ORGANIC LETTERS

2011
Vol. 13, No. 6
1382–1385

Diversity-Oriented Approach to Pyrrole-Imidazole Alkaloid Frameworks

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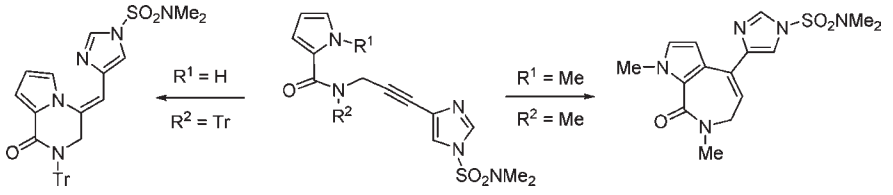
Received January 10, 2011

ABSTRACT



An exploration of imidazolylpropargyl amides as linchpin synthons for the construction of a diverse array of heterocyclic frameworks, many of which are related to those found in the oroidin derived alkaloids, is described. One such intermediate has been used in a formal total synthesis of cyclooroidin.

Nature is the ultimate synthetic chemist using a relatively limited group of building blocks with a large variety of enzymes to construct a vast array of secondary metabolites, using what can be thought of as reagent-controlled, diversity-oriented synthesis.[1,2] These so-called natural products have attracted the attention of organic chemists not only for the challenge they often present to contemporary synthetic methods[3] but also for their potential as lead compounds in medicinal chemistry endeavors.[4,5] Attempts have been made to harness the latent reactivity embedded within these building blocks in synthetic programs, but even state of the art synthetic methods cannot compete with biosynthetic machinary to produce the same levels of control, selectivity, and diversity. An additional limitation of such an approach is that using biosynthetic precursors (or close analogs) can often restrict synthetic options for accessing different cyclic frameworks or for postcyclization functionalization from a common precursor and thus can reduce structural diversity in medicinal chemistry programs. One way to circumvent these limitations is to utilize a minimally functionalized substrate which contains a functional group or groups which by suitable choice of reagents has multiple reaction pathways available to it leading to diverse cyclic frameworks and which can undergo additional postreaction chemistry.

Our group[6] has over the past few years developed an interest in inventing synthetic approaches to the oroidin family of alkaloids (e.g., **1**−**8**, Figure 1).[7,8] These marine sponge-derived natural products exhibit the characteristics described above, wherein a single building block (oroidin (**1**) in this case) gives rise to several different natural products through various modes of presumably enzyme-catalyzed cyclization or oligomerization/cyclization (to date >150 family members have been reported). As a result, oroidin monomers **4**−**6**,[9−14] dimers **7**−**8**,[15−17] and tetramers[18] are known to display a wide variety of

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(1) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48.
(2) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele, C. *Nat. Prod. Rep.* **2008**, *24*, 719.
(3) Morris, J. C.; Phillips, A. J. *Nat. Prod. Rep.* **2010**, *27*, 1186.
(4) Newman, D. J.; Cragg, G. M. *J. Nat. Prod* **2008**, *70*, 461.
(5) Capon, R. J. *Eur. J. Org. Chem.* **2001**, 633.
(6) He, Y.; Du, H.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, 965.
(7) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2010**, *27*, 165.
(8) (a) For recent reviews, see: Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scolaro, A.; Papeo, G. *Mar. Drugs* **2009**, *7*, 705. (b) Weinreb, S. M. *Nat. Prod. Rep.* **2007**, *24*, 931.
(9) Fattorusso, E.; Taglialatela-Scafati, O. *Tetrahedron Lett.* **2000**, *41*, 9917.
(10) For total synthesis, see: (a) Mukherjee, S.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J. *Org. Lett.* **2010**, *12*, 4940 and references cited therein. See also: (b) Trost, M. B.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800.
(11) Albizati, K. F.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 4163.

10.1021/ol200067e
Published on Web 02/21/2011

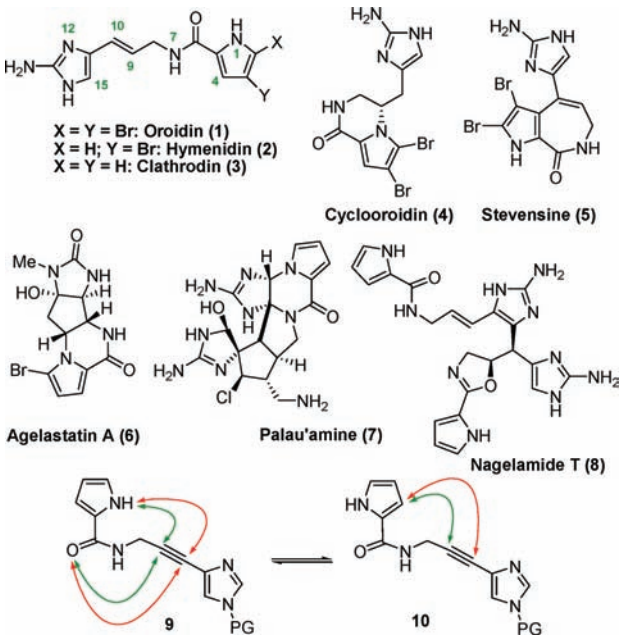
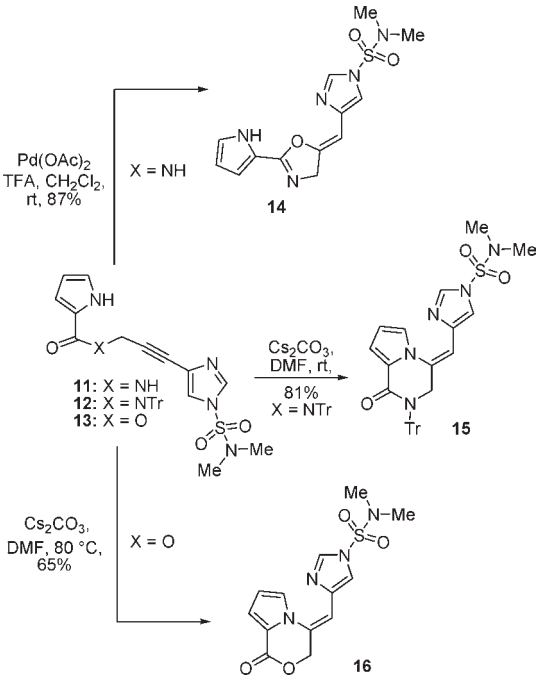


Figure 1. Selected oroidin-derived alkaloids.

connectivities and functionalization. While we and others have been interested in developing total syntheses of several members of this family of natural products, we have also developed an interest in accessing new frameworks that can be formally derived from oroidin through heretofore undiscovered cyclization pathways. It is worth noting that Lindel pointed out in a seminal review of the oroidin alkaloids that, intrisically at least, various other connectivities not yet observed in nature are not only

Scheme 1



conceivable for this family of natural products but also energetically reasonable.[19]

It is with this notion in mind that we have pursued a strategy to the oroidin alkaloids in which we have attempted to mimic nature's approach to secondary metabolite construction by utilizing a common type of building block and using reagent control to access a variety of different frameworks. To begin to accomplish these goals, our attention has been focused on imidazolylpropargyl amides (e.g., **9**, Figure 1). This substrate was selected for exploration due to a combination of ease of preparation (Sonogashira reaction with terminal acetylenes and haloimidazole derivatives), we have used such intermediates in total synthesis endeavors, and the potential spectrum of chemistry which it could undergo.[20] Specifically, intramolecular cyclization reactions were targeted for investigation, and as a result, several pathways can be identified depending on which position of the pyrrolecarboxamide (C4-carbon, N1-nitrogen, or carbonyl oxygen, Figure 1) and the mode of alkyne cyclization (*exo* vs *endo*) engage in the reaction. The specific reaction pathway followed would then depend upon the reagents chosen and the specific characteristics of the substrate.

Our initial experiments toward these goals focused on the use of a parent system **11** (Scheme 1) wherein both the pyrrole and amide nitrogen atoms were left unsubstituted; this substrate would provide an idea of the baseline reactivity of these systems. Gratifyingly, when **11** was treated with a combination of $Pd(OAc)_2$ and TFA at room temperature cyclization occurred to provide the oxazoline

(12) Xu, Y.-z.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1997**, *62*, 456.

(13) (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305. (b) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895. (c) D'Ambrosio, M.; Guerriero, A.; Ripamonti, M.; Debitus, C.; Waikedre, J.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 727. (d) Hong, T. W.; Jimenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158. (e) Tilvi, S.; Moriou, C.; Martin, M.-T.; Gallard, J.-F.; Sorres, J.; Patel, K.; Petek, S.; Debitus, C.; Ermolenko, L.; Al-Mourabit, A. *J. Nat. Prod.* **2010**, *73*, 720.

(14) For a recent synthetic contribution, see: Movassaghi, M.; Siegel, D. S.; Han, S. *Chem. Sci.* **2010**, *1*, 561.

(15) (a) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376. (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. (c) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573. (d) Grube, A.; Kock, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320. (e) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, *48*, 2127.

(16) For the total synthesis of palau'amine, see: (a) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095 and references cited therein. Also see:(b) Namba, K.; Inai, M.; Sundermeier, U.; Greshock, T. J.; Williams, R. M. *Tetrahedron Lett.* **2010**, *51*, 6557. (c) Feldman, K. S.; Nuriye, A. Y. *Org. Lett.* **2010**, *12*, 4532. Ma, Z.; Lu, J.; Wang, X.; Chen, C. *Chem. Commun.* **2011**, *47*, 427.

(17) Araki, A.; Kubota, T.; Aoyama, K.; Mikami, Y.; Fromont, J.; Kobayashi, J. *Org. Lett.* **2009**, *11*, 1785.

(18) (a) Grube, A.; Koeck, M. *Org. Lett.* **2006**, *8*, 4675. See also:(b) Buchanan, M. S.; Carroll, A. R.; Addepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **2007**, *72*, 2309.

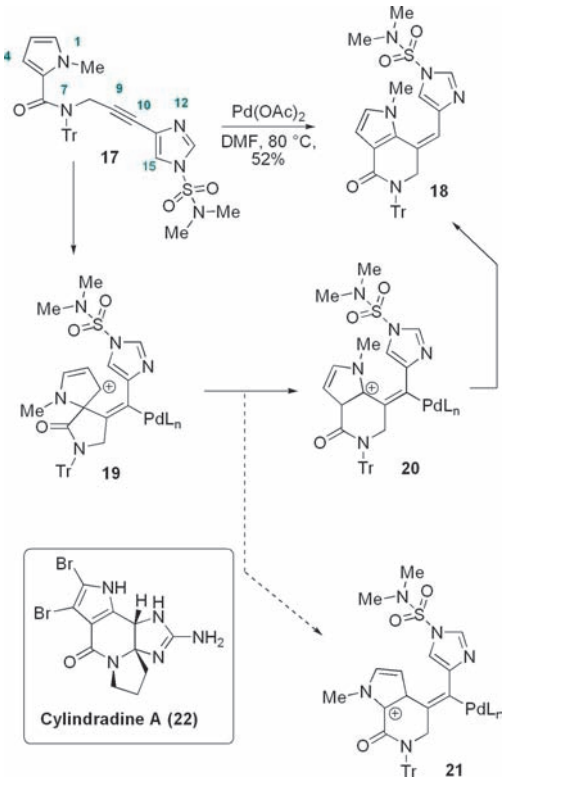
(19) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753.

(20) Bhandari, M. K.; Sivappa, R.; Lovely, C. J. *Org. Lett.* **2009**, *11*, 1535.

14 (Scheme 1).[21] A related structural fragment is found in the oroidin dimers nagelamide R and T (**8**),[17,22,23] and therefore this chemistry may have value in approaches to these natural products.[23] To redirect this cyclization manifold, two substrates were prepared in which the participation of the enol tautomer was not feasible. In the first case, the ester analog of **11** was subjected to Pd-catalyzed hydroamination ($Pd(OAc)_2$, Cs_2CO_3), leading to formation of the morpholinone ring (**13**→**16**, 45%, Scheme 1), the connectivity, and in particular the location and geometry of the olefin, was established by X-ray crystallography. Similarly, it was found that the Tr-protected amide **12** participated in the cyclization with Pd-catalysis providing the corresponding pyrazinone **16** (~80%, Scheme 1). Interestingly, we found that both reactions proceeded equally or more efficiently in the absence of the Pd-catalyst, indicating that the reaction is simply base-mediated.[24] Of particular note is the relative efficiency of the base-induced formation of **16**, which is presumably a result of the buttressing effect of the Tr-moiety.[25]

Given our success with the cyclization of substrates via the pyrrole nitrogen (Scheme 1), we decided to introduce substituents on this nitrogen to prevent cyclization via this manifold to establish whether cyclization would occur via C−H insertion at the pyrrole C4 atom (net hydroarylation).[26,27] For convenience only, an *N*-methyl group was employed. Under Pd-catalysis smooth cyclization of **17** occurred (Scheme 2) to provide what we initially anticipated was an isocyclooroidin skeleton; however, X-ray crystallography provided something of a surprise. While cyclization had occurred to provide a piperidine-type ring system, there was net acyl migration resulting in the formation of **18**. While this result was unexpected, a rearranged pyrrole moiety has been observed recently in two examples of the oroidin alkaloids, e.g., cylindradine A (**22**),[28] and this modification may in fact be a more common structural feature than currently realized. A similar type of rearrangement has been noted previously in the literature during a study of oxidative Heck-type reactions with *N*-allyl pyrrolecarboxamides.[29] This outcome was rationalized mechanistically through *ipso* addition to form a spirocyclic intermediate, which then rearranges to form fused systems. A similar mechanistic proposal through spiro adduct **19** rearranging to the more

Scheme 2

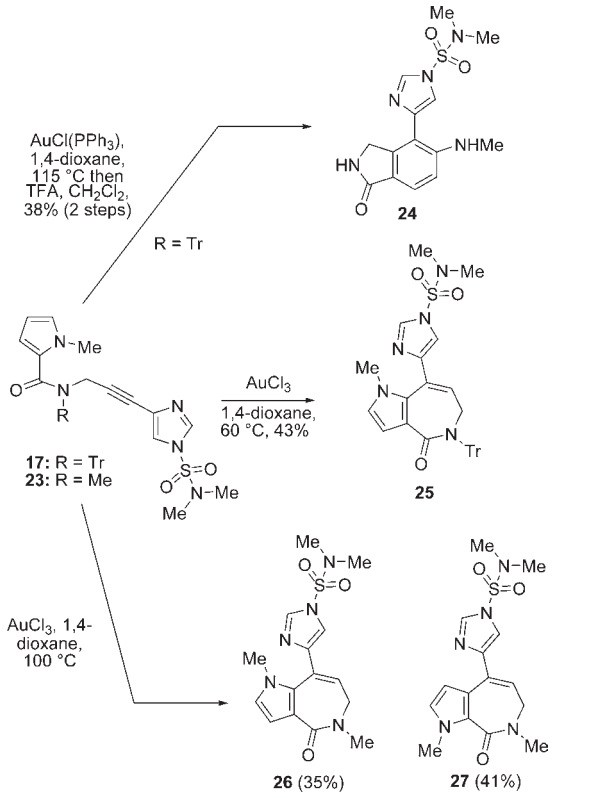


stable intermediate **20** (vis à vis the alternative rearrangement pathway to **21**) presumably accounts for the formation of the observed product **18**.

Gold-catalyzed reactions of alkynes have recently attracted considerable attention in the literature,[30] and it seemed relevant to establish the reactivity patterns of this system. In particular, we were motivated by the notion that access to stevensine-like systems (cf. **5** in Figure 1) might be possible via a gold-catalyzed addition of the pyrrole to the alkyne (hydroarylation).[31] In an initial attempt, alkyne **17** was exposed to a Au(I) precatalyst resulting in conversion of the starting material into a new cyclic product. Preliminary structural assignment was complicated by signals from the trityl moiety dominating the aromatic region of the ^{1}H NMR spectrum. Treatment of the initial product with TFA resulted in the cleavage of the trityl moiety which substantially simplified the spectroscopic data and allowed us to assign the product structure as the *N*-methyl aniline derivative **24** (Scheme 3). This structure was subsequently confirmed through X-ray crystallography. Given the relatively high temperatures required to effect this reaction, it would suggest that this product is formed as a result of an intramolecular Diels−Alder/ring-opening reaction

(21) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516.
(22) Appenzeller, J.; Tilvi, S.; Martin, M.-T.; Gallard, J.-F.; El-bitar, H.; Dau, E. T. H.; Debitus, C.; Laurent, D.; Moriou, C.; Al-Mourabit, A. *Org. Lett.* **2009**, *11*, 4874.
(23) Mukherjee, S.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J. *Synlett* **2010**, 817.
(24) Llauger, L.; Bergami, C.; Kinzel, O. D.; Lillini, S.; Pescatore, G.; Torrisi, C.; Jones, P. *Tetrahedron Lett.* **2009**, *50*, 172.
(25) Choony, N.; Dadabhoy, A.; Sammes, P. G. *Chem. Commun.* **1997**, 513.
(26) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.
(27) Gryko, D. T.; Vakuliuk, O.; Gryko, D.; Koszarna, B. *J. Org. Chem.* **2009**, *74*, 9517.
(28) Kuramoto, M.; Miyake, N.; Ishimaru, Y.; Ono, N.; Uno, H. *Org. Lett.* **2008**, *10*, 5465.
(29) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Paladino, G. *Tetrahedron* **2005**, *61*, 1077.
(30) For recent reviews of gold chemistry, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (e) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (f) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885.
(31) Gruit, M.; Michalik, D.; Krüger, K.; Spannenberg, A.; Tillack, A.; Pews-Davtyan, A.; Beller, M. *Tetrahedron* **2010**, *66*, 3341.

Scheme 3



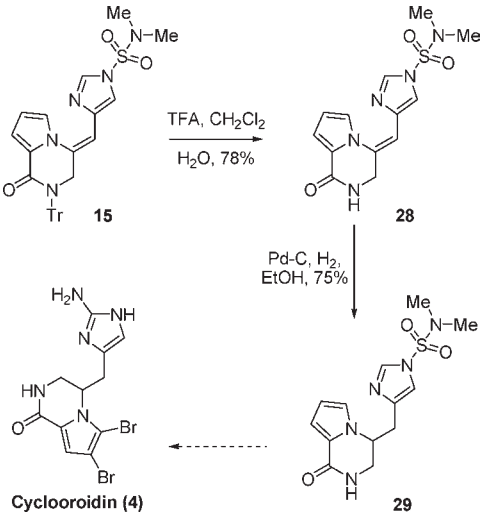
between the pyrrole and the alkyne.[32] A control reaction conducted in the absence of the Au(I) complex indicated that the cycloaddition proceeds under the same conditions, but the efficiency is somewhat attenuated and additional byproducts are formed. This result provides circumstantial evidence that there may be catalysis by Au(I). Changing the catalyst from a Au(I) to a Au(III) salt resulted in a change-over in the product, leading to the formation of the azepine derivative **25** (confirmed by X-ray analysis) as the only isolated product.[33] This result mirrors the observations of the Beller lab which reported on the cyclization reactions of related substrates.[31] As with these literature examples, rearrangement of the pyrrole carboxamide moiety occurred. Mechanistically, a similar *ipso* addition−rearrangement pathway was proposed (cf. Scheme 2) to account for the acyl migration. We noted that there was substantial loss of the trityl moiety in this chemistry, and thus we prepared and evaluated the corresponding N_{amide}-methyl derivative **23**. Interestingly, we found that this change results in the formation of two azepine derivatives **26** and **27** (confirmed by X-ray crystallography), of which the major product resembles the core framework of stevensine (**5**).

One of the reasons that we initiated this program was to use these cyclic derivatives as launching points for total

(32) Jung, M. E.; Rohloff, J. C. *J. Chem. Soc., Chem. Commun.* **1984**, 630.

(33) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358.

Scheme 4



synthesis efforts. In Scheme 4 we illustrate an application of one of these derivatives in a formal total synthesis of cyclooroidin (**4**).[10] Pyrazinone **15** was treated with TFA to remove the Tr-protecting group providing **28**; X-ray crystallography clearly indicated that the double bond was exocyclic with the geometry shown. Subjection of the resulting enamine **28** to catalytic hydrogenation resulted in the formation of the reduction product **29**, a compound which has served as an intermediate in the total synthesis of cyclooroidin (**4**) reported by our group.[10]

In this manuscript we have reported a diversity-oriented approach to several structurally distinct frameworks some of which are found in the oroidin alkaloids from a common type of building block. Our strategy is predicated on a pseudo biomimetic approach, wherein a common precursor type is employed in a number of different reagent-controlled reactions. We have demonstrated the value of this approach in a formal total synthesis of cyclooroidin (**4**). While at this stage there is room for optimization of individual cyclization manifolds, we anticipate the real value of this chemistry is the generation of multiple ring systems amenable to further elaboration and in SAR evaluations.

Acknowledgment. We thank Prof. R. Sivappa (UMAss-Dart) for valuable discussions during the initial phases of this project. This work was supported by the Robert A. Welch Foundation (Y-1362) and the NIH (GM065503). The NSF (CHE-0234811 and CHE-0840509) is thanked for partial funding of the purchases of the NMR spectrometers used in this work.

Supporting Information Available. Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. CIFs for compound **16**, **18**, **24**, **25**, **27**, **28**. This material is available free of charge via the Internet at http://pubs.acs.org.