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A Catalyst-Free One-Pot Construction of Skeletons of 5-Methoxyseselin and Alloxanthoxyletin in Water

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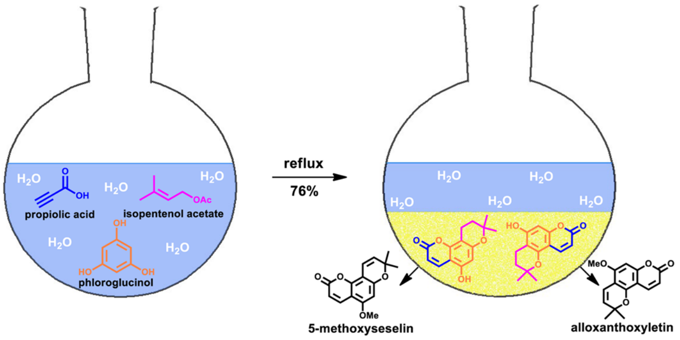
ABSTRACT



In refluxing water and without an additional catalyst, electron-rich phenols could react with alkynoic acids or alkynoates to provide coumarin structures. The skeletons of two natural pyranocoumarins, 5-methoxyseselin and alloxanthoxyletin, could be constructed (total yield up to 76%) in an aqueous multicomponent reaction in which isoprenyl acetate, propiolic acid, and phloroglucinol were simply mixed and refluxed in water.

Multicomponent reactions (MCRs) in which three or more small building blocks react together following their intrinsic reactivities offer a quick solution in the syntheses of complicated molecules.[1] Most MCRs require activation by a catalyst and are operated in organic solvents, but it was found that several MCRs, such as the Passerini and Ugi reaction, could efficiently proceed in aqueous solution without an additional catalyst.[2] Actually, in Robinson's synthesis of bridged bicyclic alkaloid tropinone reported in 1917, which was later regarded as the pioneering work of biomimetic total synthesis, glutaraldehyde, methylamine, and calcium acetone dicarboxylate were simply mixed in an aqueous buffer solution and the catalyst-free MCR produced the skeleton of tropinone with great simplicity (Scheme 1).[3] The aqueous MCRs in the literature normally use relatively reactive substrates such as aldehydes, amines, 1,3-dicarbonyl compounds, and 1,3-dinitriles. Nevertheless, examples of aqueous MCRs using less reactive substrates such as arenes, olefins, and alkynes are quite limited.[1g,2,4] Furthermore, after Robinson's synthesis of tropinone, the catalyst-free one-pot synthesis of the skeleton of natural products in aqueous solution was rarely reported and it is of general interest to broaden the scope of the natural products that can be accomplished in nature's solvent.[5]

Pyranocoumarins with a phloroglucinol core such as (+)-calanolide A, (+)-pseudocordatolide C, and nordentatin have diverse bioactivities such as anti-HIV and antibacterial activities.[6] The angled 5-methoxyseselin (**1**) and alloxanthoxyletin (**2**) are active antibacterial agents, and linear xanthoxyletin (**3**) is used in the perfume industry (Figure 1).[7] The traditional methods for syntheses of

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(1) For reviews on MCRs, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Syamala, M. *Org. Prep. Proced. Int.* **2009**, *41*, 1. (c) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (d) Yu, J.; Shi, F.; Gong, L. -Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (e) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem.—Asian J.* **2010**, *5*, 2318. (f) Slobbe, P.; Ruijter, E.; Orru, R. V. A. *Med. Chem. Commun.* **2012**, *3*, 1189. (g) Gu, Y. *Green Chem.* **2012**, *14*, 2091. (h) Eckert, H. *Molecules* **2012**, *17*, 1074.

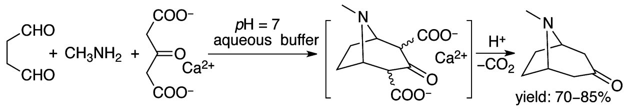
(2) (a) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444. (b) Pirrung, M. C.; Sarma, K. D. *Synlett* **2004**, 1425. (c) Pirrung, M. C.; Sarma, K. D. *Tetrahedron* **2005**, *61*, 11456. (d) Pirrung, M. C.; Wang, J. *J. Org. Chem.* **2009**, *74*, 2958.

(3) Robinson, R. *J. Chem. Soc., Trans.* **1917**, *111*, 762.

(4) Kumaravel, K.; Vasuki, G. *Curr. Org. Chem.* **2009**, *13*, 1820.

10.1021/ol401581p

Scheme 1. One-Pot Synthesis of Tropinone in Aqueous Solution



coumarins, such as the Perkin, Pechmann, or Knoevenagel reaction, were usually conducted under harsh reaction conditions.[8] The modern atom-economic syntheses of coumarins by hydroarylation reactions of alkynoates were carried out under mild conditions, but using expensive transition metals such as Pd,[7i,9a−e] Pt,[9f,g] and Au[9h] as catalysts. It was also reported that inexpensive metal salts such as Fe[10a,b] or Zn[7j,10c−e] could also be efficient catalysts. Due to our long-lasting interest in water-promoted organic reactions,[11] we investigated the reactions of electron-rich phenols with alkynoic acids or alkynoates in water and reported herein that the hydroarylation reactions of propiolic acid or propiolate worked in refluxing water and gave coumarin products in high yields. We further presented that the skeletons of two natural pyranocoumarins could be constructed in one step through an aqueous tricomponent reaction.

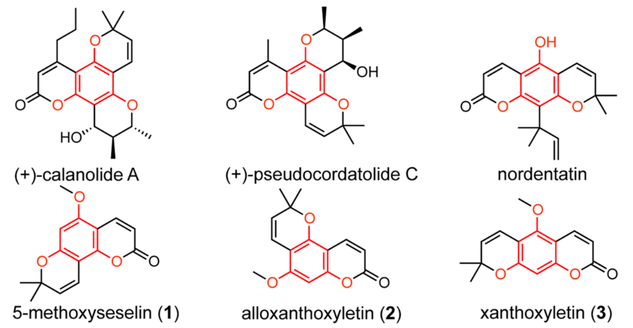


Figure 1. Natural pyranocoumarins.

Since many coumarins contain a phloroglucinol (**4a**) core (Figure 1),[6] the preliminary trial was carried out by adding **4a** and 1.2 equiv of propiolic acid (**5a**) in water (both of the two reactants can dissolve in water).[12] As the reaction proceeded under refluxing conditions, 5,7-dihydroxycoumarin (**6a**, a natural coumarin first isolated in 1982,[13] 83% yield) formed as a light yellow precipitate (entry 1, Table 1). The minor product of reaction was bicoumarin **7** (5% yield, Scheme 2). At 75 °C, only a 57% yield of **6a** was obtained with 61% conversion of phloroglucinol (entry 2). The reaction barely took place in room-temperature water or in refluxing methanol (entries 3, 4). 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) also has high ionizing power like water but can dissolve most organic compounds. When replacing water with the mixed solvent of HFIP and H_2O (v:v = 1:1), a 63% yield of **6a** was obtained with 64% conversion of phloroglucinol (entry 5). We also tested the neat conditions by heating solid **4a** in liquid **5a** in an oil bath at 110 °C. It turned out that the neat reaction gave a parallel yield with that held in aqueous solution (entry 6). For practical reasons and because of our interest of investigating the possible role of water in the natural occurrence of complicated natural products, water was chosen as the reaction medium in the current study. When using 3 equiv of propiolic acid, all phloroglucinol could be converted within 4 h under refluxing conditions (entry 7) and the cleaner but slower reaction at 75 °C gave the highest yield of 96% (entry 8). The reaction using ethyl propiolate (**5b**) proceeded equally well in refluxing water and gave an 81% yield of **6a** after 24 h (entry 9). A control experiment showed that this reaction did not proceed under neat conditions. The reaction of monomethylated phloroglucinol **4b** was slower compared with **4a**, which was probably due to its lower aqueous solubility (entry 10). Notably, the regioselectivity of the

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(5) The catalyst-free one-pot synthesis of natural products in alcoholic solvents: (a) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505. (b) De Laszlo, S. E.; Williard, P. G. *J. Am. Chem. Soc.* **1985**, *107*, 199. (c) Tsuchida, K.; Mizuno, Y.; Ikeda, K. *Heterocycles* **1981**, *15*, 883. The catalyst-free one-pot synthesis of natural-product-like molecules in water: (d) Santra, S.; Andreana, P. R. *Org. Lett.* **2007**, *9*, 5035. (e) De Silva, R. A.; Santra, S.; Andreana, P. R. *Org. Lett.* **2008**, *10*, 4541. (f) Santra, S.; Andreana, P. R. *J. Org. Chem.* **2011**, *76*, 2261. (g) Santra, S.; Andreana, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9418. (h) Gu, Y. -L.; De Sousa, R.; Frapper, G.; Bachmann, C.; Barrault, J.; Jérôme, F. *Green Chem.* **2009**, *11*, 1968.

(6) Venugopala, K. N.; Rashmi, V.; Odhav, B. *Biomed. Res. Int.* **2013**10.1155/2013/963248.

(7) The previous total syntheses of pyranocoumarins **1**, **2**, **3**: (a) Ganguly, A. K.; Joshi, B. S.; Kamat, V. N.; Manmade, A. H. *Tetrahedron* **1967**, *23*, 4777. (b) Ahluwalia, V. K.; Bhat, M. K.; Prakash, C.; Bala, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1070. (c) Tsukayama, M.; Sakamoto, T.; Horie, T.; Masumura, M.; Nakayama, M. *Heterocycles* **1981**, *16*, 955. (d) Murray, R. D. H.; Jorge, Z. D. *Tetrahedron Lett.* **1983**, *24*, 3403. (e) Murray, R. D. H.; Jorge, Z. D. *Tetrahedron* **1984**, *40*, 3129. (f) Takeuchi, Y.; Xie, L.; Cosentino, L. M.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2573. (g) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1999**, *42*, 2662. (h) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (i) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518. (j) Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A.-L.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 78.

(8) (a) Sethna, S. M.; Shah, N. M. *Chem. Rev.* **1945**, *36*, 1. (b) Fedorov, A. Y.; Nyuchev, A. V.; Beletskaya, I. P. *Chem. Heterocycl. Compd.* **2012**, *48*, 166 and the references cited therein.

(9) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074. (c) Kitamura, T.; Yamamoto, K.; Kotani, M.; Oyamada, J.; Jia, C.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1889. (d) Aoki, S.; Oyamada, J.; Kitamura, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 468. (e) Oyamada, J.; Jia, C.; Fujiwara, Y.; Kitamura, T. *Chem. Lett.* **2002**, 380. (f) Oyamada, J.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6918. (g) Oyamada, J.; Kitamura, T. *Tetrahedron Lett.* **2005**, *46*, 3823. (h) Shi, Z.-J.; He, C. *J. Org. Chem.* **2004**, *69*, 3669.

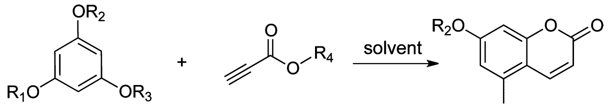
(10) (a) Li, R.; Wang, S. R.; Lu, W. *Org. Lett.* **2007**, *9*, 2219. (b) Kutubi, M. S.; Hashimoto, T.; Kitamura, T. *Synthesis* **2011**, *8*, 1283. (c) Kaufman, K. D.; Kelly, R. C. *J. Heterocycl. Chem.* **1965**, *2*, 91. (d) Leão, R. A. C.; de Moraes, P. F.; Pedro, M. C. B. C.; Costa, P. R. R. *Synthesis* **2011**, 3692. (e) Kalyanam, N.; Nagarajan, A.; Majeed, M. *Synth. Commun.* **2004**, *34*, 1909.

(11) (a) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270. (b) Wang, J.; Liang, Y.-L.; Qu, J. *Chem. Commun.* **2009**, 5144. (c) Li, G.-X.; Qu, J. *Chem. Commun.* **2010**, 2653. (d) Xu, Z.-B.; Qu, J. *Chem.—Eur. J.* **2013**, *19*, 314.

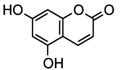
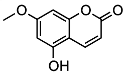
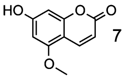
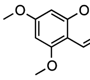
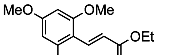
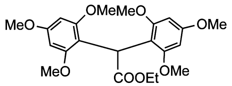
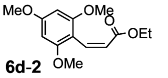
(12) The water we used to carry out the reactions was double distilled water. The pH value of the double distilled water is 5.5−6 because of the dissolved CO_2. The possible effect of dissolved CO_2 in water was evaluated by conducting the reactions under a nitrogen atmosphere with degassed water, but no difference in reactivity was found.

(13) Batsurén, D.; Batirov, É. Kh.; Malikov, V. M. *Chem. Nat. Compd.* **1982**, *18*, 616.

Table 1. Reactions of Phloroglucinol or Its Ethers with Propiolic Acid or Ethyl Propiolate



4 a $R_1 = R_2 = R_3 = H$
4 b $R_1 = CH_3$, $R_2 = R_3 = H$
4 c $R_1 = R_2 = CH_3$, $R_3 = H$
4 d $R_1 = R_2 = R_3 = CH_3$
5 a $R_4 = H$
5 b $R_4 = CH_2CH_3$

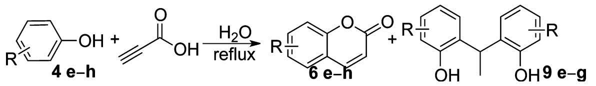
entry	4	5 (equiv)	solvent/temp	time (h)	product	yield/conv (%)[a,b]
1	**4a**	**5a** (1.2)	H_2O/reflux	24	 **6a**	83/100
2	**4a**	**5a** (1.2)	H_2O/75°C	24	**6a**	57/61
3	**4a**	**5a** (1.2)	H_2O/25°C	24	**6a**	4/4
4	**4a**	**5a** (1.2)	MeOH/reflux	24	**6a**	3/3
5	**4a**	**5a** (1.2)	H_2O:HFIP (v:v = 1:1)/reflux	24	**6a**	63/64
6	**4a**	**5a** (1.2)	neat/110°C	24	**6a**	86/100
7	**4a**	**5a** (3.0)	H_2O/reflux	4	**6a**	82/100
8	**4a**	**5a** (3.0)	H_2O/75°C	15	**6a**	96/100
9	**4a**	**5b** (3.0)	H_2O/reflux	24	**6a**	81/86[c]
10	**4b**	**5a** (3.0)	H_2O/reflux	6	 **6b-1** :  **6b-2** = 1:4.3[d]	74/100
11	**4c**	**5a** (3.0)	H_2O/reflux	15	 **6c**	39/100
12	**4d**	**5b** (3.0)	HFIP/reflux	48	 **6d-1**  **8** (1%)  **6d-2**	28/31 *E*:*Z* = 1:6.2[e]

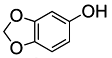
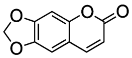
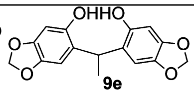
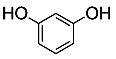
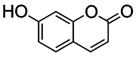
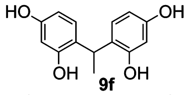
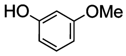
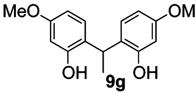
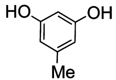
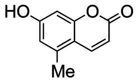
[a] General procedure: reactions were performed with 1.0 mmol of **4** and **5** in solvent (2 mL). [b] Isolated yield. [c] In water (1 mL). [d] By isolated yield. [e] By ^{1}H NMR.

formation of **6b-1** and **6b-2** (**6b-1**:**6b-2** = 1:4) was better compared with the Pd_2dba_3-catalyzed hydroarylation reaction of the similar substrates.[7i] The dimethoxy substituted **4c** reacted even worse due to its even poorer aqueous solubility. It is interesting to test if 1,3,5-trimethoxy benzene (**4d**) can react with ethyl propiolate (**5b**) in water since no acidic proton presents in both substrates and the reaction cannot be self-catalyzed. 1,3,5-Trimethoxy benzene (**4d**) does not dissolve in water, and hence no reaction took place in water. However, **4d** and **5b** did react in refluxing HFIP slowly but cleanly and gave a 1:6 mixture of **6d-1** and **6d-2** in 28% total yield and 1% of disubstituted product **8** (entry 12). Clearly, a protic solvent with high ionizing power such as HFIP could promote the hydroarylation of alkynoates.

Other electron-rich phenols could also react with propiolic acid but some of the reactions gave a different type of product (Table 2). For sesamol **4e**, a 44% yield of 4,4′-ethylidene-bisphenol **9e** was obtained as the major product. Similar products were also obtained by using resorcinol (**4f**) or *m*-guaiacol (**4g**). But for 5-methylresorcinol (**4h**), the reaction gave coumarin **6h** as the major product. The reactions between phloroglucinol and 2-butynoic acid or 3-phenylpropiolic acid did not work due to steric hindrance.

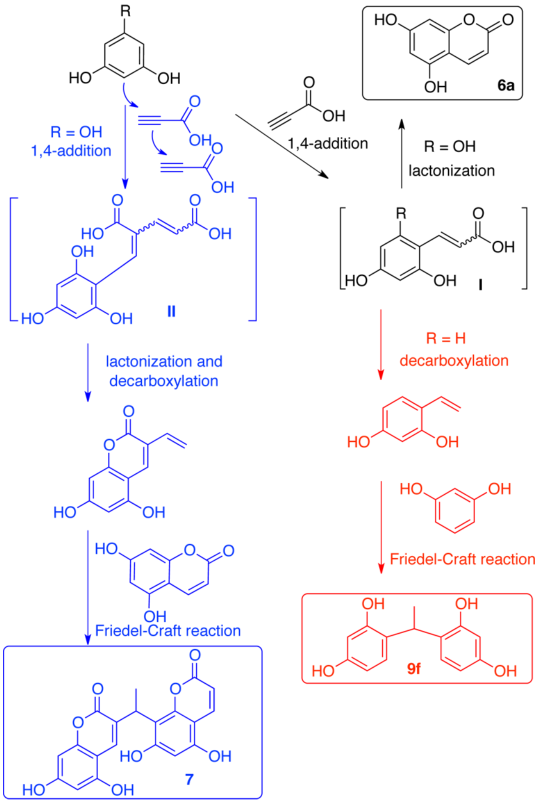
Table 2. Reactions of Other Electron-Rich Phenols with Propiolic Acid



phenol	products		time (h)	yield (%)[a,b]
 **4e**	 **6e**	 **9e**	12	**6e** (1%)/**9e** (44%)
 **4f**	 **6f**	 **9f**	21	**6f** (1%)/**9f** (27%)
 **4g**	–	 **9g**	24	**9g** (25%)
 **4h**	 **6h**	–	25	**6h** (44%)

[a] General procedure: reactions were performed with 1.0 mmol of **4** and 3 mmol of **5** in water (2 mL). [b] Isolated yield based on the quantity of **4**.

Scheme 2. Proposed Mechanism



A plausible mechanism of the reactions is drawn in Scheme 3. The electron-rich phloroglucinol attacked the triple bond of propiolic acid to form the phenyl-substituted α,β-unsaturated acid (**I**) which was immediately cyclized to give a coumarin product since no α,β-unsaturated acid was observed during the whole reaction followed by NMR techniques. However, if the phenolic hydroxyl group at the *ortho* position of the arene (such as that in **4e**, **4f**, and **4g**) is not nucleophilic enough to afford the coumarin product, the formed α,β-unsaturated acid would undergo a decarboxylation reaction[14] and produce the substituted styrene which was then attacked by another molecule of phenol to give 4,4′-ethylidene-bisphenol. The formation of 5% of byproduct **7** can be explained as being due to the direct attack of phenol at the triple bond of propiolic acid generating an anion. This anion attacks the triple bond of another molecule of propiolic acid that is nearby to give the diacid (**II**). After the lactonization and decarboxylation, the substituted styrene further reacted with coumarin formed in the reaction system and gave $C_3-C_{8'}$ linked bicoumarins.

The aqueous synthesis of coumarin could be combined with an aqueous Friedel–Crafts reaction in constructing the pyranocoumarin skeleton. The reported synthesis of 2,2-dimethylchroman (**11**) from phloroglucinol (**4a**) and isoprenyl acetate (**10**) was catalyzed by Lewis acids or Brønsted acids.[15] To our delight, this reaction proceeded in refluxing water and gave **11** in 88% yield (isoprenyl acetate (**10**) was not stable in refluxing water, so an excess amount of **4a** was needed to convert **10** in a short period of time). The isolated **11** could react with propiolic acid in refluxing water to provide a mixture of regioisomeric compounds **12**, **13**, and **14** (**12**:**13**:**14** = 1:3:0.4) with a total yield of 60% (Scheme 3). The above stepwise synthesis was then carried out as an aqueous MCR. By adding **10**, **4a**, and **5a** (**10**:**4a**:**5a** = 1:1:1.2) in water and heating the reaction mixture, a 1:3.3 mixture of regioisomers **12** and **13** (40% total yield; the amount of linear type product **14** was too small to be isolated) precipitated out as a light yellow powder. We found that 21% of **6a** and 6% of compound **15**, which is the synthetic precursor of the antibiotic natural product dipetalolactone,[16] also formed in the one-pot reaction (entry 1, Table 3). Because **6a** did not react with **10** in refluxing water and a very small amount of **11** presented in the final product, the reaction sequence in the one-pot synthesis should be as follows: **10** and **4a** first reacted and gave 2,2-dimethylchroman (**11**), which was then reacted with **5a** to give compounds **12** and **13**. Upon using an excess amount of substrates **4a** and **5a**, most of **10** was converted and the total yield of compounds **12** and **13** based on **10** was 76% (entry 5). Compounds **12** and **13** were methylated and dehydrogenated using the reported method[7i] to finish the total syntheses of 5-methoxyseselin **1** and alloxanthoxyletin **2** in three steps.

Scheme 3. Stepwise Synthesis of Pyranocoumarins in Water

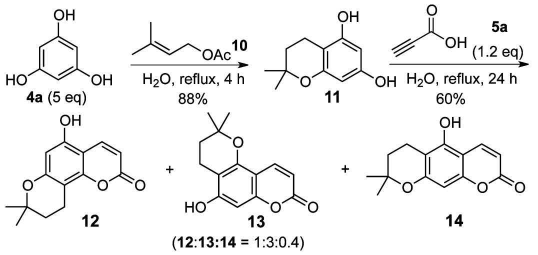
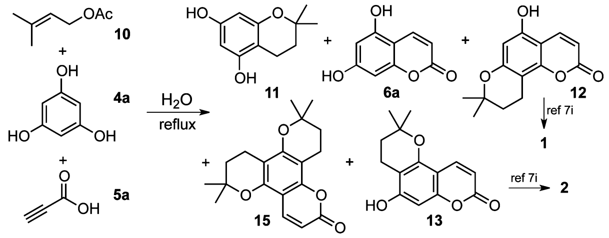


Table 3. Synthesis of Pyranocoumarins by an Aqueous MCR



entry	ratio of **10**:**4a**:**5a**	**11** (%)	**6a** (%)[c]	**15** (%)	**12**+**13** (%) (**12**:**13**)[a,b]
1	1:1:1.2	0	21	6	40 (1:3.4)
2	1:1:2	0	20	3	42 (1:3.2)
3	1:1.7:2	5	74	6	56 (1:3.3)[d]
4	1:5:4	0	71	3	71 (1:3.4)[d]
5	1:5:6	0	70	3	76 (1:3.4)[d]

[a] General procedure: 1 mmol of **10** with **4a** and **5a** were refluxed in water (2 mL). [b] Isolated yield based on the quantity of **10**. [c] Isolated yield based on the quantity of **4a**. [d] Compound **5a** was added 4 h later.

Water is an ideal solvent for MCRs involving a polar transition state/intermediate since the polarity and the ionizing power of water compared to organic solvents are far larger. For the first time, our group found that the reaction between propiolic acid (or its ester) and phloroglucinol derivatives worked in refluxing water without an additional catalyst. In an aqueous MCR, phloroglucinol, isoprenyl acetate, and propiolic acid could be self-assembled to form the skeletons of two natural pyranocoumarins. This work demonstrated the power of an aqueous MCR in the construction of the core structures of natural products, which has not been fully explored yet.

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Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Johnson, W. S.; Heinz, W. E. *J. Am. Chem. Soc.* **1949**, *71*, 2913. (b) Sinha, A. K.; Sharma, A.; Joshi, B. P. *Tetrahedron* **2007**, *63*, 960.

(15) Vece, V.; Ricci, J.; Poulain-Martini, S.; Nava, P.; Carissan, Y.; Humbel, S.; Duñach, E. *Eur. J. Org. Chem.* **2010**, *32*, 6239.

(16) (a) Sarkera, S. D.; Gray, L. I.; Waterman, P. G. *J. Nat. Prod.* **1994**, *57*, 324. (b) Sultana, N.; Sarker, S. D.; Armstrong, J. A.; Wilson, P. G.; Waterman, P. G. *Biochem. Syst. Ecol.* **2003**, *31*, 681.

The authors declare no competing financial interest.