Organic LETTERS

Letter

pubs.acs.org/OrgLett

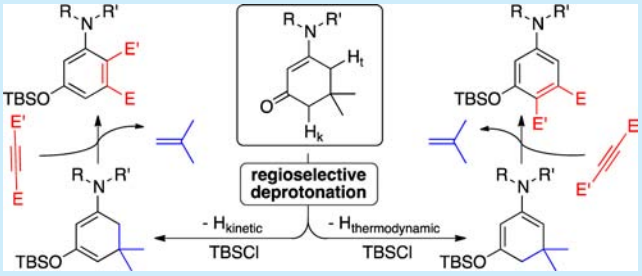
Diels–Alder Construction of Regiodifferentiated *meta*-Amino Phenols and Derivatives

Marisa G. Weaver, Wen-Ju Bai, Stephen K. Jackson, and Thomas R. R. Pettus*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106-9510, United States

Supporting Information

ABSTRACT: Synthetic access to regiodifferentiated *meta*-amino phenols is described. The strategy relies upon distinct deprotonation conditions to afford regioisomeric thermodynamic and kinetic dienes that undergo a tandem Diels–Alder and *retro*-Diels–Alder sequence with assorted acetylenic dienophiles to afford a range of aromatic products.



meta-Amino phenol (*m*-APhOH) and *meta*-amino pyridinol (*m*-APyOH) derivatives are important building blocks for natural product synthesis. They have proven themselves as privileged pharmaceutical scaffolds[1] and serve as inhibitors of JNK[2] and CGRP,[3] modulators of the delta-opioid receptor,[4] and efficacious treatment for neurological and psychiatric maladies,[5] Alzheimer's disease,[6] and various carcinomas.[7] However, differentially substituted *m*-APhOHs and *m*-APyOHs, particularly those displaying electron-deficient amino functionality, are tedious to construct by aryl nitration–reduction–protection regimes, palladium mediated cross-coupling sequences,[8] and other strategies,[9] such as conventional Diels–Alder sequences.[10]

Herein, we report a new strategy to secure these important aromatic materials by way of a regioselective deprotonation of various cyclic vinylogous amides, a plan loosely based upon Danishefsky's preliminary observations regarding the synthesis of *pseudo*-symmetric resorcinylic materials.[11]

Our process enables rapid access to regiodifferentiated aromatic materials using two isomeric dienes derived from a common cyclic vinylogous amide and uncovers equilibria between the resulting dienes, which has often been overlooked.[12] The skeletons of our regioisomeric aromatic products are found in compounds resembling tetrapetalone A (**1**) and the CGRP inhibitor (**2**) (Figure 1).[13,3]

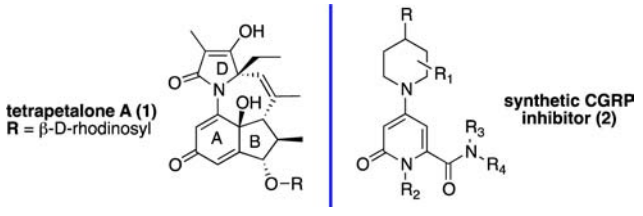
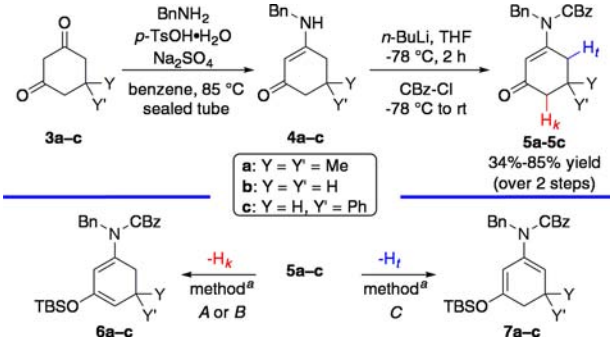


Figure 1. Products containing *m*-APhOHs and *m*-APyOHs.

Cyclic vinylogous amides (**5a–c**, Table 1) were prepared by condensation of the appropriate 1,3-cyclohexadione (**3a–3c**) with benzyl amine and acylation with benzyl chloroformate.[14] Our process continued with regioselective deprotonation of the

Table 1. Regioselective Deprotonation and Diene Formation



entry	CVA	kinetic diene (k-D)	thermodynamic diene (t-D)	deprotonation method ratio k-D/t-D
1[b,d]	**5a**	**6a**	**7a**	*C*, <1:20
2[b,d]	**5a**	**6a**	**7a**	*A*, >10:1
3[b]	**5b**	**6b**	**7b**	*C*, <1:20
4[b]	**5b**	**6b**	**7b**	*B*, ~4:1
5[c]	**5c**	**6c**	**7c**	*C*, <1:20
6[c]	**5c**	**6c**	**7c**	*B*, >10:1

[a]Method *A*: KO*t*-Bu (1.5 equiv), *n*-BuLi (1.5 equiv), −78 °C, THF (0.02 M), 20 min; **5a–c** (1.0 equiv), 10 min; TBSCl (1.4 equiv), −78 °C to rt. Method *B*: KHMDS (1.2 equiv), THF (0.02 M), −78 °C, **5a–c** (1.0 equiv), 10 min; TBSCl (1.4 equiv), −78 °C to rt. Method *C*: **5a–c** (1.3 equiv), KHMDS (1.0 equiv), THF (0.02 M), 0 °C, 5 h; TBSCl (1.1 equiv), 0 °C to rt. [b]*T* = 150 °C for DA/*r*-DA sequence. [c]*T* = 100 °C for DA/*r*-DA sequence. [d]Preferred conditions.

Received: November 27, 2013
Published: February 13, 2014

   dx.doi.org/10.1021/ol4034447 | *Org. Lett.* 2014, 16, 1294–1297

vinylogous amides (**5a–c**, Table 1) to form either the thermodynamic or the kinetic enolate.[15] Enolate interception with TBSCl furnished the corresponding dienes (**7a–c**, **6a–c**, Table 1). For example, vinylogous amide **5a** was subjected to deprotonation with KHMDS under thermodynamic enolization conditions. Addition of TBSCl afforded the diene (**7a**) as the sole product (Table 1, entry 1), which proved stable for over a month when frozen in benzene. Deprotonation of **5a** with KHMDS under kinetic enolization conditions and addition of TBSCl afforded the diene (**6a**) in an ~7:1 ratio of **6a**:**7a**. However, Schlosser's conditions (*n*-BuLi, KO*t*-Bu) reproducibly increased the ratio to >10:1, despite a lower yield (Table 1, entry 2).[16] We sought to improve the kinetic/thermodynamic diene ratio by varying the Y and Y′ substituents using vinylogous amides **5b** and **5c**. While thermodynamic dienes (**7b–c**) formed selectively as before (Table 1, entries 3, 5), the selectivity for kinetic dienes (**6b–c**) failed to improve (Table 1, entries 4, 6). We envisioned that submission of these respective dienes and a dienophile would facilitate the Diels–Alder (DA) and *retro*-Diels–Alder (*r*-DA) reaction and lead to the desired aromatic products in a controlled and predictable manner.[17]

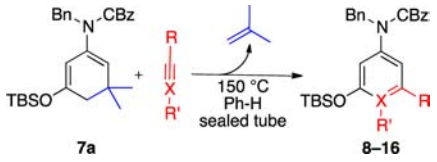
Individual submission of thermodynamic dienes (**7a–c**) and excess dimethyl acetylenedicarboxylate (DMAD) to thermal conditions facilitated the tandem DA and *r*-DA reaction to form compound **8** in all cases. However, we chose to focus on diene **7a** because of its low cost and ease of preparation. Thermodynamic diene **7a** participates in the reaction sequence with assorted dienophiles to afford desired products **8–16** in good yields (Table 2). Acetylenes mono- or disubstituted with an electron-withdrawing group both participate in the DA and subsequent *r*-DA reaction. However, the 3-bromo- and 3-chloro-propionaldehyde (entry 6) resulted in lower isolated yields. In the case employing an acetylene with nonequivalent electron-withdrawing groups (entry 7), an isomeric product mixture was obtained. The major product, **15a**, arose from the ketone acting as the predominant directing group (**15a**:**15b**, 2:1). Remarkably, ethyl cyanoformate proceeded to afford the silyl-protected *m*-APyOH **16** (entry 8), a core widely found as the corresponding pyridone in natural and synthetic products.[3]

The mixture of regioisomers **15a** and **15b** (Table 2, entry 7) proved inconsequential in one context.[18] Upon submission to potassium hexamethyldisilazide both isomers converged by cyclization to the diketone **17** in a 76% yield (Scheme 1).

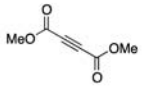
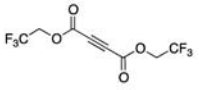
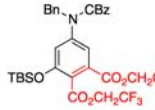
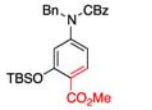
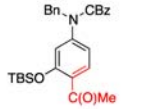
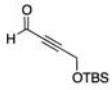
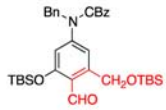
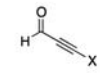
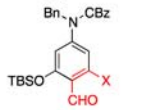
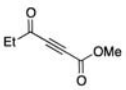
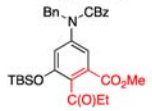
Additional chemical manipulations further demonstrate the utility of these new aromatic materials (Scheme 2). Hydrogenolysis of *bis*-protected *m*-APhOH **8** provided the aniline **18** in 96% yield, while stirring *m*-APyOH **12** with acid afforded the pyridone **19** in 90% yield.[19]

Submission of the individual kinetic dienes (**6a–c**, Table 1) to similar thermal conditions with excess DMAD dienophile gave the anticipated product **20**. However, a significant amount of undesired regioisomer **8**, resulting from diene **7a**, was also isolated. Isomeric ratios among the phenol products were nearly identical for dienes **6a–c**. As done in the thermodynamic case, we chose to focus on diene **6a**, which was submitted to the same reaction conditions as diene **7a** with a similar assortment of acetylenes (Table 3). Despite a starting diene ratio of >10:1, **6a**:**7a**, two isomeric products always formed: the expected products (**20–24**) from the kinetic diene **6a**, and their respective regioisomers resulting from the thermodynamic diene **7a**. Since the product ratios failed to reflect the initial diene ratio, we suspected that perhaps the regioisomeric dienes undergo reaction at different rates or that the ratio of **6a**:**7a**

Table 2. Cycloadditions with Thermodynamic Diene 7a

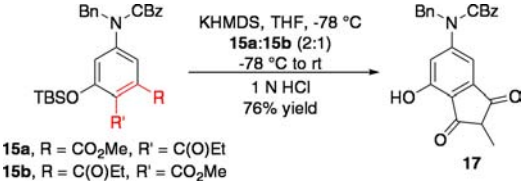


7a **8–16**

entry	dienophile	thermodynamic product	yield[a]
1[b]		 **8**	85%
2[b]		 **9**	63%
3[b]		 **10**	85%
4[b]		 **11**	79%
5[b]		 **12**	65%
6[c,e]		 **13**, X=Br **14**, X=Cl	40% 33%[f]
7[c,g]		 **15a**	67%[h]
8[d]		 **16**	61%

[a]Reaction yields based on the diene **7a** as the limiting reagent. Dienophile equivalents. [b]2 equiv. [c]4 equiv. [d]10 equiv. [e]Dienophile used without purification. [f]Yield of **14** based on the corresponding isolated phenol, characterized as such. [g]Mixture of regioisomers **15a**:**15b** (2:1); major product **15a** pictured. [h]Combined yield.

Scheme 1. Convergent Closure of Regioisomers 15a and 15b

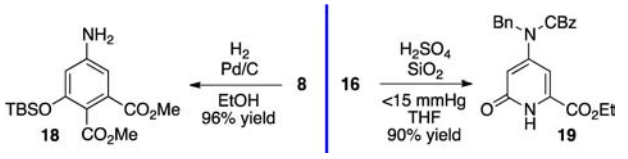


15a, R = CO_2Me, R′ = C(O)Et
15b, R = C(O)Et, R′ = CO_2Me

17

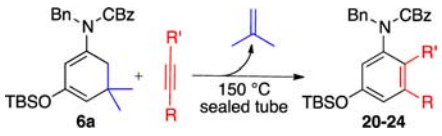
dx.doi.org/10.1021/ol4034447 | *Org. Lett.* 2014, 16, 1294–1297

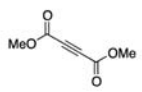
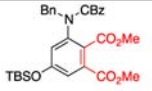
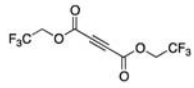
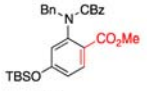
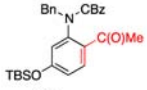
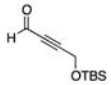
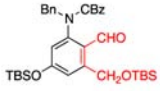
Scheme 2. Aniline and Pyridone Formation Conditions



changes during the course of the reaction. The best outcomes were observed with *bis*(trifluoroethyl)acetylene dicarboxylate (entry 2) and the propargylic aldehyde (entry 5), which are presumably more reactive dienophiles. Ethyl cyanoformate appeared to undergo successful reaction, but the product proved difficult to isolate. All isolated products (**20**–**24**) exhibit hindered rotation about the N–Ar bond due to the steric encumbrance of the neighboring group. Variable temperature experiments demonstrated free rotation, although it was difficult to fully resolve their ^{13}C spectra. A variety of Lewis acids were investigated in an attempt to improve these isomeric ratios. However, in our hands, most caused degradation of the diene to the cyclic vinylogous amide **5a**.

Table 3. Cycloadditions with Kinetic Diene 6a[a]

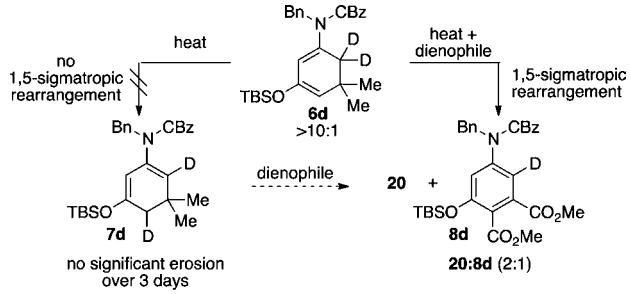


entry	dienophile	kinetic product	product ratio combined yield[b]
1[c]		 **20**	**20:8** 2:1, 80%
2[d]		 **21**	**21:9** >4:1, 59%
3[c]		 **22**	**22:10** >3:1, 73%
4[c,e]		 **23**	**23:11** >1:1, 57%
6[d]		 **24**	**24:12** ~4:1, 41%

[a]Diene ratio was >10:1 **6a**:**7a**. [b]Reaction yields based on the diene **6a** as the limiting reagent. Dienophile equivalents. [c]2 equiv. [d]4 equiv. [e]Characterized as the corresponding phenol.

To better understand the apparent isomerization,[20] a deuterated system was synthesized (Scheme 3). Diene **6d** was prepared by repetitive formation of **7a** and deuteration of the intermediate thermodynamic siloxydiene with acetic acid-d_4 to enrich the γ-position, which eventually resulted in 80% deuterium incorporation for **6d**. Upon heating, the non-deuterated diene **6a** had been found to equilibrate from >10:1 to 7:1 over 24 h to 5:1 over 3 days, and to 2:1 over 7 days. However, under strictly thermal conditions, the deuterated

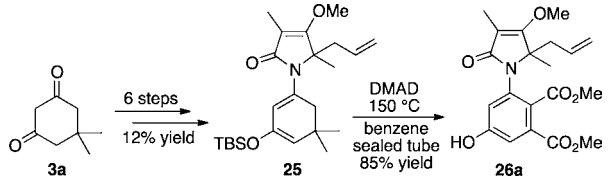
Scheme 3. Deuterium Study



diene **6d** did *not* behave similarly to afford diene **7d** (Scheme 3). Upon heating the deuterated diene **6d** with the acetylenic dienophile DMAD, aromatics **20** and **8d** arose in a 2:1 ratio by analysis of the crude NMR. This suggests that the dienophile might facilitate the formation of **7d** perhaps via a charge-transfer complex, or zwitterionic intermediate.[21] However, this notion was not probed further.

To establish the tolerance and utility of this strategy, we prepared the sophisticated diene derivative **25** in six steps and 12% yield from dimedone **3a**, using a mild SmI_2-mediated cyclization recently developed in our lab to construct the methylated tetramic acid (Scheme 4).[22] Application of our

Scheme 4. Application toward Tetrapetalone A



standard thermal conditions to a mixture of diene **25** and DMAD afforded the anticipated aromatic compound, which was desilylated by prolonged heating or exposure to fluoride and afforded compound **26a** along with its minor regioisomer (not pictured) (2:1) in an 85% combined yield.

This work demonstrates that dimedone **3a** can be used to prepare a plethora of highly functionalized *m*-APhOHs and a *m*-APyOH. This strategy is tolerant of a wide range of nitrogen appended functional groups that would not be amenable to preparation by any other existing method.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds and experimental procedures for all noncommercial dienophiles. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Pettus@chem.ucsb.edu.

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ol4034447 | *Org. Lett.* 2014, 16, 1294–1297

■ ACKNOWLEDGMENTS

T.R.R.P. is grateful that the National Institute of General Medical Sciences has supported this work (GM064831) and other studies related to the synthesis of tetrapetalones.

■ REFERENCES

(1) (a) Yang, Z.-Q.; Geng, X.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881−7889. (b) Chen, H. C.; Bai, J.; Fang, Z.-F.; Yu, S.-S.; Ma, S.-G.; Xu, S.; Li, Y.; Qu, J.; Ren, J.-H.; Li, L.; Si, Y.-K.; Chen, X.-G. *J. Nat. Prod.* **2011**, *74*, 2438−2445. (c) Dupuis, S. N.; Veinot, T.; Monro, S. M. A.; Douglas, S. E.; Syvitski, R. T.; Goralski, K. B.; McFarland, S. A.; Jakeman, D. L. *J. Nat. Prod.* **2011**, *74*, 2420−2424.

(2) Zhao, J.; Serby, M. D.; Xin, Z.; Szczepankiewicz, B. G.; Liu, M.; Kosogof, C.; Lu, B.; Nelson, L. T. J.; Johnson, E. F.; Wang, S.; Pederson, T.; Gum, R. J.; Clampit, J. E.; Haasch, D. L.; Abad-Zapatero, C.; Fry, E. H.; Rondinone, C.; Trevillyan, J. M.; Sham, H. L.; Liu, G. *J. Med. Chem.* **2006**, *49*, 4455−4458.

(3) Gottschling, D.; Dahmann, G.; Doods, H.; Heiman, A.; Mueller, S. G. U.S. Patent 065921 A2, 2009.

(4) (a) Carson, J. R.; Boyd, R. E.; Neilson, L. A. W.O. Patent 46191 A1, 2001. (b) Boyd, R. E.; Reitz, A. B. W.O. Patent 035574 A2, 2004.

(5) Aicher, T. D.; Cortez, G. S.; Groendyke, T. M.; Khilevich, A.; Knobelsdorf, J. A.; Marmsater, F. P.; Schkeryantz, J. M.; Tang, T. P. U.S. Patent 7 678 794 B2, 2010.

(6) (a) Galley, G.; Goergler, A.; Zbinden, K. G.; Norcross, R.; Stalder, H. U.S. Patent 0096906 A1, 2008. (b) Scopes, D. I. C.; Horwell, D. C. U.S. Patent 0298325 A1, 2010.

(7) (a) Bedin, M.; Gaben, A.-M.; Saucier, C.; Mester, J. *Int. J. Cancer* **2004**, *109*, 643−652. (b) Lumma, W. C. Jr.; Smith, A. M.; Sisko, J. T. U.S. Patent 6 335 343 B1, 2002.

(8) (a) Jiang, C. Ph.D. Dissertation, University of Rochester, NY, 2009. (b) Browning, R. G.; Mahmud, H.; Badarinarayana, V.; Lovely, C. J. *Tetrahedron Lett.* **2001**, *42*, 7155−7157. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (d) Kim, B. R.; Cho, S.-D.; Kim, E. J.; Lee, I.-H.; Sung, G. H.; Kim, J.-J.; Lee, S. G.; Yoon, Y.-J. *Tetrahedron* **2012**, *68*, 287−293.

(9) (a) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852−1873. (b) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 13966−13969. (c) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832−3835.

(10) *Rawal:* (a) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252−5253. *Padwa:* (b) Padwa, A.; Kissell, W. S.; Eidell, C. K. *Can. J. Chem.* **2001**, *79*, 1681−1693. (c) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088−4096. *Carter:* (d) Ashburn, B. O.; Carter, R. G. *J. Org. Chem.* **2007**, *72*, 10220−10223 ; see Supporting Information for a brief summary.

(11) (a) Geng, X.; Danishefsky, S. J. *Org. Lett.* **2004**, *6*, 413−416. (b) Yoshino, T.; Ng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 14185−14191. (c) Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S. J.; Jones, G. O.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 645−657.

(12) (a) Morrison, C. F.; Burnell, D. J. *Tetrahedron Lett.* **2001**, *42*, 7367−7369. (b) Buckle, R. N.; Burnell, D. J. *Tetrahedron* **1999**, *55*, 14829−14838. (c) Blanco, L.; Slougui, N.; Rousseau, G.; Conia, J. M. *Tetrahedron Lett.* **1981**, *22*, 645−648.

(13) *Isolation and characterization:* (a) Komoda, T.; Sugiyama, Y.; Naoki, A.; Imachi, M.; Hirota, H.; Hirota, A. *Tetrahedron Lett.* **2003**, *44*, 1659−1661. (b) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Tetrahedron Lett.* **2003**, *44*, 7417−7419. *Synthetic efforts*: (c) Wang, X.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2005**, *44*, 3067−3071. (d) Corrigenda: Wang, X.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 6607. (e) Marcus, A. P.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4560−4563. (f) Li, C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036−4039. (g) Vaidya, T.; Cheng, R.; Carlsen, P. N.; Frontier, A. J.; Eisenberg, R. *Org. Lett.* **2014**, *16*, 800−803.

(14) Edafiogho, I. O.; Hinko, C. N.; Chang, H.; Moore, J. A.; Mulzac, D.; Nicholson, J. M.; Scott, K. R. *J. Med. Chem.* **1992**, *35*, 2798−2805.

(15) (a) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979−2990 and references cited therein. (b) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *84*, 2324−2336.

(16) Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627−1634.

(17) (a) Rickborn, B. The Retro-Diels−Alder Reaction Part I. C−C Dienophiles. In *Organic Reactions*; Paquette, L., Ed.; John Wiley & Sons, Inc.: NJ, 1998; Vol. *52*, pp 1−393. (b) Rickborn, B. The Retro-Diels−Alder Reaction Part II. Dienophiles with One or More Heteroatom. In *Organic Reactions*; Paquette, L., Ed.; John Wiley & Sons, Inc.: NJ, 1998; Vol. *52*, pp 223−629.

(18) (a) Tamaru, M.; Takehi, T.; Masuyama, N.; Ryo, H. *Pestic. Sci.* **1996**, *47*, 327−336. (b) Bowden, K.; Chehel-Amiran, M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 2035−2038.

(19) Green, J. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 1603−1608.

(20) (a) Doering, W. v. E.; Zhao, X. *J. Am. Chem. Soc.* **2006**, *128*, 9080−9085. (b) Dewar, M. J. S.; Healy, E. F.; Ruiz, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 2666−2667.

(21) Harrison, R.; Rickborn, B. *Org. Lett.* **2002**, *4*, 1711−1713.

(22) Bai, W.-J.; Jackson, S. K.; Pettus, T. R. R. *Org. Lett.* **2012**, *14*, 3862−3865 ; see Supporting Information for preparation methods.