Organic LETTERS

Letter

pubs.acs.org/OrgLett

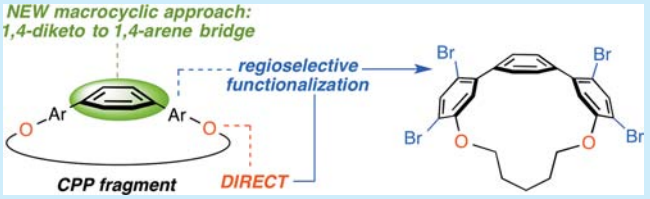
A Non-Cross-Coupling Approach to Arene-Bridged Macrocycles: Synthesis, Structure, and Direct, Regioselective Functionalization of a Cycloparaphenylene Fragment

Nirmal K. Mitra,[†] Rolande Meudom,[†] John D. Gorden, and Bradley L. Merner*

Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama 36849, United States

Supporting Information

ABSTRACT: A new synthetic strategy that employs a relatively unstrained, 1,4-diketo-bridged macrocycle as a precursor to a strained, 1,4-arene-bridged (bent *para*-phenylene) macrocycle has been developed. The distorted *p*-terphenyl nucleus (CPP fragment) of the macrocycle has been characterized by X-ray crystallography, and a direct, regioselective bromination protocol of the macrocyclic system is reported.



The synthesis of *para*-linked benzenoid macrocycles, *i.e.*, [*n*]cycloparaphenylenes (CPPs), has attracted the interest of multiple research groups around the world over the past seven years.[1] The inaugural synthesis of [9], [12], and [18] CPP by Bertozzi and Jasti[2] set this area of synthetic chemistry on fire, with the notion that these macrocyclic systems may be used as templates in the bottom−up chemical synthesis of monodisperse carbon nantotubes (CNTs).[3,4] While multiple synthetic strategies that facilitate the formation of these hoop-shaped hydrocarbons have been developed,[5] including the preparation of gram-scale quantities of [8] and [10]CPP,[6] two of the biggest challenges currently facing this field of chemical synthesis include macrocyclization strategies that tolerate functional groups/substituents in positions *ortho* to the site of bond (macrocycle) formation and the late-stage (direct), regioselective functionalization of CPP units. In the case of the former, functional groups at these positions would provide a starting point for future synthetic manipulations of potential CNT templates and the assembly of higher-order nanostructures (tube elongation). Several approaches to phenyl substituted CPPs have been reported,[7,8] as well as arene-linked[9] and dimeric[10] CPP precursors; however, the required cyclodehydrogenation reactions that would furnish bona fide CNTs have yet to come to fruition.[7,8] Furthermore, the bottom−up synthetic approach of using an [*n*]CPP macrocycle as a diameter controlling template is complicated by a lack of late-stage functionalization reactions that facilitate the synthesis of more suitable building blocks with programmed substituents for C−C bond forming reactions. Itami and co-workers have recently described the selective monofunctionalization of [9] and [12]CPP through an η^6-Cr tricarbonyl intermediate, which requires three synthetic operations from the CPP unit.[11] Herein we describe a new macrocyclic approach to [*n*]CPP fragments and the direct, regioselective functionalization of the *p*-terphenyl (CPP fragment) subunit of the macrocycle that does not require precomplexation of a benzene ring. The *meta*-alkoxy bridging group that connects the 3 and 3″-positions of the *p*-terphenyl systems plays a pivotal role in directing the substitution reactions of the terminal benzene rings.

Typically, synthetic approaches to CPPs have required four stages: [1] synthesis of bent, pre-arene subunits; [2] subunit elongation via cross-coupling reactions; [3] macrocyclization via cross-coupling reactions or direct arene−arene bond forming reactions; and [4] pre-arene to arene conversion (Figure 1a). Arguably the most challenging synthetic steps are encountered at Stages 3 and 4, and macrocyclization reactions (Stage 3) have proven to be significantly lower yielding than the corresponding aromatization reactions (Stage 4). Macrocyclization reactions that furnish strained molecular architectures are notoriously difficult transformations in chemical synthesis.[12] The high degree of organization that an acyclic precursor must attain in order for it to be converted into a macrocyclic system has proven to be a major impasse. On the other hand, aromatization protocols that facilitate the synthesis of highly strained and distorted aromatic hydrocarbons have proven to be powerful synthetic tools. Thus, our own interest in the development of new chemical tools for the synthesis of CNTs and CNT substructures led us to pursue a new approach to strained 1,4-arene-bridged macrocycles.

It was envisioned that a simple, alkylated hydroxybenzaldehyde derivative could be converted to relatively unstrained macrocyclic-1,4-dione and that the 1,4-dione bridging unit of the macrocycle would serve as an arene surrogate (Figure 1b).[13]

As such, our synthesis commenced with the dialkylation of 3-hydroxybenzaldehyde (**8**) with 1,5-diiodopentane to afford dialdehyde **9** (73%). A Grignard reaction of **9** with vinylmagnesium chloride furnished diene **10** (82%), which was then subjected to a macrocyclic ring-closing metathesis (RCM)

Received: April 15, 2015
Published: May 8, 2015

DOI: 10.1021/acs.orglett.5b01102
Org. Lett. 2015, 17, 2700−2703

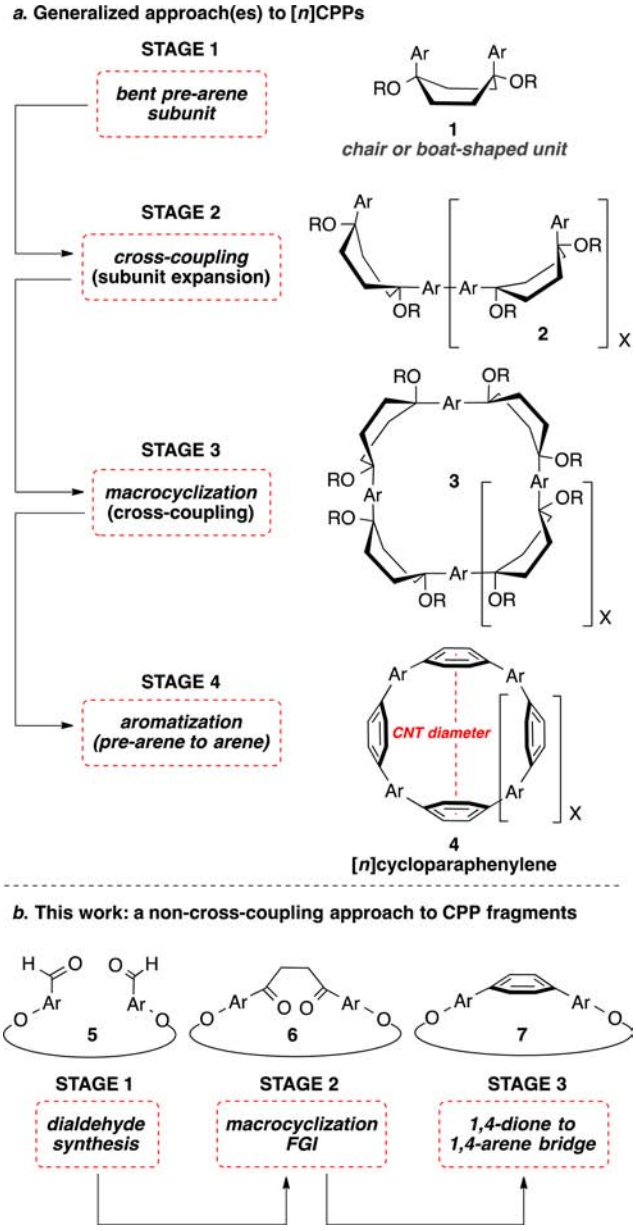
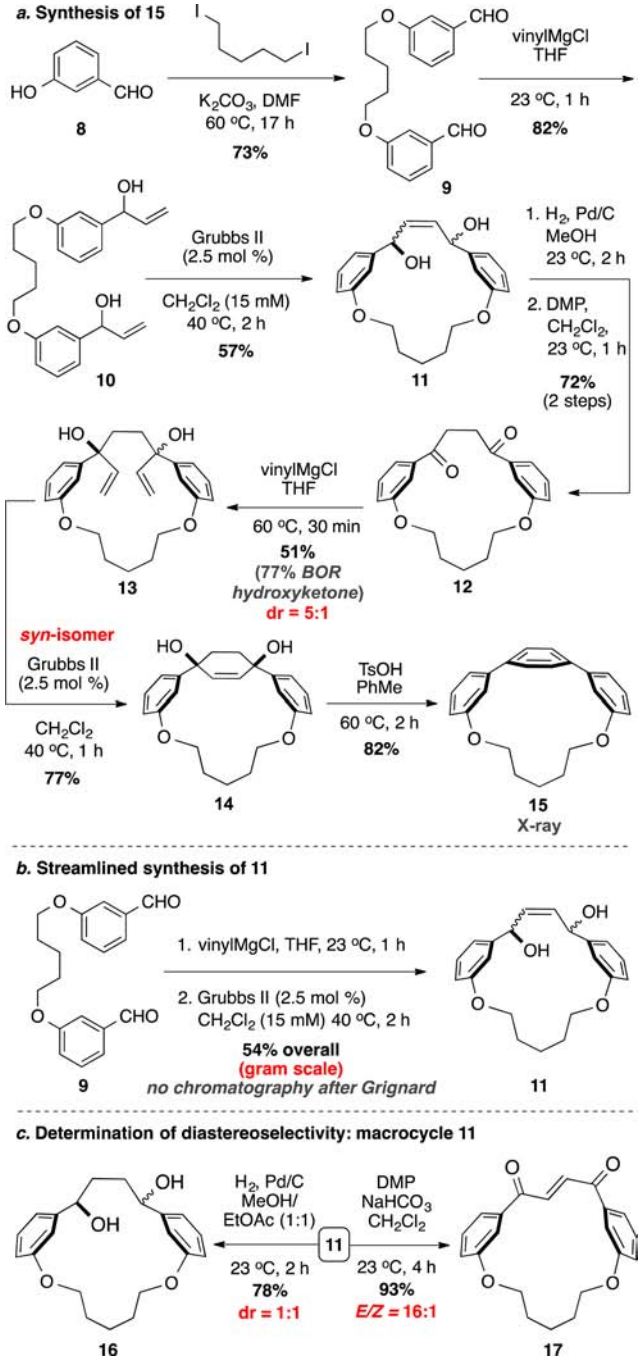


Figure 1. (a) Approaches to [*n*]CPPs and (b) macrocyclic CPP fragments.

Scheme 1. (a) Synthesis of 1,7-Dioxa[7](3,3″)*p*-terphenylophane (15); (b) Streamlined Synthesis of 11; (c) Determination of Diastereoselectivity in 11



reaction using the Grubbs second-generation catalyst. At 15 mM concentration in dichloromethane, macrocyclic diol **11** was obtained in 57% yield. This represents a rare application of the RCM reaction to furnish an [*n*.4]metacyclophane derivative.[14] During the course of our synthetic investigations it was discovered that purification (flash chromatography) of **10** resulted in only modest improvements of the purity of the RCM precursor. Since a chromatographic separation is necessary at the macrocyclization stage, we explored the possibility of exposing crude **10** to the same RCM conditions. This two-step, single chromatographic separation protocol was carried out on a gram scale to furnish **11** with an overall yield of 54% (*cf.*, 46% overall yield for **9** to **10** and **10** to **11**, Scheme 1b). Macrocycle **11** was isolated as a mixture of diastereomers, and the ratio of alcohol and alkene diastereomers was determined to be 1:1 (*syn*/*anti*), via catalytic hydrogenation of the olefin unit (**11** to **16**), and 16:1 (*E*/*Z*), via oxidation for the diastereomeric alcohols (**11** to **17**), respectively (Scheme 1c).[15] Molecular modeling suggests that the *E*-configured macrocyclic olefin is the preferred diastereomer. As such, the mixture of diastereomers (**11**) was first subjected to catalytic hydrogenation conditions and then oxidized to macrocyclic diketone **12** in 72% overall yield. A second Grignard reaction with vinylmagenium chloride afforded allylic diol **13** (51%) as a 5:1 mixture of *syn*/*anti* diastereomers.[16] Only the major diastereomer undergoes cyclization when treated with the Grubbs second-generation catalyst to afford **14**. Based on steric considerations this isomer has been assigned the *syn* (*syn*-**13** or *meso*-**13**) relative configuration, owing to its much greater likelihood of undergoing an RCM reaction. The minor

DOI: 10.1021/acs.orglett.5b01102
Org. Lett. 2015, 17, 2700−2703

(uncyclized) isomer, assigned as *anti*-(racemic)**13**, was easily removed by flash chromatography of the reaction mixture after RCM in 1:1 EtOAc/hexanes: R_f(*rac*-**13**) = 0.59, R_f(**14**) = 0.27). Aromatization of the cyclohex-2-ene-1,4-diol ring system (macrocycle **14**), in the presence of TsOH in toluene, furnished the [1,4]-benzeno-bridged macrocycle **15** in 82% yield.

Recrystallization of **15** from acetone and dichloromethane provided a single crystal suitable for X-ray crystallography. The crystal structure of **15** (Figure 2) indicates that the central

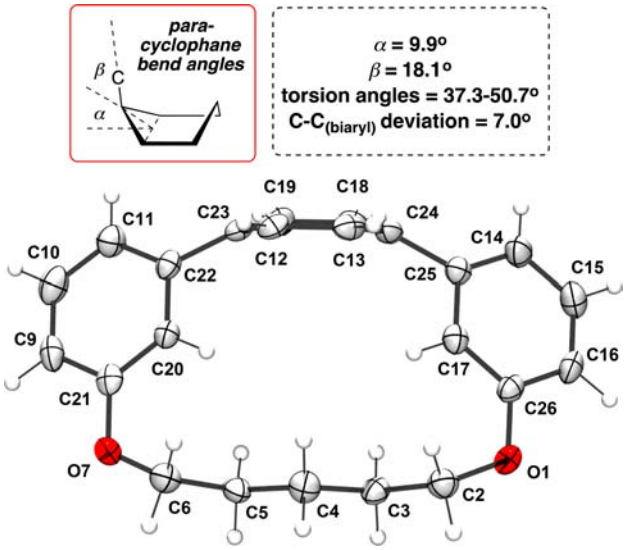


Figure 2. X-ray crystal structure and important deformation angles of **15**.

benzene ring of the *p*-terphenyl system of **15** is distorted from planarity. The *para*-carbon atoms, C-23 and C-24 (crystallographic numbering) of the central benzene ring have a mean deviation angle (α) of 9.9° from the plane defined by C-12, C-13, C-18, and C-19, respectively, and are displaced from the plane by 0.054 Å. The benzylic carbon atoms, C-22 and C-25, are distorted by an average angle (β) of 18.1°. These angles are akin to those (α and β) used for quantifying the deformation of nonplanar benzene rings in the [*n*]paracyclophanes.[17] The average twist (torsion angle) of the teraryl system ranges from 37.3° to 50.7°, and the mean C−C_{biaryl} bond deviation between the two terminal rings and the central benzene ring is 7.0°. As such, the *meta*-alkoxy bridging group cants the terminal phenyl rings away from the central arene unit. Deviation of the *p*-terphenyl system from its ideal geometry, relative to that of unperturbed 3,3″-dimethoxy-*p*-terphenyl (model), causes a blue shift in both the UV−vis and fluorescence spectrum (Figure 3): λ_{max} (**15**) = 270 nm (absorption) and 335 nm (emission), λ_{max} (model) = 278 nm (absorption) and 339 and 352 nm (emission).

Compound **15** can be viewed as a cyclophane and is, therefore, named 1,7-dioxa[7](3,3″)*p*-terphenylophane. This numbering is appropriate for a discussion of its substitution chemistry (Scheme 2). In the initial stages of our synthetic investigations, we had envisioned that incorporation of oxygen atoms at the C-3 and C-3″-positions of the *p*-terphenyl system of **15** would allow for selective functionalization of the terminal benzene rings. Furthermore, it was anticipated that the hindered C-2 and C-2″-positions would be less susceptible to substitution reactions. Indeed, the ^{1}H NMR spectrum of **15**

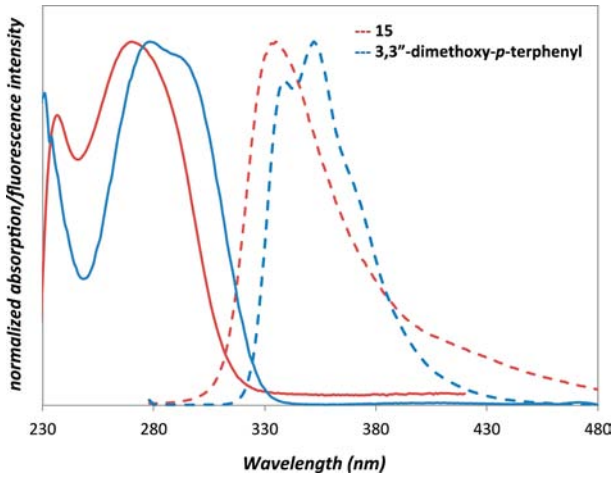
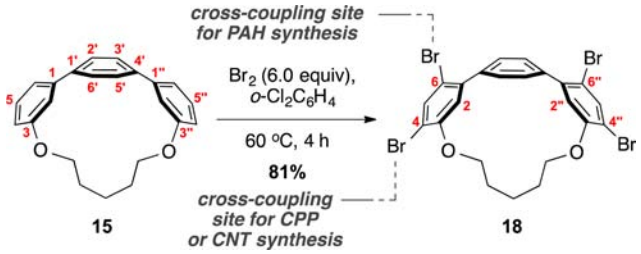


Figure 3. UV−vis and fluorescence spectra of **15** (red, 2.5 × 10^{-5} M) and 3,3″-dimethoxy-*p*-terphenyl (blue, 2.5 × 10^{-5} M). Fluorescence spectra were obtained at 270 nm excitation.

Scheme 2. Direct, Regioselective Bromination of 15



shows that the proton resonance of the (H)2 and (H)2″-positions is considerably shielded at 5.81 ppm − *cf.*, 7.20 ppm (δH-2 and H-2″) for 3,3″-dimethoxy-*p*-terphenyl.[18] This indicates that, like the solid phase structure, H-2 and H-2″ are directed toward the shielding cone of the central benzene ring in the solution phase. Treatment of **15** with an excess of bromine (6.0 equiv) in *ortho*-dichlorobenzene at 60 °C furnished only the 4,4″,6,6″-tetrabrominated product **18**. Such bromination reactions of 3,3″-substituted *p*-terphenyl systems have not been previously reported, and direct halogenation reactions of [*n*]CPPs have been cited as problematic.[10,11] These site selective bromination reactions should facilitate future two directional carbon−carbon bond-forming reactions for expanding the terphenyl unit of **15** into a PAH system and connecting the remote (*para*) arene vertices to complete nanohoop or tube construction. The fact that the arene units of **15** do not participate in strain-relief-driven rearrangement reactions is also noteworthy. Currently, we are investigating these and other regioselective functionalizations of the *p*-terphenyl system of **15**, and the conversion of **18** into an elongated (PAH containing) CNT substructure.

The use of a 1,4-diketo-bridged macrocycle (**12**) as a precursor to a strained, 1,4-arene-bridged macrocycle (**15**) represents a new approach for the synthesis of benzenoid segments of CNTs. Strategic placement of alkoxy groups on the terminal benzene rings of a distorted *p*-terphenyl system has enabled a regioselective bromination reaction of the aromatic core. To demonstrate the synthetic utility of this non-cross-coupling-based approach to arene-bridged macrocycles, we are currently pursuing the synthesis of (smaller and larger) homologues of **15**. Furthermore, an investigation of other

DOI: 10.1021/acs.orglett.5b01102
Org. Lett. 2015, 17, 2700−2703

useful regioselective functionalizations and subsequent skeletal building reactions are well underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, including ^{1}H and ^{13}C NMR spectra for all new compounds, photophysical measurements, and important X-ray crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01102.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: blm0022@auburn.edu.

Author Contributions

†N.K.M. and R.M. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We dedicate this work to Professor Stephen Hanessian on the occasion of his 80th birthday. The authors are grateful to Auburn University for financial support. R.M. would like to thank the Cellular and Molecular Biosciences Fellowship Program and NSF EPSCoR for a graduate fellowship.

■ REFERENCES

(1) For a detailed account on the work of Jasti and co-workers, see: (a) Golder, M. R.; Jasti, R. *Acc. Chem. Res.* **2015**, *48*, 557−566. For leading papers, see: (b) Evans, P. J.; Darzi, E. R.; Jasti, R. *Nat. Chem.* **2014**, *6*, 404−408. (c) Xia, J.; Jasti, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2474. (d) Sisto, T. J.; Golder, M. R.; Hirst, E. S.; Jasti, R. *J. Am. Chem. Soc.* **2011**, *133*, 15800−15802. For a detailed account on the work of Itami and co-workers, see: (e) Omachi, H.; Segawa, Y.; Itami, K. *Acc. Chem. Res.* **2012**, *45*, 1378−1389. For leading papers, see: (f) Sibbel, F.; Matsui, K.; Sagawa, Y.; Studer, A.; Itami, K. *Chem. Commun.* **2014**, *50*, 954−956. (g) Yagi, A.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 2962−2965. (h) Segawa, Y.; Miyamoto, S.; Omachi, H.; Matsurra, S.; Šenel, P.; Sasamori, T.; Tokitoh, N.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3244−3248. For representative work by Yamago and co-workers, see: (i) Patel, V. K.; Kayahara, E.; Yamago, S. *Chem.—Eur. J.* **2015**, *21*, 5742−5749. (j) Kayahara, E.; Patel, V. K.; Yamago, S. *J. Am. Chem. Soc.* **2014**, *136*, 2284−2287. (k) Iwamoto, T.; Wantanabe, Y.; Sakamoto, Y.; Suzuki, T.; Yamago, S. *J. Am. Chem. Soc.* **2011**, *133*, 8354−8361. (l) Yamago, S.; Watanabe, Y.; Iwamoto, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 757−759. For recent reviews on the synthesis CPPs and related systems, see: (m) Lewis, S. E. *Chem. Soc. Rev.* **2015**, *44*, 2221−2304. (n) Tran-Van, A. F.; Wegner, H. A. *Beilstein J. Nanotechnol.* **2014**, *5*, 1320−1333.

(2) Jasti, R.; Bhattacharjee, J.; Neaton, J. B.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 17646−17647.

(3) Jasti, R.; Bertozzi, C. R. *Chem. Phys. Lett.* **2010**, *494*, 1−7.

(4) Bunz, U. F.; Menning, S.; Martin, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 7094−7101.

(5) (a) Tran-Van, A.-F.; Huxol, E.; Basler, J. M.; Neuburger, M.; Adjizan, J.-J.; Ewels, C. P.; Wegner, H. A. *Org. Lett.* **2014**, *16*, 1594−1597. (b) Huang, C.; Huang, Y.; Akhmedov, N. G.; Popp, B. V.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2014**, *16*, 2672−2675. (c) Reference 1.

(6) Xia, J.; Bacon, J. W.; Jasti, R. *Chem. Sci.* **2012**, *3*, 3018−3021.

(7) Sisto, T. J.; Tian, X.; Jasti, R. *J. Org. Chem.* **2012**, *77*, 5857−5860.

(8) Nishiuchi, T.; Feng, X.; Enkelmann, V.; Wagner, M.; Müllen, K. *Chem.—Eur. J.* **2012**, *18*, 16621−16625.

(9) Xia, J.; Golder, M. R.; Foster, M. E.; Wong, B. M.; Jasti, R. *J. Am. Chem. Soc.* **2012**, *134*, 19709−19715.

(10) Ishii, Y.; Matsuura, S.; Segawa, Y.; Itami, K. *Org. Lett.* **2014**, *16*, 2174−2176.

(11) Kubota, N.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2015**, *137*, 1356−1361.

(12) Gulder, T.; Baran, P. S. *Nat. Prod. Rep.* **2012**, *29*, 899−834.

(13) Ziffle, V. E.; Cheng, P.; Clive, D. L. J. *J. Org. Chem.* **2010**, *75*, 8024−8038.

(14) Bodwell, G. J.; Nandaluru, P. R. *Isr. J. Chem.* **2012**, *52*, 105−138.

(15) See Supporting Information and ^{1}H NMR spectra for determination of diastereoselectivities, for compounds **16** and **17**.

(16) See Supporting Information for ^{1}H NMR spectra of compound **13**: dr = 5:1.

(17) Tobe, Y.; Kakiuchi, K.; Odaira, Y.; Hosaki, T.; Kai, Y.; Kasai, N. *J. Am. Chem. Soc.* **1983**, *105*, 1376−1377.

(18) See Supporting Information for ^{1}H NMR spectra overlay of compound **15** and 3,3″-dimethoxy-*p*-terphenyl.

DOI: 10.1021/acs.orglett.5b01102
Org. Lett. 2015, 17, 2700−2703