Organic LETTERS

Letter

pubs.acs.org/OrgLett

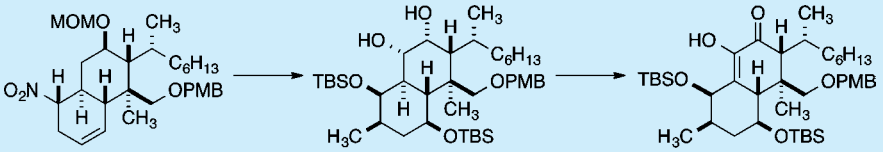
Studies toward Australifungin. A Synthesis Dilemma of Regioselective Keto−Enol Tautomerization

David R. Williams,*[,†] J. Cullen Klein,[†] Lucas C. Kopel,[†] Nhu Nguyen,[‡] and Dean J. Tantillo*[,‡]

[†]Department of Chemistry, Indiana University, Bloomington, Indiana 47405, United States

[‡]Department of Chemistry, University of California, Davis, California 95616, United States

Supporting Information



4 15 19

ABSTRACT: Studies have advanced a stereocontrolled pathway for the synthesis of australifungin. Elaboration of the *trans*-fused IMDA product **4** led to the *cis*-diol **15**, which produced the α-hydroxyenone **19** upon oxidation. Computational studies on model systems indicate that the keto−enol tautomer shown for **19** is higher in energy than the keto−enol tautomer represented by the natural product **1**. The reactivity of **19** does not permit mild isomerization and subsequent deprotection to yield **1**. These findings raise new questions regarding the synthesis and bioactivity of australifungin and related natural products.

Our synthesis investigations of australifungin (**1**, Figure 1) have focused on two objectives. The first phase of these

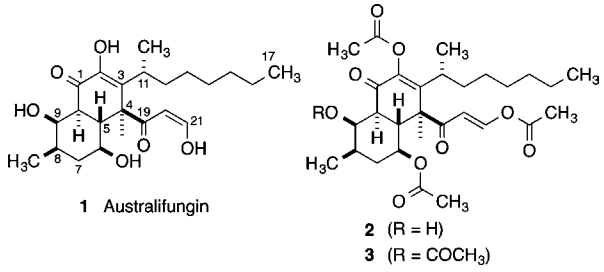


Figure 1. Australifungin and its acetate derivatives.

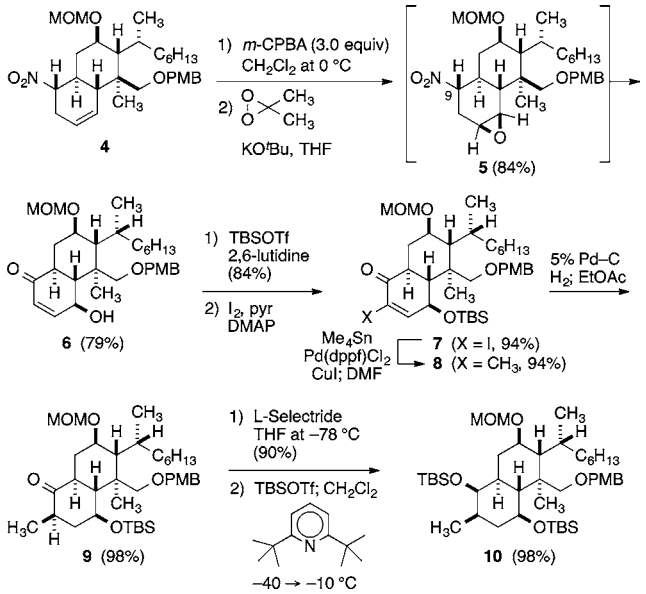
studies devised an intramolecular Diels−Alder (IMDA) approach.[1] Structural complexity in the carbon tether of a nitroalkene led to a rate acceleration in the cyclization reaction due to steric repulsions of vicinal substituents. Furthermore, the relative stereochemistry of these substituents was paramount for optimal yield of the desired *trans*-fused decalin. The second objective of our studies explored the functionalization of the decalin core, and related issues characterizing keto−enol tautomerizations within this class of natural products. Considerable efforts were undertaken by Hensens and co-workers[2] to advance the structural elucidation studies because **1** is an interconverting mixture of keto and enol isomers. Only 17 of the 23 carbons are observed in the ^{13}C NMR spectrum of **1**, and critical $^{1}H-^{1}H$ and $^{1}H-^{13}C$ connectivities are not found via the usual repertoire of 2D NMR experiments. Low temperature NMR studies at −25° to −50 °C indicate at least four to five contributing structures. As a result, the elucidation studies were advanced by the formation of triacetate **2** and tetraacetate **3**. These derivatives do not provide a straightforward solution of the problem. In fact, proton NMR spectra at −25 °C resolve two conformers in a ratio of 7:5 and 3:1 for **2** and **3**, respectively, and these mixtures have been analyzed to describe structure **1**. While conformational isomers of the B ring cannot be ruled out on the basis of *J* values and NOE effects, restricted rotation about the C3−C11 bond may be responsible for the broadening of signals and the absence of assignable ^{13}C resonances, particularly relating to this region of the proposed structure. In this letter, we have described the results of our synthesis studies toward **1**. These studies demonstrate the preparation and the characterization of derivatives of australifungin. Our computational studies have also afforded insights of potential value in advancing studies of natural products within this family.

The studies of our prior report have explored a stereoselective route to provide the *trans*-decalin core of the natural product by utilizing a nitroalkene as a surrogate ketene equivalent in an effective IMDA cycloaddition. Direct conversion of the Diels−Alder product **4** (Scheme 1) into the desired enone **6** illustrates a useful application of the Nef reaction for general construction of γ-hydroxy-α,β-unsaturated cyclohexenones proceeding via a base-induced elimination of an epoxyketone intermediate. In fact, the C=C epoxidation and the Nef oxidation[3] of **4** is achieved with excess *meta*-chloroperbenzoic acid (MCPBA) and judicious choice of base. However, the oxirane proved to be labile under acid and basic conditions, complicating the timing of these reaction events. Thus, direct oxidation of **4** is accomplished with reduced yields of **6** and with the production of several

Received: December 4, 2015
Published: January 19, 2016

DOI: 10.1021/acs.orglett.5b03464
Org. Lett. 2016, 18, 424−427

Scheme 1. Elaboration of A-Ring Substitution



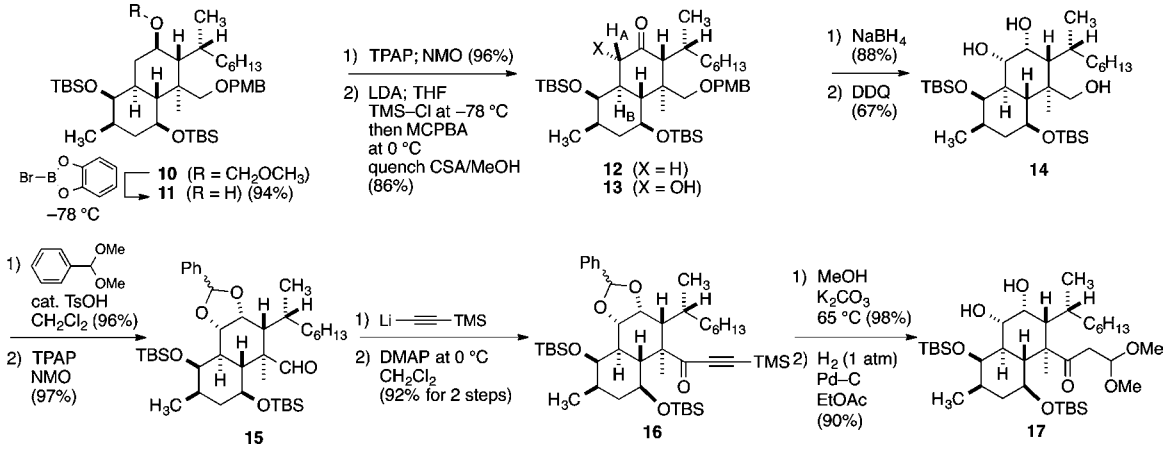
byproducts. These issues are avoided by uneventful epoxidation of **4** using excess MCPBA to give **5**, which can be isolated and characterized (84% yield) by significant improvements employing the introduction of small amounts of the radical inhibitor, 4,4′-thiobis(2-*tert*-butyl-6-methylphenol),[4] and the addition of anhydrous KF to precipitate the remaining MCPBA and *m*-chlorobenzoic acid prior to an aqueous workup. The application of the Nef reaction utilizes **5** with KO^{t}Bu in the presence of dimethyldioxirane to yield the desired enone **6** and a small quantity of the C-9 epimer of **5** (5%). After conversion of **6** to its corresponding *tert*-butyldimethylsilyl (TBS) ether, iodination[5] proceeds smoothly to **7**, and the cross-coupling of **7** with tetramethylstannane is catalyzed by Pd(dppf)Cl_2 to efficiently install α-methyl substitution in the enone **8**. The hydrogenation of **8** affords a single diastereomer **9**, and the carbonyl reduction with L-Selectride leads to the axial alcohol at C-9 for protection as its corresponding TBS ether **10**. Alternatively, the conjugate reduction of enone **6** with Stryker's reagent[6] and stoichiometric $(HMe_2Si)_2O$ is effective (>70% yields), but the subsequent α-methylation by kinetic deprotonation with LDA and addition of methyl iodide produces nearly equal amounts of the diastereomeric C-8 methylketones.

The elaboration of the B-ring substitution begins by removal of the methoxymethyl (MOM) ether of **10** upon treatment with B-bromocatecholborane at −78 °C in the presence of 2,6-di-*tert*-butylpyridine to give the alcohol **11** for TPAP oxidation[7] to the C-2 ketone **12** (Scheme 2). A regiocontrolled kinetic deprotonation of **12** leads to the formation of an intermediate TMS enol ether for Rubottom oxidation[8] with MCPBA at 0 °C to afford hydroxyketone **13**. The stereochemistry of the α-hydroxylation is assigned by the characterization of the *trans*-diaxial (J_{AB} = 11.3 Hz) relationship of the vicinal hydrogens H_A and H_B (δ 4.52 and δ 4.30, respectively) of the product.

Sodium borohydride reduction of **13** is followed by oxidative deprotection of the *para*-methoxybenzyl (PMB) ether to provide the triol **14**. This key intermediate has been utilized for acetal formation of the vicinal *cis*-diol providing an inseparable mixture (1.6:1) of the expected benzylidene acetals, and TPAP oxidation[7] of the remaining primary alcohol gives the aldehyde **15**. The steric environment of the aldehyde in **15** necessitates the use of a compact, reactive nucleophile for carbonyl addition. This requirement is met by the lithium anion derived by *n*BuLi deprotonation of trimethylsilylacetylene at −78 °C. The resulting mixture is immediately oxidized with the Dess–Martin periodinane[9] at 0 °C, and the conjugated alkynone **16** is characterized as a 1.3:1 mixture of benzylidine acetals (92% yield for 2 steps) following flash chromatography. The removal of the trimethylsilyl group and subsequent acetal formation[10] occurs upon heating **16** in anhydrous methanol in the presence of potassium carbonate, and hydrogenolysis then produces the key intermediate diol **17**.

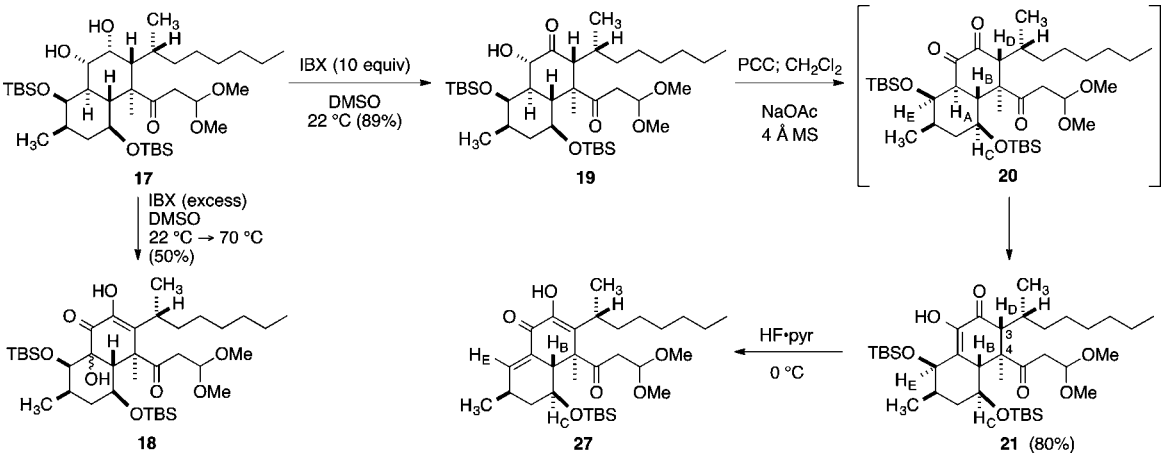
Progress toward australifungin (**1**) is advanced in Scheme 3 and reveals an unexpected enolization of the 1,2-dicarbonyl moiety within the B ring. Our initial attempts for direct formation of the desired α-hydroxyenone system, analogous to **1**, employed the diol **17** for treatment with excess IBX reagent in anhydrous DMSO. An overoxidized product was isolated in modest yield. The small quantity of sample and the coelution of impurities did not permit full characterization. However, this substance was tentatively assigned structure **18** on the basis of the high resolution mass (HRMS) data confirming the additional hydroxylation, as well as the disappearance of NMR signals for the C-3 and C-10 methine hydrogens. Indeed, other members of the natural product family exhibit this

Scheme 2. Elaboration of B-Ring Functionality



DOI: 10.1021/acs.orglett.5b03464
Org. Lett. 2016, 18, 424–427

Scheme 3. Oxidations of the Australifungin Decalin Core



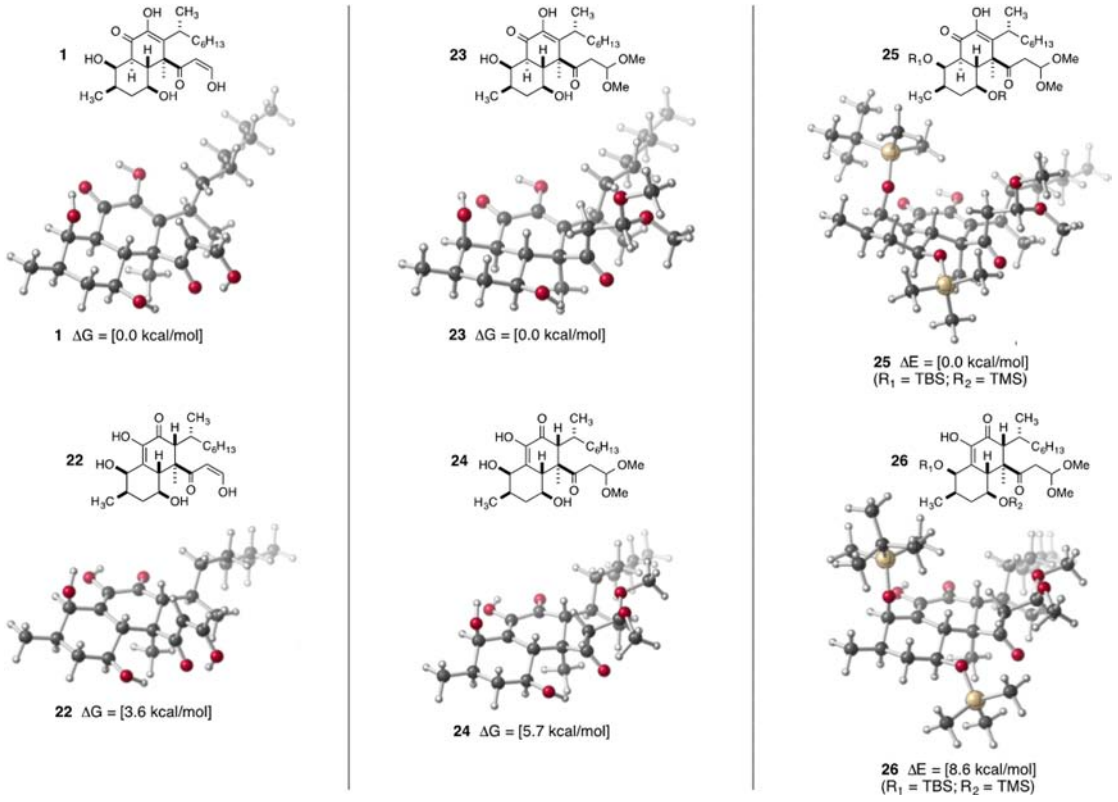


Figure 2. Computational results.[12]

oxidation pattern.[11] Unfortunately, the pseudosymmetry of the substitution pattern for the precursor α-diketone that leads to this additional hydroxylation raises ambiguities regarding the structural similarities of isomeric enols featuring the production of either C-3 or C-10 oxidation. Stepwise oxidations of the diol **17** have proven to be more fruitful. In this manner, oxidation with IBX (10 equiv) in anhydrous DMSO at 22 °C for 16 h produces the α-hydroxyketone **19** (89%). Similarities in the proton NMR data with the Rubottom product **13** advanced additional evidence for the formation of the C-2 ketone of **19**. Further treatment with PCC in methylene chloride in the presence of small amounts of NaOAc and powdered 4 Å molecular sieves resulted in formation of an unstable 1,2-diketone **20**, which was immediately characterized by proton NMR spectroscopy. Samples quickly tautomerized to the α-hydroxy enone **21** during purification by silica gel chromatography or upon standing at room temperature.

The diketone **20** is characterized by the *trans*-diaxial arrangement of the hydrogens H_A, H_B, and H_C. A diagnostic pattern of a doublet of doublets for H_A δ 2.16 (dd, J = 11.6 and 1.2 Hz) and H_B δ 3.24 (dd, J = 11.6 and 9.8 Hz) is observed. The C-6 methine H_C at δ 3.57 (ddd, J = 9.8, 9.4, 3.6 Hz) is identified by its coupling to H_B and the adjacent diastereotopic methylene. The methine hydrogen H_D is observed at δ 2.82 as a broad, poorly resolved signal due to contributions of slowly interconverting C-3/C-11 conformers, and hydrogen H_E is also seen as a broad singlet because of small coupling constants with its vicinal neighbors at δ 4.50 (dd, J = 1.3, 1.2 Hz). Enolization of **20** did not occur as we had anticipated based on numerous metabolites that have been described among this family of

DOI: 10.1021/acs.orglett.5b03464
Org. Lett. 2016, 18, 424−427

natural products. The diosphenol functionality of **21** is recognized by the absence of the bridgehead H_A of diketone **20**, and a simple doublet at δ 3.27 (d, J = 10.0 Hz) for H_B, which is coupled to the axial hydrogen H_C (d 3.63 (ddd, J = 10.9, 10.0, 3.7 Hz)). The methine hydrogen H_D appears as an unresolved multiplet at δ 2.60, indicative of the conformational restrictions imposed by the steric crowding of C-3 and C-4 substituents, which produce a slow interconversion of conformational isomers. The C-9 hydrogen H_E is observed as a doublet at δ 4.72 (J = 1.9 Hz), and the exchangeable enolic signal appears at δ 6.23 (s, 1H). The formation of the tautomer **21** is unanticipated, since we had assumed that the enolization of **1** and its acetate derivatives reflected a thermodynamic preference (*vide infra*).

To address this issue, we undertook computational studies to compare the relative free energies of australifungin (**1**) and its tautomer **22** (using the M06-2X/6-31+G(d,p) method as implemented in Gaussian09 with the SMD continuum solvent model for *n*-hexane).[12] The results of these calculations (Figure 2) indicated that **1** is indeed lower in energy than isomeric **22** by 3.6 kcal/mol. We also probed the effect of the presence of the dimethylacetal and the silyl ethers on the relative energies of the corresponding enols. Introduction of the dimethylacetal moiety (**23** and **24**) leads to an increase in the preference for the tautomer that is represented in the natural product. Upon introduction of TMS protecting groups (**25** and **26**, $R_1 = R_2$ = TMS), the australifungin arrangement is still preferred (see Supporting Information (SI)). Incorporation of the C_9-OTBS ether (modeled with a C_6-OTMS; Figure 2, structures **25** and **26**) leads to an even greater preference. Frequency calculations were not completed on this system, so the latter comparison is based on electronic energies only. The vicinal diketone, corresponding to **20**, is predicted to be higher in energy (see SI for details). Thus, the difficulty in producing **1** synthetically appears to be kinetic in nature. We have examined all of the usual conditions for TBS silyl ether deprotection of **21**, which has proven to be very labile. While most procedures lead to decomposition, the use of HF·pyridine (70% HF/30% pyridine) at 0 °C provided modest yields (31%) of the elimination product **27** (Scheme 3) at 50% conversion. The sterically hindered C_6-OTBS ether is surprisingly unreactive. The ease of elimination of the axial C_9-OTBS substituent in **21** leads to speculation that a reversible hydration involving the conjugate addition of water could provide a reaction pathway to the natural product. Moreover, the discovery of the facile elimination to **27** introduces a novel Michael acceptor that may be a key site of reactivity associated with the observed biological fate of the natural product.

Overall, our synthesis studies toward australifungin have advanced an IMDA strategy using an *E*-nitroalkene dienophile for stereocontrolled formation of a highly substituted *trans*-fused decalin. Oxidations of the $[4\pi + 2\pi]$ product provide an efficient method for preparation of a γ-hydroxy-α,β-unsaturated cyclohexenone that is readily advanced to fully functionalized australifungin derivatives. Computational studies have shown the natural product to be the thermodynamically favored tautomer. However, synthetic studies have produced the less stable keto−enol regioisomer, which undergoes facile elimination. These results pose an unexpected dilemma for our continuing studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03464.

Experimental details, ^{1}H and ^{13}C NMR spectra, additional details on computational results (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: williamd@indiana.edu.
*E-mail: djtantillo@ucdavis.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

D.R.W. acknowledges the National Science Foundation (NSF, CHE-1362561). D.J.T acknowledges computational support from the NSF's XSEDE program). The authors thank Merck and Co. (J. Obenchain) for a research sample of australifungin for comparison studies.

■ REFERENCES

(1) See preceding letter: Williams, D. R.; Klein, J. C. *Org. Lett.* **2015**, DOI: 10.1021/acs.orglett.5b03463.

(2) Hensens, O. D.; Helms, G. L.; Jones, E. T. T.; Harris, G. H. *J. Org. Chem.* **1995**, *60*, 1772−1776.

(3) For a review of the Nef oxidation: Pinnick, H. W. *Org. React.* **1990**, *38*, 655−792.

(4) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64−65.

(5) For related iodination conditions: (a) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917−918. (b) Gautier, E. C.; Lewis, N. J.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759−8760.

(6) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779−2788.

(7) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *1994*, 639−666.

(8) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319−4322. (b) Jauch, J. *Tetrahedron* **1994**, *50*, 12903−12912.

(9) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7278.

(10) Takao, K.; Nagata, S.; Kobayashi, S.; Ito, H.; Taguchi, T. *Chem. Lett.* **1998**, *27*, 447−448.

(11) For examples of related metabolites which exhibit this hydroxylation pattern: Brauers, G.; Edrada, R. A.; Ebel, R.; Proksch, P.; Wray, V.; Berg, A.; Gräfe, U.; Schächtele, C.; Totzke, F.; Finkenzeller, G.; Marme, D.; Kraus, J.; Münchbach, M.; Michel, M.; Bringmann, G.; Schaumann, K. *J. Nat. Prod.* **2000**, *63*, 739−745.

(12) (a) M06-2X: Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241. (b) *Gaussian 09*, Revision B.01; Gaussian, Inc.: Wallingford, CT, 2009 (full reference in Supporting Information). (c) SMD: Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396. (d) Structural images produced with: Legault, C. Y. *CYLview*, 1.0b; Université de Sherbrooke, 2009 (http://www.cylview.org).

DOI: 10.1021/acs.orglett.5b03464
Org. Lett. 2016, 18, 424−427