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Cobalt-Mediated Approach for the Synthesis of Terpene-Based Hybrids

Elsa Álvaro,[†] María C. de la Torre,*[,†] and Miguel A. Sierra*[,‡]

Instituto de Química Orgánica. Consejo Superior de Investigaciones Científicas (CSIC), Juan de la Cierva 3, 28006-Madrid, Spain, and Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

iqot310@iqog.csic.es; sierraor@quim.ucm.es

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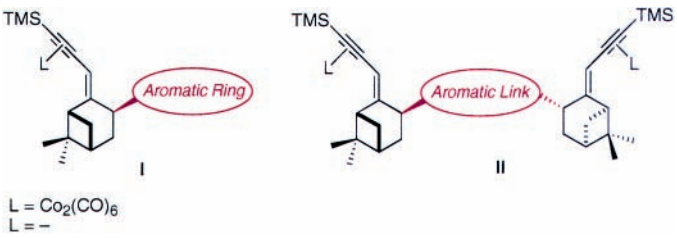
ABSTRACT



Dicobalt-β-pinene hybrids of types I and II have been prepared using a Nicholas reaction between propargyl derivatives, obtained from commercial (1*R*)-(−)-myrtenal, and different aromatic nucleophiles. The method is suitable for the preparation of densely functionalized bio-organometallic natural product-based hybrids, as demonstrated by the preparation of a β-pinene–neoclerodane hybrid.

The synthesis of hybrid natural products and analogues has emerged as a promising approach to increase the number and the diversity of structural types for applications such as pharmacological testing.[1] This concept imitates nature since many natural products having unusual biological activities are biosynthesized through mixed biogenetic pathways.[2] The interaction between the fragments, arising from the different pathways, controls and modulates conformation, recognition, transport, or solubility properties and, therefore, the biological activity.[3] Hybrids made by incorporation of a metallic fragment into organic compounds may be an interesting addition to the emerging field of bio-organometallic chemistry.[4]

Co-cluster stabilized α-carbocations[5] offer a paramount opportunity to effect the preparation of bio-organometallic hybrid structures. In fact, the Nicholas reaction has been profusely used in organic synthesis.[6] Reported herein is the development of methodology to access to monoterpene- (**I**) and dihomoterpene-aromatic hybrid analogues (**II**) (Figure 1). Our approach uses a Nicholas reaction between easily available propargyl derivatives, prepared from commercial (1*R*)-(−)-myrtenal, and different aromatic nucleophiles.

(1*R*)-(−)-Myrtenal (**1**) was selected as the terpenic component of the hybrids. The propargyl alcohol (**2**) and its acetylated derivative (**3**) were obtained, as a mixture of

* To whom correspondence should be addressed.
[†] Instituto de Química Orgánica.
[‡] Departamento de Química Orgánica.

(1) See, for example: (a) Hopen, S.; Emde, U.; Friedrich, T.; Grubert, L.; Koert, U. *Angew. Chem., Int. Ed.* **2000**, *39*, 2099. (b) Tietze, L. F.; Schneider, G.; Wölfling, J.; Nöbel, T.; Wulff, C.; Schubert, I.; Rübeling, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2469. (c) Wang, J.; De Clerq, P. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1749. (d) Depew, K. M.; Zeman, M,; Boyer, S. H.; Denhart, D. J.; Ikemoto, N.; Danishefsky, S. J.; Crothers, D. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2797.

(2) Mann, J. *Secondary Metabolism*; Clarendon Press: Oxford, 1987.

(3) Mehta, G.; Singh, V. *Chem. Soc. Rev.* **2002**, *31*, 324.

(4) For an overview of this field, see: Dagani, R. *Chem. Eng. News*, **2002**, *80*, 23.

(5) (a) Melikyan, G. G.; Nicholas, K. M. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995; p 118. (b) Caffyn, A. J. M.; Nicholas, K. M. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 685.

(6) (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. (b) Nicolaou, K. C.; Dai, W. H. *Ang. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (c) Magnus, P.; Pitterna, T. *J. Chem. Soc., Chem. Commun.* **1991**, 541. (d) Magnus, P. *Tetrahedron* **1994**, *50*, 1397. (e) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133. (f) Takai, S.; Isobe, M. *Org. Lett.* **2002**, *4*, 1183. (g) Magnus, P.; Miknis, G. F.; Press, N. J.; Grandjean, D.; Taylor, G. M.; Harling, J. *J. Am. Chem. Soc.* **1997**, *119*, 6739. (h) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032. (i) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498. (j) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353.

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epimers, by treatment of **1** with lithium trimethylsilylacetilide, followed by reaction of **2** with a mixture of Ac_2O/Pyr (Scheme 1).

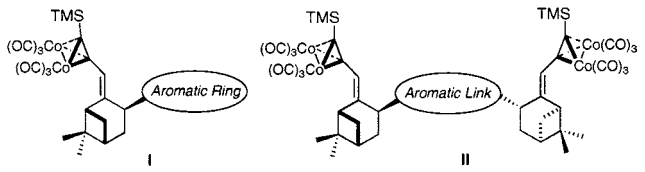
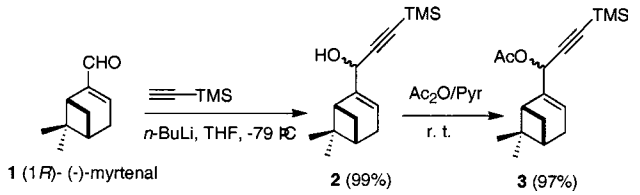


Figure 1.

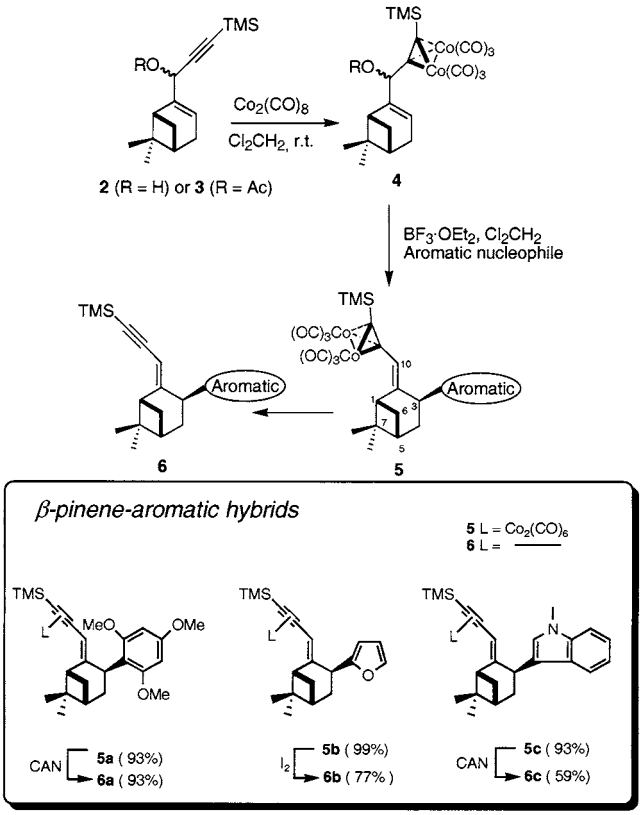
Dicobalt complex **4** was prepared in situ by reacting alkynes **2** or **3** with commercially available $Co_2(CO)_8$ in DCM at rt. Submission of **4** to Lewis acid treatment generates a carbocation that was reacted with aromatic nucleophiles. In all cases, dicobalt-hybrid compounds **5** were obtained as single products in almost quantitative yield (Scheme 2). Regeneration of the triple bond from the alkyne−$Co_2(CO)_6$ moiety was achieved by reaction with cerium(IV) ammonium nitrate (CAN)[7] or with I_2.[8] Derivatives **6** were obtained in good to excellent yields, and their structures were established unambiguously by spectroscopy (Scheme 2).[9]

Scheme 1



It is worth noting that compounds **6** were derived exclusively from the addition of the nucleophile at carbon C-3 of the β-pinene framework.[10] The stereochemistry of the double bond and the configuration at carbon C-3 of products **6** were determined on the basis of NOE experiments.

Scheme 2



Selective irradiation of H-3, for compound **6a**, caused a strong NOE increment of the signal corresponding to the *pro-s* methyl group at carbon C-7. Therefore, proton H-3 and carbon C-7 must have a syn relationship. Additionally, irradiation of the olefinic proton H-10 caused a positive NOE increment of the signal assigned to H-3. This result estab-

(7) (a) Magnus, P.; Eisenbeis, S. A.; Fairhurst, R. A.; Iliadis, T.; Magnus, N. A.; Parry, D. *J. Am. Chem. Soc.* **1997**, *119*, 5591. (b) Krafft, M. E.; Cheung, Y. Y.; Wright, C.; Cali, R. *J. Org. Chem.* **1996**, *61*, 3912.

(8) Tanaka, S.; Isobe, M. *Synthesis*, **1995**, 859.

(9) **The Preparation of 5a and 6a Is Representative.** To a solution of **3** (100 mg, 0.34 mmol) in dry DCM (8.5 mL) under argon atmosphere was added $Co_2(CO)_8$ (154 mg, 0.37 mmol) in one portion. The deep red solution was stirred at rt until no starting material was left (TLC analysis) and then cooled at 0 °C. 1,3,5-Trimethoxybenzene (87 mg, 0.37 mmol) was added, and the mixture was treated dropwise with a solution of freshly distilled $BF_3{\cdot}OEt_2$ (65 μL, 0.51 mmol) in dry DCM (4.5 mL) at 0 °C. After 30 min of stirring, TLC analysis revealed no further progress of the reaction. Then, $NaHCO_3$ (saturated solution 10 mL) was added, and the reaction mixture was allowed to reach room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexanes/CH_2Cl_2 10: 1) to give 220 mg (93%) of pure **5a** as dark green oil: IR (film) ν_{max} 2955, 2080, 2040, 2010, 1741, 1608, 1455, 1213, 1120, 841 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.17 (d, J = 2.2 Hz, 1H), 6.10 (d, J = 2.2 Hz, 1H), 5.66 (d, J = 2.4 Hz, 1H), 4.57 (ddd, J = 9.7, 7.0, 2.2 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.63 (s, 3H), 3.46 (t, J = 5.7 Hz, 1H), 2.42 (m, 1H), 2.34−2.11 (m, 3H), 1.83 (m, 1H), 1.38 (s, 3H), 1.08 (s, 3H), 0.32 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.7 (6C), 159.6 (C), 159.0 (C), 158.3 (C), 154.6 (C), 116.4 (CH), 114.0 (C), 101.6 (C), 91.6 (CH), 90.4 (CH), 79.9 (CH), 56.3 (CH_3), 55.2 (CH_3), 54.5 (CH_3), 49.0 (CH), 42.1 (CH), 39.9 (C), 33.1 (CH_2), 31.3 (CH_2), 30.8 (CH), 27.0 (CH_3), 22.6 (CH_3), 0.9 ($3CH_3$). **Oxidation of 5a To Give 6a.** To a solution of **5a** (220 mg, 0.31 mmol), in acetone (10 mL) at −78 °C, was added CAN (90 mg, 1.6 mmol) in one portion followed by the addition of 2−5 drops of water. The mixture was allowed to reach −50 °C and stirred for 2 h. $NaHCO_3$ (saturated solution 10 mL) was added, and the cooling bath was removed. The resulting mixture was extracted with DCM (3 × 20 mL). The combined organic phases were successively washed with aqueous $NaHSO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexanes/DCM 10: 1) to yield 115 mg (94%) of pure **6a** as a white solid: mp 102−105 °C; IR (KBr) ν_{max} 2957, 2935, 2127, 1606, 1588, 1463, 1215, 1205, 1156, 1124, 842, 809 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (s, 2H), 4.83 (d, J = 2.6 Hz, 1H), 4.59 (ddd, J = 10.1, 7.4, 2.6 Hz, 1H), 3.79 (s, 3H), 3.74 (sa, 6H), 3.34 (t, J = 5.7 Hz, 1H), 2.46 (m, 1H), 2.20−2.10 (m, 2H), 1.99 (ddd, J = 12.7, 6.4, 2.0 Hz, 1H), 1.83 (d, J = 9.2 Hz, 1H), 1.38 (s, 3H), 1.08 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (C), 159.8 (C), 159.1 (2C), 113.8 (C), 104.5 (C), 99.5 (CH), 95.5 (C), 91.9 (CH), 90.4 (CH), 56.2 (CH_3), 55.3 (CH_3), 55.0 (CH_3), 50.1 (CH), 42.4 (CH), 39.1 (C), 32.1 (CH_2), 30.8 (CH_2, CH), 27.4 (CH_3), 22.8 (CH_3), 0.2 ($3CH_3$); MS (EI) *m/z* (relative intensity) 398 [M$^+$] (23), 383 (8), 367 (10), 355 (10), 340 (5), 329 (100), 245 (10), 181 (18), 73 (32); $[\alpha]_D$ −27.3 (*c* 0.055, $CHCl_3$). Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60. Found: C, 72.15; H 8.43.

(10) The numbering system given here for the natural fragments is the most commonly used. See: Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*, Chapman and Hall: London, 1991; Vol. 1.

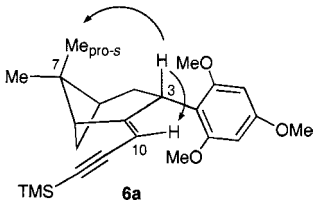
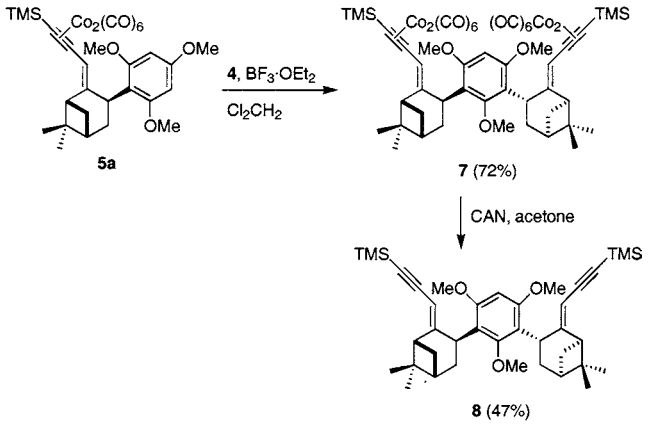


Figure 2. Main NOE increments for compound **5a**.

lished that the $\Delta^{2(10)}$ double bond has the *E* configuration (Figure 2).

The Nicholas methodology proved to be also useful for the synthesis of bis-homodimer **7**. In this case, Co complex **5a** was used as nucleophile in the Nicholas reaction (Scheme 3). Reaction of dicobalt−β-pinene−trimethoxybenzene **5a**

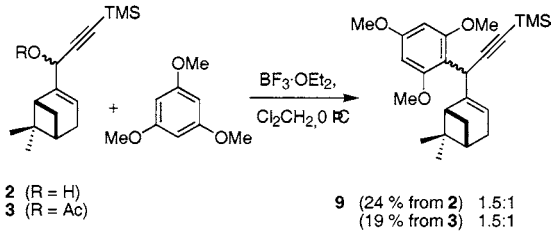
Scheme 3



with the cobalt-stabilized carbocation generated from the propargyl derivatives **2** or **3** produced the bis-homodimer in excellent yield (72%). Oxidation of the cobalt moiety with CAN yielded **8**. The structure of this new type of hybrid was based on spectroscopic means as follows. The molecular peak at *m*/*z* 628 in the EI mass spectrum and the elemental analysis account for a molecular formula $C_{39}H_{56}O_3Si_2$. The ^{1}H NMR for **8** was almost identical to **6a** except for the signal singlet at 6.25 ppm that accounts for one aromatic proton instead of two. Additionally, the ^{13}C NMR spectrum for **8** showed one signal at 94.2 ppm attributed to the aromatic methyne instead of the two signals (91.9 and 90.4 ppm) showed by **6a**. Since the ^{1}H and the ^{13}C NMR showed signals for half of the structure **8**, it is clear that it possesses a C_2 axis. Therefore, the stereochemistry of the double bond and of carbon C-3 must be the same for both terpenic fragments. The selective irradiation of H-3 (δ_H 4.44) under NOE conditions caused a strong increment of the intensity of the signal corresponding to the methyl group at 1.10 ppm. Irradiation of the signal corresponding to the olefinic proton H-10 (δ_H 4.85) caused a NOE increment at the signals corresponding to H-3 and the methoxy groups (δ_H 4.44 and 3.68 respectively). Thus, the bis-homohybrid **8** possesses the same stereochemistry at $\Delta^{2(10)}$ double bond and at carbon C-3 than hybrid **6a**.

It can be thought that reactions above may occur without the participation of the Co-cluster. To discard this possibility, the reactions of alcohol **2** and its acetyl-derivative **3** with 1,3,5-trimethoxybenzene were effected under conditions strictly identical to those used in the reaction of complex **4** with the same aromatic substrate. The reactions produced in both cases complex reaction mixtures from which we were able to isolate by column chromatography the hybrid product **9** in 24% and 19% yields, respectively. Furthermore, compound **9** was obtained in both cases as a 1.5:1 mixture of diasteromers in the newly formed chiral center (Scheme 4). These experiments were repeated twice to ensure

Scheme 4



reproducibility. It is clear then that not only the regioselectivity of the reaction is determined by the Co-complexation but that higher yields of reaction products are obtained. Finally, the stereoselectivity of the Co-mediated reaction is complete while the uncomplexed product formed a mixture of diastereomers of compound **9**.[11]

To prove that our approach is suitable for the synthesis of densely functionalized natural product based hybrids, we chose 19-acetygnaphalin (**10**) as nucleophile.[12] Compound **10** belongs to the neoclerodane diterpenoids,[13] a class of natural products having interesting antifeedant properties.[14] 19-Acetylgnaphalin (**10**) has an arrangement of functional groups that renders it extremely prone to acid or base media. In fact, different rearrangements have been reported for this product.[15]

(11) For some examples of increased reaction selectivity by using $Co_2(CO)_6$−alkyne clusters, see: (a) Ju, J.; Reddy, B. R.; Khan, M.; Nicholas, K. M. *J. Org. Chem.* **1989**, *54*, 5426. (b) Mukai, C.; Kataoaka, C.; Hanoaka, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 563. (c) Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 1143. (d) Ganesh, P.; Nicholas, K. M. *J. Org. Chem.* **1997**, *62*, 1737. (e) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153. (f) Bach, J.; Berenguer, R.; García, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021.

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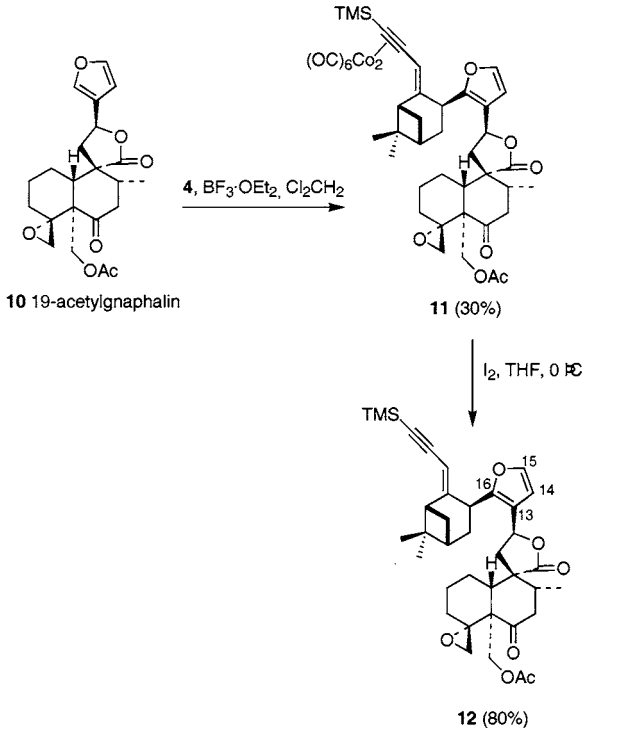
The Nicholas reaction of the dicobalt complex prepared from alcohol **2** and 19-acetylgnaphalin (**10**) gave a single reaction product (30%) whose spectroscopic data fulfill the requirements for structure **11**. Moreover, only unreacted 19-acetylgnaphalin **10** was recovered together with hybrid **11**. Neither decomposition nor rearranged derivatives from 19-acetylgnaphalin were obtained (Scheme 5).

Scheme 5



Treatment of **11** with I_2 liberates the alkyne moiety producing the terpene-based hybrid **12**. In the ^{1}H and ^{13}C NMR spectra of **12**, the signals for the two terpenic moieties were easily recognized. The pattern for the β-pinene fragment was identical to the hybrids described above. Accordingly, the addition of the furanic nucleophile has taken place at carbon C-3, following the same stereochemical course. With respect to the neoclerodane part, the ^{1}H NMR spectrum showed signals for only two furanic protons. The signal at 6.29 ppm corresponds to proton H-14, while the signal at 7.29 ppm must be attributed to one α-furane proton (H-15 or H-16), coupled each other with a J value of 1.8 Hz, as expected for a vicinal coupling. This statement was substantiated by the *g*HMBC spectrum. In particular, correlation between H-3 of the β-pinene part (δ_H 3.90) and the quaternary carbon C-16 of the neoclerodane fragment (δ_C 158.6) clearly establishes that the Nicholas reaction has proceeded exclusively through carbon C-16, yielding a dicobalt C-3,C16-β-pinene−neoclerodane hybrid **11**.

In conclusion, an efficient and general methodology to prepare new terpene−aromatic hybrids leading to potential entries to terpene-polyphenols, terpene−furyl natural products and terpene−indolic alkaloids has been developed. The suitability of applying this approach to the synthesis of complex hybrid derivatives has been demonstrated by using the sensible diterpene 19-acetylgnaphalin as substrate. Efforts to implement this methodology to prepare structurally complex hybrid molecules are being pursued in our laboratories.

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Supporting Information Available: Text describing the preparation and spectral data (^{1}H NMR, ^{13}C NMR, IR, and elemental analysis) for all organic compounds listed through this work, as well as ^{1}H NMR spectra for compounds **2**, **3**, **5a**−**c**, **7**, **9**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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