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De Novo Synthesis of Tricyclic 5,5-Benzannulated Spiroketals

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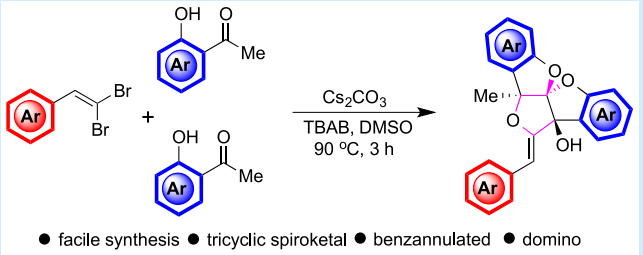
ABSTRACT: The synthesis of tricyclic 5,5-benzannulated spiroketal scaffolds was accomplished from 2′-hydroxyacetophenones and *gem*-dibromoalkenes involving a one-pot domino strategy. The hitherto unknown transformation afforded the tricyclic 5,5-benzannulated spiroketals as single diastereomers in high yields with a broad substrate scope.



Spiroketals are ubiquitous structural units present in several natural products comprising structurally simple to complex frameworks.[1,2] A few tricyclic spiroketals containing natural products were also recently isolated,[3] and benzannulated spiroketal[2]-based natural products such as purpuromycin, rubromycins, etc., are known to exhibit anticancer activity (Figure 1).[4] General synthetic methods of spiroketal synthesis[2]

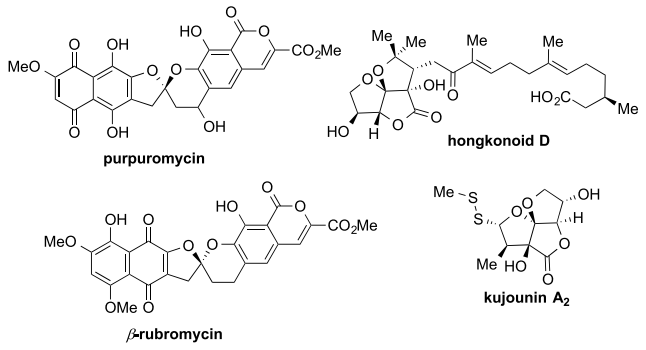
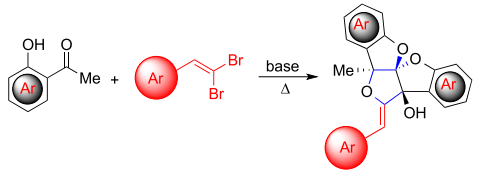


Figure 1. Four naturally occurring spiroketals.

include the ketalization of suitably substituted ketones tethered with hydroxyl groups,[5] the 4+2 cycloaddition of *o*-quinone,[6] Me_3SiI-promoted spirocyclization,[7] oxidative cyclizations,[8] metal-catalyzed hydroalkoxylation of alkynes,[9] etc.[10] Despite an array of available methods, a general method for the synthesis of tricyclic benzannulated spiroketals is still needed.

As a part of our efforts to develop new synthetic methodologies employing *gem*-dibromoalkenes and their applications in natural product synthesis,[11,12] herein, we report a novel strategy for the synthesis of tricyclic 5,5-benzannulated spiroketal scaffolds. This strategy involves the reaction of 2′-hydroxyacetophenone and *gem*-dibromoalkene under base-mediated reaction in DMSO (Scheme 1).

Scheme 1. Synthetic Strategy for Tricyclic 5,5-Benzannulated Spiroketals



At the outset, the reaction of 2′-hydroxyacetophenone **1a** and *gem*-dibromoalkene **2a** in DMSO with Cs_2CO_3 and a substoichiometric amount of TBAB afforded tricyclic 5,5-benzannulated spiroketal **3a** in 43% yield as a single diastereomer (Table 1, entry 1). The structure of tricyclic benzannulated spiroketal **3a** was confirmed by single-crystal X-ray analysis. The reaction was further screened with 1.5 equiv of *gem*-dibromoalkene, and the tricyclic spiroketal was isolated in 79% yield (Table 1, entry 2). Decreasing the amount of Cs_2CO_3 to 4 equiv provided the spiroketal in 74% yield (Table 1, entry 3). Changing the base to K_2CO_3, ^{t}BuOk, or KOAc was found to be ineffective (Table 1, entries 4−6). Changing the solvent to DMA did not yield the spiroketal (Table 1, entry 7). A mixture of 1-bromoalkyne and the corresponding terminal acetylene arising from *gem*-dibromoalkene **2a** was observed in larger amounts (Table 1, entries 4−7). Performing the reaction with different reaction times (Table 1, entries 8 and 9) revealed that the 3 h condition is suitable to furnish the spiroketal in 87% yield (Table 1, entry 9). A reaction carried out without TBAB furnished the spiroketal in lower yield

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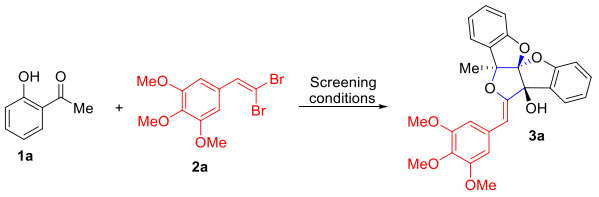
Table 1. Screening Conditions[a]



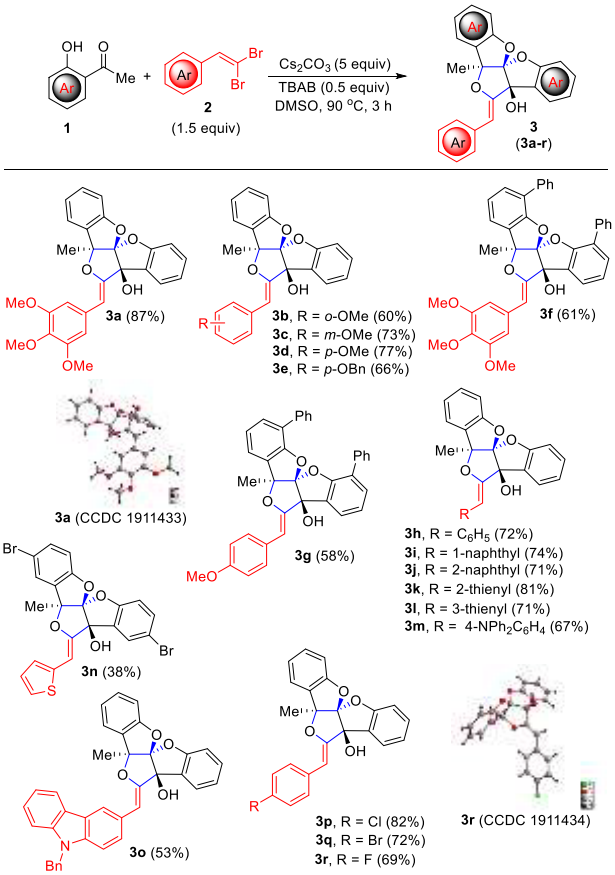
entry	base	solvent	time (h)	yield (%)
1	Cs_2CO_3	DMSO	6	43[b]
2	Cs_2CO_3	DMSO	6	79
3	Cs_2CO_3	DMSO	6	74[c]
4	K_2CO_3	DMSO	6	–
5	^tBuOK	DMSO	6	–
6	KOAc	DMSO	6	–
7	Cs_2CO_3	DMA	6	–
8	Cs_2CO_3	DMSO	5	79
9	Cs_2CO_3	DMSO	3	87
10	Cs_2CO_3	DMSO	2	78[d]

[a]Reaction conditions: **1a** (0.38 mmol, 1 equiv), **2a** (0.56 mmol, 1.5 equiv), base (1.9 mmol, 5 equiv), TBAB (0.19 mmol, 0.5 equiv), solvent (3 mL), 90 °C. Yield calculated considering 0.19 mmol of spiroketal **3a** as a 100% yield. Any excess *gem*-dibromoalkene (**2a**) transformed into terminal alkyne (**2.1a**). [b]**2a** (0.38 mmol, 1 equiv). [c]Cs_2CO_3 (1.5 mmol, 4 equiv). [d]Without TBAB.

(Table 1, entry 10). Thus, the optimized protocol for the synthesis of tricyclic 5,5-benzannulated spiroketal **3a** in high yield was found to consist of 2′-hydroxyacetophenone (1 equiv), *gem*-dibromoalkene (1.5 equiv), Cs_2CO_3 (5 equiv), and TBAB (0.5 equiv) in DMSO at 90 °C for 3 h (Table 1, entry 9). Additionally, the larger scale reaction that was carried out with 3.67 mmol of **1a** furnished spiroketal **3a** in 61% yield.

After establishing the optimized protocol, we explored the synthetic scope for the formation of tricyclic 5,5-benzannulated spiroketals using different *gem*-dibromoalkenes and 2′-hydroxyacetophenones involving 3 h conditions (Scheme 2). It was found that the *o*-, *m*-, and *p*-methoxy- and *p*-benzyloxy-functionalized *gem*-dibromoalkenes reacted well and delivered tricyclic benzannulated spiroketals **3b**–**3e**, respectively, in 60–77% yields. Further reaction of 2′-hydroxy-3′-phenylacetophenone **1b** with *gem*-dibromoalkenes provided spiroketals **3f** and **3g** in moderate yields. *gem*-Dibromoalkenes derived from simple benzaldehyde and 1- and 2-naphthaldehyde also reacted well, furnishing spiroketals **3h**–**3j**, respectively, in 71–74% yields. Reactions using *gem*-dibromoalkenes derived from thiophene-2-carbaldehyde and thiophene-3-carbaldehyde afforded tricyclic benzannulated spiroketals **3k** and **3l**, respectively, in high yields. Similarly, the reaction with 4-(2,2-dibromovinyl)-*N*,*N*-diphenylaniline also provided spiroketal **3m** in good yield. The reaction of 1-(5-bromo-2-hydroxyphenyl)ethanone **1c** with 2-(2,2-dibromovinyl)-thiophene produced spiroketal **3n** in 38% yield. The carbazole-derived *gem*-dibromoalkene, 9-benzyl-3-(2,2-dibromovinyl)-9*H*-carbazole, gave spiroketal **3o** in moderate yield. Notably, *gem*-dibromoalkenes derived from *p*-halo-benzaldehydes reacted to furnish spiroketals **3p**–**3r** in 69–82% yields. The structure of tricyclic benzannulated spiroketal **3r** was also confirmed by single-crystal X-ray analysis. However, *p*-cyano-, *p*-nitro-, and *o*-nitro-functionalized electron-deficient *gem*-dibromoalkenes with 2′-hydroxyacetophenone did not yield the spiroketal products.

Scheme 2. Tricyclic 5,5-Benzannulated Spiroketals with *gem*-Dibromoalkenes[a]



[a]Reaction conditions: 2′-hydroxyacetophenone **1** (0.38 mmol, 1 equiv), *gem*-dibromoalkene **2** (0.56 mmol, 1.5 equiv), Cs_2CO_3 (1.9 mmol, 5 equiv), TBAB (0.19 mmol, 0.5 equiv), DMSO (3 mL), 90 °C, 3 h. Yield calculated considering 0.19 mmol of spiroketal **3** as a 100% yield.

We extended the study with challenging 1,3-dienyldibromides derived from functionalized cinnamaldehydes. These *gem*-dibromoalkenes showed excellent reactivity under the optimized conditions (Scheme 3). Thus, the 1,3-dienyldibromides prepared from cinnamaldehydes containing functionalized phenyls (with R = H, 4-Me, 4-MeO, 4-Cl, and 4-Br) reacted well with 2′-hydroxyacetophenone to afford tricyclic benzannulated spiroketals **5a**–**5e**, respectively, in good yields (Scheme 3, i). 2-Naphthyl-substituted 1,3-dienyldibromide also furnished spiroketal **5f** in 68% yield. Further study using 3-en-1-ynyldibromide **6a** also afforded tricyclic 5,5-benzannulated spiroketal **7a** in 50% yield under the established conditions (Scheme 3, ii). We further demonstrated the versatility of the protocol with 1,4-disubstituted bis-dibromoalkene **8a** and 2′-hydroxyacetophenone **1a**. This reaction proceeded smoothly to give terminal acetylene-embedded tricyclic 5,5-benzannulated spiroketal **9a** in high yield (Scheme 3, iii). Interestingly, reaction of 2′-hydroxyacetophenone with 1-bromoalkyne[12c] **2aa** prepared from *gem*-dibromoalkene **2a** furnished tricyclic spiroketal **3a** in 80% yield (Scheme 3, iv). This reaction clearly indicated the in situ formation of 1-bromoalkyne during the course of the reaction from *gem*-dibromoalkene. It also further indicated the viability for the

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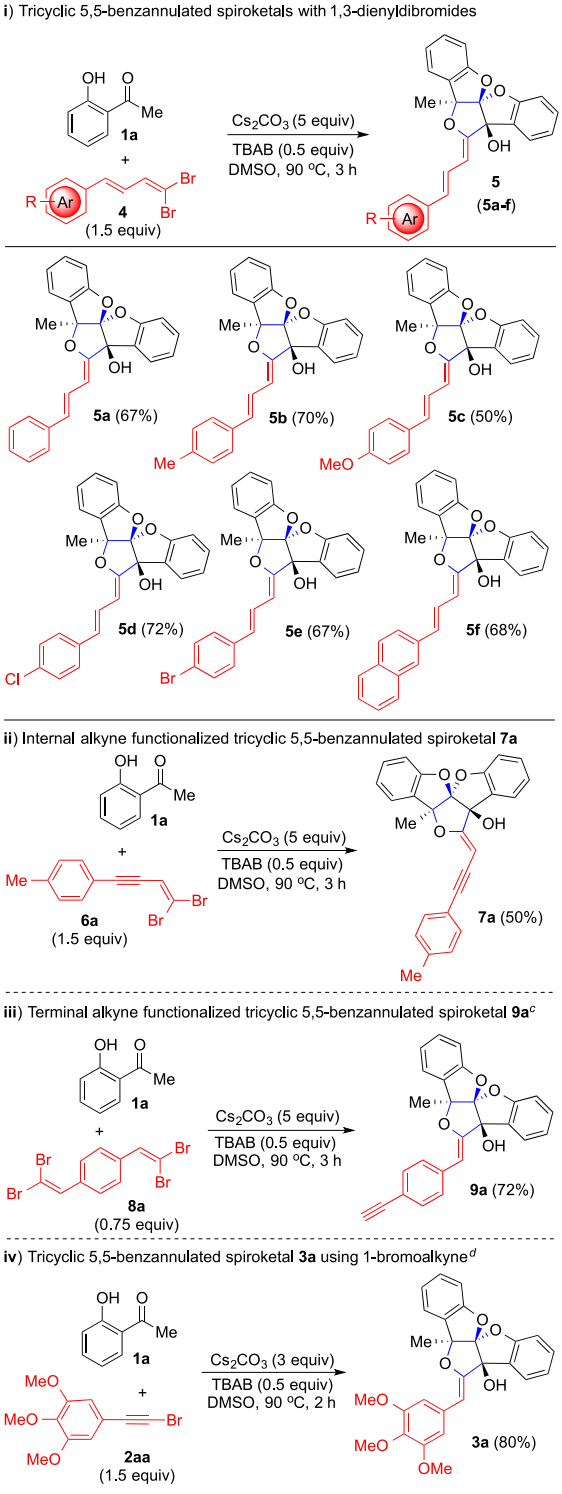
Scheme 3. Reactions with 1,3-Dienyldibromides, 3-En-1-ynyldibromide, Bis-dibromoalkene, or 1-Bromoalkyne[a,b]

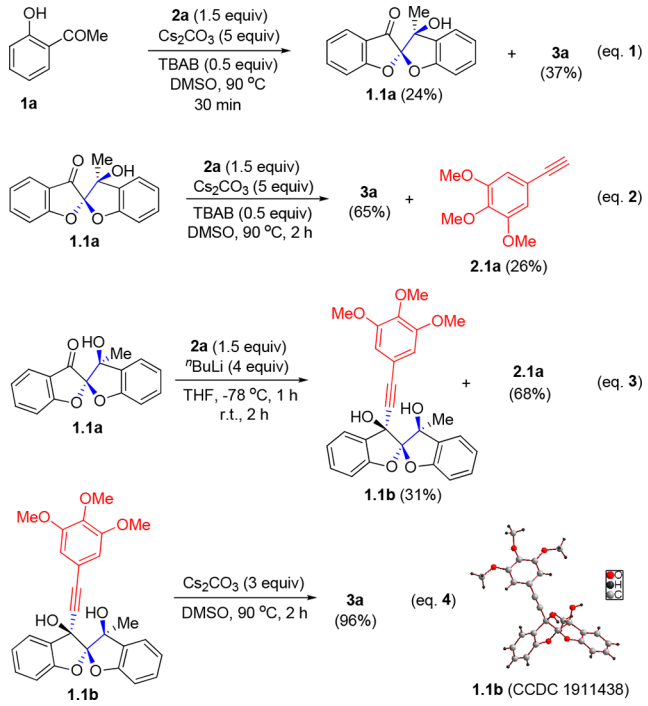


[a]Reaction conditions: **1a** (0.38 mmol, 1 equiv), **4**, **6a**, or **2aa** (0.56 mmol, 1.5 equiv), Cs_2CO_3 (1.9 mmol, 5 equiv), TBAB (0.19 mmol, 0.5 equiv), DMSO (3 mL), 90 °C, 3 h. [b]Yield calculated considering 0.19 mmol of spiroketal as a 100% yield. [c]**8a** (0.28 mmol, 0.75 equiv). [d]Cs_2CO_3 (1.12 mmol, 3 equiv), 2 h.

direct use of either *gem*-dibromoalkene or 1-bromoalkyne as the substrate in the reaction.

We also conducted additional control experiments to probe the mechanistic rationale for the formation of the tricyclic 5,5-benzannulated spiroketal (as given Scheme 4 and Scheme S1).

Scheme 4. Control Experiments



First, the reaction of a simple acetophenone **1d** and *gem*-dibromoalkene **2a** failed to give tricyclic spiroketal **3a** but instead furnished terminal alkyne **2.1a** (Scheme S1, eq 1). This indicated the requirement of an *o*-hydroxy group in acetophenone to form spiroketal **3a**. The reaction using 2′-acetoxyacetophenone **1e** (Scheme S1, eq 2) and 3′-hydroxyacetophenone **1f** (Scheme S1, eq 3) failed to produce spiroketal **3a**. In both cases, terminal alkyne **2.1a** was obtained. These reactions (Scheme S1, eqs 1−3) established the requirement of a free 2′-hydroxyacetophenone in the reaction. The successful reaction obtained with 1-bromoalkyne (vide supra) also confirms its in situ formation from *gem*-dibromoalkene during the course of the reaction (Scheme 3, iv). The reaction of terminal alkyne **2.1a** with 2′-hydroxyacetophenone **1a** failed to deliver product **3a** (Scheme S1, eq 4), indicating no role of the terminal alkyne in the reaction. We also successfully isolated intermediate **1.1a** in 24% yield along with a 37% yield of **3a** in the reaction of 2′-hydroxyacetophenone **1a** with *gem*-dibromoalkene **2a** quenched after 30 min (Scheme 4, eq 1). We also performed the reaction with intermediate **1.1a** in the presence of *gem*-dibromoalkene **2a**, and this furnished spiroketal **3a** in 65% yield (Scheme 4, eq 2), confirming the formation of spiroketal through intermediate **1.1a**. A reaction of 2′-hydroxyacetophenone **1a** (without *gem*-dibromoalkene **2a** did not furnish intermediate **1.1a** (Scheme S1, eq 5), indicating the significant role of *gem*-dibromoalkene in the formation of **1.1a**. The reaction with a substituted *gem*-dibromoalkene such as (1,1-dibromoprop-1-en-2-yl)benzene **10a** (which cannot form the 1-bromoalkyne) failed to give the tricyclic spiroketal product (Scheme S1, eq 6). This indicated the important role of 1-bromoalkyne in the reaction. It was also found that the

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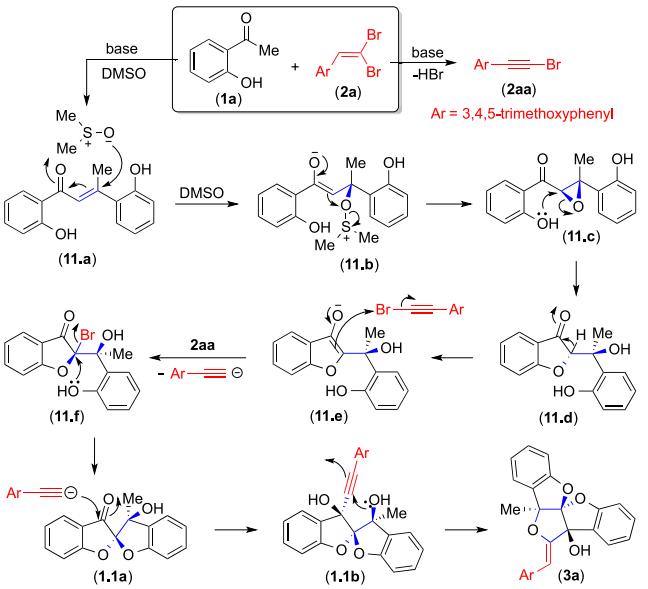
reaction of intermediate **1.1a** with *gem*-dibromoalkene **2a** in the presence of ^{n}BuLi furnished compound **1.1b** (Scheme 4, eq 3), the structure of which was also confirmed by single-crystal X-ray analysis. The reaction of **1.1b** with Cs_2CO_3 gave tricyclic 5,5-benzannulated spiroketal **3a** in excellent yield (Scheme 4, eq 4).

On the basis of these control experiments, the following mechanistic rationale is proposed for the formation of tricyclic benzannulated spiroketal **3a** (Scheme 5).

Scheme 5. Proposed Mechanistic Pathway



First, base-mediated aldol reaction of **1a** forms chalcone **11.a**, which undergoes epoxidation with DMSO[13] to yield intermediate **11.c**.[14] The intramolecular cyclization of **11.c** furnishes benzofuran-3(2*H*)-one **11.d**. Enolate **11.e** formed from **11.d** undergoes X-philic reaction with 1-bromoalkyne[15] **2aa** (formed in situ from *gem*-dibromoalkene **2a**) to give 2-bromobenzofuran-3(2*H*)-one **11.f**. Subsequent intramolecular nucleophilic bromide displacement[16] in **11.f** provides intermediate **1.1a**. The in situ-formed acetylide in turn reacts with **1.1a** to afford product **1.1b**, which undergoes 5-*exo*-*dig* cyclization[17] and yields the final tricyclic 5,5-benzannulated spiroketal **3a** product.

In conclusion, a simple strategy for the preparation of tricyclic 5,5-benzannulated spiroketals from 2′-hydroxyacetophenones and *gem*-dibromoalkenes under a base-mediated one-pot domino protocol was developed. The mechanistic rationale was proposed to explain the formation of the tricyclic 5,5-benzannulated spiroketal product. Further investigations to explore this methodology for the synthesis of spiroketal-containing natural product analogues are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01109.

Experimental section, detailed experimental procedures, and full spectroscopic data for all related compounds (PDF)

Accession Codes

CCDC 1911433−1911434 and 1911438 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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