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General Synthetic Approach to Functionalized Dihydrooxepines

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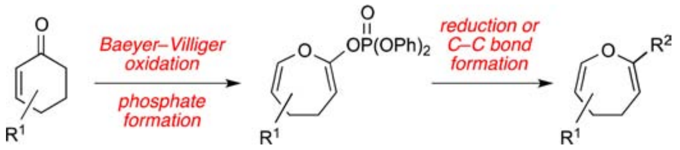
ABSTRACT



A three-step sequence to access functionalized 4,5-dihydrooxepines from cyclohexenones has been developed. This approach features a regioselective Baeyer–Villiger oxidation and subsequent functionalization via the corresponding enol phosphate intermediate.

4,5-Dihydrooxepines are featured as structural motifs within various natural products, ranging from sesquiterpenes, such as miscandenin[1] and endiadric acid derivative beilshmiedin,[2] to polyketides, such as conioxepinol A[3] (Figure 1). This framework is also found in some of the most interesting members of the epidithiodiketopiperazine family as represented by aranotin[4] (Figure 1). Consequently, a number of approaches have been developed to access this structural motif. These include acid-catalyzed cyclization,[5] Rh-catalyzed cycloisomerization,[6] ring-closing metathesis,[7] [4 + 2] cycloaddition/epoxidation/retro [4 + 2] cycloaddition,[8] Cope rearrangement,[9] fragmentation,[10] and Criegee rearrangement.[11]

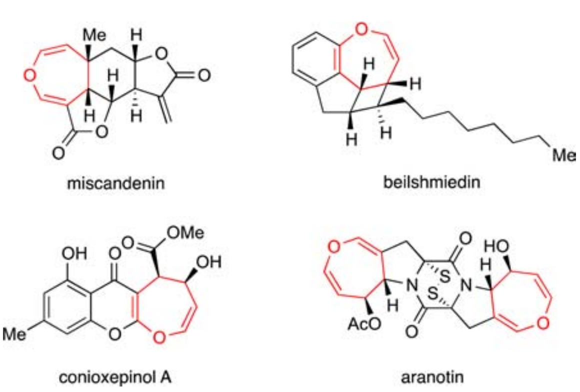


Figure 1. Selected natural products containing the 4,5-dihydrooxepine structural motif.

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Despite this progress, the synthesis of related natural products in which the dihydrooxepine unit is highly functionalized remains challenging, in part because the scope and generality of existing methods are rather limited. Postfunctionalization of preformed dihydrooxepines is also difficult due to the sensitive nature of these structural moieties. Therefore, a general approach through which substrates with a diverse array of substitution patterns can be reliably transformed into functionalized dihydrooxepines is highly desirable.

As part of our continuing efforts toward the total synthesis of members of the dihydrooxepine epidithiodiketopiperazine family,[8a,12] we opted to develop a method to synthesize 4,5-dihydrooxepines from cyclohexenones. Such a strategy would benefit from the ready availability of functionalized cyclohexenones, thus allowing access to a broad range of dihydrooxepine structures. We reasoned that ring expansion of the cyclohexenone could be achieved through a regioselective Baeyer–Villiger oxidation. Further functionalization of the resulting enol lactone through either reduction or C–C bond formation would give rise directly to the bisenol ether moiety found in 4,5-dihydrooxepines (Figure 2).[13]

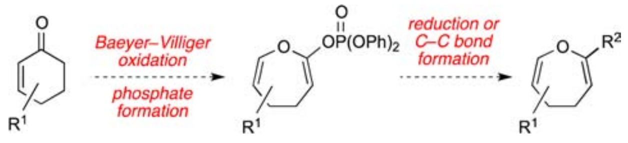
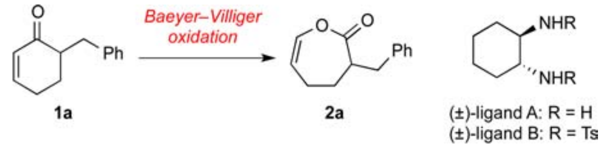


Figure 2. Proposed synthesis of functionalized 4,5-dihydrooxepines from the corresponding cyclohexenones.

Our experimentation began with the Baeyer–Villiger oxidation of enone **1a** (Table 1). Thus, reaction of **1a** with *m*CPBA gave the desired enol lactone as a single regioisomer, albeit in low conversion (Table 1, entry 1). Attempts to use stronger oxidants such as CF_3CO_3H led to partial decomposition of the product (entry 2). We then reasoned that substrate activation by a suitable Lewis acid would improve conversion under milder reaction conditions that would avoid product decomposition. Indeed, the combination of $SnCl_4$ and bis(trimethylsilyl)peroxide (BTSP), in the presense of *trans*-1,2-diaminocyclohexane (ligand A), generated the desired product **2a** in 83% yield (entry 3).[14] The use of this ligand proved to be critical as it successfully tempered the Lewis acidity of $SnCl_4$. Neither $SnCl_4$ itself nor its combination with other ligands tested, such as *trans*-1,2-di(tosylamino)cyclohexane (ligand B), led to

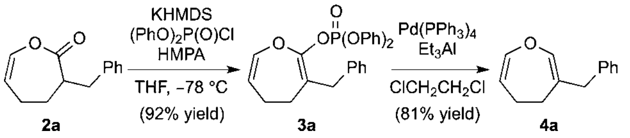
Table 1. Study of the Baeyer–Villiger Oxidation of Enones[a]



entry	conditions	yield (%)[b]
1	*m*CPBA, CH_2Cl_2	15
2	UHP, TFAA, CH_2Cl_2	decomp
3[c]	**BTSP, $SnCl_4$, ligand A, 4 Å MS, CH_2Cl_2**	**83**
4[d]	BTSP, $SnCl_4$, 4 Å MS, CH_2Cl_2	trace
5[d]	BTSP, $SnCl_4$, ligand B, 4 Å MS, CH_2Cl_2	22
6[d]	BTSP, $SnCl_4$, pyridine, 4 Å MS, CH_2Cl_2	32
7[d]	BTSP, $SnCl_4$, ligand A, CH_2Cl_2	trace

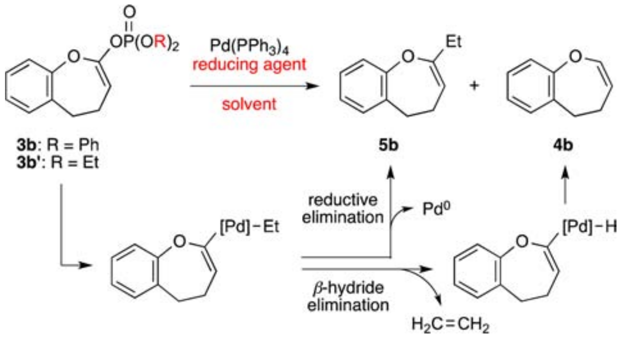
[a] Reactions were carried out on 0.25 mmol scale. [b] ^{1}H NMR yield. [c] Reactions were carried out at 0.1 M concentration with 0.5 equiv of $SnCl_4$, 0.5 equiv of ligand A, 3.0 equiv of BTSP, and 50 mg of 4 Å MS at 25 °C. [d] Reactions were carried out under the identical conditions in entry 3 with changes indicated in the table. *m*CPBA = *meta*-chloroperoxybenzoic acid, UHP = urea hydrogen peroxide, TFAA = trifluoroacetic anhydride, BTSP = bis(trimethylsilyl)peroxide.

Scheme 1. Enol Phosphate Formation and Pd-Catalyzed Reduction to 4,5-Dihydrooxepine



2a **3a** **4a**

Table 2. Optimization of Enol Phosphate Reduction[a]



entry	R	reducing agent	solvent	yield (%)[b] (**4b** + **5b**)	**4b**:**5b**[c]
1	Ph	Et_3Al	$ClCH_2CH_2Cl$	58	60:40
2	Ph	Et_3Al	CH_2Cl_2	62	37:63
3	Et	Et_3Al	$ClCH_2CH_2Cl$	70	90:10
4	Et	$LiBH_4$	THF	66	**4b** only
5	Ph	$LiBH_4$	THF	67	**4b** only

[a] Reactions were run on 0.1 mmol scale at 0.05 M concentration with 0.2 equiv of $Pd(PPh_3)_4$ and 2.5 equiv of Et_3Al at 25 °C or 10 equiv of $LiBH_4$ at 0 °C. [b] ^{1}H NMR yield. [c] Ratios determined by ^{1}H NMR spectroscopic analysis.

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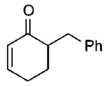
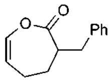
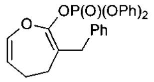
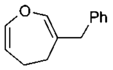
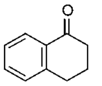
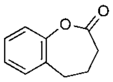
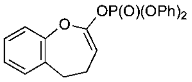
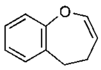
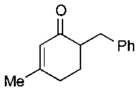
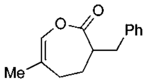
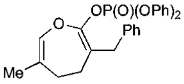
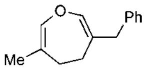
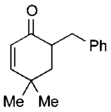
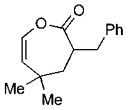
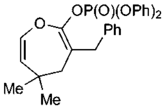
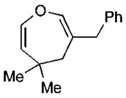
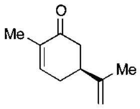
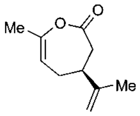
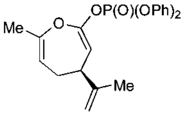
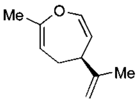
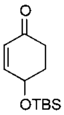
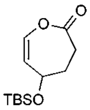
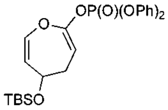
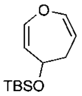
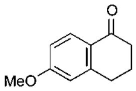
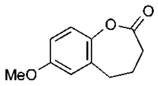
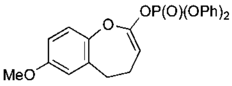
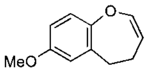
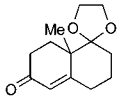
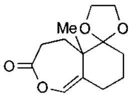
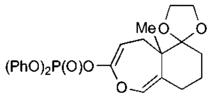
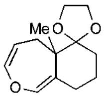
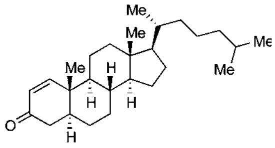
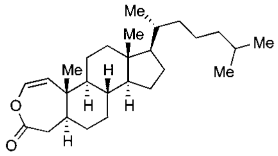
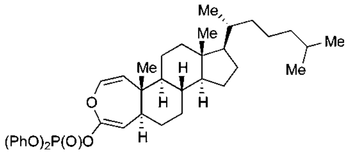
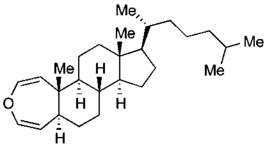
(13) In their elegant synthesis of acetylaranotin, Tokuyama et al. prepared the 4,5-dihydrooxepine structural motif of the molecule from a lactone via the corresponding enol triflate; see: Fujiwara, H.; Kurogi, T.; Okaya, S.; Okano, K.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 13062.

Table 3. Scope and Generality of the 4,5-Dihydrooxepine-Forming Sequence[a]

entry	substrate	lactone (% yield)[b]	enol phosphate (% yield)[b]	4,5-dihydrooxepine (% yield)[b]
1	 **1a**	 **2a** (83)	 **3a** (92)	 **4a** (81)[c]
2	 **1b**	 **2b** (70)	 **3b** (93)	 **4b** (67)[d,e]
3	 **1c**	 **2c** (72)	 **3c** (89)	 **4c** (90)[c]
4	 **1d**	 **2d** (70)	 **3d** (55)	 **4d** (81)[c]
5	 **1e**	 **2e** (74)[e]	 **3e** (84)	 **4e** (61)[d,e]
6	 **1f**	 **2f** [34 (46 brsm)][f]	 **3f** (75)	 **4f** (64)[d,e]
7	 **1g**	 **2g** (79)	 **3g** (83)	 **4g** (86)[d]
8	 **1h**	 **2h** (54)	 **3h** (90)	 **4h** (71)[d]
9	 **1i**	 **2i** (99)	 **3i** (57)	 **4i** (82)[d]

[a] Lactone formation: reactions were carried out on 1.0 mmol scale at 0.1 M concentration in CH_2Cl_2 with 0.5 equiv of $SnCl_4$, 0.5 equiv of ligand A, 3.0 equiv of BTSP, and 200 mg of 4 Å MS at 25 °C. Enol phosphate formation: reactions were carried out on 0.5 mmol scale at 0.1 M concentration in THF with 2.0 equiv of KHMDS, 2.0 equiv of $(PhO)_2P(O)Cl$, 3.0 equiv of HMPA at −78 °C. Dihydrooxepine formation (method A): reactions were carried out on 0.2 mmol scale at 0.05 M concentration in $ClCH_2CH_2Cl$ with 0.2 equiv of $Pd(PPh_3)_4$ and 2.5 equiv of Et_3Al. Dihydrooxepine formation (method B): reactions were carried out on 0.2 mmol scale at 0.05 M concentration in THF with 0.2 equiv of $Pd(PPh_3)_4$ and 10 equiv of $LiBH_4$ at 0 °C. [b] Isolated yield unless otherwise noted. [c] Using method A. [d] Using method B. [e] Due to the volatility of the product, the yield refers to ^{1}H NMR yield. [f] Anhydrous K_2CO_3 (200 mg) was added; brsm = based on recovered starting material.

comparable yields (entries 4–6). The presence of dry molecular sieves was essential for the success of this reaction, as in its absence, only trace amounts of the product was observed (entry 7).

Conversion of the Baeyer–Villiger product **2a** to the corresponding enol phosphate **3a** went smoothly under our previously developed conditions (Scheme 1).[15] The phosphate group was chosen over the more common triflate group because the former is well-known to be more stable than the latter.[15]

Pd-catalyzed reduction of the diphenyl phosphate **3a** proved to be unsuccessful when using either Ph_2SiH_2 or

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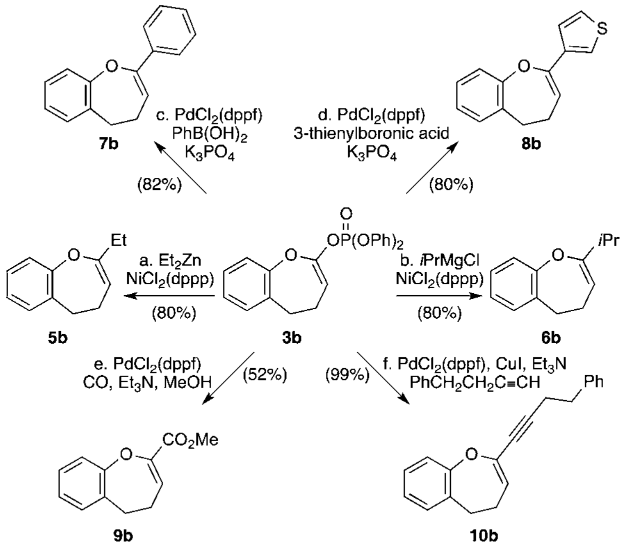
nBu$_3$SnH as the reducing agent. After extensive screening, Et$_3$Al turned out to be the optimal reducing agent, giving the desired 4,5-dihydrooxepine **4a** in 81% yield (Scheme 1). However, when applying the same reduction conditions to phosphate **3b** (Table 2), we obtained an inseparable mixture of the desired product **4b** and the ethylated product **5b** in ca. 3:2 ratio (Table 2, entry 1). This result reflects the competition between β-hydride elimination and reductive elimination of the ethylated intermediate (see Table 2).[16] Attempts to optimize the reduction of **3b** by changing the solvent (entry 2) or using the diethyl phosphate **3b′** (entry 3) gave a mixture of **4b** and **5b**, albeit in different ratios (see Table 2). We then turned to some other reducing agents and found that LiBH$_4$ proved to be the best, giving exclusively the benzodihydrooxepine **4b** in good yield [entries 4 (66% yield) and 5 (67% yield)].

With the developed optimized conditions in hand, we then proceeded to assess the generality and scope of this three-step procedure to functionalized dihydrooxepines. As shown in Table 3, a variety of substrates with diverse substitution patterns and functional groups could be reliably transformed into the corresponding 4,5-dihydrooxepines. Cyclohexenones with either a methyl group on the olefinic bond (entries 3 and 5) or *gem*-dimethyl groups on the 4-position (entry 4) are good substrates for these transformations, although the latter exhibits lower reactivity in the first and third steps as compared to the others. Functional groups such as an isolated olefinic bond, an electron-rich arene, a TBS-protected secondary alcohol, or a ketal group are all tolerated in these procedures (entries 5–8). Most notably, the current method is also applicable to relatively complex structures, including the protected Wieland–Miescher ketone **1h** and the cholesterol derivative **1i** (entries 8 and 9, respectively). Thus, application of the present method to these substrates allows rapid access to the relatively complex dihydrooxepines **4h** and **4i**, respectively.

In addition to the above Pd-catalyzed reduction, the enol phosphate intermediate also provides a platform for a series of C–C bond forming reactions, thereby allowing further functionalization of the dihydrooxepine system. Thus, as demonstrated in Scheme 2, **3b** could be successfully engaged in Ni-catalyzed Negishi (conditions a) and Kumada couplings (conditions b), leading to the corresponding alkyl-substituted products **5b** and **6b**, respectively, without competition from the β-hydride elimination pathway. Introduction of phenyl (conditions c), 3-thienyl (conditions d), and alkynyl (conditions f) substituents can also be achieved in high yields using PdCl$_2$(dppf) as the catalyst (products **7b**, **8b**, and **10b**, respectively). The same catalyst is also effective in converting the phosphate into an ester group (conditions e), albeit in moderate yield (product **9b**).

Scheme 2. Functionalization of the 4,5-Dihydrooxepine Structural Motif via the Corresponding Enol Phosphate



In summary, we have developed a three-step approach for the synthesis of functionalized dihydrooxepines from readily available cyclohexenones. This sequence features a regioselective Baeyer–Villiger oxidation, subsequent enol phosphate formation, and Pd-catalyzed functionalization. The large variety of available cyclohexenones provides the basis for the generality of this approach, while the mildness of reaction conditions ensures their reliable transformation to functionalized dihydrooxepines with minimal loss due to facile decomposition. The current method holds considerable promise for application to the synthesis of bioactive natural products and their analogues.

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Supporting Information Available. Experimental procedures, characterization, and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.