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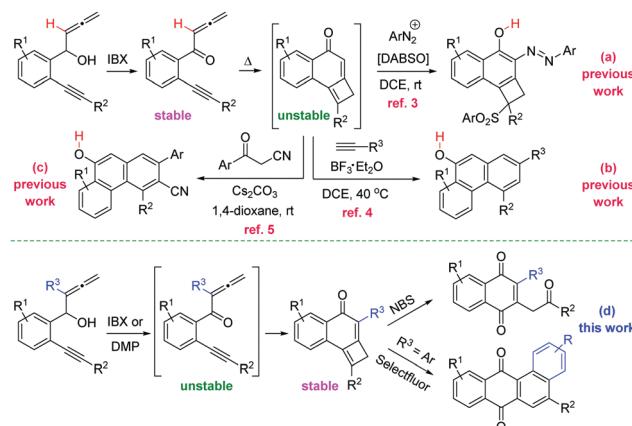
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The controlled synthesis of 1,4-naphthoquinones and tetraphene-7,12-diones, which bear the ABCD-ring of landomycins, has been accomplished directly through oxidative rearrangement of common stable precursors, namely, previously non-isolable cyclobuta[a]naphthalen-4(2H)-ones.

The ubiquity of the quinone moiety in natural products and organic materials justifies the continued interest in the synthesis of molecules containing this framework.¹ The widespread occurrence of the cyclobutene nucleus in natural products and bioactive compounds, coupled to the use of this strained carbocycle as a building block in organic synthesis, triggered a renewed activity in the synthesis of cyclobutenes.² However, the preparation of the quinone core from cyclobutenes has remained unexplored. Jiang and co-workers have recently communicated the cyclization reactions of allenynes toward naphthols using DABSO [DABCO·(SO₂)₂] and arenediazonium salts (Scheme 1a),³ or either in presence of alkynes (Scheme 1b),⁴ or β -ketonitriles (Scheme 1c),⁵ involving the generation of tricyclic cyclobutene intermediates. Aiming to extend the utility of allenynes, we planned to use allenyne precursors bearing substituents at the internal allene double bond. Worthy of note, the presence of the extra-substituent ($R^3 = Me, Ar$) did allow for the isolation of previously unstable and non-isolable tricyclic cyclobutenes ($R^3 = H$). Herein, we present a convenient method for the divergent synthesis of 1,4-naphthoquinones and tetraphene-7,12-diones through the oxidative reorganization of cyclobutene-fused naphthalen-1-ones (Scheme 1d).

Transition metal-free cyclobutene rearrangement in fused naphthalen-1-ones: controlled access to functionalized quinones^{†‡}

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Scheme 1 The allenynone framework as a platform for the synthesis of fused carbocycles: prior art and our method.

Starting substrates, allenynols **2a–k**, were prepared from alkynyl-benzaldehydes **1** and 3-substituted prop-2-ynyl bromides using an indium-mediated allenylation under Barbier conditions in aqueous media (Scheme 2). Further oxidation with IBX or Dess–Martin periodinane (DMP) to introduce the carbonyl moiety gives rise directly to cyclobutene-fused naphthalen-1-ones **3a–k** (Scheme 2). It was found that the best results were systematically obtained in the presence of DMP. Because of the great reactivity imparted by the highly conjugated system in the initially formed non-isolable allenynes, [2+2] cycloaddition reactions take place spontaneously.⁶ Tricyclic cyclobutenes **3** were obtained with complete chemo- and regioselectivity in good yields.

To explore the reactivity of cyclobutene-fused naphthalen-1-ones **3**, at the beginning of the study we selected *N*-bromo-succinimide (NBS) as a convenient electrophilic source of bromine and tricyclic cyclobutene **3a** as a model substrate. In the event, the use of THF as solvent led to reaction failure. Fortunately, the replacement of THF by acetonitrile provided 2-methyl-3-(2-oxo-2-phenylethyl)naphthalene-1,4-dione **4a**,⁷ but only in a modest 29% yield. Because of the structure of **4a**, it may be apparent that adventitious water in the reaction

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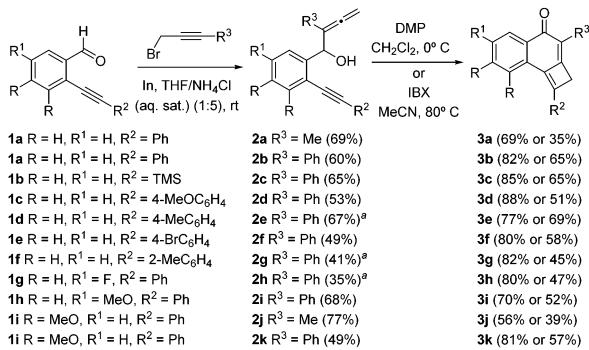
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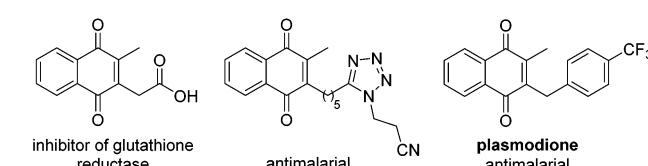
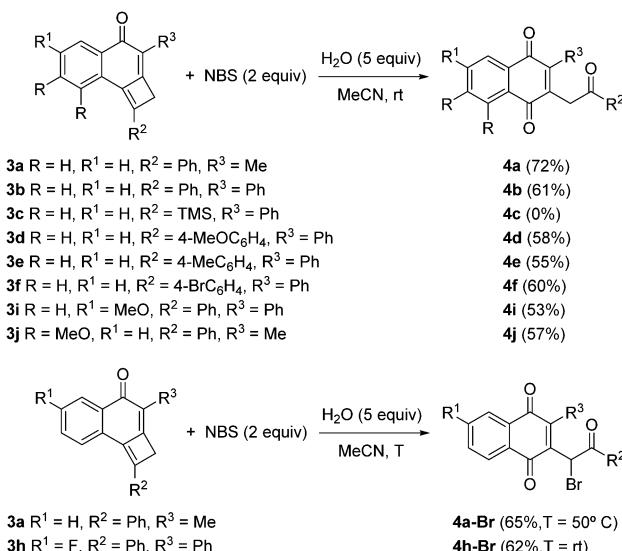
[‡] Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data, and copies of NMR spectra for all new compounds. See DOI: [10.1039/c9cc08628e](https://doi.org/10.1039/c9cc08628e)





Scheme 2 Synthesis of tricyclic cyclobutenes **3a–k**. ^aThe reaction was carried out in THF/H₂O (1 : 1).

medium was necessary. To prove this assumption, we carried out the reaction with the addition of 5.0 equiv. of water. Indeed, in this way a significant improvement of the yield of **4a** up to 72% was achieved (Scheme 3). With the optimal conditions in hand, we evaluated the influence of substituents at the different positions of tricycles **3**. A variety of aromatic moieties were well tolerated both at R² and R³, while an aliphatic substituent was accommodated at R³ (Scheme 3). Even precursor **3j** bearing two electron-donating substituents (R = MeO) on the aromatic ring, conveniently afforded naphthalene-1,4-dione **4j** after NBS treatment. By contrast, the reaction of TMS-cyclobutene **2c** was not satisfactory. Interestingly, the presence of a fluorine atom at the benzene ring such as in tricyclic cyclobutene **3h** resulted in an extra-bromination on the final adduct **4h-Br** (Scheme 3).

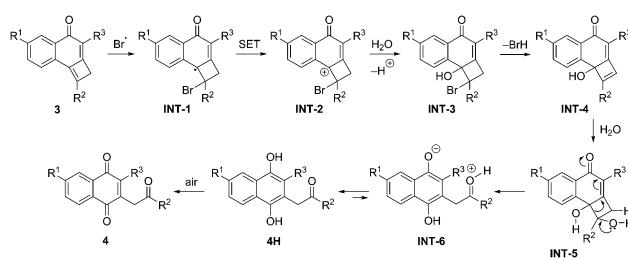


Scheme 3 Synthesis of 2-substituted-3-(2-oxo-2-arylethyl)naphthalene-1,4-diones **4** and **4-Br**.

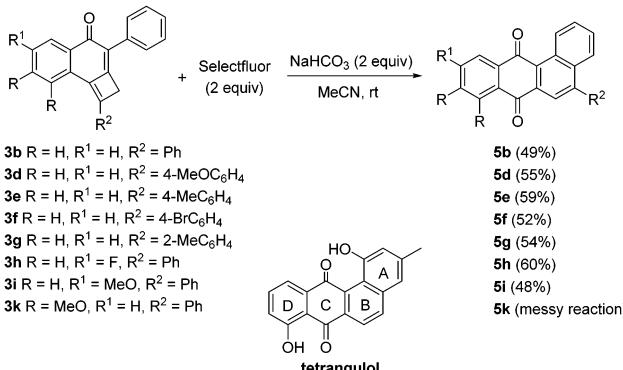
The same phenomenon was observed starting from tricycle **3a** under otherwise identical reaction conditions but through mild heating, which resulted in the formation of **4a-Br** (Scheme 3). Pleasingly, it has been reported that several 2-methyl-3-alkyl-naphthalene-1,4-diones related to bicycles **4** possess interesting biological activities.⁸

A plausible mechanism for the NBS-promoted genesis of 1,4-naphthoquinones **4** is delineated in Scheme 4. The reaction is presumed to possess a radical nature, which was based on the suspension of the transformation after the addition of TEMPO to the reaction medium. Initially, the formation of allylic radical species **INT-1** should occur by bromine radical attack. The formation of this radical should be followed by oxidation to the carbocationic species **INT-2** by single electron transfer (SET) to the succinimide. Next, water attack takes place with formation of bromohydrin **INT-3** which is followed by HBr release. Hydration of the resulting intermediate cyclobutanol **INT-4** leads to diol **INT-5**, which evolves into zwitterionic intermediate **INT-6**. According to Density Functional Theory calculations (see ESI†), this step proceeds with a low activation barrier of only 10.6 kcal mol⁻¹ (for **3a**). A subsequent proton transfer leads to dihydroquinone **4H** in a highly exergonic transformation ($\Delta G_R = -40.3$ kcal mol⁻¹, for **3a**), which is finally oxidized to its quinone form **4**.

Aiming to explore the effect of different reagents in the selective oxidative reorganization of cyclobutene-fused naphthalen-1-ones, we decided to expose tricycles **3** to the action of Selectfluor. The reaction of adduct **3a** with Selectfluor was problematic and a complex mixture was obtained. By contrast, an encouraging result was obtained when adduct **3b** having a phenyl group was used, because we unexpectedly isolated in a 19% yield tetracycle **5b** that should arise from an angular benzannulation process. The presence of sodium bicarbonate in the reaction between Selectfluor and **3b** caused an appreciable rise in the yield of **5b** (Scheme 5). On this point, we next tested the scope of this rearrangement reaction using diverse fused-cyclobutenes **3** which contain a phenyl moiety at the cyclohexenone ring. A variety of differently substituted precursors **3**, including fluoroo- and methoxy-derivatives **3h** and **3i** were suitably rearranged. By contrast, the reaction of dimethoxy-substituted precursor **3k** with Selectfluor was troublesome and the desired tetracycle **5k** was not isolated in reasonable purity. Synthetically useful yields of tetracycles **5b** and **5d–i** were attained (Scheme 5). For all examples included in Scheme 5 no products of type **4** were observed.

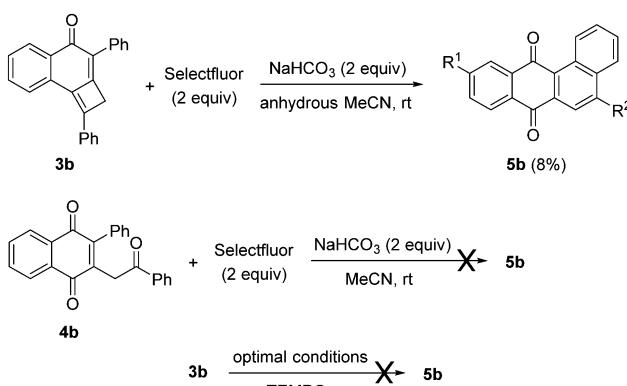


Scheme 4 Mechanistic explanation for the NBS-promoted synthesis of 2-oxo-naphthalene-1,4-diones **4**.

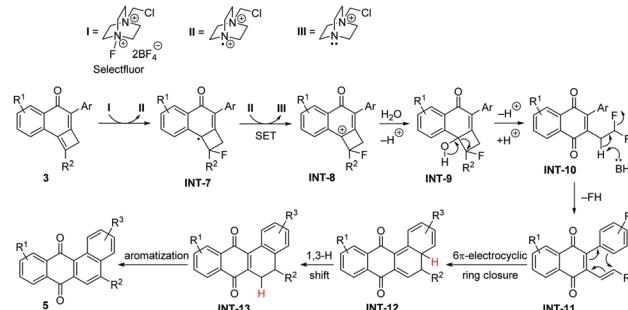
Scheme 5 Synthesis of 5-aryltetraphene-7,12-diones **5b** and **5d–i**.

Noteworthy, tetracycles **5** bear the ABCD-ring of landomycins. Landomycins such as tetrangulol are a class of natural quinones characterized by an angular conjugated tetracyclic core, which confers them with interesting bioactivities.⁹ The major difficulty associated with the synthesis of landomycins is the formation of the B-ring due to hindrance issues. This elusive aspect is easily addressed in our preparation of the landomycin core.

In order to gain some mechanistic insights, control experiments were planned (Scheme 6). First, when tricycle **3b** was treated with Selectfluor under the optimized conditions but using anhydrous acetonitrile, the yield of **5b** decreased to 8% (Scheme 6). This result unveiled the origin of the oxygen at the C-ring, that should come from ambient water. Succeeding in performing a divergent preparation of 2-substituted-3-(2-oxo-2-arylethyl)naphthalene-1,4-diones **4** and 5-aryltetraphene-7,12-diones **5**, we speculated about the possible intermediacy of 1,4-naphthoquinones **4** in the formation of angular tetracycles **5** in the presence of Selectfluor. When 1,4-naphthoquinone **4b** was treated with Selectfluor and sodium bicarbonate under the optimized reaction conditions for the formation of pentacycles **5**, the reaction failed and starting material **4b** was fully recovered (Scheme 6). From the above experiment, it may be inferred that naphthalene-1,4-diones of type **4** should be discarded as intermediates for this reaction. The radical scavenger TEMPO effectively suppressed the formation of the required product, pointing to a radical reaction mechanism.



Scheme 6 Control experiments.

Scheme 7 Mechanistic explanation for the Selectfluor-promoted synthesis of tetraphene-7,12-diones **5**.

Based on the above experiments, we assume a mechanism as presented in Scheme 7 for the reaction of aryl-substituted cyclobutene-fused naphthalen-1-ones **3** with Selectfluor. Similar to the above-described reaction involving NBS, tricycles **3** can be converted into cationic intermediates **INT-8** after Selectfluor treatment with concomitant formation of **III**. Next, this intermediate should suffer water attack to produce halohydrin **INT-9**, which evolves through cyclobutane ring opening followed by base-assisted HF release¹⁰ into the quinone **INT-11**. The so-formed polyene is able to undergo a 6 π -electrocyclic ring closure to produce **INT-12**,¹¹ which rapidly evolves into **INT-13** via a 1,3-hydrogen migration. According to DFT calculations on **3b** (see ESI \ddagger), this step proceeds with an activation barrier of 21.9 kcal mol⁻¹ in a highly exergonic transformation ($\Delta G_R = -28.2$ kcal mol⁻¹) driven by the gain in aromaticity in the system. Finally, **INT-13** is oxidized into the observed tetracycles **5**. Our calculations indicate that the concerted H₂ release from either **INT-13** or even from **INT-12** thus directly forming **5** is unfeasible ($\Delta G^\ddagger = 89.9$ and 77.4 kcal mol⁻¹, respectively). This points to a different mechanism for this final aromatization step,¹² which is not evident to us at the moment.

In conclusion, we have developed a divergent outcome transformation of the previously non-isolable cyclobuta[*a*]naphthalen-4(2H)-one system to afford either 1,4-naphthoquinones or tetraphene-7,12-diones, which has been accomplished through the reorganization of the above fused tricyclic cyclobutenes in the presence of NBS or Selectfluor.

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Conflicts of interest

There are no conflicts of interest to declare.

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