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Novel Domino Oxidative Coupling: C−C Bond Formation Sequence to Highly Functionalized Dibenzo-[*a*,*c*]cycloheptenes

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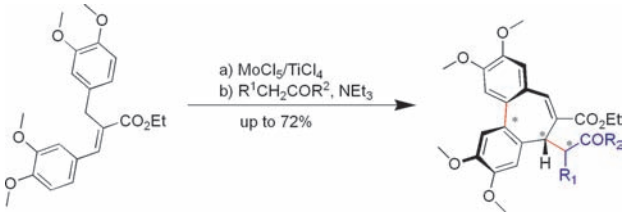
ABSTRACT



A domino sequence involving various $MoCl_5$-mediated oxidations followed by trapping and supposed [3,3]-sigmatropic rearrangement provides a fast access to the full carbon skeleton of metasequirin-B. A variety of different moieties R^1 and R^2 are tolerated.

Seven-membered ring systems with annulated benzo moieties are found in many natural products such as cycloneolignans, as well as alkaloids.[1] Among the latter colchicine is the most prominent example.[2] Colchicine derivatives, such as allocolchicine or the bicyclic analogue combretastatin, are of major medicinal and biological interest because of their pharmacological properties.[3] It is well-known that colchicine binds to the β-subunit of the protein tubulin in the protofilaments and causes destabilization of the microtubules,[4] which are required for the formation of the mitotic spindle in eukaryotic cells. The potential application of colchicine in cancer therapy is limited by its high toxicity, but this has given rise to a demand for structural analogues. The lignane steganacine, which features a lactone moiety attached to the central

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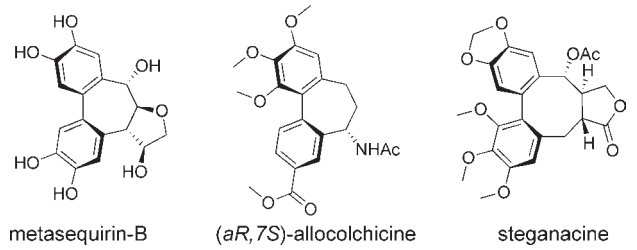


Figure 1. Structures of metasequirin-B, alllocolchicine, and steganacine.

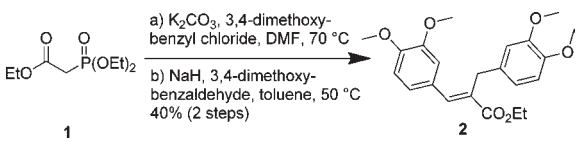
eight-membered ring system, also binds to the colchicine binding site on tubulin.[5]

Among the naturally occurring norcycloneolignans metasequrin-B is the only known natural product with a bisbenzocycloheptene skeleton fused to a tetrahydrofuran system. It was isolated from the heartwood of *Metasequoia glyptostroboides*.[6] The close structural relationship of metasequirin-B to the well investigated allocolchicine, as well as steganacine (Figure 1), promises an interesting pharmacological profile. The described tubulin-binding compounds are classified as vascular disrupting agents because of their mechanism of action. In contrast to anti-angiogenesis drugs, the vascular disrupting agents act on existing blood vessels that feed a solid tumor resulting in tumor ischemia and necrosis. Such drugs offer a nonsurgical treatment in the case of advanced disease which is of major interest in cancer therapy.[7] Most synthetic approaches construct the biaryl intermediate at an early stage, and the central seven-membered ring is subsequently formed. Synthetic efforts to these tricyclic architectures usually require many steps.[8]

Despite the atom economic nature of oxidative coupling reactions, the direct conversion of the corresponding diaryl substrates via this technology has not received much attention due to the low yields that are usually observed for such reactions.[9]

Use of the powerful oxidant $MoCl_5$ provides, in the conversion of 1,3-diaryl propanes, a fast and modular

Scheme 1. Synthesis of the Substrate



access to a variety of dibenzo[*a*,*c*]cycloheptenes.[10] $MoCl_5$ is a versatile reagent for the oxidative transformation of arenes[11] which tolerates numerous functional groups[12] and prefers a specific substitution pattern on the aryl moiety.[13] In the course of the reaction, hydrogen chloride is liberated from the reagent. In order to keep the reaction mixture electrophilic and active, Lewis acids can be used for binding the hydrogen chloride.[14] The reagent waste consists of electrophilic metal chlorides which form multinuclear clusters and may serve as templates in a stereoselective oxidative coupling process.[15]

Here we report an oxidative coupling sequence which does not stop at the intramolecular arylation product but, rather, proceeds with further C−H functionalization. In a one-pot procedure, carboxymethyl fragments can also be installed upon oxidative cyclization. The synthesis of the substrate **2** commenced with phosphono acetate **1**. After deprotonation and installation of the first aryl moiety via a benzylation, the second aryl group was introduced, using a Horner−Wadsworth−Emmons olefination. Compound **2**, prepared in a modular fashion, was formed in an *E*/*Z* ratio of 3:1 (Scheme 1).

Treatment of **2** with $MoCl_5/TiCl_4$ in CH_2Cl_2 not only affected the aryl−aryl bond formation but also brought about oxidation of the central cycloheptatriene system (**3**) to the tropylium intermediate **4**. Benzo annulations on bonds a and c of the seven-membered ring usually destabilize a tropylium system since the planar geometry is difficult to maintain.[16] However, trapping such a reactive intermediate with a carbonyl oxygen provides **5** which forms a 1,5-diene system (**6**) in the presence of a base. This might undergo a [3,3]-sigmatropic rearrangement leading to the observed product **7**.

If the workup was performed with an ethyl acetate/triethyl amine mixture the ethyloxycarbonylmethyl-modified product **8** was isolated in 70% yield (Table 1, entry 1). An increased steric demand in the alkyl portion of the ester has little influence (entry 2). The strong electrophilic reaction conditions promote elimination of secondary alkyl moieties. Therefore, other auxiliaries had to be applied but showed no diastereoselectivity

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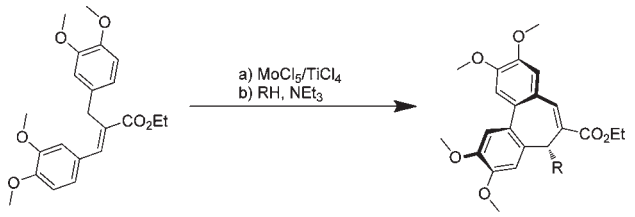
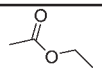
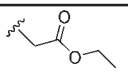
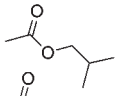
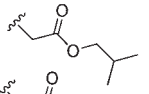
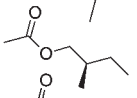
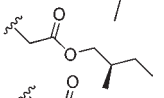
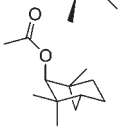
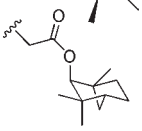
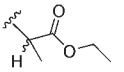
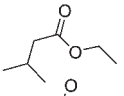
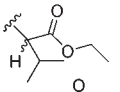
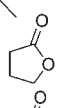
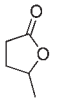
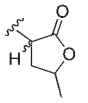
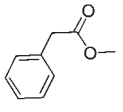
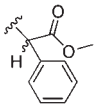
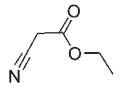
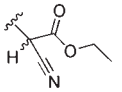
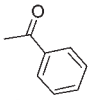
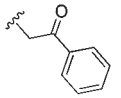
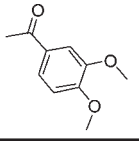
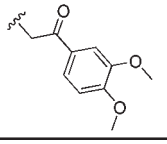
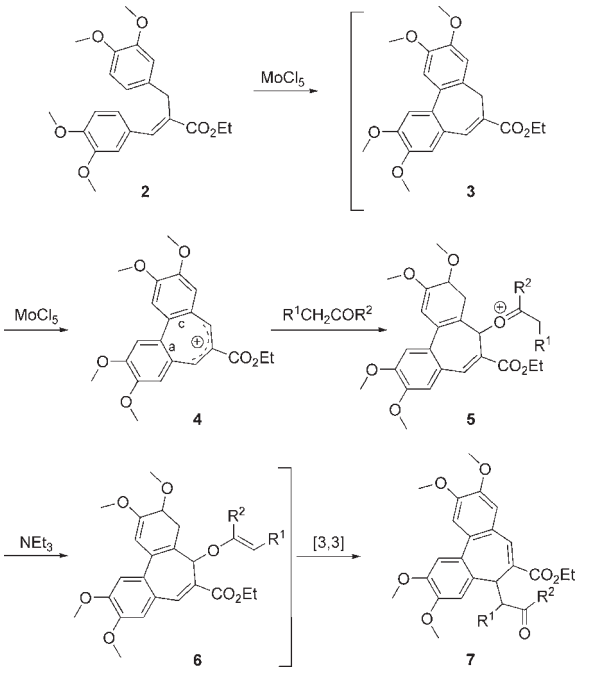
Table 1. Scope of Carbonyl Components for Domino Sequence



entry	carbonyl component	product, R =	yield [%]	*dr*
1			70 (**8**)	-
2			72 (**9**)	-
3			55 (**10**)	1/1
4			34 (**11**)	1/1
5			60 (**12**)	1/0.6
6			69 (**13**)	1/0.9
7			52 (**14**)	1/0.6
8			46 (**15**)	1/0.7/0.35
9			50 (**16**)	1/0.5
10			64 (**17**)	1/1
11			55 (**18**)	1/0.33
12			46 (**19**)	-
13			30 (**20**)	-

(entries 3 and 4). (*R*)-2-Methylbutyl acetate provided an equimolar mixture of diastereomers. A similar result was obtained when (+)-α-fenchyl acetate was used in the workup procedure. Carbonyl components with an α modification also represent suitable coupling partners

Scheme 2. Potential Mechanism for the Product Formation



for the domino sequence (entries 5−11). Ethyl propionate and isovalerate were successfully subjected to the transformation providing **12** and **13** in 60% and 69% yield, respectively. The proximity to the newly formed stereocenters caused a diastereoselectivity (entries 5 and 6). Lactones are also suitable substrates for this C−C bond formation. γ-Butyrolactone led to product **14** with a similar diastereoselectivity found for ethyl propionate (entry 7).

Introduction of further stereogenic information led to a set of three diastereomers (entry 8). Further functionalities are tolerated in the domino sequence. Phenylacetic ester was coupled to the seven-membered ring to give **16** in 50% yield and pronounced diastereoselectivity (entry 9). Remarkably, cyano esters can serve as appropriate coupling partners (entry 10). In addition, the scope can be extended to ketones as substrates. Cyclohexanone was converted to **18** in 55% yield (entry 11). Aromatic ketones were expected to support the transformation since the enolization is facilitated. Consequently, the conversion of acetophenone was achieved in almost 50% yield, whereas the 3,4-dimethoxyacetophenone reacted in lower yield since the enolate formation was disfavored by the electron-rich moieties. The anticipated course of the reaction (Scheme 2) was supported by two major observations: A stronger influence of the α-modified carbonyl components on the stereochemistry was found and moieties which stabilized the enol ether **6**; for example, electron withdrawing systems or cyclic substrates led to significantly higher yields. X-ray analyses of suitable single crystals of **15** and **16** (Figure 2) revealed a favored *anti*-conformation of the newly formed carbon−carbon bond (highlighted blue). Furthermore, we found that the carbonyl component was exclusively

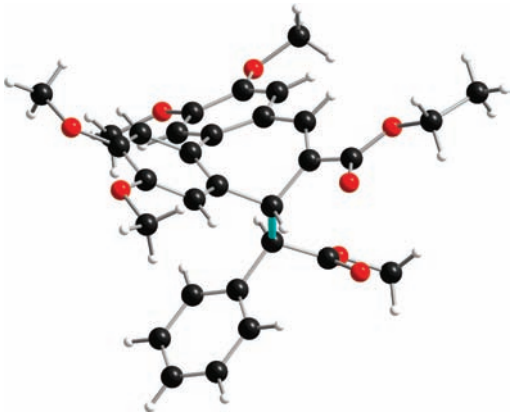


Figure 2. Molecular structure of **16** (major diastereomer) obtained by X-ray analysis.

located in the axial position at the sp^3 carbon of the seven-membered ring system. Consequently, the orientation of the biaryl axis was determined by this adjacent stereocenter in the central ring system. Because of this stereochemical preference, a sole diastereomer was obtained if an achiral primary alkyl moiety was used as a coupling partner in the domino sequence (entries 1, 2, 12, 13).

When achiral secondary alkylcarbonyl components served as reaction partners, as in the case for **16**, two diastereomers were observed (entry 9). The structure of the major diastereomer of **16** was similar to that found for **15** (Supporting Information (SI)). In **16** the biaryl axis is tilted by 41.6°. The benzylic sp^3 carbon is almost perfectly tetrahedral, arranged 109.3° with respect to its neighboring atoms in the central ring system. The geometry of **16** provides a consistent picture with the NMR data. The atropisomeric biaryl moiety forms, in all the examples investigated, the same geometric arrangement with respect to the newly formed stereogenic center in the seven-membered ring. The nucleophilic attack to the planar and *C*2 symmetric dibenzo[*a*,*c*]tropylium **4** (Scheme 2) can occur from both sides onto the central ring system creating the stereochemical relationship between the atropisomeric biaryl portion and new stereogenic center in the ring. Together with the adjacent exocyclic stereocenter a domino product with relative configuration *R*,*R*,*R* (*S*,*S*,*S*) or *R*,*R*,*S* (*S*,*S*,*R*) is formed. Only if cyclic carbonyl components or aromatic substituents on the new stereogenic center are involved, a pronounced stereoselectivity is found.

The unique character of $MoCl_5/TiCl_4$ for this domino sequence became obvious when **2** was subjected to ferrous chloride or other common electrophilic coupling media. Following the same workup protocol neither product **3**, formed by 2-fold C−H activation, nor product **7**, in consequence of the oxidative domino coupling sequence, was observed. Only traces of the domino product were detected when an analogous mixture of $FeCl_3/TiCl_4$ was applied (SI). Further indication for the domino sequence with a prior tropylium formation was found when tropylium tetrafluoroborate was subjected to the workup protocol. In the presence of $TiCl_4$ the ethyl acetate/triethylamine mixture led to the installation of an ethoxycarbonylmethyl moiety at the cycloheptatriene (SI). Recently, Cozzi et al. have demonstrated that cycloheptatriene can be organocatalytically functionalized by oxidative C−H activation.[17]

In conclusion, we have developed a fast and reliable domino sequence to highly functionalized dibenzo[*a*,*c*]cycloheptenes. The installation of the carboxy methyl moiety on the seven-membered ring can only be achieved by the $MoCl_5/TiCl_4$ mixture. The unprecedented domino transformation consists of three C−H activation steps. The sequence provides the full carbon skeleton of metasequirin-B.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds **2**−**20**. CIF files for compounds **15** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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