Organic LETTERS

Letter

pubs.acs.org/OrgLett

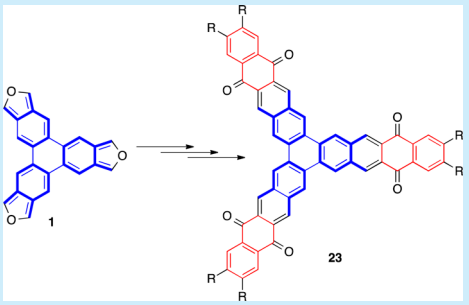
Star-Shaped Polycyclic Aromatic Ketones via 3-Fold Cycloadditions of Isobenzofuran Trimer Equivalent

Hitoshi Tozawa, Takamasa Kakuda, Kazuhiko Adachi, and Toshiyuki Hamura*

Department of Applied Chemistry for Environment, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan

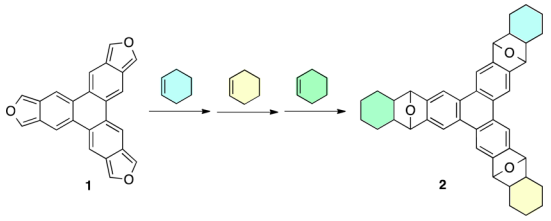
Supporting Information

ABSTRACT: Three-directional annulations of isobenzofuran trimer equivalent are developed. Importantly, the successive cycloadditions could be controlled under suitable conditions, selectively affording the dual or triple cycloadduct, which leads to the alternative preparation of the symmetrical and unsymmetrical star-shaped polycyclic aromatic ketones. ^{1}H NMR analysis of the star-shaped aromatic ketone indicated the $\pi-\pi$ interactions through the aggregation in solution.



Multidirectional annulations of two or more rings onto a reactive core ring is one of the most efficient ways to highly condensed aromatic compounds.[1,2] In this context, we became interested in the synthetic use of isobenzofuran trimer **1** or its equivalent as a reactive platform[3,4] since, through its successive cycloadditions, it would allow for rapid access to *star-shaped* polycyclic compounds[5] with potentially attractive properties derived from the unique molecular structure (Scheme 1).

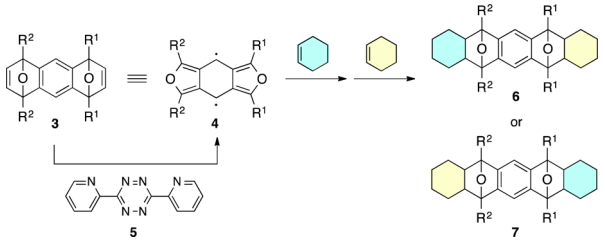
Scheme 1. Three-Fold Annulations of Isobenzofuran Trimer



In relation to this synthetic strategy, we previously reported an efficient protocol of the ring-selective generation of isobenzofuran for selective construction of *linearly* fused polycycles (Scheme 2).[2] In this process, diepoxyanthracene **3**, the synthetic equivalent to a bisisobenzofuran **4**, was treated with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (**5**) to successively generate the two isobenzofuran species in a ring-selective manner, allowing the alternative synthesis of polyacene derivatives **6** and/or **7** through the iterative [4 + 2] cycloadditions.

Herein, we disclose 3-fold annulations of isobenzofurans for preparation of *star-shaped* polycyclic aromatic compounds with six electron-withdrawing carbonyl groups onto the aromatic core. The key of this approach is the design and the synthesis of

Scheme 2. Dual Annulation of Bisisobenzofuran



the synthetic equivalent to isobenzofuran trimer **1**. Along these lines, trisepoxytrinaphthylene **8**, prepared by [4 + 2] cycloaddition and trimerization of two aryne species **9** and **11**, turned out to serve as a synthetic equivalent to **1** by thermally induced elimination of carbon monoxide and subsequent retro Diels–Alder reaction (eq 1 in Scheme 3).[6] It is important to note that protection of the double bond in epoxynaphthalene is essential for the aryne cyclotrimerization (vide infra), and the trimer **8** undergoes retro Diels–Alder reaction to generate the three isobenzofurans, which are successively trapped with dienophiles, producing the 3-fold cycloadducts. Moreover, the successive cycloadditions can be controlled under suitable conditions, selectively affording the dual or triple cycloadduct, which leads to the selective preparation of the symmetrical and unsymmetrical star-shaped polycyclic aromatic ketones.

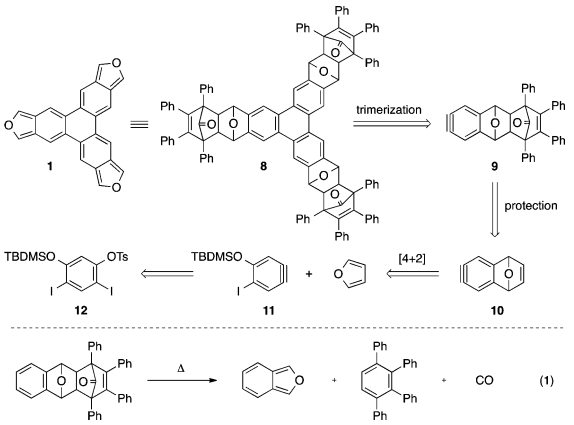
Starting from diiodide **12**,[7] corresponding to a bisbenzyne equivalent,[8] the trimer **8** was efficiently prepared (Scheme 4). Upon heating of epoxynaphthalene **13**[9] with tetraphenylcyclopentadienone, Diels–Alder reaction occurred stereoselectively to give the silyl triflate **14** as a single isomer. The

Received: June 24, 2017

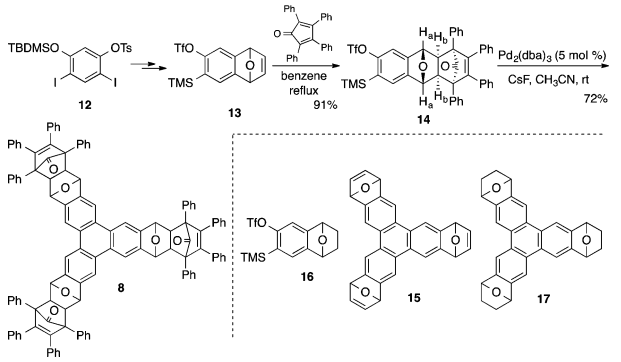
ACS Publications © XXXX American Chemical Society

DOI: 10.1021/acs.orglett.7b01932
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Strategy for Preparation of Isobenzofuran Trimer Equivalent



Scheme 4. Preparation of Isobenzofuran Trimer Equivalent

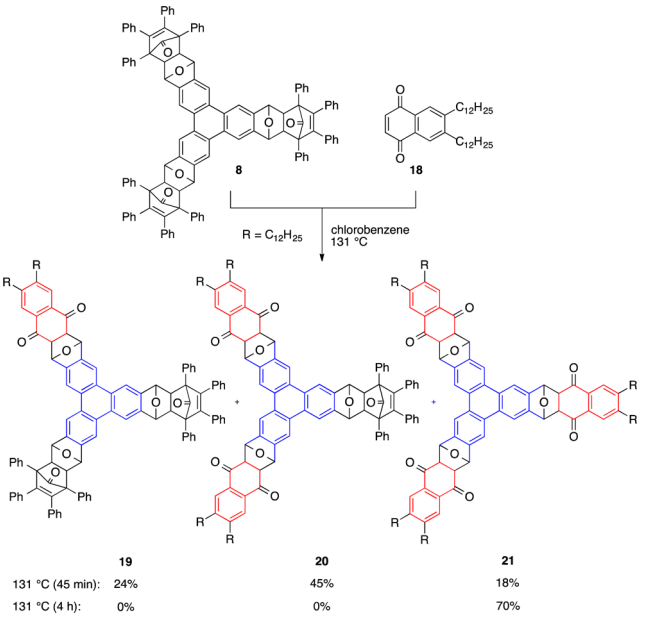


stereochemistry of **14** was determined by X-ray analysis,[10] where the two protons (H_b) on the bridge-head carbon and the carbonyl group were antioriented with respect to the epoxy bridge. This is due to the concave topology of the epoxynaphthalene **13**, which forces the tetraphenylcyclopentadienone to approach along the convex side of **13**.[11] ^{1}H NMR analysis of **14** showed the absence of vicinal coupling between H_a and H_b, indicating the dihedral angle approached 90°, which was also confirmed by the X-ray structure.

The silyl triflate **14**, thus obtained, was subjected to Pd-catalyzed aryne cyclotrimerization by treatment with CsF,[12] cleanly affording the trimer **8**, which consisted of a mixture of two diastereomers (ds 6:1) with respect to the three epoxy rings. The important point in this reaction is that tetraphenylcyclopentadienone played a key role not only as a protecting group of the double bond in **13** but also as an initiator for the generation of isobenzofuran (vide infra). Indeed, the corresponding reaction of nonprotected substrate **13** gave no trimer **15**, which would be also a suitable precursor of **1** by tetrazine methodology (Scheme 2).[3a] This is due to the existence of the double bond within the rigid oxabicyclic structure in **13**, which may react with Pd catalyst under the reaction conditions to give a complex mixture of products.[13] In this case, however, the cyclotrimerization proceeded cleanly with the saturated aryne precursor **16** under the same reaction conditions, affording triepoxytrinaphthylene **17** in 64% yield.

Scheme 5 shows the successive generation of isobenzofuran and its trapping with dienophile. Upon heating of **8** in the presence of naphthoquinone **18** (131 °C, 4 h), iterative [4 + 2] cycloadditions occurred cleanly to give the 3-fold cycloadduct

Scheme 5. Multiple Cycloadditions of Isobenzofuran Trimer Equivalent



21 in 70% yield as a mixture of stereoisomers. TLC analysis showed that the initially formed monocycloadduct **19** and dicycloadduct **20** were gradually converted to the tricycloadduct **21**. Indeed, the same reaction in a shorter reaction time (131 °C, 45 min) selectively gave the dicycloadduct **20** in 45% yield, accompanied by the mono- and tricycloadducts **19** (24%) and **21** (18%), respectively. As for the solubility of the products, introduction of the long alkyl chains into naphthoquinone is essential since the similar reaction with parent naphthoquinone produced extremely insoluble products in all common organic solvents, which precluded their characterization.

The stereochemistry of the dicycloadduct **20** was determined by NMR analysis, where two sets of the coupled aliphatic methine protons (H_c and H_d, H_e and H_f), characteristic as an *endo* isomer, were observed.[2,4f] Moreover, the two peaks of aliphatic methine protons H_b and H_b', which were noncoupled with H_a and H_a' on the right fused ring (vide supra), were independently located at 3.17 and 3.21 ppm as the doublet indicated the structure as the *endo-endo/anti* isomer with C_1 symmetry rather than the symmetrical *endo-endo/syn* isomer (Figure 1). This result showed that the two successive cycloadditions occurred in an *endo* manner, where the two dienophiles approached across opposite faces of the triphenylene core.

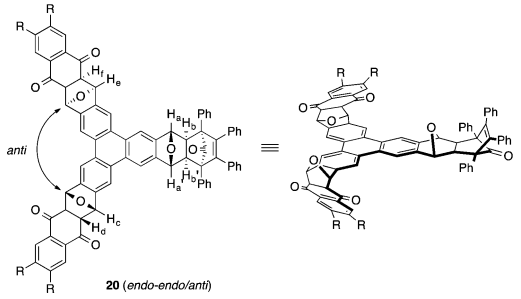


Figure 1. Stereochemistry of the dual cycloadduct **20**.

DOI: 10.1021/acs.orglett.7b01932
Org. Lett. XXXX, XXX, XXX−XXX

The 3-fold cycloadduct **21**, initially produced by heating at 131 °C for 45 min (Scheme 5), was composed of two diastereomers (ds 4:1). The major product **21a** has two *endo* and one *exo* stereochemistries on the oxabicyclomoieties, which were determined by the presence of both coupled and noncoupled aliphatic methine signals. Moreover, the six singlets corresponding to the aromatic protons on the triphenylene moiety indicated the product as a nonsymmetric *exo-endo-endo/syn-anti* isomer (Figure 2). On the other hand, the lack of

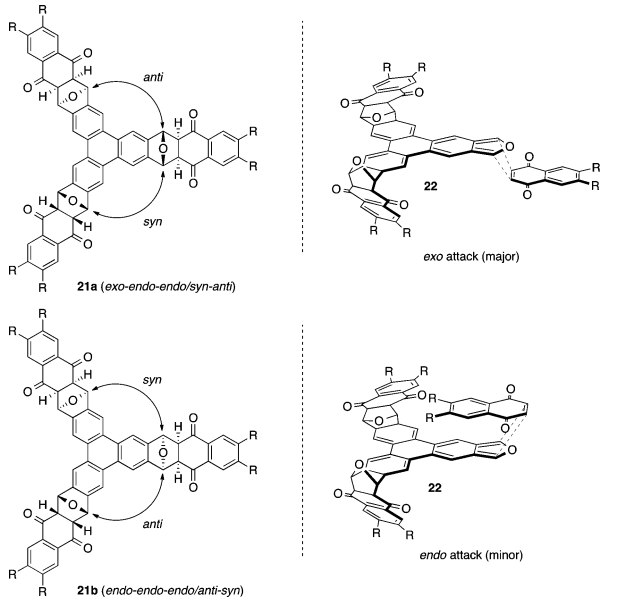


Figure 2. Stereochemistry of the 3-fold cycloadduct **21**.

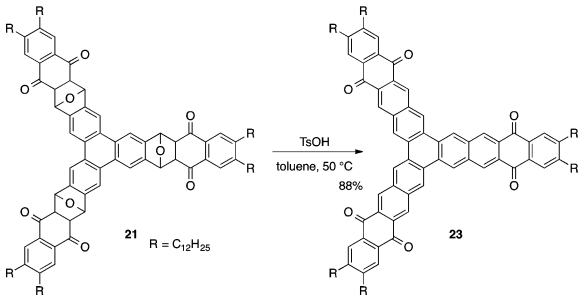
noncoupling protons on the oxabicyclo moieties and the three singlets on the aromatic protons on the triphenylene moiety established the minor product **21b** as an *endo-endo-endo/anti-syn* isomer. The formation of the major cycloadduct **21a** was explained by the *exo* attack of the dienophile to the isobenzofuran **22** to avoid the steric repulsion by both sides of the polycyclic framework in **22**.

Further study on the stereochemistry of the 3-fold cycloadduct **21** revealed that stereoisomerization was observed by heating the same reaction for a longer reaction time to produce several kinds of diastereomers (*exo-exo-endo* and *exo-exo-exo* isomers) in addition to the above-mentioned major stereoisomer **21a**,[14] which were cleanly converted to the corresponding star-shaped polyketone **23** by acid-promoted aromatization (TsOH in toluene at 50 °C). Purification of the crude product by silica-gel column chromatography gave the poly ketone **23** in high yield (Scheme 6). Owing to the six long alkyl chains introduced to three directions at the end of the aromatic rings, the product **23** was highly soluble in hexane, CH_2Cl_2, $CHCl_3$, toluene, and Et_2O.[15]

^{1}H NMR analysis of the product **23** showed that all peaks were significantly broadened at room temperature. On the other hand, these broadened signals gradually sharpened at higher temperature (90 °C). Moreover, the aromatic signals were shifted downfield by increasing the temperature (Figure 3) or decreasing concentration (Figure 4), which indicated the aggregation in solution.[16]

Finally, it should be emphasized that the unsymmetrical star-shaped polyketone **28** could be accessed by using the π-extended isobenzofuran **25** as a key intermediate (Scheme 7).

Scheme 6. Acid-Promoted Aromatization of the Cycloadduct 21 to Star-Shaped Polyketone 23



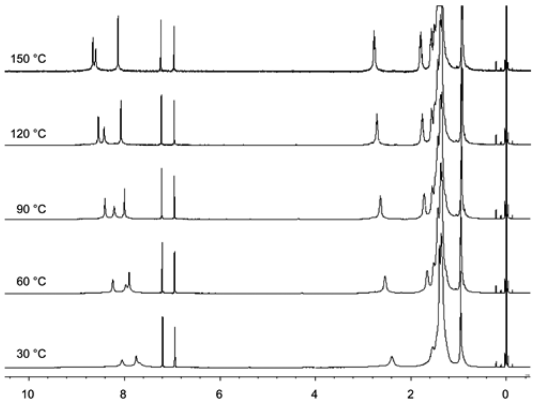


Figure 3. Temperature-dependent ^{1}H NMR spectra of **23** in *o*-$C_6D_4Cl_2$ (2.97×10^{-2} M).

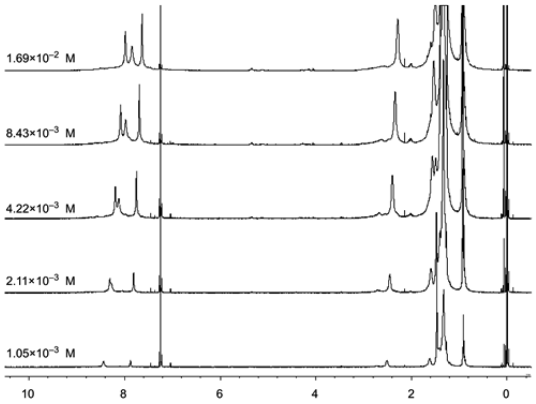


Figure 4. Concentration-dependent ^{1}H NMR spectra of **23** at 50 °C in $CDCl_3$.

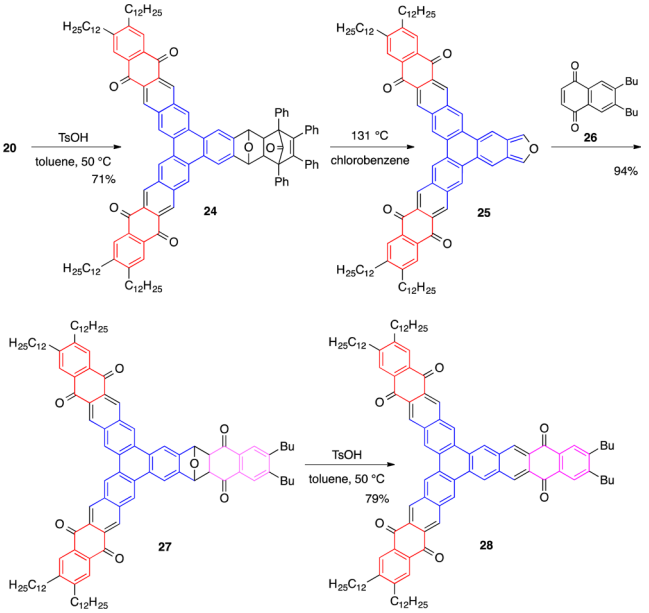
When dual-cycloadduct **20** was treated with TsOH in toluene at 50 °C, dehydrative aromatization occurred cleanly to give tetraketone **24** in 71% yield.

π-Extended polyketone **24** was then heated in chlorobenzene at 131 °C to generate the highly condensed isobenzofuran **25**,[3c] which was trapped with naphthoquinone **26** to give the unsymmetrical star-shaped polyketone **28** after acid-induced aromatization. As for the third [2 + 4] cycloaddition of the π-extended isobenzofuran **25**, aromatization of dual cycloadduct **20** to tetraketone **24** was indispensable since the corresponding thermal reaction of **20** with naphthoquinone **26** gave the desired cycloadduct in low yield due to the retro Diels–Alder reaction of **20**.

In summary, successive cycloaddition of isobenzofuran trimer equivalent allowed us to construct symmetrical and unsym-

DOI: 10.1021/acs.orglett.7b01932
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 7. Preparation of Unsymmetrical Star-Shaped Polyketone 28



metrical star-shaped polycyclic aromatic ketones with valuable synthetic potential. Further synthetic applications are under active investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01932.

Experimental procedures and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: thamura@kwansei.ac.jp.

ORCID

Toshiyuki Hamura: 0000-0003-2857-2273

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Number JP15H05840 in Middle Molecular Strategy and JST ACT-C Grant Number JPMJCR12YY, Japan.

■ REFERENCES

(1) For recent reviews, see: (a) Pérez, D.; Peña, D.; Guitián, E. *Eur. J. Org. Chem.* **2013**, *2013*, 5981. (b) Scott, L. T. *Polycyclic Aromat. Compd.* **2010**, *30*, 247.

(2) For selective examples, see: (a) Haneda, H.; Eda, S.; Aratani, M.; Hamura, T. *Org. Lett.* **2014**, *16*, 286. (b) Akita, R.; Kawanishi, K.; Hamura, T. *Org. Lett.* **2015**, *17*, 3094.

(3) For preparation of isobenzofuran, see: (a) Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346. (b) Warrener, R. N.; Shang, M.; Butler, D. N. *Chem. Commun.* **2001**, 1550. (c) Sygula, A.; Sygula, R.; Rabideau, P. W. *Org. Lett.* **2006**, *8*, 5909. (d) Pei, B. J.; Chan, W. H.; Lee, A. W. M. *Org. Lett.* **2011**, *13*, 1774. (e) Hamura, T.; Nakayama, R. *Chem. Lett.* **2013**, *42*, 1013. (f) Asahina, K.; Matsuoka, S.; Nakayama, R.; Hamura, T. *Org. Biomol. Chem.* **2014**, *12*, 9773.

(4) For selective synthetic applications of isobenzofuran, see: (a) Binger, P.; Wedemann, P.; Goddard, R.; Brinker, U. H. *J. Org. Chem.* **1996**, *61*, 6462. (b) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (c) Wong, H. N. C. *Acc. Chem. Res.* **1989**, *22*, 145. (d) Man, Y.-M.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3214. (e) Chan, S.-H.; Yick, C.-Y.; Wong, H. N. C. *Tetrahedron* **2002**, *58*, 9413. (f) Rainbolt, J. E.; Miller, G. P. *J. Org. Chem.* **2007**, *72*, 3020.

(5) (a) Kanibolotsky, A. L.; Perepichka, I. F.; Skabara, P. J. *Chem. Soc. Rev.* **2010**, *39*, 2695. (b) Zhang, H.; Wu, D.; Liu, S. H.; Yin, J. *Curr. Org. Chem.* **2012**, *16*, 2124. (c) Lynett, P. T.; Maly, K. E. *Org. Lett.* **2009**, *11*, 3726. (d) Alonso, J. M.; Díaz-Álvarez, A. E.; Criado, A.; Pérez, D.; Peña, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 173. (e) Rüdiger, E. C.; Porz, M.; Schaffroth, M.; Rominger, F.; Bunz, U. H. F. *Chem. - Eur. J.* **2014**, *20*, 12725. (f) Yao, B.; Zhou, Y.; Ye, X.; Wang, R.; Zhang, J.; Wan, X. *Org. Lett.* **2017**, *19*, 1990. (g) Tanokashira, N.; Kukita, S.; Kato, H.; Nehira, T.; Angkouw, E. D.; Mangindaan, R. E. P.; de Voogd, N. J.; Tsukamoto, S. *Tetrahedron* **2016**, *72*, 5530.

(6) (a) Fieser, L. F.; Haddadin, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 2081. (b) Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599. (c) Luo, J.; Hart, H. *J. Org. Chem.* **1989**, *54*, 1762.

(7) The diiodide **12** was prepared from resorcinol in four steps. For details, see Supporting Information.

(8) For pioneering studies by Hart on the generation and trapping of 1,4-benzdiyne equivalents, see: (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. Other examples, see: (c) Chen, Y.-L.; Sun, J.-Q.; Wei, X.; Wong, W.-Y.; Lee, A. W. M. *J. Org. Chem.* **2004**, *69*, 7190. (d) Morton, G. E.; Barrett, A. G. M. *J. Org. Chem.* **2005**, *70*, 3525. (e) Schuster, I. I.; Craciun, L.; Ho, D. M.; Pascal, R. A., Jr. *Tetrahedron* **2002**, *58*, 8875. (f) Duong, H. M.; Bendikov, M.; Steiger, D.; Zhang, Q.; Sonmez, G.; Yamada, J.; Wudl, F. *Org. Lett.* **2003**, *5*, 4433. (g) Hamura, T.; Arisawa, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6842.

(9) Epoxynaphthalene **13** was prepared by a five-step protocol including the [2 + 4] cycloaddition of benzyne with furan. For details, see Supporting Information.

(10) For details, see Supporting Information.

(11) By now, there has been no report on the determination of the stereochemistry of the Diels–Alder adduct like **14** by X-ray analysis. Among various possibilities, long-range ^{13}C–H coupling is a reliable probe to evaluate the stereochemistry of the cycloadduct. See: (a) Tan, R. Y. S.; Russell, R. A.; Warrener, R. N. *Tetrahedron Lett.* **1979**, *20*, 5031. (b) Coxon, J. M.; Battiste, M. A. *Tetrahedron* **1976**, *32*, 2053 For the X-ray structure of **14**, see Supporting Information..

(12) (a) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Org. Lett.* **1999**, *1*, 1555. (c) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E.; Castedo, L. *Org. Lett.* **2000**, *2*, 1629. (d) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **2000**, *65*, 6944. (e) Romero, C.; Peña, D.; Pérez, D.; Guitián, E. *Chem. - Eur. J.* **2006**, *12*, 5677.

(13) (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834. (b) Shih, H.-T.; Shih, H.-H.; Cheng, C.-H. *Org. Lett.* **2001**, *3*, 811. (c) Li, Y.; Yang, W.; Cheng, G.; Yang, D. *J. Org. Chem.* **2016**, *81*, 4744.

(14) For the stereoisomerization of the cycloadduct **21**, see Supporting Information.

(15) The star-shaped polyketone **23** was insoluble in polar solvents, e.g., EtOAc, acetone, DMF, and DMSO.

(16) Watson, M. D.; Fechtenkötter, A.; Müllen, K. *Chem. Rev.* **2001**, *101*, 1267.

DOI: 10.1021/acs.orglett.7b01932
Org. Lett. XXXX, XXX, XXX–XXX