ChemInform Abstract: Synthesis of Substituted 3-Iodocoumarins and 3-Iodobutenolides via Electrophilic Iodocyclization of Ethoxyalkyne Diols.

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · MAY 2013

Impact Factor: 4.72 · DOI: 10.1021/jo400499r · Source: PubMed

4 AUTHORS, INCLUDING:

Maddi Sridhar Reddy
Central Drug Research Institute
48 PUBLICATIONS **860** CITATIONS
SEE PROFILE

Madala Hari Babu
Central Drug Research Institute
6 PUBLICATIONS **55** CITATIONS
SEE PROFILE

JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

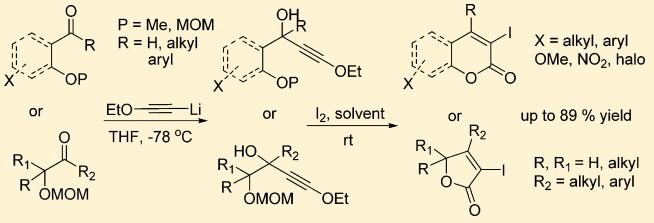
Synthesis of Substituted 3-Iodocoumarins and 3-Iodobutenolides via Electrophilic Iodocyclization of Ethoxyalkyne Diols

Maddi Sridhar Reddy,* Nuligonda Thirupathi, Madala Hari Babu, and Surendra Puri

Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, Chattar Manzil Palace, Lucknow-226 001, U.P., India

Supporting Information

ABSTRACT: A convenient and general synthesis of various 4-substituted 3-iodocoumarins and 4,5-disubstituted 3-iodobutenolides is described via an exclusive 6-*endo-dig* iodocyclization of 3-ethoxy-1-(2-alkoxyphenyl)-2-yn-1-ols and 5-*endo-dig* iodocyclization of 1-alkoxy-4-ethoxy-3-yn-1,2-diols, respectively. The reaction is carried out under very mild conditions using I_2 in CH_2Cl_2 or toluene at room temperature. Oxygens in OMe and OMOM groups were used as efficient nucleophiles for this intramolecular cyclization to obtain the products in good to excellent yields.

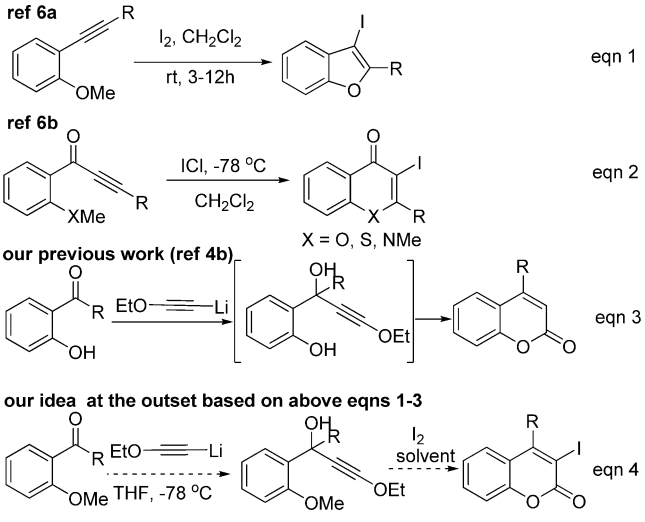


INTRODUCTION

Electrophilic cyclization of alkynols and alkynamines is intensely explored in current chemistry for the construction of various novel heterocyclic moieties and the synthesis of known structures with a substantially increased ease with novel substitution patterns.[1−4] The main reason for this is the easy access to alkyne intermediates and the identification of a variety of alkynophilic catalysts, including various metal catalysts based on Au, Ag, Pd, Pt, Fe, etc.,[1−4] apart from the standardization/control of selectivity (5-, 6-, exo, endo, etc.) in the cyclization.[2] These cyclizations together with tandem eliminations, isomerizations, and coupling reactions have proved to be powerful synthetic tools. Apart from the metal catalysts, various electrophilic halogen sources have shown enormous applications in this kind of cyclization to give halo-substituted heterocycles facilitating a lever for further substitution reactions.[3] This has further focused attention, due to the proven biological importance of halo substitutions.[5]

On the other hand, organic chemists often encounter protected hydroxyl groups which need to be deprotected before further operations. The protected hydroxy group generally acts as a weaker nucleophile, but there are precedents in which the protected oxygen acted as a nucleophile in intramolecular reactions, which thereafter facilitated the in situ cleavage of the protecting group, affording a step-economical process.[6] Recently, Larock et al. reported a synthesis of 3-iodobenzofurans from 1-(2-methoxyaryl)-1-ynes (Scheme 1, eq 1)[6a] and, 3-iodochromones from 2-methoxyaryl-alkynones (Scheme 1, eq 2),[6b] employing a methoxy group as the reactive intramolecular nucleophile. On the basis of this and on our earlier work on the synthesis of 3-unsubstituted coumarins (Scheme 1, eq 3),[4b] we devised a new approach for the synthesis of 3-iodocoumarins via an electrophilic iodocyclization (Scheme 1, eq 4).

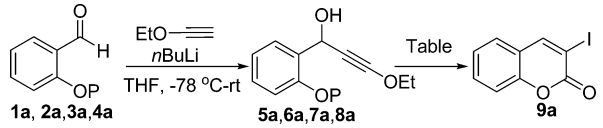
Scheme 1. Development of Our Idea at the Outset



Utilization of a coumarin substructure as a scaffold in the search for novel biologically functional molecules has been highly investigated.[7] 3-Halocoumarins are often used for the introduction of various functionalities.[8] Surprisingly, there have been no general methods for their synthesis until now. Recently, Alami et al. reported the synthesis of 3-bromocoumarins from 2-hydroxybenzaldehyde, but the method was restricted to 4-unsubstituted coumarins.[9] Moreover, the iodo group is considered as easily replaceable in comparison to bromide. 3-Halocoumarins were earlier obtained from the corresponding presynthesized 3-unsubstituted coumarins.[10] The method often leads to additional halogenation in the

Received: March 9, 2013
Published: May 24, 2013

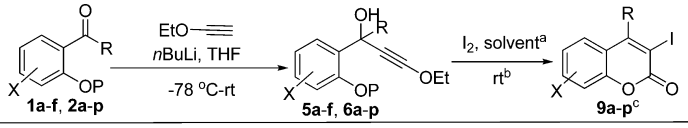
Table 1. Optimization Studies

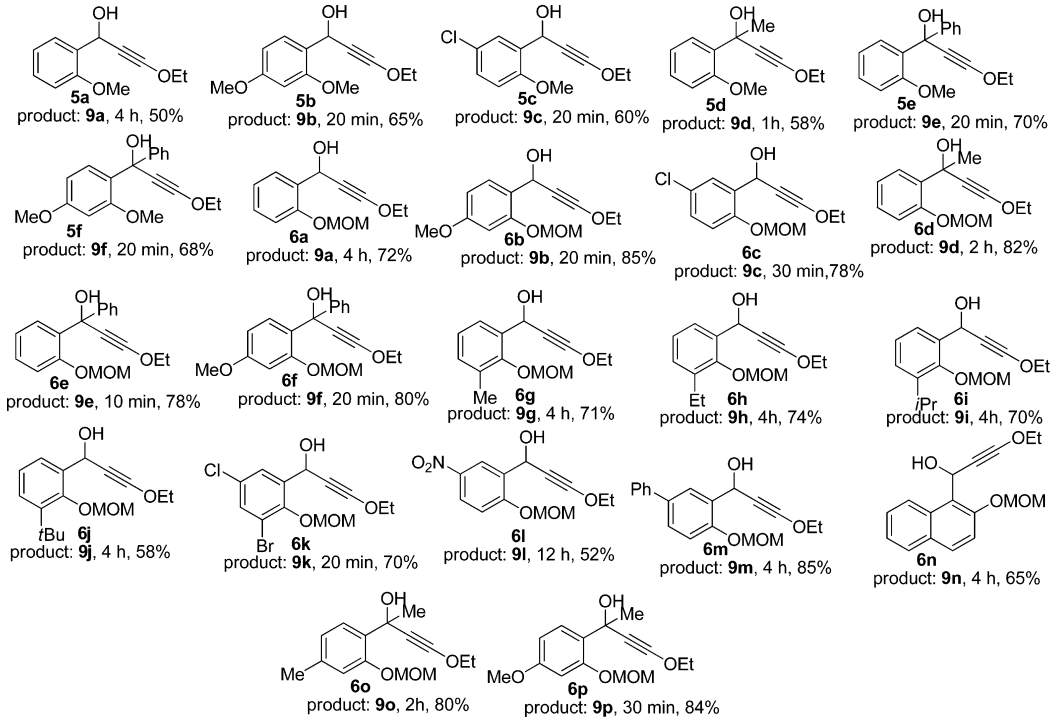


entry	substrate	P	reagent[a]	solvent	temp	time, h	yield of **9a**, %[b]
1	**5a**	Me	I_2	CH_2Cl_2	reflux	12	nr
2	**5a**	Me	I_2	DCE	reflux	4	50
3	**5a**	Me	NIS	CH_2Cl_2	reflux	4	*c*
4	**5a**	Me	NIS	DCE	reflux	12	20
5	**5a**	Me	ICl	DCE	reflux	4	*c*
6	**6a**	**MOM**	**I_2**	**CH_2Cl_2**	**room temp**	**4**	**73**
7	**6a**	MOM	I_2	DCE	room temp	4	63
8	**7a**	Bn	I_2	DCE	reflux	12	*c*
9	**7a**	Bn	NIS	DCE	reflux	12	*c*
10	**8a**	PMB	I_2	DCE	reflux	12	30
11	**8a**	PMB	ICl	DCE	reflux	12	*c*

[a]All reactions were carried out using 2 mmol of substrates with 2.6 mmol of reagent at 0.25 M concentration. [b]Isolated yields. [c]Decomposition of the SM.

Table 2. Synthesis of Substituted 3-Iodocoumarins 9 via Electrophilic Cyclization of Alkyne Diols 5 or 6





[a]DCE for **5a–f** and CH_2Cl_2 for **6a–p**. All reactions were carried out using 2 mmol of substrates with 2.6 mmol of I_2 at 0.25 M concentration. [b]Reflux temperature needed only for **5a**. [c]Isolated yields.

presence of electron-donating groups.[11] As part of our ongoing program on electrophilic cyclization of alkynols and alkynamines for the synthesis of various heterocycles,[4] we devised a new synthesis of 4-substituted 3-iodocoumarins via 6-*endo-dig* iodocyclization of 3-ethoxy-1-(2-alkoxyphenyl)-2-yn-1-ols (Scheme 1, eq 4). We not only succeeded in defining the appropriate conditions for this transformation but also found substrates with different suitable protecting groups, and the synthesis of iodobutenolides was possible via similar 5-*endo-dig* cyclizations of 1-alkoxy-4-ethoxy-3-yn-1,2-diols.

RESULTS AND DISCUSSION

Initially we chose **5a**, prepared from methoxybenzaldehyde (**1a**) and ethoxyacetylide, for our initial trials. When **5a** was

dx.doi.org/10.1021/jo400499r | J. Org. Chem. 2013, 78, 5878–5888

treated with I_2 in CH_2Cl_2, no reaction occurred. Even when the mixture was heated to reflux, no reaction but partial decomposition occurred (Table 1, entry 1). A change of reagent to NIS and ICl also proved to be unfruitful, leading only to decomposition but no trace of product (entry 4). Screening of various solvents with I_2 finally revealed that the reaction was somewhat smoother in DCE at reflux temperature, affording the product **9a**, but in a moderate yield of 50%. Other reagents such as ICl and NIS in the same solvent led only to decomposition (entry 5) or low productivity (20%, entry 4). In parallel, we tuned the reaction by changing the protecting group to MOM, Bn, and PMB. To our delight, **6a** with MOM protection cleanly formed the product (**9a**, 73%) at room temperature using I_2 as the reagent in CH_2Cl_2 (entry 6), whereas **7a** and **8a** were proven to be unsuitable substrates (poor or no yield of the product) after screening various conditions (entries 8−11).

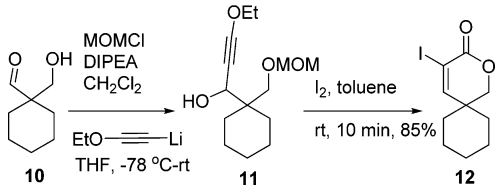
With the optimized conditions in hand, we set out to investigate the scope of the reaction with respect to substitution on the phenyl ring and at the C1 position of the substrates. The results are summarized in Table 2. As is evident from the table, various electron-rich, neutral and electron-poor substrates with cyclizing groups as OMe and OMOM smoothly underwent the reaction to give the corresponding products in good to moderate yields. Initially, we performed the reaction on methoxyphenyl derivatives **5a−f**, since various methoxyphenylcarbonyl compounds are commercially available. Thus, various 4-substituted/4-unsubstituted coumarins **9a−f** were prepared from **5a−f** in 50−72% yield. Surprisingly and to our delight, unlike the case for model substrate **5a** (in Table 1), no heating was required for any of the substrates **5b−f** and the reactions were complete in less than 1 h, affording the products in better yields (58−72% compared to 50% of **9a**).

We then tested the reaction on various substrates with OMOM as the cyclizing group. These substrates (**6a−p**) were more productive (52−85%) in comparison to their methoxy counterparts. Various electron-rich and -poor 4-substituted and unsubstituted 3-iodocoumarins were obtained with a variety of substitution patterns. A notable impact of the electron density was observed on both the rate and the yield of the reaction. Thus, electron-rich substrates **6b,f** underwent the reaction cleanly in 20 min to give **9b,f** in 85% and 80% yields, respectively, whereas the electron-poor substrate **6l** gave the product in 52% yield in 12 h. 3-Alkyl-substituted substrates (**6g−j**) also reacted at a lower rate (4 h), and this may be due to steric factors. Halogen-substituted 3-iodocoumarins **9c** (from **6c**) and **9k** (from **6k**) were obtained in 78 and 70% yields, respectively. The reaction was equally good for installing alkyl and aryl groups at C4 of coumarin, thus giving **9d−f,o,p** in 78−84% yields.

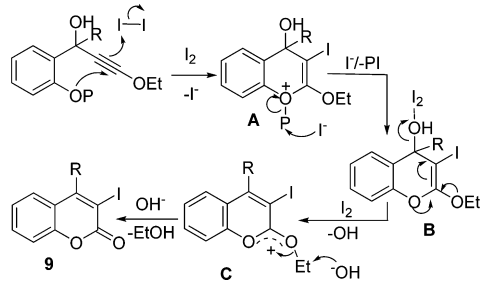
Before proposing a plausible reaction pathway, we wanted to know the influence of the aromatic system on the nucleophilicity of the alkoxy group and on the elimination of the propargyl hydroxyl group, which is also a benzylic hydroxyl system that in general is easily cleaved. For this, we prepared substrate **11** from **10**[12] and treated it with I_2 in toluene (a better solvent in comparison to CH_2Cl_2) (Scheme 2). To our pleasure, the corresponding product **12** was obtained at ambient temperature and in excellent yield of 85%, suggesting that the aromatic system plays no role in the promotion of the reaction.

On the basis of the above observation, a plausible reaction pathway is described in Scheme 3. I_2-induced *6-endo-dig*

Scheme 2. Synthesis of α,β-Unsaturated 3-Iodo-2-pyrone 12 from 11



Scheme 3. Proposed Mechanistic Pathway



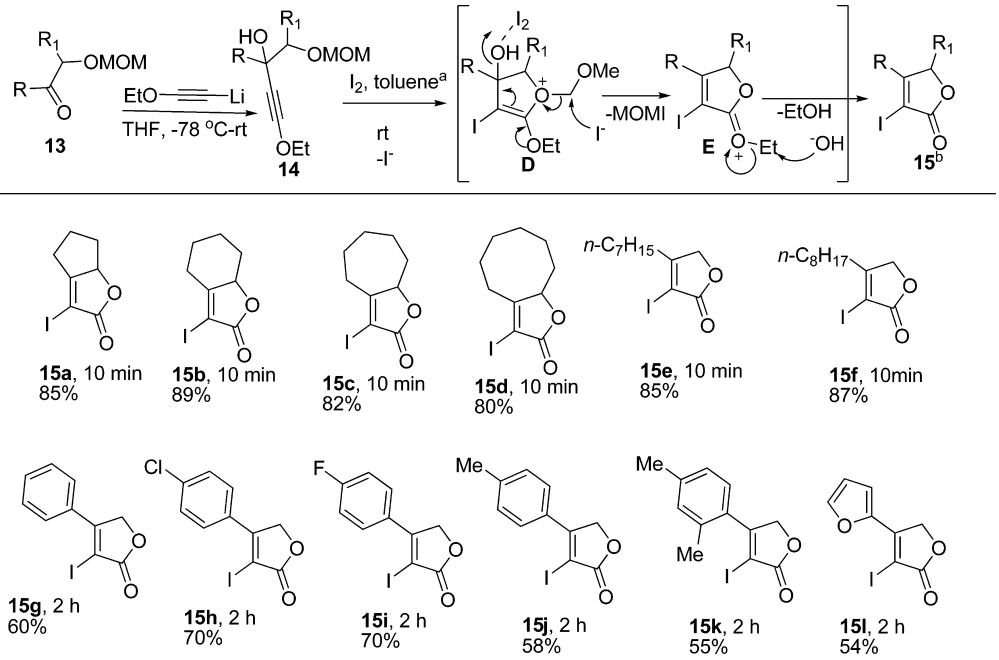
cyclization of the alkoxy group onto the alkyne group led to oxonium ion intermediate **A**, which on expulsion of the protecting group with the help of iodide ion gave **B**. The allylic hydroxy group on **B**, with its high tendency to cleave off, was eliminated in the presence of I_2 to give another oxonium intermediate, **C**. The expelled hydroxy group attacked the ethoxy group to relieve oxygen of its positive charge to yield the required product **9**.

Encouraged by the above results, we next set out to examine the reaction manifold for *5-endo-dig* cyclization, by reducing a carbon between the nucleophile (OMOM) and the alkyne moiety, to achieve the synthesis of hitherto formidable 3-iodobunenolides. Butenolides are an important class of heterocycles with a broad range of potential biological activities.[13] Recently, much attention has been focused on the efficient and diverse synthesis of these compounds.[14] Insertion of halide into such interesting small molecules facilitates the installation of various additional pharmacophores that may lead to a variety of SAR (structure activation relationship) studies. Ma et al. reported the synthesis of 4-iodobutenolides,[15] while no general report is available for the synthesis of 3-iodobutenolides.[16,17] Conversion of 3,4-dibromobutenolides to 4-substituted 3-bromobutenolides was reported by Zhang and Bellina, but the substitution was restricted to C4 and aryl groups.[18] Moreover, in light of the increased feasibility of metal-mediated substitution of the iodo group in comparison to its counterparts (Br, Cl, OTs, and OTf), installation of iodide in the intermediates always has a higher priority.

To screen the conditions for our aimed *5-endo-dig* cyclization, we chose **14a** with OMOM as the intramolecular nucleophile, as it facilitated a smooth cyclization in the above 3-iodocoumarin synthesis. After some experimentation, we found that the alkoxy alkynol **14a** smoothly reacted with I_2 in toluene at room temperature, to afford the expected product **15a** in 85% yield.[19] Similarly, various substrates **14b−f** with aliphatic substitution at C4 and C5 were also converted to the corresponding products **15b−f** in good yields (80−89%). 4-Aryl-substituted butenolides were also obtained (**15g−l** from **4g−l**) but with a slightly diminished reactivity and reduced yields. The probable pathway of the reaction is described in Table 3.

dx.doi.org/10.1021/jo400499r | J. Org. Chem. 2013, 78, 5878−5888

Table 3. Synthesis of 3-Iodobutenolides 15 via Electrophilic Iodocyclization of Alkyne Diols 14



[a]All reactions were carried out using 2 mmol of substrates with 2.6 mmol of I_2 in 0.25 M concentration. [b]Isolated yields.

CONCLUSION

In conclusion, a simple and versatile new approach to a wide variety of 3-iodocoumarins and 3-iodobutenolides has been achieved from the electrophilic iodocyclization of various semiprotected 1-ethoxy-1-alkyne diols. The reactions proceed under mild conditions and tolerate considerable functionality. A systematic study was done to optimize the conditions as well as cyclizing groups for each of the cyclizations.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with a 200 or 300 MHz spectrometer for ^{1}H NMR and a 50, 75, or 100 MHz spectrometer for ^{13}C NMR spectroscopy. Chemical shifts are reported relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/[D_6]DMSO for ^{1}H and ^{13}C NMR spectroscopy. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m); HRMS were recorded by using QTof and MALDI-ToF/ToF mass spectrometers. Column chromatography was performed with silica gel (100−200 mesh) as the stationary phase. All reactions were monitored by using TLC. The purity and characterization of compounds were further established by using HRMS.

General Procedure A for the Synthesis of Ethoxyalkynols (5a−f, 6a−p, 7a, 8a, 11, 14a−l) Taking 5a as the Model Substrate. *n*BuLi (1.6 M in THF, 9.1 mL, 2 equiv) was added slowly to ethoxyacetylene (40 wt/vol % in hexane, 2.57 mL, 2 equiv) in THF (10 mL) at −78 °C, and the mixture was stirred at the same temperature for 2 h and at 0 °C for another 2 h. Then the reaction mixture was recooled to −78 °C before adding **1a** (1 g in 10 mL of THF, 7.35 mmol, 1 equiv) to it. The mixture was then stirred at −78 °C for 1 h and at room temperature for 2 h before it was diluted with water at 0 °C. The mixture was extracted with EtOAc (2 × 25 mL), and the combined extracts were washed with brine (15 mL) and dried over Na_2SO_4. After removal of the solvent in vacuo, the crude product was purified on silica (using 10% EtOAc/hexane) to give **5a** (1.36 g, 90%) as a yellow oil.

*3-Ethoxy-1-(2-methoxyphenyl)prop-2-yn-1-ol (**5a**).* **5a** (1.36 g) was obtained from **1a**[20] (1 g, 7.35 mmol) following general procedure A: yield 90%; yellow oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, d, J = 7.3 Hz), 7.28 (1H, t, J = 7.3 Hz), 6.97 (1H, t, J = 7.3 Hz), 6.89 (1H, d, J = 8.2 Hz), 5.76 (1H, d, J = 5.3 Hz), 4.15 (2H, q, J = 7.0 Hz), 2.87 (1H, d, J = 5.3 Hz), 1.39 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 130.0, 129.3, 127.8, 120.7, 110.7, 95.1, 74.6, 60.9, 55.5, 37.9, 14.4 ppm; IR (neat) ν 3436, 3019, 2974, 2933, 2266, 1486, 1217, 1029, 670, 628 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{15}O_3$ [M + H]$^+$ 207.1021, found 207.1015.

*1-(2,4-Dimethoxyphenyl)-3-ethoxyprop-2-yn-1-ol (**5b**).* **5b** (1.27 g) was obtained from **1b**[20] (1 g, 6.02 mmol) following general procedure A: yield 90%; brown oil; R_f = 0.45 (SiO_2, 30% EtOAc/70% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (1H, d, J = 1.4 Hz), 6.80 (2H, d, J = 9.0 Hz), 5.72 (1H, d, J = 5.5 Hz), 4.14 (2H, q, J = 7.0 Hz), 3.83 (3H, s), 3.78 (3H, s), 2.98 (1H, d, J = 5.5 Hz), 1.38 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 149.7, 130.1, 112.8, 112.5, 110.8, 93.9, 73.6, 59.7, 55.0, 54.6, 36.9, 13.3 ppm; IR (neat) ν 3432, 3019, 2969, 2266, 1464, 1217, 1042, 761, 670 cm^{-1}; ESI-MS m/z 259 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}NaO_4$ 259.0946, found 259.0941.

*1-(5-Chloro-2-methoxyphenyl)-3-ethoxyprop-2-yn-1-ol (**5c**).* **5c** (993 mg) was obtained from **1c**[20] (800 mg, 4.70 mmol) following general procedure A: yield 88%; brown oil; R_f = 0.32 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, d, J = 2.4 Hz), 7.21 (1H, dd, J = 8.7, 2.4, Hz), 6.79 (1H, d, J = 8.7 Hz), 5.70 (1H, d, J = 5.2 Hz), 4.14 (2H, q, J = 7.08 Hz), 3.85 (3H, s), 2.84 (1H, d, J = 5.2 Hz), 1.38 (3H, t, J = 7.08 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 131.7, 128.8, 127.9, 125.8, 111.9, 95.4, 74.8, 60.3, 55.9, 37.4, 14.4 ppm; IR (neat) ν 3408, 3017, 2934, 2265, 1485, 1217, 1125, 758, 669 cm^{-1}; ESI-MS m/z 263 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{12}H_{13}NaClO_3$ 263.0451, found 263.0443.

*4-Ethoxy-2-(2-methoxyphenyl)but-3-yn-2-ol (**5d**).* **5d** (1.31 mg) was obtained from **1d**[20] (1 g, 6.66 mmol) following general procedure A: yield 90%; brown oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, d, J = 8.9 Hz), 7.27 (1H, dd, J = 15.6, 1.4 Hz), 6.98−6.92 (2H, m), 4.46 (1H, s), 4.12 (2H, q, J = 7.1 Hz), 3.93 (3H, s), 1.85 (3H, s), 1.38 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 133.6, 128.7, 126.7, 120.9, 11.5,

dx.doi.org/10.1021/jo400499r | J. Org. Chem. 2013, 78, 5878−5888

93.3, 74.4, 69.8, 55.5, 42.1, 31.1, 14.4 ppm; IR (neat) ν 3412, 2928, 2263, 1599, 1455, 1384, 1238, 912, 860 cm^{-1}; ESI-MS m/z 243 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{16}NaO_3$ 243.0997, found 243.0989.

*3-Ethoxy-1-(2-methoxyphenyl)-1-phenylprop-2-yn-1-ol (**5e**).* **5e** (1.19 g) was obtained from **1e**[20] (1 g, 4.71 mmol) following general procedure A: yield 90%; brown oil; R_f = 0.50 (SiO_2, 30% EtOAc/70% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (3H, t, J = 5.4 Hz), 7.30−7.21 (4H, m), 6.95 (1H, t, J = 7.4 Hz), 6.89 (1H, d, J = 8.2 Hz), 4.82 (1H, s), 4.13 (2H, q, J = 7.0 Hz), 3.70 (3H, s), 1.36 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 146.2, 133.6, 129.2, 128.6, 127.8, 127.0, 126.0, 120.8, 112.1, 74.8, 74.7, 55.7, 41.3, 14.5 ppm; IR (neat) ν 3497, 3018, 2929, 2266, 1597, 1382, 1217, 759, 670 cm^{-1}; ESI-MS m/z 283 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{19}O_3$ 283.1334, found 283.1328.

*1-(2,4-Dimethoxyphenyl)-3-ethoxy-1-phenylprop-2-yn-1-ol (**5f**).* **5f** (1 g) was obtained from **1f**[20] (900 mg, 3.71 mmol) following general procedure A: yield 87%; yellow oil; R_f = 0.46 (SiO_2, 30% EtOAc/70% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (2H, d, J = 7.7 Hz), 7.38 (1H, d, J = 8.2 Hz), 7.28 (2H, t, J = 7.7 Hz), 7.22 (1H, t, J = 7.1 Hz), 6.45 (2H, d, J = 7.4 Hz), 4.68 (1H, s), 4.12 (2H, q, J = 6.7 Hz), 3.79 (3H, s), 3.68 (3H, s), 1.35 (3H, t, J = 6.7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 157.6, 146.4, 129.2, 127.7, 126.9, 126.3, 125.9, 103.9, 100.0, 96.2, 74.6, 74.3, 55.6, 55.3, 41.5, 14.4 ppm; IR (neat) ν 3504, 3009, 2265, 1609, 1499, 1211, 1159, 1122, 700, 668 cm^{-1}; ESI-MS m/z 335 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{20}NaO_4$ 335.1259, found 335.1254.

*3-Ethoxy-1-(2-(methoxymethoxy)phenyl)prop-2-yn-1-ol (**6a**).* **6a** (1.17 g) was obtained from **2a**[21] (1 g, 6.02 mmol) following general procedure A: yield 83%; brown oil; R_f = 0.38 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, dd, J = 1.3, 7.5 Hz), 7.26 (1H, t, J = 7.5 Hz), 7.10 (1H, d, J = 8.0 Hz), 7.02 (1H, t, J = 7.5 Hz), 5.77 (1H, d, J = 5.7 Hz), 5.25 (2H, dd, J = 10.1, 6.6 Hz), 4.13 (2H, q, J = 7.1 Hz), 3.50 (3H, s), 2.85 (1H, d, J = 5.7 Hz), 1.38 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 129.9, 128.3, 126.8, 121.0, 113.4, 93.9, 93.6, 73.6, 59.7, 55.2, 37.0, 13.4 ppm; IR (neat) ν 3401, 3018, 2927, 2265, 1632, 1263, 1217, 1154, 770, 669 cm^{-1}; ESI-MS m/z 259 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{16}NaO_4$ 259.0946, found 259.0949.

*3-Ethoxy-1-(4-methoxy-2-(methoxymethoxy)phenyl)prop-2-yn-1-ol (**6b**).* **6b** (1.12 g) was obtained from **2b**[22] (1 g, 5.10 mmol) following general procedure A: yield 83%; yellow oil; R_f = 0.45 (SiO_2, 30% EtOAc/70% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, d, J = 8.3 Hz), 6.69 (1H, s), 6.55 (1H, d, J = 8.3 Hz), 5.72 (1H, d, J = 5.4 Hz), 5.23 (2H, dd, J = 9.8, 6.5 Hz), 4.14 (2H, q, J = 7.0 Hz), 3.79 (3H, s), 3.50 (3H, s), 2.66 (1H, d, J = 5.4 Hz), 1.38 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 154.3, 127.6, 122.6, 105.3, 100.6, 93.8, 93.7, 73.6, 59.2, 55.2, 54.4, 37.2, 13.4 ppm; IR (neat) ν 3433, 3019, 2969, 2265, 1608, 1259, 1216, 1158, 1111, 760 cm^{-1}; ESI-MS m/z 289 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_5$ 289.1052, found 289.1044.

*1-(5-Chloro-2-(methoxymethoxy)phenyl)-3-ethoxyprop-2-yn-1-ol (**6c**).* **6c** (756 mg) was obtained from **2c**[23] (700 mg, 3.5 mmol) following general procedure A: yield 80%; yellow oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, J = 2.3 Hz), 7.21 (1H, dd, J = 8.7, 2.3 Hz), 7.04 (1H, d, J = 8.7 Hz), 5.73 (1H, d, J = 5.6 Hz), 5.22 (2H, dd, J = 10.7, 6.8 Hz), 4.15 (2H, q, J = 7.1 Hz), 3.49 (3H, s), 2.67 (1H, d, J = 5.6 Hz), 1.39 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 132.7, 128.9, 127.8, 127.0, 115.8, 95.1, 94.8, 74.8, 60.0, 56.3, 37.6, 14.4 ppm; IR (neat) ν 3431, 3020, 2977, 2266, 1535, 1262, 1216, 1122, 761, 670 cm^{-1}; ESI-MS m/z 293 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{15}NaClO_4$ 293.0557, found 293.0553.

*4-Ethoxy-2-(2-(methoxymethoxy)phenyl)but-3-yn-2-ol (**6d**).* **6d** (1.19 g) was obtained from **2d**[24] (1 g, 5.55 mmol) following general procedure A: yield 86%; yellow oil; R_f = 0.47 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, J = 7.5 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.14 (1H, d, J = 8.0 Hz), 6.99 (1H, d, J = 6.9 Hz), 5.30 (2H, dd, J = 7.8, 6.8 Hz), 4.28 (1H, s), 4.10 (2H, q, J = 7.1 Hz), 3.53 (3H, s), 1.87 (3H, s), 1.36 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 134.0, 128.7, 126.5, 121.8, 114.7, 94.6, 93.1, 74.4, 69.4, 56.3, 42.2, 30.9, 14.4 ppm; IR (neat) ν 3428, 3017, 2928, 2264, 1600, 1385, 1216, 1158, 669 cm^{-1}; ESI-MS m/z 273 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_4$ 273.1103, found 273.1107.

*3-Ethoxy-1-(2-(methoxymethoxy)phenyl)-1-phenylprop-2-yn-1-ol (**6e**).* **6e** (1.10 g) was obtained from **2e**[25] (1 g, 4.13 mmol) following general procedure A: yield 86%; yellow oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, dd, J = 1.2, 7.5 Hz), 7.48 (2H, d, J = 7.5 Hz), 7.30−7.18 (4H, m), 7.06 (1H, d, J = 8.2 Hz), 7.01 (1H, t, J = 7.5 Hz), 4.99 (2H, dd, J = 26.5, 6.6 Hz), 4.54 (1H, s), 4.14 (2H, q, J = 7.1 Hz), 3.13 (3H, s), 1.36 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 145.4, 132.8, 128.1, 127.4, 126.7, 125.9, 124.7, 120.5, 113.7, 95.5, 93.0, 73.6, 73.4, 66.9, 54.9, 40.0, 13.4 ppm; IR (neat) ν 3515, 3062, 2960, 2266, 1595, 1230, 1157, 1080 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{20}NaO_4$ 335.1259, found 335.1248.

*3-Ethoxy-1-(4-methoxy-2-(methoxymethoxy)phenyl)-1-phenylprop-2-yn-1-ol (**6f**).* **6f** (1.09 g) was obtained from **2f**[25] (1 g, 3.67 mmol) following general procedure A: yield 87%; brown oil; R_f = 0.36 (SiO_2, 30% EtOAc/70% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, J = 8.6 Hz), 7.48 (2H, d, J = 7.8 Hz), 7.28 (3H, t, J = 6.4 Hz), 6.66 (1H, s), 6.53 (1H, d, J = 8.6 Hz), 4.97 (2H, dd, J = 24.1, 6.7 Hz), 4.42 (1H, s), 4.13 (2H, q, J = 6.9 Hz), 3.79 (3H, s), 3.13 (3H, s), 1.35 (3H, t, J = 6.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 155.0, 146.7, 129.1, 127.7, 126.8, 126.6, 125.8, 105.3, 102.2, 96.4, 94.2, 74.6, 74.1, 55.9, 55.3, 41.3, 14.4 ppm; IR (neat) ν 3522, 3016, 2929, 2265, 1608, 1449, 1298, 1217, 1159, 1116, 669, 630, 589 cm^{-1}; ESI-MS m/z 365 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{22}NaO_5$ 365.1365, found 365.1357.

*3-Ethoxy-1-(2-(methoxymethoxy)-3-methylphenyl)prop-2-yn-1-ol (**6g**).* **6g** (716 mg) was obtained from **2g**[26] (600 mg, 3.33 mmol) following general procedure A: yield 86%; yellow oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, J = 7.4 Hz), 7.15 (1H, d, J = 7.3 Hz), 7.07 (1H, t, J = 7.4 Hz), 5.82 (1H, d, J = 4.5 Hz), 5.08 (1H, d, J = 5.9 Hz), 4.97 (1H, d, J = 5.9 Hz), 4.15 (2H, q, J = 7.1 Hz), 3.63 (3H, s), 3.44 (1H, d, J = 4.5 Hz), 2.28 (3H, s), 1.38 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 135.7, 131.3, 130.9, 126.1, 124.8, 99.6, 94.9, 74.6, 59.8, 57.5, 38.2, 16.8, 14.4 ppm; IR (neat) ν 3430, 3016, 2932, 2267, 1593, 1389, 1218, 1159, 991, 858, 760, 669 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{18}NaO_4$ 273.1103, found 273.1094.

*3-Ethoxy-1-(3-ethyl-2-(methoxymethoxy)phenyl)prop-2-yn-1-ol (**6h**).* **6h** (819 mg) was obtained from **2h**[27] (700 mg, 3.60 mmol) following general procedure A: yield 86%; yellow oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, dd, J = 7.5, 1.6 Hz), 7.19 (1H, dd, J = 7.5, 1.6 Hz), 7.12 (1H, t, J = 7.5 Hz), 5.83 (1H, d, J = 4.8 Hz), 5.08 (1H, d, J = 5.9 Hz), 4.96 (1H, d, J = 5.9 Hz), 4.15 (2H, q, J = 7.1 Hz), 3.64 (3H, s), 3.46 (1H, d, J = 4.8 Hz), 2.64 (2H, q, J = 7.6 Hz), 1.38 (3H, t, J = 7.1 Hz), 1.22 (3H, t, J = 7.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 136.9, 135.8, 129.5, 126.1, 125.0, 100.1, 94.9, 74.6, 60.6, 59.7, 57.4, 38.3, 23.1, 14.6 ppm; IR (neat) ν 3406, 2927, 2265, 1650, 1456, 1219, 1157, 1065, 759, 668 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{20}NaO_4$ $[M + Na]^+$ 287.1259, found 287.1253.

*3-Ethoxy-1-(3-isopropyl-2-(methoxymethoxy)phenyl)prop-2-yn-1-ol (**6i**).* **6i** (534 mg) was obtained from **2i**[28] (500 mg, 2.40 mmol) following general procedure A: yield 84%; brown oil; R_f = 0.47 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, dd, J = 1.5, 7.5 Hz), 7.25 (1H, dd, J = 1.5, 7.5 Hz), 7.15 (1H, t, J = 7.5 Hz), 5.84 (1H, d, J = 4.0 Hz), 5.09 (1H, d, J = 5.9 Hz), 4.95 (1H, d, J = 5.9 Hz), 4.15 (2H, q, J = 7.0 Hz), 3.65 (3H, s), 3.44 (1H, d, J = 4.0 Hz), 3.23 (1H, sp, J = 6.7 Hz), 1.39 (3H, t, J = 7.0 Hz), 1.25 (6H, d, J = 6.7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 141.8, 135.8, 126.9, 126.0, 125.3, 100.6, 95.0, 74.6, 59.9, 57.6, 41.9, 38.3, 23.5, 14.4 ppm; IR (neat) ν 3401, 2926, 2265, 1652, 1384, 1217, 1155, 1021, 769, 668 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{16}H_{22}NaO_4$ $[M + Na]^+$ 301.1416, found 301.1409.

*1-(3-tert-Butyl-2-(methoxymethoxy)phenyl)-3-ethoxyprop-2-yn-1-ol (**6j**).* **6j** (526 mg) was obtained from **2j**[29] (500 mg, 2.25 mmol)

dx.doi.org/10.1021/jo400499r | J. Org. Chem. 2013, 78, 5878−5888

following general procedure A: yield 80%; brown oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, dd, J = 7.5, 1.5 Hz), 7.32 (1H, dd, J = 7.8, 1.5 Hz), 7.11 (1H, t, J = 7.8 Hz), 5.84 (1H, d, J = 5.0 Hz), 5.09 (1H, d, J = 5.9 Hz), 4.95 (1H, d, J = 5.9 Hz), 4.14 (2H, q, J = 7.0 Hz), 3.69 (3H, s), 3.44 (1H, d, J = 5.0 Hz), 1.39 (12 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 143.0, 136.8, 127.6, 127.5, 124.6, 100.9, 94.8, 74.7, 59.6, 57.4, 39.1, 35.1, 31.3, 14.5 ppm; IR (neat) ν 3430, 3018, 2960, 2265, 1637, 1392, 1216, 1156, 854, 757, 669 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{24}NaO_4$ [M + Na]$^+$ 315.1572, found 315.1580.

*1-(3-Bromo-5-chloro-2-(methoxymethoxy)phenyl)-3-ethoxyprop-2-yn-1-ol (**6k**).* **6k** (969 mg) was obtained from **2k**[30] (900 mg, 3.24 mmol) following general procedure A: yield 86%; brown oil; R_f = 0.42 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 2.4 Hz), 5.80 (1H, d, J = 4.2 Hz), 5.13 (2H, dd, J = 48.0, 6.0 Hz), 4.18 (2H, q, J = 7.1 Hz), 3.66 (1H, s), 3.54 (1H, d, J = 4.2 Hz), 1.40 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 139.1, 132.7, 130.7, 128.0, 117.6, 100.4, 95.5, 74.9, 59.5, 58.0, 37.1, 14.4 ppm; IR (neat) ν 3456, 3036, 2928, 2266, 1314, 1232, 1125, 872, 732, 580 cm^{-1}; ESI-MS m/z 370 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{14}NaBrClO_4$370.9662, found 370.9657.

*3-Ethoxy-1-(2-(methoxymethoxy)-5-nitrophenyl)prop-2-yn-1-ol (**6l**).* **6l** (1.14 g) was obtained from **2l**[31] (1 g, 4.73 mmol) following general procedure A: yield 85%; yellow oil; R_f = 0.40 (SiO_2, 50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (1H, s), 8.17 (1H, d, J = 9.1 Hz), 7.20 (1H, d, J = 9.1 Hz), 5.79 (1H, s), 5.35 (2H, s), 4.17 (2H, q, J = 7.1 Hz), 3.51 (3H, s), 2.54 (1H, s), 1.40 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.2, 124.7, 123.7, 122.8, 113.8, 95.5, 94.5, 75.0, 59.7, 56.7, 37.4, 14.4 ppm; IR (neat) ν 3432, 2938, 2254, 1632, 1542, 1442, 1368, 1311, 1232, 1178, cm^{-1}; ESI-MS m/z 304 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}NaNO_6$ 304.0797, found 304.0791.

*3-Ethoxy-1-(4-(methoxymethoxy)biphenyl-3-yl)prop-2-yn-1-ol (**6m**).* **6m** (665 mg) was obtained from **2m**[32] (600 mg, 2.47 mmol) following general procedure A: yield 86%; yellow oil; R_f = 0.48 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.56 (2H, d, J = 7.8 Hz), 7.48 (1H, dd, J = 8.4, 1.4 Hz), 7.42 (2H, t, J = 7.5 Hz), 7.31 (1H, t, J = 7.5 Hz), 7.18 (1H, d, J = 8.4 Hz), 5.83 (1H, d, J = 5.1 Hz), 5.29 (2H, dd, J = 11.5, 6.7 Hz), 4.14 (2H, q, J = 7.1 Hz), 3.53 (3H, s), 2.81 (1H, d, J = 5.1 Hz), 1.38 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 140.6, 135.0, 131.3, 128.7, 127.7, 126.8, 126.6, 114.8, 95.0, 94.7, 74.6, 60.7, 56.3, 38.2, 14.4 ppm; IR (neat) ν 3406, 2926, 2264, 1611, 1482, 1227, 1153, 1006, 763 cm^{-1}; ESI-MS m/z 335 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{20}NaO_4$ 335.1259, found 335.1255.

*3-Ethoxy-1-(2-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (**6n**).* **6n** (575 mg) was obtained from **2n**[33] (500 mg, 2.31 mmol) following general procedure A: yield 87%; yellow oil; R_f = 0.42 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (1H, d, J = 8.5 Hz), 7.77 (2H, t, J = 7.3 Hz), 7.51 (1H, t, J = 7.3 Hz), 7.38 (2H, t, J = 4.6 Hz), 6.49 (1H, d, J = 6.4 Hz), 5.31 (2H, dd, J = 8.7, 6.7 Hz), 4.04 (2H, q, J = 7.05 Hz), 3.56 (3H, s), 3.11 (1H, d, J = 6.4 Hz), 1.30 (3H, t, J = 7.05 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 130.1, 129.3, 128.9, 127.4, 125.3, 123.4, 123.2, 123.1, 115.5, 94.7, 93.5, 73.4, 56.4, 55.4, 38.6, 13.3 ppm; IR (neat) ν 3421, 3016, 2933, 2261, 1626, 1467, 1217, 1154, 1012, 923, 759, 669 cm^{-1}; ESI-MS m/z 309 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{18}NaO_4$ 309.1103; found; 309.1098.

*4-Ethoxy-2-(2-(methoxymethoxy)-4-methylphenyl)but-3-yn-2-ol (**6o**).* **6o** (1.14 g) was obtained from **2o**[34] (1 g, 5.15 mmol) following general procedure A: yield 84%; yellow oil; R_f = 0.55 (SiO_2, 30% EtOAc/70% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (1H, d, J = 7.8 Hz), 6.96 (1H, s), 6.80 (1H, d, J = 7.8 Hz), 5.28 (2H, s), 6.80 (1H, d, J = 7.8 Hz), 5.28 (2H, s), 4.27 (1H, s), 4.09 (2H, q, J = 7.2 Hz), 3.53 (3H, s), 2.32 (3H, s), 1.85 (3H, s), 1.36 (3H, t, J = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 138.9, 131.2, 126.3, 122.4, 115.4, 94.5, 92.6, 74.4, 69.2, 56.4, 42.3, 30.9, 21.2, 14.4 ppm; IR (neat) ν 3411, 3018, 2927, 2264, 1612, 1245, 1216, 1156, 927, 853, 753 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{20}NaO_4$ 287.1259, found 287.1252.

*4-Ethoxy-2-(4-methoxy-2-(methoxymethoxy)phenyl)but-3-yn-2-ol (**6p**).* **6p** (655 mg) was obtained from **2p**[24] (600 mg, 2.85 mmol) following general procedure A: yield 82%; brown oil; R_f = 0.38 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (1H, d, J = 8.5 Hz), 6.74 (1H, d, J = 2.3 Hz), 6.51 (1H, dd, J = 2.3, 8.5 Hz), 5.28 (2H, s), 4.16 (1H, s), 4.10 (2H, q, J = 7.0 Hz), 3.79 (3H, s), 3.52 (3H, s), 1.84 (3H, s), 1.36 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 155.4, 127.1, 126.8, 105.6, 102.2, 94.7, 92.9, 74.4, 69.0, 56.4, 55.4, 42.4, 31.1, 14.4 ppm; IR (neat) ν 3422, 2933, 2263, 1610, 1254, 1217, 1158, 1129, 923, 851, 760 cm^{-1}; ESI-MS m/z 303 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{20}NaO_5$ 303.1208, found 303.1202.

*1-(2-(Benzyloxy)phenyl)-3-ethoxyprop-2-yn-1-ol (**7a**).* **7a** (1.11 g) was obtained from **3a**[35] (1 g, 4.71 mmol) following general procedure A: yield 84%; yellow oil; R_f = 0.55 (SiO_2, 30% EtOAc/70% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, d, J = 6.6 Hz), 7.38−7.16 (6H, m), 6.88 (2H, t, J = 8.7 Hz), 5.72 (1H, d, J = 5.8 Hz), 5.07−5.04 (2H, m), 4.04 (2H, q, J = 7.0 Hz), 2.83 (1H, d, J = 5.8 Hz), 1.29 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 136.6, 130.4, 129.1, 128.5, 127.9, 127.8, 127.1, 121.0, 112.0, 94.9, 74.5, 40.1, 60.9, 38.1, 14.3 ppm; IR (neat) ν 3486, 2988, 2254, 1568, 1378, 1323, 1254, 812 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{18}NaO_3$ 301.1154, found 301.1145.

*3-Ethoxy-1-(2-(4-methoxybenzyloxy)phenyl)prop-2-yn-1-ol (**8a**).* **8a** (825 mg) was obtained from **4a**[36] (800 mg, 3.30 mmol) following general procedure A: yield 80%; brown oil; R_f = 0.50 (SiO_2, 30% EtOAc/70% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 7.2 Hz), 7.37 (2H, d, J = 8.3 Hz), 7.28−7.24 (1H, m), 6.99−6.95 (2H, m), 6.91 (2H, d, J = 8.3 Hz), 5.76 (1H, d, J = 5.7 Hz), 5.06 (2H, d, J = 36. Hz), 4.12 (2H, q, J = 7.01 Hz), 3.81 (3H, s), 2.92 (1H, d, J = 5.7 Hz), 1.37 (3H, t, J = 7.08 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 155.8, 130.5, 129.2, 129.0, 128.7, 127.8, 120.9, 114.0, 112.1, 94.9, 74.6, 70.1, 61.1, 55.2, 38.0, 14.3 ppm; IR (neat) ν 3410, 2929, 2263, 1609, 1455, 1241, 1175, 827, 756 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{20}NaO_4$ 335.1259, found 335.1254.

*1-(Ethoxyethynyl)-2-(methoxymethoxy)cyclopentanol (**14a**).* **14a** (624 mg) was obtained from **13a**[37] (500 mg, 3074 mmol) following general procedure A: yield 84%; yellow oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (2H, dd, J = 27.6, 6.3 Hz), 4.06 (2H, q, J = 7.0 Hz), 3.96 (1H, t, J = 7.1 Hz), 3.40 (3H, s), 2.84 (1H, s), 2.00−1.57 (6H, m), 1.34 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.9, 91.3, 83.4, 73.4, 72.4, 54.4, 39.7, 37.7, 27.5, 18.3, 13.3 ppm; IR (neat) ν 3445, 2968, 2274, 1352, 1251, 1202, 1135 cm^{-1}; ESI-MS m/z 237 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{11}H_{18}NaO_4$ 237.1103, found 237.1094.

*1-(Ethoxyethynyl)-2-(methoxymethoxy)cyclohexanol (**14b**).* **14b** (496 mg) was obtained from **13b**[38] (400 mg, 2.5 mmol) following general procedure A: yield 86%; yellow oil; R_f = 0.52 (SiO_2, 30% EtOAc/70% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (2H, dd, J = 27.7, 6.6 Hz), 4.07 (2H, q, J = 7.1 Hz), 3.59 (1H, dd, J = 7.6, 3.6 Hz), 3.40 (3H, s), 2.73 (1H, s), 1.94−1.39 (8H, m), 1.34 (3H, t, J = 7.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.1, 96.0, 92.9, 87.0, 80.5, 74.3, 71.8, 69.3, 55.5, 50.5, 40.9, 38.6, 37.5, 27.7, 24.2, 23.5, 22.9, 21.8, 21.6, 14.2 ppm; IR (neat) ν 3488, 2978, 2263, 1388, 1336, 1264, 1163, 1032, cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{20}NaO_4$ 251.1259, found 251.1250.

*1-(Ethoxyethynyl)-2-(methoxymethoxy)cycloheptanol (**14c**).* To a mixture of 2-hydroxyheptanone[39] (450 mg, 3.51 mmol) and DIPEA (680 mg, 5.27 mmol) in CH_2Cl_2 (6 mL) was added MOMCl (365 mg, 4.56 mmol) at 0 °C, and the contents were stirred at room temperature overnight. After it was diluted with water, the mixture was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with brine (6 mL) and dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was filtered through a silica bed using 20% EtOAc/80% hexanes. The product **13c** was used as such (considering 100% yield) in the next step without further purification and analysis.

dx.doi.org/10.1021/jo400499r | J. Org. Chem. 2013, 78, 5878−5888

14c (590 mg) was obtained from **13c** (600 mg, 3.48 mmol) following general procedure A: combined yield 70%; yellow oil; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (2H, dd, J = 14.9, 6.6 Hz), 4.07 (2H, q, J = 7.0 Hz), 3.69 (1H, d, J = 7.8 Hz), 3.421 (3H, s), 3.09 (1H, s), 1.89−1.66 (10H, m), 1.35 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.3, 91.4, 83.6, 73.3, 71.5, 54.8, 40.9, 37.6, 27.0, 26.5, 21.9, 20.1, 13.3 ppm; IR (neat) ν 3434, 3016, 2933, 2261, 1387, 1216, 1150, 1098 cm^{-1}; ESI-MS m/z 265 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{22}NaO_4$ 265.1416, found 265.1408.

*1-(Ethoxyethynyl)-2-(methoxymethoxy)cyclooctanol (**14d**).* To a mixture of 2-hydroxyoctanone[40] (305 mg, 2.14 mmol) and DIPEA (414 mg, 3.21 mmol) in CH_2Cl_2 (5 mL) was added MOMCl (222 mg, 2.78 mmol) at 0 °C, and the contents were stirred at room temperature overnight. After it was diluted with water, the mixture was extracted with CH_2Cl_2 (2 × 8 mL) and the combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was filtered through a silica bed using 20% EtOAc/80% hexanes. The product **13d** was used as such (considering 100% yield) in the next step without further purification and analysis.

14d (374 mg) was obtained from **13d** (400 mg, 2.15 mmol) following general procedure A: combined yield 68%; yellow oil; R_f = 0.48 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81−4.62 (3H, m), 4.18−4.03 (2H, m), 3.79 (1H, d, J = 8.5 Hz), 3.43 (2H, s), 3.34 (1H, s), 3.07 (1H, s), 2.48−2.44 (1H, m), 2.15−1.39 (16H, m), 1.34 (4H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.9, 94.9, 91.2, 81.5, 79.5, 73.3, 71.8, 54.8, 54.7, 40.5, 38.8, 33.6, 30.5, 28.3, 27.0, 25.9, 24.9, 24.6, 24.0, 23.8, 21.8, 20.9, 13.3 ppm; IR (neat) ν 3452, 3017, 2932, 2259, 1620, 1334, 1215, 1150, 1033 cm^{-1}; ESI-MS m/z 279 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{24}NaO_4$ 279.1572, found 279.1565.

*1-Ethoxy-3-((methoxymethoxy)methyl)dec-1-yn-3-ol (**14e**).* To a mixture of 1-hydroxy-2-nonanone[41] (547 mg, 3.46 mmol) and DIPEA (670 mg, 5.19 mmol) in CH_2Cl_2 (8 mL) was added MOMCl (360 mg, 4.49 mmol) at 0 °C, and the contents were stirred at room temperature overnight. After it was diluted with water, the mixture was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with brine (8 mL) and dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was filtered through a silica bed using 20% EtOAc/80% hexanes. The product **13e** was used as such (considering 100% yield) in the next step without further purification and analysis.

14e (660 mg) was obtained from **13e** (700 mg, 3.46 mmol) following general procedure A: combined yield 70%; brown oil; R_f = 0.40 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (2H, s), 4.08 (2H, q, J = 6.8 Hz), 3.61−3.46 (2H, m), 3.40 (3H, s), 2.82 (1H, s), 1.38−1.25 (18H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.1, 92.4, 74.9, 73.5, 69.4, 54.4, 38.1, 38.1, 30.8, 28.6, 28.2, 23.3, 21.6, 21.6, 13.3, 13.0 ppm; IR (neat) ν 3424, 3020, 2928, 2858, 2262, 1642, 1462, 1216, 1152 cm^{-1}; ESI-MS m/z 295 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{28}NaO_4$ 295.1885, found 295.1877.

*1-Ethoxy-3-((methoxymethoxy)methyl)undec-1-yn-3-ol (**14f**).* To a mixture of 1-hydroxy-2-decanone[41] (398 mg, 2.31 mmol) and DIPEA (447 mg, 3.47 mmol) in CH_2Cl_2 (6 mL) was added MOMCl (240 mg, 3.00 mmol) at 0 °C, and the contents were stirred at room temperature overnight. After it was diluted with water, the mixture was extracted with CH_2Cl_2 (2 × 8 mL) and the combined organic layers were washed with brine (6 mL) and dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was filtered through a silica bed using 20% EtOAc/80% hexanes. The product **13f** was used as such (considering 100% yield) in the next step without further purification and analysis.

14f (430 mg) was obtained from **13f** (500 mg, 2.31 mmol) following general procedure A: yield 65%; yellow oil; R_f = 0.48 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (2H, dd, J = 10.9, 6.5 Hz), 4.08 (2H, q, J = 6.9 Hz), 3.54 (2H, dd, J = 35.9, 10.1 Hz), 3.40 (3H, s), 2.80 (3H, s), 1.64−1.29 (18H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.0, 92.4, 74.9, 73.5, 69.4, 54.4, 38.1, 38.1, 30.8, 28.8, 28.5, 28.2, 23.3, 21.6, 13.3, 13.0 ppm; IR (neat) ν 3429, 3019, 2929, 2263, 1638, 1466, 1215, 1151, 1112, cm^{-1}; ESI-MS m/z 309 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{30}NaO_4$ 309.2042, found 309.2035.

*4-Ethoxy-1-(methoxymethoxy)-2-phenylbut-3-yn-2-ol (**14g**).* **14g** (1.16 g) was obtained from **13g**[42] (1g, 5.55 mmol) following general procedure A: yield 84%; yellow oil; R_f = 0.37 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, J = 7.3 Hz), 7.35 (2H, t, J = 7.3 Hz), 7.29 (1H, d, J = 7.3 Hz), 4.69 (2H, dd, J = 17.1, 6.5 Hz), 4.14 (2H, q, J = 7.0 Hz), 3.70 (2H, dd, J = 40.5, 10.3 Hz), 3.44 (1H, s), 3.35 (3H, s), 1.38 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 128.1, 127.7, 126.0, 97.1, 94.5, 78.1, 74.7, 72.2, 55.5, 39.8, 14.4 ppm; IR (neat) ν 3431, 3017, 2928, 2264, 1625, 1216, 1153, 1110, 704, 669 cm^{-1}; ESI-MS m/z 273 [M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{18}NaO_4$ 273.1103, found 273.1094.

*2-(4-Chlorophenyl)-4-ethoxy-1-(methoxymethoxy)but-3-yn-2-ol (**14h**).* **14h** (708 mg) was obtained from **13h**[43] (600 mg, 2.80 mmol) following general procedure A: yield 89%; brown oil; R_f = 0.50 (SiO_2, 30% EtOAc/70% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 7.4 Hz), 4.67 (2H, dd, J = 12.7, 6.6 Hz), 4.13 (2H, q, J = 6.9 Hz), 3.74−3.59 (3H, m), 3.34 (3H, s), 1.38 (3H,t, J = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 133.4, 128.0, 127.4, 97.0, 94.5, 77.8, 74.7, 71.7, 55.4, 39.4, 14.3 ppm; IR (neat) ν 3472, 2966, 2234, 1464, 1312, 1252, 1178, 712 cm^{-1}; ESI-MS m/z 307[M + Na]$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{17}NaClO_4$ 307.0713, found 307.0708.

*4-Ethoxy-2-(4-fluorophenyl)-1-(methoxymethoxy)but-3-yn-2-ol (**14i**).* **14i** (595 mg) was obtained from **13i**[43] (500 mg, 2.52 mmol) following general procedure A: yield 88%; yellow oil; R_f = 0.52 (SiO_2, 30% EtOAc/70% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, d, J = 5.4 Hz), 7.61 (1H, d, J = 5.4 Hz), 7.02 (2H, t, J = 8.6 Hz), 4.69 (2H, dd, J = 16.1, 6.6 Hz), 4.14 (2H, q, J = 7.0 Hz), 3.67 (2H, dd, J = 42.7, 10.3 Hz), 3.56 (1H, s), 3.53 (3H, s), 1.39 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 161.2, 138.3, 127.9, 127.8, 114.9, 114.7, 97.1, 94.6, 78.1, 74.8, 71.9, 55.6, 39.6, 14.8 ppm; IR (neat) ν 3466, 2968, 2242, 1502, 1379, 1312, 1245, 1136, 1012 cm^{-1}; ESI-MS m/z 269[M + H]$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{18}FO_4$ 269.1189, found 269.1180.

*4-Ethoxy-1-(methoxymethoxy)-2-p-tolylbut-3-yn-2-ol (**14j**).* **14j** (591 mg) was obtained from **13j**[43] (500 mg, 2.57 mmol) following general procedure A: yield 87%; brown oil; R_f = 0.47 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, J = 7.9 Hz), 7.15 (2H, d, J = 7.9 Hz), 4.68 (2H, dd, J = 16.4, 6.5 Hz), 4.13 (2H, q, J = 7.0 Hz), 3.68 (2H, dd, J = 38.5, 10.3 Hz), 3.41 (1H, s), 3.36 (3H, s), 2.34 (3H, s), 1.38 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.3, 128.7, 125.8, 97.0, 94.3, 78.0, 74.6, 72.0, 55.4, 39.9, 21.0, 14.4 ppm; IR (neat) ν 3426, 2930, 2263, 1613, 1450, 1383, 1216, 1153, 818, 757, 667 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd $C_{15}H_{21}NaO_4$ 287.1259, found 287.1250.

*2-(2,4-Dimethylphenyl)-4-ethoxy-1-(methoxymethoxy)but-3-yn-2-ol (**14k**).* To a mixture of hydroxy 2,4-dimethyl-2′-hydroxyacetophenone[25] (473 mg, 2.88 mmol) and DIPEA (558 mg, 4.32 mmol) in CH_2Cl_2 (6 mL) was added MOMCl (300 mg, 3.74 mmol) at 0 °C, and the contents were stirred at room temperature overnight. After it was diluted with water, the mixture was extracted with CH_2Cl_2 (2 × 8 mL) and the combined organic layers were washed with brine (6 mL) and dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was filtered through a silica bed using 20% EtOAc/80% hexanes. The product **13k** was used as such (considering as 100% yield) in the next step without further purification and analysis.

14k (600 mg) was obtained from **13k** (600 mg, 2.88 mmol) following general procedure A: combined yield 75%; brown oil; R_f = 0.45 (SiO_2, 20% EtOAc/80% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 8.5 Hz), 6.98 (2H, d, J = 6.8 Hz), 4.72 (2H, dd, J = 17.3, 6.5 Hz), 4.10 (2H, q, J = 6.9 Hz), 3.85 (2H, dd, J = 24.1, 10.3 Hz), 3.38 (3H, s), 2.58 (3H, s), 2.29 (3H, s), 1.35 (3H, t, J = 6.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.5, 135.8, 133.0, 126.3, 126.2, 97.1, 94.5, 75.3, 74.5, 71.6, 55.5, 39.8, 21.3, 20.8, 14.4 ppm; IR (neat) ν 3412, 3017, 2929, 2264, 1614, 1442, 1384, 1216,

dx.doi.org/10.1021/jo400499r | J. Org. Chem. 2013, 78, 5878−5888

1151, 926, 756 cm^{-1}; ESI-MS m/z 301 $[M + Na]^+$; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{22}NaO_4$ 301.1416, found 301.1409.

*4-Ethoxy-2-(furan-2-yl)-1-(methoxymethoxy)but-3-yn-2-ol (**14l**).* To a mixture of 1-(furan-2-yl)-2-hydroxyethanone[44] (370 mg, 2.94 mmol) and DIPEA (569 mg, 4.41 mmol) in CH_2Cl_2 (5 mL) was added MOMCl (305 mg, 3.82 mmol) at 0 °C, and the contents were stirred at room temperature overnight. After it was diluted with water, the mixture was extracted with CH_2Cl_2 (2 × 6 mL) and the combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was filtered through a silica bed using 20% EtOAc/80% hexanes. The product **13l** was used as such (considering as 100% yield) in the next step without further purification and analysis.

14l (444 mg) was obtained from **13l** (500 mg, 2.94 mmol) following general procedure A: combined yield 63%; brown oil; R_f = 0.38 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.18 (2H, m), 6.97 (1H, t, J = 4.3 Hz), 4.72 (2H, dd, J = 9.9, 6.6 Hz), 4.17 (2H, q, J = 7.0 Hz), 3.86 (1H, s), 3.82−3.77 (2H, m), 3.40 (3H, s), 1.41 (3H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 126.5, 125.1, 124.6, 97.1, 94.2, 78.0, 74.8, 69.9, 55.6, 39.4, 14.4 ppm; IR (neat) ν 3412, 3019, 2929, 2400, 1618, 1264, 1215, 1152, 928, 757, 669 cm^{-1}; HRMS (ESI): (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{12}H_{16}NaO_5$ 263.0895, found 263.0889.

General Procedure for the Synthesis of 3-Iodocoumarins 9a−p from 5a−f or 6a−p and the Synthesis of 3-Iodobutenolides 15a−l from 14a−l. Iodine (657 mg, 2.6 mmol) was added to a solution of substrate (2 mmol of **5a−f**, **6a−p**, **11**, or **14a−l**) in 8 mL of DCE (**5a−f**), CH_2Cl_2 (**6a−p**), or toluene (**11** or **14a−l**). The resulting mixture was stirred at room temperature (reflux temperature for **5a**) until the reaction was complete as indicated by TLC (for the time see Table 2). Then the reaction was quenched by adding a saturated aqueous solution of $Na_2S_2O_3$ and extracted with DCM (for **5a−f** and **6a−p**) or EtOAc (for **11** and **14a−l**). The combined organics were washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure the crude product was purified by column chromatography with silica gel using a mixture of ethyl acetate and hexanes.

*3-Iodo-2H-chromen-2-one (**9a**):*[10] yield 72% (390 mg); white solid; mp 86−88 °C; R_f = 0.50 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.57 (t, 1 H, J = 7.7 Hz), 7.44 (d, 1H, J = 7.1 Hz), 7.34−7.30 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 154.5, 152.2, 132.4, 126.9, 124.8, 120.2, 116.9, 86.3 ppm; IR (KBr): ν 3021, 1606, 1127, 952, 669 cm^{-1}; ESI-MS m/z 272.7 $[M + H]^+$.

*3-Iodo-7-methoxy-2H-chromen-2-one (**9b**):*[11e] yield 85% (511 mg); brown solid; mp 150−153 °C; R_f = 0.45 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.32 (d, 1H, J = 8.3 Hz), 6.85 (dd, 1H, J = 8.3, 2.3 Hz), 6.80 (d, 1H, J = 2.3 Hz), 3.87 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.3, 157.8, 155.9, 152.1, 127.9, 114.1, 113.0, 100.8, 81.2, 56.0 ppm; IR (KBr): ν 3020, 1617, 923, 669 cm^{-1}; ESI-MS m/z 302.7 $[M + H]^+$.

*6-Chloro-3-iodo-2H-chromen-2-one (**9c**):* yield 78% (475 mg); yellow solid; mp 103−105 °C; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.51 (dd, 1H, J = 8.8, 2.2 Hz), 7.42 (d, 1H, J = 2.2 Hz), 7.27 (d, 1H, J = 8.8 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 152.4, 150.9, 132.2, 130.1, 126.0, 121.0, 118.3, 88.1 ppm; IR (KBr): ν 3021, 1605, 1083, 926, 669 cm^{-1}; ESI-MS m/z 306.7 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_9H_4ClIO_2$ $[M + H]^+$ 306.9023, found 306.9026.

*3-Iodo-4-methyl-2H-chromen-2-one (**9d**):* yield 82% (467 mg); yellow solid; mp 88−90 °C; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 7.7 Hz), 7.58 (t, 1H, J = 7.4 Hz), 7.36 (d, 1H, J = 7.4 Hz), 7.30 (t, 1H, J = 7.7 Hz), 2.72 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 156.6, 152.6, 132.3, 125.2, 124.8, 119.4, 117.0, 93.2, 25.5 ppm; IR (KBr): ν 3019, 2400, 1598, 929, 624 cm^{-1}; ESI-MS m/z 286.7 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{10}H_8IO_2$ $[M + H]^+$ 286.9569, found 286.9565.

*3-Iodo-4-phenyl-2H-chromen-2-one (**9e**):* yield 78% (541 mg); yellow solid; mp 94−96 °C; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.58−7.53 (m, 4H,) 7.39 (d, 1H, J = 7.7 Hz), 7.24 (d, 2H, J = 6.6 Hz), 7.15 (t, 1H, J = 7.7 Hz), 7.05 (d, 1H, J = 7.7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 157.7, 153.0, 138.8, 132.3, 129.2, 128.8, 127.8, 127.7, 124.5, 119.9, 116.5, 92.2 ppm; IR (KBr) ν 3021, 1601, 1333, 928, 669 cm^{-1}; HRMS (MALDI-TOF/TOF) calcd for $C_{15}H_{10}IO_2$ $[M + H]^+$ 348.9725, found 348.9717.

*3-Iodo-7-methoxy-4-phenyl-2H-chromen-2-one (**9f**):* yield 80% (603 mg); yellow solid; mp 110−112 °C; R_f = 0.50 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$): = 7.56−7.54 (m, 3H), 7.25−7.21(m, 2H), 6.94 (d, 1H, J = 8.9 Hz), 6.88 (d, 1H, J = 2.6 Hz), 6.70 (dd, 1H, J = 8.9, 2.6 Hz) 3.87 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 160.8, 158.4, 155.0, 139.3, 129.2, 129.0, 128.9, 127.9, 114.0, 112.8, 100.5, 87.6, 55.9, 53.5 ppm; IR (KBr): ν 3021, 2401, 1611, 954, 669 cm^{-1}; ESI-MS m/z 378.4 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{16}H_{12}IO_3$ $[M + H]^+$ 378.9831, found 378.9824.

*3-Iodo-8-methyl-2H-chromen-2-one (**9g**):* yield 71% (404 mg); colorless gum; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.41 (d, 1H, J = 7.1 Hz), 7.25 (d, 1H, J = 6.3 Hz), 7.18 (t, 1H, J = 7.5 Hz), 2.45 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 152.5, 152.3, 133.6, 126.3, 124.6, 124.4, 119.9, 85.9, 15.3 ppm; IR (KBr): ν 2963, 1599, 1131, 943, 669 cm^{-1}; ESI-MS m/z 286.5 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{10}H_8IO_2$ $[M + H]^+$ 286.9569, found286.9565.

*8-Ethyl-3-iodo-2H-chromen-2-one (**9h**):* yield 74% (442 mg); white solid; mp 80−82 °C; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.43 (dd, 1H, J = 7.5, 1.2 Hz), 7.27 (d, 1H, J = 7.5 Hz), 7.21 (t, 1H, J = 7.5 Hz), 2.88 (q, 2H, J = 7.5 Hz), 1.28 (t, 3H, J = 7.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 152.6, 152.0, 132.4, 132.1, 128.8, 124.6, 120.1, 85.9, 22.4, 14.1 ppm; IR (KBr): ν 3019, 1597, 1046, 929, 625 cm^{-1}; ESI-MS m/z 300.7 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{11}H_{10}IO_2$ $[M + H]^+$ 300.9725, found 300.9720.

*3-Iodo-8-isopropyl-2H-chromen-2-one (**9i**):* yield 70% (438 mg); white solid; mp 131−133 °C; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.49 (t, 1H, J = 4.59 Hz), 7.24 (d, 2H, J = 4.5 Hz), 3.61 (sp, 1H, J = 6.9 Hz), 1.29 (d, 6H, J = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 152.8, 151.3, 136.8, 129.5, 124.7, 124.6, 120.1, 85.7, 26.5, 22.6 ppm; IR (KBr): ν 3020, 1595, 1131, 942, 669 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{12}IO_2$ $[M + H]^+$ 314.9882, found 314.9884.

*8-tert-Butyl-3-iodo-2H-chromen-2-one (**9j**):* yield 58% (380 mg); colorless gum; R_f = 0.50 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.56 (d, 1H, J = 7.4 Hz), 7.28 (d, 1H, J = 7.7 Hz), 7.21 (t, 1H, J = 7.4 Hz), 1.49 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 153.1, 152.8, 138.3, 130.0, 125.4, 124.4, 120.8, 85.3, 53.5, 35.1 ppm; IR (KBr): ν 2963, 1410, 1095, 931, 670 cm^{-1}; ESI-MS m/z 329.2 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{13}H_{14}IO_2$ $[M + H]^+$ 329.0038, found 329.0036.

*8-Bromo-6-chloro-3-iodo-2H-chromen-2-one (**9k**):* yield 70% (536 mg); white solid; mp 174−176 °C; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, [D6]DMSO) δ 8.74 (s, 1H), 8.07 (d, 1H, J = 2.3 Hz), 7.81 (d, 1H, J = 2.3 Hz) ppm; ^{13}C NMR (75 MHz, [D_6]DMSO) δ 156.3, 150.7, 149.1, 133.9, 128.6, 126.0, 122.1, 109.9, 89.9 ppm; IR (KBr): ν 3019, 1600, 1124, 853, 626 cm^{-1}; HRMS (MALDI-TOF/TOF) calcd for $C_9H_4BrClIO_2$ $[M + H]^+$ 384.8128, found 384.8138.

*3-Iodo-6-nitro-2H-chromen-2-one (**9l**):* yield 52% (328 mg); colorless gum; R_f = 0.40 (SiO_2, 30% EtOAc/70% hexanes); ^1H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.6 (d, 1H, J = 2.7 Hz), 8.4 (dd, 1H, J = 9.2, 2.7 Hz), 7.6 (d, 1H, J = 9.2 Hz) ppm; ^{13}C NMR (75 MHz, [D_6]DMSO) δ 157.5, 156.9, 151.7, 144.0, 127.1, 123.6, 120.8, 118.3, 90.4 ppm; IR (KBr): ν 2928, 1613, 1346, 930, 624 cm^{-1}; ESI-MS m/z 317.3 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_9H_4INO_4$ $[M + H]^+$: 317.9263, found 317.9255.

*3-Iodo-6-phenyl-2H-chromen-2-one (**9m**):* yield 85% (589 mg); yellow solid; mp 155−157 °C; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.78 (dd, 1H, J = 8.5, 2.0 Hz), 7.60 (d, 1H, J = 2.0 Hz), 7.56 (d, 1H, J = 8.5 Hz), 7.7 (t, 2H, J = 7.0 Hz), 7.41 (t, 3H, J = 8.5 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 153.4, 152.3, 139.1, 138.2, 131.3, 129.2, 128.1, 127.1,

dx.doi.org/10.1021/jo400499r | J. Org. Chem. 2013, 78, 5878−5888

125.0, 120.4, 117.3, 86.8 ppm; IR (KBr): ν 3021, 2401, 1611, 954, 669 cm^{-1}; ESI-MS m/z 348.5 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{15}H_{10}IO_2$ $[M + H]^+$ 348.9725, found 348.9733.

*2-Iodo-3H-benzo[f]chromen-3-one (**9n**):* yield 65% (417 mg); white solid; mp 148−150 °C; R_f = 0.50 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.20 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 8.9 Hz), 7.92 (d, 1H, J = 8.3 Hz), 7.71 (t, 1H, J = 7.3 Hz), 7.59 (t, 1H, J = 7.3 Hz), 7.44 (d, 1H, J = 8.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 154.0, 148.2, 133.8, 130.4, 129.1, 128.7, 127.9, 126.5, 121.3, 116.8, 114.4, 85.5 ppm; IR (KBr): ν 3019, 1551, 928, 669, 625 cm^{-1}; ESI-MS m/z 322.5 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{13}H_8IO_2$ $[M + H]^+$ 322.9569, found 322.9565.

*3-Iodo-4,7-dimethyl-2H-chromen-2-one (**9o**):* yield 80% (478 mg); yellow solid; mp 144−146 °C; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 8.1 Hz), 7.14 (s, 1H), 7.11 (d, 1H, J = 8.1 Hz), 2.68 (s,3H), 2.43 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.5, 152.5, 143.6, 125.9, 124.8, 116.9, 114.0, 91.4, 25.3, 21.7. ppm; IR (KBr): ν 3019, 2400, 1598, 929, 624 cm^{-1}; ESI-MS m/z 300.7 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{11}H_{10}IO_2$ $[M + H]^+$ 300.9725, found 300.9720.

*3-Iodo-7-methoxy-4-methyl-2H-chromen-2-one (**9p**):*[11f] yield 84% (529 mg); white solid; mp 159−162 °C; R_f = 0.45 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 1H, J = 8.9 Hz), 6.85 (dd, 1H, J = 8.9, 2.5 Hz), 6.81 (d, 1H, J = 2.5 Hz), 3.88 (s, 3H), 2.65 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 157.9, 156.5, 154.1, 126.3, 113.0, 112.7, 100.4, 86.6, 55.9, 25.4 ppm; IR (KBr): ν 3020, 1617, 923, 669 cm^{-1}; ESI-MS m/z 316.6 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{11}H_{10}IO_3$ $[M + H]^+$ 316.9674, found 316.9671.

*4-Iodo-2-oxaspiro[5.5]undec-4-en-3-one (**12**):* yield 85% (537 mg); colorless gum; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 4.22 (s, 2H), 1.69−1.39 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 159.9, 87.6, 75.3, 40.1, 32.5, 25.4, 21.2 ppm; HRMS (ESI-TOF) calcd for $C_{10}H_{13}NaIO_2$ $[M + Na]^+$ 314.9858, found 314.9850.

*3-Iodo-4,5,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (**15a**):* yield 85% (408 mg); colorless gum; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (t, 1H, J = 7.9 Hz), 2.68−2.06 (m, 4H), 1.45−1.32 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.6, 171.9, 86.9, 78.0, 29.57, 24.4, 22.7 ppm; IR (KBr): ν 3021, 1605, 1272, 951, 669 cm^{-1}; ESI-MS m/z 250.7 $[M + H]^+$; HRMS (ESI) calcd for $C_7H_8IO_2$ $[M + H]^+$ 250.9569, found 250.9564.

*3-Iodo-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one (**15b**):* yield 89% (468 mg); colorless gum; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (dd, 1H, J = 6.2, 5.0 Hz), 2.82 (dt, 1H, J = 14.0, 2.1 Hz), 2.48−2.43 (m, 1H), 2.27 (ddd, 1H, J = 13.6, 7.6, 6.0 Hz), 2.07−1.93 (m, 2H), 1.56−1.27 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 169.9, 83.7, 79.3, 34.3, 30.3, 26.0, 22.9 ppm; IR (KBr): ν 3020, 1638, 1037, 669 cm^{-1}; HRMS (MALDI-TOF/TOF) calcd for $C_8H_{10}IO_2$ $[M + H]^+$ 264.9725, found 264.9731.

*3-Iodo-4,5,6,7,8,8a-hexahydro-2H-cyclohepta[b]furan-2-one (**15c**):* yield 82% (454 mg); colorless gum; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (d, 1H, J = 6.8 Hz), 2.68−2.3 (m, 4H), 1.9−1.47 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 169.9, 86.8, 83.2, 33.5, 32.3, 29.5, 26.1, 25.1 ppm; IR (KBr): ν 3019, 1619, 1015, 668 cm^{-1}; ESI-MS m/z 278.3 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_9H_{12}IO_2$ $[M + H]^+$ 278.9882, found 278.9877.

*3-Iodo-5,6,7,8,9,9a-hexahydro-2H-cycloocta[b]furan-2-one (**15d**):* yield 80% (467 mg); yellow color gum; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.01 (t, 1H, J = 5.2 Hz), 3.66 (s, 1H), 2.74−2.68 (m, 1H), 2.43−2.34 (m, 1H), 2.29 (t, 1H, J = 7.5 Hz), 2.20−2.13 (m, 1H), 2.12−2.01 (m, 1H), 1.82−1.70 (m, 3H), 1.41−1.29 (m,3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 85.9, 84.7, 30.1, 28.6, 26.7, 26.3, 25.0, 20.7 ppm; IR (KBr): ν 3019, 1752, 1620, 1216, 669 cm^{-1}; ESI-MS m/z 293.5 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{10}H_{14}IO_2$ $[M + H]^+$ 293.0038, found 293.0035.

*4-Heptyl-3-iodofuran-2(5H)-one (**15e**):* yield 85% (523 mg); brown oil; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.8 (s, 2H), 2.48 (t, 2H, J = 7.2 Hz), 1.4−1.24 (m, 13H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.8, 82.2, 73.2, 30.5, 30.1, 28.6, 27.8, 25.9, 21.5, 13.0 ppm; IR (KBr): ν 3018, 2860, 1358, 1047, 668 cm^{-1}; ESI-MS m/z 309.1 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{11}H_{18}IO_2$ $[M + H]^+$ 309.0351, found 309.0345.

*3-Iodo-4-octylfuran-2(5H)-one (**15f**):* yield 85% (547 mg); brown oil; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 2H), 2.47 (t, 2H, J = 7.6 Hz), 1.57−1.51 (m, 2H), 1.40−1.20 (m, 13H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 170.9, 83.2, 77.5, 31.7, 31.1, 29.3, 29.1, 29.0, 26.9, 22.6, 14.1 ppm; IR (KBr): ν 3019, 1625, 1143, 668 cm^{-1}; ESI-MS m/z 323.1$[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{12}H_{20}IO_2$ $[M + H]^+$ 323.0508, found 323.0501.

*3-Iodo-4-phenylfuran-2(5H)-one (**15g**):* yield 60% (342 mg); yellow solid; mp 110−112 °C; R_f = 0.45 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 2H, J = 6.0 Hz), 7.54−7.52 (m, 3H), 5.20 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 162.8, 131.7, 130.2, 129.1, 127.0, 80.9, 73.8 ppm; IR (KBr): ν 3019, 1756, 1046, 626 cm^{-1}; ESI-MS m/z 286.6 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{10}H_8IO_2$ $[M + H]^+$ 286.9569, found 286.9560.

*4-(4-Chlorophenyl)-3-iodofuran-2(5H)-one (**15h**):* yield 70% (446 mg); brown solid; mp 175−177 °C; R_f = 0.50 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, J = 8.3 Hz), 7.50 (d, 2H, J = 8.3 Hz), 5.18 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 161.6, 137.4, 129.4, 128.5, 128.3, 81.5, 73.6 ppm; IR (KBr): ν 3021, 1760, 1606, 1095, 627 cm^{-1}; ESI-MS m/z 320.8 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{10}H_7ClIO_2$ $[M + H]^+$ 320.9179, found 320.9170.

*4-(4-Fluorophenyl)-3-iodofuran-2(5H)-one (**15i**):* yield 70% (424 mg); brown solid; mp 121−123 °C; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, 2H, J = 8.4, 6.0 Hz), 7.23 (t, 1H, J = 8.4 Hz), 5.2 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 165.7, 163.1, 161.7, 129.3, 129.3, 126.3, 126.3, 116.4, 116.2, 80.6, 80.6, 73.7 ppm; IR (KBr): ν 2927, 1604, 1243, 1032, 669 cm^{-1}; ESI-MS m/z 304.1 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{10}H_7FIO_2$ $[M + H]^+$ 304.9475, found 304.9467.

*3-Iodo-4-p-tolylfuran-2(5H)-one (**15j**):* yield 58% (346 mg); yellow solid; mp 170−172 °C; R_f = 0.60 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 7.6 Hz), 7.32 (d, 2H, J = 7.6 Hz), 5.19 (s, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 162.7, 142.5, 129.7, 127.2, 126.8, 79.4, 73.7, 21.6 ppm; IR (KBr): ν 3020, 1755, 1609, 1034, 670 cm^{-1}; ESI-MS m/z 300.6 $[M + H]^+$; HRMS (ESI) calcd for $C_{11}H_{10}IO_2$ $[M + H]^+$ 300.9725, found 300.9723.

*4-(2,4-Dimethylphenyl)-3-iodofuran-2(5H)-one (**15k**):* yield 55% (344 mg); yellow solid; mp 96−98 °C; R_f = 0.55 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.14−7.01 (m, 3H), 4.98 (s, 2H), 2.37 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 169.5, 140.3, 134.7, 131.8, 128.4, 127.1, 127.0, 86, 75.3, 21.3, 19.9 ppm; IR (KBr): ν 3019, 2344, 1628, 1047, 669 cm^{-1}; ESI-MS m/z 314.7 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_{12}H_{12}IO_2$ $[M + H]^+$ 314.9882, found 314.9873.

*4-(Furan-2-yl)-3-iodofuran-2(5H)-one (**15l**):* yield 54% (297 mg); yellow solid; mp 115−117 °C; R_f = 0.50 (SiO_2, 20% EtOAc/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 4.4 Hz), 7.63 (d, 1H, J = 2.4 Hz), 7.24 (dd, 1H, 4.8, 4.0 Hz), 5.22 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 157.0, 132.3, 131.2, 129.8, 127.9, 77.5, 73.2 ppm; IR (KBr): ν 3019, 1600, 1048, 669 cm^{-1}; ESI-MS m/z 276.7 $[M + H]^+$; HRMS (ESI-TOF) calcd for $C_8H_6IO_3$ $[M + H]^+$ 276.9362, found 276.9358.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*M.S.R.: tel, 91-5222612411-8, ext 2358; fax, 91-5222623405; e-mail, msreddy@cdri.res.in, sridharreddymaddi@yahoo.com.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

N.T., M.H.B., and S.P. thank the CSIR for Ph.D. fellowships. We thank Dr. T. K. Chakraborty, Director CDRI, for his encouragement. We thank the SAIF division CSIR-CDRI for analytical support. We gratefully acknowledge financial support by the CSIR-Network project "BSC0104i" (CSIR-CDRI-SPLenDID) and by the DST under "Fast Track Proposal Scheme for Young Scientists". CDRI Communication No. 8462.

REFERENCES

(1) (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Inamoto, K.; Asano, N.; Nakamura, Y.; Yonemoto, M.; Kondo, Y. *Org. Lett.* **2012**, *14*, 2622. (c) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173. (d) Alcaide, B.; Almendros, P.; Alonso, J. M. *Org. Biomol. Chem.* **2011**, *9*, 4405. (e) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (f) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 15720. (g) Nishizawa, M.; Imagawa, H.; Yamamoto, H. *Org. Biomol. Chem.* **2010**, *8*, 511. (h) Gabriele, B.; Veltri, L.; Mancuso, R.; Aresta, B. M. *J. Org. Chem.* **2012**, *77*, 4005. (i) Loh, C. C. J.; Enders, D. *Chem. Eur. J.* **2012**, *18*, 10212. (j) Susanti, D.; Koh, F.; Kusuma, J. A.; Kothandaraman, P.; Chan, P. W. H. *J. Org. Chem.* **2012**, *77*, 7166.

(2) (a) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513−6556. (b) Patil, N. T.; Nijamudheen, A.; Datta, A. *J. Org. Chem.* **2012**, *77*, 6179−6185.

(3) See for example: (a) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937. (b) Gabriele, B.; Mancuso, R.; Salerno, G.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 7640. (c) Spina, R.; Colacino, E.; Gabriele, B.; Salerno, G.; Martinez, J.; Lamaty, F. *Org. Biomol. Chem.* **2012**, *10*, 9085. (d) Mphahlele, M. J. *Molecules* **2009**, *14*, 4814. (e) Bew, S. P.; Taeb, G. M. M. E.; Jones, S.; Knight, D. W.; Tan, W. F. *Eur. J. Org. Chem.* **2007**, 5759. (f) Yang, F.; Jin, T.; Bao, M.; Yamamoto, Y. *Chem. Commun.* **2011**, *47*, 4541. (g) Kothandaraman, P.; Koh, B. Q.; Limpanuparb, T.; Hirao, H.; Chan, P. W. H. *Chem. Eur. J.* **2013**, *19*, 1978. (h) Kothandaraman, P.; Mothe, S. R.; Toh, S. S. M.; Chan, P. W. H. *J. Org. Chem.* **2011**, *76*, 7633. (i) Sharma, S. K.; Mandadapu, A. K.; Kumar, B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 798.

(4) (a) Reddy, M. S.; Kumar, Y. K.; Thirupathi, N. *Org. Lett.* **2012**, *14*, 824. (b) Reddy, M. S.; Thirupathi, N.; Babu, M. H. *E. J. Org. Chem.* **2012**, 5803. (c) Reddy, M. S.; Thirupathi, N.; Kumar, Y. K. *RSC Adv.* **2012**, *2*, 3986. (d) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178. (e) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *J. Org. Chem.* **2011**, *76*, 1269. (f) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420. (g) Reddy, M. S.; Thirupathi, N.; Babu, M. H. *Beilstein J. Org. Chem.* **2013**, *9*, 180.

(5) (a) Hernandes, M. Z.; Melo, S.; Cavalcanti, T.; Rodrigo, D.; Moreira, M.; Junior, W. F. A.; Leite, A. C. L. *Curr. Drug Targets* **2010**, *11*, 303. (b) Margosis, M.; Tanner, J. T.; Lambert, J. P. F. *J. Pharm. Sci.* **1971**, *60*, 1550. (c) Adriani, J.; Yarbrough, W. M. *J. Med. Assoc. Ga.* **1972**, *61*, 347. (c) Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.

(6) See for example: (a) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (b) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626. (c) Valerio, V.; Petkova, D.; Madelaine, C.; Maulide, N. *Chem. Eur. J.* **2013**, *19*, 2606. (d) Chen, Z.; Huang, G.; Jiang, H.; Huang, H.; Pan, X. *J. Org. Chem.* **2011**, *76*, 1134. (e) Okamoto, N.; Yanada, R. *J. Org. Chem.* **2012**, *77*, 3944. (f) Chuang, H.-L.; Sawant, R. C.; Luo, S.-Y. *Synlett* **2013**, *24*, 522.

(7) (a) Chimenti, F.; Secci, D.; Bolasco, A.; Chimenti, P.; Bizzarri, B.; Granese, A.; Carradori, S.; Yanez, M.; Orallo, F.; Ortuso, F.; Alcaro, S. *J. Med. Chem.* **2009**, *52*, 1935. (b) Emam, A. M.; Swelam, E. S.; Megally, N. Y. *J. Nat. Prod.* **2009**, *2*, 10.

(8) (a) Schiedel, M.-S.; Briehn, C. A.; Bauerle, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4677. (b) Welser, K.; Grilj, J.; Vauthey, E.; Aylott, J. W.; Chan, W. C. *Chem. Commun.* **2009**, 671. (c) Zhang, L.; Meng, T.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 7279.

(9) Audisio, D.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 1046.

(10) Elangovan, A.; Lin, J.-H.; Yang, S.-W.; Hsu, H.-Y.; Ho, T.-I. *J. Org. Chem.* **2004**, *69*, 8086.

(11) (a) Aquila, B. M. *Tetrahedron Lett.* **1997**, *38*, 2795. (b) Besson, T.; Ruiz, N.; Coudert, G.; Guillaumet, G. *Tetrahedron* **1995**, *51*, 3177. (c) Chilin, A.; Battistutta, R.; Bortolato, A.; Cozza, G.; Zanatta, S.; Poletto, G.; Mazzorana, M.; Zagotto, G.; Uriarte, E.; Guiotto, A.; Pinna, L. A.; Meggio, F.; Moro, S. *J. Med. Chem.* **2008**, *51*, 752. (d) Ghantwal, S. R.; Samant, S. D. *Indian J. Chem., Sect. B* **1999**, *38*, 1242. (e) Fukuyama, N.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4363. (f) Lele, S. S.; Sethna, S. *J. Org. Chem.* **1958**, *23*, 1731. (g) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis* **2005**, 1103. (h) Das, B.; Krishnaiah, M.; Venkateswarlu, K.; Reddy, S. *Tetrahedron Lett.* **2007**, *48*, 81. (i) Das, B.; Venkateswarlu, K.; Krishnaiah, M.; Holla, H. *Tetrahedron Lett.* **2006**, *47*, 8693.

(12) Jha, A.; Huang, P.-J. J.; Mukherjee, C.; Paul, N. K. *Synlett* **2007**, *20*, 3127.

(13) (a) Sorbera, L. A.; Rabasseda, X.; Castaner, J. *Drugs Fut.* **1998**, *23*, 1287. (b) Sun, L.; Vasilevich, N. I.; Fuselier, J. A.; Coy, D. H. *Anticancer Res.* **2004**, *24*, 179. (c) Otsuka, H.; Kotani, K.; Bando, M.; Kido, M.; Takeda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1180. (d) Juan Hikawczuk, V. E.; Saad, J. R.; Giordano, O. S.; Garcia, C.; Martin, T.; Martin, V. S.; Sosa, M. E.; Tonn, C. E. *J. Nat. Prod.* **2008**, *71*, 190. (e) Parvatkar, R. R.; D'Souza, C.; Tripathi, A.; Naik, C. G. *Phytochemistry* **2009**, *70*, 128. (f) Pour, M.; Spulak, M.; Buchta, V.; Kubanova, P.; Voprasalova, M.; Wsol, V.; Fakova, H.; Koudelka, P.; Pourova, H.; Schiller, R. *J. Med. Chem.* **2001**, *44*, 2701. (g) Koo, K. A.; Lee, M. K.; Kim, S. H.; Jeong, E. J.; Oh, T. H.; Kim, Y. C. *Br. J. Pharmacol.* **2007**, *150*, 65−71;(h) Kaushik, M. P.; Thavaselvam, D.; Nivsarkar, M.; Acharya, B. N.; Prasanna, S.; Sekhar, K. *PCT Int. Appl.* WO 2007039915, 2007; *Chem. Abstr.* **2007**, *146*, 408201. (i) Son, J. K.; Kim, D. H.; Woo, M. H. *J. Nat. Prod.* **2003**, *66*, 1369. (j) Kikuchi, H.; Tsukitani, Y.; Nakanishi, H.; Shimizu, I.; Saitoh, S.; Iguchi, K.; Yamada, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1172.

(14) (a) Li, S.; Miao, B.; Yuan, W.; Ma, S. *Org. Lett.* **2013**, *15*, 977. (b) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295. (c) Bellina, F.; Marchetti, C.; Rossi, R. *E. J. Org. Chem.* **2009**, 4685. (d) Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 778. (e) Browne, D. M.; Niyomura, O.; Wirth, T. *Org. Lett.* **2007**, *9*, 3169. (f) Alfonsi, M.; Arcadi, A.; Chiarini, M.; Marinelli, F. *J. Org. Chem.* **2007**, *72*, 9510. (g) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Chem. Commun.* **2005**, 3295. (h) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2003**, *42*, 1955. (i) Beck, B.; Lachaux, M. M.; Lachaux, M.; Herdtweck, E.; Domling, A. *Org. Lett.* **2001**, *3*, 2875.

(15) (a) Ma, S.; Wu, B.; Shi, Z. *J. Org. Chem.* **2004**, *69*, 1429. (b) Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2005**, 3942. (c) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137.

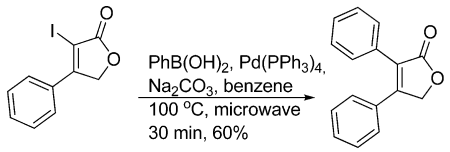
(16) An example of unsubstituted 3-iodobutenolide is reported in both of the following references: (a) Boukouvalas, J.; Loach, R. P. *J. Org. Chem.* **2008**, *73*, 8109. (b) Carter, N. B.; Mabon, R.; Richecoeur, A. M. E.; Sweeney, J. B. *Tetrahedron* **2002**, *58*, 9117.

(17) Li et al and Larock et al. reported the synthesis of 3-iodospirobutenolides in the following references: (a) Tang, B.-X.; Yin, Q.; Tang, R.-Y.; Li, J.-H. *J. Org. Chem.* **2008**, *73*, 9008. (b) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230.

(18) (a) Zhang, J.; Blazecka, P. G.; Belmont, D.; Davidson, J. G. *Org. Lett.* **2002**, *4*, 4559. (b) Bellina, F.; Anselmi, C.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997.

(19) Products were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS analysis. Comparison of the data of a few of the examples with those of

the corresponding bromobutenolides reported in the literature[18b] also helped in the structure confirmation. To further confirm, one of the examples of our iodobutenolides, **15g**, was subjected to Suzuki coupling, as given below, to give the known 3,4-diphenylbutenolide.[18a]



15 g **16**

(20) Commercially available.
(21) Kitade, M.; Tanaka, H.; Takahashi, T. *Heterocycles* **2007**, *73*, 183.
(22) Granados-Covarrubias, E. H.; Maldonado, L, A. *J. Org. Chem.* **2009**, *74*, 5097.
(23) Wang, G.; Wu, W.; Peng, F.; Cao, D.; Yang, Z.; Ma, L.; Qiu, N.; Ye, H.; Han, X.; Chen, J.; Qiu, J.; Sang, Y.; Liang, X.; Ran, Y.; Peng, A.; Wei, Y.; Chen, L. E. *J. Med. Chem.* **2012**, *54*, 793.
(24) Kobayashi, T.; Sasaki, S.; Tomita, N.; Kiba, A.; Takatsu, Y.; Ohtaki, T.; Baba, A.; Fukui, S.; Kuroda, N.; Nakayama, M.; Itoh, F. *Bioorg. Med. Chem.* **2010**, *18*, 3841.
(25) Forrester, A. R.; Gill, M.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 621.
(26) Nomura, N.; Aoyama, T.; Ishii, R.; Kondo, T. *Macromolecules* **2005**, *38*, 5363.
(27) Mori, K.; Kawasaki, T.; Sueoka, S.; Akiyama, T. *Org. Lett.* **2010**, *12*, 1732.
(28) Kobayashi, S.; Arai, K.; Shimizu, H.; Ihori, Y.; Ishitani, H.; Yamashita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 761.
(29) Nomura, N.; Ishii, R.; Yamamoto, Y.; Kondo, T. *Chem. Eur. J.* **2007**, *13*, 4433.
(30) Awasthi, A. K.; Boys, M. L.; Cain-Janicki, K. J.; Colson, P.-J.; Doubleday, W. W.; Duran, J. E.; Farid, P. N. *J. Org. Chem.* **2005**, *70*, 5387.
(31) Tsubaki, K.; Tanaka, H.; Kinoshita, T.; Fuji, K. *Tetrahedron* **2002**, *58*, 1679.
(32) Harvey, R. G.; Cortez, C.; Ananthanarayan, T. P.; Schmolka, S. *J. Org. Chem.* **1988**, *53*, 3936.
(33) Syper, L. *Synthesis* **1989**, 167.
(34) Srikrishna, A.; Ravi, G.; Krishnan, H. S. *Synlett* **2008**, 1199.
(35) Mori, K.; Kawasaki, T.; Sueoka, S.; Akiyama, T. *Org. Lett.* **2010**, *12*, 1732.
(36) Lopez-Valdez, G.; Olguin-Uribe, S.; Millan-Ortiz, A.; Miranda, L. D.; Gamez-Montano, R. *Tetrahedron* **2011**, *67*, 2693.
(37) Gasparski, C. M.; Herrinton, P. M.; Overman, L. E.; Wolfe, J. P. *Tetrahedron Lett.* **2000**, *41*, 9431.
(38) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030.
(39) (a) Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287. (b) Stankovic, S.; Espenson, J. H. *J. Org. Chem.* **1998**, *63*, 4129.
(40) Matsuo, K.; Shindo, M. *Org. Lett.* **2010**, *12*, 5346.
(41) Rangappa, P.; Shine, H. J.; Marx, J N.; Ould-Ely, T.; Kelly, A. T.; Whitmire, K. H. *J. Org. Chem.* **2005**, *70*, 9764.
(42) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716.
(43) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100.
(44) Wong, F. F.; Chang, P.-W.; Lin, H.-C.; You, B.-J.; Huang, J.-J.; Lin, S.-K. *J. Organomet. Chem.* **2009**, *694*, 3452.

dx.doi.org/10.1021/jo400499r | *J. Org. Chem.* 2013, 78, 5878−5888