ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: D. Wang, Z. Ma, N. Wang, C. Li, T. Wang, Y. Liang and Z. Zhang, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC04452K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/D0CC04452K

COMMUNICATION

Synthesis of 7-hydroxy-6*H*-naphtho[2,3-*c*]coumarin *via* TsOH-Mediated Tandem Reaction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Ding Wang, Zhishuang Ma, Nana Wang, Chenyu Li, Tao Wang, Yong Liang‡ and Zunting Zhang*

A concise and efficient method for the synthesis of 7-hydroxy-6*H*-naphtho[2,3-*c*]coumarin using available 1-(2-hydroxyphenyl)-2-phenylethanone and meldrum's acid has been developed. This transformation involves tandem Aldol reaction/Lactonization/ Friedel-crafts reaction to form a lactone ring and a benzene ring. It showed high atom-economical with water and acetone as the byproducts. Mechanism studies demonstrate dual roles of meldrum's acid: i) as the reagent for the tandem reaction; ii) as the catalyst for the Friedel-crafts reaction. Moreover, the hydroxyl group of 7-hydroxy-6*H*-naphtho[2,3-*c*]coumarin was further functionalized efficiently by arylethynyl, aryl, cyano groups to furnish D-π-A compounds with excellent fluorescence emissions (ΦF = 0.14–0.78).

Polycyclic conjugated coumarins are wildly found in the natural products that have significant pharmacological and biological activities.[1] And it also showed interesting applications in materials science due to its unique photophysical properties.[2] In particular, 6*H*-naphtho[2,3-*c*]coumarins, a new kind of coumarin skeleton which are subunits embedded in chartreusin-type glycosides[3] and axially chiral molecules (**Fig. 1**), have attracted considerable attention. For example, the chartreusin (**I**) was isolated from *Streptomyces chartreusis* strain and found to possess a significant anticancer and antibacterial activity.[3c] As for the material field, the chiral and fluorescent columnar mesogen (**II**) bearing a 6*H*-naphtho[2,3-*c*]coumarin could emit fluorescent blue light. This liquid crystal comprises a C_2-symmetric chiral core with two staggered aromatic planes.[2f] Because of their importance, the preparation of 6*H*-naphtho[2,3-*c*]coumarins is of interest to the synthetic chemists.

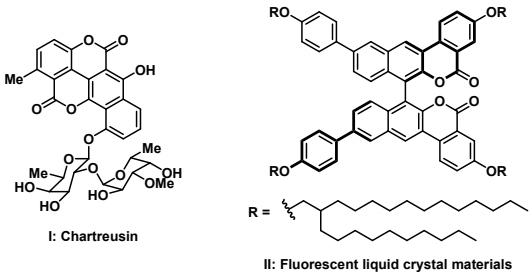
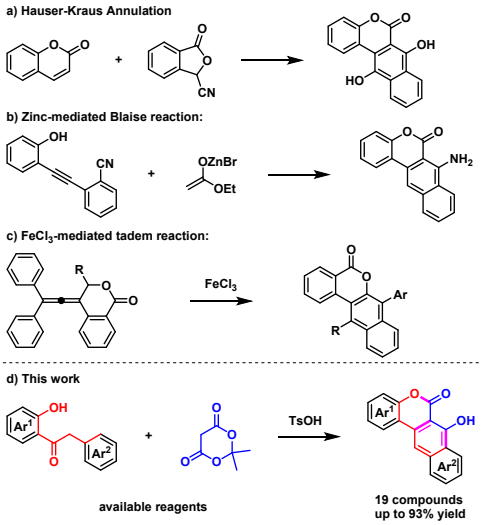


Fig. 1 Importance of polycyclic conjugated coumarins.

The general method to synthesize 6*H*-naphtho[2,3-*c*]coumarins relies on the lactonization of biaryl compounds through transition-metal-catalysed cross-coupling reactions as the key step.[4] However, tedious steps are required to prepare the aryl halides and organometallic reagents, resulting in complicated manipulation and high costs. In order to avoid these limitations, tandem reactions for construction of these frameworks using available substrates were seen as an attractive alternative. In this regard, the synthesis of 7,12-dihydroxy-6*H*-naphtho[2,3-*c*]coumarins via Hauser-Kraus reaction has been developed[3a-d, 5] (**Scheme 1a**). In addition, Fan reported the preparation of 7-amino-6*H*-naphtho[2,3-*c*]coumarins through tandem reaction of 2-phenylenylbenzonitriles and Reformatsky reagent[6] (**Scheme 1b**). More recently, Ren and co-workers revealed a $FeCl_3$-mediated tandem reaction for transformation of available 1-isochromanones bearing a diaryl allenic moiety at the C_4-position to functionalized 5*H*-naphtho[2,3-*c*]isocoumarins[7] (**Scheme 1c**). Despite these approaches are efficient and reliable, a motivation on develop more streamlined and practical methods from the available reagents is highly desirable. Herein, we would like to report a TsOH-mediated tandem reaction to synthesize 7-hydroxy-6*H*-naphtho[2,3-*c*]coumarins using available 1-(2-hydroxyphenyl)-2-phenylethanone and meldrum's acid (**Scheme 1d**).

Initially, the 1-(2-hydroxy-4-isopropoxyphenyl)-2-phenylethanone **1a** was chosen as the model substrate to optimize reaction conditions. The desired product **3a** was obtained in 17% yield with *p*-toluenesulfonic acid (TsOH) as the acid catalyst in *p*-xylene at 150 °C (**Table 1**, entry 1). An appropriate acid might be the key factor for the reaction efficiency. Various Lewis acid catalysts were screened, only $Yb(OTf)_3$ led to the desired product **3a**, but in a slightly lower yield than TsOH (entry 2). All other Lewis acid

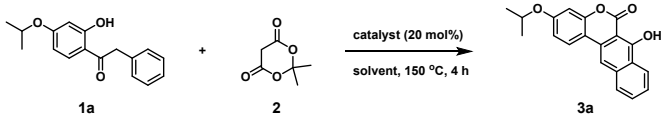
Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, National Engineering Laboratory for Resource Development of Endangered Crude Drugs in Northwest of China, School of Chemistry and Chemical Engineering, and Basic Experimental Teaching Center, Shaanxi Normal University, Xi'an 710119, China
E-mail: zhangzt@snnu.edu.cn
Electronic Supplementary Information (ESI) available: CCDC 2005596. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x
‡Present address: Department of Molecular Medicine, Beckman Research Institute of City of Hope, Duarte, California 91010, USA.



Scheme 1 The synthesis of polycyclic conjugated coumarins via tandem reaction.

catalysts did not work at all, such as MsOH, H_2SO_4, TFA, $FeCl_3$ and $AlCl_3$ (entries 3-7). Changing the amount of TsOH catalyst and meldrum's acid did not promote the reaction efficiency (see SI, Table S1, entries 1-7). Then, a series of solvents were evaluated. The results showed that toluene yielded **3a** in 21% (entry 8), while other solvents either gave lower yield or did not work at all (entries 9-14).

Table 1 Optimization of reaction conditions[a]



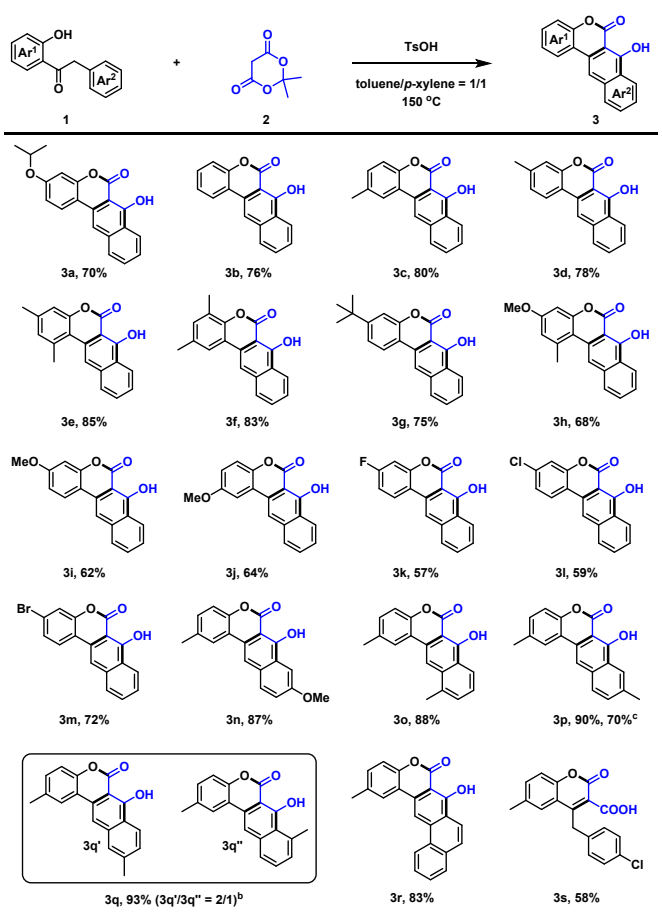
1a 2 3a

Entry	catalyst	solvent	Yield[b]
1	TsOH	*p*-xylene	17%
2	$Yb(OTf)_3$	*p*-xylene	10%
3	MsOH	*p*-xylene	ND
4	H_2SO_4	*p*-xylene	ND
5	TFA	*p*-xylene	ND
6	$FeCl_3$	*p*-xylene	ND
7	$AlCl_3$	*p*-xylene	ND
8	TsOH	toluene	21%
9	TsOH	$PhCF_3$	7%
10	TsOH	mesitylene	mess
11	TsOH	PhCl	14%
12	TsOH	DMF	ND
13	TsOH	1,4-dioxane	ND
14	TsOH	DCE	ND
15	TsOH	*p*-xylene/toluene (1/1, v/v)	31%
16[c]	TsOH	*p*-xylene/toluene (1/1, v/v)	63%
17[d]	TsOH	*p*-xylene/toluene (1/1, v/v)	72%
18[e]	TsOH	*p*-xylene/toluene (1/1, v/v)	73%(70%)[f]

[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol, 2.0 equiv), catalyst (20 mol%), 5.0 mL solvent, 150 °C, 4 h. [b]The yields were determined by ^{1}H NMR analysis with dibromomethane and 1,1,2,2-tetrachloroethane as the internal standard. [c]Another batch of TsOH (20 mol%) and **2** (2.0 equiv) was added when the reaction was stirred for 1 h. [d]The third batch of TsOH (20 mol%) and **2** (2.0 equiv) was added when the reaction was stirred for 2 h. [e]The third batch of TsOH (10 mol%) and **2** (1.0 equiv) was added when the reaction was stirred for 2 h. [f]Isolated yield. ND: no detected product.

Interestingly, the yield of **3a** was boosted to 31% with mixture of *p*-xylene/toluene (entry 15). Finally, the reaction temperature was optimized as well. Increasing the temperature to 170 °C resulted in a slightly poor yield (17%), while lowing the temperature to 120 °C only gave trace amount of product (see SI, Table S1, entries 10-12). The rapid decomposition of meldrum's acid under high reaction temperature might be responsible for the low yield. Thus, multiple batches of meldrum's acid and TsOH were added to the reaction to improve the yield (entries 16-18). Finally, the yield of **3a** was significantly improved (70%) when meldrum's acid/TsOH was added in three times (entry 18).

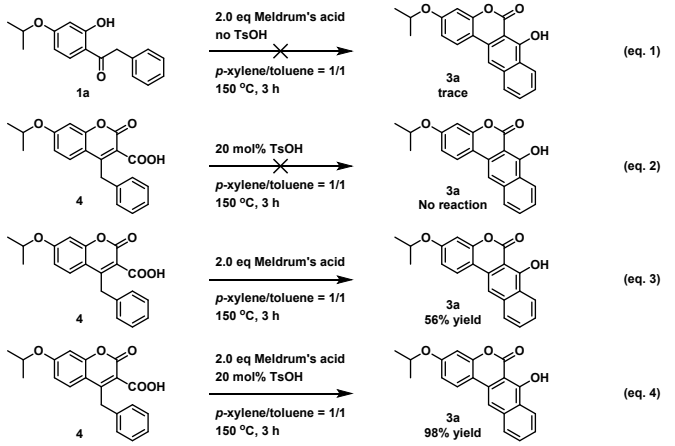
Table 2 Scope of substrates[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), TsOH (20 mol%), toluene/*p*-xylene (10 mL, 1/1, v/v), 150 °C for 1h. Another batch of **2** (2.0 mmol) and TsOH (20 mmol%) was added to the reaction, and stirred at 150 °C for 1 h. Third batch of **2** (1.0 mmol) and TsOH (10 mmol%) was added to the reaction, and stirred at 150 °C for 2 h. [b]The ratio of **3q'**/**3q''** was detected by ^{1}H NMR. [c]4.5 mmol scale of **1p** for the gram-scale reaction.

With the optimized reaction conditions, the substrate scope was investigated. Various 1-(2-hydroxyaryl)-2-phenylethanones were investigated, and the corresponding products were obtained in moderate to good yields (**Table 2**). Different substituents on the Ar^1 ring were well tolerated, including electron-neutral or electron-rich groups, such as methyl, *tert*-butyl, methoxyl, isopropoxyl (**3a-3j**) and electron-poor groups, such as fluoro, chloro and bromo (**3k-3m**). Notable, the *tert*-butyl group (**3g**) is tolerated as well, which could easily occur the alkyl migration, rearrangement or to be removed in

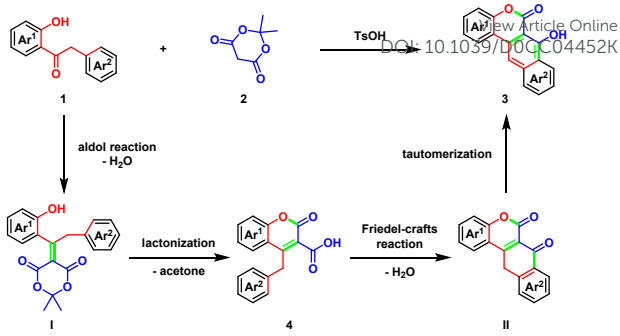
the Friedel-Crafts reaction. In addition, the products with halogen atoms give the potential chance for late-stage functionalization by well-established transition-metal-catalyzed cross-coupling reactions (**3k-3m**). The substituent effect on the Ar^2 ring was also studied. The results indicated that substrates with *ortho*- or *para*-substituents give desired products in good yields (**3n-3p**). When the substrate bearing a *meta*-methyl substituent on Ar^2 ring was tested, a mixture of regioisomers was obtained with 3:1 ratio in a total yield of 93% (**3q'** and **3q''**). The 1-naphthalene ring is also compatible to furnish **3r** in 83%. However, when the *para* position of Ar^2 ring was substituted with the chloro group, the reaction completely halted at the Friedel-crafts reaction step to give 3-carboxy-4-benzylcoumarin product **3s** in 58%.The steric effect of the *ortho*-position substituents on the Ar^1 or Ar^2 rings was not observed (**3e**, **3f** and **3o**), which is contrast to the lactonization of 2-arylbenzoic acids.[4a, 4e, 4h, 8] To further investigate the synthetic application, a gram-scale synthesis using substrate **1p** was performed, furnishing the corresponding product **3p** in 70%. This result indicated this method had great potential application in practical organic synthesis.



Scheme 2 Control experiments.

To gain insight into the reaction process, some control experiments were carried out. As shown in **Scheme 2**, only trace amount of product **3a** was observed without TsOH (eq.1), indicated TsOH played a crucial role in the tandem reaction. However, the TsOH could not catalyze the Friedel-crafts reaction, due to no product **3a** was observed when the key intermediate (3-carboxyl-4-benzylcoumarin derivatives **4**) was used (eq.2). On the other hand, the desired product **3a** was obtained in 56% yield in the presence of two equivalents meldrum's acid (eq.3). In addition, the combination of meldrum's acid and TsOH provided nearly quantitative conversion to the product **3a** (eq. 4), which indicated that TsOH could promote the Friedel-crafts reaction in the presence of meldrun's acid.

Based on these results, a plausible mechanism involves aldol reaction, lactonization and Friedel-crafts reaction was depicted in **Scheme 3**. First, the α,β-Unsaturated dicarbonyl compound **I** was formed via the Aldol reaction of 1-(2-hydroxyphenyl)-2-phenylethanone 1 and meldrum's acid **2**, following the lactonization process to produce the key intermediate 3-carboxyl-4-benzylcoumarin **4**. In the presence of meldrum's acid, the compound

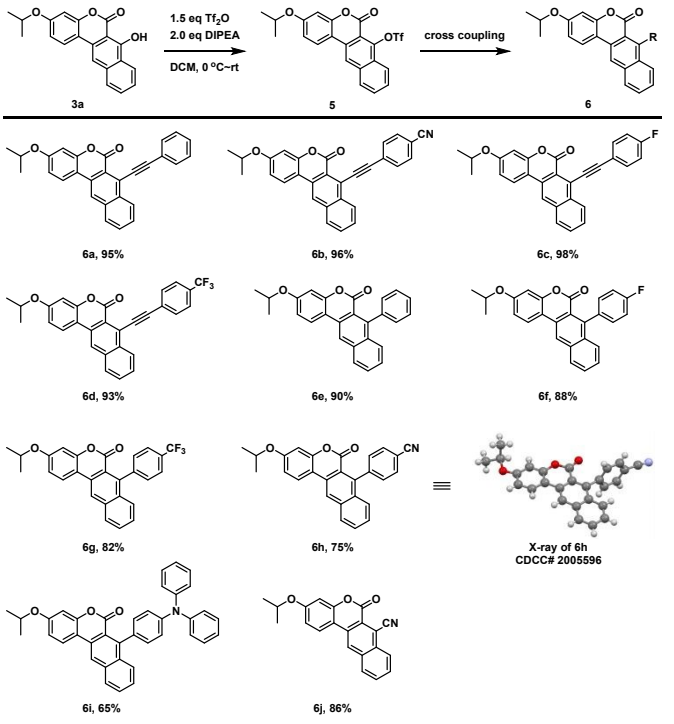


Scheme 3 Plausible mechanism for the tandem reaction.

II was generated through intramolecular Friedel-crafts reaction. Finally, the desired product **3** was obtained after tautomerization.

All the synthesized 7-hydroxy-6*H*-naphtho[2,3-*c*]coumarins **3** displayed brightly fluorescent under sunlight in organic solvent, which indicated these compounds might possess the potential application as fluorescent material. The generally methods to improve the fluorescent properties of coumarin materials mainly focused on following aspects: (1) enhanced fluorescence intensity of coumarin derivatives *via* introducing the electron-donor group at 7-position and electron-acceptor group at 3-position to the coumarin π-conjugated skeleton to generate a D-π-A molecule;[9] (2) pursued the significant bathochromic shifts in emission by extending the

Table 3 Transformation of the 7-hydroxy-6H-naphtho[2,3-c]chromen-6-one by cross coupling[a,b]



[a]Reaction condition: Trifluoromethylation: **3a** (0.5 mmol), Tf_2O (1.5 equiv), DIPEA (2.0 equiv) in 5.0 mL DCM, 0 °C, 1 h. Alkynylation: **5** (0.5 mmol), alkyne arene (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (3.0 mmol%), CuI (6.0 mol%) in 10 mL Et_3N, 90 °C, 12 h. Arylation: **5** (0.5 mmol), $ArB(OH)_2$ (1.3 equiv), $Pd(PPh_3)_4$ (3.0 mmol%), K_3PO_4 (1.6 equiv) in 5.0 mL 1,4-dioxane, 100 °C, 12 h. Cyanation: **5** (0.5 mmol), $ZnCN_2$ (2.0 equiv), $Pd(PPh_3)_4$ (5.0 mmol%) in 5.0 mL 1,4-dioxane, 100 °C, 12 h. [b]Isolated yield over two steps.

conjugate system to lower the HOMO-LUMO gap;[10] (3) largeStokes shifts, which play a decisive role in the field of optical whiteners and brighteners.[11] In this article, in order to explore the photophysical properties of these naphtho[*c*]coumarin derivatives, further modification were conducted. According to principles discussed above, we introduced a π-conjugated system (arylethynyl or aryl groups) or electron-acceptor group (cyano group) to the 7-position of compound **3a**, which has owned an electron-donor group (isopropoxyl group) at 3-position, to improve the fluorescence properties. As shown in **Table 3**, the compound **3a** could easily transform to triflate **5**, followed by cross-coupling reactions of compound **5** with various coupling partners, such as alkyne arene, arylboronic acid and zinc cyanide to give the corresponding alkylation products (**6a-d**), arylation products (**6e-i**), and the cyanidation product (**6j**) in good yields. The structure of **6h** was confirmed by the X-ray crystallographic analysis.

As expected, the emission wavelengths of all of the coupling products (**6a-j**) are bathochromically shifted compared to **3a**, and the fluorescence quantum yields were improved (**Table 4**). The compounds containing arylethynyl groups (**6a-d**) exhibited dramatic high fluorescence quantum yield up to 78%. Furthermore, most of these naphtho[2,3-*c*]coumarins showed blue-green flurescence in the range of approximately 460-570 nm with large Stokes shift. Surprisingly, the compound **6i**, bearing a 4-(diphenylamino)phenyl substituent group at 7-position, exhibited fluorescence maximum at 563 nm with Stockes shift of 173 nm.

Table 4 Spectral properties of 5 in dichloromethane solution (10^{-5} mol/L)

No.	λ_{abs} (nm)	λ_{ex} (nm)	λ_{em} (nm)	Stokes shift (nm)	ΦF (%)
3a	390	389	459	70	17
5	394	392	483	91	19
6a	413	415	496	81	78
6b	419	420	511	91	77
6c	412	414	496	82	78
6d	415	417	502	85	74
6e	384	386	463	77	28
6f	385	386	464	78	31
6g	386	387	472	85	36
6h	388	387	480	93	39
6i	392	390	563	173	14
6j	413	412	514	102	39

In conclusion, an efficient and easily operated synthetic procedure to construct the 7-hydroxy-6*H*-naphtho[2,3-*c*]coumarin derivatives was developed *via* TsOH-mediated aldol reaction, lactonization, Friedel-crafts reaction using available 1-(2-hydroxyphenyl)-2-phenylethanone and meldrum's acid. Control experiments indicated the meldrum's acid served as both reagent and catalyst in the reaction, and the TsOH promoted the total process. Furthermore, transformations of compounds **3** by cross-coupling reaction were achieved to afford three types of 7-substituted-6*H*-naphtho[2,3-*c*]coumarin derivatives in good to equivalent yield. Most of these compounds have significantly bathochromic shifts, and exhibit high fluorescence quantum yields and large Stokes shifts. Further studies on the synthetic application and physical properties examination are currently ongoing.

We gratefully acknowledge the financial support by the National Natural Science Foundation of China (21672132), China Postdoctoral Science Foundation (2018M631119) and the Fundamental Research Funds for the Central Universities (GK202003026).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) Y. S. Wang, B. Zhang, J. Zhu, C. L. Yang, Y. Guo, C. L. Liu, F. Liu, H. Huang, S. Zhao, Y. Liang, R. H. Jiao, R. X. Tan, H. M. Ge, *J. Am. Chem. Soc.* **2018**, *140*, 10909; (b) T. A. Unzner, A. S. Grossmann, T. Magauer, *Angew. Chem. Int. Ed.* **2016**, *55*, 9763; (c) A. J. Demuner, L. C. Barbosa, A. C. Miranda, G. C. Geraldo, C. M. da Silva, S. Giberti, M. Bertazzini, G. Forlani, *J. Nat. Prod.* **2013**, *76*, 2234; (d) M. Altemoller, J. Podlech, *J. Nat. Prod.* **2009**, *72*, 1288.

2 (a) L. Kowalik, J. K. Chen, *Nat. Chem. Biol.* **2017**, *13*, 587; (b) J. X. Chen, W. Liu, C. J. Zheng, K. Wang, K. Liang, Y. Z. Shi, X. M. Ou, X. H. Zhang, *ACS Appl. Mater. Interfaces* **2017**, *9*, 8848; (c) M. J. Jurow, C. Mayr, T. D. Schmidt, T. Lampe, P. I. Djurovich, W. Brutting, M. E. Thompson, *Nat. Mater.* **2016**, *15*, 85; (d) A. Nadler, D. A. Yushchenko, R. Muller, F. Stein, S. Feng, C. Mulle, M. Carta, C. Schultz, *Nat. Commun.* **2015**, *6*, 10056; (e) J. Chan, S. C. Dodani, C. J. Chang, *Nat. Chem.* **2012**, *4*, 973; (f) C. W. Yang, T. H. Hsia, C. C. Chen, C. K. Lai, R. S. Liu, *Org. Lett.* **2008**, *10*, 4069.

3 (a) N. Ueberschaar, Z. Xu, K. Scherlach, M. Metsa-Ketela, T. Bretschneider, H. M. Dahse, H. Gorls, C. Hertweck, *J. Am. Chem. Soc.* **2013**, *135*, 17408; (b) N. Ueberschaar, H. M. Dahse, T. Bretschneider, C. Hertweck, *Angew. Chem. Int. Ed.* **2013**, *52*, 6185; (c) S. Ray, A. Patra, D. Mal, *Tetrahedron* **2008**, *64*, 3253; (d) D. Mal, A. Patra, H. Roy, *Tetrahedron Lett.* **2004**, *45*, 7895; (e) S. Christmann-Franck, H. O. Bertrand, A. Goupil-Lamy, P. A. der Garabedian, O. Mauffret, R. Hoffmann, S. Fermandjian, *J. Med. Chem.* **2004**, *47*, 6840.

4 (a) K. Wadekar, S. Aswale, V. R. Yatham, *Org. Biomol. Chem.* **2020**, *18*, 983; (b) L. Fu, S. Li, Z. Cai, Y. Ding, X.-Q. Guo, L.-P. Zhou, D. Yuan, Q.-F. Sun, G. Li, *Nat. Catal.* **2018**, *1*, 469; (c) A. Shao, N. Li, Y. Gao, J. Zhan, C.-W. Chiang, A. Lei, *Chin. J. Chem.* **2018**, *36*, 619; (d) A. Shao, J. Zhan, N. Li, C. W. Chiang, A. Lei, *J. Org. Chem.* **2018**, *83*, 3582; (e) L. Zhang, Z. Zhang, J. Hong, J. Yu, J. Zhang, F. Mo, *J. Org. Chem.* **2018**, *83*, 3200; (f) Q. Yang, Z. Jia, L. Li, L. Zhang, S. Luo, *Org. Chem. Front.* **2018**, *5*, 237; (g) N. P. Ramirez, I. Bosque, J. C. Gonzalez-Gomez, *Org. Lett.* **2015**, *17*, 4550; (h) S. Luo, F. X. Luo, X. S. Zhang, Z. J. Shi, *Angew. Chem. Int. Ed.* **2013**, *52*, 10598; (i) T. H. Lee, J. Jayakumar, C. H. Cheng, S. C. Chuang, *Chem. Commun.* **2013**, *49*, 11797; (j) Y. Li, Y. J. Ding, J. Y. Wang, Y. M. Su, X. S. Wang, *Org. Lett.* **2013**, *15*, 2574.

5 X. Huang, T. Zhu, Z. Huang, Y. Zhang, Z. Jin, G. Zanoni, Y. R. Chi, *Org. Lett.* **2017**, *19*, 6188.

6 (a) Y. He, X. Zhang, X. Fan, *Chem. Commun.* **2014**, *50*, 5641; (b) Y. He, X. Zhang, X. Fan, *Asian J. Org. Chem.* **2014**, *3*, 1284.

7 M. Miao, M. Jin, H. Xu, P. Chen, S. Zhang, H. Ren, *Org. Lett.* **2018**, *20*, 5718.

8 M. Zhang, R. Ruzi, N. Li, J. Xie, C. Zhu, *Org. Chem. Front.* **2018**, *5*, 749.

9 (a) M.-S. Schiedel, C. A. Briehn, P. Bäuerle, *Angew. Chem. Int. Ed.* **2001**, *40*, 4677; (b) A. Elangovan, J.-H. Lin, S.-W. Yang, H.-Y. Hsu, T.-I. Ho, *J. Org. Chem.* **2004**, *69*, 8086; (c) K. Sivakumar, F. Xie, B. M. Cash, S. Long, H. N. Barnhill, Q. Wang, *Org. Lett.* **2004**, *6*, 4603; (d) D. J. Yee, V. Balsanek, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 2282; (e) X. Liu, J. M. Cole, P. G. Waddell, T.-C. Lin, J. Radia, A. Zeidler, *J. Phys. Chem. A* **2012**, *116*, 727.

10 M. Staderini, M. A. Martín, M. L. Bolognesi, J. C. Menéndez, *Chem. Soc. Rev.* **2015**, *44*, 1807.

11 L. Chen, T.-S. Hu, Z.-J. Yao, *Eur. J. Org. Chem.* **2008**, *2008*, 6175.

View Article Online
DOI: 10.1039/D0CC04452K

Table of contents

7-hydroxy-6*H*-naphtho[2,3-*c*]coumarin derivatives were synthesized using 1-(2-hydroxyphenyl)-2-phenylethanone and Meldrum's acid *via* TsOH-mediated tandem reaction, including Aldol reaction, Lactonization and Friedel-crafts reaction.