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Synthesis of Cyclopropanoids via Substrate-Based Cyclization Pathways

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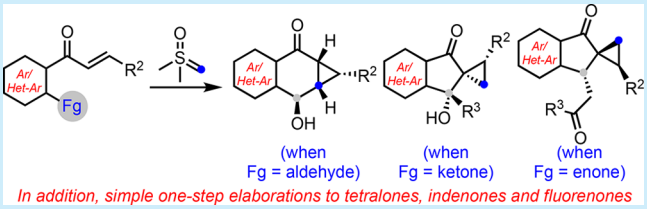
Supporting Information

ABSTRACT: A series of unexpected reactions triggered by the dimethyloxosulfonium methylide led to the discovery of unconventional approaches for the synthesis of cyclopropa-fused tetralones and indeno-spirocyclopropanes. These highly functionalized structures were further elaborated in one step to privileged scaffolds such as tetralones, indenones, and fluorenones. As a whole, the results presented herein establish new diversity-oriented folding pathways.

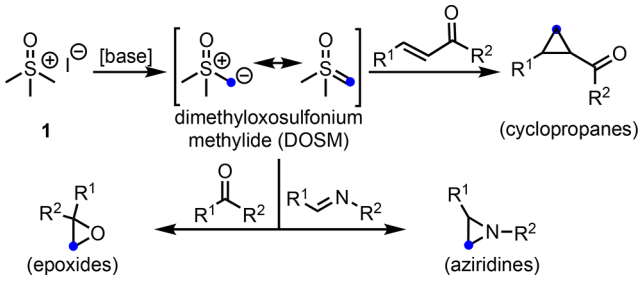


Small molecules with broader scaffold diversity demonstrated their significance in several drug discovery programs.[1] A synthetic challenge therefore is to develop contemporary and pertinent approaches to generate novel molecular architectures which can cover large areas of chemical space. Toward this end, the "folding strategy" in diversity-oriented synthesis (DOS) is an efficient method to assemble skeletally diverse compound libraries for chemical biology and medicinal chemistry.[2] According to Schreiber, the folding strategy is the conversion of a collection of substrates with preinstalled skeletal information into products having distinct molecular frameworks by employing a common set of reaction conditions.[3]

Among the privileged compound collections, cyclopropanes undoubtedly receive serious consideration.[4] The enhanced metabolic stability and conformational rigidity of cyclopropanes over unsubstituted methylene units offer distinct advantages to medicinal chemists. Further, cyclopropanes are structural units of several bioactive natural products and pharmaceutically important compounds including many marketed drugs.[5] In addition, due to their unique steric and electronic properties, the strained three-membered carbocycles can undergo a variety of ring transformations to generate new molecular entities.[6] These impressive features prompted chemists to develop several inspirational methods for the synthesis of cyclopropanes.[7]

In this context, it is worth mentioning about the versatile methylene group-transfer agent, dimethyloxosulfonium methylide (DOSM) [famously known as the Corey−Chaykovsky reagent], which can be conveniently prepared *in situ* from **1** (Scheme 1).[8] By far, the most common application of this reagent is toward the conversion of carbonyls, imines, and electron-deficient olefins to epoxides, aziridines, and cyclopropanes, respectively. In addition to the traditional synthetic transformations, a few unexpected reactions initiated by the DOSM were also documented.[9]

Scheme 1. Some of the Common Synthetic Applications of the Corey−Chaykovsky Reagent



Through the present work, we elucidate the development of a new substrate-based diversity-oriented folding strategy[10] leading to the synthesis of cyclopropa-fused tetralones (**3**) and indeno-spirocyclopropanes (**5** and **7**),[11] originating out of the reaction between DOSM and the enone-tethered substrates **2**, **4**, and **6**, respectively (Scheme 2). The cyclopropanoids were subsequently elaborated in one step to privileged scaffolds such as tetralones, indenones, and fluorenones. Remarkably, these transformations take place under mild and straightforward conditions and involve unusual rearrangements facilitated by multiple proton transfers.

As part of our ongoing research programs in catalysis,[12] it necessitated us to access the cyclopropyl keto-aldehyde **8a**, for which we opted to perform cyclopropanation of the enone-aldehyde **2a**[13] with **1** (Scheme 3a). However, an unexpected product **3a** was isolated in 94% yield, as a separable mixture of diastereomers. The structure of the major diastereomer and the relative stereochemistry were established from the X-ray diffraction analysis of **3a** (CCDC 1855673). Interestingly,

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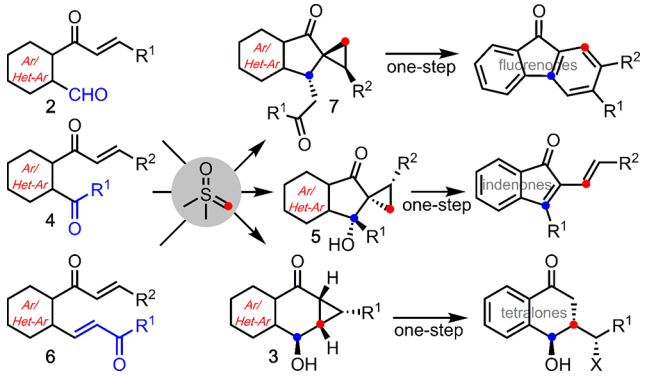
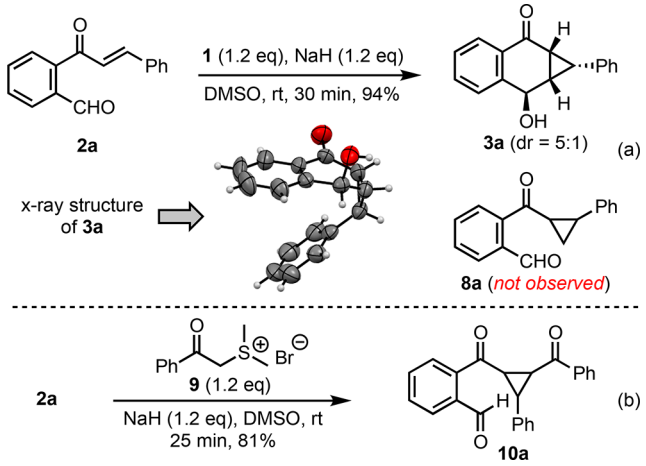
Scheme 2. Unexpected Transformations Triggered by the DOSM, and Elaboration of Cyclopropanoids: This Work



Scheme 3. An Unexpected Reaction of DOSM with the Enone-Aldehyde 2a

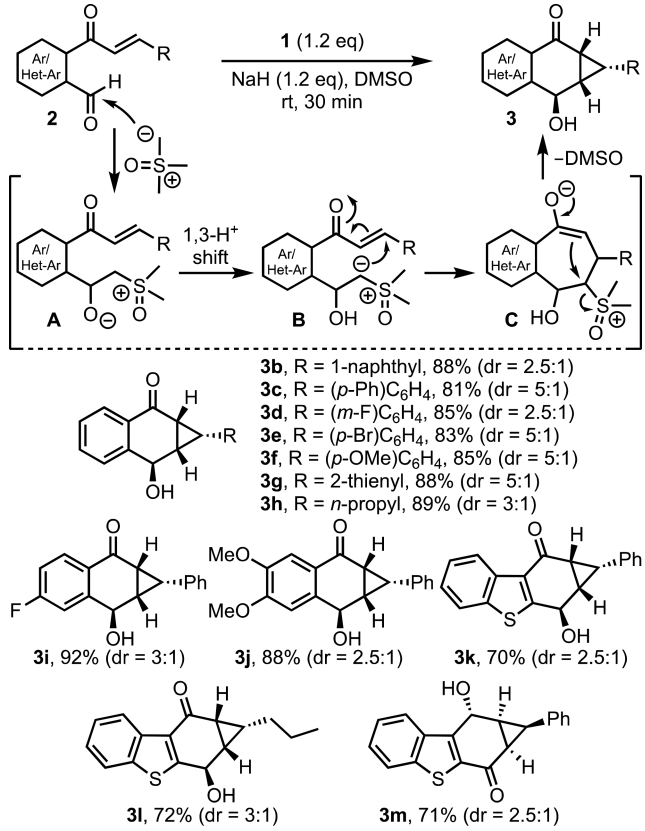


when **2a** was treated with a stabilized ylide such as **9**, the cyclopropane **10a** was realized (Scheme 3b).

Having realized the unprecedented nature of the formation of **3a** from **2a**, the reaction parameters were optimized.[14] Under the standardized conditions, the scope and generality of the reaction were investigated, and the representative results are summarized in Scheme 4. A variety of enone-aldehydes (**2**) appended to the aromatic backbone generated the respective cyclopropa-fused tetralones in good to excellent yields (**3b**–**3j**). Both electron-withdrawing and -donating substituents (including aliphatic groups) on the enone moiety as well as on the aromatic backbone were well-tolerated. This method can even be extended for the preparation of cyclopropa-fused dihydrodibenzothiophenones (**3k**–**3m**). As of the mechanism of the formation of **3**, an initial aldol-type reaction of the ylide (DOSM) with **2** generates the 1,4-zwitterionic species **A**. A subsequent 1,3-proton shift followed by an intramolecular Michael addition to the enone functionality provides the enolate **C**, which enables the formation of **3** via the nucleophilic displacement of the dimethylsulfoxonium group.

Interestingly, the reaction of enone-ketones **4** under the optimized conditions generated indeno-spirocyclopropanes **5** in an unexpected manner (Scheme 5).[15] The mechanism leading to the formation of **5** involves a sequential intermolecular Michael reaction of the ylide followed by an intramolecular aldol reaction of the intermittent enolate, thereby furnishing the 1,6-zwitterion **D**. An eventual 1,3-

Scheme 4. Scope for Cyclopropa-Fused Tetralones and Cyclopropa-Fused Dihydrodibenzothiophenones[a,b,c]



[a]See the Supporting Information for details. [b]Isolated yields. [c]Diastereomeric ratio (dr) is determined from the crude ^{1}H NMR.

proton shift generates the enolate **E**, which, by displacing the dimethylsulfoxonium group, delivers the product **5**. In this manner, a diverse set of indeno-spirocyclopropanes were synthesized (**5a**–**5j**). The structures including the relative stereochemistry of the major isomers were assigned based on the X-ray diffraction analysis of **5i** (CCDC 1855911). Some of the salient features of this method are (i) both alkyl and aryl ketones (R^1) could be employed as substrates with only marginal impact on the yield (**5a**–**5d** vs **5e**–**5j**), (ii) enones bearing alkyl, aryl, and heteroaryl groups at the β-position (R^2) fared equally well (**5d** vs **5b** vs **5c**), and (iii) even the presence of strong-electron donating groups on the aromatic backbone (**5h** and **5i**), which could be undesired for nucleophile-triggered reactions, displayed no noticeable impact; indeed, the reactions were complete within 30 min.

Encouraged by the results obtained for enone-aldehydes (**2**) and enone-ketones (**4**), the reaction of enone-eneone **6a** under the prototypical conditions was considered (Scheme 6). To our surprise, the indeno-spirocyclopropane **7a** was isolated in 90% yield.[15] The structure and the relative stereochemistry of the major isomer were assigned based on the X-ray structure obtained for **7e** (*vide supra*; CCDC 1855912). The formation of **7a** can be rationalized by considering a Michael/Michael sequence on **6a**, initiated by the DOSM.[16] The so formed zwitterion **F** then undergoes a 1,5-proton shift, and the resultant enolate **G** facilitates the formation of **7a** by eliminating DMSO.

Subsequently, few other enone–enones (**6**) were prepared and the corresponding indeno-spirocyclopropanes (**7b**–**7i**)

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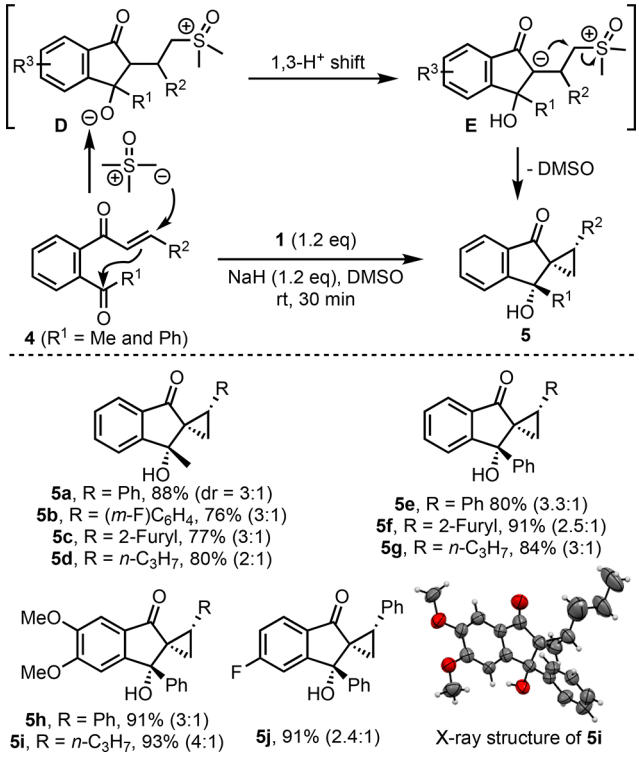
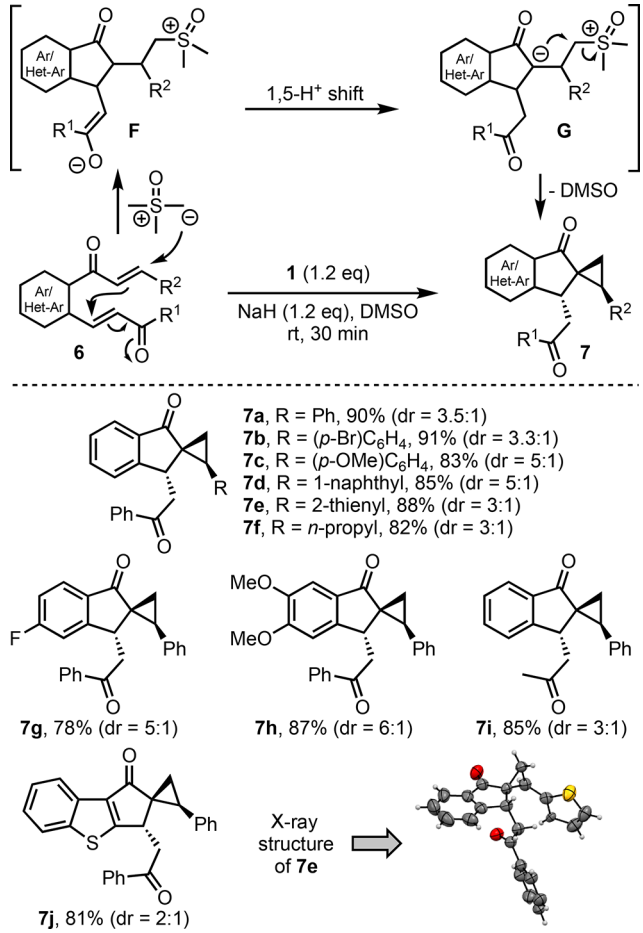
Scheme 5. Scope for Indeno Spirocyclopropanes from Enone-Ketones[a,b,c]



[a]See the Supporting Information for details. [b]Isolated yields. [c]Diastereomeric ratio (dr) is determined from the crude ^{1}H NMR.

Scheme 6. Scope for Indeno Spirocyclopropanes from Enone−Enones[a,b,c]



[a]See the Supporting Information for details. [b]Isolated yields. [c]Diastereomeric ratio (dr) is determined from the crude ^{1}H NMR.

and 2-spirocyclopropyl-cyclopenta[*b*]benzothiophene-1-ones (**7j**) were obtained in excellent yields in less than 30 min (Scheme 6). This method was realized to be less influenced by the steric or electronic effects of the substituents and provided products in consistently good yields. For example, (i) aryl or alkyl groups at R^1, (ii) aryl, heteroaryl, or alkyl groups at R^2, and (iii) electron-donating or -withdrawing groups on the aromatic backbone were well-tolerated.

Having successfully established a short and efficient synthesis of otherwise difficult-to-access cyclopropanoids such as **3**, **5**, and **7**,[11] we turned our attention to further demonstrate the generality and synthetic utility of the products obtained herein by considering a few elaborations.

With the presence of a cyclopropyl ketone moiety in **3**, ring opening of the cyclopropane was expected under metal/liq. NH_3 conditions (Scheme 7a). It is well-established that the cyclopropane bond that has maximum overlap with the π-orbital system of the carbonyl group preferentially cleaves.[17] Thus, when **3a** was treated under Li/liq.NH_3 conditions, the *trans*-1,2-disubstituted tetralone **11a** was isolated as hypothesized, the structure of which was confirmed by the X-ray diffraction analysis (CCDC 1855913). In a similar fashion, few other analogues (**11b−11e**) were quickly assembled in high yields.[18]

It was also anticipated that the reaction of **3** in the presence of an appropriate nucleophile under acidic conditions could possibly undergo ring opening of cyclopropane (Scheme 7b).[19] Indeed, we were delighted to find that the reaction of **3a** in the presence of a catalytic amount of PTSA in methanol generated the *trans*-1,2-disubstituted tetralone **12a** possessing three contiguous stereogenic centers. Employing the same reaction conditions, tetralones **12b−12e** were also synthesized in good yields (CCDC 1871641 for **12b**). These results indicate that the strategy could perhaps be applicable to other analogous nucleophile-mediated ring openings for the synthesis of a diverse range of tetralones.

Next, a synthetic elaboration of indeno-spirocyclopropanes **5** was considered (Scheme 8). It was hypothesized that the bisbenzylic *tert*-alcohol could be activated under acidic conditions and the cyclopropane moiety might anchimerically assist the developing cationic center, thereby a skeletally reorganized product could be observed. Accordingly, when **5a** was treated with a catalytic amount of PTSA at an elevated temperature, the 2-styrylindenone **13a** was realized. The mechanistic rationale for the product formation is presented in **H**. Under the optimized conditions, two more indenone derivatives (**13b** and **13c**) were prepared. This method thus provides an efficient alternative to access 2-styryl-3-arylindenones.[20]

As part of our efforts to demonstrate the synthetic utility of indeno-spirocyclopropanes **7** obtained herein, we made a remarkable observation (Scheme 9). The reaction of **7a** in the presence of a catalytic amount of PTSA with azeotropic removal of water furnished the 2,3-diarylfluorenone **14a** in a serendipitous manner. The structure was confirmed in analogy with the single crystal X-ray diffraction analysis obtained for

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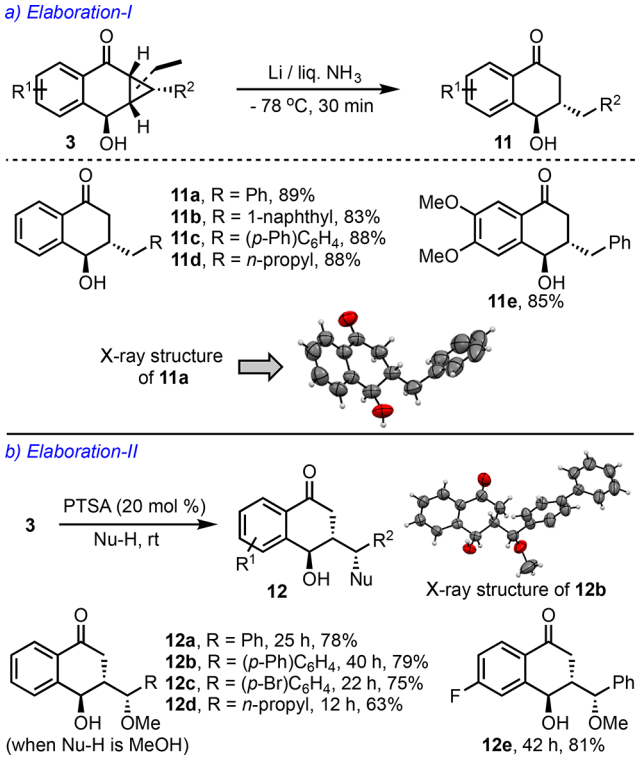
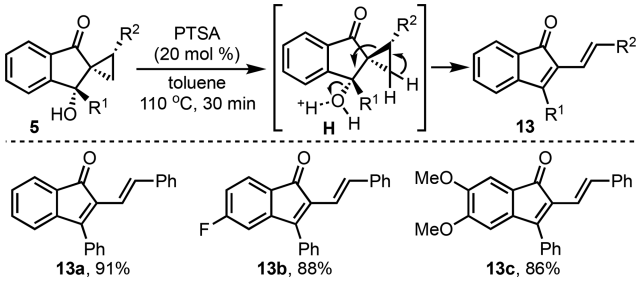
Scheme 7. Elaboration of Cyclopropa-Fused Tetralones 3 to 1,2-Disubstituted Tetralones 11[a,b]



[a]See the Supporting Information for general procedures. [b]Isolated yields.

Scheme 8. Elaboration of Indeno-Spirocyclopropanes 5 to 2-Styrylindenones 13[a,b]



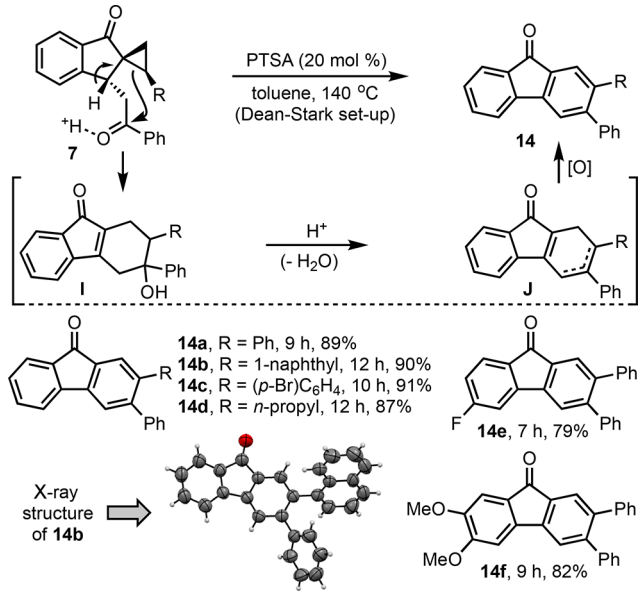
[a]See the Supporting Information for the general procedure. [b]Isolated yields.

14b (CCDC 1855918). Having realized the significance of the observation, a few more fluorenone analogues (**14b**−**14f**) were synthesized. The occurrence of several bioactive natural products and the relevance of fluorenones in materials chemistry renders this an attractive strategy.[12c,21]

As indicated on the structure **7** (Scheme 9), the reaction is believed to involve a sequential proton elimination, cyclopropane ring opening, and nucleophilic attack onto ketone to generate the tetrahydrofluorenone **I**. The acid further promotes water elimination to form the dihydrofluorenone **J**, which upon oxidative aromatization produces **14**.

In conclusion, we presented a series of unprecedented diastereoselective transformations triggered by the DOSM for the synthesis of complex and otherwise difficult-to-access cyclopropanoids. Further, new one-step synthetic elaborations were established to access privileged structures such as

Scheme 9. An Unprecedented Conversion of Indeno-Spirocyclopropanes 7 to Fluorenones 14[a,b]



[a]See the Supporting Information for the general procedure. [b]Isolated yields.

tetralones, indenones, and fluorenones incorporated with unusual substitution patterns. The methods described herein are operationally straightforward and mechanistically intriguing and symbolize novel substrate-based diversity-oriented strategies. We are in the process of applying these methods for the synthesis of bioactive natural products. Efforts to extend the concepts to new substrate classes are also in progress, and the details will be communicated in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03537.

Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR) (PDF)

Accession Codes

CCDC 1855673, 1855911−1855913, 1855918, and 1871641 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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(11) The scaffolds **3**, **5**, and **7** are without precedence and can present themselves as new pharmacophores.

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(14) See the Supporting Information for details.

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