Dess–Martin Periodinane Promoted Oxidative Coupling of Baylis–Hillman Adducts with Silyl Enol Ethers: A Novel Synthesis of *cis*-Fused Dihydropyrans

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Abstract: Baylis–Hillman adducts undergo smooth oxidative Mukaiyama–Michael addition and a subsequent cyclization with silyl enol ethers in the presence of Dess–Martin periodinane (DMP) and pyridine under mild reaction conditions to afford a new class of dihydropyran derivatives in good yields with high diastereoselectivity. This is the first report on the preparation of *cis*-fused dihydropyrans from Baylis–Hillman adducts and silyl enol ethers.

Key words: Baylis–Hillman adducts, hypervalent iodine, enol ethers, oxidative Mukaiyama–Michael addition

The dihydropyran ring system is frequently found in various natural products.[1] They are normally prepared by means of carbonyl-Diels–Alder reaction.[2] The ready availability and versatility of Baylis–Hillman adducts and their acetates makes them valuable synthetic intermediates for the synthesis of a variety of heterocycles such as quinolines, pyrimidones, isoxazolines, pyrazolones, pyrrolidines, indolizines, azetidinone, diazacyclophanes, and chromanones as well as biologically active natural products including α-alkylidene-β-lactams, α-methylene-γ-butyrolactones and mikanecic acids, frontalin, trimethoprim, sarkomycin, ilmofosine nuciferol, and many others.[3,4] Consequently, various nucleophiles such as metal hydrides, halides, azides, cyanides, alcohols, amines, arenes, and active methylene compounds have been used to prepare a wide range of synthetic intermediates.[5–7] However, there have been no reports on the preparation of fused dihydropyrans from Baylis–Hillman adducts and silyl enol ethers via an oxidative reaction.

In recent years, hypervalent iodine reagents have occupied an important place in the reactions of natural and synthetic organic chemistry because of their potential applications in the construction of carbon–carbon and carbon–heteroatom bonds.[8] One of the most significant advances in the field, discovery of the Dess–Martin periodinane (DMP) reagent, opened the door to a mild oxidation procedure allowing alcohols to be converted into the corresponding carbonyl compounds.[9] Its widespread use over the past decade attests to its benign nature and its ability to succeed under mild oxidation circumstances. The Dess–Martin periodinane is an oxidizing agent that overcomes many of the disadvantages associated with oxidative methods developed so far.[10]

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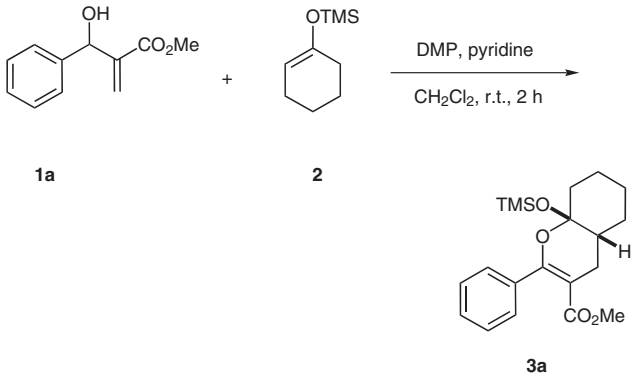
In this article, we report a direct and one-pot method for the preparation of fused dihydropyrans from Baylis–Hillman adducts and electron-rich silyl enol ethers using DMP and pyridine as a novel reagent system. Initially, we attempted an oxidative Michael and a tandem cyclization of methyl 2-[hydroxy(phenyl)methyl] acrylate (**1**) with 1-cyclohexenyl(1,1,1-trimethylsilyl) ether (**2**) in the presence of 1.2 equivalents Dess–Martin periodinane in dichloromethane. The reaction went to completion within two hours at room temperature; however, the cyclized product **3a** was obtained in 60% yield together with Mukaiyama–Michael adduct in 25% yield. Surprisingly, upon addition of 1.5 equivalents of pyridine, the cyclized product **3a** was obtained exclusively in 82% yield (Scheme 1).



Scheme 1 Preparation of product **3a**

The product **3b** was thoroughly studied using various NMR techniques including ^{1}H-decoupling experiments, double-quantum-filtered correlation spectroscopy (DQF-COSY), nuclear Overhauser effect spectroscopy (NOESY) and heteronuclear single-quantum correlation spectroscopy (HSQC). Though four protons in between 1.83–2.69 ppm were easily noticed, which contained the resonances from the allylic protons at C6 as well, other seven proton resonances crowded a region of about 0.37 ppm (between 1.28 to 1.65 ppm), resulting in extensive overlap. Resonances of the five methylene proton pairs in the molecule could be easily observed with the help of HSQC experiments. Once these protons were located, the assignments were carried out with the help of the splitting patterns, coupling constants as well as the DQFCOSY and NOESY experiments. For the cyclohexane ring fused to oxygen containing six-membered ring, all the characteris-

tic signatures of a $^1C_4$ chair form are observed from the NMR spectra. Emphatic support comes from couplings, $^3J_{H1a–H2a}$ = ca. 12.8 Hz, $^3J_{H1a–H2e}$ = 3.8 Hz, $^3J_{H1e–H2a}$ = ca. 3.6 Hz, $^3J_{H1e–H2e}$ = ca. 3.6 Hz, $^3J_{H2a–H3a}$ = ca. 12.6 Hz, $^3J_{H2a–H3e}$ = ca. 3.5 Hz, $^3J_{H3a–H4a}$ = ca. 12.3 Hz, $^3J_{H3e–H4a}$ = 3.2 Hz, $^3J_{H4a–H5}$ = 10.5 Hz, $^3J_{H4e–H5}$ = 4.2 Hz, and 1, 3-diaxial NOE enhancement, H1a/H3a, H1a/H5a and H3a/H5a. Furthermore, the $SiCH_3$/H1a and $SiCH_3$/H1e NOE cross peaks, provide evidence for O–C(Si) bond in an equatorial orientation in the cyclohexane ring, thus confirming the *cis* fusion of the two six-membered rings. In addition, the presence of a Ph group adjacent to oxygen is confirmed by NOE correlations for Ph/$SiCH_3$. Further support comes from energy-minimized structure (Figure 1).

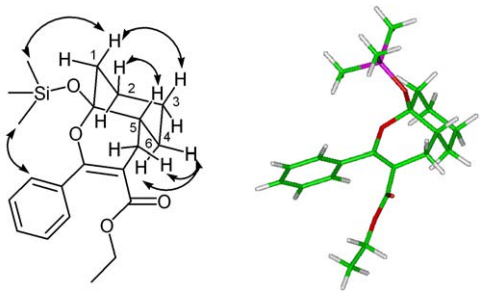
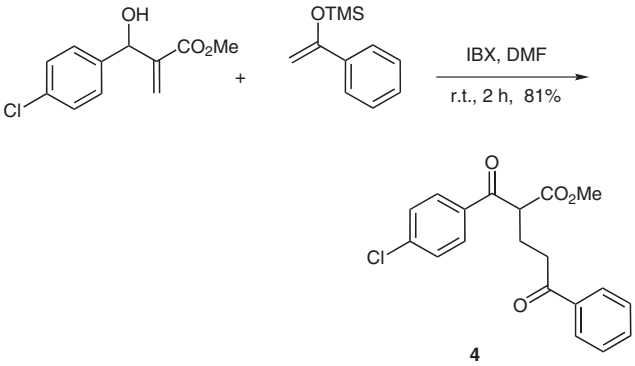


Figure 1 The characteristic NOEs and energy-minimized structure of **3b**

This result encouraged us to examine other substituted Baylis–Hillman adducts (Table 1). Interestingly, this method worked well with substrates derived from both aliphatic and aromatic aldehydes. As with cyclohexenyl(trimethylsilyl) ether, other silyl enol ethers derived from acetophenone and cyclopentanone also reacted readily with Baylis–Hillman adducts under the influence of DMP and pyridine. The *cis*-fused dihydropyran was formed exclusively in each reaction, the structure of which has been confirmed by NOE studies. However, silyl enol ethers underwent exclusively Mukaiyama–Michael addition with Baylis–Hillman adducts when using 1.2 equivalents of IBX in DMF (Scheme 2).



Scheme 2 Preparation of product **4**

Table 1 Preparation of *cis*-Fused Dihydropyrans from Baylis–Hillman Adducts and Silyl Enol Ethers Promoted by DMP and Pyridine

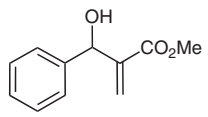
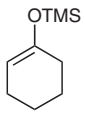
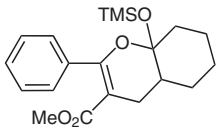
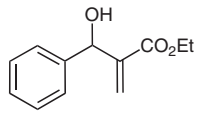
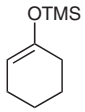
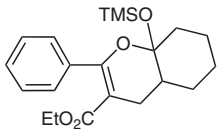
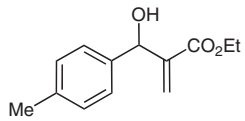
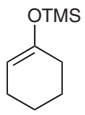
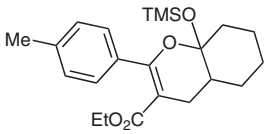
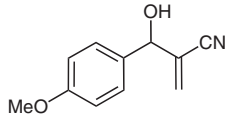
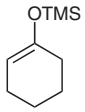
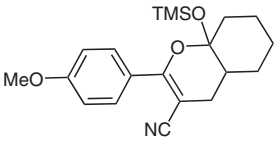
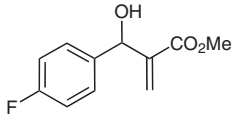
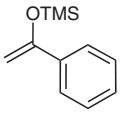
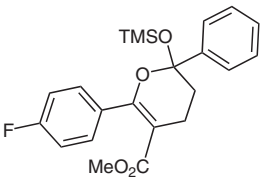
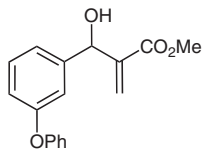
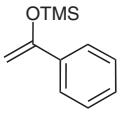
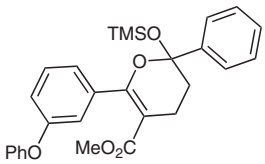
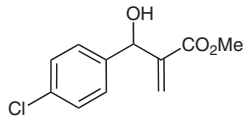
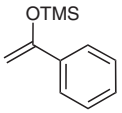
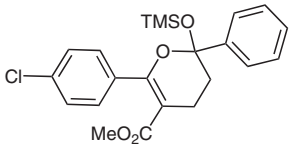
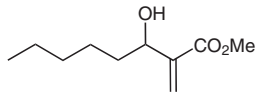
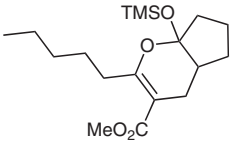
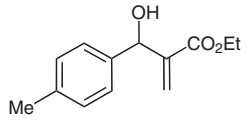
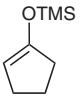
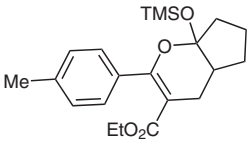
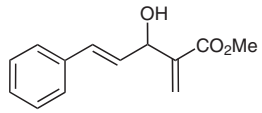
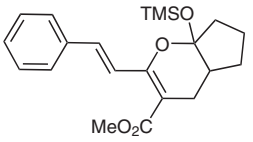
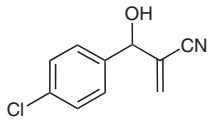
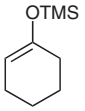
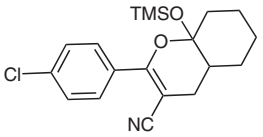
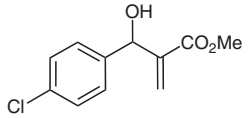
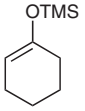
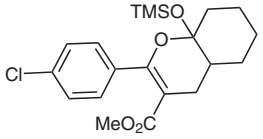
Entry	Baylis–Hillman adduct **1**	Enol ether **2**	Product **3**[a]	Time (h)	Yield (%)[b]
a				2.0	82
b				2.0	80
c				3.0	78
d				3.0	79
e				2.0	84

Table 1 Preparation of *cis*-Fused Dihydropyrans from Baylis–Hillman Adducts and Silyl Enol Ethers Promoted by DMP and Pyridine (continued)

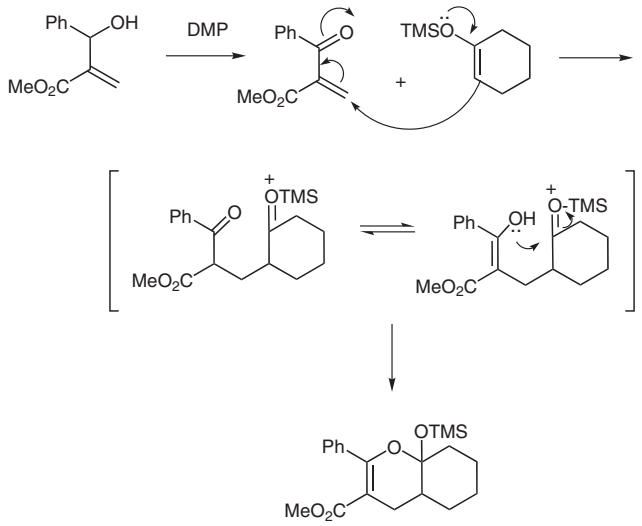
Entry	Baylis–Hillman adduct **1**	Enol ether **2**	Product **3**[a]	Time (h)	Yield (%)[b]
f				3.0	82
g				2.0	81
h				6.0	78
i				3.0	78
j				2.0	80
k				3.0	79
l				2.0	86

[a] All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

In all cases, the reactions were clean and afforded the Michael adducts in good yields. The reaction conditions were compatible with various functionalities such as halides, nitriles, aryl methyl ethers, esters, and alkenes (Table 1). All the products were characterized by ^{1}H NMR, IR, and mass spectrometry. Of the various hypervalent iodine reagents examined, including iodosobenzene (PhIO), iodobenzene diacetate [PhI(OAc)$_2$], and 2-iodoxybenzoic acid (IBX), Dess–Martin periodinane (DMP) was found to be the best in terms of conversion. Other oxidants such as Oxone®, CAN, MnO_2, and $KBrO_3$ failed to produce the desired product. As solvent, dichloromethane gave the best results. The scope of the DMP- and pyridine-promoted oxidative tandem reaction was investigated with respect to various Baylis–Hillman adducts and silyl enol ethers, and the results are presented in Table 1.[11] The reaction most likely proceeds via an initial DMP oxidation of Baylis–Hillman adducts and then Mukaiyama–Michael addition with silyl enol ethers and a subsequent cyclization to afford the product (Scheme 3).

A similar type of cyclization was reported previously to prepare *cis*-fused pyranopyrrole derivatives via an inverse-electron-demand hetero-Diels–Alder reaction.[12]

In conclusion, we have described a one-pot oxidative Michael addition and a tandem cyclization of Baylis–Hillman adducts with silyl enol ethers using DMP and pyridine as a novel reagent system. The method offers several advantages such as high regioselectivity, operational simplicity, mild reaction conditions, cleaner reaction profiles, simple workup procedure, and the use of readily available reagents which makes it a useful and attractive strategy



Scheme 3 A plausible reaction mechanism

for the preparation of highly functionalized dihydropyrans in a single-step operation.

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(11) **General Experimental Procedure**
A mixture of Baylis–Hillman adduct (1 mmol), DMP (1.2 mmol), and pyridine (1.5 mmol) in anhyd CH_2Cl_2 (10 mL) was stirred at r.t. until complete oxidation took place. To this, trimethylsilyl enol ether (1.5 mmol) was added and stirred until complete addition (as indicated by TLC) took place. The reaction mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 15 mL). The combined ether layer was washed with sat. aq $NaHCO_3$ soln (1 × 15 mL), brine (1 × 10 mL), dried over Na_2SO_4, and evaporated. The crude product was purified by silica gel column chromatography using a gradient mixture of hexane–EtOAc (9:1) as eluent to afford pure substituted dihydropyran derivatives.
Spectral Data of Selected Compounds
Compound **3a** (Table 1): colorless liquid. IR (KBr): ν_{max} = 2954, 2838, 1738, 1454, 1234, 1207, 1153, 1017, 781 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.0 (s, 9 H), 1.20–1.58 (m, 8 H), 1.61–1.76 (m, 1 H), 2.06 (dd, 1 H, *J* = 1.4, 16.4 Hz), 2.56 (dd, 1 H, *J* = 5.8, 16.8 Hz), 3.32 (s, 3 H), 7.14–7.18 (m, 5 H). ESI-MS: *m/z* = 361 [M + 1], 383 [M + Na]. HRMS: *m/z* calcd for $C_{20}H_{28}O_4NaSi$: 383.1654; found: 383.1641.
Compound **3b** (Table 1): ^1H NMR (600 MHz, $CDCl_3$): δ = 7.33 (m, 5 H, Ph), 3.92 (q, 2 H, *J* = 7.2 Hz, OCH_2), 2.72 (dd, 1 H, *J* = 16.7, 6.2 Hz, H6), 2.23 (dd, 1 H, *J* = 16.7, 2.0 Hz, H6′), 2.12 (dt, 1 H, *J* = 13.0, ca. 3.6 Hz, H1e), 1.85 (dddd, 1 H, *J* = 10.5, 6.2, 4.2, 2.0 Hz, H5a), 1.65 (m, 1 H, H3e), 1.62 (m, 1 H, H2e), 1.57 (m, 1 H, H4e), 1.55 (dt, 1 H, *J* = 3.8, ca. 12.8 Hz, H1a), 1.44 (tq, 1 H, *J* = ca. 3.5, ca. 12.6 Hz, H2a), 1.34 (dq, 1 H, *J* = 3.2, ca. 12.3 Hz, H4a), 1.28 (m, 1 H, H3a). 0.91 (t, *J* = 7.2 Hz, 1 H, CH_3), 0.15 (s, 9 H, 3 × CH_3).
Compound **3f** (Table 1): colorless liquid. IR (KBr): ν_{max} = 3029, 2948, 2865, 1718, 1495, 1265, 1217, 1137, 1037, 854 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.0 (s, 9 H), 1.80 (ddd, 1 H, *J* = 1.8, 5.6, 13.4 Hz), 2.21 (ddd, 1 H, *J* = 3.5, 5.4, 13.4 Hz), 2.52 (ddd, 1 H, *J* = 3.5, 5.6, 16.9 Hz), 2.66 (ddd, 1 H, *J* = 5.4, 11.3, 16.8 Hz), 3.59 (s, 3 H), 7.07–7.13 (m, 5 H), 7.22 (td, 1 H, *J* = 1.1, 7.9 Hz), 7.3–7.43 (m, 6 H), 7.50 (dd, 2 H, *J* = 1.5, 7.7 Hz). HRMS: *m/z* calcd for $C_{28}H_{31}O_5Si$: 475.1940; found: 475.1954.
Compound **3h** (Table 1): colorless liquid. IR (KBr): ν_{max} = 2928, 2857, 1715, 1504, 1433, 1151, 1039, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.0 (s, 9 H), 0.78 (t, 3 H, *J* = 6.8 Hz), 1.10–1.27 (m, 6 H), 1.33–1.72 (m, 6 H), 1.86–2.02 (m, 1 H), 2.07 (dd, 1 H, *J* = 6.0, 12.0 Hz), 2.16 (dd, 1 H, *J* = 6.0, 12.0 Hz), 3.55 (s, 3 H).
Compound **4** (Scheme 2): colorless liquid. IR (KBr): ν_{max} = 2920, 2851, 1739, 1683, 1506, 1443, 1226, 1157, 1019, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.20–2.39 (m, 2 H), 2.94–3.19 (m, 2 H), 3.61 (s, 3 H), 4.67 (dd, 1 H, *J* = 6.0, 7.5 Hz), 7.33–7.52 (m, 5 H), 7.87 (d, 2 H, *J* = 7.5 Hz), 7.99 (d, 2 H, *J* = 9.0 Hz). ESI-MS: *m/z* = 345 [M + 1], 367 [M + Na]. HRMS: *m/z* calcd for $C_{19}H_{17}O_4NaCl$: 367.0713; found: 367.0715.

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