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Total Synthesis of Waltherione F, a Nonrutaceous 3-Methoxy-4-quinolone, Isolated from *Waltheria indica* L. F.

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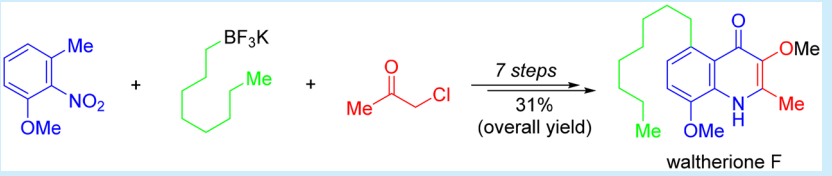
Supporting Information



ABSTRACT: Waltherione F was totally synthesized in seven steps and 31% overall yield from 2-nitro-3-methylanisole without the use of protecting groups. Key steps in the sequence were a Suzuki−Miyaura coupling to attach the *n*-octyl chain and a microwave-promoted cyclization of an acetonyl anthranilate to give the heterocyclic core whose 3-OH was *O*-methylated.

Natural products carrying the 3-methoxy-4-quinolone motif were initially found in Rutaceae; however, nonrutaceous related heterocycles have also been found in other plant families, such as the Malvaceae. The first example of such nonrutaceous alkaloids was melochinone, isolated in 1975 from *Melochia tomentosa* L.[1]

In 2005, Farias Morel et al. obtained the waltheriones A (**1**) and B (**2**) from *Waltheria douradinha* S.-Hill (Malvaceae). Compound **1** (Figure 1), also found in *M. odorata* L. F. and *M. chamaedris* St.-Hill, displays a broad spectrum of antifungal activity.[2] In 2014, the related waltheriones C (**3**) and D (**4**) were identified in *M. odorata*. The heterocycle **3**, also found in *M. umbellata*,[3] is a cancer chemopreventive agent that inhibits the NF-κB transcription factor (IC_{50} ∼ 50 μM) and is cytoprotective against HIV infection and also active toward *Trypanosoma cruzi*.[4]

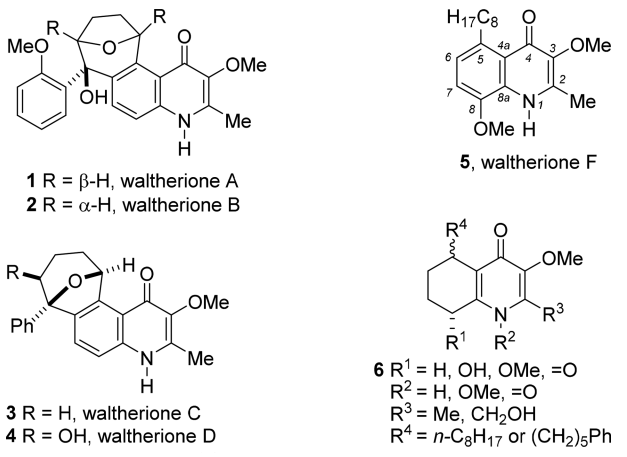


Figure 1. Waltherione F (**5**) and related natural products.

Further, the roots of *Waltheria indica* L. afforded the waltheriones E−L,[5] which except for waltherione F (**5**) share the structural motif **6**, differing in its decoration; they have anti-*T. cruzi* activity. Additional heterocycles exhibiting this framework, such as the waltheriones M−Q[6] and others, are included in this small but fast-growing family.[7] Many of them also exhibit interesting bioactivity.[8]

Taking into account our continuous interest in the synthesis of natural products,[9] considering the originality of the structures of this family members, and the scarcity of synthetic activity in the field,[10] we decided to undertake the total synthesis of waltherione F (**5**).

In the retrosynthetic analysis of **5** (Scheme 1), the disconnection of the C2−C3 moiety revealed the acetonyl anthranilate **7** as a suitable precursor, which should give the quinolone core through a Friedländer-type cyclization and rearrangement.[11] Disconnection of the *n*-octyl moiety and the ester group in **7** unveiled the *o*-nitrobenzoic acid derivative **8** as a suitable intermediate, fitted with a proper activating group (AG) to anchor the side chain.

Final retrosynthetic considerations led to 2-methyl-3-nitroanisole (**9**) as the most suitable starting material, which should be oxidizable to the related acid and also properly functionalized *ortho* to the carboxyl group.[12]

Our synthetic efforts began with oxidation of the anisole **9** with $KMnO_4$ in H_2O (Scheme 2); this gave the benzoic acid **10** in 67% yield.[13] Taking into account that the proposed strategy heavily relies on a final selective *O*-methylation of a tridentate substrate, and that this is a challenging task,[14a] a simple model was first built, implementing an approach analogous to that of Hradil et al.[14b]

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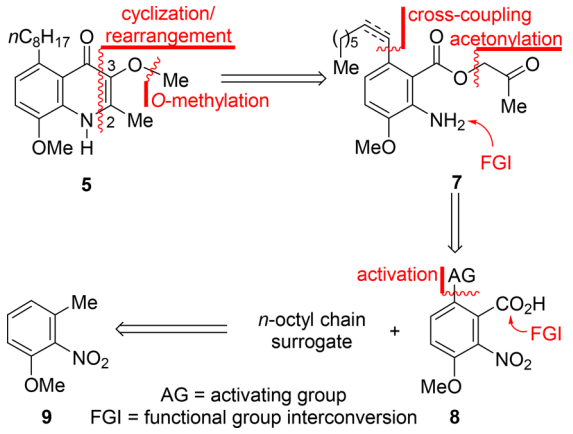
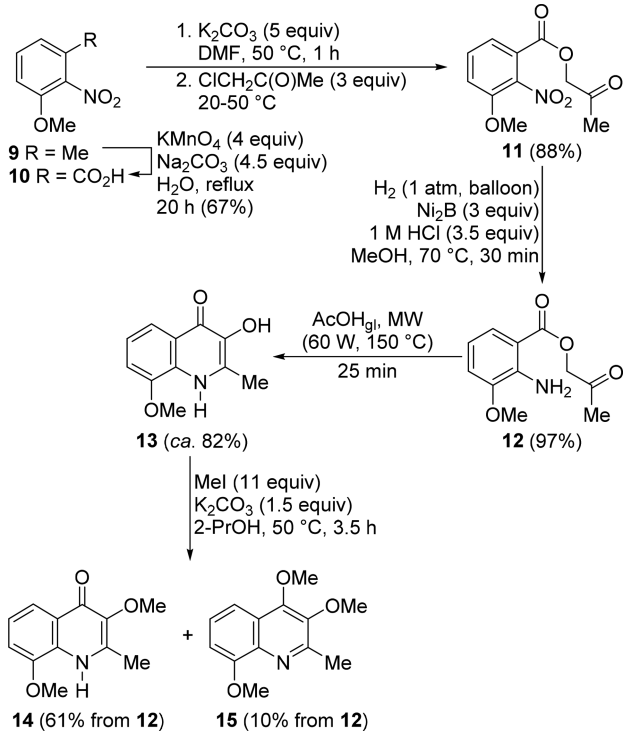
Scheme 1. Retrosynthetic Strategy toward Waltherione F (5)



Scheme 2. Synthesis of Model Compound 14



Therefore, the acid **10** was acetonylated (88% yield) with freshly prepared chloroacetone,[15] and the nitro group of the resulting ester **11** was subjected to a chemoselective reduction. However, the tested reducing agents (H_2, 10% Pd/C, Zn^0/NH_4HCO_2, TES/$CHCl_3$, $SnCl_2$, Fe^0/NH_4Cl)[16] afforded complex mixtures of esters and acids containing partial reduction derivatives of the nitro moiety. The anthranilic ester **12** was also detected, albeit in low yield.

An insightful analysis of the literature revealed that nickel boride (Ni_2B)[17a] has been used for the efficient conversion of aromatic nitro groups to the corresponding anilines in the presence of alkenes, halides, and esters.[17b] Delightfully, the reduction of **11** with 3 equiv of freshly prepared Ni_2B gave the anthranilate **12** in 97% yield.

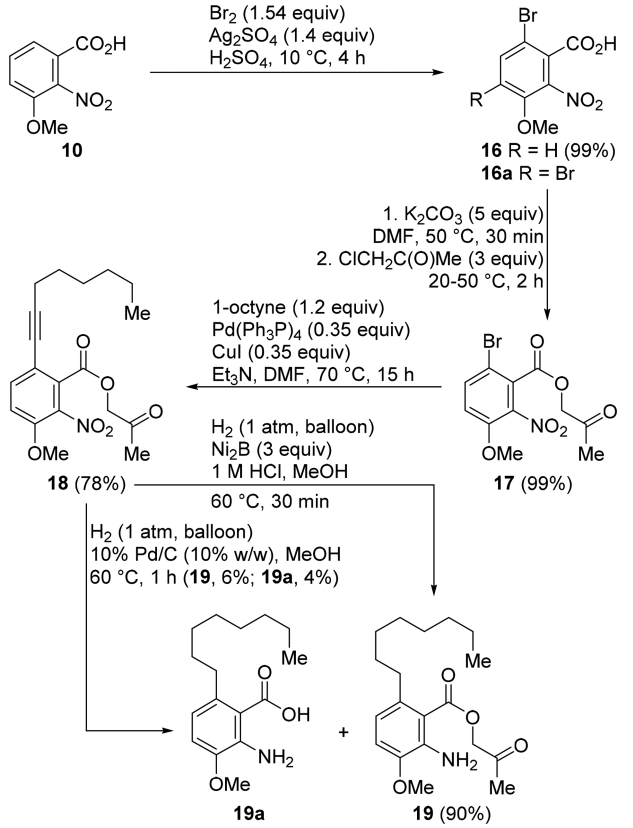
Next, the cyclization step was explored, but carrying the reaction in NMP afforded a meager 34% yield of **13**; hence, alternative conditions were sought.[18] After experimenting with different solvents (TFA, AcOH, Ph_2O) under conventional and microwave heating, it was found that AcOH was an efficient promoter of the microwave-assisted (60 W, 150 °C) cyclization/rearrangement sequence,[19] which furnished **13** in 80% yield.

Quinolone **13** bears three different alkylation positions (N, O_3, O_4), and overalkylated products are possible, depending on the reaction conditions. A literature survey revealed that conditions for 3-OH alkylation in 3-hydroxy-4-quinolones are scarce. Therefore, an optimization needed to be performed, with alcoholic solvents being preferred over polar aprotic media (DMF, MeCN, Me_2CO),[18] and mild bases (K_2CO_3, Na_2CO_3, $NaHCO_3$) needed to be used to ensure selectivity since NaH and the like promoted dialkylation.[20]

It was found that reaction of **13** with MeI in 2-PrOH gave a 61% yield of **14**, accompanied by 10% of **15**. Efforts to perform the transformation **12** → **14** as a "two step-one pot" process[21] did not improve the yields. The methylation position was determined unambiguously by NOE and HMBC experiments. The remainder of the total synthesis of **5** was thus undertaken.

Treatment of the acid **10** with Br_2 in concentrated H_2SO_4, under Ag_2SO_4 promotion,[22] provided **16** in 99% yield (Scheme 3). Occasionally, the dibrominated derivative **16a** was obtained

Scheme 3. Synthesis of the Key Intermediate 19



as a byproduct. Following Hradil's strategy, the bromide **16** was acetonylated with chloroacetone, giving the ester **17** in excellent yield (99%). Then the introduction of the *n*-octyl group was attempted[23a] under conditions compatible with acetonyl esters.[23b]

Due to the commercial availability of 1-octyne, a Sonogashira reaction was initially performed. Thus, the bromoarene **17** was treated with 1-octyne in DMF under

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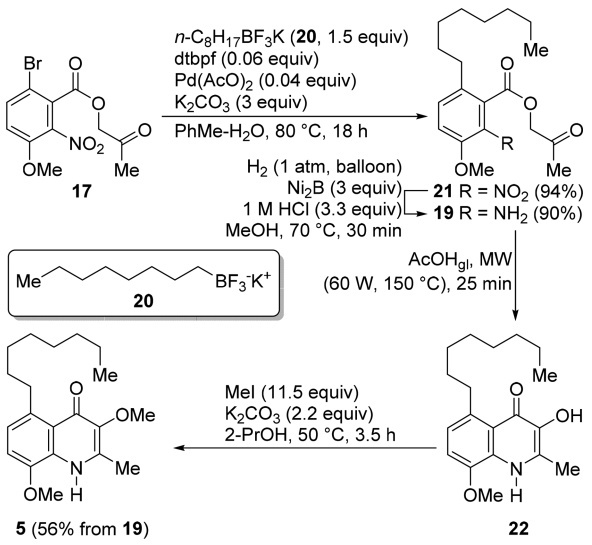
$Pd(PhP_3)_4$ and CuI catalysis (0.35 equiv each),[24] affording 78% yield of the coupled product **18** and ca. 4% of **11**. The alkyne **18** proved to be unstable to the chromatographic purification conditions; therefore, the crude reaction product was carried to the next step of the sequence.

Here, a simultaneous hydrogenation of the alkyne moiety and reduction of the nitro group was envisioned, to provide the corresponding 3-octylaniline derivative. Unfortunately, under Pd catalysis (H_2, 10% Pd/C, MeOH) a complex mixture of products was obtained where **19** was identified in a disappointing yield of 6%, at best.

A small amount of anthranilic acid **19a** (4%) was also isolated and unequivocally identified by conversion to its *O*-acetonyl ester **19** (Scheme 3). Presumably, this byproduct arose from hydrolysis of the acetonyl ester, which occurred after the alkyne hydrogenation and nitro group reduction stages. In light of these results, the strategy toward installation of the *n*-octyl group was revised.

The cross-coupling of properly activated arenes with alkyltrifluoroborate salts under palladium catalysis[25] is one of the most powerful emerging methodologies to build C_{sp^3}–C_{sp^2} bonds. Hence, potassium *n*-octyltrifluoroborate (**20**) was synthesized from *n*-octyl bromide[26] and further cross-coupled with **17** using dppf as ligand.[27] After the system was stirred overnight at 80 °C, the coupled product **21** was obtained in 81% yield (Scheme 4), accompanied by some of the proto-debrominated precursor **11** and a small amount of the related benzoic acid **10**.

Scheme 4. Synthesis of Waltherione F (5)



In order to suppress the formation of byproducts, the reaction was performed in the presence of dtbpf since sterically hindered phosphine ligands increase the oxidative insertion pathway.[12] This ligand change gave access to the desired product **21** in an improved 94% yield.

With the coupled product **21** in hand, its reduction was performed with freshly prepared Ni_2B (3 equiv) under a H_2 atmosphere to give the anthranilate **19** in 90% yield.

Next, **19** was dissolved in AcOH and subjected to microwave heating, smoothly cyclizing to **22** after 25 min at 150 °C. Unexpectedly, the chromatographic purification of **22** on SiO_2 proved troublesome;[28] therefore, the solvent was removed under high vacuum, and the final methylation step was performed on this crude material with MeI and K_2CO_3 in 2-PrOH at 50 °C during 3.5 h. This furnished synthetic waltherione F (**5**) in 56% overall yield from **19** after silica gel chromatography. The ^1H and ^{13}C NMR spectral data of the synthetic compound in MeOH-d_4 were in full agreement with those of the natural product.[5]

In conclusion, the first total synthesis of waltherione F has been accomplished in seven steps and 31% overall yield from commercial 3-methyl-2-nitroanisole without the use of protecting groups. The sequence involved the preparation of 2-nitro-3-methoxy-6-bromobenzoic acid, the synthesis of its acetonyl ester, and its subsequent Suzuki–Miyaura coupling with potassium *n*-octyltrifluoroborate under palladium catalysis using dtbpf as ligand. A chemoselective nitro group reduction with Ni_2B, AcOH-promoted cyclization of the resulting acetonyl anthranilate under microwave irradiation, and final 3-OH methylation completed the heterocyclic pseudane core.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02221.

Detailed experimental procedures and characterization data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kapadia, G. J.; Paul, B. D.; Silverton, J. V.; Fales, H. M.; Sokoloski, E. A. *J. Am. Chem. Soc.* **1975**, *97*, 6814–6819. (b) Kapadia, G. J.; Shukla, Y. N.; Basak, S. P.; Fales, H. M.; Sokoloski, E. A. *Phytochemistry* **1978**, *17*, 1444–1445.

(2) (a) Hoelzel, S. C. S. M.; Vieira, E. R.; Giacomelli, S. R.; Dalcol, I. I.; Zanatta, N.; Morel, A. F. *Phytochemistry* **2005**, *66*, 1163–1167. (b) Gressler, V.; Stüker, C. Z.; de O. C. Dias, G.; Dalcol, I. I.; Burrow, R. A.; Schmidt, J.; Wessjohann, L.; Morel, A. F. *Phytochemistry* **2008**, *69*, 994–999. (c) Dias, G. C. D.; Gressler, V.; Hoenzel, S. C. S. M.; Silva, U. F.; Dalcol, I. I.; Morel, A. F. *Phytochemistry* **2007**, *68*, 668–672. (d) Emile, A.; Waikedre, J.; Herrenknecht, C.; Fourneau, C.; Gantier, J.-C.; Hnawia, E.; Cabalion, P.; Hocquemiller, R.; Fournet, A. *Phytother. Res.* **2007**, *21*, 398–400.

(3) Erwin, E.; Noor, A.; Soekamto, N. H.; van Altena, I.; Syah, Y. M. *Biochem. Syst. Ecol.* **2014**, *55*, 358–361.

(4) (a) Jadulco, R. C.; Pond, C. D.; Van Wagoner, R. M.; Koch, M.; Gideon, O. G.; Matainaho, T. K.; Piskaut, P.; Barrows, L. R. *J. Nat. Prod.* **2014**, *77*, 183–187. (b) Monteillier, A.; Cretton, S.; Ciclet, O.; Marcourt, L.; Ebrahimi, S. N.; Christen, P.; Cuendet, M. *J. Ethnopharmacol.* **2017**, *203*, 214–225. (c) Cretton, S.; Bréant, L.;

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Org. Lett. XXXX, XXX, XXX–XXX

Pourrez, L.; Ambuehl, C.; Perozzo, R.; Marcourt, L.; Kaiser, M.; Cuendet, M.; Christen, P. *Fitoterapia* **2015**, *105*, 55−60.
(5) Cretton, S.; Breant, L.; Pourrez, L.; Ambuehl, C.; Marcourt, L.; Ebrahimi, S. N.; Hamburger, M.; Perozzo, R.; Karimou, S.; Kaiser, M.; Cuendet, M.; Christen, P. *J. Nat. Prod.* **2014**, *77*, 2304−2311.
(6) Cretton, S.; Dorsaz, S.; Azzollini, A.; Favre-Godal, Q.; Marcourt, L.; Ebrahimi, S. N.; Voinesco, F.; Michellod, E.; Sanglard, D.; Gindro, K.; Wolfender, J.-L.; Cuendet, M.; Christen, P. *J. Nat. Prod.* **2016**, *79*, 300−307.
(7) (a) Wang, G. C.; Li, T.; Wei, Y.-R.; Zhang, Y.-B.; Li, Y.-L.; Sze, S. C. W.; Ye, W. C. *Fitoterapia* **2012**, *83*, 1643−1647. (b) Buske, A.; Busemann, S.; Mühlbacher, J.; Schmidt, J.; Porzel, A.; Bringmann, G.; Adam, G. *Tetrahedron* **1999**, *55*, 1079−1086. (c) Bringmann, G.; Schlauer, J.; Rischer, H.; Wohlfarth, M.; Mühlbacher, J.; Buske, A.; Porzel, A.; Schmidt, J.; Adam, G. *Tetrahedron* **2000**, *56*, 3691−3695.
(8) (a) Zongo, F.; Ribuot, C.; Boumendjel, A.; Guissou, I. *J. Ethnopharmacol.* **2013**, *148*, 14−26. (b) Jang, J. Y.; Le Dang, Q.; Choi, Y. H.; Choi, G. J.; Jang, K. S.; Cha, B.; Luu, N. H.; Kim, J. C. *J. Agric. Food Chem.* **2015**, *63*, 68−74. (c) Jang, J. Y.; Le Dang, Q.; Choi, Y. H.; Choi, G. J.; Jang, K. S.; Cha, B.; Luu, N. H.; Kim, J. C. *J. Agric. Food Chem.* **2015**, *63*, 3803−3803. (d) Al Muqarrabun, L. M. R.; Ahmat, N. *Eur. J. Med. Chem.* **2015**, *92*, 514−530.
(9) (a) Méndez, M. V.; Heredia, D. A.; Larghi, E. L.; Bracca, A. B. J.; Kaufman, T. S. *RSC Adv.* **2017**, *7*, 28298−28307. (b) Pergomet, J. L.; Bracca, A. B. J.; Kaufman, T. S. *Org. Biomol. Chem.* **2017**, *15*, 7040−7049. (c) Pergomet, J. L.; Larghi, E. L.; Kaufman, T. S.; Bracca, A. B. J. *RSC Adv.* **2017**, *7*, 5242−5250. (d) Simonetti, S. O.; Larghi, E. L.; Bracca, A. B. J.; Kaufman, T. S. *Org. Biomol. Chem.* **2012**, *10*, 4124−4134.
(10) Mäkinen, M. E.; Mallik, R.; Siitonen, J. H.; Kärki, K.; Pihko, P. M. *Synlett* **2017**, *28*, 1209−1213.
(11) (a) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M. C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652−2671. (b) Fallah-Mehrjardi, M. *Mini-Rev. Org. Chem.* **2017**, *14*, 187−196.
(12) Cleaver, L.; Nimgirawath, S.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1976**, *29*, 2003−2021.
(13) Glossop, S. C. *Synthesis* **2007**, *2007*, 981−983.
(14) (a) Morel, A. F.; Larghi, E. L.; Selvero, M. M. *Synlett* **2005**, 2755−2758. (b) Hradil, P.; Hlaváč, J.; Lemr, K. *J. Heterocycl. Chem.* **1999**, *36*, 141−144.
(15) Clamens, S.; Teissier, R. Patent FR2633614, 1988.
(16) (a) Hradil, P.; Vaněček, J.; Hlaváč, J.; Ševčík, J. *Collect. Czech. Chem. Commun.* **1999**, *64*, 257−264. (b) Gowda, D. C.; Mahesh, B.; Gowda, S. *Indian J. Chem.* **2001**, *40B*, 75−77. (c) Mandal, P. K.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6599−6601. (d) Chandrappa, S.; Vinaya, K.; Ramakrishnappa, T.; Rangappa, K. S. *Synlett* **2010**, *2010*, 3019−3022. (e) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839−842. (f) Du, Z.; Hintermann, S.; Hurth, K.; Jacquier, S.; Lehmann, H.; Moebitz, H.; Soldermann, N.; Stojanovic, A. Patent WO010641, 2015.
(17) (a) Khurana, J. M.; Gogia, A. *Org. Prep. Proced. Int.* **1997**, *29*, 1−32. (b) Seltzman, H. H.; Berrang, S. D. *Tetrahedron Lett.* **1993**, *34*, 3083−3086.
(18) Vaňková, B.; Hlaváč, J.; Soural, M. *J. Comb. Chem.* **2010**, *12*, 890−894.
(19) (a) Nishi, T. *Chem. Pharm. Bull.* **1983**, *31*, 798−810. (b) Kiyama, R.; Kanda, Y.; Tada, Y.; Fujishita, T.; Kawasuji, T.; Takechi, S.; Fuji, M. Patent WO016275, 2003.
(20) Hodgkinson, J. T.; Gross, J.; Baker, Y. R.; Spring, D. R.; Welch, M. *Chem. Sci.* **2016**, *7*, 2553−2562.
(21) Hodgkinson, J. T.; Galloway, W. R. J. D.; Welch, M.; Spring, D. R. *Nat. Protoc.* **2012**, *7*, 1184−1192.
(22) Manthey, M. K.; Pyne, S. G.; Truscott, R. J. W. *J. Org. Chem.* **1990**, *55*, 4581−4585.
(23) (a) Chinchilla, R.; Nàjera, C. *Chem. Rev.* **2014**, *114*, 1783−1826. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417−1492.
(24) Wei, W.-G.; Zhang, Y.-X.; Yao, Z.-J. *Tetrahedron* **2005**, *61*, 11882−11886.
(25) Molander, G. A. *J. Org. Chem.* **2015**, *80*, 7837−7848.
(26) Reichle, M. A.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 5730−5734.
(27) Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75−78.
(28) Maurer, C. K.; Steinbach, A.; Hartmann, R. W. *J. Pharm. Biomed. Anal.* **2013**, *86*, 127−134.

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Org. Lett. XXXX, XXX, XXX−XXX