ChemComm

COMMUNICATION

Check for updates

Cite this: Chem. Commun., 2019, 55, 5171

Received 6th March 2019, Accepted 8th April 2019

DOI: 10.1039/c9cc01833f

rsc.li/chemcomm

Organocatalytic enantioselective direct alkylation of phloroglucinol derivatives: asymmetric total synthesis of (+)-aflatoxin B_2 [†]

Zhonglei Wang and Liansuo Zu®*

The organocatalytic enantioselective Friedel–Crafts alkylation of phloroglucinol derivatives with enals is reported, providing general access to the benzylic chiral centers shown in a variety of phloro-glucinol natural products. The synthetic utility is demonstrated by the very concise asymmetric total synthesis of aflatoxins B₂.

The naturally occurring molecules containing phloroglucinol moieties represent an important class of natural products with a vast array of biological activities.¹ About 700 phloroglucinol natural products have been isolated from various natural resources with broad structural diversity. One subset of phloroglucinol molecules that has received significant attention features the presence of benzylic chiral centers (Fig. 1). Representative examples include the 4-aryl-3,4-dihydrocoumarin natural product calomelanol F (1),² semisynthetic clinical candidates flavopiridol (2) and riviciclib (3),³

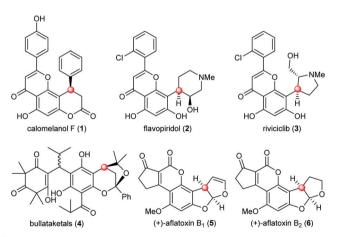


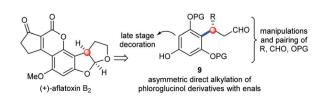
Fig. 1 Representative phloroglucinol natural products and drug candidates.

 \dagger Electronic supplementary information (ESI) available. CCDC 1893156 (9b). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc01833f

bullataketals $(4)^4$ and the carcinogenic substances aflatoxin B₁ (5) and B₂ (6).⁵ Progress in the asymmetric construction of the benzylic chiral centers and total synthesis of related natural products has been elegantly achieved, providing valuable insights and inspiration from different aspects for the chemical synthesis of this subset of phloroglucinol molecules.⁶

The examination of the chemical structures of the molecules in Fig. 1 revealed some common structural patterns, including the benzylic chiral centers, the eastern heterocyclic rings and the western decoration of the phloroglucinol phenyl rings. Based on these shared structural features and lessons learned from the previous synthetic work, we envisioned a general strategy to address the synthesis of this subset of phloroglucinol molecules at three different phases. Specifically, as depicted in Scheme 1, we envisioned that the direct asymmetric para-selective alkylation of phloroglucinol derivatives⁷ with enals could build up the benzylic chiral center and introduce several functional groups into the key intermediate 9. Subsequent synthetic manipulations and pairing of the functional groups (R, CHO and OPG) in 9 could furnish the eastern heterocyclic rings. Finally, the late stage decoration could install the required moieties in the western parts. Herein, we report our efforts to explore this concept in the context of developing a total synthesis of aflatoxins B₂.

One of the key elements in our design was to utilize iminium catalysis⁸ to control the benzylic chiral center in **9**. While the LUMO-lowering activation of enals *via* iminium ions has become a general strategy for asymmetric catalysis, the Friedel–Crafts alkylation of phenols with enals represents a significant challenge. Notable progress on the Friedel–Crafts alkylations of naphthols with enals has been realized by the groups of Wang,



Scheme 1 Designed strategy to synthesize phloroglucinol natural products.



View Article Online

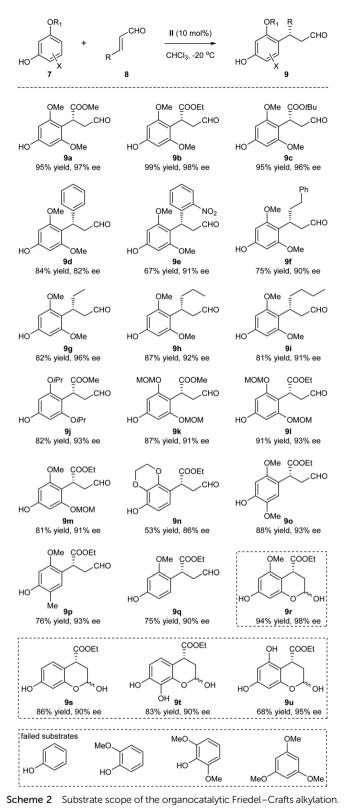
School of Pharmaceutical Sciences, Key Laboratory of Bioorganic Phosphorus, Chemistry & Chemical Biology (Ministry of Education), Beijing Frontier Research, Center for biological Structure, Tsinghua University, Beijing 100084, China. E-mail: zuliansuo@tsinghua.edu.cn

$HO = \begin{bmatrix} OHC & Ph \\ HO & OHC \\ + \\ OMe \end{bmatrix} = \begin{bmatrix} R = TMS (I) \text{ or } DPMS (II) \\ HO & additive (10 \text{ mol}\%), \text{ solvent} \\ HO & HO & OMe \end{bmatrix} = \begin{bmatrix} OHC & COOMe \\ \hline COOMe & additive (10 \text{ mol}\%), \text{ solvent} \\ HO & OMe \end{bmatrix}$						
Entry	Catalyst	Additive	Solvent	<i>T</i> (°C)	Yield ^a	ee ^b
Entry	Catalyst	Additive	Solvent	1(0)	Helu	ee
1	I	PhCOOH	EtOH	rt	51	40
2	Ι	PhCOOH	THF	rt	46	48
3	Ι	PhCOOH	Toluene	rt	25	62
4	Ι	PhCOOH	DCM	rt	76	77
5	Ι	PhCOOH	DCE	rt	71	62
6	Ι	PhCOOH	$CHCl_3$	rt	79	78
7	Ι	None	CHCl ₃	rt	88	82
8	Ι	None	$CHCl_3$	0	90	93
9	Ι	None	$CHCl_3$	-20	89	96
10	II	None	$CHCl_3$	-20	95	97
^{<i>a</i>} Isolated yield (%). ^{<i>b</i>} Determined by the chiral HPLC analysis.						

Jørgensen and others,⁹ but very limited success has been achieved on phenols with sesamol as the sole reported substrate.^{9b,c} Of note, all these reported reactions are *ortho*-selective and accompanied with subsequent cascade reactions due to the close proximity of the OH and other functional groups. In order to render the alkylation process amenable to natural product synthesis, two fundamental problems have to be addressed: (1) applying the phloroglucinol derivatives as the substrates; (2) obtaining *para*-selectivity to avoid the uncontrolled pairing of the OH and neighboring functional groups.

With these concerns in mind, a model reaction of 7a and 8a was carried out first to identify the optimized reaction conditions for the Friedel-Crafts alkylation (Table 1). The diphenylprolinol TMS ether I was selected as the initial organocatalyst¹⁰ due to its exceptional ability in activating enals. To our delight, in the presence of benzoic acid as the additive, this catalyst I could indeed enable the desired para-selective alkylation in various solvents with moderate yields and enantioselectivities (entries 1-6). These results validated the feasibility of the direct alkylation of the phloroglucinol derivatives with enals and identified chloroform as the choice of solvent. Further optimizations of the yield and ee were then carried out. Surprisingly, improvements in both the reaction yield and ee were observed without using benzoic acid as the additive (entry 7). Then, we observed that the reaction temperature had a marked effect on the enantioselectivity of the reaction, affording 96% ee at -20 °C (entries 8 and 9). Finally, by switching to a bulkier organocatalyst II, excellent results in terms of both reaction vield and enantioselectivity were achieved (entry 10).

With the optimized reaction conditions identified, the substrate scope of the Friedel–Crafts alkylation was next examined (Scheme 2). The method turned out to be a general approach for the generation of the benzylic chiral centers with good to excellent yields and enantioselectivities. The structural variations of the enals 8 were well tolerated: the R group could be esters, aryl and alkyl groups with varied steric and electronic properties (9a–9i). The absolute configuration of 9b was determined by

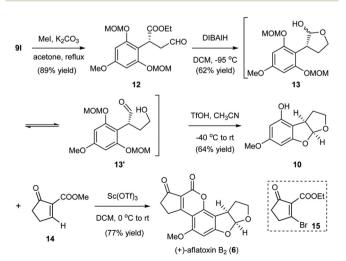


single-crystal X-ray diffraction.¹¹ The different *O*-alkylated phloroglucinol derivatives also proved to be efficient substrates (**9j–9m**). Of note, the sterically hindered MOM (methoxymethyl) protecting group could be tolerated, thus generating products amenable to subsequent synthetic transformations (**9k–9m**).

In addition to the phloroglucinol derivatives, several other polyphenolic derivatives could also participate in the alkylation processes, significantly expanding the scope of the phenolic partners (**9n–9q**). When $R_1 = H$, hemiacetals **9r–9u** were obtained through subsequent internal interactions between the OH and aldehyde. Several substrates that could not participate in the process are listed in the bottom of Scheme 2. It seemed that the presence of at least one electron-donating oxygen at the *meta* position of phenols was essential for the reaction to occur. Whether such structural requirement also dictated the *para*-selectivity of the Friedel–Crafts alkylation was not clear at this moment.

Finally, we turned to the chemical synthesis of aflatoxin B_2 , which is a representative member of the aflatoxin natural products. While significant progress in the total synthesis of racemic aflatoxins has been achieved since the 1960s,¹² relatively limited success in the catalytic enantioselective total synthesis of this class of natural products has been realized.⁶ In 2003, the group of Trost successfully achieved the asymmetric total synthesis of aflatoxin B₁ in 9 steps utilizing the palladium catalyzed transformation of γ -acyloxybutenolides.^{6a} Later, in 2005, the group of Corey completed the asymmetric total synthesis of aflatoxin B₂ in 8 steps by the application of an elegant oxazaborolidium catalyzed [3+2] cycloaddition.^{6b} Most recently, the group of Hong reported an organocatalytic approach for enantioselective synthesis of the aflatoxin system.^{6c} In this work, remarkable efficiency could be achieved by telescoping several synthetic operations into a one-pot reaction, and thus the concise formal total synthesis of aflatoxin B2 was realized.

Our developed organocatalytic Friedel–Crafts alkylation of the phloroglucinol derivatives with enals offered a direct approach for the efficient generation of the benzylic chiral center shown in aflatoxin B_2 . Furthermore, the method successfully introduced several functional groups into the alkylation product, thus providing synthetic handles for the rapid generation of the furobenzofuran ring system through manipulations and pairing of these functional groups. As depicted in Scheme 3, from the alkylation product **9**, methylation of the OH produced intermediate **12**. Reduction of the aldehyde and partial reduction of the ester could then generate



Scheme 3 Asymmetric total synthesis of aflatoxin B₂.

hemiacetal 13 and the equilibrated hydroxyl aldehyde 13' as inseparable mixtures,13 which were treated with triflic acid (TfOH) to afford 10 via cleavage of the MOM groups and subsequent cyclization to the acetal. At this stage, the remaining task of aflatoxin B2 was to install the annulated cyclopentanocoumarin ring. The single step transformation of 10 to aflatoxin B₂ reported by Corey^{6b} through Buchi's Pechmann type annulation^{12d} using the brominated precursor **15** represents by far the most efficient known approach. The bromine served as the activating group for the annulation and later a leaving group for the generation of the aromatic coumarin system. While the annulation was very concise, the process proceeded with low yield (36%).^{6b} To increase the overall synthetic efficiency of the late stage annulation, we envisioned to use a simpler precursor 14. We surmised that a similar Pechmann type annulation followed by spontaneous aerobic oxidation would generate the cyclopentanocoumarin ring. After the systematic screening of a variety of Lewis acids, we could successfully realize the desired transformation in 77% yield using $Sc(OTf)_3$ as the promoter, thus completing the total synthesis of (+)-aflatoxin B_2 (6) in only five steps from the MOMprotected phloroglucinol. The newly developed annulation protocol for the incorporation of the coumarin ring utilizing a simpler precursor and proceeding with better yield represents a marked improvement when compared to previous methods.

In summary, we have developed an organocatalytic enantioselective direct alkylation of the phloroglucinol derivatives with enals for the rapid generation of the benzylic chiral centers existing in a variety of phloroglucinol natural products. The synthetic manipulations and pairing of the functional groups of an alkylation product along with a newly developed late-stage annulation protocol have enabled the very concise asymmetric total synthesis of aflatoxins B₂, demonstrating the synthetic potential of the developed chemistry in preparing phloroglucinol natural products.

This work is supported by the National Natural Science Foundation of China (Grant No. 21871161) and the Drug Innovation Major Project (Grant No. 2018ZX09711-001).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- For selected reviews, see: (a) I. P. Singh and S. B. Bharate, Nat. Prod. Rep., 2006, 23, 558–591; (b) R. Ciochina and R. B. Grossman, Chem. Rev., 2006, 106, 3963–3986; (c) I. P. Singh, J. Sidana, P. Bansal and W. J. Foley, Expert Opin. Ther. Pat., 2009, 19, 847–866; (d) I. P. Singh, J. Sidana, S. B. Bharate and W. J. Foley, Nat. Prod. Rep., 2010, 27, 393–416; (e) S. Quideau, D. Deffieux, C. Douat-Casassus and L. Pouysegu, Angew. Chem., Int. Ed., 2011, 50, 586–621; (f) J. M. Estrela, S. Mena, E. Obrador, M. Benlloch, G. Castellano, R. Salvador and R. W. Dellinger, J. Med. Chem., 2017, 60, 9413–9436.
- 2 F. Asai, M. Inuma, T. Tanaka, M. Takenaka and M. Mizuno, *Phytochemistry*, 1992, **31**, 2487–2490.
- 3 (a) B. A. Christian, M. R. Grever, J. C. Byrd and T. S. Lin, *Curr. Opin.* Oncol., 2007, **19**, 573–578; (b) N. P. Shirsath, S. M. Manohar and K. S. Joshi, *Mol. Cancer*, 2012, **11**, 77–88.
- 4 (a) L. Larsen, M. H. Benn, M. Parvez and N. B. Perry, Org. Biomol. Chem., 2005, 3, 3236–3241; (b) H. Tan, H. Liu, X. Chen, Y. Yuan, K. Chen and S. Qiu, Org. Lett., 2015, 17, 4050–4053.

- 5 For reviews, see: (a) R. E. Minto and C. A. Townsend, *Chem. Rev.*, 1997, **97**, 2537–2556; (b) S. Brase, A. Encinas, J. Keck and C. F. Nising, *Chem. Rev.*, 2009, **109**, 3903–3990.
- 6 For the asymmetric total synthesis of aflatoxins, see: (a) B. M. Trost and F. D. Toste, J. Am. Chem. Soc., 2003, 125, 3090–3100; (b) G. Zhou and E. J. Corey, J. Am. Chem. Soc., 2005, 127, 11958–11959; (c) W. Huang, A. Raja, B. Hong and G. Lee, Org. Lett., 2017, 19, 3494–3497. For the asymmetric formal total synthesis of aflatoxins, see: (d) J. P. Marino, Pure Appl. Chem., 1993, 65, 667–674; (e) E. R. Civitello and H. Rapoport, J. Org. Chem., 1994, 59, 3775–3782; (f) T. Bando and K. Shishido, Synlett, 1997, 665–666; (g) J. P. Marino, K. A. Kieler and M.-W. Kim, Tetrahedron, 2011, 67, 837–841. For the selected asymmetric total synthesis of other phloroglucinol natural products, see: (h) M. Charpentier, M. Hans and J. Jauch, Eur. J. Org. Chem., 2013, 4078–4084; (i) M. Charpentier and J. Jauch, Tetrahedron, 2017, 73, 6614–6623; (j) M. Cheng, J. Cao, X. Yang, L. Zhong, L. Hu, X. Lu, B. Hou, Y. Hu, Y. Wang, X. You, L. Wang, W. Ye and C. Li, Chem. Sci., 2018, 9, 1488–1495; (k) Y. Guo, Y. Zhang, M. Xiao and Z. Xie, Org. Lett., 2018, 20, 2509–2512.
- 7 For recent ortho-selective asymmetric transformations of phloroglucinol derivatives, see: (a) L. Albrecht, L. K. Ransborg, V. Lauridsen, M. Overgaard, T. Zweifel and K. A. Jørgensen, Angew. Chem., Int. Ed., 2011, 50, 12496–12500; (b) Z. Yang, Y. He and F. D. Toste, J. Am. Chem. Soc., 2016, 138, 9775–9778; (c) G. Li, Z. Li, Q. Gu and S. You, Org. Lett., 2017, 19, 1318–1321; (d) X. Han, C. Ye, F. Chen, Q. Chen, Y. Wang and X. Zeng, Org. Biomol. Chem., 2017, 15, 3401–3407.
- 8 For selected reviews on iminium catalysis, see: (a) G. Lelais and D. W. C. MacMillan, *Aldrichimica Acta*, 2006, **39**, 79–87; (b) A. Erkkila, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416–5470; (c) A. Moyano and R. Rios, *Chem. Rev.*, 2011, **111**, 4703–4832; (d) P. Melchiorre, *Angew. Chem., Int. Ed.*, 2012, **51**, 9748–9770; (e) S. Meninno and A. Lattanzi, *Chem. Commun.*, 2013, **49**, 3821–3832.
- 9 For ortho-selective reactions of naphthols and sesamol with enals, see: (a) L. Hong, L. Wang, W. Sun, K. Wong and R. Wang, J. Org. Chem., 2009, 74, 6881–6884; (b) P. H. Poulsen, K. S. Feu, B. M. Pza, F. Jensen and K. A. Jørgensen, Angew. Chem., Int. Ed., 2015, 54, 8203–8207; (c) B. M. Paz, L. Klier, L. Nasborg, V. H. Lauridsen, F. Jensen and K. A. Jørgensen, Chem. Eur. J., 2016, 22, 16810–16818;

- (*d*) M. Giardinetti, J. Marrot, C. Greck, X. Moreau and V. Coeffard, *J. Org. Chem.*, 2018, **83**, 1019–1025. For the organocatalytic cross-coupling-like reactions of bromo-phenols with enals, see: (*e*) X. Song, A. Song, F. Zhang, H. Li and W. Wang, *Nat. Commun.*, 2011, **2**, 524; (*f*) H. Zhang, C. Ma, Z. Zheng, R. Sun, X. Yu and J. Zhao, *Chem. Commun.*, 2018, **54**, 4935–4938.
- 10 For the pioneering works on the diarylprolinol silyl ethers, see: (a) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, 44, 794–797; (b) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, 44, 4212–4215; (c) H. Gotoh, R. Masui, H. Ogino, M. Shoji and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2006, 45, 6853–6856.
- 11 CCDC 1893156 (9b)†.
- 12 For selected racemic chemical synthesis of aflatoxins, see: (a) G. Buchi, D. M. Foulkes, M. Kurono and G. F. Mitchell, J. Am. Chem. Soc., 1966, 88, 4534-4536; (b) G. Buchi, D. M. Foulkes, M. Kurono, G. F. Mitchell and R. S. Schneider, J. Am. Chem. Soc., 1967, 89, 6745-6753; (c) J. C. Roberts, A. H. Sheppard, J. A. Knight and P. Roffey, J. Chem. Soc. C, 1968, 22-24; (d) G. Buchi and S. M. Weinreb, J. Am. Chem. Soc., 1971, 93, 746-752; (e) A. J. Castellino and H. Rapoport, J. Org. Chem., 1986, 51, 1006-1011; (f) G. Weeratunga, S. Home and R. Rodrigo, J. Chem. Soc., Chem. Commun., 1988, 721-722; (g) S. Home, G. Weeratunga and R. Rodrigo, J. Chem. Soc., Chem. Commun., 1990, 39-41; (h) M. Koreeda, L. A. Dixon and J. D. Hsi, Synlett, 1993, 555-556; (i) M. C. Pirrung and Y. R. Lee, Trtrahedron Lett., 1996, 37, 2391-2394; (j) L. K. Casillas and C. A. Townsend, J. Org. Chem., 1999, 64, 4050-4059; (k) T. L. Graybill, E. G. Casillas, K. Pal and C. A. Townsend, J. Am. Chem. Soc., 1999, 121, 7729-7746; (l) W. E. Noland and B. L. Kedrowski, Org. Lett., 2000, 2, 2109-2111; (m) D. W. Udwary, L. K. Casillas and C. A. Townsend, J. Am. Chem. Soc., 2002, 124, 5294-5303; (n) S. A. Eastham, S. P. Ingham, M. R. Hallett, J. Herbert, A. Modi, T. Morley, J. E. Painter, P. Patel, P. Quayle, D. C. Ricketts and J. Raftery, Tetrahedron, 2008, 64, 936-948.
- 13 The hemiacetal **13** and the opened hydroxyl aldehyde **13**' should be in equilibrium with each other and could not be separated by chromatography. The yield was reported for the mixtures, and the mixtures were used for the next step.