is depicted in Scheme 1. A chirality center (blue asterisk) acts as the chirality source. The two components (green in formula **A**) are joined by the linker X to facilitate the DDA reaction. Furthermore, the chirality center and one of the ortho positions of the lower benzene ring are bridged by the unit Y to ensure an efficient asymmetric induction. In the first step a C–C single bond is formed between the alkynes giving the 1,4-diradical **B**. At this stage the chirality axis is already



Scheme 1. Concept for an ADDA reaction.

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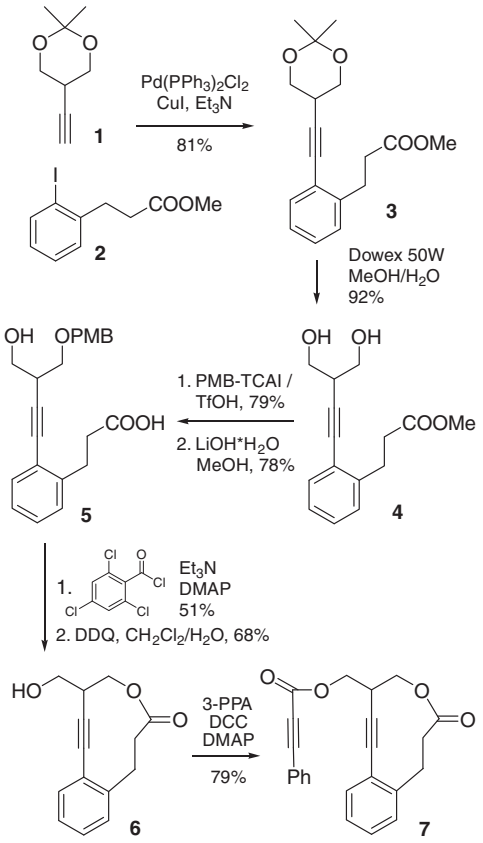


Scheme 2. Synthesis of lactone **7**. (PMB-TCAI = *p*-methoxybenzyl trichloroacetimidate, 3-PPA = 3-phenylpropiolic acid).

present (red asterisk) but the rotational barrier is still low. In the subsequent second C–C-bond formation to the cycloallene **C** the final carbon skeleton is formed and rotation around the chirality axis is now strongly hindered. The target structure **D** is formed from **C** by hydrogen migration.

It is obvious that the success of our ADDA approach should critically depend on the length of the linker X and we, therefore, prepared two different compounds **A** with different linkers X and investigated their DDA reaction.

The synthesis of the first system begins with a Sonogashira reaction[7] between the known alkyne **1**[8] and methyl 3-(2-iodophenyl)propanoate **2**[5d,9] to give the alkyne **3** with good yield. After hydrolytic cleavage of the acetal moiety and PMB protection of one of the hydroxy groups of the diol **4** the ester group was saponified providing the hydroxycarboxylic acid **5**.

We previously[10] found that the Yamaguchi macrolactonization[11] is the method of choice for the ring closure of θ-hydroxycarboxylic acids such as **5**, whereas other methods mainly gave a dimeric dilactone. Applying this method to **5** furnished, after oxidative cleavage of the PMB group with DDQ, the macrolactone **6** with good yield. In the final step to the DDA reactant **7** the alcohol **6** was coupled with 3-phenylpropiolic acid (Scheme 2).

Irradiation of macrolactone **7** in acetone as triplet sensitizer,[5b,12] gave **8** with 36% yield. Unfortunately, we observed no diastereoselectivity at all and the diastereomers **8a** and **8b** were formed in similar amounts (Scheme 3). Obviously, the six-membered dihydropyran-2-one ring, which is formed in the PDDA, is

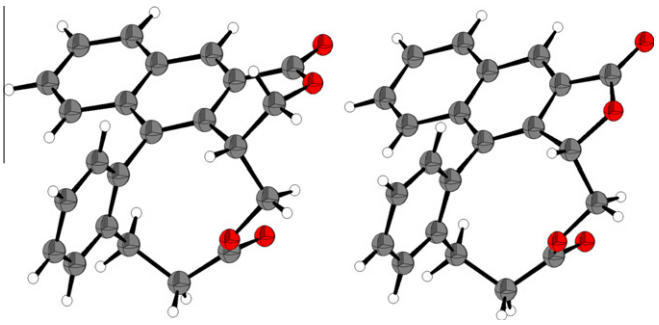
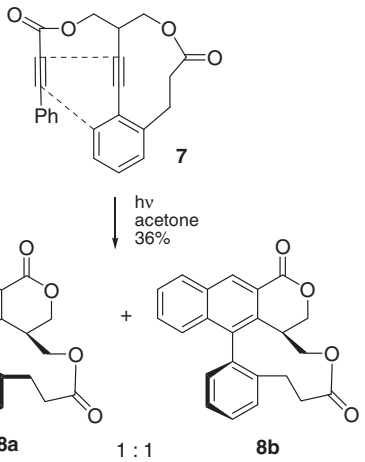
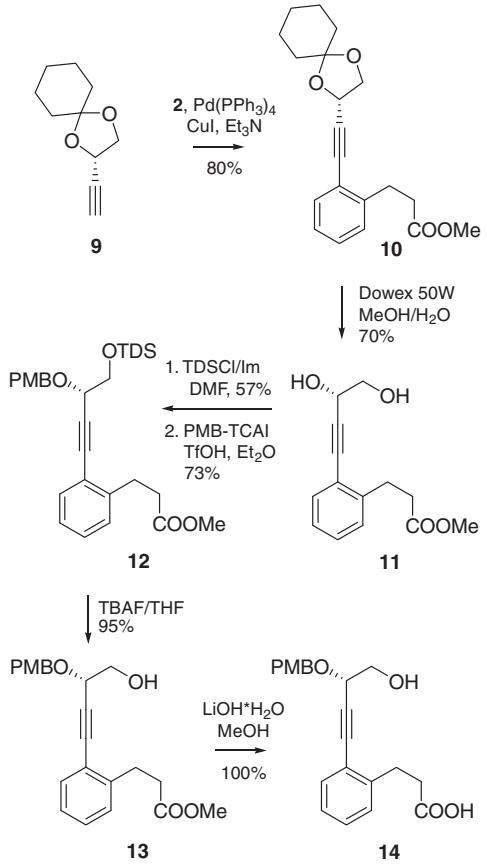


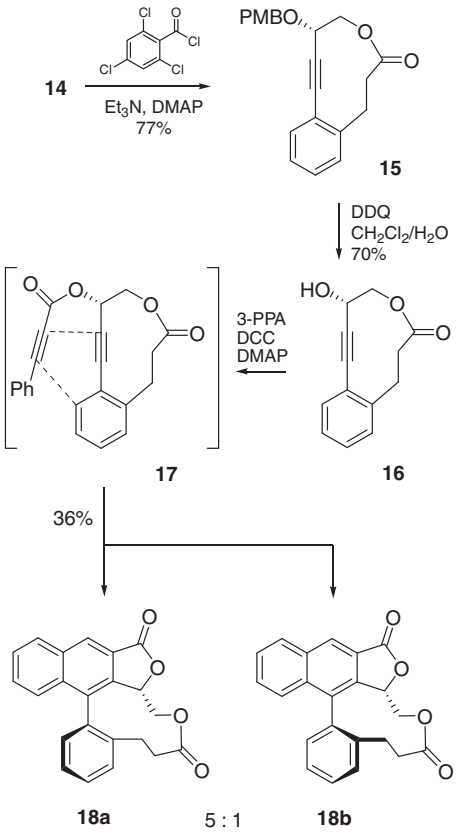
Figure 1. X-ray crystal structures of **8a** (left) and **18a** (right).



Scheme 3. PDDA reaction of **7** to **8**.



Scheme 4. Synthesis of hydroxycarboxylic acid **14**. (TDS = thexyl-dimethyl-silyl).



Scheme 5. ADDA reaction to compounds **18a**,**b**.

too large to route the reaction preferably to the isomer **8a** (cf. Fig. 1).[13]

After this rather deflating result we postulated that decreasing the ring size of the newly formed lactone ring from six to five in the second system could resolve this problem.

The synthesis of the second system commences with a Sonogashira coupling between the chiral alkyne **9**[14] and methyl 3-(2-iodophenyl)-propanoate **2** giving compound **10**. It should be noted that **9** is easily accessible from D-mannitol in three steps. The ring closure to the macrocyclic lactone **15** (see Scheme 5) required a protected secondary hydroxy group and an unprotected primary hydroxy group.

To achieve this goal we converted **10** in four steps consisting of cleavage of the cyclohexylidene acetal, silylation of the primary hydroxy group of diol **11**, PMB protection of the secondary hydroxy group and desilylation of the primary hydroxy group to give **13**. Saponification of the ester group provided the θ-hydroxycarboxylic acid **14** (Scheme 4).

Once again, we subjected **14** to the conditions of the Yamaguchi macrolactonization and obtained the macrocyclic lactone **15** with good yield. After oxidative cleavage of the PMB group we coupled the alcohol **16** with 3-phenylpropiolic acid and expected the formation of DDA reactant **17**. To our surprise, we were unable to isolate compound **17** but directly obtained the DDA products **18** with a diastereomeric ratio of 5:1, determined by NMR spectroscopy (Scheme 5). The completely different behavior of **7** and the (hypothetical) ester **17** can be explained by the different number of atoms between the alkyne moieties. The reduction from four atoms in **7** to three atoms in **17** dramatically decreases the activation barrier of the thermal DDA reaction. This behavior is well known from the Bergmann cyclization,[15] the first step of which is also a C–C-bond formation between two alkynes.

The unequivocal structural assignment of compounds **8** and **18** was possible by X-ray crystal structure analysis of **8a** and **18a** (Fig. 1).[16] These structures also clarify the reason for the different stereoselectivity of **7** and **17**. Whereas the dihydropyran-2-one ring in **8a** is puckered and adopts a half-chair conformation, the dihydrofuran-2-one ring in **18a** is nearly planar. Consequently, the dihydropyran-2-one ring may exist in two different conformations depending on whether the chirality axis has *P*- or *M*-configuration explaining the lack of asymmetric induction.

In summary, we reported on the dehydro-Diels–Alder (DDA) reaction of two compounds (**7**, **17**). We found that both the activation barrier and the stereoselectivity of the DDA reaction critically depend on the linker X (see Scheme 1). Whereas compound **7** bearing four atoms between the alkyne moieties required photochemical activation and afforded only a 1:1 mixture of diastereomeric products **8**, compound **17** with a shorter linker spontaneously underwent the DDA reaction with a remarkable diastereomeric ratio of 5:1. To the best of our knowledge this is the first example of an atropselective dehydro-Diels–Alder reaction.

Acknowledgment

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Supplementary data

Supplementary data (detailed experimental procedures and characterization data of compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.024.

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16. Compound **8a** crystallizes in the centrosymmetric space group $P2_1/c$ so that both enantiomers exist in the same crystal. Compound **18a** crystallizes in the chiral orthorhombic space group $P2_12_12_1$ with C2 in the *R* configuration. For details see the Supplementary data, Section 4.