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One-Pot Transition-Metal-Free Synthesis of Dibenzo[*b*,*f*]oxepins from 2-Halobenzaldehydes

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ABSTRACT

A one-pot transition-metal-free, base-mediated synthesis of dibenzo[*b*,*f*]oxepins was developed. The reaction of 2-halobenzaldehydes with (2-hydroxyphenyl)acetonitriles proceeds via a sequential aldol condensation and intramolecular ether formation reaction in the presence of Cs_2CO_3 and molecular sieves in toluene.

Dibenzo[*b*,*f*]oxepin is an important motif in natural and medicinal compounds (Figure 1). Recently, pacharin (**1**) and bauhiniastatins 1−4 (**2**) were isolated from the plant *Bauhinia purpurea*, and these compounds were shown to significantly inhibit cancer cell growth.[1] These compounds are similar to the natural products bauhinoxepin B (**3**)[2] and artocarpol A (**4**),[3] which have been shown to exhibit antimycobacterial and anti-inflammatory activities, respectively. Notably, molecules containing the dibenzo[*b*,*f*]oxepin moiety have received considerable interest from the medicinal community due to these compounds' potent biological properties, such as antipsychotic,[4] antidepressant,[5] antihypertensive,[6] antiestrogenic,[7] anti-inflammatory,[8] and insecticidal activities.[9] For example, compound **5** is a nonpeptide angiotensin II receptor antagonist that can regulate blood pressure and electrolyte homeostasis.[6] CGP 3466 (**6**) exhibits strong neuroprotective activity as the result of its ability to prevent neuronal apoptosis in the adult brain.[10]

Synthetic methodologies for the construction of a dibenzo[*b*,*f*]oxepin scaffold have been focused primarily on the combination of Ullmann coupling and the

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(1) (a) Pettit, G. R.; Numata, A.; Iwamoto, C.; Usami, Y.; Yamada, T.; Ohishi, H.; Cragg, G. M. *J. Nat. Prod.* **2006**, *69*, 323–327. (b) Anjaneyula, A. S. R.; Reddy, A. V. R.; Reddy, D. S. K.; Cameron, T. S.; Roe, S. P. *Tetrahedron* **1986**, *42*, 2417–2420.

(2) Kittakoop, P.; Nopichai, S.; Thongon, N.; Charoenchai, P.; Thebtaranonth, Y. *Helv. Chim. Acta* **2004**, *87*, 175–179.

(3) (a) Chung, M.-I.; Ko, H.-H.; Yen, M.-H.; Lin, C.-N.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2000**, *83*, 1200–1204. (b) Ko, H.-H.; Lin, C.-N.; Yang, S.-Z. *Helv. Chim. Acta* **2000**, *83*, 3000–3005. (c) Ko, H.-H.; Yang, S.-Z.; Lin, C.-N. *Tetrahedron Lett.* **2001**, *42*, 5269–5270. (d) Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2003**, *86*, 2566–2572.

(4) (a) Fernández, J.; Alonso, J. M.; Andrés, J. I.; Cid, J. M.; Díaz, A.; Iturrino, L.; Gil, P.; Megens, A.; Sipido, V. K.; Trabanco, A. A. *J. Med. Chem.* **2005**, *48*, 1709–1712. (b) Trabanco, A. A.; Alonso, J. M.; Cid, J. M.; Font, L. M.; Megens, A. *Il Farm.* **2005**, *60*, 241–248. (c) Trabanco, A. A.; Alonso, J. M.; Andrés, J. I.; Cid, J. M.; Fernández, J.; Iturrino, L.; Megens, A. *Chem. Pharm. Bull.* **2004**, *52*, 262–265. (d) Harris, T. W.; Smith, H. E.; Mobley, P. L.; Manier, D. H.; Sulser, F. *J. Med. Chem.* **1982**, *25*, 855–858. (e) Ueda, I.; Sato, Y.; Maeno, S.; Umio, S. *Chem. Pharm. Bull.* **1978**, *26*, 3058–3070. (f) Ueda, I.; Sato, Y.; Maeno, S.; Umio, S. *Chem. Pharm. Bull.* **1975**, *23*, 2223–2231.

(5) Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Spaulding, T. C.; Wilker, J. C.; Geyer, H. M., III; Kruse, H. *J. Med. Chem.* **1980**, *23*, 494–501.

(6) Kiyama, R.; Honma, T.; Hayashi, K.; Ogawa, M.; Hara, M.; Fujimoto, M.; Fujishita, T. *J. Med. Chem.* **1995**, *38*, 2728–2741.

(7) Acton, D.; Hill, G.; Tait, B. S. *J. Med. Chem.* **1983**, *26*, 1131–1137.

(8) Nagai, Y.; Irie, A.; Nakamura, H.; Hino, K.; Uno, H.; Nishimura, H. *J. Med. Chem.* **1982**, *25*, 1065–1070.

(9) Roeder, T.; Nathanson, J. A. *Neurochem. Res.* **1993**, *18*, 921–925.

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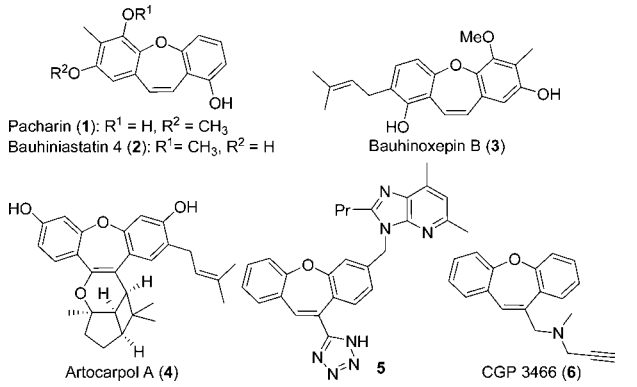
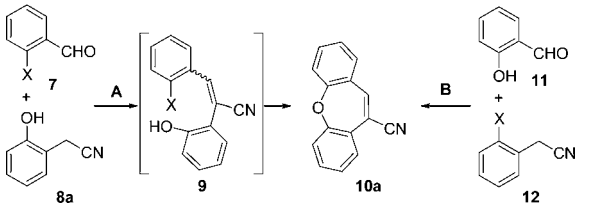


Figure 1. Dibenzo[*b*,*f*]oxepins in natural and medicinal compounds.

Friedel–Crafts reaction.[4d,5,8,11] For example, Paduraru and Wilson published a synthesis of artocarpol A and D analogs following this strategy.[12] In addition, the nucleophilic aromatic substitution reaction (S_NAr) has been widely used for the formation of biaryl ethers.[6,10a,13] Simultaneously, the ring expansion route from xanthenes has been reported, employing Wagner–Meerwein rearrangement[14] or Mn(III)-based oxidative radical rearrangement.[15] Guy et al. described the synthesis of dibenzo[*b*,*f*]oxepin based on a sequential Heck reaction and Pd-catalyzed etheration.[16] However, these strategies typically require lengthy reaction steps, yield products with low regioselectivities, and are compatible with few functional groups. As part of a research program to develop a one-pot metal-catalyzed reaction/aldol condensation reaction,[17] we sought to develop an efficient synthesis of dibenzo[*b*,*f*]oxepin via a one-pot Cu-catalyzed aryl ether formation/aldol condensation reaction. Serendipitously, we observed that the formation of dibenzo[*b*,*f*]oxepin occurred even in the absence of a copper catalyst. Herein, we report the transition-metal-free synthesis of dibenzo[*b*,*f*]oxepin from 2-halobenzaldehyde and (2-hydroxyphenyl)acetonitrile.[18]

At the outset, we envisioned two possible routes for the one-pot synthesis of dibenzo[*b*,*f*]oxepin in which the coupling partners, aryl halides and phenols, are switched, as illustrated in Table 1.

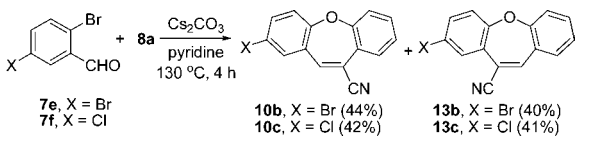
Table 1. One-Pot Synthesis of Dibenzo[*b*,*f*]oxepin[a]



entry	X (**7** or **12**)	pathway	temp (°C)	yield (%)[b]
1	F (**7a**)	A	130	98
2	Cl (**7b**)	A	130	96
3	Br (**7c**)	A	130	95
4	I (**7d**)	A	130	93
5	F (**12a**)	B	150	59
6	Cl (**12b**)	B	150	49
7	Br (**12c**)	B	150	46
8	I (**12d**)	B	150	21

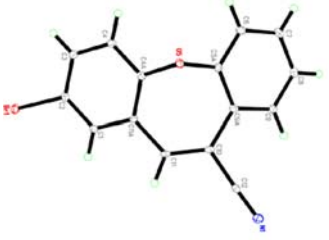
[a] Reaction conditions: (Pathway A) halobenzaldehyde **7** (0.36 mmol, 1.2 equiv), phenylacetonitrile **8a** (0.3 mmol), Cs_2CO_3 (0.6 mmol), pyridine (3 mL), 4 h; (Pathway B) benzaldehyde **11** (0.36 mmol, 1.2 equiv), phenylacetonitrile **12** (0.3 mmol), Cs_2CO_3 (0.9 mmol), pyridine (3 mL), 4 h. [b] Isolated yield.

Table 2. Isomerization of the Nitrile Group[a]



entry	solvent	additive	time (h)	yield (%)[b]	ratio of **10c**/**13c**[c]
1	pyridine	–	4	83	1:1
2	pyridine	MS (4 Å)	4	ND[d]	1:0.2
3	toluene	–	4	88	1:0.2
4	toluene	MS (4 Å)	4	72	1:0
5	toluene	MS (4 Å)	24	93	1:0

[a] Reaction conditions: halobenzaldehyde **7f** (0.36 mmol, 1.2 equiv), phenylacetonitrile **8a** (0.3 mmol), Cs_2CO_3 (0.6 mmol), MS (4 Å, 300 mg), solvents (3 mL). [b] Isolated yield. [c] ^1H NMR ratio of **10c** and **13c**. [d] Not determined.



X-ray structure of **10b**

(10) (a) Zimmermann, K.; Waldmeier, P. C.; Tatton, W. G. *Pure Appl. Chem.* **1999**, *71*, 2039–2046. (b) Zimmermann, K.; Roggo, S.; Kragten, E.; Fürst, P.; Waldmeier, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1195–1200. (c) Sagot, Y.; Toni, N.; Perrelet, D.; Lurot, S.; King, B; Rixner, H.; Mattenberger, L.; Waldmeier, P. C.; Kato, A. C. *Br. J. Pharmacol.* **2000**, *131*, 721–728.

(11) (a) Manske, R. H. F.; Ledingham, A. E. *J. Am. Chem. Soc.* **1950**, *72*, 4797–4799. (b) Olivera, R.; SanMartin, R.; Churruca, F.; Domínguez, E. *J. Org. Chem.* **2002**, *67*, 7215–7225.

(12) Paduraru, M. P.; Wilson, P. D. *Org. Lett.* **2003**, *5*, 4911–4913.

(13) (a) Hoyer, H.; Vogel, M. *Monatch. Chem.* **1962**, *93*, 766–774. (b) Samet, A. V.; Marshalkin, V. N.; Lyssenko, K. A.; Semenov, V. V. *Russ. Chem. Bull. Int. Ed.* **2009**, *58*, 347–350.

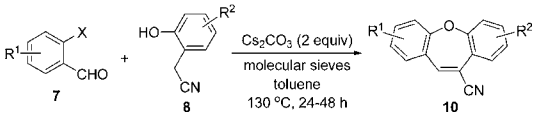
(14) (a) Storz, T.; Vangrevelinghe, E.; Dittmar, P. *Synthesis* **2005**, 2562–2570. (b) Anet, F. A. L.; Bavin, P. M. G. *Can. J. Chem.* **1957**, *35*, 1084–1087. (c) Bavin, P. M. G.; Bartle, K. D.; Jones, D. W. *J. Heterocycl. Chem.* **1968**, *5*, 327–330. (d) Hess, B. A., Jr.; Bailey, A. S.; Boekelheide, V. *J. Am. Chem. Soc.* **1967**, *89*, 2746–2747.

(15) (a) Cong, Z.; Miki, T.; Urakawa, O.; Nishino, H. *J. Org. Chem.* **2009**, *74*, 3978–3981. (b) Nishino, H.; Kamachi, H.; Baba, H.; Kurosawa, K. *J. Org. Chem.* **1992**, *57*, 3551–3557.

(16) Arnold, L. A.; Luo, W.; Guy, R. K. *Org. Lett.* **2004**, *6*, 3005–3007.

(17) (a) Kim, Y. H.; Lee, H.; Kim, Y. J.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2008**, *73*, 495–501. (b) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.-N. *Org. Lett.* **2008**, *10*, 3543–3546. (c) Choi, Y. L.; Yu, C.-M.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2009**, *74*, 3948–3951. (d) Goh, Y.-H.; Kim, G.; Kim, B. T.; Heo, J.-N. *Heterocycles* **2010**, *80*, 669–677.

Table 3. Scope of the One-Pot Synthesis of Dibenzo[*b*,*f*]oxepin[a]



7 8 10

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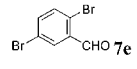
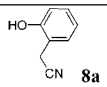
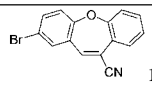
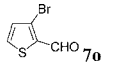
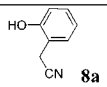
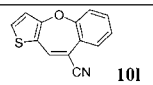
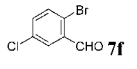
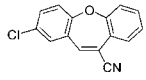
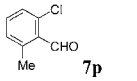
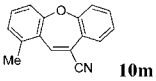
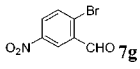
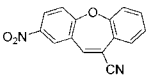
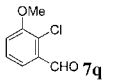
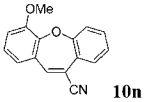
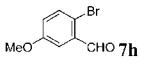
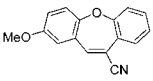
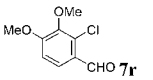
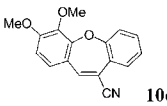
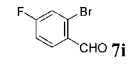
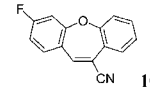
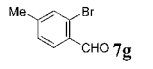
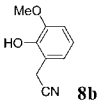
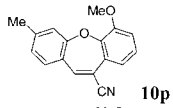
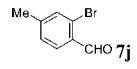
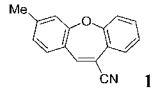
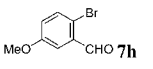
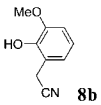
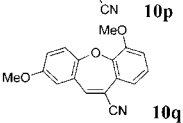
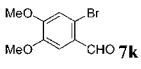
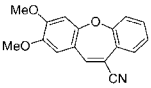
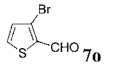
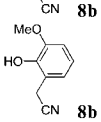
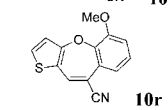
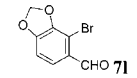
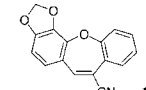
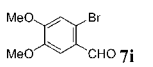
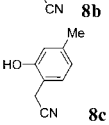
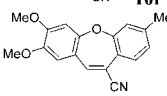
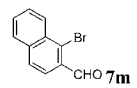
1	 7e	 8a	 10b	93	11	 7o	 8a	 10l	82
2	 7f	8a	 10c	93	12	 7p	8a	 10m	70[c,d]
3	 7g	8a	 10d	73	13	 7q	8a	 10n	80
4	 7h	8a	 10e	81	14	 7r	8a	 10o	66[c,d]
5	 7i	8a	 10f	55	15	 7g	 8b	 10p	90[d]
6	 7j	8a	 10g	77	16	 7h	 8b	 10q	76[d]
7	 7k	8a	 10h	72[c]	17	 7o	 8b	 10r	91[d]
8	 7l	8a	 10i	58[c]	18	 7i	 8c	 10s	61[d]
9	 7m	8a	10j	72	19	7f	8d	10t	57[d]
10	7n	8a	10k	64	20	7n	8e	10u	75[d]

[a] Reaction conditions: halobenzaldehyde **7** (0.72 mmol, 1.2 equiv), phenylacetonitrile **8** (0.6 mmol), Cs_2CO_3 (1.2 mmol, 2.0 equiv), molecular sieves (4 Å, 300 mg), toluene (3 mL), 130 °C, 24 h. [b] Isolated yield. [c] Reaction temperature of 150 °C. [d] Reaction time of 48 h.

Based on the electronic properties of the substrates, we thought that pathway A would be favored, primarily due to both the higher nucleophilicity of phenol **8a** and the increased electrophilicity of halobenzaldehydes **7**. After screening numerous reaction conditions for pathway A using 2-bromobenzaldehyde (**7c**), we found that Cs_2CO_3 in pyridine at 130 °C gave the best result (Table 1, entry 3).

Other halo-substituents (**7a**–**b**, **d**) for the ether formation gave similar results, producing **10a** with excellent yields (entries 1, 2, and 4). Surprisingly, aldol condensation was faster than aryl ether formation, a result that was confirmed by the isolation of intermediate **9** under mild reaction conditions. As expected, pathway B was less effective and provided less of the desired product, **10a**, with yields in the range of 21% to 59% (Table 1, entries 5–8), even at a higher reaction temperature of 150 °C. A comparison of the reaction yields from halo-substituted benzaldehydes **12a**–**d** indicated a significant halogen dependence in the following order: F > Cl ≈ Br > I. We believe that this observation supports the hypothesis that the aryl ether formation proceeds via the S_NAr mechanism.[19]

While exploring the substrate scope, we found that the reaction of 2,5-dibromobenzaldehyde (**7e**) with **8a**

(18) For a review of the transition-metal-free reaction, see: (a) Shirakawa, E.; Hayashi, T. *Chem. Lett.* **2012**, *41*, 130–134. For recent representative examples of the C–O bond formation, see: (b) Jalalian, N.; Ishikawa, E. E.; Silva, L. F., Jr.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552–1555. (c) Li, F.; Wang, Q.; Ding, Z.; Tao, F. *Org. Lett.* **2003**, *5*, 2169–2171. (d) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99–102. For C–N bond formation, see: (e) Thomé, I.; Bolm, C. *Org. Lett.* **2012**, *14*, 1892–1895. (f) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515–3517. (g) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403–1412. (h) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654–660.

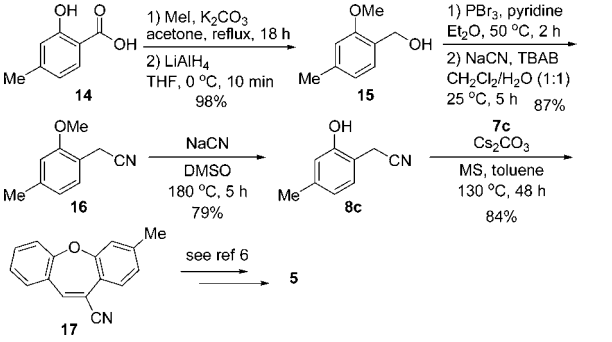
provided a ~1:1 mixture of the cyclized products **10b** and **13b** due to the concomitant isomerization of the nitrile group, as depicted in Table 2.[20]

The structure of **10b** was clearly elucidated by X-ray crystallography. When using **7f** with a 5-chloro substituent, nitrile migration also occurred to give a mixture of **10c** and **13c**[21] in a similar ratio (Table 2, entry 1). We first thought that the nitrile migration would be caused by H_2O formed during the aldol condensation. Consequently, the reaction of **7f** with **8a** in the presence of molecular sieves resulted in the suppression of the nitrile migration, yielding products in a 1:0.2 ratio (entry 2). When the solvent was changed to toluene, the migration still occurred but at a reduced ratio (entry 3). Finally, we were pleased to find that the use of molecular sieves in toluene could completely prevent this migration, although the reaction was slower (entries 4–5).

To further extend the scope, the optimized protocol was employed to obtain various dibenzo[*b*,*f*]oxepins from a broad range of substituted 2-bromo- and 2-chlorobenzaldehydes and (2-hydroxyphenyl)acetonitriles. A variety of both electron-withdrawing and -donating substituents were well tolerated, and the results are summarized in Table 3. When highly electron-rich dimethoxy and dioxalyl groups were used, an elevated reaction temperature was needed for complete conversion (entries 7–8 and 14). It is noteworthy that sterically hindered *o*-methyl and *o*-methoxy groups could be added with excellent yields, although a longer reaction time at a higher temperature was required for these reactions (entries 12–14 and 15–17). Notably, the use of aryl bromides or chlorides such as **7** is important because most of these compounds are commercially available at low cost or can be easily prepared.

With a highly efficient protocol in hand, our attention turned to the formal synthesis of the angiotensin II antagonist **5** on a gram scale (Scheme 1).[6]

Scheme 1. Synthesis of the Key Intermediate **17** of Compound **5**



The requisite starting phenylacetonitrile **8c** was easily prepared using straightforward methodologies from benzoic acid **14**. The methylation of **14** followed by the reduction of the corresponding methyl ester provided benzyl alcohol **15** with an excellent yield.[22,23] The sequential bromination–cyanization of **15** produced (2-methoxyphenyl)acetonitrile **16** with a 87% yield.[24] The demethylation of **16** with NaCN provided phenol **8c**,[25] which was subjected to the optimized one-pot base-mediated cyclization to furnish dibenzo[*b*,*f*]oxepin **17** with a good yield. Thus, the key intermediate **17** was prepared in six steps with a 56.6% overall yield.[26]

In summary, we developed a one-pot transition-metal-free, base-mediated synthesis of dibenzo[*b*,*f*]oxepins from substituted 2-halobenzaldehydes and (2-hydroxyphenyl)-acetonitriles. Importantly, this protocol is applicable to a wide range of 2-bromo- and 2-chloro-substituted benzaldehydes. Additionally, we demonstrated the synthesis of the key intermediate **17** on a gram scale. Further applications of this method for the synthesis of medicinally useful compounds are currently being investigated.

Acknowledgment. Financial support provided by the KRICT and Ministry of Knowledge Economy, Korea is gratefully acknowledged.

Supporting Information Available. Experimental procedures and NMR spectra for all compounds, including a CIF file of **10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(19) For reviews of S_NAr ether formation: (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273–412. (b) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1–32. (c) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045–5065.

(20) Isomerization of nitrile: (a) Ayub, K.; Zhang, R.; Robinson, S. G.; Twamley, B.; Williams, R. V.; Mitchell, R. H. *J. Org. Chem.* **2008**, *73*, 451–456. (b) Feng, L; Kumar, D.; Kerwin, S. M. *J. Org. Chem.* **2003**, *68*, 2234–2242.

(21) Dibenzo[*b*,*f*]oxepins **13c** was identical with the synthetic compound, which was obtained in 92% yield by the reaction of **7c** with **8e** under the optimized conditions.

(22) (a) Snider, B. B.; Gao, X. *J. Org. Chem.* **2005**, *70*, 6863–6869. (b) Itoh, Y.; Kitaguchi, R.; Ishikawa, M.; Naito, M.; Hashimoto, Y. *Bioorg. Med. Chem.* **2011**, *19*, 6768–6778.

(23) Gensini, M.; Altamura, M.; Dimoulas, T.; Fedi, V.; Giannotti, D.; Giuliani, S.; Guidi, A.; Harmat, N. J. S.; Meini, S.; Nannicini, R.; Pasqui, F.; Tramontana, M.; Triolo, A.; Maggi, C. A. *ChemMedChem* **2010**, *5*, 65–78.

(24) Kelley, J. L.; Linn, J. A.; Selway, J. W. T. *J. Med. Chem.* **1989**, *32*, 1757–1763.

(25) McCarthy, J. R.; Moore, J. L.; Cregge, R. J. *Tetrahedron Lett.* **1978**, *52*, 5183–5186.

(26) According to the procedure reported by Kiyama and co-workers (ref 6), the intermediate **17** was prepared from 3-methylphenol and 2-chloro-5-nitrobenzaldehyde in 12 steps with a 12.8% overall yield.