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Synthesis of the human aldose reductase inhibitor rubrolide L

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ABSTRACT

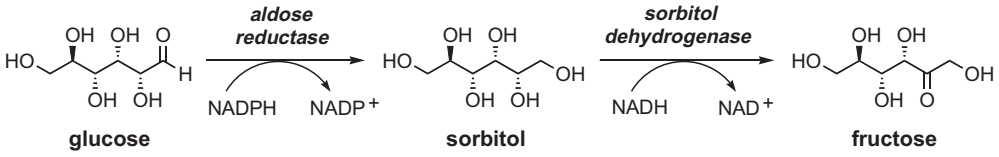
The first synthesis of rubrolide L, a marine ascidian butenolide and a potent inhibitor of human aldose reductase, has been achieved by two tactically distinct pathways in 4–5 steps and 37–42% overall yield from commercially available 3-chlorotetronic acid.

All forms of diabetes are characterized by high levels of blood glucose that can be caused by defects in insulin production, insulin action, or both. The resulting hyperglycemia overwhelms the normal glycolytic pathway and an increased flux of glucose through the polyol pathway occurs (Scheme 1).[1] Aldose reductase (ALR2), the first and rate-determining enzyme of the polyol pathway, catalyzes the reduction of glucose to sorbitol which is then converted to fructose by sorbitol dehydrogenase (SDH).

Mounting evidence suggests that the polyol pathway plays a pivotal role in the long-term development of diabetic complications such as neuropathy, renal failure, blindness, and cardiovascular disease.[1] Thus, aldose reductase inhibitors (ARIs) offer the possibility of preventing or arresting these complications even in the presence of elevated blood glucose.[2] Furthermore, recent in vitro and animal studies suggest that ARIs could be clinically beneficial for preventing inflammatory diseases including asthma, sepsis, and colon cancer.[3]

So far, all ARIs taken to clinical trials on diabetic patients are either spiroimides or carboxylic acids, as represented by sorbinil, fidarestat, and epalrestat (Fig. 1).[4] Although epalrestat was launched in Japan in 1992, where it is still used for the treatment of diabetic neuropathy,[5] none of these ARIs were proven safe or effective enough to meet FDA's standards.[4] The low tolerability of some of these drugs (e.g., sorbinil)[3a] may arise from poor selectivity for ALR2 over aldehyde reductase (ALR1), a closely related enzyme that plays a role in the detoxification of aldehydes.[2b,4a] Also, many spiroimides cause skin reactions or liver toxicity limiting the doses usable in humans to subtherapeutic.[6] On the other hand, the low pK_a values of the carboxylic acids (ca. 3–4) lead to poor tissue penetration and pharmacokinetic profiles.[3a,6] Hence, attention is currently focused on new ARIs that are neither spiroimides nor carboxylic acids.[6,7]

One such compound is rubrolide L (**1**, Fig. 1), first described by Salvá in 2000 as an antitumor metabolite of the red tunicate *Synoicum blochmanni*, collected near the Spanish island of Tarifa.[8] In 2006, it was discovered that **1** inhibits human ALR2 at the submicromolar level with a 5-fold greater potency than sorbinil.[9] Seven congeners of **1**, including rubrolide C and M (**2**–**3**), were also tested



Scheme 1. Polyol pathway.

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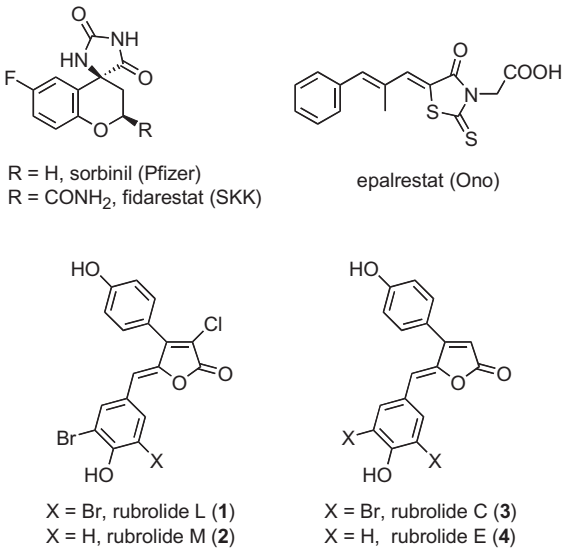
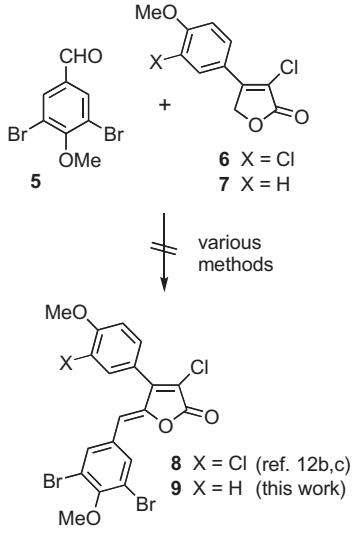


Figure 1. Structures of some synthetic ARIs and rubrolides.

but none were nearly as potent.[9] These findings were recently corroborated by molecular docking studies indicating that the binding mode of **1** to hALR2 is different from that of other rubrolides.[10]

Besides ALR2 inhibition and tumor cell toxicity, members of the rubrolide family have been known to possess other potentially useful biological properties, including antibacterial and anti-inflammatory activities.[11] Not surprisingly, their synthesis has captured the attention of several groups, including our own.[12–15] Three of the sixteen known rubrolides have been synthesized (C, E, and M)[12] along with the putative structure of rubrolide N (shown to be incorrect)[13] and various analogs.[14,15]

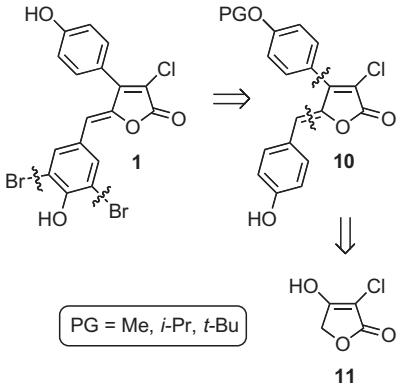
However, no synthesis of rubrolide L has been reported to date. Nor is there irrefutable proof for the proposed structure **1**.[16,17] Previous attempts by Bellina et al. to synthesize a close relative of **1** have been unsuccessful due to the difficulties in attaching the benzylidene unit onto the butenolide nucleus through aldol reaction of **5** with **6** (Scheme 2).[12b,c] In sharp contrast, the aldol condensation of **5** with butenolides lacking an α-halo substituent works well,[12a] as does the condensation of the parent 4-methoxybenzaldehyde with a host of substituted butenolides,[12a,13,18] including **6** and **7**.[12b,c]



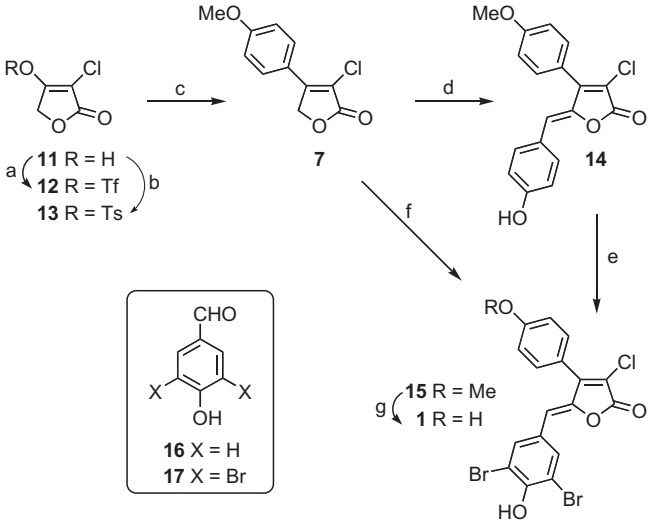
Scheme 2. Attempted synthesis of butenolides **8** and **9**.

Given the dismal prospects of arriving at **1** from **5** and **7** (Scheme 2, also vide infra), we opted for a customized strategy that hinged upon installation of the bromo-substituents to a fully assembled rubrolide scaffold **10** (Scheme 3). The desired regioselectivity in the bromination step would arise from the more powerful directing effect of the free phenol group over that of its protected counterpart. Moreover, a bulky protecting group (PG), such as *i*-propyl or *t*-butyl, could further improve the selectivity, if necessary.[19] Practical access to **10** was envisioned from commercial 3-chlorotetronic acid (**11**) by the sequential attachment of the β- and γ-substituents.[12a,20]

The synthesis commenced with the conversion of **11** to triflate **12**, obtained in 73% yield after purification by Kugelrohr distillation[21] (Scheme 4). Since triflates can undergo hydrolysis under harsher Suzuki conditions,[22,23] we also prepared the more robust, crystalline tosylate **13** (91%).[24] Both of these reagents were subjected to Suzuki–Miyaura coupling with 4-methoxyphenylboronic acid (**18**) under a variety of conditions, including those shown in Table 1. With either sulfonate, the best results were obtained using Fu's $Pd(OAc)_2/P(Cy)_3$ catalyst system,[25] albeit under different base/

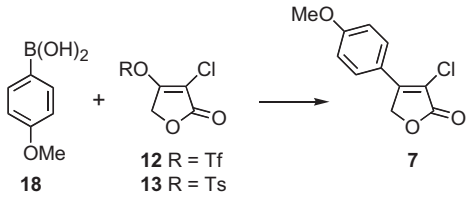


Scheme 3. Retrosynthetic analysis of rubrolide L (**1**).



Scheme 4. Reagents and conditions: (a) Tf_2O/Et_3N (1.2 equiv each), CH_2Cl_2, 0 °C→rt, 2 h (73%); (b) $TsCl/Et_3N$ (1.2 equiv each), CH_2Cl_2, 0 °C→rt, 2 h (91%); (c) see entries 5 and 8 in Table 1 (87% from **12**, 55% from **13**); (d) TBSOTf (2.2 equiv), **16** (1.2 equiv), *i*-Pr_2NEt (3 equiv), CH_2Cl_2, rt, 1 h; DBU (2 equiv), rt, 3 h; aq HCl (3 N)/THF (1:5), rt, 12 h (72%); (e) Br_2 (2.1 equiv), KBr (0.2 equiv), dioxane/H_2O (8:1), 5 °C→rt, 1 h (96%); (f) as in (d) but using **17** instead of **16** (61%); (g) BBr_3 (3 equiv), CH_2Cl_2, −78 °C to rt, 16 h, (95%).

Table 1
Condition screen for the Suzuki–Miyaura coupling of boronic acid **18** with sulfonates **12** and **13**[a]



Entry	Sulfonate	Palladium catalyst	Ligand	Base/solvent	Reaction temp. (°C)/time (h)	Yield of **7**[b] (%)
1	**12**	$PdCl_2(PPh_3)_2$	—	Na_2CO_3/THF-H_2O	60/24	18
2	**12**	$PdCl_2(PPh_3)_2$	—	KF/THF-H_2O	60/12	9
3[c]	**12**	$Pd(PPh_3)_4$	—	Na_2CO_3/PhMe-H_2O[b]	80/12	54
4[c]	**12**	$Pd(PPh_3)_4$	$P(Cy)_3$	Na_2CO_3/PhMe-H_2O[b]	24/12	59
5[c]	**12**	$Pd(OAc)_2$	$P(Cy)_3$	Na_2CO_3/PhMe-H_2O[b]	24/3	87
6[c]	**13**	$Pd(OAc)_2$	$P(Cy)_3$	Na_2CO_3/PhMe-H_2O[b]	60/2	<5
7[d]	**13**	$Pd(OAc)_2$	$P(Cy)_3$	Na_2CO_3/MeOH	60/2→24/10	25
8[d]	**13**	$Pd(OAc)_2$	$P(Cy)_3$	$NaHCO_3$/MeOH	60/2→24/10	55
9	**13**	$PdCl_2$(dppf)	—	Cs_2CO_3/THF-H_2O	60/24	18

[a] Boronic acid (1.2 equiv); Pd-cat. (5 mol %); $P(Cy)_3$ (5 mol %); base (3 equiv).
[b] Yields are based on the sulfonate; they refer to isolated **7** after flash chromatography (except for entry 6).
[c] $BnEt_3N^+Cl^-$ (5 mol %) was used in these experiments (entries 3–6).
[d] A larger amount of $P(Cy)_3$ (10 mol %) was used (entries 7–8).

solvent/temperature combinations (entries 5 and 8). However, the triflate proved substantially more reactive affording the highest yield of 7[26] (87% vs 55%) under milder reaction conditions.

Appendage of the benzylidene unit proceeded without incident by application of our one-pot vinylogous aldol condensation protocol, originally developed during the synthesis of rubrolides C and E.[12a] Thus, aldol reaction of **7** with 4-hydroxybenzaldehyde (**16**) in the presence of TBSOTf and *i*-Pr_2NEt, followed by in situ β-elimination with DBU and eventual treatment of the crude product with aq HCl provided the corresponding (*Z*)-benzylidenebutenolide **14**[27] as a single stereoisomer in 72% yield (Scheme 4). Next, bromination of **14** with KBr_3[28] generated in situ from Br_2 (2.1 equiv) and a catalytic amount of KBr delivered lactone **15**[29] as the only detectable product in excellent yield (96%).

In an ancillary study, a more convergent pathway to the brominated rubrolide scaffold was also explored. As we had anticipated on the basis of Bellina's work,[12c] all attempts to accomplish aldol condensation of **7** with 3,5-dibromo-4-methoxybenzaldehyde (**5**) by using several variants of our method,[12a,18a,b] and other procedures (e.g., heating with Na_2CO_3 in MeOH),[30] failed to give **9** (Scheme 2). We were therefore pleased to discover that by simply replacing **5** with unprotected 3,5-dibromo-4-hydroxybenzaldehyde (**17**), from which **5** is prepared,[12a] the desired product **15**[29] was obtained in a decent yield of 61% (Scheme 4). It is worthy of note that despite numerous applications of our method in recent years, there have been no examples involving unprotected hydroxybenzaldehydes.[13,15b,c,18]

Finally, demethylation of **15** with boron tribromide afforded rubrolide L (**1**) as an amorphous yellow-orange solid (95%, Scheme 4) whose ^1H and ^{13}C NMR properties[31] were in excellent agreement with those reported in the literature.[8]

To conclude, the first synthesis of rubrolide L has been achieved from commercially available 3-chlorotetronic acid by two tactically distinct pathways in 4 or 5 steps and overall yields of 37% and 42%, respectively. The synthesis confirms the proposed structure (**1**) while making the natural product accessible for further biological studies, such as ALR2/ALR1 selectivity, and efficacy in diabetic mice. In conjunction with the existing SAR picture on a series of rubrolides[9] and supporting computational studies,[10] the above chemistry provides the groundwork for production of new, custom-designed analogs of improved therapeutic performance.

Acknowledgments

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References and notes

1. (a) Oates, P. J. *Curr. Drug Targets* **2008**, *9*, 14–36; (b) Ramasamy, R.; Goldberg, I. J. *Circ. Res.* **2010**, *106*, 1449–1458.
2. (a) de la Fuente, J. Á.; Manzanaro, S. *Nat. Prod. Rep.* **2003**, *20*, 243–251; (b) Van Zandt, M. C.; Doan, B.; Sawicki, D. R.; Sredy, J.; Podjarny, A. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2006–2008.
3. (a) Alexiou, P.; Pegklidou, K.; Chatzopoulou, M.; Nicolaou, I.; Demopoulos, V. A. *Curr. Med. Chem.* **2009**, *16*, 734–752; (b) Ramana, K. V.; Srivastava, S. K. *Int. J. Biochem. Cell Biol.* **2010**, *42*, 17–20.
4. (a) Oates, P. J. *Curr. Opin. Invest. Drugs* **2010**, *11*, 402–416; (b) Schemmel, K. E.; Padiyara, R. S.; D'Souza, J. J. *J. Diabetes Complications*, in Press.
5. (a) Ramirez, M. A.; Borja, N. L. *Pharmacotherapy* **2008**, *28*, 646–655; (b) Kawai, T.; Takei, I.; Tokui, M.; Funae, O.; Miyamoto, K.; Tabata, M.; Hirata, T.; Saruta, T.; Shimada, A.; Itoh, H. *J. Diabetes Complications*, in Press.
6. (a) Mylari, B. L.; Armento, S. J.; Beebe, D. A.; Conn, E. L.; Coutcher, J. B.; Dina, M. S.; O'Gorman, M. T.; Linhares, M. C.; Martin, W. H.; Oates, P. J.; Tess, D. A.; Withbroe, G. J.; Zembrowski, W. J. *J. Med. Chem.* **2005**, *48*, 6326–6339; (b) Sun, W.; Oates, P. J.; Coutcher, J. B.; Gerhardlinger, C.; Lorenzi, M. *Diabetes* **2006**, *55*, 2757–2762.
7. (a) La Motta, C.; Sartini, S.; Muganaini, L.; Simorini, F.; Taliani, S.; Salerno, S.; Marini, A. M.; Da Settimo, F.; Lavecchia, A.; Novellino, E.; Cantore, M.; Failli, P.; Ciuffi, M. *J. Med. Chem.* **2007**, *50*, 4917–4927; (b) Alexiou, P.; Nicolaou, I.; Stefek, M.; Kristl, A.; Demopoulos, V. J. *Bioorg. Med. Chem.* **2008**, *16*, 3926–3932; (c) Saito, R.; Tokita, M.; Uda, K.; Ishikawa, C.; Satoh, M. *Tetrahedron* **2009**, *65*, 3019–3026; (d) Cosconati, S.; Marinelli, L.; La Motta, C.; Sartini, S.; Da Settimo, F.; Olson, A. J.; Novellino, E. *J. Med. Chem.* **2009**, *52*, 5578–5581; (e) Pegklidou, K.; Koukoulitsa, C.; Nicolaou, I.; Demopoulos, V. J. *Bioorg. Med. Chem.* **2010**, *18*, 2107–2114.
8. Ortega, M. J.; Zubía, E.; Ocaña, J. M.; Naranjo, S.; Salvá, J. *Tetrahedron* **2000**, *56*, 3963–3967.
9. Manzanaro, S.; Salvá, J.; de la Fuente, J. Á. *J. Nat. Prod.* **2006**, *69*, 1485–1487.
10. Wang, Z.; Ling, B.; Zhang, R.; Suo, Y.; Liu, Y.; Yu, Z.; Liu, C. *J. Mol. Graphics Model.* **2009**, *28*, 162–169.
11. (a) Miao, S.; Andersen, R. J. *J. Org. Chem.* **1991**, *56*, 6275–6280; (b) Pearce, A. N.; Chia, E. W.; Berridge, M. V.; Mass, E. W.; Page, M. J.; Webb, V. L.; Harper, J. L.; Copp, B. R. *J. Nat. Prod.* **2007**, *70*, 111–113.
12. Synthesis of natural rubrolides: (a) Boukouvalas, J.; Lachance, N.; Ouellet, M.; Trudeau, M. *Tetrahedron Lett.* **1998**, *39*, 7665–7668; (b) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2002**, *43*, 2023–2027; (c) Bellina, F.; Anselmi, C.; Martina, F.; Rossi, R. *Eur. J. Org. Chem.* **2003**, 2290–2302; (d) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2284–2286; (e) Chavan, S. P.; Pathak, A. B.; Pandey, A.; Kalkote, U. R. *Synth. Commun.* **2007**, *37*, 4253–4263; (f) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sferrazza, A. *Synlett* **2009**, 1277–1280.
13. Bellina, F.; Anselmi, C.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997–10007.

14. Diacetates of rubrolides A, C, D and E: Kotora, M.; Negishi, E. *Synthesis* **1997**, 121–128.
15. Rubrolide analogs and relatives: (a) Prim, D.; Fuss, A.; Kirsch, G.; Silva, A. M. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1175–1180; (b) Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 670–673; (c) Boukouvalas, J.; Pouliot, M. *Synlett* **2005**, 343–345; (d) Sofikiti, N.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. *Tetrahedron* **2006**, *62*, 5308–5317; (e) Kumar, N.; Iskander, G. PCT Int. Appl., WO 2008040097, 2008.; (f) Marchal, E.; Uriac, P.; Brunel, Y.; Poigny, S.; PCT Int. Appl., WO 2010034827, 2010.
16. Recent reviews on misassigned NP structures: (a) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044; (b) Maier, M. E. *Nat. Prod. Rep.* **2009**, *26*, 1105–1124.
17. For our own contributions to the correction of NP structures by total synthesis, see: (a) Boukouvalas, J.; Pouliot, R.; Fréchette, Y. *Tetrahedron Lett.* **1995**, *36*, 4167–4170; (b) Boukouvalas, J.; Wang, J.-X.; Marion, O.; Ndzi, B. *J. Org. Chem.* **2006**, *71*, 6670–6673; (c) Boukouvalas, J.; Pouliot, M.; Robichaud, J.; MacNeil, S.; Snieckus, V. *Org. Lett.* **2006**, *8*, 3597–3599; (d) Boukouvalas, J.; Wang, J.-X.; Marion, O. *Tetrahedron Lett.* **2007**, *48*, 7747–7750; (e) Boukouvalas, J.; Wang, J.-X. *Org. Lett.* **2008**, *10*, 3397–3399.
18. Recent examples: (a) Boukouvalas, J.; Beltrán, P. P.; Lachance, N.; Côté, S.; Maltais, F.; Pouliot, M. *Synlett* **2007**, 219–222; (b) Teixeira, R. R.; Barbosa, L. C. A.; Forlani, G.; Piló-Veloso, D.; Carneiro, J. W. M. *J. Agric. Food Chem.* **2008**, *56*, 2321–2329; (c) Teixeira, R. R.; Pinheiro, P.; Barbosa, L. C. A.; Carneiro, J. W. M.; Forlani, G. *Pest Manag. Sci.* **2010**, *66*, 196–202.
19. McDonald, M. G.; Rettie, A. E. *Chem. Res. Toxicol.* **2007**, 1833–1842.
20. For related work from this group, see: (a) Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897–7900; (b) Boukouvalas, J.; Maltais, F. *Tetrahedron Lett.* **1994**, *35*, 5769–5770; (c) Boukouvalas, J.; Maltais, F. *Tetrahedron Lett.* **1995**, *36*, 7175–7176; (d) Boukouvalas, J.; Lachance, N. *Synlett* **1998**, 31–32; (e) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228–229; (f) Boukouvalas, J.; Robichaud, J.; Maltais, F. *Synlett* **2006**, 2480–2482; (g) Boukouvalas, J.; Côté, S.; Ndzi, B. *Tetrahedron Lett.* **2007**, *48*, 105–107; (h) Boukouvalas, J.; Loach, R. P. *J. Org. Chem.* **2008**, *73*, 8109–8112.
21. *Data for* **12**: colorless oil, bp (Kugelrohr internal temp) 72 °C/0.1 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 159.3, 118.5 (q, J_{CF} = 321 Hz), 112.0, 67.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.87; HRMS: calcd for $C_5H_2ClF_3O_5S$ (m/z): 265.9264, found: 265.9274.
22. Recent review on Suzuki–Miyaura cross coupling: Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013–2030.
23. For some recent examples on the Suzuki arylation of related sulfonates, see: (a) Yoon-Miller, S. J. P.; Opalka, S. M.; Pelkey, E. T. *Tetrahedron Lett.* **2007**, *48*, 827–830; (b) Dorward, K. M.; Guthrie, N. J.; Pelkey, E. T. *Synthesis* **2007**, 2317–2322; (c) Bellina, F.; Marchetti, C.; Rossi, R. *Eur. J. Org. Chem.* **2009**, 4685–4690.
24. *Data for* **13**: white powder (mp 88–89 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 5.06 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 160.7, 147.6, 131.0, 130.6, 128.4, 108.0, 67.3, 21.8; HRMS: calcd for $C_{11}H_9ClO_5S$ (m/z): 287.9859, found: 287.9867.
25. (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; (b) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555–1564.
26. *Data for* **7**: white powder (mp 173–175 °C, lit.[12c] 174–175 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 5.19 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 162.5, 151.6, 129.3, 121.5, 115.0, 114.9, 70.2, 55.8; Anal. Calcd for $C_{11}H_9ClO_3$: C, 58.81; H, 4.04. Found: C, 58.52; H, 4.24.
27. *Data for* **14**: amorphous yellow solid (mp 225 °C, dec); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.89 (br s, 1H) 7.70 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.23 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.9, 162.3, 159.8, 151.0, 145.5, 133.7, 131.8, 125.7, 121.2, 116.8, 116.7, 115.4, 115.3, 55.9; HRMS: calcd for $C_{18}H_{13}ClO_4$ (m/z): 328.0502, found: 328.0507.
28. Kumar, L.; Sharma, V.; Mahajan, T.; Agarwal, D. D. *Org. Process Res. Dev.* **2010**, *14*, 174–179.
29. *Data for* **15**: amorphous light-orange solid (mp 228 °C, dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 2H) 7.48 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.13 (br s, 1H), 5.97 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 161.7, 150.4, 149.6, 146.7, 134.2, 130.9, 128.0, 120.0, 118.3, 114.8, 111.4, 110.6, 55.7; HRMS: calcd for $C_{18}H_{11}Br_2ClO_4$ (m/z): 483.8713, found: 483.8702.
30. Xu, H.-W.; Wang, J.-F.; Liu, G.-Z.; Hong, G.-F.; Liu, H.-M. *Org. Biomol. Chem.* **2007**, *5*, 1247–1250.
31. *Data for* **1**: amorphous reddish-orange solid (mp 238 °C, dec); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.05 (s, 2H) 7.52 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 6.28 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.9, 159.9, 151.7, 150.1, 146.7, 134.6, 131.3, 128.1, 119.0, 117.1, 116.1, 111.1 (×2); Anal. Calcd for $C_{17}H_9Br_2ClO_4$: C, 43.21; H, 1.92. Found: C, 43.49; H, 2.30.