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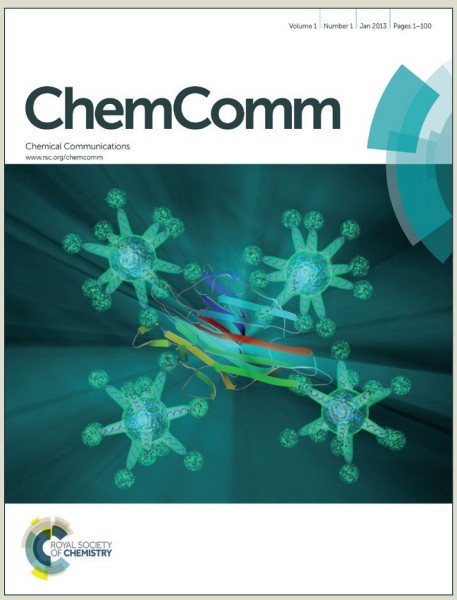

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New Synthetic Route to Substituted Tetracenes and Pentacenes via Stereoselective [4+2] Cycloadditions of 1,4-Dihydro-1,4-epoxynaphthalene and Isobenzofuran

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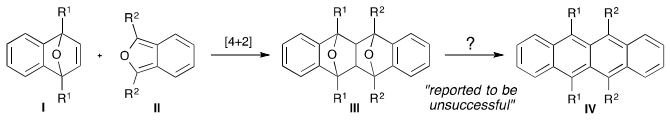
Shohei Eda, Fumiaki Eguchi, Hiroshi Haneda, and Toshiyuki Hamura*

Stereoselective [4+2] cycloadditions of 1,4-dihydro-1,4-epoxynaphthalene and isobenzofuran were described. Among several possibilities, *syn-exo* and/or *anti-endo* isomers were selectively produced depending on the substitution pattern of the reactants. Importantly, the *syn-exo* isomer underwent acid promoted aromatization, affording the corresponding tetracene. These findings enabled us to prepare a substituted pentacene with electron withdrawing groups.

Due to the inherent strain, 1,4-epoxynaphthalenes **I** show potentially interesting reactivities in organic syntheses.[1] The [4+2] cycloaddition of **I** with dienes is one of their representative reactions for construction of polycyclic compounds.[2] Among various dienes, isobenzofuran **II**, a 10π electron system, is an attractive reactive partner of **I**, since it can readily cyclize with **I** to give diepoxytetracene **III**,[3] which can be viewed as an efficient precursor to substituted tetracenes (Scheme 1). However, conversions of **III** to tetracenes **IV** was reported to be unsuccessful, resulting in the formation of ring cleaved products.[3b,3d,4] These unfortunate results discouraged the syntheses of various functionalized derivatives of **III**.



Scheme 1 The [4+2] cycloaddition of 1,4-epoxynaphthalene **I** and isobenzofuran **II**.

In this context, we recently exploited a one-pot synthetic method of 1,3-diarylisobenzofurans[5,6] by sequential reaction of methyl 2-formylbenzoate with two identical or different aryl metal species.[7] In addition, successive [4+2] cycloadditions of benzyne and dibromoisobenzofuran were developed, allowing a rapid construction of polycyclic structures.[8] These findings can offer various opportunities to open up a new way to polycyclic aromatic compounds.

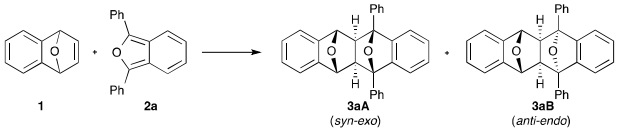
In this study, we re-examined the [4+2] cycloaddition of 1,4-epoxynaphthalene and isobenzofuran to elucidate the stereochemical course of the reaction, and more importantly, to develop the synthetic utility of the cycloadducts (*vide supra*). The important points that were uncovered during the course of the investigation are that 1) *syn-exo* and/or *anti-endo* cycloadducts are selectively produced depending on the substitution patterns of the 1,4-epoxynaphthalene and isobenzofuran, and 2) *syn-exo* isomer can be cleanly converted to the corresponding tetracene under the acidic conditions. These findings enable us to prepare a substituted pentacene with electron-withdrawing groups, which is described in this communication.

Table 1 shows the initial model reaction. Upon heating of epoxynaphthalene **1** and diphenylisobezofuran (**2**) in toluene at 110 °C, the [4+2] cycloaddition occurred smoothly to give the cycloadduct **3** in 96% yield (entry 1). In this case, *syn-exo* isomer **3aA** was selectively obtained as a major product, accompanied by a small amount of the *anti-endo* isomer **3aB**. Same reaction performed at lower reaction temperature slightly improved the *syn-exo* selectivity, although the prolonged reaction time was required to consume the starting material (entries 2 and 3). Use of another solvents showed little effect on the stereoselectivity (entries 4–8).

These observed stereoselectivity is due to the concave topology of the epoxynaphthalene **1**, which would force the isobenzofuran to approach along the convex side of **1**. The stereochemistry of each cycloadduct was determined by X-ray analysis (Figure 1). These cycloadducts were thermally stable

and retro Diels–Alder reaction did not occur at all under the reaction conditions (toluene, 110 °C).

Table 1 Initial model study



Entry[a]	Solvent	Temp.	Time	Yield (%)	**3aA** : **3aB**
1	toluene	110	0.5 h	96	75 : 25
2	toluene	25	8 h	86	79 : 21
3	toluene	0	8 d	83	81 : 19
4	benzene	80	3 h	95	77 : 23
5	hexane	69	3.2 h	93	76 : 24
6	CH_3CN	82	3.5 h	94	67 : 23
7	EtOH	78	2 h	96	76 : 24
8	THF	65	3.5 h	95	77 : 23

[a]1.2 equiv of **1** and 1.0 equiv of **2a**. [b]*Syn* and *anti* represent the relative relationship between the two oxygen bridges.

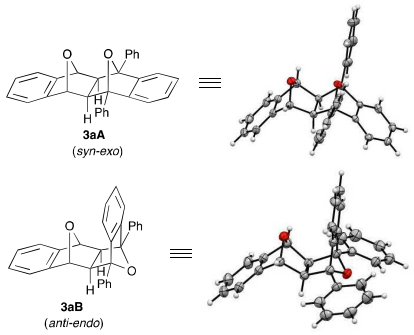
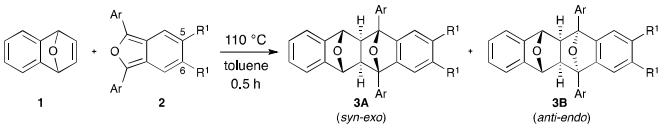


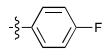
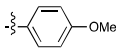
Figure 1 X-ray structures of cycloadducts **3aA** and **3aB**. The thermal ellipsoids are scaled at a 50% probability level.

This [4+2] cycloaddition could be applicable to various substrate combinations. Upon heating of epoxynaphthalene **1** with diarylisobenzofurans **2b** and **2c**,[9] having a fluoro or a methoxy group on the aromatic ring at *para* position (toluene, 110 °C, 0.5 h), the [4+2] cycloadditions occurred stereoselectively to give cycloadducts **3bA** and **3cA** as major products, respectively (entries 1 and 2). Isobenzofuran **2d**,[9] having a sterically congested *o*-tolyl group, cyclized slowly with **1** (110 °C, 30 h) to give cycloadduct **3d** in 82% yield (entry 3).

Furthermore, substituents at C_5 and C_6 position on the isobenzofuran slightly influenced the stereoselectivity. The cycloadditions of isobenzofurans **2f** and **2g**, having a chloro or methoxy group, with **1** occurred smoothly to give the cycloadducts **3f** and **3g** with moderate stereoselectivities (entries 5 and 6). On the other hands, the corresponding reaction of fluoride **2e** resulted in the poor selectivity (entry 4).

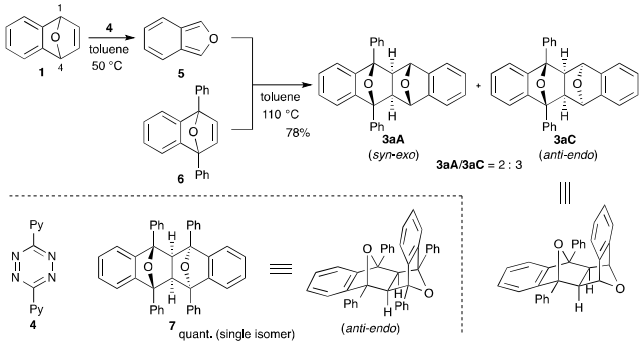
Table 2 [4+2] cycloaddition of epoxynaphthalene and isobenzofuran



Entry	Furan	Ar	R^1	Product	Yield/%
1	**2b**		H	**3b**	94 (75 : 25)[b]
2	**2c**		H	**3c**	95 (76 : 24)[b]
3[a]	**2d**		H	**3d**	82 (80 : 20)[b]
4	**2e**		F	**3e**	87 (57 : 43)[b]
5	**2f**		Cl	**3f**	97 (68 : 32)[b]
6	**2g**		OMe	**3g**	98 (76 : 24)[b]

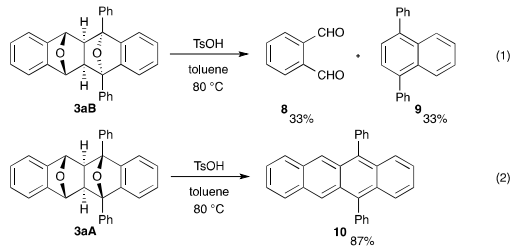
[a]The reaction was performed for 30 h. [b]*syn-exo* : *anti-endo*.

Further investigation revealed that introduction of the substituent at C_1 and C_4 position in epoxynaphthalene switched the stereoselectivity (Scheme 2). Upon treatment of epoxynaphthalene **1** with tetrazine **4** in toluene at 50 °C, isobenzofuran **5** was generated,[6c] which was intercepted by 1,4-diphenylepoxynaphthalene **6** to give *anti-endo* isomer **3aC** as a major stereoisomer (**3aA**/**3aC** = 2 : 3). Remarkably, heating of 1,4-diphenylepoxynaphthalene **6** and diphenylisobenzofuran **2a** in toluene at 110 °C gave *anti-endo* isomer **7** as an exclusive product, whose stereochemistry was unequivocally confirmed by X-ray analysis.[10,11]



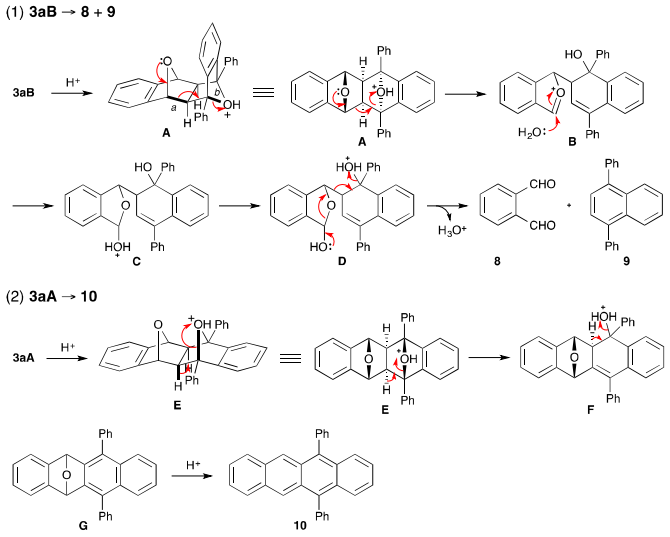
Scheme 2 Stereoselective [4+2] cycloaddition of 1,4-disubstituted epoxynaphthalene.

We next focused our attention to the conversion of [4+2] cycloadducts to the corresponding tetracenes (Scheme 3). All attempts on acid promoted aromatization of *anti-endo* isomers **3B** to the corresponding tetracenes have failed. In these cases, however, ring cleavage occurred predominantly. For example, treatment of **3aB** with TsOH (toluene, 80 °C, 1.5 h) gave the phthalaldehyde **8** and diphenylnaphthalene **9** in 33% and 33% yields, respectively (Eq. 1). In sharp contrast, we were pleased to find that the *syn-exo* isomer **3aA** could be cleanly aromatized under the same reaction conditions, affording substituted tetracene **10**[12] in 87% yield (Eq. 2).



Scheme 3 Attempts on acid promoted aromatization of the [4+2] cycloadducts.

A possible reaction course of the [4+2] cycloadducts **3aA** and **3aB** to the ring cleaved or the aromatized products **8**–**10** is shown in Scheme 4.

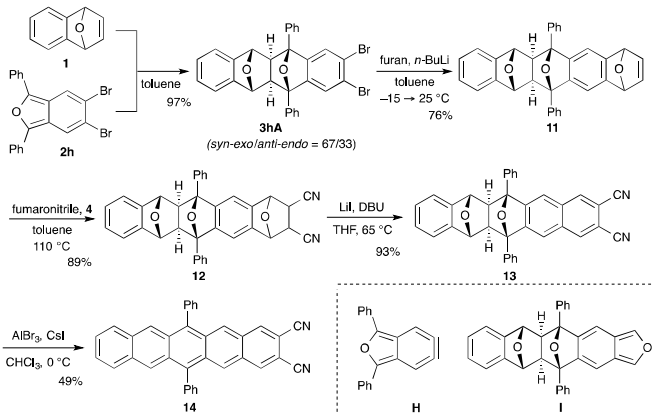


Scheme 4 A possible reaction course to the ring cleaved or the aromatized products.

The formation of the ring cleaved products **8** and **9** can be explained by Grob type fragmentation,[13] since the *anti* orientation of the two epoxides bridges in the protonated intermediate **A** would facilitate the cleavage of the carbon–carbon bond *a* and the carbon–oxygen bond *b* with an *anti*-periplanar relationship.[3d] The intermediate **B**, thus formed, underwent the nucleophilic addition of water, and subsequent proton transfer and fragmentation of the resulting lactol **D** gave the phthalaldehyde (**8**) and 1,4-diphenylnaphthalene (**9**).

On the other hand, the conversion of **3aA** to the tetracene **10** is ascribed to the *anti* orientation of the two protons on the bridge-head carbon with respect to the two epoxide bridges in **3aA**, which would facilitate the dehydration of the protonated intermediate **E**, affording the epoxytetracene **G**. Second acid induced aromatization of the epoxytetracene **G** led to the clean formation of the tetracene **10**.[14]

Lastly, an important point to emphasize is that this synthetic method could be applied to the synthesis of a substituted pentacene (Scheme 5).[15] Starting from dibromoisobenzofuran **2h**, served as a synthetic equivalent of didehydroisobenzofuran **H**,[8] the precursor of pentacene was rapidly constructed by successive [4+2] cycloadditions. Thus, the first [4+2] cycloaddition of epoxynaphthalene **1** and isobenzofuran **2h** smoothly gave cycloadduct **3hA** in high yield. In this case, *syn-exo* isomer was again a major stereoisomer. The second [4+2] cycloaddition of benzyne, generated by treatment of *syn-exo* isomer **3hA** with *n*-BuLi, and furan afforded the [4+2] cycloadduct **11**. Subsequent cyanation through the generation of isobenzofuran **I** by treatment of **11** with tetrazine **4** and its trapping with fumaronitrile gave the product **12** in 89% yield. The cycloadduct **12**, thus obtained, was converted to the corresponding tetraepoxypentacene **13** under the basic conditions (LiI, DBU, THF, 65 °C). Final acid-promoted aromatization of **13** under the above mentioned conditions, however, was not satisfied, affording the pentacene **14** only in 12% yield. Re-investigation of the aromatized conditions revealed that Lewis-acid promoted conditions ($AlBr_3$, CsI, $CHCl_3$, 0 °C)[8] improved the yield of the desired product **14**.[16,17]



Scheme 5 Synthesis of a substituted pentacene.

In summary, stereoselevtive [4+2] cycloaddition of epoxynaphthalene and isobenzofuran allowed rapid construction of highly functionalized diepoxytetracenes, which were amenable to selective transformation en route to substituted tetracene and pentacene derivatives. Further

synthetic applications are under active investigation in our laboratories.

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Notes and references

Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan, Tel and Fax: (+81) 79-565-7591, E-mail: thamura@kwansei.ac.jp

†Electronic Supplementary Information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/c000000x/

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10 For details, see supporting information.

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17 The same reaction of **3aA** by treatment with $AlBr_3$ and CsI gave the tetracene **10** in 51% yield.

