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Phenylboronic Acid Mediated Triple Condensation Reactions of Phloroglucinol and Unsaturated Carbonyl Compounds

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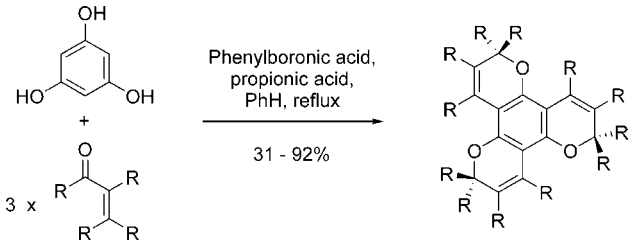
ABSTRACT



A remarkable phenylboronic acid mediated triple condensation reaction of phloroglucinol (1,3,5-trihydroxybenzene) with a series of α,β-unsaturated carbonyl compounds is reported. This experimentally simple reaction afforded novel C_3-symmetric 2*H*-chromene derivatives. These derivatives represent structural analogues of the natural product xyloketal A, which has been reported to be a potent inhibitor of acetylcholine esterase.

The isolation and structural characterization of the natural products xyloketal A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**), from a mangrove fungus of the *Xylaria* species, was reported by Lin and co-workers in 2001 (Figure 1).[1] Xyloketal A (**1**) has a novel chiral, C_3-symmetric molecular structure and was shown to be a potent inhibitor of acetylcholine esterase. We have previously reported the synthesis of (±)-11-norxyloketal D, the first total synthesis of (±)-xyloketal D (±)-**4**, and asymmetric syntheses of this natural product and its enantiomer.[2] In addition, we have also described model studies toward the total synthesis of xyloketal A (**1**).[2] These syntheses involved the cycloaddition reactions of appropriately functionalized *ortho*-quinone methides and dihydrofurans as a key step. Recently, Krohn and co-workers have reported an alternative asymmetric synthesis of (−)-xyloketal

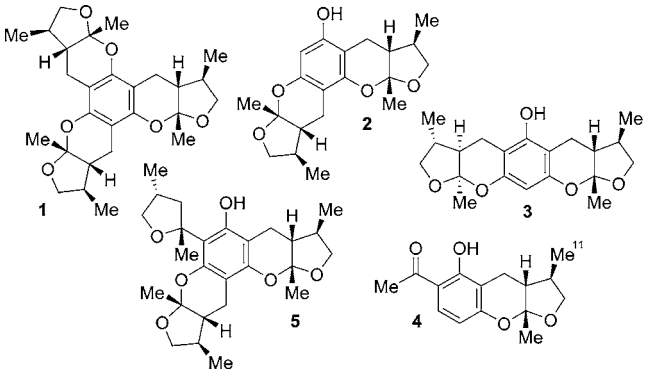


Figure 1. Xyloketal A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**).

(1) Lin, Y.; Wu, X.; Feng, S.; Jiang, G.; Luo, J.; Zhou, S.; Vrijmoed, L. L. P.; Jones, E. B. G.; Krohn, K.; Steingröver, K.; Zsila, F. *J. Org. Chem.* **2001**, *66*, 6252.

(2) (a) Pettigrew, J. D.; Bexrud, J. A.; Freeman, R. P.; Wilson, P. D. *Heterocycles* **2004**, *62*, 445. (b) Pettigrew, J. D.; Freeman, R. P.; Wilson, P. D. *Can. J. Chem.* **2004**, *82*, 1640.

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D (**4**) from (3*R*)-3-methylbutyrolactone and 2,4-dihydroxyacetophenone as well as model studies toward the total synthesis of xyloketal A (**1**).[3]

Our continued interest in the total synthesis of xyloketal A (**1**) has led us to consider that it could be prepared from the C_3-symmetric 2*H*-chromene derivative **6** by a stereoselective hydrogenation reaction (Figure 2). Here it would

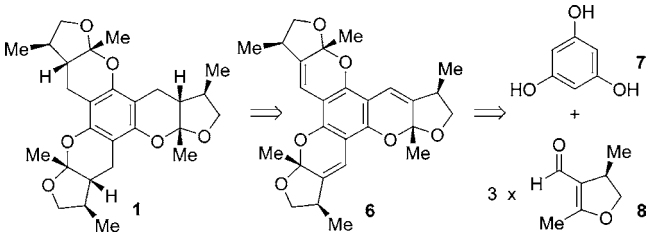
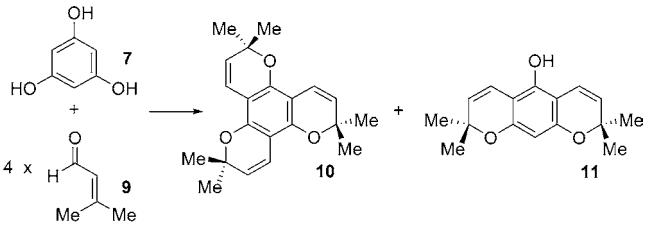


Figure 2. Retrosynthetic analysis of xyloketal A (**1**).

be expected that hydrogen would be added to the convex face of the molecule. The chromene derivative **6** could be prepared from phloroglucinol (1,3,5-trihydroxybenzene) **7** and 3 equiv of the α,*β*-unsaturated aldehyde **8**. This process would involve three electrophilic aromatic substitution reactions and three subsequent dehydrative-cyclization reactions.[4]

In this paper, we describe an unprecedented phenylboronic acid mediated triple condensation reaction of phloroglucinol **7** with a series of α,*β*-unsaturated carbonyl compounds. Our initial studies involved the attempted condensation reaction of phloroglucinol **7** (1 equiv) with senecialdehyde (3-methyl-2-butenal) **9** (4 equiv) (Table 1).[5] We discovered that the use of phenylboronic acid (0.25 equiv), in the presence of propionic acid in benzene at reflux with azeotropic removal of water, afforded a mixture of the condensation products **10** and **11** in good yield (entry 1).[6,7] These reaction products have the core ring systems of xyloketal A (**1**) and C (**3**),

Table 1. Reaction of Phloroglucinol **7** with Senecialdehyde **9**



entry	reagents and conditions[a]	yield (%)[b] 10	11
1	$PhB(OH)_2$ (0.25 equiv), $CH_3CH_2CO_2H$, PhH	55	39
2	$PhB(OH_2)$ (1 equiv), $CH_3CH_2CO_2H$, PhH	74	23
3	$PhB(OH)_2$ (2 equiv), $CH_3CH_2CO_2H$, PhH	81	11
4	**$PhB(OH)_2$ (3 equiv), $CH_3CH_2CO_2H$, PhH**	**92**	**6**
5	$PhB(OH)_2$ (3 equiv), PhH	tr	tr
6	$CH_3CH_2CO_2H$, PhH	tr	tr
7	$B(OH)_3$ (0.25 equiv), $CH_3CH_2CO_2H$, PhH	45	30
8	B(OH)3 (1 equiv), $CH_3CH_2CO_2H$, PhH	50	25
9	$B(OH)_3$ (3 equiv), $CH_3CH_2CO_2H$, PhH	44	27

[a] All reactions were performed with 1 equiv of phloroglucinol **7** and 4 equiv of senecialdehyde **9** at reflux in a Dean−Stark trap for ∼22 h. [b] Isolated yield after separation and purification by flash chromatography.

respectively. Increasing the amount of phenylboronic acid used in this reaction led to an increase in the amount of the triple condensation product **10** that was formed (entries 2−4).[8] Only trace amounts of these reaction products were formed when propionic acid or phenylboronic acid were omitted from the reaction mixture (entries 5 and 6). The reaction could also be effected with boric acid (entries 7−9).[7a] However, the yields of the reaction products were lower.

In the example where 3 equiv of phenylboronic acid is employed (entry 4), presumably three electrophilic aromatic substitution reactions occur prior to the cyclization reactions. The formation of significant quantities of the disubstituted product **11**, when less than 3 equiv of phenylboronic acid is used, can be attributed to the formation and subsequent cyclization reactions of intermediate **12** (Figure 3).[6a] The

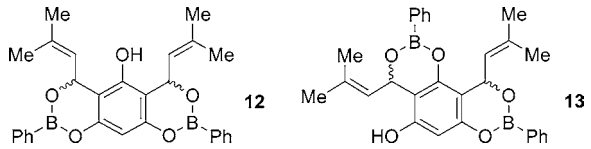


Figure 3. Borate ester reaction intermediates **12** and **13**.

disubstituted product **11** cannot undergo a subsequent phenylboronic acid directed electrophilic aromatic substitu-

(3) (a) Krohn, K.; Riaz, M. *Tetrahedron Lett.* **2004**, *45*, 293. (b) Krohn, K.; Riaz, M.; Flörke, U. *Eur. J. Org. Chem.* **2004**, 1261.

(4) For reviews on the synthesis of 2*H*-chromene derivatives, see: (a) Merlini, L. *Adv. Heterocycl.* Chem. **1975**, *18*, 159. (b) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, pp 737−883. (c) Lévai, A.; Tímár, T.; Sebök, P.; Eszenyi, T. *Heterocycles* **2000**, *53*, 1193. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 734 and references therein. (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939 and references therein.

(5) Our preliminary investigations also involved the use of calcium hydroxide in methanol (Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768), magnesium sulfate and allylamine in tetrahydrofuran (Paduraru, M. P.; Wilson, P. D. *Org. Lett.* **2003**, *5*, 4911), and calcium chloride hydrate and triethylamine in ethanol (Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481) as reagents. However, these reactions afforded complex mixtures of products that contained only trace amounts of compounds **10** and **11**.

(6) For references on the use of phenylboronic acid to prepare 2*H*-chromenes, see: (a) Bissada, S.; Lau, C. K.; Bernstein, M. A.; Dufresne, C. *Can. J. Chem.* **1994**, *72*, 1866. (b) Chauder, B. A.; Lopes, C. C.; Lopes, R. S. C.; da Silva, A. J. M.; Snieckus, V. *Synthesis* **1998**, 279.

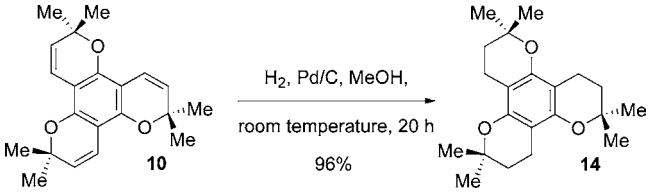
(7) For references regarding the pioneering use of boric acid and phenylboronic acid in *ortho*-selective electrophilic aromatic substitution reactions of phenols with aldehydes, see: (a) Peer, H. G. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 825. (b) Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365 and references therein.

(8) Heating phloroglucinol **7** (1 equiv) with senecialdehyde **9** (4 equiv) and propionic acid in toluene at 80 °C, without the azeotropic removal of water (or in the presence of 4 Å molecular sieves), only afforded trace amounts of the desired products **10** and **11**.

tion reaction as the *ortho*-positions (with respect to the remaining phenol moiety) are blocked.[7b,9] Of note, the unsymmetrical disubstituted intermediate **13** (or the product formed from subsequent cyclization reactions) can react further with senecialdehyde **9**.

The structure of the chromene derivative **10** was confirmed on conversion of this compound to the known hexahydro-analogue **14** by means of a hydrogenation reaction (Scheme 1).[10]

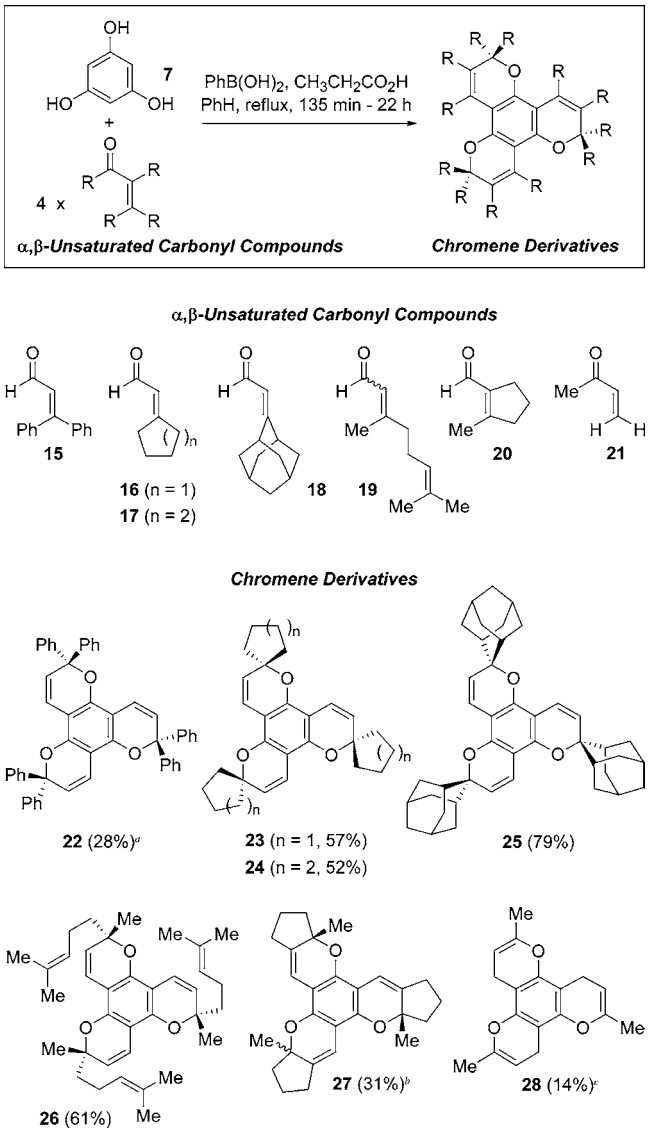
Scheme 1. Hydrogenation Reaction of Compound **10**



To examine the generality of this efficient and novel reaction, a series of α,*β*-unsaturated carbonyl compounds were condensed with phloroglucinol **7** (Scheme 2). Commercially available *β*-phenylcinnamaldehyde **15** reacted rapidly (<150 min) with phloroglucinol **7** under the optimized reaction conditions and afforded the triple condensation product **22**. As this particular compound proved to be unstable to purification (using flash chromatography on silica gel), the crude reaction mixture was hydrogenated directly to afforded the corresponding hexahydro-analogue in 28% overall yield. The reaction of cyclopentylideneacetaldehyde **16** and cyclohexylideneacetaldehyde **17** with phloroglucinol **7** afforded the corresponding spirocyclic triple condensation products **23** (57%) and **24** (52%), respectively.[11] Moreover, reaction of the adamantanone-derived α,*β*-unsaturated aldehyde **18** afforded the remarkable product **25** in excellent yield.[11] Of note, the yields of these synthetic transformations are particularly encouraging when one considers that they involve, minimally, six individual reactions.[6a]

When the commercially available unsymmetrical α,*β*-unsaturated aldehyde **19** (citral, *E*:*Z* = ~2:1) was employed, the triple condensation product **26** was isolated. Interestingly, this chromene derivative was formed (based on inspection of the ^{1}H NMR spectrum of the crude reaction product) and isolated as a single C_3-symmetric diastereoisomer. In addition, reaction of 2-methylcyclopentene-1-carboxaldehyde **20** with phloroglucinol **7** afforded the heptacyclic xyloketal A analogue **27**.[12] In this case, the C_3-symmetric diastereoisomer was the minor reaction product. Finally, the reaction of

Scheme 2. Condensation Reactions of Phloroglucinol **7** with α,*β*-Unsaturated Carbonyl Compounds



[a] Isolated as the corresponding hexahydro-analogue following hydrogenation (H_2, Pd/C MeOH, 18 h). [b]Isolated by flash chromatography as an inseparable mixture of two diastereoisomers (α:*β*, 20:1). [c]In this instance, using an α,*β*-unsaturated ketone as a reaction precursor, an isomeric 4*H*-chromene derivative was isolated from a complex mixture of products.

methyl vinyl ketone **21** with phloroglucinol **7** led to the isolation of the isomeric 4*H*-chromene derivative **28**, in relatively low yield, from a complex mixture of reaction products. In this instance, the reaction substrate employed was an α,*β*-unsaturated ketone and presumably the isolated product was formed by a different reaction mechanism. Of note, the corresponding double condensation reaction products were not isolated from any of the above condensation reactions.

(9) For additional discussion on the "*ortho*-specific" electrophilic aromatic substitution reaction of phenols with aldehydes via 1,3,2-benzodioxaborins, see: Lau, C. K.; Williams, H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Bélanger, P. C. *Can. J. Chem.* **1989**, *67*, 1384.

(10) (a) Wolfrom, M. L.; Wildi, B. S. *J. Am. Chem. Soc.* **1951**, *73*, 235. (b) Al-Khayat, I.; Dean, F. M.; Parvizi, B.; Sutcliffe, L. H. *J. Chem. Soc., Chem. Commun.* **1979**, 213.

(11) The aldehydes **16**−**18** were prepared in three steps from cyclopentanone, cyclohexanone and adamantanone, based on a literature procedure; see: Snowden, R. L.; Linder, S. M.; Würst, M. *Helv. Chim. Acta* **1989**, *72*, 892.

(12) The aldehyde **20** was prepared in four steps from 1-methylcyclohexene on modification of a literature procedure; see: (a) White, J. D.; Ruppert, J. F.; Avery, M. A.; Torii, S.; Nokami, J. *J. Am. Chem. Soc.* **1981**, *103*, 1813. (b) Hudlicky, T.; Ranu, B. C.; Naqvi, S. M.; Srnak, A. *J. Org. Chem.* **1985**, *50*, 123.

In conclusion, an unprecedented phenylboronic acid mediated triple condensation reaction of phloroglucinol **7** with a series of α,β-unsaturated aldehydes has been developed. This experimentally simple reaction afforded novel C_3-symmetric chromene derivatives that represent structural analogues of the natural product xyloketal A (**1**). Current investigations involve the synthesis and triple condensation reactions of additional α,β-unsaturated aldehydes. In addition, current studies are also being directed toward the synthesis of aldehyde **8** (Figure 2). This compound is required for our proposed synthesis of xyloketal A (**1**). The results of these investigations will be reported in due course.

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Supporting Information Available: Detailed experimental procedures and full product characterization data for all of the compounds synthesized; ^{1}H and ^{13}C NMR spectra for compounds **10**, **11**, **14**, **23**−**28**, and the hexahydro-analogue of compound **22**; and selected preparative details and characterization data for the α,β-unsaturated aldehydes **16**−**18** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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