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Versatile Route to Benzoannulated Medium-Ring Carbocycles via Aryne Insertion into Cyclic 1,3-Diketones: Application to a Synthesis of Radermachol

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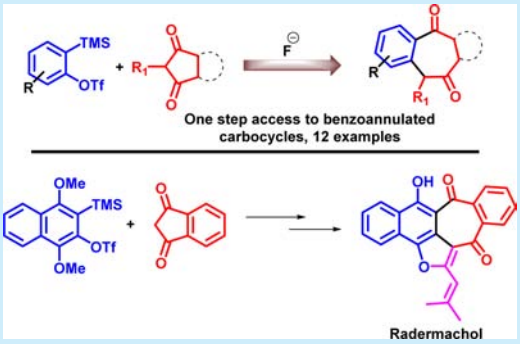
Supporting Information

ABSTRACT: A general approach involving the insertion of in situ generated aryne into the C−C bond of cyclic 1,3-diketones for rapidly assembling functionalized benzo-fused medium ring carbocycles is delineated. The efficacy of the methodology has been demonstrated through a concise total synthesis of pentacyclic natural product radermachol.



Frameworks based on mono- and dibenzoannulated medium-sized carbocyclic rings have been found among a relatively small but rapidly growing group of natural products.[1] Besides embodying interesting structural features, some members of this class exhibit broad and varied range of bioactivity profile. Some of the notable natural products in this group are rubialatin (**1**) (modulator of TNF-α and NF-κB pathways),[1a] hamigeran G (**2**) (H-60 active against human myelocytic leukemic cell lines),[1b] merochlorin A (**3**) (antibacterial activity against MRSA),[1c] diptoindonesin D (**4**) (cytotoxic against P-388 murine leukemia cells),[1d] radermachol (**5**) (folk medicines in China, India),[1e] and amurensinine (**6**) (CNS activity related to Parkinson's and Alzheimer's diseases)[1f,g] (Figure 1).

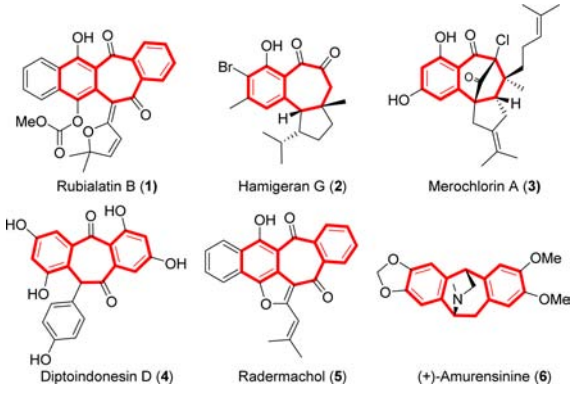


Figure 1. Representative examples for benzoannulated carbocyclic natural products.

Over the years, several synthetic approaches to benzoannulated medium rings bearing carbocyclic frameworks have been devised.[2−7] These involve intramolecular Friedel−Crafts reaction,[2] ring-closing metathesis,[3] intermolecular cationic cyclization reactions,[4] intramolecular ene reactions,[5] intramolecular cycloadditions,[6] and intramolecular Rh- and Pt-mediated hydroacylation,[7] among others. However, structural and bioactivity attributes of some of the recently isolated natural products (Figure 1) embodying the benzoannulated medium ring motifs and their bioactivity have rekindled interest in rapidly accessing these natural products through generally applicable strategies.

We were drawn to explore a short, simple, and generally applicable approach to mono- and dibenzocycloheptanes and cyclooctanes from readily available precursors employing an aryne insertion reaction[8−10] as the key step. Stoltz et al.[10a] have reported a protocol based on aryne insertion into the C−C bond of cyclic β-ketoesters to access mono- and dibenzocycloheptanes and applied it for the synthesis of natural product (+)-amurensinine (**6**)[10b] (Figure 2). Very recently, Zeng et al.[10c] have reported similar aryne insertion into the C−C bond of α-arylated cyclic ketones (Figure 2). This report prompts us to disclose our findings of smooth aryne insertion into the C−C bond of cyclic β-diketones to furnish mono- and dibenzocycloheptanes and cyclooctanes (Figure 2). A distinctive advantage of this strategy is that it directly installs a very desirable and differentiated 1,5-diketo functionality on the medium ring for orchestrating further

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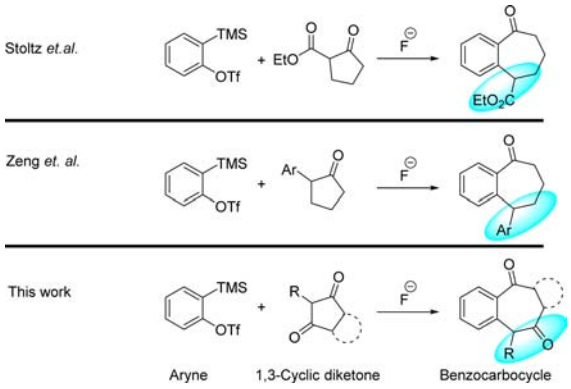
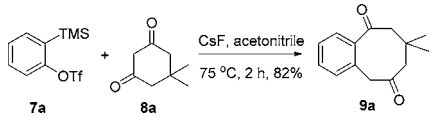


Figure 2. Aryne insertion based approaches for benzoannulated carbocyclic motifs.

functional group manipulations. As a demonstration of the utility of this aryne insertion approach and the advantage it offers in terms of carbonyl group disposition on the medium ring, we outline a short synthesis of natural product radermachol (**5**).[1e]

As an initial demonstrator of our projected theme, reaction of aryne generated from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **7a** in the presence of CsF[11] with dimedone **8a** as the 1,3-dicarbonyl-bearing reaction partner was investigated to furnish the benzocyclooctanone **9a** in decent yield (Scheme 1). Although several reaction conditions, solvents, and

Scheme 1. Ready Access to Benzoannulated Cyclooctane-1,5-dione from an Aryne Precursor with Dimedone

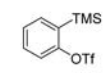
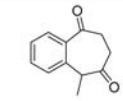
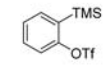
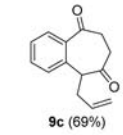
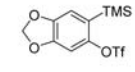
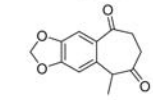
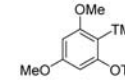
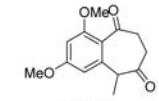
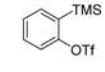
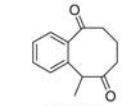
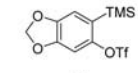
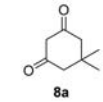
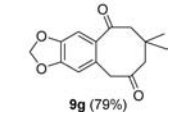


different fluoride sources (KF, KF-18-Crown-6, TBAF, TBAT, etc.) were explored, it was found that the reported[11] conditions using CsF and acetonitrile as solvent were the most productive and gave consistent outcomes. This set the stage for studying the reaction between various arynes **7a–c** and diverse cyclic 1,3-dicarbonyl partners **8b–d** and demonstrated a fair degree of generalization. Thus, insertion of arynes **7a–c** into the C–C bond of 1,3-cyclopentane diones **8b** led to benzoannulated cycloheptane-1,5-diones **9b,d,e** (Table 1), and insertion of aryne **7a** into the 1,3-diketone **8c** led to **9c**, respectively. Similarly, reaction of aryne **7a** with 2-methylcyclohexane-1,3-dione **8d** and aryne **7b** with dimedone **8a** delivered benzocyclooctanoids **9f** and **9g**, respectively (Table 1). In all cases, reactions were scalable, yields were preparatively exploitable, and isolation of products was straightforward.

For the formation of benzoannulated medium-ring products through formal C–C insertion, it is reasonable to extend the previously[10c] advanced mechanism for the reaction. Thus, nucleophilic attack of in situ generated enolate of 1,3-diketone onto aryne results in the formation of intermediate aryl anion **A**, which undergoes intramolecular nucleophilic attack onto the carbonyl group and forms a cyclobutane intermediate **B** which on fragmentation undergoes ring expansion to furnish the benzoannulated carbocycle (Scheme 2).

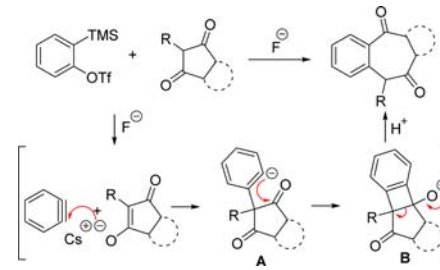
Since many natural products bear a dibenzo-fused cycloheptanoid scaffold (Figure 1), it was relevant to extend our

Table 1. Accessing Simple Benzoannulated Carbocycles by Reaction of Aryne with Cyclic 1,3-Diketones[a]

entry	aryne precursor **7**	1,3-diketone **8**	time (h)	product **9** (yield)[b]
1	 **7a**	 **8b**	2	 **9b** (75%)
2	 **7a**	 **8c**[c]	2	 **9c** (69%)
3	 **7b**	 **8b**	2	 **9d** (79%)
4	 **7c**	 **8b**	2	 **9e** (71%)
5	 **7a**	 **8d**	2	 **9f** (72%)
6	 **7b**	 **8a**	1	 **9g** (79%)

[a]Standard reaction conditions: aryne presursor (0.125 mmol), cyclic 1,3-diketone (0.1 mmol), and CsF (0.25 mmol) in acetonitrile at 80 °C. [b]Yield of the isolated product. [c]Prepared by following the known procedure.[12a]

Scheme 2. General Mechanism



aryne-1,3-diketone C–C insertion approach and validate it to access such tricyclic systems. For this purpose, several indan-1,3-diones (**10a,b**) were exposed to aryne generated from precursors **7a,b** to furnish dibenzocycloheptane diones **11a–d** in fair yields in a one-pot protocol (Table 2). Similarly, aryne generated from **7a** was treated with **10c** to result in allylated dibenzocycloheptane dione **11e**. The resulting tricyclic scaffolds are useful and versatile constructs. For example, **11c** represents the core framework present in the natural product diptoindonesin D (**4**) (Figure 1). On the other hand, the allylated dibenzocycloheptanoid **11e** could be readily elaborated to furano-fused tetracyclic system **12** through the intermediacy of Wacker oxidation[13] product and acid-mediated cyclodehydration of the 1,4-dicarbonyl moiety (Scheme 3).

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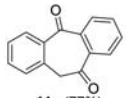
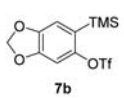
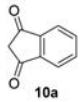
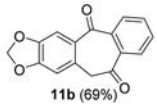
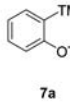
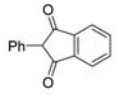
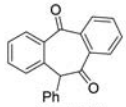
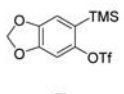
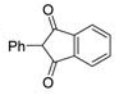
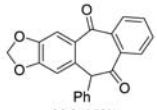
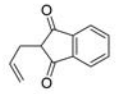
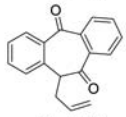
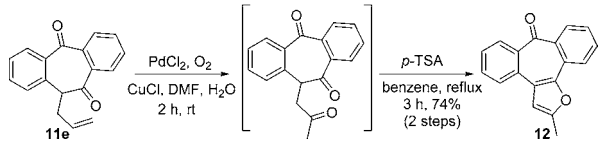
Table 2. Accessing Fused Benzoannulated Carbocycles by Reaction of Aryne with Benzofused Cyclic 1,3-Diketones[a]

entry	aryne presursor **7**	1,3-diketone **10**	time (h)	product **11** (yield)[b]
1	 **7a**	 **10a**	1	 **11a** (77%)
2	 **7b**	 **10a**	1	 **11b** (69%)
3	 **7a**	 **10b**	1.5	 **11c** (73%)
4	 **7b**	 **10b**	1.5	 **11d** (65%)
5	 **7a**	 **10c**[c]	1.5	 **11e** (67%)

[a]Standard reaction conditions: aryne presursor (0.125 mmol), cyclic 1,3-diketone (0.1 mmol), and CsF (0.25 mmol) in acetonitrile at 65 °C. [b]Yield of the isolated product. [c]Prepared by the known procedure.[12b]

Scheme 3. Synthesis of Furano-Fused Benzocarbocycle

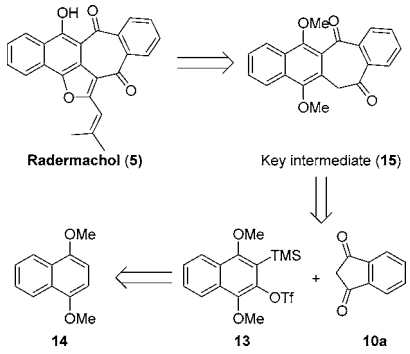


To demonstrate the efficacy of the present aryne strategy for complex synthesis, dibenzo-annulated cycloheptanoid dione radermachol (**5**)[1e] was chosen as an interesting natural product target. Radermachol (**5**)[1e] is a red pigment isolated from two different Indian plant sources, *Radermachera xylocarpa* K. *Schum* and *Tecomella undulate*, described and used in folk medicine. The pentacyclic structure of **5** was secured from X-ray crystallographic analysis,[1e] and to date, three total syntheses[14] have been documented employing PPA mediated intramolecular acylation,[14a] condensation of isobenzofuranone with preformed benzocycloheptenone,[14b] and $Yb(OTf)_3$-mediated furannulation−intramolecular nucleophilic acylation[14c] as the key steps, respectively.

A retrosynthetic perspective on our approach to radermachol (**5**) is outlined in Scheme 4 and can be traced to the insertion of napthyne (generated from precursor **13** prepared from readily available 1,4-dimethoxynaphthalene **14**) onto indan-1,3-dione **10a**. The resulting advanced naphtho- and benzoannulated cycloheptanedione **15** can be further elaborated to the pentacyclic natural product radermachol (**5**) following routine steps.

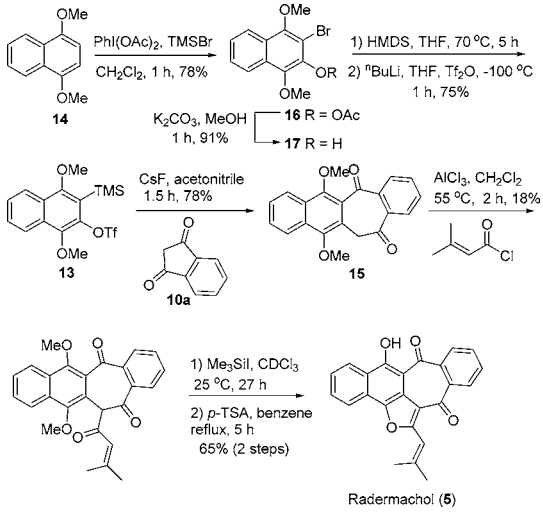
Commercially available 1,4-dimethoxynaphthalene **14** was subjected to a one-pot bromoacetoxylation reaction with iodobenzene diacetate and trimethylsilyl bromide (TMSBr) to

Scheme 4. Retrosynthetic Analysis of Radermachol (5)



provide bromoacetoxylated compound **16**[15] in 78% yield. Acetate hydrolysis to the corresponding bromonaphthol **17** and further one-pot HMDS-mediated *O*-silylation of the phenolic hydroxyl group, lithium−halogen exchange using *n*-BuLi with concomitant *O*- to *C*-silyl group migration, and *O*-triflation[16] gave *o*-trimethylsilyl naphthyl triflate **13** (Scheme 5). The *O*-silyl naphthyl triflate **13** on exposure to 1,3-

Scheme 5. Total synthesis of Radermachol (5)



indandione **10a** in the presence of CsF led to the desired tetracyclic C−C insertion product **15** in 78% yield. The key tetracyclic compound **15** was evolved to the natural product radermachol (**5**) through precedented steps, i.e., *C*-acylation with 3-methylcrotonoyl chloride, trimethylsilyl iodide mediated demethylation, and acid-induced cyclo-dehydration of the 1,4-dicarbonyl functionality to generate the fused furanoid moiety (Scheme 5). The resulting product **5** was found to be spectroscopically (^1H and ^{13}C NMR) identical to the natural product radermachol (**5**), thus leading to a short synthesis.

In short, we have meaningfully extended the aryne insertion strategy to access a range of benzoannulated 7- and 8-membered carbocycles by partnering with varied cyclic 1,3-diketones. The advantage in using cyclic 1,3-diketone as co-reactants is the facilitation of installation of desirable 1,5-diketo functionality on the medium ring with enhanced functional group maneuverability. The protocol has been successfully utilized for a short synthesis of the pentacyclic natural product radermachol (**5**).

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01078.

Detailed experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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