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Stereospecific Synthesis of Tetrahydronaphtho[2,3-*b*]furans Enabled by a Nickel-Promoted Tandem Reductive Cyclization

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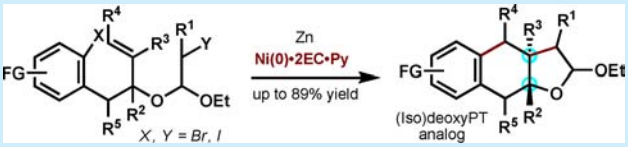
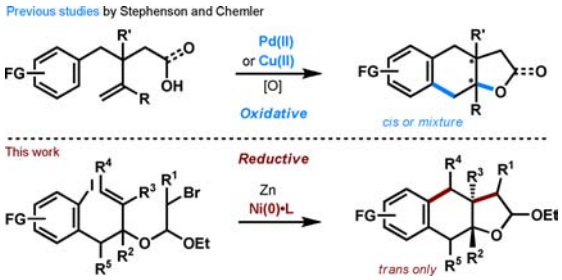
Supporting Information

ABSTRACT: A Ni-mediated cascade to a stereoselective synthesis of *trans*-tetrahydronaphtho[2,3-*b*]furans is efficiently achieved for the first time. The mild reductive system can be easily generated from inexpensive and air-stable materials and shows a broad positional tolerance of substituents that were previously difficult or impossible to access by other methods. Facile syntheses toward new analogues of therapeutic agents (iso)deoxypodophyllotoxin are also reported. In addition, the inherent substrate control is disclosed for the observed unique stereoselectivities during cyclizations.



Privileged skeletons with tetrahydronaphtho[2,3-*b*]furans (tetrahydronaphtho = THN) can be found in a wide array of natural products, pharmaceuticals, and agrochemicals.[1] Several synthetic methodologies toward the construction of this scaffold have thus emerged, such as [2 + 2] cycloaddition followed by Baeyer−Villiger oxidation,[2a] oxo-Pauson−Khand reactions of *o*-allyl aryl ketones,[2b] and Friedel−Crafts cyclization of acid chloride.[2c] Recently, several groups reported new tactics using oxidative cyclizations catalyzed by transition metals (Scheme 1, top).[3] A Pd(II)-catalyzed cascade that generated

Scheme 1. Oxidative versus Reductive Cyclization



C−O and C−C bonds successively for construction of THN[2,3-*b*]furan-2-ones was first developed by Stephenson and co-workers.[3a] However, these researchers demonstrated only two examples, both as a mixture of almost 1:1 *cis*/*trans*-fused isomers. Some oxidative dearomatization side products were also observed, especially in the case of substrates bearing electron-rich benzene rings. Later, Chemler et al. expanded the scope of THN[2,3-*b*]furan via a Cu(II)-catalyzed, MnO_2-mediated alkene carboetherification.[3b,c] The good *cis*-stereoselectivity diminished severely when substituent groups at ring-junction positions were removed (i.e., R, R′ = H). Notably, the above reactions involved Csp^2−H functionalization; therefore, the formation of regioisomeric products cannot be avoided when substrates had *o*- or *m*-aryl substituents. Efficient and complementary synthetic methods are still in high demand.

Recently, Ni-catalyzed reductive coupling of alkyl (pseudo)-halides have become a valuable tool for the formation of C−C bonds.[4−10] Our previous research mainly focused on intramolecular reactions and stereoselective tandem cyclizations.[11] Herein, we present an unprecedented and stereospecific synthesis of *trans*-THN[2,3-*b*]furans with the sequential formation of two C−C bonds enabled by Ni/EC (ethyl crotonate) (Scheme 1, bottom). This method led to a convenient preparation of (iso)deoxypodophyllotoxin analogues.

First, optimization studies of the proposed reductive cascade were carried out (Table 1) with the *β*-bromo acetal **1a** that was easily prepared from 1-*o*-iodobenzyl allyl alcohol and ethyl vinyl ether (EVE). We chose Ni(0)·2EC·Py to perform this transformation, and the desired tandem cyclization of **1a** indeed occurred in DMF at room temperature, affording tricylic acetal **2a** in 51% isolated yield within 12 h (entry 1). A facile oxidation of **2a** as a pair of inconsequential diastereomers mediated by *m*-CPBA and $BF_3{\cdot}Et_2O$[12] led to the sole lactone **3a** in almost quantitative yield. The unique *trans*-fused stereochemistry was confirmed through its single-crystal structure (Table 1 inset).[13] By comparison, less reactive dibromide **1aa** resulted in the lower yield of **2a** under identical conditions (entry 2). The utilization of 2,2′-bipyridine as a ligand also caused a decrease in yield (entry 3). To our delight, CH_3CN was identified as a superior solvent for this cascade. The yield of **2a** increased substantially, up to 70% when the reaction time was shortened to a half, presumably due to the unstable nature of this acetal product upon long periods in the reaction medium (entries 4 and 5 versus entry 1). Further evaluation of solvents proved that DMA is the best choice, and **2a** was isolated in 78% yield (entry 6). A slight decrease of yield was observed when the reaction was run

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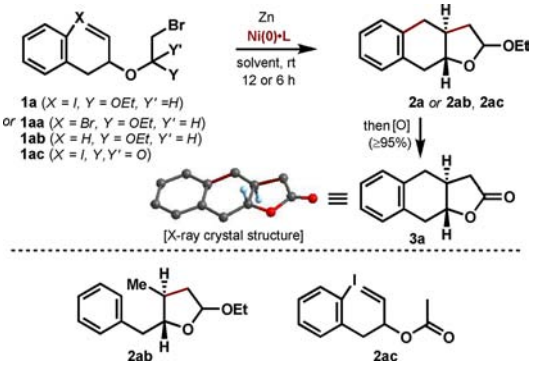
Table 1. Optimization of Cyclization Conditions



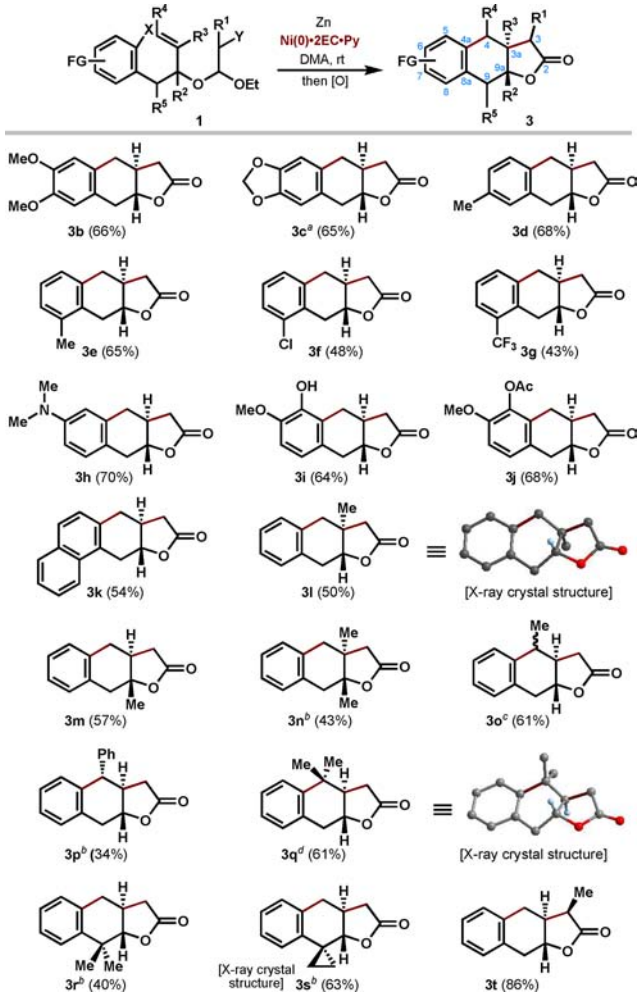
entry	compd	ligand	solvent	2a, yield[a] (%)
1	**1a**	EC	DMF	51
2	**1aa**	EC	DMF	28
3	**1a**	2,2′-bipy	DMF	20
4	**1a**	EC	CH_3CN	63
5	**1a**	EC	CH_3CN	70
6	**1a**	**EC**	**DMA**	**78**
7[b]	**1a**	EC	DMA	63
8	**1a**	4,4′-di-*t*Bu-2,2′-bipy	DMA	14
9	**1a**	4,4′-di-OMe-2,2′-bipy	DMA	17
10	**1a**	1,10-phen	DMA	6
11	**1a**	4,7-di-Ph-1,10-phen	DMA	46
12	**1ab**	EC	DMA	0[c]
13	**1ac**	EC	DMA	0[d]

[a]Isolated yield with 1 equiv of Ni complexes. [b]The reaction was conducted at 40 °C. [c]**2ab** was isolated in 50% yield. [d]**2ac** was isolated in 80% yield.

at elevated temperature in order to accelerate the transformation (entry 7). Screening of other bidentate ligands including phenanthrolines gave no improvements (entries 8−11). No **2a** could be observed when the C−I bond was replaced by the C−H bond in **1ab**. Instead, monocyclization product **2ab** was obtained in 50% yield (entry 12), suggesting that a homolytic aromatic substitution process[14] during the second cyclization seems impossible. Attempts to direct access to tricylic lactone **3a** from α-bromo ester **1ac** only afforded the partial reduction product **2ac** in 80% yield (entry 13). The attempted catalytic reactions and a gram-scale experiment are included in the SI. We were pleased to find that this bicylization event still proceeded smoothly under substoichiometric Ni, providing **2a** in 72% yield.

With these optimized conditions in hand, a scope of this tandem cyclization mediated by nickel was then investigated. As shown in Scheme 2, reductive cascades of various β-bromo acetals **1** can give *trans*-THN[2,3-*b*]furan-2-ones **3** in moderate and good yields after oxidation of the intermediate tricyclic acetals **2** (not shown). We first studied the tolerance of functional groups on the benzene ring of substrates (**3b−k**). The reaction of dimethoxyphenyl iodide **1b** worked well under the present conditions, and a single crystal of one of the resulting diastereomeric acetals was obtained, clearly demonstrating that two tertiary hydrogen atoms at C3a and C9a adopt a *trans*-orientation.[13] Upon oxidation, lactone **3b** was generated in 66% overall yield. Other electron-rich benzene-derived precursors also gave similar results, as exemplified in the cases of **3d** and **3e** with a Me group at either C7 or C8 position. Phenyl iodides bearing typical electron-withdrawing groups like

Scheme 2. Synthesis of *trans*-THN[2,3-*b*]furan-2-ones*



*The substrate **1** (X = I, Y = Br) and Ni complexes (1 equiv) were used generally unless otherwise stated. Overall yields of **3** were reported, and monocyclization side products (10−20%) similar to **2ab** were observed in some cases. [a]**1c** (X,Y = Br) was used at 35 °C. [b]**1n**, **1p**, **1r**, and **1s** (X, Y = I) were used at 40 °C. [c]dr = 1.1:1. [d]1,10-phen was used.

CF_3 and Cl were also suitable, leading to **3f** and **3g** in moderate yields. In particular, phenyl bromide **1c** with a methylenedioxy group also worked well under the identical conditions except at slightly elevated temperature, in sharp contrast to that of dibromide **1aa**. The substrates bearing NMe_2, OH, and OAc groups afforded **3h−j** in good yields as well. The naphthalene derivative **1k** also participated in this transformation to deliver the tetracyclic lactone **3k** in a serviceable yield.

In light of the limited exploration in previous reports,[3] the compatibility of substituents at two aliphatic rings in targets **3** was next evaluated (**3l−t**). When **1l** derived from 1-*o*-iodobenzyl 2-methylallyl alcohol was exposed to the indicated system, the tricyclic lactone **3l** with an all-carbon quaternary stereocenter at C3a could be successfully obtained in 50% overall yield. More importantly, a *trans*-relationship between H9a and Me was still maintained, which was unambiguously established by its single-crystal analysis.[13] The angular-methyl group could also be incorporated into the C9a position, thus generating **3m** with an oxo-quaternary carbon in a higher yield. Amazingly, the present methodology allowed for the con-

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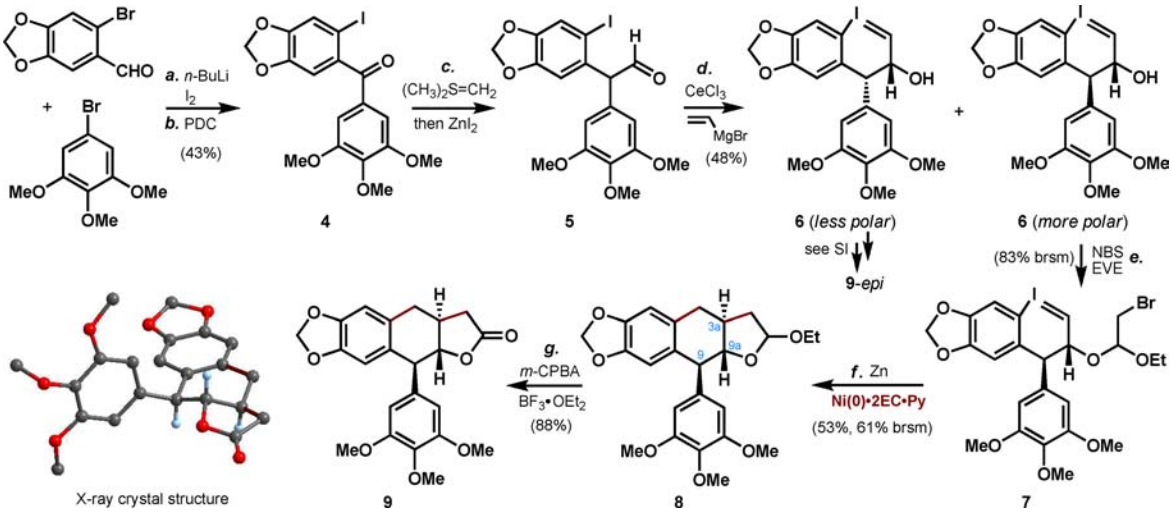
Scheme 3. Total Synthesis of Isodeoxypodophyllotoxin Analogue

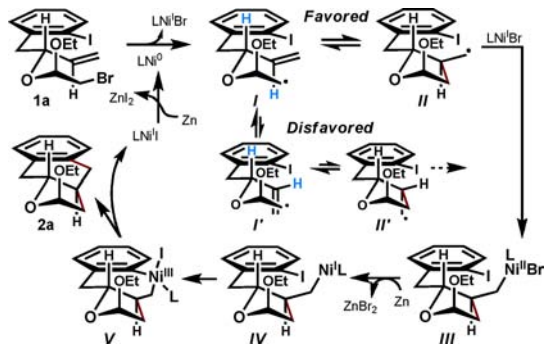


struction of vicinal quaternary C3a and C9a with steric congestion in **3n** when the diiodide **1n** was used. Besides the substrates containing a terminal alkene, *β*-bromo acetals **1o** and **1p** derived from 1-*o*-iodobenzyl crotyl and cinnamyl alcohols were compatible as well, providing C4-substituted lactones **3o** and **3p** successfully albeit the latter had a lower yield. However, subjection of **1q** from prenyl alcohol to the Ni·Phen system led to *trans*-fused lactone **3q** in a normal yield, thus generating an aryl-quaternary carbon.[13] It is noteworthy that this unprecedented transformation represented the first Ni-promoted *intramolecular* reductive cross-coupling of a formal tertiary alkyl bromide and an aryl iodide.[15] Moreover, the decoration of the *gem*-dimethyl group at C9 in **3r** also worked, although its yield diminished as compared to 61% of **3q**. Nonetheless, the dehydrogenation congener of **3r**, that is, cyclopropane **3s**, could be synthesized more efficiently. The expected *trans*-fused stereochemistry of this THN[2,3-*b*]furan-2-one and its interesting spiro-quaternary carbon structure were determined by single-crystal analysis.[13] Pleasingly, the Ni-triggered reductive cascade of secondary bromide **1t** gave the highest yield. Oxidation of separable diastereomers of the resulting tricylic acetal eventually afforded lactone **3t** in 86% overall yield.

Podophyllotoxin (PT) has been paid extensive attention for over half a century by the academic and industrial community. Its derivatives have been developed as drugs for the treatment of lung and testicular cancer, leukemia, etc.[16] Not surprisingly, numerous total syntheses of PT have appeared to date,[17] and the preparation of diverse analogues[18,11c] is also in high demand in order to obtain superior therapeutic agents. Based on the reductive cascade shown in Scheme 2, we next demonstrated a versatile application in the synthesis of new isodeoxyPT analogue **9** (Scheme 3). Our synthesis commenced with the assembly of commercially or easily available 6-bromopiperonal (6-BrPi) and 3,4,5-trimethoxybromobenzene (TpBr), according to a series of standard protocols including Tp-Br/Li exchange, the lithium reagent addition to the aldehyde, and Pi-Br/I exchange reaction. The resulting carbinol was then converted to the diaryl ketone **4** in 43% overall yield by oxidation with PDC. The one-carbon homologation of **4** to the diaryl acetaldehyde **5** was realized by a Corey−Chaykovsky epoxidation and the subsequent rearrangement mediated by ZnI_2.[19] The resulting labile aldehyde was directly subjected to a freshly prepared organocerium reagent from vinylmagnesium bromide and anhydrous $CeCl_3$ to afford two separable allyl alcohols **6** (dr = 1:1) in 48% overall yield. These two diastereomers that are differentiated at C9 could be elaborated independently. For example, upon exposure of the more polar isomer to a mixture of NBS and EVE,[20] *β*-bromo acetal **7** was obtained in 56% yield, thus setting the stage for the key reductive cyclization enabled by nickel. Smooth cascade of **7** with a C9-aryl substitution was observed, affording the desired THN[2,3-*b*]furan **8** bearing three contiguous stereocenters (C9−C9a−C3a) in 53% yield with partial recovery (12%) of the starting material. The expected *trans*-ring fusion was established by single-crystal analysis (Scheme 3 inset) of **9**[13] resulting from the oxidation of **8**. To that end, a new analogue **9** of isodeoxyPT[21] was achieved by this seven-step synthetic sequence. In addition, a similar route starting from **6** (less polar) also delivered the corresponding analogue **9**-*epi* of deoxyPT[22] (see the Supporting Information for details).

On the basis of the work of others[4f,5a,c] and our proposed mechanism regarding intermolecular reductive coupling enabled by nickel,[11a,d] a rational explanation for the intramolecular cascade here is illustrated in Scheme 4 with **1a** as an example.

Scheme 4. Proposed Mechanism



Homolysis of the Csp^3−Br bond through a single-electron-transfer process with in situ generated Ni^0 complex provides radical **I**, which adopts a pseudo-half-chair conformation.[17d] The next stereospecific 5-*exo*-*trig* cyclization would quickly occur to give a unique *trans*-substituted THF **II**. An alternative pathway to the *cis*-isomer from **I′** and **II′** is a disfavored process since the subsequent cyclization would be impossible. Radical **II** would

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then combine with $LNi^{I}Br$ to afford Ni^{II} intermediate **III**, which can be reduced to Ni^{I} species **IV** by Zn. The following oxidative addition of the C_{aryl}–I bond in an intramolecular fashion would furnish Ni^{III}acycle **V**,[23] which would undergo a facile reductive elimination to form the tricyclic acetal **2a** while regenerating Ni^{0} upon the eventual reduction. The competitive protonation and direct reduction to form **2ab** (vide supra) during the transformation of **IV** to **V** could occur when a less reactive aryl bromide like **1aa** was employed. On the other hand, a corresponding secondary radical from **1q** allowed the whole cascade to proceed more efficiently due to its high reactivity, therefore leading to the product in the highest yield. Inclusion of TEMPO led to almost no formation of **2a**, implying possible involvement of radical intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02665.

Experimental procedures and characterization data (PDF)
$^{1}H/^{13}C$ NMR (PDF)
X-ray data for **2b** (CIF)
X-ray data for **3a** (CIF)
X-ray data for **3l** (CIF)
X-ray data for **3q** (CIF)
X-ray data for **3s** (CIF)
X-ray data for **9** (CIF)

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Notes

The authors declare no competing financial interest.

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