Organic LETTERS

Letter

pubs.acs.org/OrgLett

Regenerative γ-Lactone Annulations: A Modular, Iterative Approach to Oligo-tetrahydrofuran Molecular Stairs and Related Frameworks

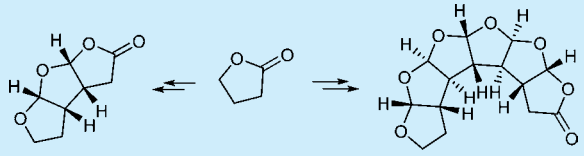
Showkat Rashid,[†] Bilal A. Bhat,*[,†] and Goverdhan Mehta*[,‡]

[†]Medicinal Chemistry Division, Indian Institute of Integrative Medicine (CSIR), Sanatnagar, Srinagar 190005, India

[‡]School of Chemistry, University of Hyderabad, Hyderabad 500046, India

Supporting Information

ABSTRACT: A unified, stereocontrolled, regenerative γ-butyrolactone annulation approach has been conceptualized and validated through syntheses of a range of oligo-THFs. The new protocol is short (four steps), simple (table-top reagents), and efficient (50−61% overall yields). Although the scope of this approach is unlimited, it has been demonstrated up to five iterations on commercial γ-butyrolactone to assemble six fused tetrahydrofuran moieties in a staircase-like architecture. A selection of exploratory transformations is presented to exemplify the potential applications of this protocol.



Natural products and synthetic molecules embodying diverse furofuranone subunits have been surfacing in the literature with regular frequency. Among them, furo[2,3-*b*]furanone based prototypical natural products such as norrisolide **1**,[1] conosilane A **2**,[2] and a synthetic antiviral drug darunavir **3**,[3] a protease inhibitor clinically used in HIV infections, are notable examples. Higher "oligologues" of furo[2,3-*b*]furanone have a very limited presence with garcilin C **4**[4] and paracaseolide A **5**[5] being the only two examples of natural products bearing three repeating THF units. However, recent observation that synthetic compound GRL-0519A **6**,[6] based on tricyclic *bis*-acetal substructure, exhibits an exceptional protease inhibitory profile has drawn further attention toward oligocyclic motifs bearing repeating THF units (Figure 1).

In the non-natural product arena, oligo-THF constructs offer possibilities for creating novel, aesthetically pleasing architecture, and forays in this context have led to the assembly of "bowl-like" all *syn* polycyclic polyacetals **7** (tetraoxa[4]peristylane),[7] **8** (pentaoxa[5]perystylane),[8] and more recently the all *anti* polycyclic oligo-THF **9** (molecular stair)[9] (Figure 2).

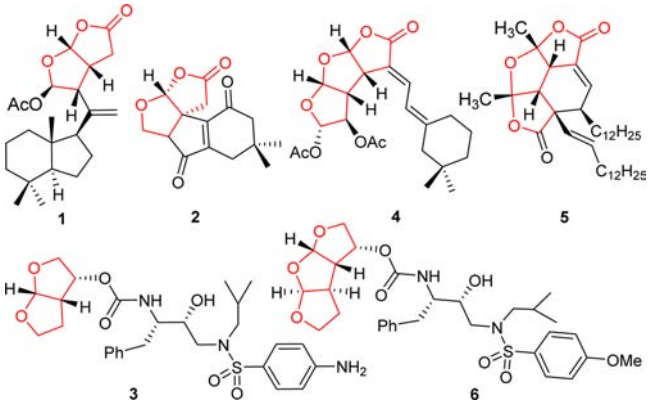


Figure 1. Oligocyclic-THF based natural products and synthetic bioactive entities.

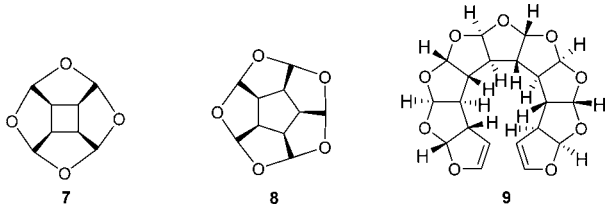


Figure 2. Oligo-THF based aesthetically pleasing creations.

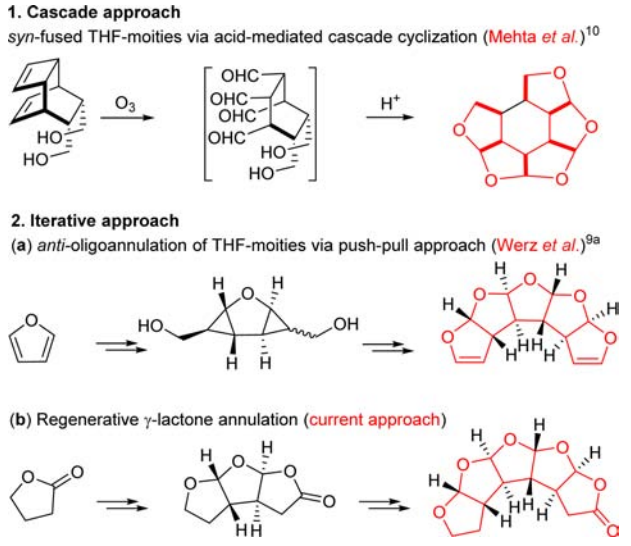
Several synthetic approaches to polycyclic oligo-THF frameworks have been developed but mostly in the context of a particular target. However, there are very few strategies of general applicability, involving either cascade or iterative processes, for the rapid assembly of polycyclic oligo-THF frameworks. These approaches lead to either all *syn* or *syn,anti*- arrangements, as schematically captured in Scheme 1, along with the present offering, to put our effort in proper perspective. In this letter, we disclose a short, versatile, stereocontrolled strategy for the oligoannulation of γ-butyrolactones to deliver a range of fused THF entities in a staircase-like arrangement.[9] The distinctive feature of the present approach is the self-perpetuating regeneration of the γ-butyrolactone moiety, functional group variability, and subtle stereocontrol to deliver either the *syn,anti* or all *syn* arrangement of fused THFs.

Our synthetic efforts toward polycyclic oligo-THFs have commenced from cheap, commercially available, γ-butyrolac-

Received: June 11, 2015
Published: July 7, 2015

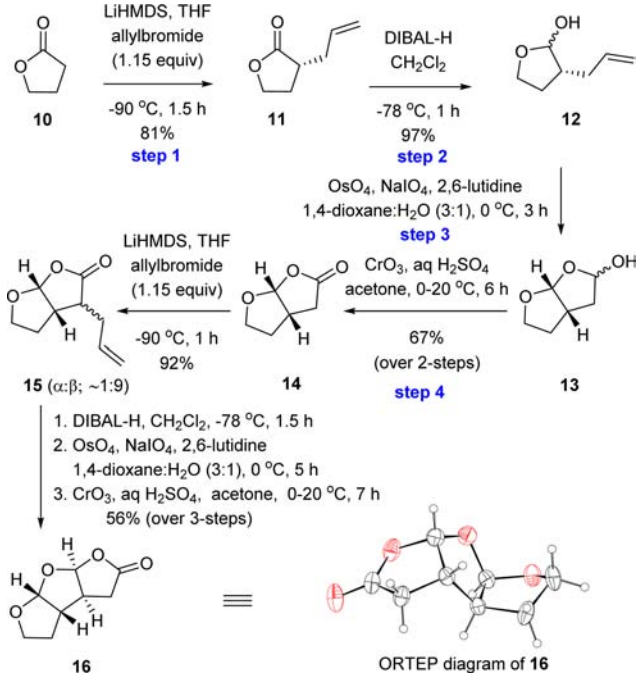
DOI: 10.1021/acs.orglett.5b01707
Org. Lett. 2015, 17, 3604−3607

Scheme 1. General Approaches To Access Polycyclic Oligo-THF Frameworks



tone **10** which was subjected to allylation (step 1) under kinetically controlled conditions to deliver monoallylated product **11** (Scheme 2).[11] DIBAL-H reduction (step 2) of

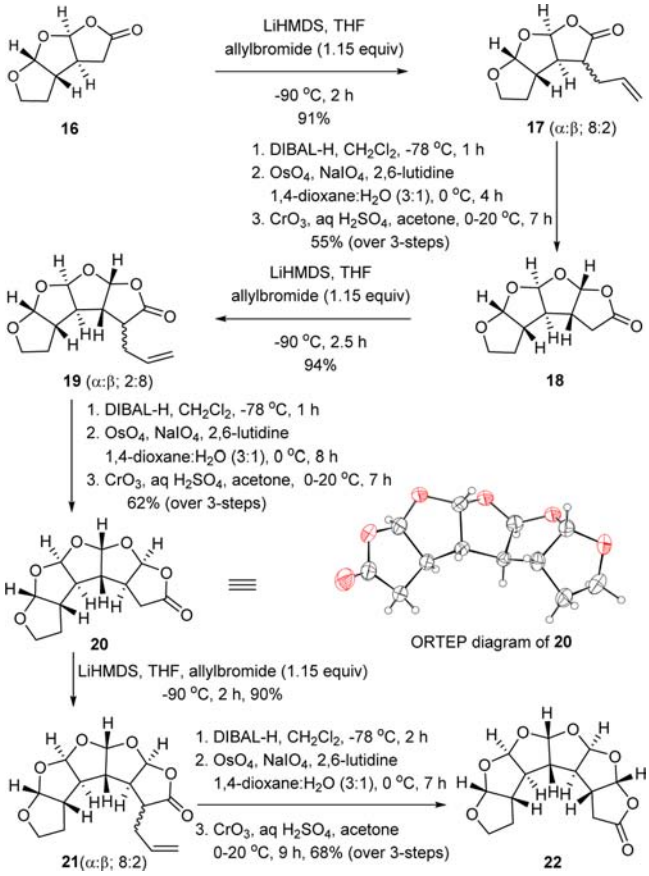
Scheme 2. Regenerative γ-Butyrolactone Annulation to *syn,anti,syn*-Tricyclic Oligo-THF Lactone



11 led to lactol **12** in near-quantitative yield. Sequential OsO_4-mediated dihydroxylation of the terminal alkene moiety in **12** and *in situ* oxidative cleavage (step 3) of the resulting diol with $NaIO_4$[12] led to lactol **13**. Further exposure to CrO_3 in aq H_2SO_4 (Jones reagent)[13] (step 4) delivered the bicyclic lactone **14** in decent yield. The regenerated γ-butyrolactone moiety in **14** was subjected to stereoselective *exo*-face directed allylation (step 1) under kinetically controlled conditions to furnish allylated product **15** (*α*:*β* ratio; ~1:9). Iteration of steps 2−4 involving DIBAL-H reduction, OsO_4-dihydroxylation, oxidative cleavage, and Jones oxidation resulted in the formation of *syn,anti,syn*-tricyclic lactone **16** in good overall yield, and its structure was confirmed by X-ray structure determination.

Three more iterations of the four-step strategy for regenerative γ-butyrolactone annulations were implemented to demonstrate the generality of the strategy. This endeavor smoothly furnished tetracyclic fused-THF **18**, pentacyclic fused-THF **20** (X-ray structure determination), and hexacyclic fused-THF **22** as depicted in Scheme 3. Indeed, there were

Scheme 3. Reiterative γ-Butyrolactone Annulation to Hexacyclic Oligo-THF Lactone



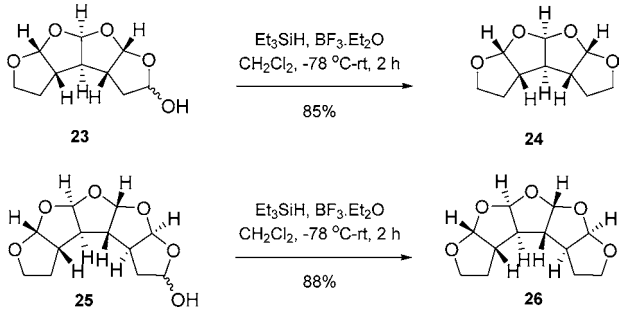
no limits or impediments to carrying out further iterations, more or less perpetually, so to speak, but it was considered more expedient to explore some new possibilities around this newly developed protocol.

At this point it was considered appropriate to demonstrate that parent, unsubstituted polycyclic oligo-THFs could also be readily prepared following a minor deviation at step 3 of the strategy outlined above. Thus, triethylsilane-mediated reductive deoxygenation[14] of the intermediate lactols **23** and **25** en route from **18** and **20** delivered **24** and **26** respectively (Scheme 4).

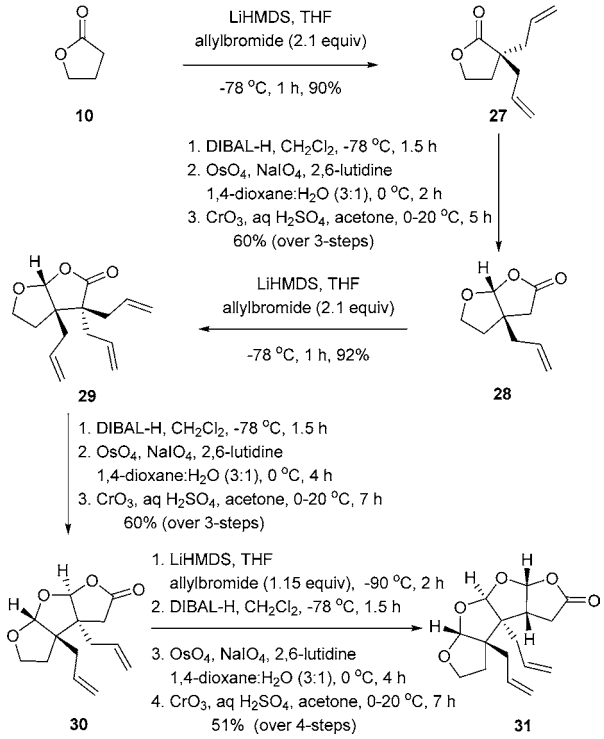
It was of interest to explore whether appropriate substituents could be installed at the ring junction on the oligo-THFs to generate interesting new functionality on this scaffold. For this purpose, γ-butyrolactone **10** was subjected to allylation in the presence of excess allyl bromide at a slightly elevated temperature to furnish geminally diallylated product **27** as an exclusive product (Scheme 5). Subsequent

DOI: 10.1021/acs.orglett.5b01707
Org. Lett. 2015, 17, 3604−3607

Scheme 4. Deoxygenation of Oligo-THF Lactols to Parent Oligo-THFs



Scheme 5. Regenerative γ-Butyrolactone Annulation to Substituted Tetracyclic Oligo-THF Lactones

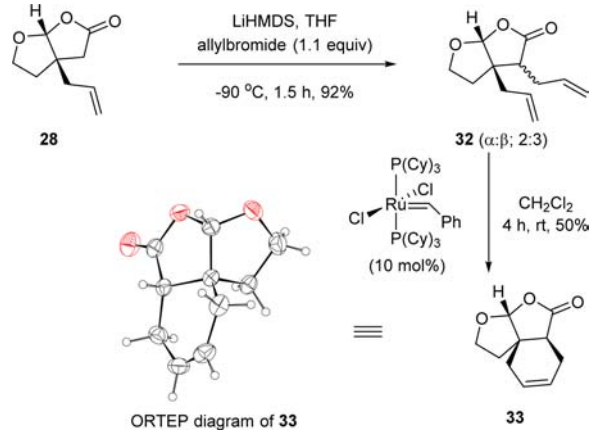


implementation of steps involving DIBAL-H reduction, regioselective oxidative cleavage, and Jones oxidation delivered the bridgehead substituted bicyclic lactone **28**. Reiteration of step 1 (Scheme 2) in the presence of excess allyl bromide on compound **28** resulted in the formation of a triallylated compound **29** and set the stage for the implementation of steps 2−4 to eventuate in the diallylated *syn,anti,syn*-tricyclic lactone **30** with two allyl appendages for further elaboration. The regenerated γ-lactone moiety in **30** was further elaborated to allylated *syn,anti,syn,anti,syn*-tetracyclic lactone **31** through the implementation of steps 1−4 (Scheme 5).

The conceptual intent behind introducing allyl groups on the oligo-THF framework is indicated here through a model study. The allylated bicyclic lactone **28** was further allylated to furnish vicinally diallylated compound **32** (Scheme 6). RCM was smoothly implemented in **32** employing G-I catalyst to furnish angular tricyclic γ-lactone **33** (X-ray structure), a motif encountered in many bioactive natural products.[15]

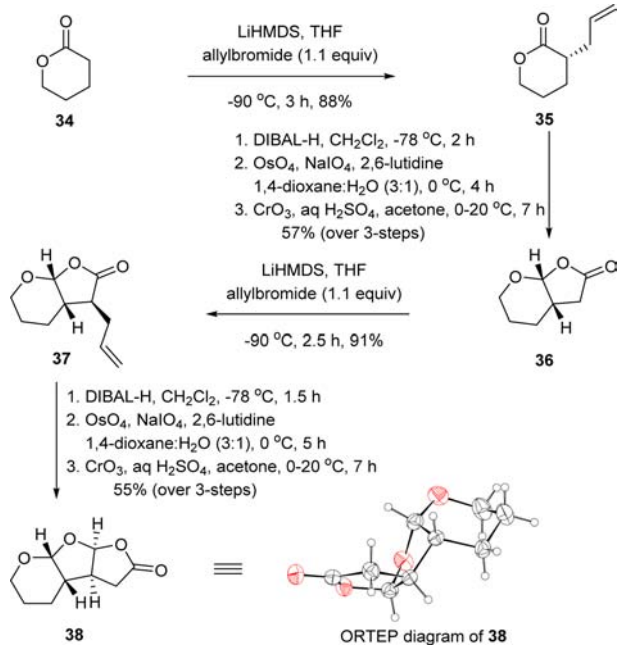
In another variant of the regenerative γ-lactone annulation strategy, the sequence was implemented (steps 1−4) on the

Scheme 6. Construction of Angularly Fused Tricyclic γ-Butyrolactone Framework



homologous valerolactone **34** to furnish **36** and further reiteration led to a new and potentially useful *syn,anti,syn*-tricyclic scaffold **38** (X-ray structure), amenable to further diversity creation (Scheme 7).

Scheme 7. Regenerative γ-Lactone Annulation on Valerolactone

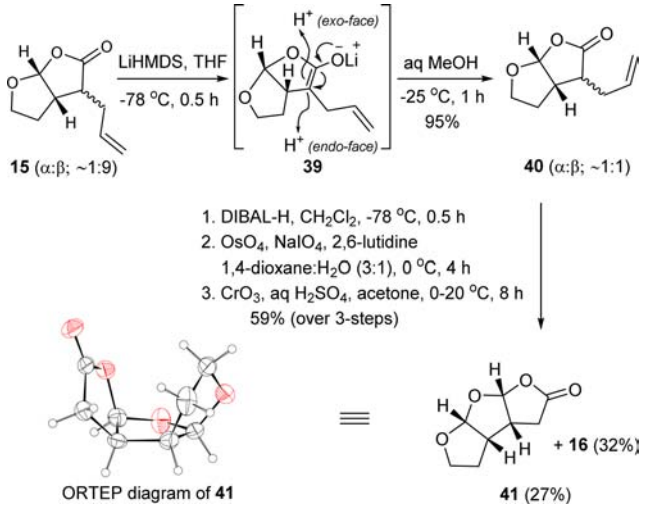


Lastly, we raised the question whether the γ-lactone annulation protocol disclosed here, leading to oligo-THFs with a *syn,anti,syn* stereochemical pattern determined by the *exo*-face preference during the allylation, could be adapted to deliver the all *syn* stereochemical array present in natural products, e.g. **4** (Figure 1). Indeed, it can be, and for this purpose monoallylated bicyclic adduct **15** was subjected to a deprotonation−reprotonation protocol. The enolate **39** generated from **15** exhibited little face selectivity and led to **40** as an ∼1:1 mixture with proton capture from both the *exo* and the *endo* face with equal facility.[16] Iteration of steps 2−4 on the diastereomer mixture led to chromatographically separable all *syn* **41** (X-ray structure) and *syn,anti,syn* **16** in almost equal ratios (Scheme 8). This outcome lends the

DOI: 10.1021/acs.orglett.5b01707
Org. Lett. 2015, 17, 3604−3607

possibility of generating the desired all *syn* stereochemical pattern on the oligo-THF framework present in some natural products.

Scheme 8. Regenerative γ-Butyrolactone Annulation to all *syn*-Tricyclic Oligo-THF Lactone



In conclusion, we have developed a short (four steps) and simple "regenerative γ-lactone annulation" strategy to access an array of "staircase-like" oligo-THFs. This efficient protocol employs table-top reagents and routine bench level operations. A few transformations have been probed to demonstrate the potential of this strategy to gain access to useful scaffolds present in natural products and other bioactive entities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of compounds, spectra and crystal data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01707.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: bilal@iiim.ac.in (B.A.B.).
*E-mail: gmehta43@gmail.com (G.M.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We wish to acknowledge the financial support from the Department of Science and Technology, India (GAP 1199) and Eli Lilly-Jubilant Bhartia Foundations. X-ray structures were determined with assistance from Dr. Saikat Sen (DRILS) and Mr. Nagarjuna Kumar Srungavruksham (UoH).

■ REFERENCES

(1) Hochlowski, J. E.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1983**, *48*, 1141.
(2) Yang, X.-Y.; Feng, T.; Li, Z.-H.; Sheng, Y.; Yin, X.; Leng, Y.; Liu, J.-K. *Org. Lett.* **2012**, *14*, 5382.
(3) (a) Ghosh, A. K.; Dawson, Z. L.; Mitsuya, H. *Bioorg. Med. Chem.* **2007**, *15*, 7576. (b) Ghosh, A. K.; Anderson, D. D.; Weber, I. T.; Mitsuya, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1778.
(4) Mayol, L.; Piccialli, V.; Sica, D. *J. Nat. Prod.* **1986**, *49*, 823.
(5) (a) Chen, X.-L.; Liu, H.-L.; Li, J.; Xin, G.-R.; Guo, Y.-W. *Org. Lett.* **2011**, *13*, 5032. (b) Vasamsetty, L.; Khan, F. A.; Mehta, G. *Tetrahedron Lett.* **2013**, *54*, 3522.
(6) Ghosh, A. K.; Xu, C.-X.; Rao, K. V.; Baldridge, A.; Agniswamy, J.; Wang, Y.-F.; Weber, I. T.; Aoki, M.; Miguel, S. G. P.; Amano, M.; Mitsuya, H. *ChemMedChem* **2010**, *5*, 1850.
(7) Mehta, G.; Vidya, R.; Venkatesan, K. *Tetrahedron Lett.* **1999**, *40*, 2417.
(8) (a) Mehta, G.; Vidya, R. *Tetrahedron Lett.* **1997**, *38*, 4173. (b) Mehta, G.; Vidya, R. *J. Org. Chem.* **2001**, *66*, 6905.
(9) (a) Schneider, T. F.; Kaschel, J.; Dittrich, B.; Werz, D. B. *Org. Lett.* **2009**, *11*, 2317. (b) Schneider, T. F.; Kaschel, J.; Awan, S. I.; Dittrich, B.; Werz, D. B. *Chem. - Eur. J.* **2010**, *16*, 11276.
(10) Mehta, G.; Vidya, R. *J. Org. Chem.* **2001**, *66*, 6913.
(11) Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094.
(12) Zhao, Y.; Zhou, Y.; Liang, L.; Yang, X.; Du, F.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 555.
(13) Lone, A. M.; Bhat, B. A.; Mehta, G. *Tetrahedron Lett.* **2013**, *54*, 5619.
(14) Wang, J.; Qian, P.; Hu, Y.; Yang, J.; Jiang, J.; Chen, S.; Zhang, Y.; Zhang, S. *Tetrahedron Lett.* **2015**, *56*, 2875.
(15) ZDero, C.; Bohlmann, F.; King, R. M.; Haegi, L. *Phytochemistry* **1988**, *27*, 2251.
(16) As suggested by a reviewer, employing a bulky proton source (2,6-di-*tert*-butyl-4-methyl phenol, BHT) or acetic acid to quench **39** made only a marginal difference to the face selectivity and **40** was obtained with nearly the same ratio of α,β-isomers (see Table 1 and supporting spectra in the Supporting Information).

DOI: 10.1021/acs.orglett.5b01707
Org. Lett. 2015, 17, 3604−3607