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Tungsten-Catalyzed Heterocycloisomerization Approach to 4,5-Dihydro-benzo[*b*]furans and -indoles

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Supporting Information

ABSTRACT: A $W(CO)_5$·THF-catalyzed cycloisomerization of bicyclo[4.1.0] substrates to afford mono C4-substituted 4,5-dihydro-benzo[*b*]furans and -indoles is reported. The title compounds are versatile intermediates that lead to a range of fused bicycles including the cores of various furan-, benzofuran-, and indole-containing natural products. In many cases, the functionalization of the dihydro-benzo[*b*]furans and -indoles is orthogonal to that of the corresponding benzofurans and indoles and, thus, offers complementary approaches for synthesis.

The 4,5-dihydrobenzo[*b*]furans and the corresponding 4,5-dihydroindoles (see boxed compound in Figure 1) may represent versatile intermediates in the synthesis of complex molecules. This is largely because multiple options for functionalization of these bicyclic motifs could be possible as shown in Figure 1, which could lead to the cores of myriad natural products and pharmaceutical substances. For example, dehydrogenation could yield benzofurans or indoles (**A**). Alternatively, the double bond moiety may be selectively engaged in various addition reactions to give functionalized annelated furans or pyrroles (**B**). Of perhaps even greater significance, the heteroaromatic portion of the 4,5-dihydro-benzo[*b*]furans and -indoles may undergo reactions that are either not possible (e.g., cycloadditions; see **C**) or are complementary (see **D**) for the corresponding benzofurans and indoles. As a result, dihydro-benzofurans and -indoles may offer novel strategies for the synthesis of various substituted fused bicycles including decalin derivatives, indoles, and benzofurans.

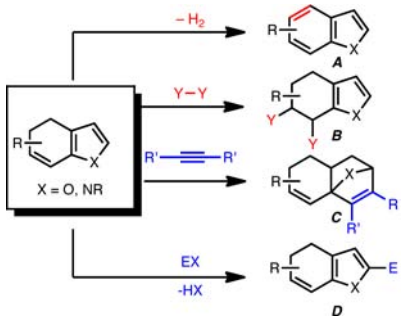
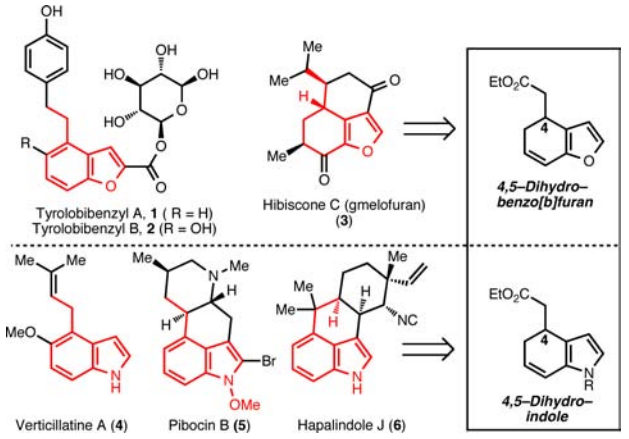


Figure 1. Versatile reactions of 4,5-dihydro-benzo[*b*]furans and -indoles.

As a part of a general program aimed at the total synthesis of benzofuran natural products such as tyrolobibenzyls A and B (**1** and **2**, respectively, Scheme 1)[1] and furanoterpenoids including hibiscone C (**3**),[2] as well as indole natural products such as verticillatine A (**4**),[3] pibocin B (**5**),[4] and the hapalindoles (e.g., **6**),[5] we were drawn to the use of 4,5-dihydro-benzo[*b*]furan and -indole derivatives as precursors. Specifically, we envisioned a methylene carboethoxy substituent at C4 (see boxed structures in Scheme 1) that could be transformed to a range of groups including prenyl and reverse prenyl substituents. In the context of indole alkaloid synthesis, this would be highly significant given the expense and challenge associated with accessing C4-prenyl and reverse prenyl substituents,[6] which form the basis of the synthesis of many indole alkaloids.[7]

Scheme 1. Potential Utility of 4,5-Dihydro-benzo[*b*]furans and -indoles



Our inspection of the literature has revealed only one prior report of a synthetically useful synthesis of mono C4-substituted 4,5-dihydroindoles.[8,9] Reported by Semmelhack and co-workers in 1982, this preparation involved the intermediacy of stoichiometric η_6-Cr arene complexes, which limits the practical utility of this route (especially for the large-scale preparation of C4-substituted 4,5-dihydroindoles) for complex molecule applications. To the best of our knowledge, outside of the vacuum pyrolysis studies of Weber,[9] there are no prior examples of 4,5-dihydrobenzo[*b*]furans bearing a single substituent at C4. In this manuscript, we report the preparation

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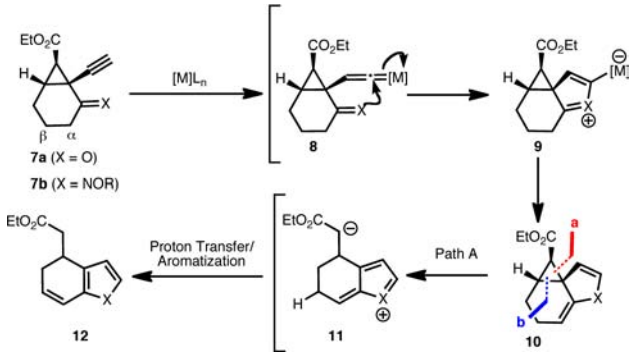
of these versatile synthetic intermediates, which takes advantage of a unique $W(CO)_5$·THF-catalyzed heterocycloisomerization. Furthermore, we demonstrate the conversion of the dihydro-benzo[*b*]furan and -indole compounds to the value-added products outlined in Figure 1, which could set the stage for numerous applications in complex molecule synthesis.

On the basis of well-established studies of metallo-vinylidene formation from terminal alkynes,[10] we envisioned that [4.1.0] bicycles such as **7** could be transformed to **12** (Scheme 2). In

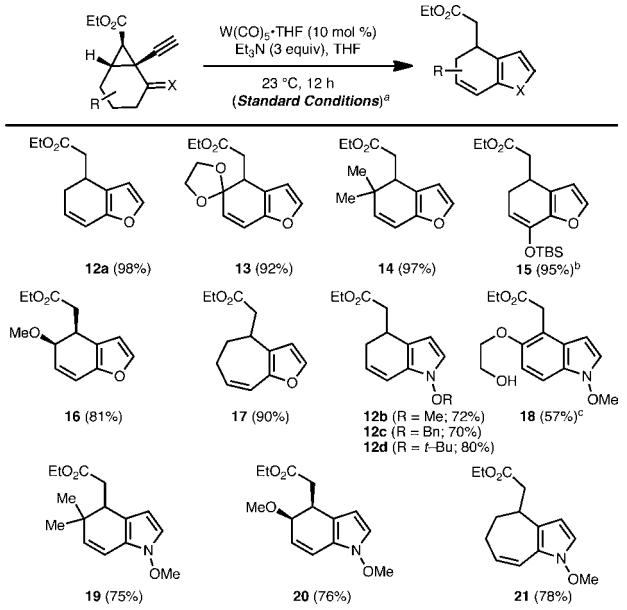
Scheme 2. Possible Cycloisomerization Mechanism for the Formation of Dihydro-benzo[*b*]furans and -indoles



the presence of an appropriate metal complex, **7** could first be converted to metallo-vinylidene **8**, which could then be engaged by the proximal heteroatom (O or N) to provide zwitterionic intermediate **9**. Proto-demetalation of **9** could potentially yield spiro-fused tricycle **10**. At this stage, strain release fragmentation of the cyclopropane to afford **11** (likely assisted by the heteroatom), followed by proton transfer (and concomitant aromatization), would provide the desired dihydro-benzo[*b*]furans or -indoles. Several aspects of this proposed sequence are noteworthy. First, remote C−H functionalization *β* to the carbonyl or oxime group of **7a**/**b** is achieved in the overall transformation. Second, it is also possible that the metallo-vinylidene moiety in **8** could undergo a vinyl cyclopropane rearrangement,[11] or be engaged by the carboethoxy group (instead of X), which would lead to a heteroatomic variant of the divinylcyclopropane rearrangement.[12] Third, although numerous reports have appeared in the literature that describe cycloisomerization of cyclopropyl ketones related to **7**,[13] to the best of our knowledge, the previously reported transformations of bicyclo-1-(1-alkynyl)-cyclopropyl ketones proceed with formal cleavage of the endocyclic cyclopropane bond (i.e.,"b", see **10**).[14] In contrast, cleavage of bond "a" is required for our purposes. However, we expected the presence of the carboethoxy group in **7** to make Path A more favorable by better stabilizing the developing negative charge (see **11**).[15]

We initiated our studies with [4.1.0] bicycle **7a** (prepared from cyclohexenone in 61% yield over four steps),[16] which was subjected to a range of ruthenium and rhodium metal complexes that have been established as catalysts for vinylidene formation, including $RhCl(PPh_3)_3$[17] and $[RuCl_2(cymene)]_2$.[18,19] In the end, the conditions of Ohe and Uemura,[20] which employ a tungsten complex (10 mol % $W(CO)_5$·THF, 3 equiv of Et_3N, rt, 12 h), were found to be the most effective and general. As illustrated in Table 1 (only products are shown), substrates bearing substitution on the six-membered ring provide access to the corresponding 4,5-

Table 1. Substrate Scope of the Heterocycloisomerization



[a]The standard conditions (10 mol % $W(CO)_5$·THF, 3 equiv of Et_3N, rt, 12 h) were used unless otherwise stated. [b]Reaction was conducted using 20 mol % of $W(CO)_5$·THF. [c]The reported yield of *N*-alkoxy indole **18** was obtained upon stirring the crude reaction product with oxalic acid and SiO_2 in wet CH_2Cl_2 for 3 h (see the Supporting Information for more details).

dihydrobenzo[*b*]furans in good to excellent yields (see **12a**, **13**−**16**). Both heteroatom (see **13**, **15**, and **16**) and alkyl substitution (see **14**) are well tolerated. In addition, a bicyclo[5.1.0] substrate readily participates in the cycloisomerization to provide **17**, illustrating the potential generality of this transformation beyond dihydro-benzo[*b*]furans.[21] Furthermore, *N*-alkoxy-4,5-dihydroindoles are also readily accessed using this methodology (see **12b**−**d**, **19**, and **20**).[22] The scope of the *N*-alkoxy-4,5-dihydroindole formation is generally analogous to that observed for the formation of 4,5-dihydrobenzo[*b*]furans. One exception is the formation of *N*-methoxy indole **18**,[23] where the ketal group of the crude product (compare to **13**) unravels upon purification on silica gel, presumably because of the pronounced electron-rich nature of the alkoxypyrrole group relative to the corresponding furan.

The versatility of the 4,5-dihydro-benzo[*b*]furans and -indoles as synthetic intermediates is evident in the range of reactions that they undergo as illustrated in Scheme 3. For example, **12a** is easily transformed to disubstituted benzofuran **23**, which provides a starting point for the synthesis of tyrolobibenzyl A (**1**, Scheme 1). The short sequence proceeds from **12a** in good overall yield (57% yield over 3 steps) by a formal carbomethoxylation and DDQ-mediated oxidation. Also, highly functionalized furans such as diol **24** are readily obtained with good diastereoselectivity (9:1 d.r.)[24] under standard dihydroxylation conditions, which are selective for the double bond over the furan moiety.[25] In addition, methylation of ketone **25** (obtained from **15**)[26,27] provides *α*-methyl ketone **26** (78% yield, 3.5:1 d.r.), which may serve as a starting point for the synthesis of furanoterpenoids such as hibiscone C (**3**, Scheme 1).

N-alkoxyindoles (e.g., **27**, Scheme 3), which may be employed in the synthesis of indole alkaloids including pibocin B (**5**, Scheme 1), can be realized from the dehydrogenation of

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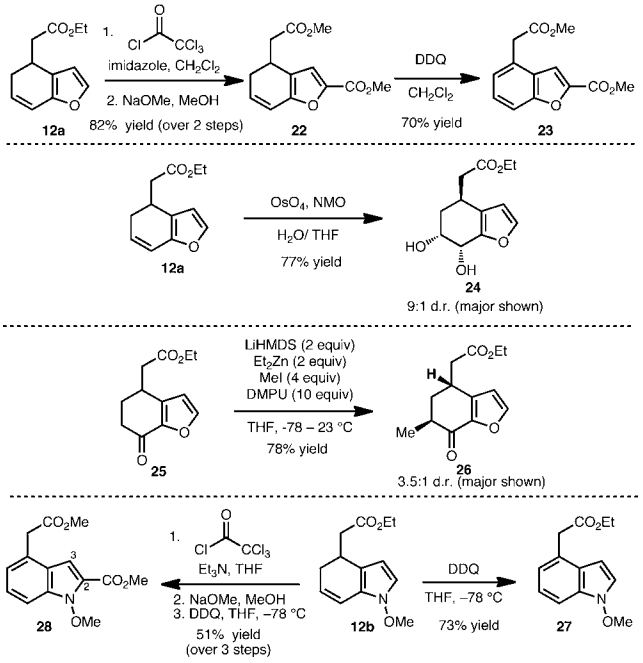
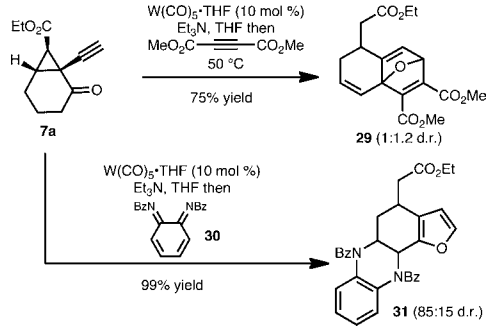
Scheme 3. Transformations of 4,5-Dihydro-benzo[*b*]furans and -indoles



the corresponding *N*-alkoxy-4,5-dihydroindoles (i.e., **12b**). Importantly, formal C2 indole functionalization is also easily achieved, which is complementary to the normally observed C3 regioselectivity for *N*-alkoxyindoles,[28] (see **12b** → **28** for sequential acylation/oxidation).

Significantly, several transformations may be carried out in one pot from the precursor bicyclo [4.1.0] substrates without isolation of, for example, the 4,5-dihydrobenzo[*b*]furan intermediate. As shown in Scheme 4, decalin derivative **29** is

Scheme 4. One-Pot Sequential Reactions of [4.1.0] Substrates



obtained in good yield from **7a** following cycloaddition of the furan moiety of the intermediate 4,5-dihydrobenzo[*b*]furan with dimethylacetylene dicarboxylate in a one-pot process. Alternatively, fused tetracycle **31** (85:15 d.r.)[29] is formed in a single pot sequence following selective cycloaddition of the alkene group of the intermediate 4,5,-dihydrobenzo[*b*]furan with **30**.[30]

In conclusion, we report a general entry to the synthesis of mono C4-substituted 4,5-dihydro-benzo[*b*]furans and -indoles, which are readily obtained through the $W(CO)_5$·THF-catalyzed heterocycloisomerization of bicyclo[4.1.0] substrates. These compounds have proven to be versatile synthetic intermediates that offer access to functionalized furans, benzofurans, pyrroles, and indoles. In addition, one-pot sequential additions involving the bicyclo[4.1.0] substrates that proceed via the intermediacy of the 4,5-dihydrobenzo[*b*]-furans can be achieved and proceed in high yield. A comprehensive study of the reactivity of the mono C4-substituted 4,5-dihydrobenzo[*b*]furan and 4,5-dihydroindole compounds, as well as their applications in natural products synthesis, is currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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