Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

Two Competitive but Switchable Organocatalytic Cascade Reaction Pathways: The Diversified Synthesis of Chiral Acetal-Containing Bridged Cyclic Compounds

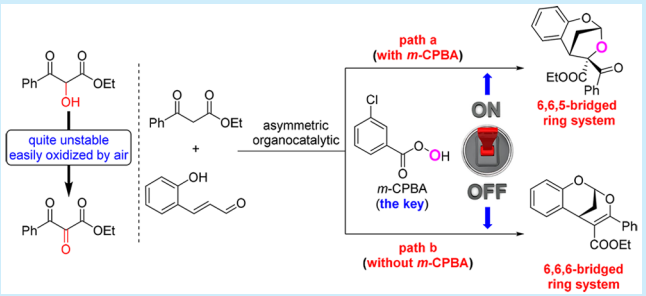
Xue-Jiao Lv,[†] Ying-Han Chen,[†] and Yan-Kai Liu*[,†,‡]

[†]Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China

[‡]Laboratory for Marine Drugs and Bioproducts of Qingdao National Laboratory for Marine Science and Technology, Qingdao 266003, China

Supporting Information

ABSTRACT: The organocatalytic enantioselective synthesis of methanobenzodioxepine derivatives bearing a 6,6,5-bridged ring system is presented. The *m*-CPBA-triggered in situ α-oxidation of β-oxoesters to provide the required but unstable α-hydroxy-β-dicarbonyl substrates is the key to this three-step sequence, providing the desired cyclic acetals with excellent stereoselectivities containing two bridgehead and one fully substituted stereocenters. It is noteworthy that the absence of *m*-CPBA furnished the acetal products bearing a 6,6,6-bridged ring system with similar good results from the same starting materials.

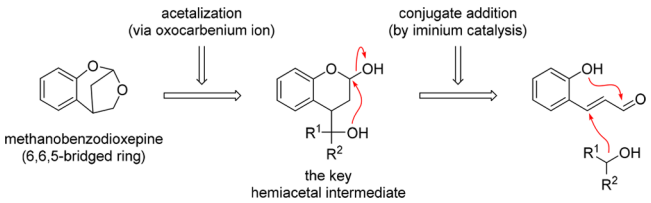


The chiral methanobenzodioxepine scaffold, containing two bridgehead carbon stereogenic centers, constitutes a privileged structural unit in many bioactive natural products and pharmaceuticals.[1] As a result, it has received considerable attention from chemists for the synthesis of this bridged cyclic acetal skeleton.[2] However, although a number of strategies have been developed, it has been found that the enantioselective construction of such a cyclic acetal moiety is quite challenging since almost no asymmetric catalytic approaches have been reported, which may be ascribed to the structural complexity and rigidity of the bridged cyclic system.[3]

In 2016, Jørgensen and co-workers reported the first example of an asymmetric iminium-catalytic Friedel–Crafts reaction to prepare chiral methanobenzodioxepine scaffolds.[4] However, the reaction was demonstrated as a competitive process between the synthesis of fused cyclic ketal and bridged cyclic acetal and thus limited to particular substrates bearing an aryl side chain for the regioselectivity. To the best of our knowledge, there is no other report on the enantioselective construction of chiral methanobenzodioxepine derivatives. Therefore, given their biological relevance, asymmetric synthetic strategies to construct chiral methanobenzodioxepine scaffold in a practical and efficient manner are still in great demand.

As shown in Scheme 1, a general retrosynthetic analysis of the methanobenzodioxepine scaffold possessing 6,6,5-bridged ring system leads to the key intermediate bearing a hemiacetal moiety and a free hydroxy group, which can be accessed by iminium-catalyzed conjugate addition of 2-hydroxycinnamaldehyde to a hydroxy-containing nucleophile followed by the acid-catalyzed intramolecular acetal formation.

Scheme 1. Retrosynthetic Analysis for the Synthesis of the Methanobenzodioxepine Scaffold



We recently focused on the application of hemiacetals in asymmetric organocatalysis[5] and found that 2-hydroxycinnamaldehyde could serve as a precursor of the 6,6-fused ring system in the synthesis of chiral polycyclic architectures via hemiacetal-containing intermediates.[6] We thus proposed that the application of α-hydroxy-β-dicarbonyl compounds as hydroxy-containing nucleophiles to react with 2-hydroxycinnamaldehyde seemed promising,[7] since α-hydroxy-β-dicarbonyl compounds have emerged as valuable synthons in many important chemical transformations.[8] It should be noted that α-hydroxy-β-dicarbonyl compound has never been used as a competent nucleophile in analogous reactions pathways.[9]

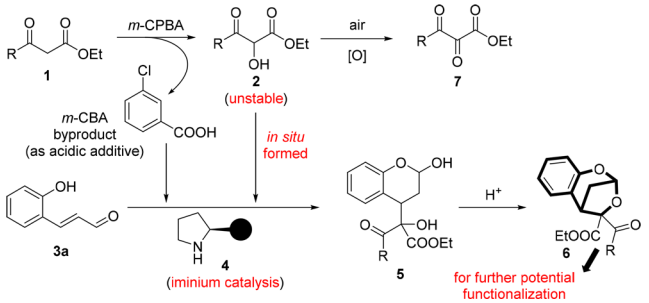
However, from the outset of our studies, the concept is considered to be particularly challenging because we found

Received: November 15, 2018

DOI: 10.1021/acs.orglett.8b03654
Org. Lett. XXXX, XXX, XXX–XXX

that α-hydroxy-β-dicarbonyl compound **2** was quite unstable toward air oxidation and easily converted into α,β-dioxocarbonyl **7** during the purification process by silica gel column chromatography (Scheme 2). We envisioned that the

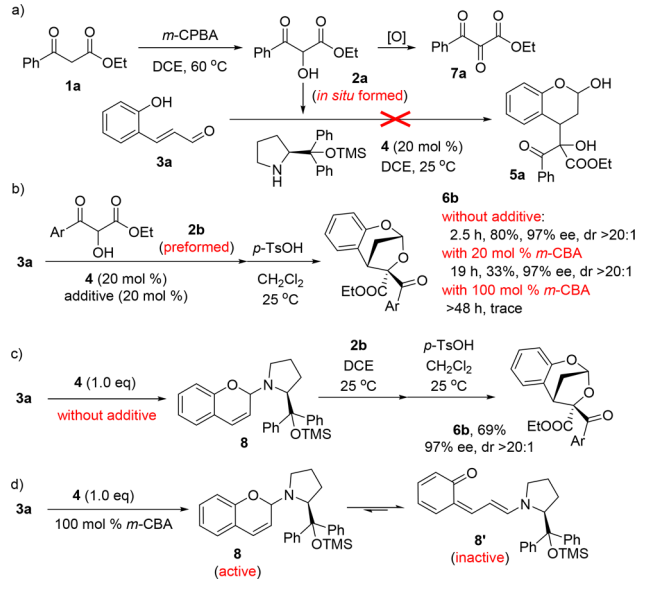
Scheme 2. Design of Synthetic Strategies



challenging issue could be addressed via the in situ oxidation of β-oxoesters **1** by *m*-chloroperbenzoic acid (*m*-CPBA),[10] where the byproduct *m*-chlorobenzoic acid (*m*-CBA) can further act as an acidic additive in the aminocatalyst **4** triggered iminium catalysis[11] to promote the reaction of 2-hydroxycinnamaldehyde **3a** and the in situ formed **2**, thus enabling a milder access to target the chiral methanobenzodioxepine scaffold **6** after oxocarbenium ion induced ring closure of the key intermediate **5**. Herein, we report our efforts to address this issue, which led to chiral methanobenzodioxepine scaffolds with a wide substrate scope in good yields and with excellent stereoselectivities. Nevertheless, there are still several issues with this design: (1) the undesired side reaction Baeyer−Villiger-type oxidation of β-oxoesters; (2) the oxidation of aminocatalyst resulting in complete loss of catalytic activity; and (3) the stereocontrolled creation of two bridgehead and one fully substituted stereocenters.

With these considerations in mind, we initially investigated the in situ oxidation of ethyl benzoylacetate **1a** with *m*-CPBA in 1,2-dichoroethane (DCE) at 60 °C (Scheme 3a). However, upon complete consumption of **1a**, the subsequent conjugate addition of **3a** and **2a** catalyzed by aminocatalyst **4** (20 mol %,

Scheme 3. Control Experiments

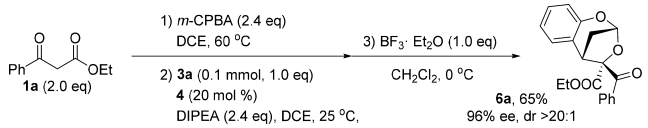


TMS = trimethylsilyl) at 25 °C in DCE did not provide the expected key intermediate hemiacetal **5a**. Meanwhile, most of **2a** was oxidized into **7a**. However, this is rather surprising because the electron induction of the hydroxy moiety could be expected to increase the acidity of the hydrogen atom at the α-position and the propensity toward an alkylation pathway.[12]

Indeed, when the preformed α-hydroxy-β-dicarbonyl **2b**, which was somewhat stable because of the strong electron-donating effect of the methoxy group, was used in the sequential reaction with **3a** in the presence of catalyst **4** and without acidic or basic additives (Scheme 3b, Ar = 4-$MeOC_6H_4$), the desired product **6b** was obtained in 80% yield with excellent stereoselectivity (97% ee, dr >20:1). When *m*-CBA (20 mol %) was used as the acidic additive, the reaction became sluggish (19 h, 33% yield), albeit with a high level of stereocontrol (97% ee, dr >20:1). Almost no reaction occurred (>48 h) when 100 mol % of *m*-CBA was used. Additionally, it is proposed that an active aminal intermediate **8** was formed from the reaction of **3a** with catalyst **4** in an almost quantitative yield,[13] and we also found that the preformed **2b** could be converted cleanly into **6b** by the reaction with aminal **8** (Scheme 3c, Ar = 4-$MeOC_6H_4$), and similar good results were obtained as compared to the direct sequential reaction path, which indicates that aminal **8** is involved in the catalytic process. However, to our surprise, a large amount of acidic additives, such as 100 mol % of *m*-CBA, significantly suppressed the reaction rate for the generation of the active aminal intermediate **8**, while the reaction between **3a** and catalyst **4** led to a mixture of **8** and *o*-quinone methides **8′**,[14] which is inactive for the conjugate addition with α-hydroxy-β-dicarbonyl **2** (Scheme 3d). In fact, this could explain why no hemiacetal **5a** was obtained due to the existence of 2.4 equiv of *m*-CBA in the reaction mixture as the byproducts.

Based on the above observations, we envisioned that the use of base would be essential, which plays two roles: (1) accelerating the formation of the active aminal intermediate **8** and (2) the deprotonative activation of α-hydroxy-β-dicarbonyl **2**. Much to our delight (Scheme 4), with the

Scheme 4. Sequential Synthesis of Chiral Methanobenzodioxepine Scaffold

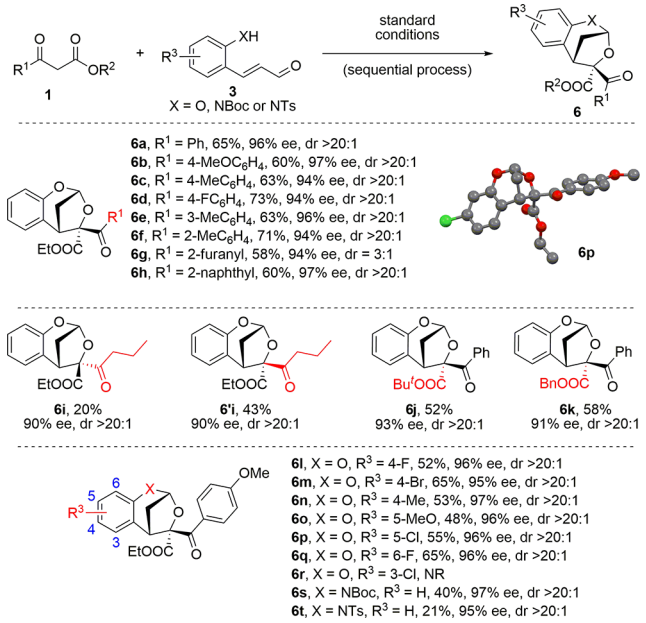


addition of *N*,*N*-diisopropylethylamine (DIPEA) to neutralize the byproducts *m*-CBA, the in situ oxidation triggered sequential reaction proceeded smoothly, providing the key intermediate **5a**, and the subsequent $BF_3{\cdot}Et_2O$-catalyzed acetal formation via oxocarbenium ion delivered the desired bridged cyclic acetal product **6a** in good isolated yield with excellent enantioselectivity as a single diastereoisomer.

Inspired by the success of the above model reaction, we next explored the substrate scope of the reaction sequence between 2-hydroxycinnamaldehydes **3** and the in situ formed **2**. As shown in Scheme 5, regardless of the electronic properties and the position of substituents on the phenyl ring of **1**, the reaction proceeded smoothly, providing products **6a−f** in good yields with good to excellent stereoselectivities. The heteroaryl- and naphthyl-substituted **1** also worked well in the reaction

DOI: 10.1021/acs.orglett.8b03654
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Substrate Scope of the Sequential Reaction of 2-Hydroxycinnamaldehydes 3 and in Situ Formed 2[a]

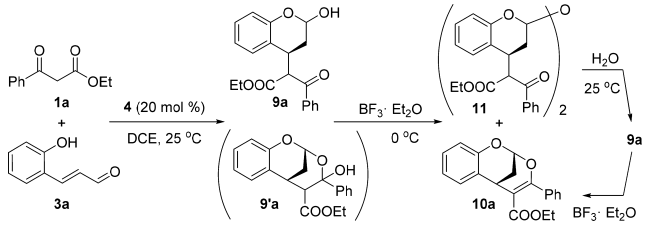


[a]All reactions were carried out using **1** (0.2 mmol, 2.0 equiv) and *m*-CPBA (0.24 mmol, 2.4 equiv) in DCE (0.2 mL) at 60 °C for 20 h to give the required *α*-hydroxy-*β*-dicarbonyl compound **2**. Then DIPEA (0.24 mmol, 2.4 equiv) was added to remove *m*-chlorobenzoic acid followed by the addition of **3** (0.10 mmol, 1.0 equiv) and **4** (20 mol %) to afford product **5**, which was cyclized in the presence of BF_3·Et_2O (1.0 equiv) at 0 °C in CH_2Cl_2 (1 mL) leading to product **6**. Isolated yields are given. Enantiomeric excesses (ee) are determined by chiral HPLC analysis. Diastereomeric ratios (dr) are determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Boc = *tert*-butoxycarbonyl; Ts = 4-toluenesulfonyl.

sequence, delivering the bridged cyclic products **6g** and **6h** in good results. It should be noted that **6g** was obtained as two inseparable diastereoisomer (3:1), while by using an alkyl group instead of an aryl group, the desired product was obtained as two separable epimers, **6i** and **6′i**, with slightly decreased enantioselectivity. Furthermore, the benzyl and *tert*-butyl benzoylacetates were tolerated in this sequential process (**6j** and **6k**), albeit with slightly lower enantioselectivities. For the 2-hydroxycinnamaldehyde substrates, both electron-donating and electron-withdrawing groups at different positions on the aromatic rings were compatible with this transformation, affording the products **6l−q** in good yield with excellent enantioselectivity. It should be noted that no reaction (NR) was observed with 3-Cl-substituted **3**, probably for steric reasons (**6r**) Furthermore, Boc- and Ts-protected 2-amino-cinnamaldehyde **3** were also found to be suitable substrates, and the desired bridged aminal-containing product **6s** and **6t** were obtained with excellent stereoselectivity, albeit in lower yield.

Indeed, during the optimization of reaction conditions for the synthesis of **6a**, a small amount of the undesired enol-containing bridged cyclic acetal **10a** was observed when there was an incomplete oxidation of ethyl benzoylacetate **1a**, and this original structure attracted our attention, which possesses a 6,6,6-bridged ring system. We then tested the reaction of 2-hydroxycinnamaldehyde **3a** and ethyl benzoylacetate **1a** in the presence of catalyst **4** in DCE at 25 °C (Scheme 6), leading to the hemiacetal intermediate **9a**, which was distinguished from

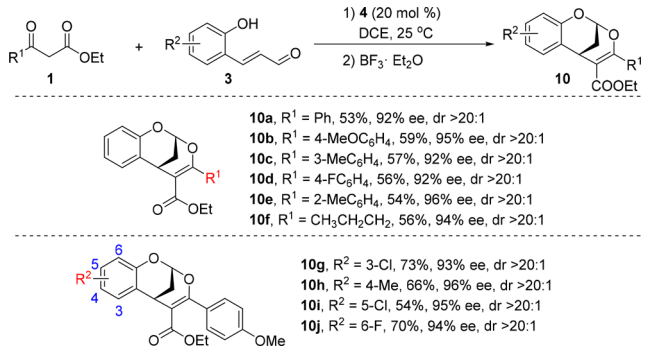
Scheme 6. Sequential Synthesis of Chiral 6,6,6-Bridged Ring Scaffold



the hemiketal isomer **9′a** by NMR spectroscopy (characteristic carbon of the ketone carbonyl moiety at δ 196.2 ppm).[15] Unexpectedly, when **9a** was treated with an excess of BF_3·Et_2O, the reaction mixture showed two new spots on TLC, and the more polar one gradually converted to the less polar one, which was confirmed to be the expected bridged cyclic acetal **10a** (92%, 53% ee, dr >20:1), while the more polar intermediate **11**, which was somewhat unstable to isolation, was characterized to be the dimer of **9a** by mass spectroscopy. Interestingly, we found that, in the presence of BF_3·Et_2O, the dimer **11** was first hydrolyzed to give **9a**, followed by ring-closure to afford **10a**.[16]

Encouraged by these initial results, we next focused on the scope of this sequential cascade transformation, involving a Michael addition, ketalization, and dehydration reaction sequence. As shown in Scheme 7, ethyl benzoylacetate **1**,

Scheme 7. Substrate Scope of the Sequential Reaction of 2-Hydroxycinnamaldehydes 3 and *β*-Oxoesters 1[a]



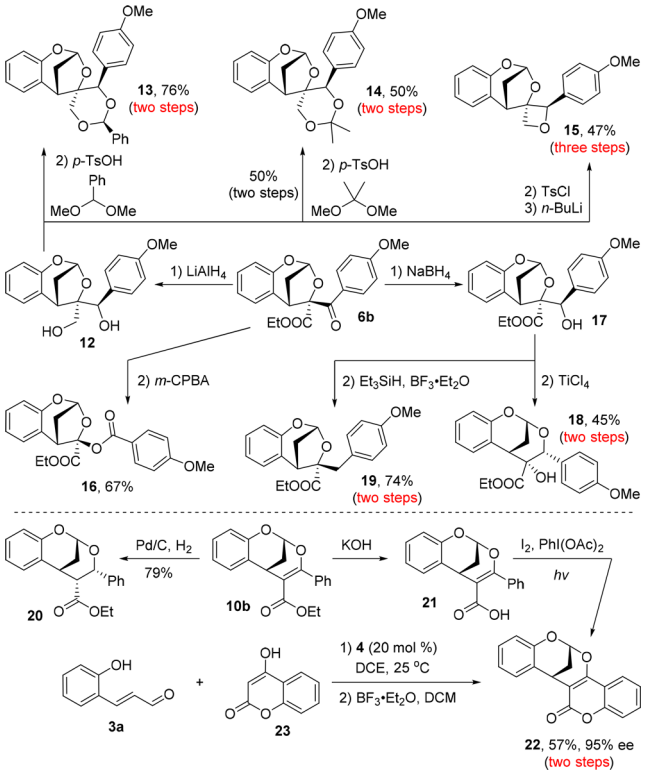
[a]Performed on 0.2 mmol scale with 1.1 equiv of **1** and 1.0 equiv of **3**. Isolated yields are given. Enantiomeric excess (ee) are determined by chiral HPLC analysis. Diastereomeric ratios (dr) are determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

bearing electronically different substituents at various positions of the aromatic ring, reacted smoothly with 2-hydroxycinnamaldehyde **3**, affording the enol-containing bridged cyclic acetal in good yield with high enantioselectivity as a single diastereoisomer (**10a−e**). This reaction sequenced is applicable to alkyl-substituted *β*-dicarbonyl (**10f**). Similar good results were also obtained regardless of the substituents on the aryl moiety of 2-hydroxycinnamaldehyde (**10g−j**).

As previously mentioned, the *β*-dicarbonyl moiety has emerged as a valuable synthon in many important chemical transformations, and then selected transformations were performed to demonstrate the synthetic utility of the corresponding cascade products **6b** and **10a** (Scheme 8). By using $LiAlH_4$ in THF at 0 °C, the reduction of **6b** gave the dihydroxy-bridged acetal **12** with an additional stereocenter

DOI: 10.1021/acs.orglett.8b03654
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 8. Useful Transformations



with complete stereocontrol. Compound **12** reacted with (dimethoxymethyl)benzene and 2,2-dimethoxypropane, respectively, in the presence of *p*-TsOH to produce **13** and **14**, both of which contained a spiro fully substituted stereogenic center. Notably, **13** was obtained as a single diastereoisomer with the creation of one new asymmetric center. Additionally, the regioselective tosylation of the primary hydroxyl group in **12** followed by *n*-BuLi-triggered ring closure via intramolecular O-nucleophilic substitution provided the spirocyclic product**15** containing a four-membered oxetane ring in 47% total yield over three steps. The Bayer−Villiger oxidation of the aryl ketone functionality with *m*-CPBA as the oxidant delivered the acyl-protected ketal **16** in 67% yield, maintaining excellent stereoselectivity. Moreover, a highly chemo- and stereoselective reduction of the ketone group with $NaBH_4$ resulted in secondary alcohol product **17**, followed by $TiCl_4$-catalyzed intramolecular transacetalization to generate 6,6,6-benzannulated bridged cyclic acetal **18** containing a fully substituted stereogenic center with a free hydroxy group. It is noteworthy that the newly formed bridged stereocenter of **18** can be introduced with complete stereoselectivity. Furthermore, in the presence of Et_3SiH and $BF_3{\cdot}Et_2O$, compound **17** was smoothly dehydroxylated to give enantiopure bridged acetal **19**. On the other hand, Pd/C-catalyzed hydrogenation of the double bond in **10b** yielded **20** as the only stereoisomeric product with two new chiral centers. Additionally, hydrolysis of **10b** afforded acid **21**, and when acid **21** was exposed to blue LED in the presence of $PhI(OAc)_2$ and I_2, oxidative cross coupling between C−H and O−H took place to afford the polycyclic coumarin-containing product **22** in 57% yield (two steps) with excellent stereoselectivity.[17] It should be noted that, starting from **3a** and 4-hydroxycoumarin **23**, product **22** could also be obtained, however, with poor results (45%, 28% ee).

The structure and stereochemistry of **6p** (CCDC 1878221) were unambiguously determined by single-crystal X-ray analysis (Scheme 5; the H atoms are omitted for clarity). All other compound structures were assigned by analogy to **6p** assuming a uniform reaction pathway. The absolute configuration of compounds **6i**, **13**, **18**, and **20** was determined by chemical correlation (see the Supporting Information for details).

In summary, we have developed a highly efficient organocatalytic three-step sequence for the construction of chiral methanobenzodioxepine derivatives containing two bridgehead and one fully substituted stereogenic centers with a wide substrate scope and with high stereoselectivity. The key to the success of this strategy was the in situ formed *α*-hydroxy-*β*-dicarbonyl **2** via the metal-free *α*-hydroxylation of *α*-unsubstituted *β*-dicarbonyl compounds by using *m*-CPBA as the oxidant. For the first time, *α*-hydroxy-*β*-keto esters were used in asymmetric organocatalytic cascade reactions to construct polyheterocyclic compounds bearing a 6,6,5-bridged ring system. Interestingly, the reaction sequence could proceed smoothly in the absence of *m*-CPBA, leading to different types of polycyclic acetals that possess a 6,6,6-bridged ring system. Moreover, based on the dicarbonyl functionality, several valuable transformations were realized to furnish spiro-bridged polycyclic acetals with high levels of structural complexity. The application of this in situ oxidation strategy to construct complex heterocyclic compounds is currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03654.

Detailed optimization, experimental procedures, spectroscopic data for all new compounds, and X-ray data (PDF)

Accession Codes

CCDC 1878221 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuyankai@ouc.edu.cn.

ORCID

Yan-Kai Liu: 0000-0002-6559-2348

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC−Shandong Joint Fund for Marine Science Research Centers (No. U1606403) and the Scientific and Technological Innovation Project Financially Supported by Qingdao National Laboratory for Marine Science and Technology (No. 2015ASKJ02-06).

DOI: 10.1021/acs.orglett.8b03654
Org. Lett. XXXX, XXX, XXX−XXX

REFERENCES

(1) (a) Castagnino, C.; Vercauteren, J. Castavinol, a new series of polyphenols from Bordeaux red wines. *Tetrahedron Lett.* **1996**, *37*, 7739. (b) Larsen, L.; Benn, M. H.; Parvez, M.; Perry, N. B. A cytotoxic triketone−phloroglucinol−bullatenone hybrid from Lophomyrtus bullata. *Org. Biomol. Chem.* **2005**, *3*, 3236. (c) Luo, W.; Yu, Q.-S.; Holloway, H. W.; Parrish, D.; Greig, N. H.; Brossi, A. Syntheses of tetrahydrofurobenzofurans and dihydromethanobenzodioxepines from 5-hydroxy-3-methyl-3*H*-benzofuran-2-one. Rearrangement and ring expansion under reductive conditions on treatment with hydrides. *J. Org. Chem.* **2005**, *70*, 6171. (d) Luo, W. M.; Yu, Q.-S.; Zhan, M.; Parrish, D.; Deschamps, J. R.; Kulkarni, S. S.; Holloway, H. W.; Alley, G. M.; Lahiri, D. K.; Brossi, A.; Greig, N. H. Novel anticholinesterases based on the molecular skeletons of furobenzofuran and methanobenzodioxepine. *J. Med. Chem.* **2005**, *48*, 986. (e) Luo, W.; Yu, Q.-S.; Kulkarni, S. S.; Parrish, D. A.; Holloway, H. W.; Tweedie, D.; Shafferman, A.; Lahiri, D. K.; Brossi, A.; Greig, N. H. Inhibition of human acetyl- and butyrylcholinesterase by novel carbamates of (−)- and (+)-tetrahydrofurobenzofuran and methanobenzodioxepine. *J. Med. Chem.* **2006**, *49*, 2174. (f) Kamal, M. A.; Qu, X.; Yu, Q.-s.; Tweedie, D.; Holloway, H. W.; Li, Y.; Tan, Y.; Greig, N. H. Tetrahydrofurobenzofuran cymserine, a potent butyrylcholinesterase inhibitor and experimental Alzheimer drug candidate, enzyme kinetic analysis. *J. Neural Transm.* **2008**, *115*, 889. (g) Woollard, J. M. R.; Perry, N. B.; Weavers, R. T.; van Klink, J. W. Bullatenone, 1,3-dione and sesquiterpene chemotypes of Lophomyrtus species. *Phytochemistry* **2008**, *69*, 1313. (h) Chaudhaery, S. S.; Roy, K. K.; Shakya, N.; Saxena, G.; Sammi, S. R.; Nazir, A.; Nath, C.; Saxena, A. K. Novel carbamates as orally active acetylcholinesterase inhibitors found to improve scopolamine-induced cognition impairment: pharmacophore-based virtual screening, synthesis, and pharmacology. *J. Med. Chem.* **2010**, *53*, 6490. (i) El Hattab, M.; Genta-Jouve, G.; Bouzidi, N.; Ortalo-Magné, A.; Hellio, C.; Maréchal, J.-P.; Piovetti, L.; Thomas, O. P.; Culioli, G. Cystophloroketals A−E, unusual phloroglucinol−meroterpenoid hybrids from the brown alga cystoseira tamariscifolia. *J. Nat. Prod.* **2015**, *78*, 1663. (j) Yang, D.; Xie, H.; Jiang, Y.; Wei, X. Phenolics from strawberry cv. Falandi and their antioxidant and α-glucosidase inhibitory activities. *Food Chem.* **2016**, *194*, 857.

(2) (a) Chen, P. N.; Kingston, D. G. I.; Vercellotti, J. R. Reduction of sterigmatocystin and versicolorin A hemiacetals with sodium borohydride. *J. Org. Chem.* **1977**, *42*, 3599. (b) Graybill, T. L.; Pal, K.; McGuire, S. M.; Brobst, S. W.; Townsend, C. A. The timing of aromatic deoxygenation in aflatoxin biosynthesis. *J. Am. Chem. Soc.* **1989**, *111*, 8306. (c) Graybill, T. L.; Casillas, E. G.; Pal, K.; Townsend, C. A. Silyl triflate-mediated ring-closure and rearrangement in the synthesis of potential bisfuran-containing intermediates of aflatoxin biosynthesis. *J. Am. Chem. Soc.* **1999**, *121*, 7729. (d) Schnermann, M. J.; Beaudry, C. M.; Egorova, A. V.; Polishchuk, R. S.; Sütterlin, C.; Overman, L. E. Golgi-modifying properties of macfarlandin E and the synthesis and evaluation of its 2,7-dioxabicyclo[3.2.1]octan-3-one core. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 6158. (e) Tan, H.; Liu, H.; Chen, X.; Yuan, Y.; Chen, K.; Qiu, S. Concise construction of the tricyclic core of bullataketals enabled by a biomimetic intermolecular (3 + 3) type cycloaddition. *Org. Lett.* **2015**, *17*, 4050. (f) Ievlev, M. Y.; Ershov, O. V. Synthesis of 2,7-dioxabicyclo[3.2.1]octanes (microreview). *Chem. Heterocycl. Compd.* **2016**, *52*, 213. (g) Ivanov, K. L.; Vatsouro, I. M.; Bezzubov, S. I.; Melnikov, M. Y.; Budynina, E. M. Domino construction of a bullataketal core via double bond cleavage in activated dihydrofurans. *Org. Chem. Front.* **2018**, *5*, 1655.

(3) Zhu, Y.; Zhou, J.; Jin, S.; Dong, H.; Guo, J.; Bai, X.; Wang, Q.; Bu, Z. Metal-free diastereoselective construction of bridged ketal spirooxindoles via a Michael addition-inspired sequence. *Chem. Commun.* **2017**, *53*, 11201.

(4) Paz, B. M.; Klier, L.; Næsborg, L.; Lauridsen, V. H.; Jensen, F.; Jørgensen, K. A. Enantioselective organocatalytic cascade approach to different classes of benzofused acetals. *Chem. - Eur. J.* **2016**, *22*, 16810.

(5) (a) Liu, Y.-K.; Li, Z.-L.; Li, J.-Y.; Feng, H.-X.; Tong, Z.-P. Open−close: an alternative strategy to α-functionalization of lactone via enamine catalysis in one pot under mild conditions. *Org. Lett.* **2015**, *17*, 2022. (b) Cai, P.-W.; You, Z.-H.; Xie, L.-H.; Tan, R.; Tong, Z.-P.; Liu, Y.-K. The attractive application of lactol chemistry: from racemic lactol to natural product skeleton. *Synthesis* **2016**, *48*, 2581. (c) Li, J.-Y.; Li, Z.-L.; Zhao, W.-W.; Liu, Y.-K.; Tong, Z.-P.; Tan, R. One-pot, highly efficient, asymmetric synthesis of ring-fused piperidine derivatives bearing N,O- or N,N-acetal moieties. *Org. Biomol. Chem.* **2016**, *14*, 2444. (d) Li, J.-Y.; Yu, K.-W.; Xie, C.-C.; Liu, Y.-K. Lactols in an asymmetric aldol-desymmetrization sequence: access to tetrahydro-4*H*-furo[2,3-*b*]pyran-2-one and tetrahydro-4*H*-furo[2,3-*b*]furan-2-one derivatives. *Org. Biomol. Chem.* **2017**, *15*, 1407. (e) Liu, C.; Liu, Y.-K. Asymmetric organocatalytic one-pot, two-step sequential process to synthesize chiral acetal-containing polycyclic derivatives from cyclic hemiacetals and enones. *J. Org. Chem.* **2017**, *82*, 10450. (f) You, Z.-H.; Chen, Y.-H.; Wu, X.-N.; Liu, Y.-K. Lactols in asymmetric sequential organo- and gold-catalysis: synthesis of densely functionalized epimeric bicyclic O,O-acetals. *Adv. Synth. Catal.* **2017**, *359*, 4260. (g) Zhao, W.-W.; Liu, Y.-K. Enantio- and diastereoselective synthesis of tetrahydrofuro[2,3-*b*]furan-2(3*H*)-one derivatives and related oxygen heterocycles via an asymmetric organocatalytic cascade process. *Org. Chem. Front.* **2017**, *4*, 2358. (h) Pei, J.-P.; Chen, Y.-H.; Liu, Y.-K. Asymmetric organocatalytic sequential reaction of structurally complex cyclic hemiacetals and functionalized nitro-olefins to synthesize diverse heterocycles. *Org. Lett.* **2018**, *20*, 3609. (i) Wu, X.-N.; You, Z.-H.; Liu, Y.-K. Different hybridized oxygen atoms controlled chemoselective formation of oxocarbenium ions: synthesis of chiral heterocyclic compounds. *Org. Biomol. Chem.* **2018**, *16*, 6507.

(6) (a) Sun, X.-L.; Chen, Y.-H.; Zhu, D.-Y.; Zhang, Y.; Liu, Y.-K. Substrate-controlled, one-pot synthesis: access to chiral chroman-2-one and polycyclic derivatives. *Org. Lett.* **2016**, *18*, 864. (b) Chen, Y.-H.; Sun, X.-L.; Guan, H.-S.; Liu, Y.-K. Diversity-oriented one-pot synthesis to construct functionalized chroman-2-one derivatives and other heterocyclic compounds. *J. Org. Chem.* **2017**, *82*, 4774. (c) You, Z.-H.; Chen, Y.-H.; Tang, Y.; Liu, Y.-K. Organocatalytic asymmetric synthesis of spiro-bridged and spiro-fused heterocyclic compounds containing chromane, indole, and oxindole moieties. *Org. Lett.* **2018**, *20*, 6682.

(7) (a) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. Organocatalytic asymmetric synthesis of á,á-disubstituted á-amino acids and derivatives. *J. Am. Chem. Soc.* **2008**, *130*, 12031. (b) Lee, Y.; Seo, S. W.; Kim, S.-G. Highly enantioselective conjugate addition−cyclization cascade reaction of malonates with *o*-hydroxycinnamaldehydes: asymmetric synthesis of 4-substituted chromanols. *Adv. Synth. Catal.* **2011**, *353*, 2671. (c) Cruz Cruz, D.; Mose, R.; Villegas Gómez, C.; Torbensen, S. V.; Larsen, M. S.; Jørgensen, K. A. Organocatalytic cascade reactions: towards the diversification of hydroisochromenes and chromenes through two different activation modes. *Chem. - Eur. J.* **2014**, *20*, 11331. (d) Kim, Y. S.; Kim, S. M.; Wang, B.; Companyó, X.; Li, J.; Moyano, A.; Im, S.; Tošner, Z.; Yang, J. W.; Rios, R. Expanding the scope of the organocatalytic addition of fluorobis(phenylsulfonyl)-methane to enals: enantioselective cascade synthesis of fluoroindane and fluorochromanol derivatives. *Adv. Synth. Catal.* **2014**, *356*, 437. (e) Ackrill, T. D.; Sparkes, H. A.; Willis, C. L. Synthesis of diarylheptanoid scaffolds inspired by calyxins I and J. *Org. Lett.* **2015**, *17*, 3884. (f) Næsborg, L.; Tur, F.; Meazza, M.; Blom, J.; Halskov, K. S.; Jørgensen, K. A. Synergistic catalysis for the asymmetric [3 + 2] cycloaddition of vinyl aziridines with α,β-unsaturated aldehydes. *Chem. - Eur. J.* **2017**, *23*, 268. (g) Maity, R.; Pan, S. C. Organocatalytic asymmetric Michael/hemiacetalization/acyl transfer reaction of α-nitroketones with *o*-hydroxycinnamaldehydes: synthesis of 2,4-disubstituted chromans. *Org. Biomol. Chem.* **2018**, *16*, 1598.

(8) For a review, see: (a) Christoffers, J.; Baro, A.; Werner, T. α-Hydroxylation of β-dicarbonyl compounds. *Adv. Synth. Catal.* **2004**, *346*, 143. For selected examples of α-hydroxy-β-dicarbonyl compounds in reactions, see: (b) Zhu, J.; Klunder, A. J. H.;

DOI: 10.1021/acs.orglett.8b03654
Org. Lett. XXXX, XXX, XXX−XXX

Zwanenburg, B. Stereospecific total synthesis of (−)-kjellmanianone and a revision of its absolute configuration. *Tetrahedron Lett.* **1994**, *35*, 2787. (c) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. Chemistry of Sponges. 19. Novel Bioactive Metabolites from Hamigera tarangaensis. *J. Nat. Prod.* **2000**, *63*, 79. (d) Christoffers, J.; Werner, T.; Frey, W.; Baro, A. Straightforward synthesis of (*R*)-(−)-kjellmanianone. *Chem. - Eur. J.* **2004**, *10*, 1042. (e) Park, J.-H.; Chang, J.-S.; El-Gamal, M. I.; Choi, W.-K.; Lee, W. S.; Chung, H. J.; Kim, H.-I.; Cho, Y.-J.; Lee, B. S.; Jeon, H.-R.; Lee, Y. S.; Choi, Y. W.; Lee, J.; Oh, C.-H. Novel amides and esters prodrugs of olmesartan: Synthesis, bioconversion, and pharmacokinetic evaluation. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5895.

(9) Companyó, X.; Mazzanti, A.; Moyano, A.; Janecka, A.; Rios, R. First one-pot organocatalytic synthesis of α-methylene-γ-lactones. *Chem. Commun.* **2013**, *49*, 1184.

(10) Asahara, H.; Nishiwaki, N. Metal-free α-hydroxylation of α-unsubstituted β-oxoesters and β-oxoamides. *J. Org. Chem.* **2014**, *79*, 11735.

(11) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New strategies for organic catalysis: the first highly enantioselective organocatalytic Diels−Alder reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(12) Bergonzini, G.; Melchiorre, P. Dioxindole in asymmetric catalytic synthesis: routes to enantioenriched 3-substituted 3-hydroxyoxindoles and the preparation of maremycin A. *Angew. Chem., Int. Ed.* **2012**, *51*, 971.

(13) Zu, L.; Zhang, S.; Xie, H.; Wang, W. Catalytic Asymmetric oxa-Michael−Michael Cascade for Facile Construction of Chiral Chromans via an Aminal Intermediate. *Org. Lett.* **2009**, *11*, 1627.

(14) Ramachary, D. B.; Shiva Prasad, M.; Vijaya Laxmi, S.; Madhavachary, R. Asymmetric synthesis of drug-like spiro[chroman-3,3′-indolin]-2′-ones through aminal-catalysis. *Org. Biomol. Chem.* **2014**, *12*, 574.

(15) See the Supporting Information for more details.

(16) No product formation of **10a** from **11** was observed in the presence of molecular sieves, which indicated H_2O is crucial for the transformation processes.

(17) (a) Kim, K. E.; Li, J.; Grubbs, R. H.; Stoltz, B. M. Catalytic anti-markovnikov transformations of hindered terminal alkenes enabled by aldehyde-selective wacker-type oxidation. *J. Am. Chem. Soc.* **2016**, *138*, 13179. (b) Andersen, T. L.; Frederiksen, M. W.; Domino, K.; Skrydstrup, T. Direct access to α,α-difluoroacylated arenes by palladium-catalyzed carbonylation of (hetero)aryl boronic acid derivatives. *Angew. Chem., Int. Ed.* **2016**, *55*, 10396. (c) Wang, S.; Xi, C. Nickel-catalyzed arylative carboxylation of alkynes with arylmagnesium reagents and carbon dioxide leading to trisubstituted acrylic acids. *Org. Lett.* **2018**, *20*, 4131.

DOI: 10.1021/acs.orglett.8b03654
Org. Lett. XXXX, XXX, XXX−XXX