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Ring Selective Generation of Isobenzofuran for Divergent Access to Polycyclic Aromatic Compounds

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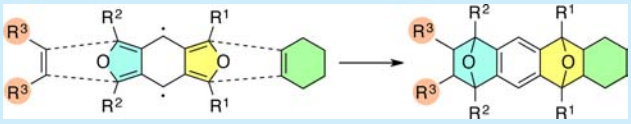
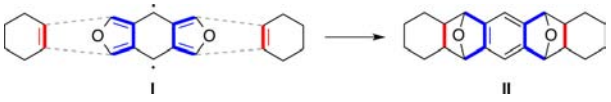
Supporting Information

ABSTRACT: Ring selective generation of isobenzofuran, a formal equivalent to bis-isobenzofuran, was developed. Importantly, selective introduction of functionalities and/or fused rings in the isobenzofuran core by iterative cycloadditions can achieve the divergent construction of polycyclic compounds. This selective approach enables us to prepare a regioisomeric pair of pentacenes.



Construction of polycyclic structures with diverse functionalities is one of the important subjects often faced in the natural and unnatural product syntheses.[1] In this context, we were interested in the dual annulation and/or functionalization onto a reactive core ring[2] since it would allow for the rapid assembly of polycycles. In particular, we were intrigued by the use of bis-isobenzofuran **I**,[3−5] which could serve as a reactive platform for linearly fused polycyclic compounds **II** (Scheme 1).

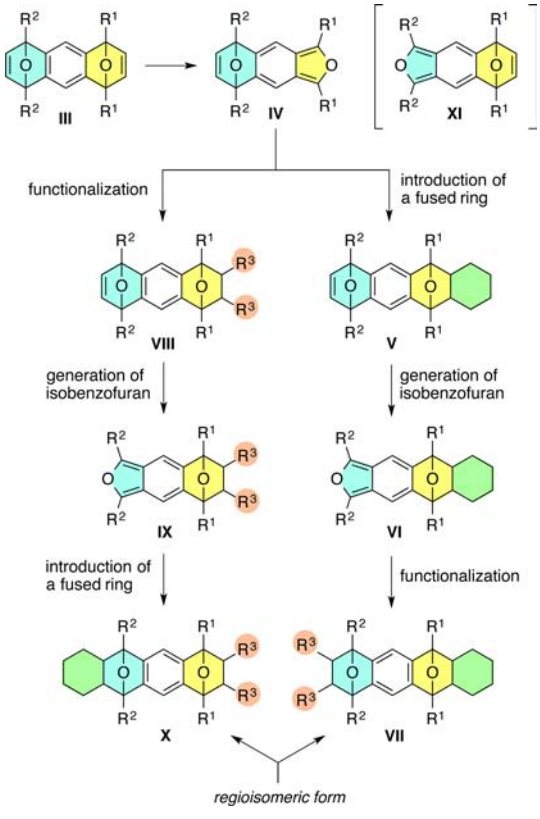
Scheme 1. Dual Annulation of Bis-isobenzofuran



In this study, we focus on the formal use of bis-isobenzofuran **I** by sequential generation of two isobenzofurans from diepoxyanthracene **III** (Scheme 2). Selective introduction of functionalities and/or fused rings in **III** by iterative cycloadditions can achieve the divergent construction of polycyclic compounds. The fundamental issue that should be established in this process is the "ring selectivity", that is, the relative susceptibilities of the two oxa-bicyclo rings in **III** toward the generation of isobenzofuran. If the more reactive oxa-bicyclo ring (yellow) in **III** would undergo selective Diels−Alder or retro-Diels−Alder reaction with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (vide infra), the isobenzofuran **IV**, selectively generated, can cyclize with a dienophile to give the [4 + 2] cycloadduct **V**. Subsequent second generation of isobenzofuran **VI** at the remaining oxa-bicyclo ring (blue) in **V** and trapping with a dienophile selectively affords the bis-cycloadduct **VII**. By switching the order of the dienophiles in each cycloaddition, the isomer **X** would also be accessible.

Now, we disclose the selective access to polycyclic aromatic compounds by using the *ring selective* generation of isobenzofurans. This divergent approach enables us to prepare a regioisomeric pair of substituted pentacenes, one of which

Scheme 2. Ring Selective Generation and Trapping of Isobenzofuran



turned out to have higher solubility and stability, which is described in this communication.

First, three diepoxyanthracenes **1a**−**1c**[6] with different substitution patterns on the epoxy rings were examined for

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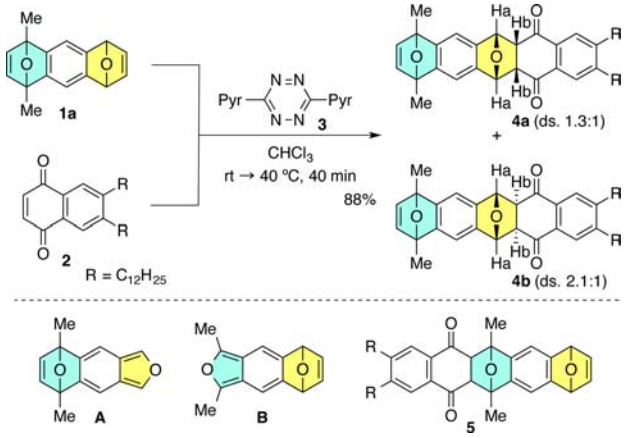
exploiting the ring selective generation of isobenzofurans. Upon heating of diepoxyanthracene **1a** with tetrazine **3** in the presence of naphthoquinone **2**[7] ($CHCl_3$, 40 °C, 40 min), the less substituted oxa-bicyclo ring (yellow ring) underwent the exclusive generation of isobenzofuran **A** and subsequent cycloaddition of **A** with **2** to give the monocycloadduct **4** in high yield with perfect ring selectivity (Scheme 3). In this case,

Scheme 3. Ring Selective Generation of Isobenzofuran from 1a



the cycloadduct **5**, based on the generation of isobenzofuran **B**, was not produced at all.[8] In addition to the ring selectivity, this cycloaddition was stereoselective to give *endo* isomer **4a** as a major product (**4a**/**4b** = 80:20). The structure of **4a** was determined by ^{1}H NMR analysis, where an AA′XX′ pattern of the aliphatic methine protons (two sets of doublet-of-doublet signals for H_a and H_b, J = 1.7, 3.5 Hz), characteristic as an *endo* isomer, was observed. In the case of cycloadduct **4b**, HMBC correlations revealed the connection between the naphthoquinone and the right epoxy ring in **1a**, differentiating **4b** from regioisomer **5**. Moreover, the absence of vicinal coupling between H_a and H_b in **4b** indicated the dihedral angle approached 90°, thereby determining the structure as an *exo* isomer.

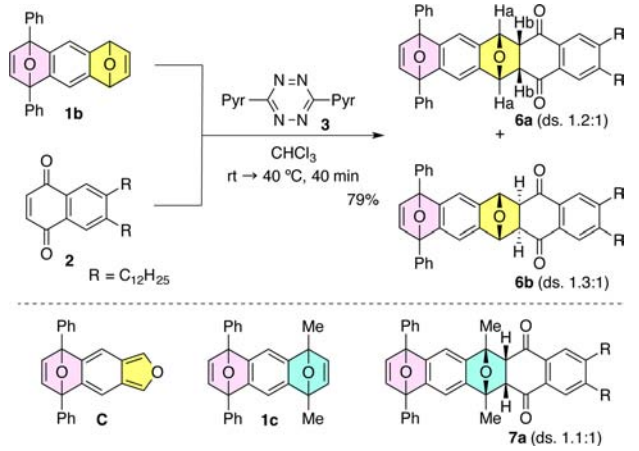
This observed ring selectivity in the generation of isobenzofuran **A** from the yellow ring over that of the blue ring can be explained by the facile nature of the interaction between the double bond in the less substituted oxa-bicyclo ring and the diene in tetrazine **3**.

Similarly, diepoxyanthracene **1b**, possessing the two phenyl groups in the left ring (pink ring), reacted with tetrazine **3** at the less substituted right ring to generate isobenzofuran **C**, which was intercepted with **2** to give cycloadducts **6a** and **6b** (**6a**/**6b** = 64:36), respectively (Scheme 4). Again, the structure of **6a** was confirmed by ^{1}H NMR spectroscopy, showing vicinal coupling of the two aliphatic protons, H_a and H_b. The *exo* isomer **6b** was determined after conversion to the pentacenequinone **11** (vide infra).

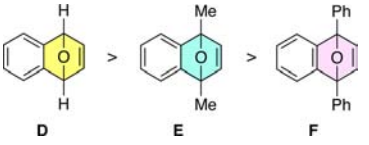
Moreover, ring selectivity was observed for the reaction of tetrasubstituted derivative **1c**, having methyl and phenyl groups at the two epoxy rings, which led to the selective formation of the *endo* cycloadduct **7** in moderate yield (43%).[9]

These results indicate the order of the reactivity of the epoxy ring: **D** > **E** > **F**, which is based on the steric effect of the substituents in each epoxy ring (Scheme 5).

Scheme 4. Ring Selective Generation of Isobenzofurans from 1b and 1c

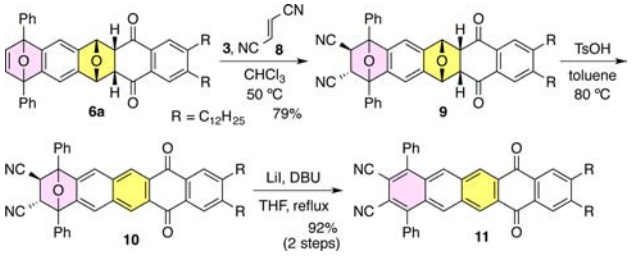


Scheme 5. Order of the Reactivity



The monocycloadducts, thus selectively obtained, were further functionalized by the second [4 + 2] cycloaddition (Scheme 6). For example, treatment of *endo* adduct **6a** with

Scheme 6. Second [4 + 2] Cycloaddition



tetrazine **3** in the presence of fumaronitrile (**8**) ($CHCl_3$, 50 °C) gave the [4 + 2] cycloadduct **9** as a mixture of diastereomers, which were smoothly converted to pentacenequinone **11** through the two-step sequence of aromatization. Upon treatment of cycloadduct **9** with TsOH (toluene, 80 °C), the dehydration occurred smoothly at the central epoxy ring to give the quinone **10**. Subsequent base-induced aromatization (LiI, DBU, THF, reflux)[10] at the remaining epoxy ring cleanly produced the pentacenequinone **11** in 92% yield.[11] Similar functionalization−aromatization protocol of the cycloadduct **6b** also gave **11** in high yield. At this stage, the structure of **6b** could be unambiguously determined as an *exo* isomer.

It is important to note that isomeric pentacenequinone **15** was selectively synthesized by switching the order of the addition of trapping agents in each cycloaddition (Scheme 7). The first [4 + 2] cycloaddition of isobenzofuran **C** with **8** at the less substituted yellow ring gave functionalized epoxyanthracene **13** after aromatization of the right epoxy ring in **12** under the basic conditions. Since the attempt at aromatization of the bis-cycloadduct **16** obtained by the dual cycloaddition of **1b** turned out to be unsuccessful, the monocycloadduct **12** was

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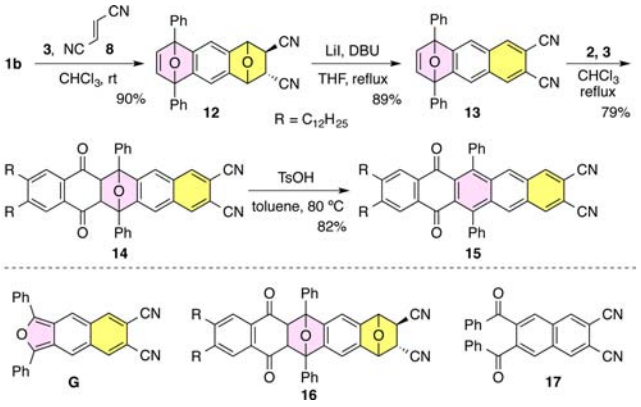
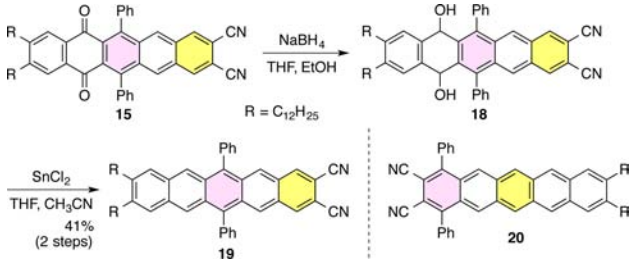
Scheme 7. Second [4 + 2] Cycloaddition



aromatized before the second [4 + 2] cycloaddition. Epoxyanthracene **13**, thus obtained, was treated with tetrazine **3** to generate isonaphthofuran **G**,[12] a structurally attractive π-extended isoheterol, which was cleanly trapped with naphthoquinone **2** to give pentacenequinone **15** after acid treatment. For the conversion of **14** to **15**, prolonged reaction time was required to complete the aromatizaion because the retro-Diels–Alder reaction occurred upon heating of **14**.[13] In this case, insufficient reaction time caused the formation of the ring-cleaved oxidized diketone **17**.

Lastly, an important point to emphasize is that, as one of the synthetic applications, pentacenequinone **15** was converted to the pentacene **19** through the reduction of two carbonyl groups by treatment with $NaBH_4$ followed by Sn^{II}-mediated reductive aromatization (Scheme 8). Attaching the two long alkyl chains

Scheme 8. Selective Synthesis of Substituted Pentacenes



and the two cyano groups at the 2,3 and 9,10 positions sufficiently improved the solubility and the stability of the product in comparison with nonsubstituted pentacene.[14] Indeed, purification of **19** by preparative thin layer chromatography with a stringent exclusion of air and light gave the pure product, whose half-life turned out to be around 288 min.[15,16] In sharp contrast, pentacene **20**, an isomer of **19**, similarly synthesized by this two-step sequence, was fairly unstable and immediately underwent photo-oxidation.[17,18]

In summary, ring selective generation and iterative cycloaddition of isobenzofuran allowed us to rapidly construct functionalized polycyclic compounds, which were amenable to selective transformation en route to substituted pentacene derivatives. Further synthetic applications are under active investigation in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01364.

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Notes

The authors declare no competing financial interest.

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(6) Diepoxyanthracenes **1a–1d** were prepared by the iterative [4 + 2] cycloadditions of benzyne and two kinds of furans. For details, see Supporting Information. See also: (a) Hart, H.; Ok, D. *J. Org. Chem.* **1986**, *51*, 979. (b) Hart, H.; Lai, C.-Y.; Nwokogu, G.; Shamouilian, S.; Teuerstein, A.; Zlotogorski, C. *J. Am. Chem. Soc.* **1980**, *102*, 6649.

(7) For preparation, see Supporting Information.

(8) Similar reaction of nonsubstituted diepoxyanthracene gave a sizable amount of the dual cycloadduct (20%) in addition to the desired monocycloadduct (47%).

(9) The structure of the *endo* cycloadduct **7a** was determined by NOE. The chemical shifts of aromatic protons of **7a** are similar to those of the *endo* isomer **6a**.

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