Cyclizations

Highly Modular Construction of Differently Substituted Dihydrodibenzo[*a*,*c*]cycloheptenes: Fast and Efficient Access to Derivatives of 2,2′-Cyclo-7,8′-neolignans**

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Dedicated to Professor Julius Rebek, Jr.
on the occasion of his 60th birthday

Although cyclolignans containing seven-membered carbocycles, like colchinol derivatives, inhibit the polymerization of tubulin in vitro, they have received scant attention in the

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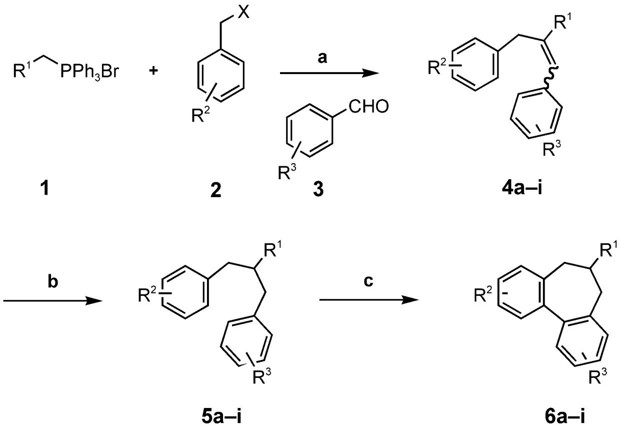
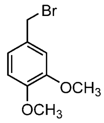
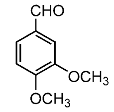
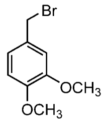
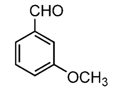
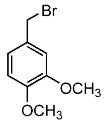
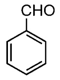
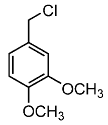
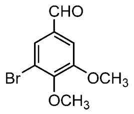
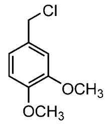
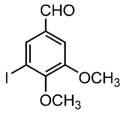
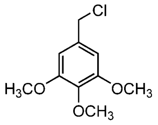
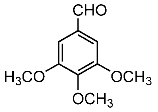
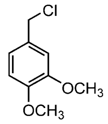
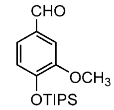
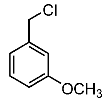
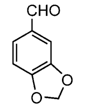
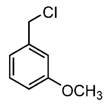
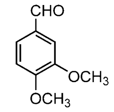
past.[1] Earlier strategies started with the biaryl synthesis developed by Meyers and yielded the seven-membered ring system after a multistep sequence.[2] Because of the many steps and the low overall yields, this pathway is less attractive for the construction of analogues and natural products of the metasequirin B series. Spectroscopic, crystallographic, and theoretical investigations indicate that 2,2′-cyclo-7,8′-neolignans are comparable to their corresponding eight-membered-ring derivatives, which exhibit a preferential twist-boat-chair conformation, in terms of their structure and biological activity.[3] Therefore, easily accessible molecules from this class of 2,2′-cycloneolignans may serve as surrogates for the interesting eight-membered lignans.

We report an efficient and highly modular route to dihydrodibenzo[*a*,*c*]cycloheptenes **6**. Simple and readily available components like the appropriately substituted benzyl halides, benzaldehydes, phosphonium salts, and phosphonates were used as starting materials. The reaction sequence of the one-pot procedure commenced with the alkylation of the deprotonated phosphorus reagent employing benzyl halides (Scheme 1). Base was added again, and the subsequent Wittig reaction with benzaldehyde derivatives resulted in an isolable mixture of olefins **4**, in which all three components are properly connected. In the succeeding hydrogenation with palladium on charcoal the reaction mixture could be used directly, but it was beneficial to remove the salts and triphenylphosphane oxide.[4] In the case of the iodo-substituted substrate **4e** dehalogenation and deactivation of the catalyst could be avoided when the double bond was reduced by treatment with triethylsilane in trifluoroacetic acid,[5] whereas the reduction of the bromo derivative **4d** succeeded with the Adams catalyst. All hydrogenations proceeded quantitatively and provided the analytically pure 1,3-diarylpropanes.[6]



Scheme 1. a) THF, 0°C, *n*BuLi, 2 h; then **2**, 0°C, 2 h; then *n*BuLi, 0°C, 2 h; then **3**, 15 h, RT; b) THF, Pd/C, H_2, 1 atm, 10 h, RT; **5d:** THF, PtO_2, H_2, 1 atm, 10 h, RT; **5e:** TFA, Et_3SiH, CH_2Cl_2, 10 h, RT; c) CH_2Cl_2, $MoCl_5$, $TiCl_4$. RT = room temperature, TFA = trifluoroacetic acid.

Table 1: Results of the alkylation/Wittig olefination sequence and subsequent hydrogenation.

Entry	R^1	**2**	**3**	**5**	Yield [%]
1	CH_3			**5a**	74
2	CH_3			**5b**	73
3	CH_3			**5c**	75
4	CH_3			**5d**	35
5	CH_3			**5e**	56
6	CH_3			**5f**	64
7	CH_3			**5g**	43
8	CH_3			**5h**	51
9	COOEt[a]			**5i**	72

[a] Triethyl phosphonoacetate was employed instead of the phosphonium salt **1**.

Employing benzyl chlorides[7] for the alkylation of **1** gave lower yields for **5d**–**h**, whereas the corresponding benzyl bromides[8] always provided better results (see Table 1, entries 1–3). The first benzyl moiety could also be introduced with the phosphonoacetate,[9] and the subsequent Horner olefination was performed with sodium hydride in toluene.

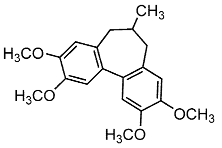
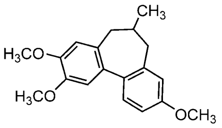
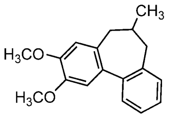
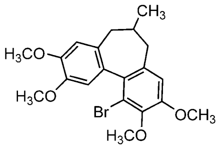
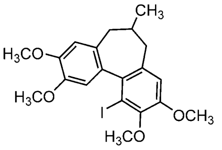
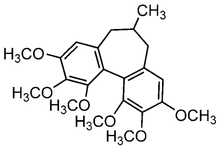
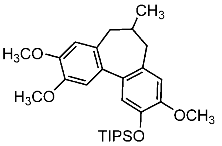
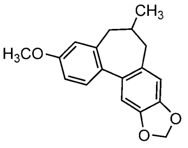
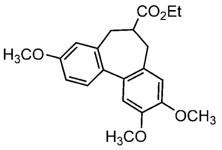
Toxic thallium or vanadium reagents are often applied for the intramolecular coupling reaction of electron-rich aryl groups.[10] The transformation is much better with either hypervalent iodine systems[11] or the biocompatible $MoCl_5$. If the latter reagent is used, the substrate must have a 1,2-dialkoxy substitution pattern for the dehydrodimerization reaction to succeed.[12] The synthetic power of $MoCl_5$ in the oxidative cyclization reaction was demonstrated in the construction of the 2,2′-cyclolignans (eight-membered-ring systems), which proceeded in the moderate yields typical for this class of compounds.[13] The addition of Lewis acids like $TiCl_4$ enhance the synthetic potential of $MoCl_5$ significantly.[14]

In contrast to the synthesis of eight-membered lignans, the oxidative conversion of the 1,3-diarylpropanes using $MoCl_5$/$TiCl_4$ reagent mixtures gave the corresponding seven-membered ring systems in excellent yields, and the reaction tolerated a broad range of functional groups. The construction of the seven-membered carbocycle **6a** was realized in good yields. Previous procedures for the preparation of similar compounds with thallium reagents gave substantially lower yields.[15] Surprisingly, the oxidative coupling reaction providing the less electron-rich trimethoxy derivative **6b** was accomplished quantitatively. Even a nonactivated phenyl moiety was successfully subjected to the oxidative cyclization process (see Table 2, entry 3). Increasing the amount of the reagent did not lead to better results for the desired product but rather the formation of a dimeric species.[16] The $MoCl_5$-mediated oxidative coupling reaction tolerated the valuable bromo and iodo substituents,[17] which are handles for subsequent modification of the cyclized products by transition-metal-catalyzed reactions. Very electron-rich biphenyl moieties equipped with six methoxy groups (**6f**) are found in many natural products and were obtained in almost quantitative yield by this methodology (see Table 2, entry 6). The reaction conditions of the $MoCl_5$-mediated transformation were compatible with a variety of different protective groups for the phenolic oxygen.[18] When a triisopropylsilyl group was used, some protolytic desilylation occurred (see Table 2, entry 7). Homogeneous materials in over 90% yield were obtained either by subsequent resilylation or by deprotection of the crude product. Substrates containing benzodioxole moieties could be cyclized to provide the desired compound **6h** in impressive yield despite the oxidation-sensitive methylene group.

The reaction of **5i** with the oxidizing agent was significantly slower, since the electrophilic metal center, which typically binds to the methoxy groups of the substrate, may coordinate intramolecularly to the ester moiety. Prolonged reaction times at room temperature also facilitated almost complete cyclization of **5i** to give the seven-membered-ring system **6i**.

We have described the first highly modular construction of dihydrodibenzo[*a*,*c*]cycloheptenes **6**. Simple and inexpensive building blocks were connected successfully and efficiently in a one-pot procedure, which was followed by an oxidative cyclization reaction. The dehydrodimerization reaction was accomplished with $MoCl_5$/$TiCl_4$ reagent mixtures in almost quantitative yield, and it tolerated a broad variety of functional groups. This route for the construction of such dihydrodibenzo[*a*,*c*]cycloheptenes is the most efficient strategy to date with overall yields of up to 72%.

Table 2: Results of the $MoCl_5$-mediated oxidative coupling reaction.

Entry	Starting material	Reaction conditions	Product		Yield [%]
1	**5a**	0°C, 40 min		**6a**	87
2	**5b**	0°C, 25 min		**6b**	99
3	**5c**	0°C, 30 min		**6c**	56
4	**5d**	0°C, 30 min		**6d**	95
5	**5e**	−5°C, 5 min		**6e**	92
6	**5f**	0°C, 50 min		**6f**	95
7	**5g**	−25°C, 20 min		**6g**	57 (+35)[a]
8	**5h**	0°C, 20 min		**6h**	87
9	**5i**	25°C, 3.5 h		**6i**	96

[a] The amount of desilylated product isolated is given in parentheses.

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Keywords: biaryls · C–C coupling · cyclization · lignans · molybdenum

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