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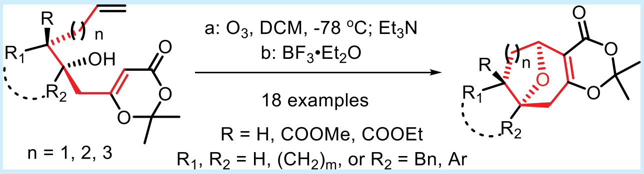
Synthesis of Oxa-Bridged Medium-Sized Carbocyclic Rings via Prins Cyclization

Min-Shou Wang, Zheng Wang, Wen Chen, Xiaodong Yang,* and Hongbin Zhang*

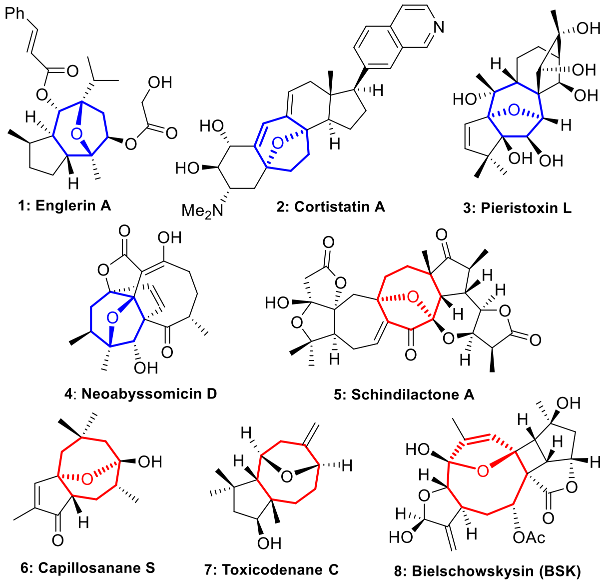
Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education and Yunnan Province, State Key Laboratory for Conservation and Utilization of Bio-Resources in Yunnan, School of Chemical Science and Technology, Yunnan University, Kunming, Yunnan 650091, P. R. China

Supporting Information

ABSTRACT: Herein, we report a new method for the synthesis of oxa-bridged carbocyclic units based on intramolecular Prins reaction of dioxinones. Our new synthetic approach is flexible and practical and has been successfully applied to the preparation of highly functionalized seven-, eight-, and nine-membered carbocycles. The potential utility of this approach has also been demonstrated in a model study toward construction of the 7,8-fused ring system presented in neoabyssomicin D.



In nature, there are a large number of natural products containing oxa-bridged bicyclic (OBB) structure units.[1] Among them, the seven- and eight-membered ring derivatives are especially attractive due to their existence in a number of highly bioactive natural products.[2] In Figure 1, some representative compounds are illustrated, such as englerin A (**1**), which exhibits potent and selective inhibitory activity (GI_{50} < 20 nm) against renal cell carcinoma;[3] cortistatin A (**2**), which inhibits the proliferation of human umbilical vein endothelial cells (HUVECs, IC_{50} = 1.8 nM);[4] and toxicodenane C (**7**), which exhibits antidiabetic nephropathy activity.[5] Due to their unique structures as well as their biological importance, these oxa-bridged medium-sized carbocycles have attracted considerable attention from the synthetic community.[6] To date, numerous methodologies, such as gold-catalyzed alkyne cycloisomerization reactions,[7] Lewis acid mediated intramolecular cross-cycloadditions,[8] photoinduced cyclizations,[9] 1,3-dipolar cycloadditions,[10] [5 + 2] dipolar cycloaddition of oxidopyrylium ylides,[11,6c] ring-closing metathesis (RCM),[12] Prins-type cyclizations,[13] and [4 + 3] cycloadditions[14] have been developed for the synthesis of OBB ring systems. Despite the above-mentioned methods, practical and flexible strategies (i.e., short steps, cheap commercially available starting materials and reagents, easy-to-handle reaction conditions, gram-scale procedure, and stereoselectivity) leading to the synthesis of seven-, eight-, and nine-membered rings are still in great demand.[6a,14e] In this paper, we report a Lewis-acid-mediated Prins cyclization approach for constructing medium-sized carbocycles bearing oxa-bridged bicyclic structural units.



1: Englerin A
2: Cortistatin A
3: Pieristoxin L
4: Neoabyssomicin D
5: Schindilactone A
6: Capillosanane S
7: Toxicodenane C
8: Bielschowskysin (BSK)

Figure 1. Representative natural products bearing seven-, eight-, and nine-membered OBB rings.

In 1991, Molander's group reported an elegant vinylogous aldol-addition/Prins-cyclization annulative approach[6i,15] toward the synthesis of oxa-bridged seven- and eight-membered ring systems via the reaction of a *β*-dicarbony1-l,3-dianionic equivalent, normally bis(trimethylsilyl) enol ether, with 1,4- or 1,5-dielectrophiles under the catalysis of Lewis acids (Scheme 1, eq 1). The asymmetric version for the synthesis of seven- and eight-membered rings based on this annulation was also developed by using chiral substrates (Scheme 1, eq 2). Recently, we initiated a research program toward the synthesis of neoabyssomicin D. A practical method for the construction of the oxa-bridged bicyclic ring system is required. We noticed that the volatile and unstable dicarbonyl compounds were

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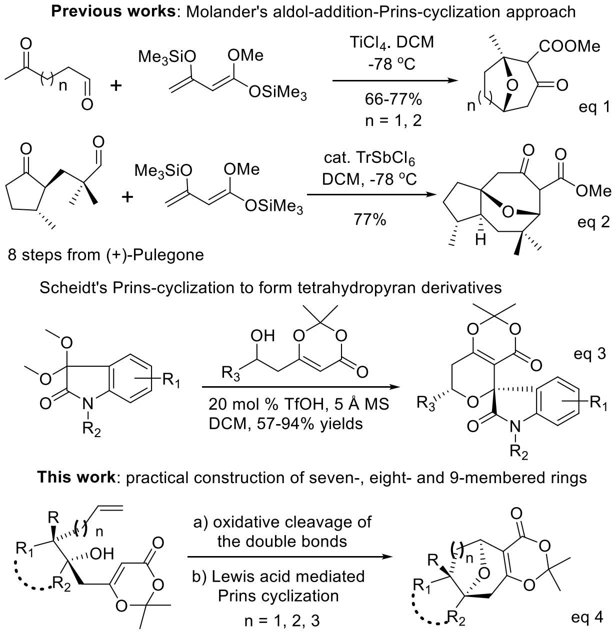
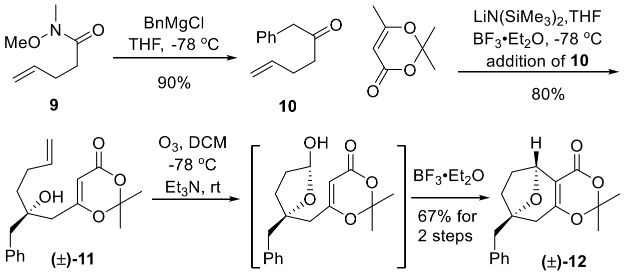
Scheme 1. Synthetic Approaches toward Medium-Sized Rings



difficult to handle.[16] Inspired by Molander's work and Scheidt's recent application of β-hydroxy dioxinones in the synthesis of tetrahydropyran-4-ones (Scheme 1, eq 3),[17] we proposed an oxidative-cleavage/Prins-cyclization approach toward the synthesis of highly functional oxa-bridged seven-, eight-, and nine-membered rings aiming for the core structures indicated in Figure 1. We envisioned that an olefin substrate bearing a dioxinone moiety would be much easier to handle, after oxidative cleavage of the double bond, and an intramolecular Prins reaction would provide the desired products. Our synthetic methodology is outlined in Scheme 1 (eq 4).

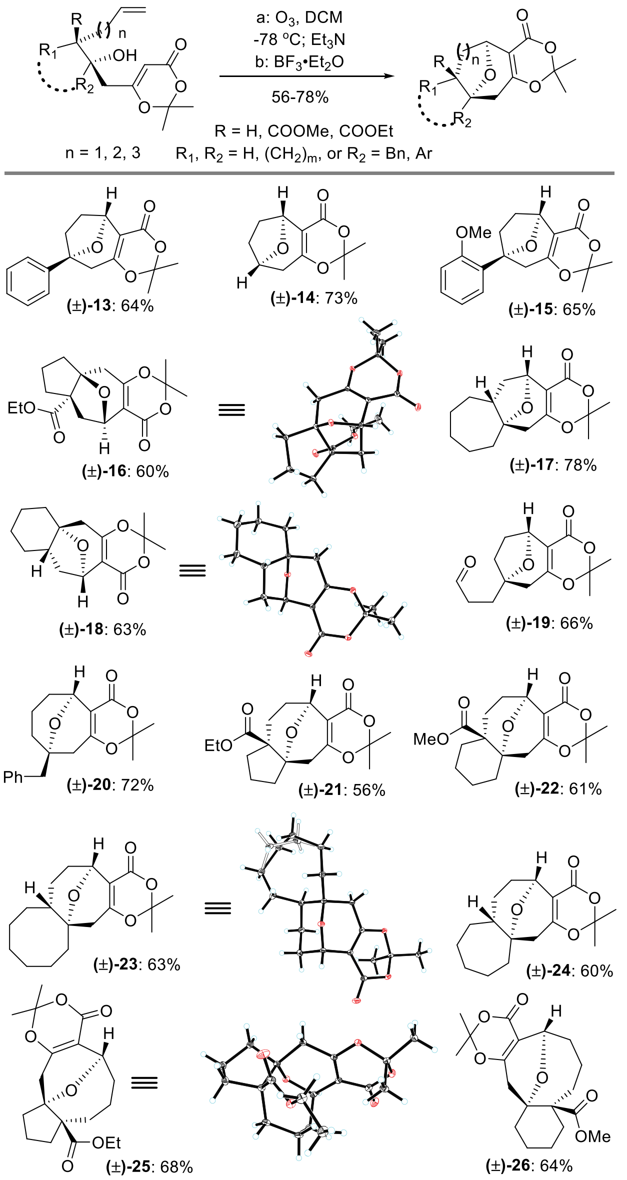
To test the intramolecular Prins reaction, we used amide **9** as starting material for initial studies. Reaction of amide **9** with benzyl magnesium chloride afforded ketone **10** in 90% yield (Scheme 2). Next we conducted the vinylogous addition according to our previously established reaction conditions.[18] Alcohol **11** was obtained in 87% yield. This two-step procedure quickly set the stage for the proposed oxidative cleavage and Prins cyclization. Ozonolysis of the double bond provided the semiketal, which presumably formed an oxonium ion upon treatment with $BF_3 \cdot Et_2O$, and finally cyclization gave the desired oxa-bridged compound **12** in a two-step operation (67% yield). The stereochemistry was totally controlled by the orientation of the hydroxyl group through formation of a semiketal intermediate.

Scheme 2. Initial Studies toward Medium-Sized Ring Synthesis



Having established the procedure based on intramolecular Prins reaction, we next turned our attention to extending the general utility of this process toward the synthesis of other medium-sized ring systems. Due to the unfavorable entropic and enthalpic factors, synthesis of eight- and nine-membered rings is challenging.[6] To our delight, a number of polycyclic compounds containing eight-membered rings could be synthesized under the optimal reaction conditions (Scheme 3). The substrates bearing cyclopentane, cyclohexane, cycloheptane, and cyclooctane (**16**−**18**, **21**−**26**) also worked well and afforded the corresponding tetracyclic products in 56−78% yields (two steps). Notably, the seven−eight fused (**24**) and eight−eight fused (**23**) ring systems could be constructed, and even nine-membered carbocycles (Scheme 3, **25** and **26**) were obtained by this methodology. The angular carbome-

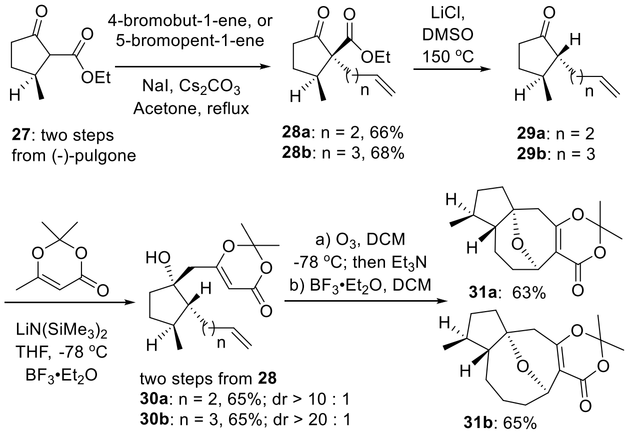
Scheme 3. Synthesis of 7/8/9-Membered Oxa-Bridged Rings



thoxy (or carboethoxy) containing substrates also provided the desired products in good yields (**16**, **21**, **22**, **25**, and **26**).

Having demonstrated the versatility of intramolecular dioxinone Prins reaction in the synthesis of the medium-sized ring system, we next examined the diastereoselectivity of this methodology through gram-scale asymmetric synthesis of the 5,8-fused and 5,9-fused bicyclic rings. Treatment of β-ketoester **27**, obtained in 2 steps from (−)-pulgone,[19] with 4-bromo-1-butene and 5-bromo-1-pentene afforded olefins **28a** and **28b** (Scheme 4). Ketones **29a** and **29b** were obtained under Krapcho conditions.[20] After reaction with dioxinone-derived lithium dienolate, alcohols **30a** and **30b** were obtained both in 65% yields, respectively. The diastereoselectivities in the vinylogous addition step were excellent, with the desired product being isolated as the major products. Ozonolysis of **30a** and **30b** followed by treatment of the crude aldehydes with BF$_3$·Et$_2$O afforded the desired carbocycles in good yields (Scheme 4).

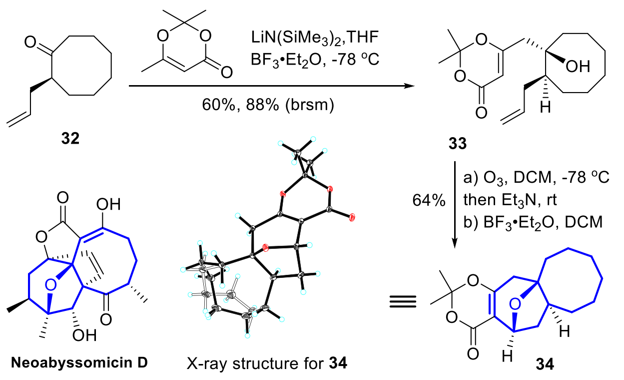
Scheme 4. Asymmetric Synthesis of 5/8- and 5/9-Fused Carbocycles from Chiral Starting Material



Finally, we conducted a model study to construct the 7,8-fused ring system presented in neoabyssomicin D. Starting from ketone **32**, the vinylogous addition provided **33** in 60% yield. After ozonolysis and treatment with BF$_3$·Et$_2$O, the desired 7,8-fused ring product was obtained in 64% yield (Scheme 5).

In conclusion, we have developed a practical and straightforward method for the synthesis of medium-sized OBB rings presented in a number of natural products based on an oxidative-cleavage/Prins-cyclization procedure. This annulation approach is flexible and enables entry to a number of highly functionalized fused carbocycles. Reactions in this new methodology are easy to handle and highly diastereoselective and can be carried out in gram scales. Finally, the utility of this approach has also been demonstrated in a model study toward rapid construction of the core skeleton of neoabyssomicin D. Our new process would be applicable for the synthesis of natural products containing oxa-bridged bicyclic seven-, eight-, and nine-membered rings.

Scheme 5. Model Study toward Neoabyssomicin D



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00491.

Experimental procedures, characterization data, and spectra of all key intermediates (PDF)

Accession Codes

CCDC 1895118–1895120 and 1895122–1895123 contain 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 Authors

*E-mail: zhanghb@ynu.edu.cn.
*E-mail: xdyang@ynu.edu.cn.

ORCID

Hongbin Zhang: 0000-0002-2516-2634

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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