Organic LETTERS

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A Chiral Pentenolide-Based Unified Strategy toward Dihydrocorynantheal, Dihydrocorynantheol, Protoemetine, Protoemetinol, and Yohimbane

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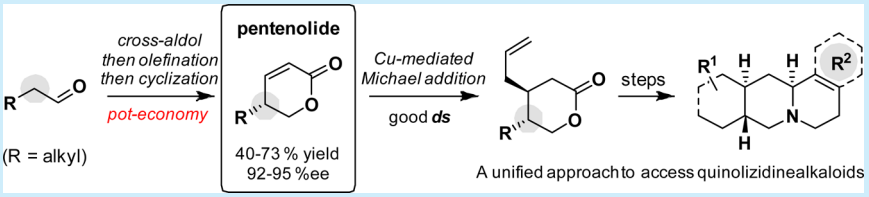
Supporting Information



ABSTRACT: An organocatalytic cross-aldol reaction of formaldehyde (formalin) with alkyl aldehydes, followed by the *Z*-selective Horner−Wadsworth−Emmons (HWE) reaction and immediate lactonization, afforded γ-alkylated pentenolides in good overall yields and excellent enantioselectivities. Based on this scalable sequence, five quinolizidine alkaloids were synthesized in a unified and concise manner. The development of an in situ activation of a tertiary amide to improve the efficiency of the Bischler−Napieraiski (B−N) reaction was also noteworthy due to the generality to sensitive substrates for a variety of target molecules.

δ-Lactones are widely embedded in numerous natural products and pharmaceutical intermediates and are versatile building blocks for organic synthesis.[1] Given the wealth of substituent patterns on the ring system, the development of efficient methods to synthesize δ-lactones has become a topic of constant interest in the synthetic community. Among the literature precedents to access δ-lactones, pentenolide (**1**) (IUPAC name: 5,6-dihydro-2*H*-pyran-2-one) is a common precursor to readily implement a variety of functional groups (Scheme 1a). For instance, new stereogenic centers can be readily installed through a stereoselective Michael addition at C4 and subsequent alkyl or aldol reactions at C3. Indeed, its versatile reactivity has been recognized by the synthetic community in the past several decades.[2] Among all novel synthetic methods to access chiral pentenolides, ring closing metathesis (RCM) has been widely adopted due to the readily availability of chiral allylic alcohols.[3] We noticed, however, that the diluted reaction system would be a bottleneck for the scalability of this protocol. Recently, Liu and co-workers developed an Evan's chiral auxiliary-based Michael addition/elimination cascade to complete the preparation of chiral 5-methyl-pentenolide (**2a**, R = Me).[4] Although the reaction was readily scalable, a catalytic asymmetric variant to access such versatile chiral lactones is still of great interest.

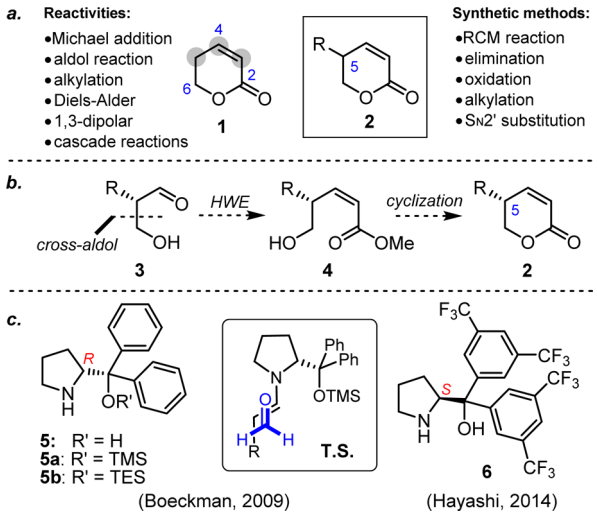
We envisioned a potentially short and practical approach to construct the requisite structure (Scheme 1b). In this proposal, aldol product **3** should be immediately used for olefination to give *Z*-isomer **4**, which is expected to carry out the ensuing lactonization to deliver pentenolide **2**. To our surprise, this combination was not fully developed despite the individual transformations being well-documented for decades.[5] The main challenge in this proposal, however, is the cross-aldol reaction of formaldehyde to form β-hydroxy aldehyde **3** due to the inherent low reactivities of the oligomerized formaldehyde, the potential condensation and self-aldol reactions of the parent aldehyde, and the oligomerization of the corresponding product (see **3**). To our delight, Boeckman and co-workers reported a highly enantioselective cross-aldol reaction of formaldehyde (formalin) using the Jørgensen−Hayashi catalyst (**5a**/**5b**) (Scheme 1c).[6,7] The corresponding hemiacetal was further converted into *E*-conjugated esters by trapping with a variety of Wittig reagents in good yields. Interestingly, Hayashi and co-workers applied organocatalyst **6** to synthesize similar products in higher enantioselectivities.[8] With a secure aldol reaction in excellent enantioselectivity, the remaining problem would be the *Z*-selective olefination to deliver a designed conjugated ester (see **4**), which will be readily cyclized under suitable conditions. Here, we report such an effort to successfully access chiral γ-substituted pentenolides in high enantioselectivities in a "pot-economy" manner,[9] and we further exemplified the short syntheses (5−6 total steps) of several biologically interesting alkaloids (*vide infra*), which have been typically prepared in >10 steps in previous reports.

Boeckman's protocol[7] was chosen due to a lower catalyst loading (5−30 mol % of **5a** or **5b**) and cheaper catalyst ($60/25 g

Received: May 24, 2017

DOI: 10.1021/acs.orglett.7b01573
Org. Lett. XXXX, XXX, XXX−XXX

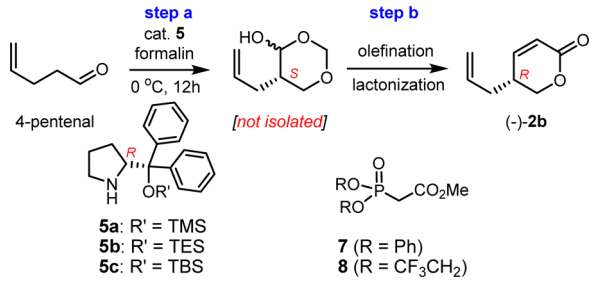
Scheme 1. (a) Pentenolide: Reactivities and Synthetic Methods; (b) Proposed Synthetic Route toward Pentenolide 2; (c) Organocatalysts for the Cross-Aldol Reaction of Formaldehyde (the Stereochemistry Rationale with 5a Highlighted in the Box; Also See Ref 7b)[a]



[a]TMS = trimethylsilyl; TES = triethylsilyl.

of **5**) in comparison to Hayashi's system (30 mol %, $110/1 g of **6**).[8] 4-Pentenal was therefore subjected to a buffered biphasic system in the presence of trimethylsilyl diphenylprolinol **5a** (entry 1, Table 1). The aldol reaction was performed at 0 °C for 12 h and diluted with toluene. The hemiacetal (*not isolated*) was extracted into the organic layer and then treated with phosphate **7**[10] in the presence of NaH (entry 1). The resultant *Z*-conjugated ester (see **4**) was immediately cyclized to release 5-allyl-pentenolide **2b** in 46% overall yield and 90% ee (entry 1). When diisopropylethylamine (DIPEA) was used for the subsequent olefination, a dramatic drop of enantioselectivity was observed (entry 3 vs 1 and 2). When catalyst **5b** (R′ = TES) was examined, the enantioselectivity was improved (entry 4 vs 2). Reactions with catalyst **5c** (R′ = TBS) or phosphate **8** did not give better results (entries 5 and 6). A contamination of noncyclized free alcohol was found during the direct neutral workup procedure. Therefore, a stoichiometric amount of HCl (aq) was introduced, providing **2b** in 73% yield (entry 7 vs 4). The "three-step, one-column" procedure was readily scalable while maintaining a good yield and excellent enantioselectivity (entry 8). The optimized conditions proved to be effective for other chiral pentenolides **2c−f** in good yields and excellent enantioselectivity (Scheme 2). For instance, chiral pentenolide **2f** was readily isolated in 40% overall yield (*unoptimized*), which drastically improves the step-economic efficiency of the previous synthesis.[3a]

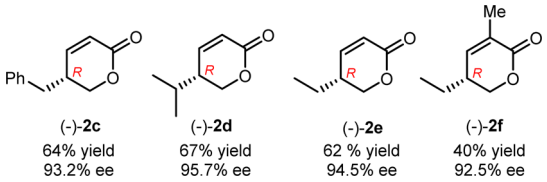
Table 1. Optimization of the Reaction Conditions for the Preparation of Chiral Pentenolide 2b



entry	step a: catalyst (equiv)	step b: HWE olefination and lactonization	ee % (**2b**)[a]	yield (%, **2b**)[b]
1	**5a** (0.2)	**7**, NaH, THF, 0 °C	90.1	46
2	**5a** (0.2)	**7**, NaI, DBU, THF, −78 °C to rt	90.2	50
3	**5a** (0.2)	**7**, NaI, DIPEA, THF, −78 °C to rt	58.0	n.d.[c]
4[d]	**5b** (0.2)	**7**, NaI, DBU, THF, 0 °C	95.6	49
5	**5c** (0.2)	**7**, NaI, DBU, THF, 0 °C	93.0	26
6	**5b** (0.2)	**8**, NaI, DBU, THF, 0 °C	92.4	30
7	**5b** (0.2)	**7**, NaI, DBU, THF; HCl (1.0 equiv), 0 °C	93.2	73
8[e]	**5b (0.2)**	**7, NaI, DBU, THF; HCl (1.3 equiv), 0 °C**	**94.8**	**68**

[a]Enantiomeric excess (ee) of **2b** was determined by chiral HPLC (see the Supporting Information for details); the absolute configuration was assigned by Boeckman's model (ref 7b) and the following synthetic transformation. [b]Isolated yield. [c]Not determined (n.d.). [d]4-Pentenal was freshly distilled. [e]The reaction was run on a 2-g scale for 48h. TBS = *tert*-butyldimethylsilyl; THF = tetrahydrofuran; rt = room temperature; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Scheme 2. Preliminary Exploration on Substrate Scope (50−200 mg Scale)

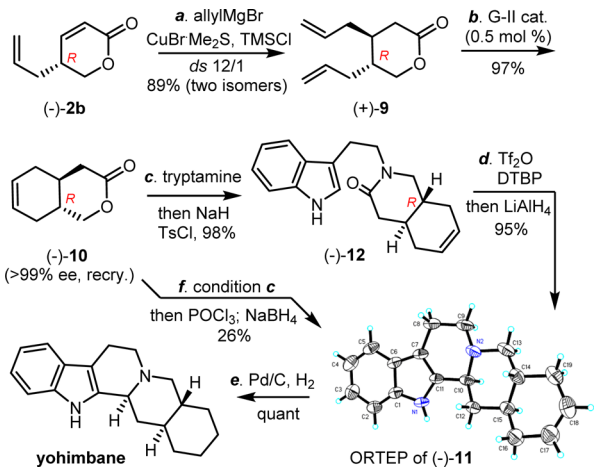


Having established a method to access chiral pentenolides, we sought to devise a new strategy to synthesize bioactive natural products. Yohimbane is a congener of the yohimbine family, a class of pentacyclic alkaloids exerting an extensive array of biological activities.[11] Continuing interest in this intriguing architecture has resulted in dozens of synthetic routes as well as biological evaluations over the past six decades.[12,13] However, the previous routes were not suitable for the supply of materials due to the generally long synthetic sequences and/or low overall yields. Recently, Ghosh and co-workers reported a divergent route to access yohimbane and alloyohimbane via enzymatic desymmetrization.[12e] The total yield of the yohimbane synthesis was impressively 11%, while the synthetic route still required 13 LLS (longest linear steps). To quickly establish a library of natural product-like compounds, an efficient synthesis remains in high demand.[14] We proposed pentenolide **2b** would be an ideal starting point to reach this objective.

At the outset, the copper(I)-promoted Michael addition[15] of pyranone **2b** generated lactone **9** in 89% yield with good diastereoselectivity (*ds* 12/1) (Scheme 3). The subsequent RCM reaction proceeded smoothly with the Grubbs-II catalyst[16] (0.5 mol %) to deliver a fused *trans*-lactone **10** in excellent yield (97%). The conventional aminolysis and "one-pot" lactamization/Bischler−Napieraiski (B−N) cyclization/reduction sequence were adapted to deliver dehydroyohimbane **11** in 26% isolated yield. A contamination of unidentified side products was observed, which might be derived from the harsh conditions using phosphorus oxychloride ($POCl_3$), particularly for the reactive indole moiety.[17] Therefore, a survey of the activation of the tertiary amide was undertaken. Encouraged by Banwell's work on the activation of amides,[18] as well as the recent explorations by

DOI: 10.1021/acs.orglett.7b01573
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of Yohimbane[a]



[a]*ds* = diastereoselectivity; TMSCl = trimethylsilyl chloride; TsCl = *para*-methylphenylsulfonyl chloride; Tf_2O = trifluoromethanesulfonic anhydride; DTBP = 2,6-di-*tert*-butylpyridine; $LiAlH_4$ = lithium aluminum hydride.

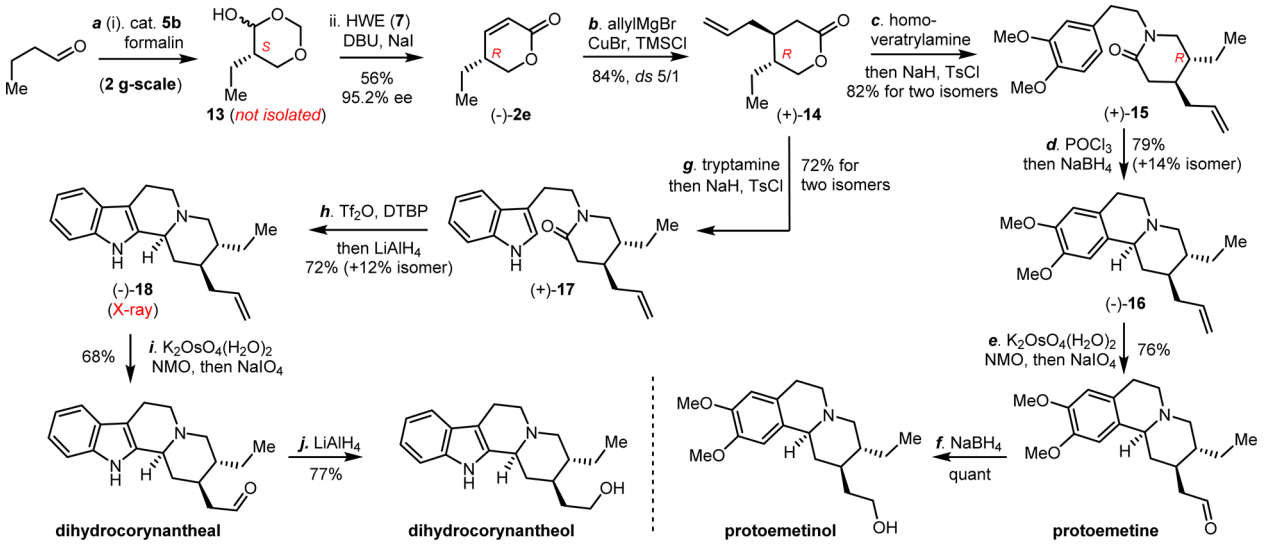
the Movassaghi and Huang groups,[19] a combination of Tf_2O and 2,6-di-*tert*-butylpyridine (DTBP) proved to be effective to promote the B−N cyclization in excellent yield. Therefore, a two-step protocol (conditions *c* and *d*) through intermediate **12** was validated to complete the synthesis of **11** in 93% overall yield. The excellent stereoselectivity (*ds* > 20/1) is attributed to the boat conformation adapted for α-hydride delivery. Hydrogenation of the alkene proceeded smoothly to deliver yohimbane, and the characterization was consistent with the reported data.[12] The total synthesis described here with 50% overall yield from simple 4-pentenal represents the most efficient route reported so far.

The rapid synthesis of chiral pentenolide **2b** encouraged us to construct other quinolizidine alkaloids that were previously accessed by other synthetic sequences. A 2-g scale synthesis of **2e** was secured with high enantioselectivity (95.2% ee). The following copper(I)-promoted allylation of pentenolide **2e** afforded the adducts **14** (*trans*- and *cis*-isomers) in 84% combined yield with a good diastereoselectivity (*ds* 5/1) (Scheme 4). Aminolysis with homoveratrylamine and the ensuing cyclization delivered lactam **15** in a combined 82% yield for two inseparable diastereomers. The subsequent B−N cyclization with $POCl_3$ proceeded smoothly, and the subsequent reduction with $NaBH_4$ afforded the desired *cis, trans*-product **16** in 79% yield (*ds* > 20/1 for the reduction step) along with the *cis, cis*-isomer in 14% yield.[20] Cleavage of the terminal alkene to reveal the aldehyde proved to be challenging in the presence of an electron-rich aromatic ring.[21] After intensive optimization, an interrupted extraction with *n*-BuOH after dihydroxylation proved crucial to achieve a high yield for the water-soluble dihydroxylated product. Thus, catalytic dihydroxylation in acetone−H_2O cosolvent and cleavage of the corresponding diol with silica-gel-supported[22] $NaIO_4$ gave protoemetine in 76% yield. The following reduction by $NaBH_4$ delivered protoemetinol[23] in quantitative yield.

When homoveratrylamine was substituted with tryptamine, the above synthesis sequence remained effective. Accordingly, aminolysis of **14** with tryptamine and cyclization with in situ activation of the primary alcohol afforded lactam **17** in 72% yield (a mixture of *trans*- and *cis*-isomers). The subsequent B−N cyclization with Tf_2O/DTBP and reduction by $LiAlH_4$ smoothly gave the requisite tetracyclic *cis, trans*-product **18** in 72% yield, whose structure was further confirmed by X-ray crystallography.[20] Following the above procedure for the oxidative cleavage of the terminal alkene, dihydrocorynantheal[22] was obtained in good yield. The subsequent reduction of aldehyde with $LiAlH_4$ resulted in dihydrocorynantheol[23] in 77% yield, and the spectral data were identical with the previous literature report.

In summary, we devised a unified approach to access intriguing alkaloids from γ-alkylated pentenolides, which were enabled by an organocatalytic cross-aldol reaction, achieving good yields and excellent enantioselectivities. The new protecting-group-free[24] syntheses improved the overall efficiency compared to other known synthetic routes. Compared with the conventional B−N cyclization, the newly developed "two-step" procedure, including tosylation/lactamization and B−N cyclization/reduction, was practical for sensitive substrates (e.g., the *N*1-unprotected indole

Scheme 4. Concise Syntheses of Dihydrocorynantheal, Dihydrocorynantheol, Protoemetinol, and Protoemetine[a]



[a]NMO = *N*-methylmorpholine *N*-oxide.

DOI: 10.1021/acs.orglett.7b01573
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derivative) and thus can further complement a strategy to construct more complex quinolizidine alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01573.

Full experimental details and analytical data including NMR spectra and X-ray diffraction of compounds **10**, **11**, and **18** (PDF)

Crystallographic data (ZIP)

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§C.X. and J.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21290184 and 21672246 to R.H., 21302208 to L.Z.), the Strategic Priority Research Program (XDB20000000), and the Key Research Program of Frontier Sciences (QYZDY-SSW-SLH026) of the Chinese Academy of Sciences are greatly appreciated. We also thank Jie Sun (SIOC) for X-ray analysis and Yuping Zhang (Shanghai Institute of Technology) for experimental assistance.

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DOI: 10.1021/acs.orglett.7b01573
Org. Lett. XXXX, XXX, XXX−XXX