Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

A Bioinspired Cascade Sequence Enables Facile Assembly of Methanodibenzo[*b*,*f*][1,5]dioxocin Flavonoid Scaffold

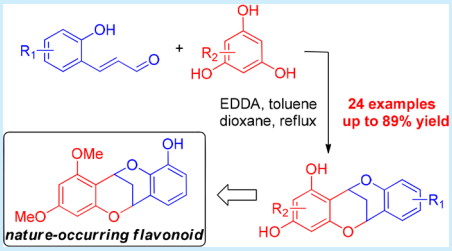
Hongxin Liu,[†,‡] Yu Wang,[†] Xueying Guo,[†] Luqiong Huo,[†] Zhifang Xu,[†] Weimin Zhang,[‡] Shengxiang Qiu,[†] Bao Yang,*[,†] and Haibo Tan*[,†]

[†]Program for Natural Products Chemical Biology, Key Laboratory of Plant Resources Conservation and Sustainable Utilization, Guangdong Provincial Key Laboratory of Applied Botany, South China Botanical Garden, Chinese Academy of Sciences, Guangzhou 510650, China

[‡]State Key Laboratory of Applied Microbiology Southern China, Guangdong Provincial Key Laboratory of Microbial Culture Collection and Application, Guangdong Open Laboratory of Applied Microbiology, Guangdong Institute of Microbiology, Guangzhou 510070, China

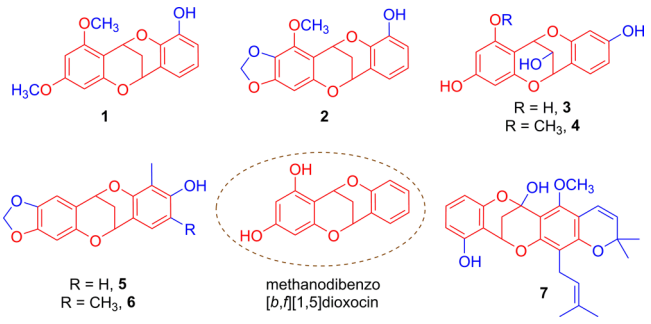
Supporting Information

ABSTRACT: A remarkable bioinspired EDDA-mediated method for the selective construction of biologically interesting and highly strained bridged methanodibenzo[*b*,*f*][1,5]dioxocin flavonoid scaffold was uncovered by starting from a variety of readily available acylphloroglucinol and 2-hydroxycinnamaldehyde substrates. This method merges a fascinating olefin isomerization/hemiacetallization/dehydration/[3 + 3]-type cycloaddition cascade reaction driven by an in situ generated chromenylium intermediate and provides a convenient and viable synthetic strategy for the efficient access of such flavonoid analogues.



The architectural complexity of natural products has fascinated synthetic scientists, and the challenges associated with their intricate structure have continuously served as a powerful vehicle to fuel synthetic methodology innovation.[1] Among the greatest achievements in accessing structural complexity stands the emergence of tandem reactions and biomimetic synthetic pathways in recent years.[2,3] The methanodibenzo[*b*,*f*][1,5]dioxocin skeleton represents a diverse family of structurally privileged motifs that are prevalent in many interesting bioactive natural products and pharmaceuticals (highlighted in Scheme 1).[4,5] Although they are useful scaffolds with potential usefulness for the treatment of many diseases,[6] the protocols for efficient creation of such bridged methanodibenzo[*b*,*f*][1,5]dioxocin skeleton are less explored probably due to their cleft-shaped structure and rigidity.[7] Thus, a fairly novel strategy toward convergent assembly of these tetracyclic bridged core by bold retrosynthetic disconnection inspired by nature will be a highly desirable and challenging task.

Scheme 1. Biologically Active Natural Products Featuring a Methanodibenzo[*b*,*f*][1,5]dioxocin Ring System

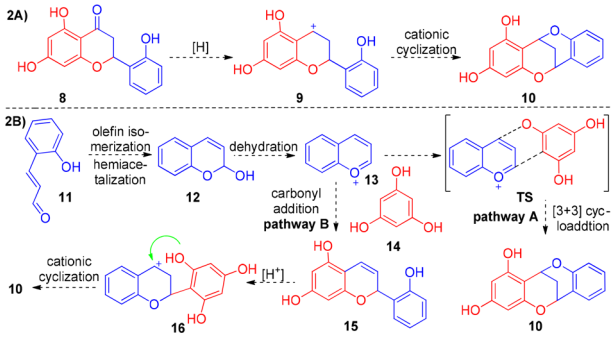


Motivated by our ongoing research program on efficiently accessing such similar polycyclic skeletons in a biomimetic [3 + 3] cycloaddition pathway,[8] we are intrigued by the possibility of forging these complex bridged scaffolds through a biomimetic strategy. The proposed biogenetic pathway for the formation of methanodibenzo[*b*,*f*][1,5]dioxocin skeleton usually proceeds through a carbonyl reduction followed by a cationic cyclization from the common flavonoid as shown in Scheme 2A. On the basis of this scenario, we anticipated that an olefin isomerization/hemiacetalization/dehydration sequence will transform 2-hydroxycinnamaldehyde **11** to a highly reactive chromenylium intermediate **13** (Hückel aromatic compound),[9,10] which can "click" on a phloroglucinol nucleophile to trigger the crucial [3 + 3]-type cycloaddition or carbonyl addition/biomimetic cationic cycloaddition cascade downstream (Scheme 2B), leading to the methanodibenzo[*b*,*f*][1,5]dioxocin flavonoid skeleton in a highly efficient manner. If this proposal is successful, it will allow us to synthesize an array of these novel and biologically meaningful flavonoid analogues without further elaboration. Herein, we report the experimental details of the selective olefin isomerization/hemiacetalization/dehydration/[3 + 3] cycloaddition bioinspired cascade sequence with readily

Received: November 22, 2017

DOI: 10.1021/acs.orglett.7b03630
Org. Lett. XXXX, XXX, XXX−XXX

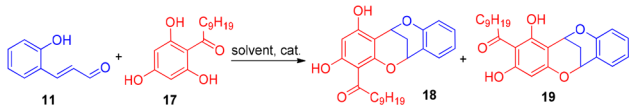
Scheme 2. Proposed Biogenetic Pathway and the Design of a Bioinspired Cascade Reaction



accessible phloroglucinol and 2-hydroxy cinnamaldehyde derivatives as substrates (Scheme 2B).

To verify this hypothesis, the readily accessible decanoylphloroglucinol **17**[11] and 2-hydroxycinnamaldehyde **11** were chosen as model substrates to implement the putative cascade sequence by judicious selection and modification of reaction conditions (Table 1). To our delight, when PTSA was used as

Table 1. Optimization of Reaction Conditions.[a]



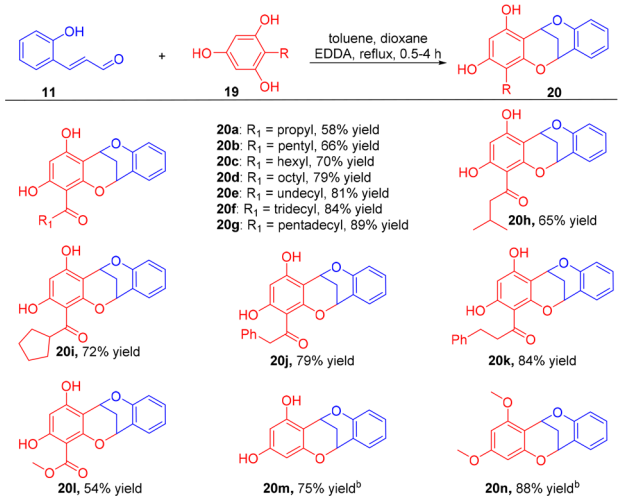
entry	solvent	catalyst	cat. loading (equiv)	t (°C)	time (h)	yield (%)[b]	ratio (**18**:**19**)[c]
1	toluene	PTSA	0.1	reflux	1	21	1:1
2	toluene	TFA	1	reflux	1	27	1:1
3	toluene	BzOH	1	reflux	1	30	1:1
4	toluene	AcOH	1	reflux	1	33	5:1
5	toluene	proline	0.1	reflux	1	58	10:1
6	toluene	EDDA	0.1	reflux	1	78	10:1
7	toluene	EDDF	0.1	reflux	1	70	10:1
8	toluene	EDDP	0.1	reflux	1	64	10:1
9	toluene	EDDA	0.1	90	3	75	10:1
10	toluene	EDDA	0.1	rt	3	NR	-
11	dioxane	EDDA	0.1	reflux	1	<10%	-
12	THF	EDDA	0.1	reflux	1	NR	-
13	DCE	EDDA	0.1	reflux	1	NR	-
14	ACN	EDDA	0.1	reflux	1	NR	-
15	toluene+dioxane[d]	EDDA	0.1	60	1.0	83	>20:1

[a]Reaction conditions: **11** (0.2 mmol), **17** (0.22 mmol), solvent (6 mL), rt, 0.5−3 h. [b]Yield of isolated product. [c]The ratio was determined by ^{1}H NMR spectra of the crude mixture. [d]Toluene (5 mL), dioxane (1 mL). EDDA: ethylenediamine diacetate. EDDF: ethylenediamine ditrifluoroacetate. EDDP: ethylenediamine di(*p*-toluenesulfonate). NR: no reaction.

the tentative catalyst to trigger the proposed cascade sequence in reflux toluene, two regioisomers **18** and **19**,[12] both featuring the fascinating tetracyclic bridged skeleton, were formed albeit in low yield (21% yield, entry 1). The formation of the regioisomers **18** and **19** could be rationally attributed to the reactive *o*- or *p*-phenol group existing in decanoylphloroglucinol **17**, respectively.[13] In order to improve its synthetic efficiency and selectivity, some other protic acids TFA, BzOH, and AcOH were subsequently evaluated. Unfortunately, all of them gave inferior results (entries 2−4).[14] Further catalyst screening proved that ammonium salts outperformed protic acids in terms of both yield and regioselectivity (entries 5−8) because of the weaker acidic conditions. In particular, EDDA provided the highest level (entry 6). Variation in the temperature and the reaction solvents did not improve the yield (entries 9−14). Satisfyingly, when dioxane was used as a cosolvent with toluene (entry 15), the cascade sequence rendered *ortho*-product **18** in higher than 80% yield and showed an excellent regioselective profile (>20:1), thereby laying a solid foundation in terms of practicality and operational simplicity.

With the optimized conditions established, we surveyed the scope and versatility of this reaction with respect to various phloroglucinol derivatives **19**.[11] As shown in Scheme 3, a wide

Scheme 3. Surveying the Substrate Scope of Phloroglucinols[a]



[a]**11** (0.2 mmol), **19** (0.22 mmol), EDDA (0.02 mmol), toluene (5 mL), dioxane (1 mL), reflux, 0.5−4 h. [b]**19** (0.22 mmol), PTSA (0.02 mmol), toluene (5 mL), dioxane (1 mL), reflux, 1 h.

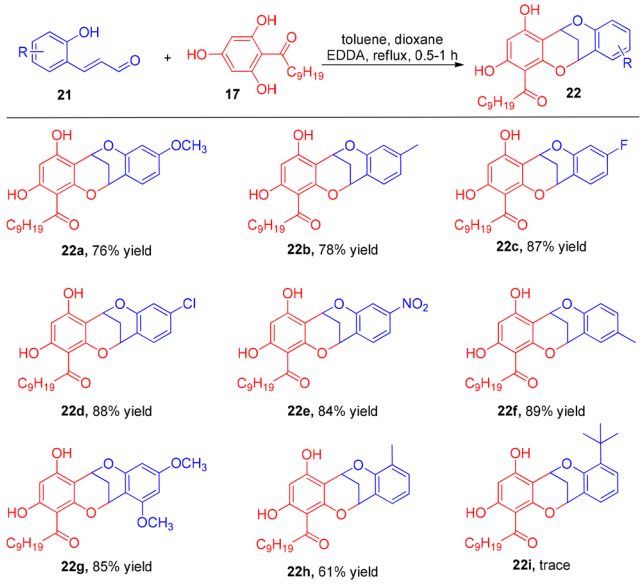
range of phloroglucinols bearing different substituents could be well tolerated, wherein the corresponding desired tetracyclic bridged products **20a−n** were delivered in moderate to excellent yields ranging from 54% to 89% within 0.5−4 h. Moreover, the reaction appeared to be quite selective almost without detectable amount of possible regioisomer for every case. It was noticeable that the acetyl substituents on phloroglucinol substrates **19** have posed a considerable influence on the reaction efficiency. An obvious increase in reaction yield was observed, when a more lipophilic acetyl substituent was introduced to the phloroglucinol skeleton (**19a−g**), whereas the steric hindrance of the substituent seemed to have little influence (**19h−k**). These results could be rationally ascribed to the solubility of the in situ generated chromenylium−phloroglucinol intermediates[9] before the crucial [3 + 3] cycloaddition step. It merited attention that substrates with a nucleophilic acetyl substituent (**19a−g,j,k**), which held the potential to generate competitive aldol condensation or Michael addition byproducts with chromenylium,[15] showed no notable loss in reactivity and selectivity. Meanwhile, when an ester group was installed on the phloroglucinol unit (**19l**), this protocol could also be well tolerated and delivered the desired product **20l** with moderate yield. Notably, simple phloroglucinols **19m** and **19n** seemed to be troublesome cases for this methodology, but an alternative switch of catalyst EDDA to 0.1 equiv of PTSA would successfully address this issue and furnish the corresponding products **20m** and **20n** in a highly efficient manner. Collectively, the availability of this well-orchestrated cascade

DOI: 10.1021/acs.orglett.7b03630
Org. Lett. XXXX, XXX, XXX−XXX

sequence exemplified by the aforementioned remarkable results enabled a broad spectrum of phloroglucinols to be substrates.

Subsequently, we further extended the substrates to a variety of substituted 2-hydroxycinnamaldehydes **21** for the construction of the structurally diverse and functionalized methanodibenzo[*b*,*f*][1,5]dioxocin system (Scheme 4). It was

Scheme 4. Surveying the Substrate Scope of 2-Hydroxycinnamaldehydes[a]

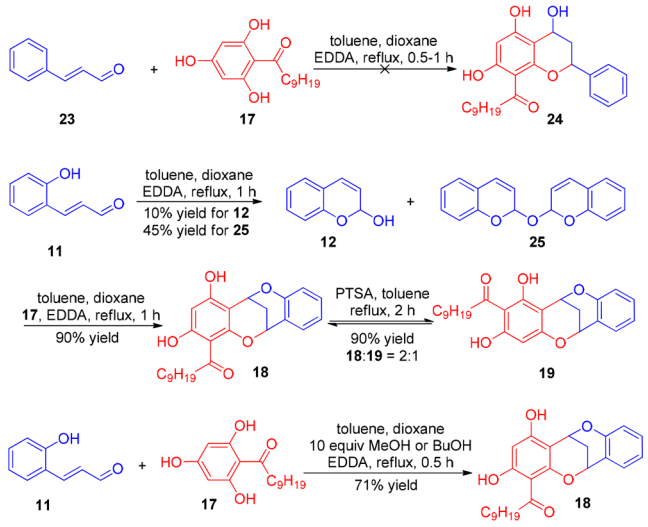


[a]**11** (0.2 mmol), **19** (0.22 mmol), EDDA (0.02 mmol), toluene (5 mL), dioxane (1 mL), reflux, 0.5−1 h.

observed that substrates bearing an electron-withdrawing substituent (−F, −Cl, and $-NO_2$) gave the corresponding products (**22c**−**e**) in 84−88% yields, which mainly outperformed those of the substrates (**21a**,**b**) bearing an electron-donating substituent, probably due to the higher reactivity of the in situ generated chromenylium intermediates for the former ones. Meanwhile, the tested substrates with a substituent at the C_3 or C_4 position (**21f** or **21g**) were also effective for this transformation, providing the corresponding products **22f** or **22g** in more than 85% yields. However, it was noteworthy that a functional group ($-CH_3$ or $-C(CH_3)_3$) located at the C_6 position (**21h** or **21i**) would significantly influence both their reaction efficiency and the selectivity, resulting in 61% yield for **22h** and a trace amount (not isolated) of **22i**.[16]

After evaluating the reaction scope, mechanistic experiments were then conducted to shed light on the potential reaction pathways, as summarized in Scheme 5. Replacing 2-hydroxycinnamaldehyde **11** with cinnamaldehyde **23** resulted in a complete inhibition of the intended reaction and any Michael addition products, strongly implying the involvement of the chromenylium intermediate in the cascade process. To probe this speculation, 2-hydroxycinnamaldehyde **11** was subjected to the standard conditions in the absence of phloroglucinol. Satisfyingly, the hemiacetal intermediate **12**[17] and its dimer derivative **25**[18,19] were then successfully isolated in 10% and 45% yields, respectively. Both the hemiacetal intermediate **12** and its dimer derivative **25** could be leveraged to react with phloroglucinol **17** under the established EDDA-

Scheme 5. Experimental Probes on Reaction Mechanism



catalyzed conditions to generate the desired product with 90% yield, thus further confirming the aforementioned deduction.

Interestingly, when the tetracyclic product **18** was heated in the presence of PTSA, the regioisomer **19** which could also be interconverted to **18** was isolated in 30% yield (about 2:1 ratio with **18**), implying that a competitive cationic trapping process of the *o*- and *p*-hydroxyl groups in phloroglucinol **17** would be inevitable when cationic intermediate **16** (Scheme 2) generated. Moreover, when an excess amount of methanol or butanol was used as the cationic-trapping reagent under the standard conditions, the reaction proceeded smoothly to provide **18** without any obvious effect and detection of the cationic trapping products. Due to these informative results and the better selectivity for the weak acidic conditions (entries 5 and 6, Table 1) than that for the stronger ones (entries 1−4, Table 1), the pathway involving a concerted [3 + 3]-type cycloaddition (pathway A in Scheme 2B) seemed to be much more conclusive for this reaction mechanism. Collectively, the aforementioned conceivable results strongly indicated that this cascade reaction probably proceeded involving a remarkable olefin isomerization/hemiacetalization/dehydration/[3 + 3]-type cycloaddition sequence through a chromenylium intermediate.

In summary, inspired by the fascinating biosynthetic hypotheses of the flavonoids bearing a novel methanodibenzo-[*b*,*f*][1,5]dioxocin skeleton, we have developed an efficient EDDA-catalyzed olefin isomerization/hemiacetalization/dehydration/[3 + 3]-type cycloaddition cascade reaction driven by an in situ generated chromenylium intermediate acting as a "click" role. The culmination of this developed downstream sequence interpreted the brevity of synthetic route, which provides a convenient and practical methodology to selectively construct highly complex and strained bridged methanodibenzo[*b*,*f*][1,5]dioxocin flavonoid skeleton with readily accessible phloroglucinol and 2-hydroxycinnamaldehyde derivatives. Moreover, we have also established a viable synthetic strategy for the efficient synthesis of such flavonoid analogues, the availability of which would be highly beneficial to both biological and medicinal chemistry. The diversity-oriented total synthesis of natural products in this family along with their structure−activity relationship study toward drug discovery is now underway and will be reported in due course.

DOI: 10.1021/acs.orglett.7b03630
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03630.

Experimental section, detailed experimental procedures, and full spectroscopic data for all related compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*Tel: +86-20-37081190. E-mail: yangbao@scbg.ac.cn.
*Tel: +86-20-37081190. E-mail: tanhaibo@scbg.ac.cn.

ORCID

Haibo Tan: 0000-0002-1652-5544

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (NSFC) (81773602, 31600271, and 81502949), Natural Science Foundation of Guangdong Province (2015A030310482, 2016A030313149, and 2016A010105015), Pearl River Science and Technology New Star Fund of Guangzhou (201605120849569), and the Frontier Science Key Program of Chinese Academy of Sciences (QYZDB-SSW-SMC018) for financial support.

■ REFERENCES

(1) (a) Davies, H. M. L. *Nature* **2009**, *459*, 786. (b) Hamann, L. G. *Nat. Chem.* **2014**, *6*, 460. (c) Razzak, M.; De Brabander, J. K. *Nat. Chem. Biol.* **2011**, *7*, 865. (d) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829. (e) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442. (f) Davies, H. M. L.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 2981. (g) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (h) Trost, B. M. *Science* **1991**, *254*, 1471.

(2) For selected reviews of cascade reaction in total synthesis, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (d) Anderson, E. A. *Org. Biomol. Chem.* **2011**, *9*, 3997. (e) Kim, J.; Movassaghi, M. *Chem. Soc. Rev.* **2009**, *38*, 3035. (f) Ardkhean, R.; Caputo, D. F.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. *Chem. Soc. Rev.* **2016**, *45*, 1557. (g) Li, X. W.; Nay, B. *Nat. Prod. Rep.* **2014**, *31*, 533.

(3) For representative recent reports on biomimetic total synthesis, see: (a) Reichl, K. D.; Smith, M. J.; Song, M. K.; Johnson, R. P.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2017**, *139*, 14053. (b) Lachkar, D.; Denizot, N.; Bernadat, G.; Ahamada, K.; Beniddir, M. A.; Dumontet, V.; Gallard, J. F.; Guillot, R.; Leblanc, K.; N'nang, E. O.; Turpin, V.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G. *Nat. Chem.* **2017**, *9*, 793. (c) Han, Y. X.; Jiang, Y. L.; Li, Y.; Yu, H. X.; Tong, B. Q.; Niu, Z.; Zhou, S. J.; Liu, S.; Lan, Y.; Chen, J. H.; Yang, Z. *Nat. Commun.* **2017**, *8*, 14233. (d) Newton, C. G.; Tran, D. N.; Wodrich, M. D.; Cramer, N. *Angew. Chem., Int. Ed.* **2017**, *56*, 13776. (e) Day, A. J.; Lam, H. C.; Sumby, C. J.; George, J. H. *Org. Lett.* **2017**, *19*, 2463. (f) Kotammagari, T. K.; Gonnade, R. G.; Bhattacharya, A. K. *Org. Lett.* **2017**, *19*, 3564. (g) Song, L. Y.; Huang, F.; Guo, L.; Ouyang, M. A.; Tong, R. B. *Chem. Commun.* **2017**, *53*, 6021.

(4) (a) Bam, M.; Ferreira, D.; Brandt, E. V. *Phytochemistry* **1988**, *27*, 3704. (b) Zheng, Z. P.; Xu, Y.; Qin, C.; Zhang, S.; Gu, X.; Lin, Y.; Xie, G.; Wang, M.; Chen, J. *J. Agric. Food Chem.* **2014**, *62*, 5519. (c) Sasaki, H.; Kashiwada, Y.; Shibata, H.; Takaishi, Y. *Phytochemistry* **2012**, *82*, 136. (d) Eastmond, R.; Gardner, R. J. *Phytochemistry* **1974**, *13*, 1477.

(5) For representative bioactive natural products, see: (a) Lin, C. N.; Lu, C. M.; Huang, P. L. *Phytochemistry* **1995**, *39*, 1447. (b) Cui, Y. M.; Wang, H.; Liu, Q. R.; Han, M.; Lu, Y.; Zhao, C. Q. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4400. (c) Chen, L.; Zhou, Q.; Li, B.; Liu, S. J.; Dong, J. X. *Nat. Prod. Res.* **2015**, *29*, 1217. (d) Sasaki, H.; Kashiwada, Y.; Shibata, H.; Takaishi, Y. *Phytochemistry* **2012**, *82*, 136. (e) Zhang, X. Q.; Jing, Y.; Wang, G. C.; Wang, Y.; Zhao, H. N.; Ye, W. C. *Fitoterapia* **2010**, *81*, 813. (f) Rashid, M. A.; Armstrong, J. A.; Gray, A. I.; Waterman, P. G. *Phytochemistry* **1992**, *31*, 3583. (g) Waterman, P. G.; Mahmoud, E.-H. N. *Phytochemistry* **1987**, *26*, 1189.

(6) (a) Chen, J. R.; Yang, D. Y. *Org. Lett.* **2009**, *11*, 1769. (b) Hennis, H. E. US 3551424 A 19701229, 1970.

(7) (a) Hennis, H. E.; Wang, C. S. *J. Org. Chem.* **1969**, *34*, 1907. (b) Hennis, H. E.; Thompson, L. R.; Wang, C. S.; Priddy, D. B. *J. Org. Chem.* **1970**, *35*, 3127. (c) Bhatia, G. D.; Mukerjee, S. K.; Seshadri, T. R. *Tetrahedron* **1966**, *22*, 139.

(8) (a) Liu, H. X.; Huo, L. Q.; Yang, B.; Yuan, Y. F.; Zhang, W. M.; Xu, Z. F.; Qiu, S. X.; Tan, H. B. *Org. Lett.* **2017**, *19*, 4786. (b) Tan, H. B.; Liu, H. X.; Chen, X. Z.; Yuan, Y. F.; Chen, K.; Qiu, S. X. *Org. Lett.* **2015**, *17*, 4050. (c) Tan, H. B.; Liu, H. X.; Chen, X. Z.; Chen, H. Y.; Qiu, S. X. *Org. Biomol. Chem.* **2015**, *13*, 9977. (d) Tan, H. B.; Chen, X. Z.; Chen, H. Y.; Liu, H. X.; Qiu, S. X. *Eur. J. Org. Chem.* **2015**, *2015*, 4956.

(9) (a) Yang, Z.; He, Y.; Toste, F. D. *J. Am. Chem. Soc.* **2016**, *138*, 9775. (b) Schmid, M.; Trauner, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 12332. (c) Chand Ganguly, N.; Roy, S.; Mondal, P. *RSC Adv.* **2014**, *4*, 42078.

(10) Selenski, C.; Pettus, T. R. *Tetrahedron* **2006**, *62*, 5298.

(11) Chauthe, S. K.; Bharate, S. B.; Periyasamy, G.; Khanna, A.; Bhutani, K. K.; Mishra, P. D.; Singh, I. P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2251.

(12) Both the structures of compounds **18** and **19** were fully characterized by 2D NMR and HMRS spectra. The difference in regiochemistry between **18** and **19** and the previous examples (refs 9 and 10) might be attributed to the less steric hindered substrate of the 2-hydroxycinnamaldehyde as well as different reaction conditions.

(13) Morkunas, M.; Dube, L.; Götz, F.; Maier, M. E. *Tetrahedron* **2013**, *69*, 8559.

(14) The strong acids usually leaded complex mixtures, and the weaker acids might result in a mixture of regioisomers or no reaction.

(15) Zhu, Y.; Zhou, J.; Jin, S.; Dong, H.; Guo, J.; Bai, X.; Wang, Q.; Bu, Z. *Chem. Commun.* **2017**, *53*, 11201.

(16) The low yield for **22i** was attributed to the steric hindrance of the **21i**, which resulted in the failure of the coupling of **21i** with **17**, leading to recovery of most of the start material **17**.

(17) Padhi, B.; Reddy, D. S.; Mohapatra, D. K. *Eur. J. Org. Chem.* **2015**, *2015*, 542.

(18) Compound **25** existed as a mixture of inseparable enantiomers with ratio ~1:1.

(19) (a) Jacquot, Y.; Refouvelet, B.; Blacque, O.; Kubicki, M. M.; Xicluna, A. *C. R. Acad. Sci., Ser. IIc: Chim.* **2001**, *4*, 375. (b) Lončar, L.; Mintas, M.; Hergold-Brundić, A.; Nagl, A.; Trötsch, T.; Mannschreck, A. *Croat. Chem. Acta* **1995**, *68*, 233.

DOI: 10.1021/acs.orglett.7b03630
Org. Lett. XXXX, XXX, XXX−XXX