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A Rapid and Efficient Sonogashira Protocol and Improved Synthesis of Free Fatty Acid 1 (FFA1) Receptor Agonists

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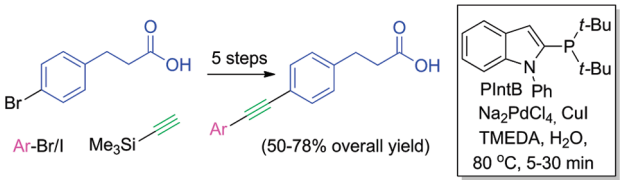
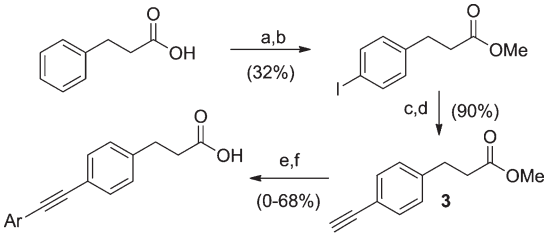


A protocol for rapid and efficient Pd/Cu-catalyzed coupling of aryl bromides and iodides to terminal alkynes has been developed with use of 2-(di-*tert*-butylphosphino)-*N*-phenylindole (cataCXium PIntB) as ligand in TMEDA and water. The new protocol successfully couples substrates which failed with standard Sonogashira conditions, and enables an efficient general synthetic route to free fatty acid 1 (FFA1) receptor ligands from 3-(4-bromophenyl)-propionic acid.

Since its discovery more than three decades ago, the Sonogashira reaction has attained the position as the most important method for synthesis of substituted alkynes.[1,2] Originally referring to the cross-coupling of terminal alkynes with vinyl or aryl halides cocatalyzed by palladium and copper, the name has lately been used broadly for any metal-catalyzed C−C bond-forming cross-coupling with terminal alkynes. The original reaction conditions are generally efficient and tolerant to a wide variety of functional groups and are still widely used, but a large number of modified protocols have also appeared which have been aimed at solving various limitations, such as broadening the scope of possible sp^2-partners to include unactivated aryl bromides and chlorides, and developing more efficient catalytic systems and environmentally friendly reaction conditions, including ligand-free, copper-free, amine-free, and aqueous conditions.[2,3] Nonetheless, unreactive substrates and problems related to alkyne homocoupling are still frequently encountered. We recently reported a series of free fatty acid 1 (FFA1 or GPR40) receptor agonists with potential antidiabetic properties.[4] The original synthesis of these compounds, which relied on the Sonogashira coupling in two central steps, frequently resulted in low or no yields, precluding upscaling and access to new analogues (Scheme 1). Thus, we set out to optimize the general synthetic route to these compounds.

SCHEME 1. Original Synthetic Route to Alkyne FFA1 Agonists[a]



[a]Reagents and conditions: (a) I_2, KIO_3, H_2SO_4, H_2O, AcOH, reflux, 5 h (33%); (b) MeOH, HCl (cat.), rt, 2 h (98%); (c) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, TMSA (added at 70 °C), DMF, 70→90 °C, 3 h; (d) K_2CO_3, MeOH, rt, 2.5 h (90% over 2 steps); (e) aryl halide, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 50 °C; (f) LiOH, 1,4-dioxane, H_2O, rt.

The low-yielding iodination step resulting in synthesis of the common alkyne intermediate **3** in only 29% yield represented a general problem in the original synthetic route (Scheme 1). We therefore decided to substitute the iodo intermediate by the readily available 3-(4-bromophenyl)-propionic acid (**1**). Unfortunately, coupling of **1** with trimethylsilylacetylene (TMSA) by the standard Sonogashira protocol resulted in only 48% conversion (Table 1, entry 1). Furthermore, both TMS-alkyne **2** and the deprotected alkyne intermediate **3** turned out to be very difficult to separate from **1**, thus, complete conversion was required. The outcome was only marginally influenced by the exchange of DMF and Et_3N by TMEDA (entry 2). Other catalytic systems like $Pd(OAc)_2$ with Xantphos (entry 3) or tri-*tert*-butylphosphine (entry 4) resulted in further reduced conversion.[5] Recently, Beller and co-workers

(1) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

(2) For recent reviews of the Sonogashira reaction, see: (a) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834–871. (b) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874–922. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017. (d) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (e) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954–6956. (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489. (g) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566–1568.

(3) Recent improved Sonogashira protocols: (a) Schulz, T.; Torborg, C.; Enthaler, S.; Schaeffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Boerner, A.; Beller, M. *Chem.—Eur. J.* **2009**, *15*, 4528–4533. (b) Torborg, C.; Huang, J.; Schulz, T.; Schäffner, B.; Zapf, A.; Spannenberg, A.; Börner, A.; Beller, M. *Chem.—Eur. J.* **2009**, *15*, 1329–1336. (c) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793–3796. (d) Mori, S.; Yanase, T.; Aoyagi, S.; Monguchi, Y.; Maegawa, T.; Sajiki, H. *Chem.—Eur. J.* **2008**, *14*, 6994–6999. (e) Huang, H.; Liu, H.; Jiang, H.; Chen, K. *J. Org. Chem.* **2008**, *73*, 6037–6040. (f) Finke, A. D.; Elleby, E. C.; Boyd, M. J.; Weissman, H.; Moore, J. S. *J. Org. Chem.* **2009**, *74*, 8897–8900. (g) Bolligera, J. L.; Frech, C. M. *Adv. Synth. Catal.* **2009**, *351*, 891–902.

(4) Christiansen, E.; Urban, C.; Merten, N.; Liebscher, K.; Karlsen, K. K.; Hamacher, A.; Spinrath, A.; Bond, A. D.; Drewke, C.; Ullrich, S.; Kassack, M. U.; Kostenis, E.; Ulven, T. *J. Med. Chem.* **2008**, *51*, 7061–7064.

(5) (a) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731. (b) Köllhofer, A.; Plenio, H. *Adv. Synth. Catal.* **2005**, *347*, 1295–1300. (c) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679–3681.

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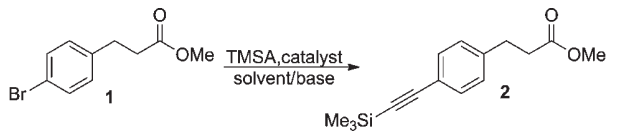
TABLE 1. Optimizing the Coupling of 1 with Trimethylsilylacetylene



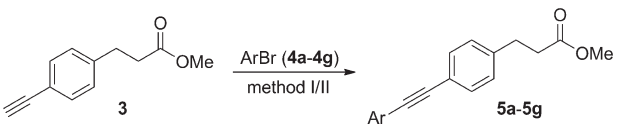
entry	catalyst[a]	solvent/base (equiv)	TMSA (equiv)	temp (°C)	conv (%)[b]
1	A	DMF/Et_3N (3)	2[c]	90	48
2	B	TMEDA	2[c]	80	54
3	C	DMF/Et_3N (22)	1.2	25	3
4	D	dioxane/Et_3N (1.2)	1.2	25	18
5	E	TMEDA	1.2	80	67
6	E	TMEDA	2	80	80
7	E	TMEDA	1.2[c]	80	98
8	E	TMEDA	2[c]	80	100[d]
9	F	TMEDA	2[c]	80	24

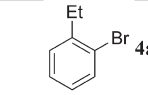
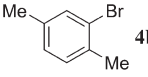
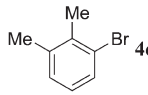
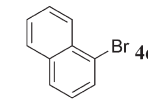
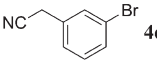
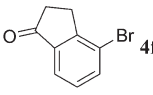
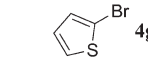
[a]Catalyst A: $Pd(PPh_3)_2Cl_2$ (1 mol %), CuI (2 mol %). Catalyst B: $Pd(PPh_3)_2Cl_2$ (0.5 mol %), CuI (1 mol %). Catalyst C: $Pd(OAc)_2$ (3 mol %), Xantphos (6.5 mol %), CuI (2 mol %). Catalyst D: $Pd(OAc)_2$ (3 mol %), P(*t*-Bu)$_3$ (6.5 mol %), CuI (2 mol %). Catalyst E: Na_2PdCl_4 (0.5 mol %), PIntB (1 mol %), CuI (1 mol %). Catalyst F: $Pd(OAc)_2$ (0.5 mol %), PIntB (1 mol %), CuI (1 mol %). [b]Determined by HPLC. [c]Added at 70 °C. [d]**3** was isolated in 86% overall yield from **1**.

reported an efficient catalyst system for the Sonogashira reaction using Na_2PdCl_4, 2-(di-*tert*-butylphosphino)-*N*-phenylindole (cataCXium PIntB), and CuI in TMEDA.[6,7] Applying these conditions to our system brought the conversion up to a promising 67% (entry 5). Alkyne homocoupling was a suspected competing reaction, and the amount of TMSA was increased to 2 equiv, resulting in a moderate increase in conversion (entry 6). It was found for the original procedure (Scheme 1) that addition of TMSA at 70 °C was crucial to obtain good yield. Addition of TMSA at 70 °C with Beller's procedure increased the conversion to 98% (entry 7). Full conversion was realized by using 2 equiv of TMSA, and the pure central intermediate **3** was isolated in 86% yield over two steps (entry 8). The palladium source is critical in this reaction, as exchange of Na_2PdCl_4 for $Pd(OAc)_2$ resulted in a dramatic drop in conversion (entry 9).

The second problem in the original synthesis of the alkyne FFA1 agonists was that the central intermediate **3** turned out to be a surprisingly unwilling Sonogashira substrate, even though the 3-propionic ester side chain is believed to be only moderately electron donating. Sonogashira reactions are usually performed with excess alkyne because of the competing Glaser homocoupling. However, since remaining **3** frequently coelutes with the product, we chose to rather perform the reactions with a small excess of the aryl halide to ensure complete conversion of the alkyne, which made suppression of alkyne homocoupling essential. Although most aryl iodides produced the desired products in satisfactory

TABLE 2. Coupling of 3 with Aryl Bromides



entry	ArBr	method[a]	yield (%)[b]
1	 **4a**	I	0
2		II	88
3	 **4b**	I	0
4		II	84
5	 **4c**	I	14
6		II	86
7	 **4d**	I	24
8		II	83
9	 **4e**	II	71
10	 **4f**	II	69
11	 **4g**	II	71

[a]Method I: ArBr (0.55 mmol), **3** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (1 mol %), CuI (2 mol %), Et_3N (2.4 equiv), DMF (1 mL), 50 °C. Method II: ArBr (0.55 mmol), **3** (0.5 mmol), Na_2PdCl_4 (1 mol %), PIntB (2 mol %), CuI (2 mol %), TMEDA (1 mL), 80 °C. [b]Isolated yields.

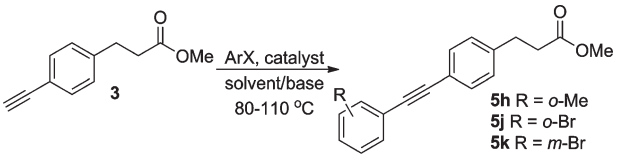
yields, the aryl bromides performed poorly, and in several cases failed completely (e.g., Table 2, entries 1 and 3). The optimized conditions from the TMSA coupling were investigated with the aryl bromides which had failed or performed poorly with the original catalyst system. The new conditions proved efficient for aryl bromide with both electron donating and electron withdrawing substituents (Table 2), including yields above 80% in cases where the original protocol had failed completely (entries 1−4).

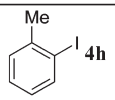
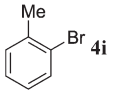
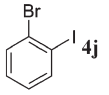
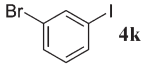
The potent FFA1 agonist TUG-424 is synthesized via intermediate **5h**, which was obtained in only 31% yield from coupling of *o*-iodotoluene (**4h**) with **3** by the original Sonogashira protocol (Table 3, entry 1).[4] Applying the optimized coupling conditions with this reaction surprisingly led to further decreased yield (entry 2). Substantial amounts of alkyne dimerization were observed with both the new and the original conditions. Since alkyne dimerization is known to be promoted by Cu(I), a copper-free protocol was investigated.[8] This resulted in a yield only comparable to the original procedure (entry 3). Other aryl iodides also produced unsatisfactory results. This was surprising, since aryl iodides normally are significantly more reactive substrates than aryl bromides in the Sonogashira reaction. Noticing that the original report by Beller and co-workers only included aryl bromides, we replaced **4h** by the bromo-analogue **4i**, which raised the yield to 67% (entry 4). To investigate the idea that the coupling conditions might prefer aryl bromides to aryl

(6) Torborg, C.; Zapf, A.; Beller, M. *ChemSusChem* **2008**, *1*, 91–96.
(7) Other studies involving PIntB (cataCXium P): (a) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2983–2990. (b) Choi, Y. L.; Yu, C.-M.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2009**, *74*, 3948–3951. (c) Schulz, T.; Torborg, C.; Enthaler, S.; Schäffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Börner, A.; Beller, M. *Chem.—Eur. J.* **2009**, *15*, 4528–4533. (d) Harkal, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237–3240. (e) Ebran, J.-P.; Hansen, A. L.; Gogsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931–6942.

(8) Komáromi, A.; Novák, Z. *Chem. Commun.* **2008**, *40*, 4968–4970.

TABLE 3. Reactivity Differences of Aryl Iodides and Bromides[a]



entry	ArX	cat[b]	solvent/base (equiv)	yield (%)
1	 **4h**	G	DMF/Et_3N (3)	31[c]
2	**4h**	E	TMEDA	22
3	**4h**	H	DMSO/K_2CO_3 (1.5)	28[d]
4	 **4i**	E	TMEDA	67
5	 **4j**	E	TMEDA	40
6	 **4k**	E	TMEDA	15
7	**4h**	E	DMF/TMEDA[e]	40
8	**4h**	I	DMF/TMEDA[e]	<10

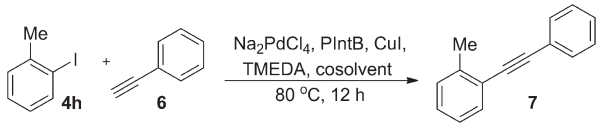
[a]Reaction conditions: **4h**−**k** (0.55 mmol), **3** (0.5 mmol), 80 °C, volume (1 mL). [b]Catalyst G: $Pd(PPh_3)_4$ (1 mol %), CuI (2 mol %). Catalyst E: Na_2PdCl_4 (1 mol %), PIntB (2 mol %), CuI (2 mol %). Catalyst H: Pd/C (1 mol %), SPhos (1 mol %). Catalyst I: Na_2PdCl_4 (1 mol %), PIntB (2 mol %). [c]Performed at 90 °C. [d]Performed at 110 °C. [e]10 vol % of DMF.

iodides, the substrates **4j** and **4k** were employed, resulting in isolation of the bromo-substituted products in 40% and 15% yield, respectively, accompanied by the dicoupled products (entries 5−6). Thus, aryl iodides react preferentially, but yields were invariably poor. It was observed that a solid precipitate was formed in all reactions with aryl bromides, while a sticky syrup was formed in the reactions with aryl iodides. We hypothesized that the poor yields with the aryl iodides were a consequence of the catalyst complex or essential components being trapped in the syrup, and we initiated a search for conditions that would produce a homogeneous reaction mixture. Addition of 10% DMF to the reaction increased the yield from 22% to 40% (entry 7), but only reduced the alkyne dimerization slightly. Removal of CuI to suppress competing alkyne homocoupling was fatal for the reaction (entry 8).

Phenylacetylene (**6**) was chosen as a less precious substrate for rapidly screening different conditions that would dissolve the syrup without having detrimental effects on the reaction. This usually excellent Sonogashira substrate only gave 84% conversion in coupling with **4h** in pure TMEDA. Adding 50% DMSO or ethyl acetate as cosolvents reduced the conversion considerably (Table 4, entries 2 and 3), while 50% PEG-400 and DMF led to a slight decrease in conversion compared to pure TMEDA (entries 4 and 5). On the other hand, addition of water (entry 6) resulted in a homogeneous reaction mixture and almost full conversion to the desired coupling product.

Addition of 50% water as cosolvent with TMEDA more than doubled the yield of **5h** (Table 5, entry 1). Reducing the amount of water to 20% brought the yield up to 76%,

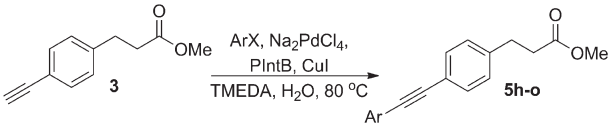
TABLE 4. Screening of Cosolvents[a]

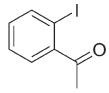
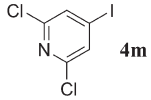
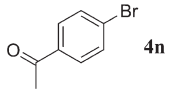
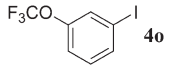


entry	cosolvent	**7** (%)[c]	dimer (%)[c]
1	none	84	11
2	DMSO	46	54
3	EtOAc	46	42
4	PEG-400	77[b]	19
5	DMF	78[b]	12
6	H_2O	98	2

[a]Reaction conditions: **4h** (0.55 mmol), **6** (0.5 mmol), Na_2PdCl_4 (1 mol %), PIntB (2 mol %), CuI (2 mol %), TMEDA/cosolvent (1 mL, 1:1, v/v), 80 °C. [b]Reaction not complete. [c]Determined by HPLC.

TABLE 5. Optimization of Water Content[a]



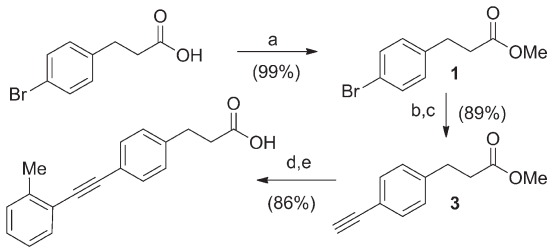
entry	ArX	water (vol%)	yield (%)
1	**4h**	50	53
2	**4h**	20	76
3	**4h**	10	79
4	**4k**	10	35[b]
5	 **4l**	0	26
6		10	85
7	 **4m**	0	55
8		10	89
9	 **4n**	10	80
10	 **4o**	10	87

[a]Reaction conditions: ArX (0.55 mmol), **3** (0.5 mmol), Na_2PdCl_4 (1 mol %), PIntB (2 mol %), CuI (2 mol %), solvent/base (1 mL), 80 °C. [b]The double-coupled product was isolated in 48% yield on the basis of **3** together with the 3-bromo-substituted **5k**.

whereas 10% water increased the yield further to 79% (entry 3). The corresponding bromide **4i** gave 86% yield with the same conditions (Scheme 2). Coupling with **4k** (entry 4) resulted in isolation of the iodo-coupled and the double-coupled products in equal amounts, indicating that a preference for coupling of iodides over bromides still exists. The beneficial effect of 10% water was found to be general for both aryl iodides and bromides (entries 5−10). Likewise, addition of 10% water to the coupling of **1** to TMSA further increased the yield to 89% over two steps, and the reaction time decreased from 2 h to 5 min (Scheme 2).

In conclusion, we have identified an efficient general protocol for Pd/Cu-catalyzed coupling of aryl bromides and iodides to alkynes, using the recently reported ligand cataXCium PIntB[6] and TMEDA/water as reaction medium.

SCHEME 2. Optimized Synthesis of TUG-424[a]



[a]Reagents and conditions: (a) MeOH, HCl (cat.), rt, 2 h (99%); (b) TMSA, Na_2PdCl_4 (1 mol %), PIntB (2 mol %), CuI (2 mol %), TMEDA, H_2O, 80 °C, 5 min; (c) K_2CO_3, MeOH, rt, 2.5 h (89% over 2 steps); (d) 2-bromotoluene (**4i**), Na_2PdCl_4 (1 mol %), PIntB (2 mol %), CuI (2 mol %), TMEDA, H_2O, 80 °C, 30 min (86%); (e) LiOH, 1,4-dioxane, H_2O, rt (100%).

The reactions proceed cleanly, usually with no detectable alkyne homocoupling, and are complete in less than 30 min. It was observed in previous reactions that longer reaction times often resulted in more of the homocoupled product, and it appears likely that suppression of homocoupling is at least partly a consequence of the high Sonogashira cross-coupling rate obtained with the new conditions. Whereas the original protocol produces discolored products, even if pure by NMR and HPLC, the new protocol generally produces white or yellow products. Implementation of the new Sonogashira protocol resulted in a vastly improved synthesis of the FFA1 receptor ligands by enabling efficient synthesis of the central intermediate **3** from 3-(4-bromophenyl)propionic acid, and by providing a rapid, reliable, practical, and efficient method for coupling of this intermediate with diverse aryl bromides and iodides.

Experimental Section

General Procedure for Sonogashira Coupling. A Schlenk flask charged with Na_2PdCl_4 (1 mol %), 2-(di-*tert*-butylphosphino)-*N*-phenylindole (PIntB, 2 mol %), CuI (2 mol %), alkyne (1 equiv), aryl halide (1.1 equiv), H_2O (0.2 mL/mmol), and TMEDA (1.8 mL/mmol) was evacuated and backfilled with argon three times, then heated to 80 °C. After consumption of the starting material (< 30 min), the reaction mixture was cooled to rt, then water was added and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated, and the residue was purified by flash chromatography.

Methyl 3-(4-((2,6-Dichloropyridin-4-yl)ethynyl)phenyl)-propanoate (5m). 5m was prepared from **3** (190 mg, 1.01 mmol) and **4m** (302 mg, 1.10 mmol) according to the general procedure to give 301 mg (89%) of a white solid after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:7): R_f 0.11 (EtOAc:petroleum ether, 1:7); ^{1}H NMR ($CDCl_3$) δ 7.48−7.45 (m, 2H), 7.34 (s, 1H), 7.24−7.22 (m, 2H), 3.68 (s, 3H), 2.99 (t, J = 7.7 Hz, 2H), 2.65 (t, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 172.9, 150.7, 142.9, 136.6, 132.3, 128.7, 124.4, 119.1, 96.9, 81.4, 51.7, 35.2, 30.9; ESI-HRMS calcd for $C_{17}H_{13}Cl_2NO_2$ ($M + Na^+$) 356.0216, found 356.0222.

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Supporting Information Available: Additional experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.