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Total Synthesis of Diptoindonesin G via a Highly Efficient Domino Cyclodehydration/Intramolecular Friedel−Crafts Acylation/Regioselective Demethylation Sequence

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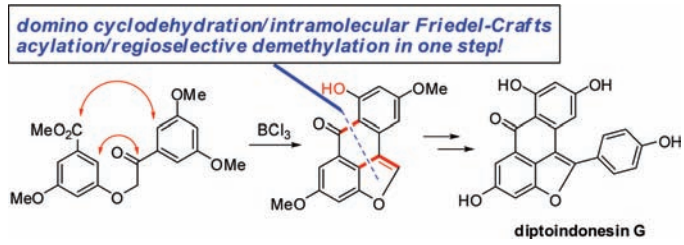
ABSTRACT



A highly efficient total synthesis of diptoindonesin G is described employing a domino dehydrative cyclization/intramolecular Friedel−Crafts acylation/regioselective demethylation reaction of aryloxyketone 7 by the action of BCl_3 wherein the tetracyclic 6*H*-anthra[1,9-*bc*]furan-6-one skeleton was constructed via the 3-arylbenzofuran in a one-pot manner. This is the first example of the strategic combination of these three reactions in a cascade fashion. The routes presented here allow for direct access to diptoindonesin G and its analogues.

Dipterocarpaceae is known to be a rich source of a variety of biologically active oligostilbenoids.[1] Indeed, a number of oligomeric stilbenes have been isolated with distinct modes of connectivity of their basic 1,2-diphenylethylene skeleton. Not surprisingly, many interesting pharmacological functions of this family have been also identified including antiinflammatory, antibacterial, antifungal, and anticancer activities.[2] Despite their intriguing biological properties as well as unique molecular structures, only a few chemical approaches to oligostilbene natural products have been reported.[3]

Recently, we described a modular approach to benzofuran-containing oligostilbenoids that led to the syntheses of permethylated analogues of viniferifuran, malibatol A, and sho-

(1) For recent reviews on natural stilbenes, see: (a) Takaya, Y.; Niwa, M. *Trends Heterocycl. Chem.* **2001**, *7*, 41. (b) Seo, E.-K.; Kinghorn, A. D. *Stud. Nat. Prod. Chem.* **2000**, *23* (Bioactive Natural Products (Part D)), 531. (c) Lin, M.; Yao, C.-S. *Stud. Nat. Prod. Chem.* **2006**, *33* (Bioactive Natural Products (Part M)), 601. (d) Shen, T.; Wang, X.-N.; Lou, H.-X. *Nat. Prod. Rep.* **2009**, *26*, 916.

(2) (a) Samaraweera, U.; Sotheeswaran, S.; Sultanbawa, M. U. S. *Phytochemistry* **1982**, *21*, 2585. (b) Bokel, M.; Diyasena, M. N. C.; Gunatilaka, A. A. L.; Kraus, W.; Sotheeswaran, S. *Phytochemistry* **1987**, *26*, 377. (c) Kurihara, H.; Kawabata, J.; Ichikawa, S.; Mishima, M.; Mizutani, J. *Phytochemistry* **1991**, *30*, 649. (d) Oshima, Y.; Namao, K.; Kamijou, A.; Matuoka, S.; Nakano, M.; Terao, K.; Ohizumi, Y. *Experientia* **1995**, *51*, 63. (e) Ohyama, M.; Tanaka, T.; Ito, T.; Iinuma, M.; Bastow, K. F.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3057. (f) Huang, K.-S.; Lin, M.; Cheng, G.-F. *Phytochemistry* **2001**, *58*, 357. (g) Meng, Y.; Bourne, P. C.; Whiting, P.; Šik, V.; Dinan, L. *Phytochemistry* **2001**, *57*, 393. (h) Luo, H.-F.; Zhang, L.-P.; Hu, C.-Q. *Tetrahedron* **2001**, *57*, 4849. (i) Privat, C.; Telo, J. P.; Bernades-Genisson, V.; Vieira, A.; Souchard, J. P.; Nepveu, F. J. *Agric. Food Chem.* **2002**, *50*, 1213. (j) Wang, S.; Ma, D.; Hu, C. *Helv. Chim. Acta* **2005**, *88*, 2315. (k) Yamada, M.; Hayashi, K.-i.; Hayashi, H.; Tsuji, R.; Kakumoto, K.; Ikeda, S.; Hoshino, T.; Tsutsui, K.; Ito, T.; Iinuma, M.; Nozaki, H. *Chem. Pharm. Bull.* **2006**, *54*, 354. (l) Yamada, M.; Hayashi, K.-i.; Ikeda, S.; Tsutsui, K.; Ito, T.; Iinuma, M.; Nozaki, H. *Biol. Pharm. Bull.* **2006**, *29*, 1504.

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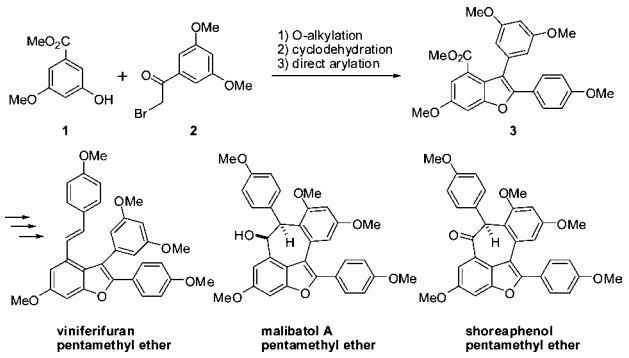
Scheme 1. Our Previous Synthetic Approach to Oligostilbenoids Bearing a Benzofuran Unit

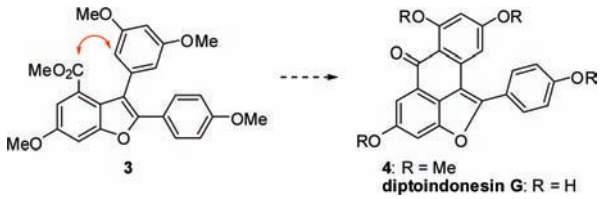


reaphenol (Scheme 1).[4] Thus, coupling of **1** and **2**, dehydrative cyclization, and subsequent direct arylation at the C2 position of the benzofuran moiety provided a key intermedate **3** which, upon further elaboration, was converted to the pentamethyl ethers of three natural products.

A few months after this publication, isolation of a novel oligostilbenoid possessing strong cytotoxic activity, diptoindonesin G, from the tree bark of *Hopea mengarawan* was reported by Syah and co-workers.[5] More recently, this natural product has been shown to exhibit potent immunosuppressive activity.[6] Alongside these interesting biological activities, the structural relationship of diptoindonesin G with **3** prompted us to pursue the total synthesis of diptoindonesin G, which is the topic of this paper.

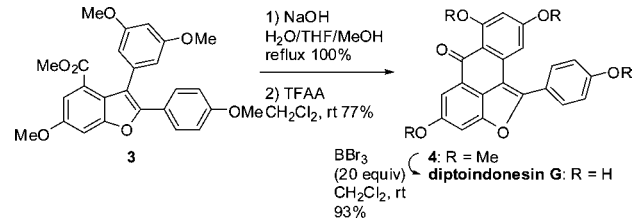
It was initially envisaged that diptoindonesin G would be easily synthesized from **3** by intramolecular Friedel−Crafts acylation[7] followed by global demethylation (Scheme 2).

Scheme 2. Initial Synthetic Plan



With this notion in mind, a large quantity of **3** was prepared by adopting the reported procedure.[4] We were pleased to find that acid obtained by hydrolysis of ester **3**[8] underwent smooth cyclization in the presence of trifluoroacetic anhydride at room temperature to afford **4** in 77% yield (Scheme 3). Unmasking of four phenolic

Scheme 3. Initial Synthetic Route to Diptoindonesin G



hydroxyl groups in **4** occurred upon exposure to BBr_3, delivering diptoindonesin G in 93% yield. Spectral data of synthetic samples are in good agreement with those of natural diptoindonesin G.[5]

At this point, we attempted to synthesize much simpler analogues which can be derived from synthetic intermediates for pharmacological evaluation.[9] In this respect, **5** was also exposed to BBr_3 to produce the corresponding trihydroxy compound. Surprisingly, however, tetracyclic compound **6** was isolated as a major product instead of expected methyl ester shown in the box of Scheme 4. This result certainly arises from the action of BBr_3 to coordinate to the carbonyl group to promote Friedel−Crafts-type cyclization in addition to its demethylation ability.[10] Similarly, subjection of **3** to the identical conditions directly provided diptoindonesin G in 92% yield. Since BCl_3-mediated cyclodehydration of aryloxyketones to benzofurans (for example, **7** to **5**) is plausible, we anticipated that more direct synthesis of **6** might be realized from **7** by modifying the reported procedure.[11] Thus, BBr_3 was added to the reaction mixture after formation of benzofuran was confirmed by TLC upon treatment of **7** with BCl_3.[12,13] To our delight, 93% of the desired product was obtained in this case.

(3) (a) Kraus, G. A.; Kim, I. *Org. Lett.* **2003**, *5*, 1191. (b) Yao, C.-S.; Zhou, L.-X.; Lin, M. *Chem. Pharm. Bull.* **2004**, *52*, 238. (c) Takaya, Y.; Terashima, K.; Ito, J.; He, Y.-H.; Tateoka, M.; Yamaguchi, N.; Niwa, M. *Tetrahedron* **2005**, *61*, 10285. (d) Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186. (e) Velu, S. S.; Buniyamin, I.; Ching, L. K.; Feroz, F.; Noorbatcha, I.; Gee, L. C.; Awang, K.; Abd. Wahab, I.; Weber, J.-F. F. *Chem.—Eur. J.* **2008**, *14*, 11376. (f) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753. (g) Nicolaou, K. C.; Wu, T. R.; Kang, Q.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3440. (h) Kraus, G. A.; Gupta, V. *Tetrahedon Lett.* **2009**, *50*, 7180. (i) Nicolaou, K. C.; Kang, Q.; Wu, T. R.; Lim, C. S.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 7540.

(4) Kim, I.; Choi, J. *Org. Biomol. Chem.* **2009**, *7*, 2788.

(5) Juliawaty, L. D.; Sahidin; Hakim, E. H.; Achmad, S. A.; Syah, Y. M.; Latip, J.; Said, I. M. *Nat. Prod. Commun.* **2009**, *4*, 947.

(6) Ge, H. M.; Yang, W. H.; Shen, Y.; Jiang, N.; Guo, Z. K.; Luo, Q.; Xu, Q.; Ma, J.; Tan, R. X. *Chem.—Eur. J.* **2010**, *16*, 6338.

(7) For recent examples, see: (a) Olah, G. A.; Mathew, T.; Farnia, M.; Prakash, G. K. S. *Synlett* **1999**, 1067. (b) Fillion, F.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144. (c) Lan, K.; Shao, F.; Shan, Z. *Aust. J. Chem.* **2007**, *60*, 80. (d) Fillion, E.; Fishlock, D. *Tetrahedron* **2009**, *65*, 6682. (e) Yadav, J. S.; Ravindar, A. R. K.; Reddy, B. V. S. *Synthesis* **2010**, 797. (f) Prinz, H.; Böhm, K. J.; Müller, K. *J. Org. Chem.* **2010**, *75*, 3867. (g) Malik, H.; Rutjes, F. P. J. T.; Zwanenburg, B. *Tetrahedron* **2010**, *66*, 7198.

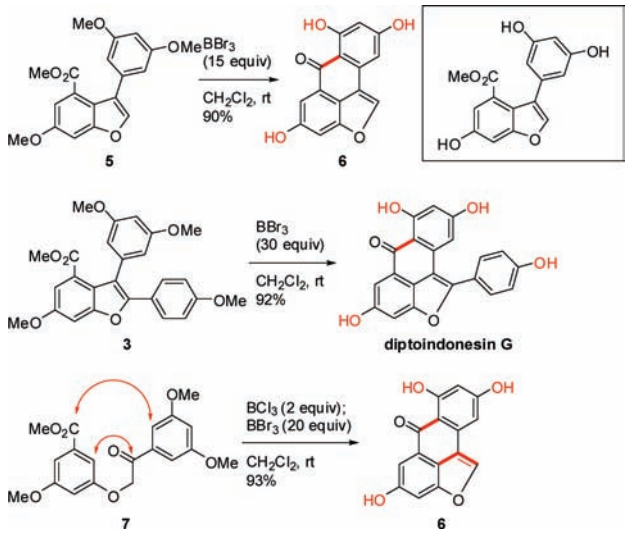
(8) Direct cyclization of **3** was also attempted with trifluoroacetic acid. Thus, exposure of **3** to refluxing trifluoroacetic acid resulted in clean conversion to **4** although long reaction time was required (36 h).

(9) For concepts on diverted total synthesis, see: (a) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329. (b) Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3224. (c) Wilson, R. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 6032.

(10) For a recent report on the use of BBr_3 as an activator of imide carbonyl group to initiate electrophilic cyclization without demethylation, see: Selvakumar, J.; Makriyannis, A.; Ramanathan, C. R. *Org. Biomol. Chem.* **2010**, *8*, 4056.

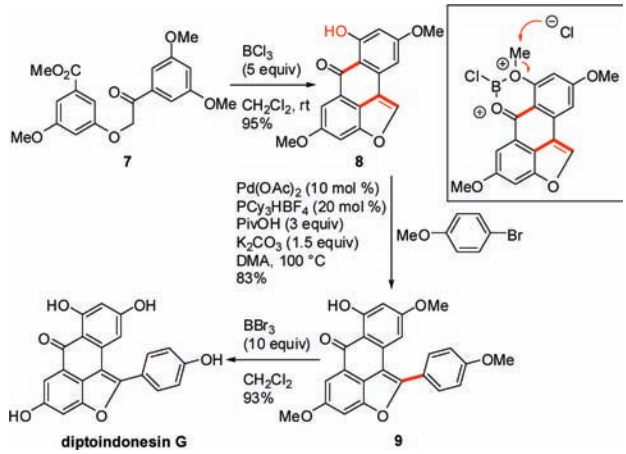
(11) Kim, I.; Lee, S.-H.; Lee, S. *Tetrahedron Lett.* **2008**, *49*, 6579.

Scheme 4. Direct Approaches to Diptoindonesin G by BBr_3



With these exciting results in hand, we further reasoned that BCl_3 alone might also trigger Friedel−Crafts-type ring closure after the cyclodehydration event on aryloxyketone **7**. Indeed, when **7** was treated with 5 equiv of BCl_3, **8** was isolated in excellent yield (Scheme 5).[14] Mechanistically,

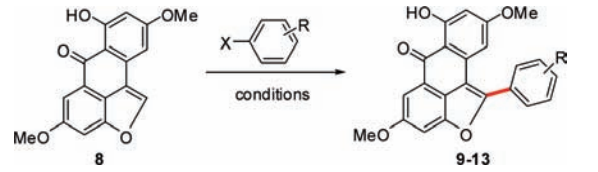
Scheme 5. Concise Route to Diptoindonesin G



successive formation of two rings set the stage for regioselective demethylation by BCl_3 as shown in the box of Scheme 5. Notably, construction of 6*H*-anthra[1,9-*bc*]furan-6-one[15] by use of a domino[16,17] cyclodehydration/intramolecular Friedel−Crafts acylation process of aryloxyketones such as **7** is unprecedented in the literature.[18]

At this point, compound **8** was also advanced to diptoindonesin G via the route illustrated in Scheme 5. Direct arylation[19] under palladium catalysis was attempted to install an aryl group at the C2 position of the benzofuran[20] unit of **8**. Initial reaction of **8** under the conditions employed in our previous syntheses of oligostilbenoids only furnished **9** in 18−22% yield (entry 1, Table 1).[21] Subjection of **8** to

Table 1. Reaction Optimization



entry	X	R	product	yield[e]
1[a]	Br	4-OMe	**9**	18−22
2[b]	I	4-OMe	**9**	28−31
3[c]	Br	4-OMe	**9**	26
4[d]	I	4-OMe	**9**	39
5[d]	Br	4-OMe	**9**	83
6[d]	Br	4-Me	**10**	78
7[d]	Br	3,4,5-$(OMe)_3$	**11**	42
8[d]	Br	4-*n*-Bu	**12**	44
9[d]	Br	4-*t*-Bu	**13**	56

[a] A mixture of **8** (0.1 mmol), aryl halide (2 equiv), $Pd(OAc)_2$ (10 mol %), and KOAc (2 equiv) in DMA (1 mL) was heated at 80 °C for 13 h. [b] A mixture of **8** (0.1 mmol), aryl halide (2 equiv), $Pd(OAc)_2$ (10 mol %), $NaHCO_3$ (2 equiv), and TBAC (1 equiv) in DMF (1 mL) was heated at 100 °C for 13 h. [c] A mixture of **8** (0.1 mmol), aryl halide (2 equiv), $Pd(OAc)_2$ (10 mol %), PCy_3HBF_4 (20 mol %), PivOH (30 mol %), and K_2CO_3 (1.5 equiv) in DMA (1 mL) was heated at 100 °C for 1 h. [d] A mixture of **8** (0.17 mmol), aryl halide (2 equiv), $Pd(OAc)_2$ (10 mol %), PCy_3HBF_4 (20 mol %), PivOH (3 equiv), and K_2CO_3 (1.5 equiv) in DMA (3 mL) was heated at 100 °C for 1 h. [e] Isolated yield (%).

Jeffery's ligandless conditions[22] gave a similar yield (entry 2). We were delighted to observe that cross coupling with

(12) See the Supporting Information for detailed experimental procedures.

(13) Direct exposure of **7** to excess BBr_3 resulted in very low yield of product.

(14) Gram-scale reaction of **7** also proceeded smoothly.

(15) (a) Mainagashev, I. Y.; Klimenko, L. S. *Izv. Akad. Nauk, Ser. Khim.* **1996**, 2710. (b) Gotzhein, F.; Kirmse, W. *Tetrahedron Lett.* **1998**, *39*, 6675.

(16) For books and reviews on domino or tandem reactions, see: (a) Ho, T.-L. *Tandem Organic Reactions*; John Wiley & Sons: New York, 1992. (b) Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (e) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (f) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (g) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (h) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (i) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1.

(17) (a) Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron* **2008**, *64*, 664. (b) Kim, I.; Kim, K.; Choi, J. *J. Org. Chem.* **2009**, *74*, 8492. (c) Kim, I.; Kim, K. *Org. Lett.* **2010**, *12*, 2500.

(18) Formation of this skeleton under Lewis or Brønsted acid catalysis in a cascade fashion is currently being investigated.

(19) For reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (f) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (h) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (i) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677.

aryl bromide under slightly modified Fagnou's conditions[23] dramatically increased the isolated yield (entries 3−5).[24] Several aryl groups were introduced under these conditions to afford the corresponding products (entries 6−9). Deprotection of three methyl groups of **9** by BBr_3 produced diptoindonesin G.

In summary, we have accomplished the first total synthesis of diptoindonsin G via several concise and flexible routes by which diptoindonesin G analogues should be easily prepared. In particular, exploitation of a novel BCl_3-facilitated domino cyclodehydration/intramolecular Friedel−Crafts acylation/regioselective demethylation sequence allows for ready access to the key tetracyclic core in one reaction step with remarkable efficiency. Subsequent direct arylation at the C2 site of the benzofuran moiety followed by demethylation led to diptoindonesin G in good overall yield (70%, four linear steps) from **1** and **2**. Extension of this protocol to the assembly of other carbo- and heterocycles as well as biological evaluation of diptoindonesin G and its analogues is currently underway and will be reported in the near future.

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Supporting Information Available: Full experimental details, characterization data, and copies of ^1H and ^{13}C NMR spectra of **4**, **6**, **8**−**13**, and synthetic diptoindonesin G. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Direct C2-arylation of benzofurans is less studied. (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951. (b) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257. (c) Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, *49*, 1045. (d) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (e) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (f) Matsuda, S.; Takahashi, M.; Monguchi, D.; Mori, A. *Synlett* **2009**, 1941. For direct C3-arylation of benzofurans, see: (g) Ionita, M.; Roger, J.; Doucet, H. *ChemSusChem* **2010**, *3*, 367.

(21) No homodimer was observed in this case as compared with direct arylation of **5**. See ref 4.

(22) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (c) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051. (d) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(23) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

(24) Studies on the reason and reaction scope under these modified conditions are in progress.