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Concise Construction of the Tricyclic Core of Bullataketals Enabled by a Biomimetic Intermolecular (3 + 3) Type Cycloaddition

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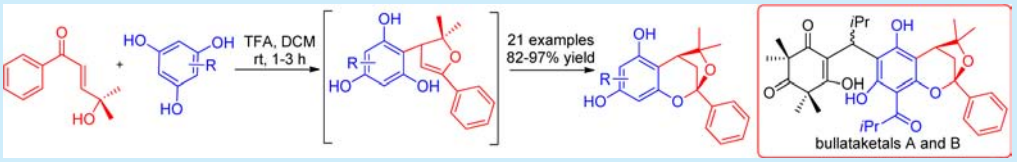
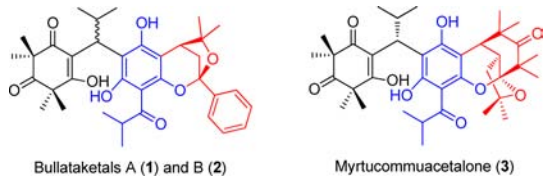
Supporting Information



ABSTRACT: A remarkable TFA-mediated method for the construction of a biologically interesting tricyclic ketal skeleton was uncovered by starting from a variety of readily available acylphloroglucinol and diacylphloroglucinol substrates. This approach, which mimics a biosynthetic olefin isomerization/hemiacetalization/dehydration/(3 + 3) type cycloaddition sequence through a 2*H*-furan-1-ium intermediate, establishes a viable synthetic strategy for efficient synthesis of bullataketals' analogs.

Structurally complex natural products continuously serve as a powerful vehicle for the invention of novel synthetic strategies; a broad variety of classic sequence reactions developed for the construction of complex molecule skeletons and biomimetic total synthesis have emerged in recent years.[1,2] Tricyclic ketal skeleton and their architectural derivatives represent frequently encountered complex motifs[3] that are present in many interesting bioactive natural products (highlighted with color in Scheme 1).[4] Among these, bullataketals A (**1**) and B (**2**) with a fascinating tricyclic ketal skeleton have shown potent cytotoxic activity against the P388 cell line with IC_{50} = 1.0 μg/mL and excellent antimicrobial activity against *Bacillus subtilis*.[4a,5] Myrtucommuacetalone **3** exhibited significant inhibitory effects against nitric oxide (NO·) production and antiproliferative activity (IC_{50} < 0.5 μg/mL).[4b] Inspired by their excellent biological activity and novel structure complexity, much effort has been undertaken to develop approaches for ketal formation, but there is still a lack of efficient methods to rapidly access this key skeleton.[6] Therefore, the development of a novel strategy which facilitates convergent assembly of the tricyclic ketal core unit is desirable.

Scheme 1. Biologically Active Natural Products Featuring Tricyclic Ketal Ring System



Bullataketals A (**1**) and B (**2**) Myrtucommuacetalone (**3**)

In contrast to the former aldol condensation/acetalation biosynthetic proposal,[4a] our efforts to construct the tricyclic ketal core have focused on disclosing the biomimetic synthesis of bullataketals by deciphering their biogenetic pathway. As highlighted in Scheme 2, we supposed that the (3 + 3) type cycloaddition between isobutyrylphloroglucinol **5** and 2*H*-furan-1-ium[7] (**TS-1**) ought to be the crucial biosynthetic transformation for bullataketals A (**1**), B (**2**) and myrtucommuacetalone **3**. Moreover, 2*H*-furan-1-ium was suggested to originate from α,β-unsaturated ketone **6** through an olefin isomerization/hemiacetalization/dehydration sequence based on the confirmed presence of isobutyrylphloroglucinol **5** in this plant.[8] Based on the speculation and inspection of the underlying biogenetic transformations, we have successfully developed a remarkable biomimetic sequence to efficiently construct the tricyclic ketal core unit of bullataketals A (**1**) and B (**2**). Herein we report the experimental details.

The challenge in the experimental realization of this sequence clearly lies in identifying reaction conditions that are conducive for simultaneously supporting operations of the stepwise reactions and avoiding side products. With readily accessible isobutyrylphloroglucinol **5**[9] and α,β-unsaturated ketone **6**[10] as the model substrate and TFA as the tentative catalyst,[11] products **4** and **9** were initially isolated with 15% yield and 2:1 ratio in THF (entry 1). Based on the NMR

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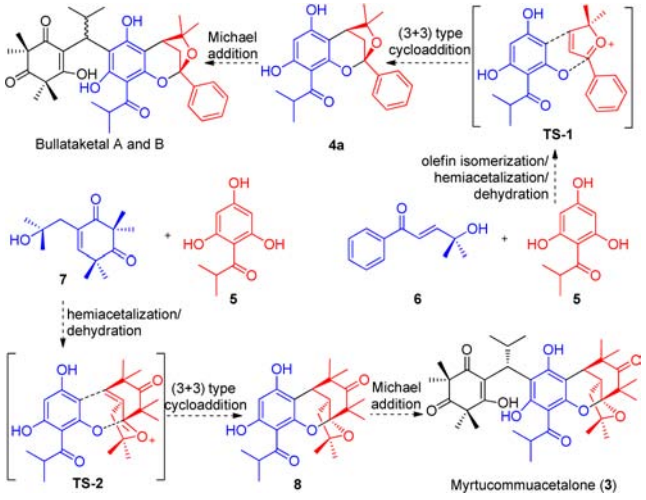
Scheme 2. Proposed Biogenetic Pathways of Bullataketals A, B and Myrtucommuacetalone

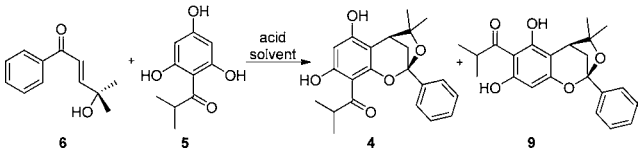


spectroscopy, both of them featured the fascinating tricyclic ketal skeleton and presumably formed due to the alternative regioselectivity of the two phenol group in either the ortho- or para-position.[12] It merits attention that **4** and **9** could be successfully separated by silica gel column chromatography but tautomerized rapidly under neat or $CDCl_3$ conditions.[13] In an attempt to improve the yield of this sequence, the reaction conditions such as solvents, substrate loadings, and catalysts were optimized. As a result, the solvent effect was shown to be fairly significant during this transformation. When apolar solvents were used, the desirable products **4** and **9** were obtained with better yields under otherwise comparable conditions, especially in DCM (73% yield, entry 7). During the optimization process, the most intractable problem was the poor solubility of acylphloroglucinol **5** in apolar solvents, which led to the formation of a double (3 + 3) type cycloaddition byproduct. The critical solution was to dissolve acylphloroglucinol **5** and α,β-unsaturated ketone **6** in THF first and then DCM after removing THF.[14] With this operation, the yield was dramatically increased to greater than 90% (entry 12, Table 1).

With the optimal conditions established, we next surveyed the scope of this biomimetic sequence. A series of structurally variable acylphloroglucinol derivatives **10**[15] were then subjected to the above-defined conditions, and the results were compiled in Figure 1. The reactivity appeared to be quite general, yielding the corresponding tricyclic ketals **11** and **12** for each case in excellent yields in the range 82−96% and with isomeric ratios of nearly 3:2. Neither the length nor the steric hindrance of acetyl substituents in the phloroglucinol ring seemed to have posed a significant influence on the reaction efficiency and isomeric ratios (**11a−11k**, **12a−12k**). Notably, we observed that as the more lipophilic acetyl substituents were induced to the acylphloroglucinol substrates, better yields would be provided. Moreover, the comparably competent substrates with a more nucleophilic acetyl substituent (**10a−10e** and **10j−10k**), which tended to generate aldol condensation or Michael addition byproducts with 2*H*-furan-1-ium, showed no notable loss in the reactivity and selectivity.

When a range of diacylphloroglucinols[16] had been examined, the reactivity is virtually irrespective of the diacetyl substitution, as the corresponding cycloaddition products **11l−11s** were all consistently isolated in almost quantitative yields. In contrast to

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	catalyst	cat. loading	*t*	time	yield[b]	ratio (**4**:**9**)[c]
1	THF	TFA	7.0 equiv	rt	12 h	15%	2:1
2	H_2O	TFA	7.0 equiv	rt	12 h	<10%	–
3	ACN	TFA	7.0 equiv	rt	12 h	<10%	–
4	$CHCl_3$	TFA	7.0 equiv	rt	2.0 h	68%	2:1
5	toluene	TFA	7.0 equiv	rt	1.0 h	45%	3:2
6	DCE	TFA	7.0 equiv	rt	1.0 h	56%	2:1
7	DCM	TFA	7.0 equiv	rt	1.0 h	73%	2:1
8	DCM	AcOH	7.0 equiv	rt	1.0 h	<10%	2:1
9	DCM	MsA	7.0 equiv	rt	1.0 h	33%	2:1
10	DCM[d]	TFA	7.0 equiv	rt	1.0 h	75%	2:1
11	DCM	TFA	20 equiv	rt	1.0 h	54%	2:1
12	DCM[e]	TFA	7.0 equiv	rt	1.0 h	91%	2:1

[a]Conditions: **6** (0.2 mmol), acylphloroglucinol **5** (0.24 mmol), TFA (1.4 mmol, 0.1 mL), solvent (7.0 mL), rt, 1.0 h. [b]Yields of isolated products. [c]The ratio (**4**:**9**) was accorded to the crude product and measured by ^{1}H NMR [d]2.0 equiv of **5** were used. [e]**5** and **6** were dissolved in THF (1.0 mL) first and dissolved again in DCM after removing THF.

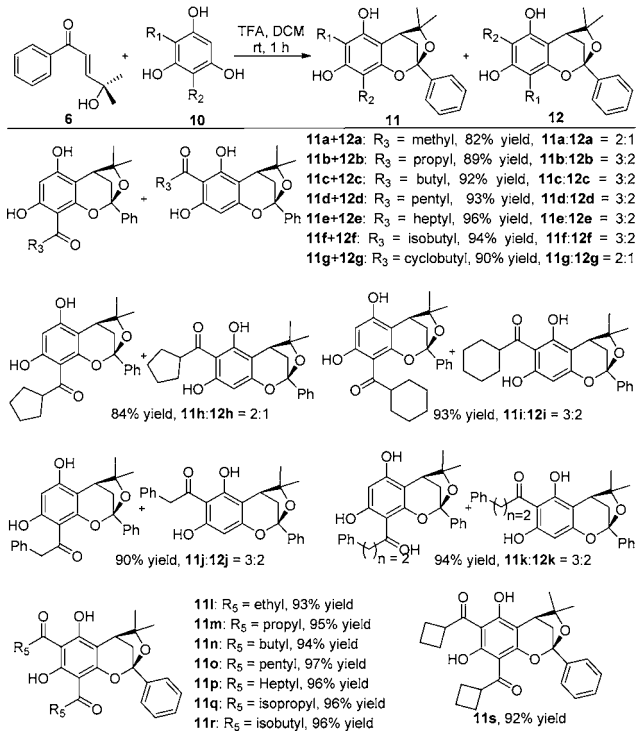


Figure 1. Surveying the scope of phloroglucinol substrates. Conditions: **6** (0.2 mmol), acylphloroglucinol **10** (0.24 mmol), TFA (1.4 mmol, 0.1 mL), DCM (7.0 mL), rt, 1−3 h. Yields of isolated products. The ratio (**11**:**12**) was estimated by ^{1}H NMR measurements of the crude product.

acylphloroglucinols, the inseparable regioisomers **12** were not observed in the diacylphloroglucinols attributed to their symmetrical structures. Moreover, all the yields of diacylphloroglucinols were slightly higher than those of acylphloroglucinols,

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because the generation of the trace double (3 + 3) type cycloaddition byproduct was prevented by the additionally introduced acetyl substituents. The TFA-mediated biomimetic (3 + 3) type cycloaddition sequence clearly tolerates a broad spectrum of phloroglucinol partners.

To further extend the scope of this protocol, various α,β-unsaturated ketone **13** analogs were also examined (Figure 2).

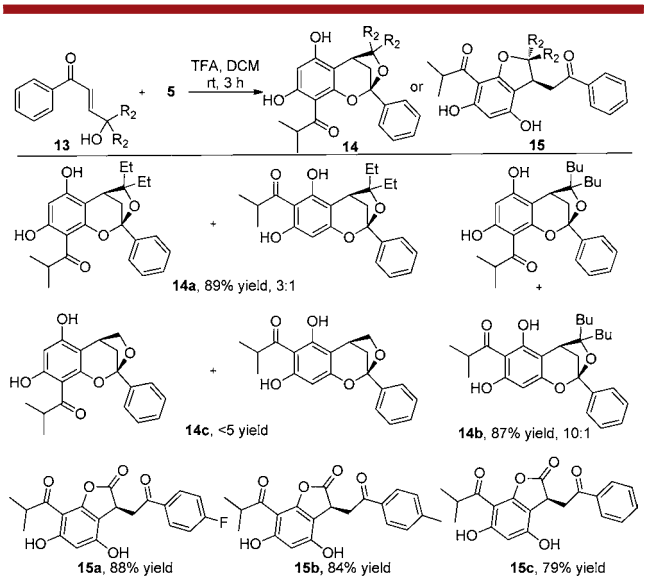
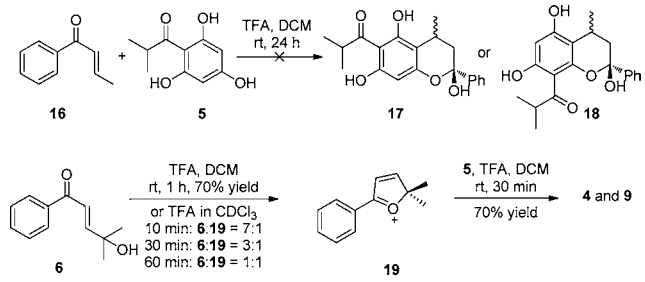


Figure 2. Surveying the scope of α,β-unsaturated ketone substrates. Conditions: **13** (0.2 mmol), acylphloroglucinol **5** (0.24 mmol), TFA (1.4 mmol, 0.1 mL), DCM (7.0 mL), rt, 1−12 h. The ratio was accorded to the crude product and measured by ^{1}H NMR.

This reaction tends to provide the corresponding tricyclic ketal products **14a**−**14b** with a lower yield but better regioselectivity as the steric bulk of α,β-unsaturated ketone **13** was increased. Moreover, the tertiary hydroxyl group in α,β-unsaturated ketone **13** played a crucial role in this transformation. Indeed, when the (*E*)-4-hydroxy-1-phenylbut-2-en-1-one was used, the (3 + 3) type cycloaddition almost did not proceed (**14c**, Figure 2). This could be attributed to the weaker stability of the generated 2*H*-furan-1-ium intermediate, which led to the formation of the 2-phenylfuran byproduct. When (*E*)-4-oxo-4-phenylbut-2-enoic acid derivatives were explored, the reaction proceeded cleanly in 12 h. It was notable that, unlike the case of (*E*)-4-hydroxy-1-phenylbut-2-en-1-one substrates, the tricyclic ketal products were not observed in (*E*)-4-oxo-4-phenylbut-2-enoic acid, but instead the corresponding linear lactone **15a**−**15c** was isolated as the only product in excellent yields ranging from 79% to 88%. The above discovery could be used as an efficient protocol to synthesize biologically significant benzofuran-2(3*H*)-one derivative.

Mechanistic experiments were then conducted to shed light on the potential reaction pathways, as summarized in Scheme 3. With phloroglucinol **5** as the model substrate, using α,β-unsaturated ketone **16** instead of **6** has led to complete inhibition of the intended reaction. The result had strongly implied the involvement of the 2*H*-furan-1-ium intermediate during the reaction process. In order to further confirm this speculation, the α,β-unsaturated ketone **6** was treated with TFA in DCM at room temperature. To our delight, the 2*H*-furan-1-ium intermediate **19**, which was fully characterized by NMR and HRMS analysis,[17] was formed in nearly 70% yield after 1 h.

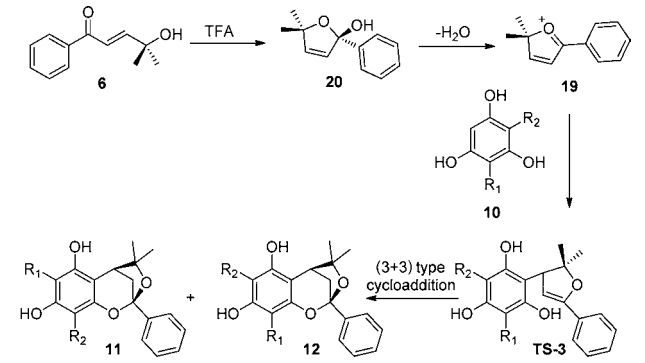
Scheme 3. Experimental Probes on Reaction Mechanism



Moreover, the detection of this transformation in $CDCl_3$ was also conducted by NMR. It ambiguously disclosed that **6** could rapidly be transformed to **19** after treatment with TFA. Finally, after treating the freshly generated 2*H*-furan-1-ium **19** with acylphloroglucinol **5**, the corresponding cycloaddition products **4** and **9** would be produced smoothly. The readily conceivable results indicated that the 2*H*-furan-1-ium **19** has played the key role in this sequence process.

The reactivity coupled with the mechanistic investigations collectively pointed to a plausible mechanism shown in Scheme 4. The sequence would be initiated by a proton acid-catalyzed

Scheme 4. Proposed Mechanism



tandem olefin *E*/*Z* isomerization and hemiacetalization to generate the hemiacetal precursor **20**. The further dehydration of **20** under acidic conditions gave rise to the critical 2*H*-furan-1-ium **19** and in turn induced the (3 + 3) type cycloaddition with acylphloroglucinol **10** to afford the desirable products **11** and **12**, which could rapidly tautomerize at room temperature. It is noted that the (3 + 3) type cycloaddition was possibly the rate-determining step from the obvious observation of 2*H*-furan-1-ium **19** during the reaction process.

In summary, motivated by the fascinating biosynthetic hypotheses of bullataketals A, B and myrtucommuacetalone, we have developed a remarkable TFA-mediated approach, which mimics a biosynthetic olefin isomerization/hemiacetalization/dehydration/(3 + 3) type cycloaddition sequence, for rapid construction of the tricyclic ketal core unit of bullataketals A and B. The key point of this discovery would be the reliable generation and application of the 2*H*-furan-1-ium intermediate. Moreover, we have also established a viable synthetic strategy for the efficient synthesis of bullataketals analogs and their potential uses in medicinal chemistry as well as diversity-oriented natural product synthesis. The total synthesis of bullataketals A, B and myrtucommuacetalone, along with solving the intractable chiral control and regio-isomerization problem, is now underway and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01970.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews of cascade reactions in total synthesis, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186. (c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993−3009. (d) Anderson, E. A. *Org. Biomol. Chem.* **2011**, *9*, 3997−4006. (e) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757−4778.

(2) For representative recent reports on biomimetic total synthesis, see: (a) Strych, S.; Journot, G.; Pemberton, R. P.; Wang, S. C.; Tantillo, D. J.; Trauner, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 5079−5083. (b) Matsuura, B. S.; Keylor, M. H.; Li, B.; Lin, Y. X.; Allison, S.; Pratt, D. A.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 3754−3757. (c) Norris, M. D.; Perkins, M. V.; Sorensen, E. J. *Org. Lett.* **2015**, *17*, 668−671. (d) Meier, R.; Strych, S.; Trauner, D. *Org. Lett.* **2014**, *16*, 2634−2637. (e) Barrett, T. N.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2014**, *136*, 17013−17015.

(3) (a) Jonek, A.; Berger, S.; Haak, E. *Chem. - Eur. J.* **2012**, *18*, 15504−15511. (b) Lazarski, K. E.; Hu, D. X.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2010**, *12*, 3010−3013. (c) Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. *Org. Lett.* **2004**, *6*, 3617−3619. (d) Zaugg, H. E.; Michaels, R. J. *J. Org. Chem.* **1963**, *28*, 1801−1805. (e) Xu, Z. L.; Li, Y. Y.; Xiang, Q.; Pei, Z.; Liu, X. L.; Lu, B. T.; Chen, L.; Wang, G. L.; Pang, J. Y.; Lin, Y. C. *J. Med. Chem.* **2010**, *53*, 4642−4653. (f) Ren, J. W.; Niu, S. B.; Li, L.; Geng, Z. F.; Liu, X. Z.; Che, Y. S. *J. Nat. Prod.* **2015**, *78*, 1316−1321.

(4) For representative bioactive natural products, see: (a) Larsen, L.; Benn, M. H.; Parvez, M.; Perry, N. B. *Org. Biomol. Chem.* **2005**, *3*, 3236−3241. (b) Choudhary, M. I.; Khan, N.; Ahmad, M.; Yousuf, S.; Fun, H. K.; Soomro, S.; Asif, M.; Mesaik, M. A.; Shaheen, F. *Org. Lett.* **2013**, *15*, 1862−1865. (c) Castagnino, C.; Vercauteren, J. *Tetrahedron Lett.* **1996**, *37*, 7739−7742. (d) Wang, W.; Zeng, Y. H.; Osman, K.; Shinde, K.; Rahman, M.; Gibbons, S.; Mu, Q. *J. Nat. Prod.* **2010**, *73*, 1815−1820. (e) Lin, Y. C.; Wu, X. Y.; Feng, S.; Jiang, G. C.; Luo, J. H.; Zhou, S. N.; Vrijmoed, L. L. P.; Jones, E. B. G.; Krohn, K.; Steingroever, K.; Zsila, F. *J. Org. Chem.* **2001**, *66*, 6252−6256.

(5) Woollard, J. M. R.; Perry, N. B.; Weavers, R. T.; van Klink, J. W. *Phytochemistry* **2008**, *69*, 1313−1318.

(6) For a selection of recent work on constructing oxygen-bridged tricyclic ketal skeletons, see: (a) Xing, S. Y.; Li, Y.; Li, Z.; Liu, C.; Ren, J.; Wang, Z. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 12605−12609. (b) Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12932−12936. (c) Čorić, I.; List, B. *Nature* **2012**, *483*, 315−319. (d) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413−1419. (e) Ramana, C. V.; Reddy, C. N.; Gonnade, R. G. *Chem. Commun.* **2008**, 3151−3153. (f) Foot, J. S.; Giblin, G. M. P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 4441−4444. (g) Sun, Z. K.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074−8077. (h) Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *127*, 13796−13797.

(7) (a) Martin-Matute, B.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4754−4757. (b) Zofia, W. T. *Polym. J. Chem.* **1993**, *67*, 1595−1607.

(8) Ghisalberti, E. L. *Phytochemistry* **1996**, *41*, 7−22.

(9) Müller, H.; Paul, M.; Hartmann, D.; Huch, V.; Blaesius, D.; Koeberle, A.; Werz, O.; Jauch, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2045−2049.

(10) (a) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 46−48. (b) Balamraju, Y. N.; Sun, M. J.; Salomon, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 11522−11528.

(11) (a) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *Org. Lett.* **2002**, *4*, 2389−2391. (b) Jiang, H.; Ferrara, G.; Zhang, X.; Oniwa, K.; Islam, A.; Han, L. Y.; Sun, Y. J.; Bao, M.; Asao, N.; Yamamoto, Y.; Jin, T. N. *Chem. - Eur. J.* **2015**, *21*, 4065−4070. (c) Yokosaka, T.; Nakayama, H.; Nemoto, T.; Hamada, Y. *Org. Lett.* **2013**, *15*, 2978−2981. (d) Yokosaka, T.; Nemoto, T.; Hamada, Y. *Chem. Commun.* **2012**, *48*, 5431−5433. (e) Wen, B.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2011**, *13*, 168−171. (f) Haga, N.; Endo, Y.; Kataoka, K.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 9795−9806. (g) Singh, T. P.; Bhattarcharya, S.; Singh, O. M. *Org. Lett.* **2013**, *15*, 1974−1977.

(12) Morkunas, M.; Dube, L.; Götz, F.; Maier, M. E. *Tetrahedron* **2013**, *69*, 8559−8563.

(13) The pure **4** can rapidly equilibrate to a mixture (**4**:**9** = 2:1) with 6 h in neat conditions and 12 h in $CDCl_3$.

(14) After removing the THF solvent, the mixture of acylphloroglucinol **5** and α,β-unsaturated ketone **6** could be readily obtained as a creamy oil which can be adequately dissolved again in DCM.

(15) Tyrrell, E.; Archer, R.; Tucknott, M.; Colston, K.; Pirianov, G.; Ramanthan, D.; Dhillon, R.; Sinclair, A.; Skinner, G. A. *Phytochem. Lett.* **2012**, *5*, 144−149.

(16) 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*, 2251−2256.

(17) The methine proton at δ_H 8.94 (1 H, J = 5.0 Hz) and δ_H 7.89 (1 H, J = 5.0 Hz) demonstrated that there was a *cis* double bond attaching to a strong electron-withdrawing group, and the carbon signal at δ_C 202.2, 181.4, 111.7 indicated that there were an oxonium group and a double bond. The HR-ESI-MS (Positive mode; $[M + H]^+ m/z$ 173.0871, calcd 173.1039) established its molecular formula as $C_{12}H_{13}O_3^+$.

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