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Utilization of Aldoses as a Carbonyl Source in Cyclocarbonylation of Enynes

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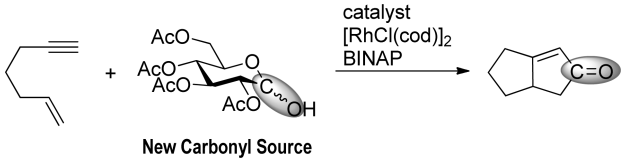

The reaction of enynes with acetyl-masked aldoses in the presence of a rhodium(I) catalyst resulted in cyclocarbonylation, thus avoiding the direct use of carbon monoxide, to afford bicyclic cyclopentenones. In rhodium catalysis, aldoses serve as a carbon monoxide equivalent by donating their carbonyl moieties on the acyclic aldehyde form to enynes. A variety of aldoses, including D-glucose, D-mannose, D-galactose, D-xylose, and D-ribose, can be used as a carbonyl source. Using the method, a wide variety of enynes were cyclocarbonylated in 22−67% yields. An asymmetric variant also proceeded with moderate to high enantioselectivity.

The cyclocarbonylation of enynes with carbon monoxide, so-called the Pauson−Khand reaction, is a powerful tool for the direct one-step synthesis of bicyclic cyclopentenones.[1] In the original method, enynes were reacted with stoichiometric amounts of transition metals containing a carbonyl ligand. Numerous subsequent studies reported on transition-metal-catalyzed reactions in which carbon monoxide itself was used as a carbonyl source. Recent progress has disclosed that various formyl compounds, such as aldehydes[2] and formates,[3] can be used as a substitute for carbon monoxide, leading to much more approachable and easily handled transformations, without the need to use toxic carbon monoxide. The strategies involve the decarbonylation of the formyl compounds by transition-metal catalysts to produce an isolated carbonyl moiety or metal−carbonyl species, which serves as a substitute for carbon monoxide. In this study, we envisioned the use of aldoses, in which the aldehyde form is present in trace amounts at equilibrium, as a carbonyl source in the cyclocarbonylation of enynes. Aldoses are widespread in nature, in the forms of oligosaccharides, polysaccharides, glycoproteins, lipopolysaccharides, nucleotidyl sugars, and nucleic acids, and they are one of the most reliable and sustainable carbon resources. Therefore, aldoses can be regarded as the most favorable carbonyl source. Their conventional synthetic applications can be broadly classified into the following two types: synthetic tools such as organocatalysts, ligands, and auxiliaries for asymmetric synthesis,[4] and synthetic building blocks for the synthesis of biologically active compounds and glycosides.[5] Quite recently, Chung et al. developed a cyclocarbonylation reaction of an enyne using just glucose as a carbonyl source, which is based on the same strategy as mentioned above.[2l] We describe herein a novel utilization of aldoses in the cyclocarbonylation of enynes and the development of the strategy into an asymmetric reaction, based on the catalytic decarbonylation of the acyclic aldehyde form.[6] This represents the first asymmetric variant using aldoses as a carbonyl source in the cyclocarbonylation of enynes.

We first attempted the cyclocarbonylation of enyne **1a** with D-glucose (**2a**) in the presence of 5 mol % of of [RhCl(cod)]$_2$ and 10 mol % of BINAP in 1,4-dioxane/dimethylacetamide (DMA) (1/1) at 130 °C for 40 h. The resulting

(1) For recent reviews of the Pauson−Khand reaction, see: (a) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800–1810. (b) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328–2336. (c) Lee, H. W.; Kwong, F. Y. *Eur. J. Org. Chem.* **2010**, 789–811.

(2) (a) Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3806–3807. (b) Shibata, T.; Toshida, N.; Takagi, K. *Org. Lett.* **2002**, *4*, 1619–1621. (c) Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.* **2002**, *67*, 7446–7450. (d) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2409–2411. (e) Jeong, N.; Kim, D. H.; Choi, J. H. *Chem. Commun.* **2004**, *40*, 1134–1135. (f) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Tetrahedron Lett.* **2004**, *45*, 9163–9166. (g) Kwong, F. Y.; Li, Y. M.; Lam, W. H.; Qiu, L.; Lee, H. W.; Yeung, C. H.; Chan, K. S.; Chan, A. S. C. *Chem.—Eur. J.* **2005**, *11*, 3872–3880. (h) Shibata, T.; Toshida, N.; Yamasaki, M.; Maekawa, S.; Takagi, K. *Tetrahedron* **2005**, *61*, 9974–9979. (i) Kwong, F. Y.; Lee, H. W.; Qiu, L.; Lam, W. H.; Li, Y.-M.; Kwong, H. L.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1750–1754. (j) Kwong, F. Y.; Lee, H. W.; Lam, W. H.; Qiu, L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2006**, *17*, 1238–1252. (k) Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *Pure Appl. Chem.* **2008**, *80*, 1079–1087. (l) Quite recently, Chung's group has reported on the use of alcohols as a carbonyl source in a rhodium-catalyzed cyclocarbonylation. In this case, aldehydes generated in situ via dehydrogenation of alcohols act as a carbonyl source: Park, J. H.; Cho, Y.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5138–5141.

(3) (a) Park, K. H.; Son, S. U.; Chung, Y. K. *Chem. Commun.* **2003**, *39*, 1898–1899. (b) Lee, H. W.; Chan, A. S. C.; Kwong, F. Y. *Chem. Commun.* **2007**, *43*, 2633–2635.

(4) For recent reviews, see: (a) Hollingsworth, R. I.; Wang, G. *Chem. Rev.* **2000**, *100*, 4267–4282. (b) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189–3215. (c) Boysen, M. M. K. *Chem.—Eur. J.* **2007**, *13*, 8648–8659.

(5) For reviews, see: (a) Inch, T. D. *Adv. Carbohydr. Chem. Biochem.* **1972**, *27*, 191–225. (b) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159–165. (c) Frase-Reid, B.; Sun, K. M.; Tam, T. F. *Bull. Soc. Chim. Fr.* **1981**, 238–246. (d) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161–3213. (e) Williams, N. R.; Davidson, B. E.; Ferrier, R. J.; Furneaux, R. H. *Carbohydr. Chem.* **1985**, *17*, 244–255. (f) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624.

(6) For reports on decarbonylation of aldoses by a rhodium complex, see: (a) Andrews, M. A.; Klaeren, S. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1266−1267 (stoichiometric). (b) Beck, R. H. F.; Elseviers, M. Lemmens, H. O. J. EP 0716066A1, **1996** (stoichiometric). (c) Andrews, M. A. *Organometallics* **1989**, *8*, 2703−2708 (stoichiometric). (d) Andrews, M. A.; Gould, G. L.; Klaeren, S. A. *J. Org. Chem.* **1989**, *54*, 5257−5264 (stoichiometric). (e) Monrad, R. N.; Madsen, R. *J. Org. Chem.* **2007**, *72*, 9782−9785 (catalytic).

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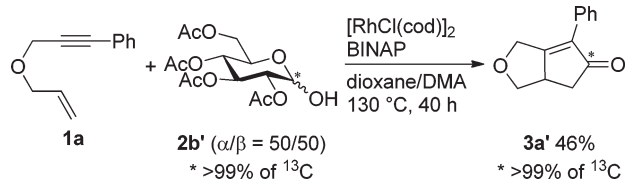
SCHEME 1. ^{13}C Labeling Experiment



mixture included the targeted carbonylated product **3a** in only 7% yield, along with the dimer of **1a** as the main product, which is formed via a [2 + 2 + 2] cycloaddition.[7] During the course of the reaction, the reaction mixture was heterogeneous because of the extremely low solubility of **2a** in organic solvents.[8] In order to increase the participation of the CO substitute in the reaction, we used tetracetyl-D-glucose **2b** as a carbonyl source, which can be readily prepared in two steps from D-glucose (**2a**).[9] The use of **2b** resulted in a dramatic increase in the yield, leading to the formation of the carbonylated product **3a** in 55% yield. Under the conditions, the cationic precursor, $[Rh(cod)_2]OTf$, which is reported to catalyze efficiently even under a lower concentration of carbon monoxide,[10] did not catalyze the sequence of the decarbonylation−cyclocarbonylation to the production of **3a**.

In order to verify the origin of the carbonyl groups introduced into the product **3a**, we performed the reaction using acetyl-masked D-glucose **2b′**, enriched at C-1 (the anomeric position) with ^{13}C (>99%). Under the aforementioned conditions, the catalytic reaction of **1a** with **2b′** resulted in cyclocarbonylation to give the carbonylated product **3a′** in 46% yield (Scheme 1). In this reaction, the introduced carbonyl group in **3a′** was labeled with >99% ^{13}C. Thus, this clearly indicates that the origin of the carbonyl moiety is not from the acetyl group of DMA (solvent) or the masked glucose, but from the anomeric carbon of the masked glucose **2b′**.

We further investigated the effect of the stereochemistry of the anomeric carbon on the efficiency of the reaction (Scheme 2). When either a mixture of α- and β-anomers (α/β = 30/70) or the β-anomer was used, the desired product was obtained in 52% yield in both cases, and therefore, no difference between the reactivities of the different anomers was observed. These results can be rationalized by the observation that, in 1,4-dioxane/DMA (1/1) at 130 °C, both the α/β-mixture and the β-anomer are converted quantitatively within 1 h into a mixture of α- and β-anomers in an α/β ratio of 77/23. Extending the reaction time (40 h) led to no change in the ratio between α- and β-anomers. Thus, α/β-interconversion via an acyclic aldehyde form would occur rapidly and reach equilibrium under the conditions of the present catalysis, despite the initial ratio of the mixture, and

SCHEME 2. Effect of Anomeric Configuration on Reaction Efficiency

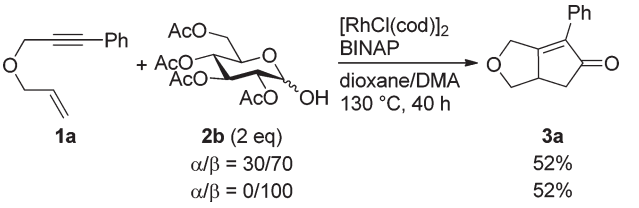
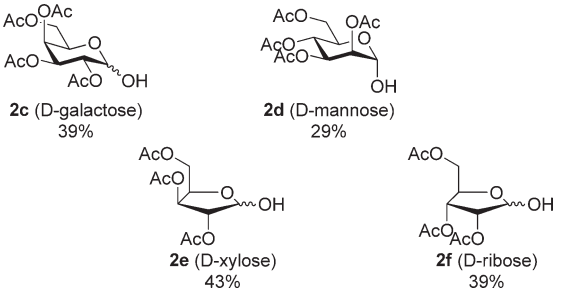


CHART 1



it can be safely concluded that both anomers function equally well as a carbonyl source.

The present reaction tolerated the use of other acetyl-masked aldoses **2c**−**f**, which are easily produced from readily available hexoses (D-galactose and D-mannose) as well as pentoses (D-xylose and D-ribose).[11] Under otherwise identical conditions, **2c**−**f** all functioned as a carbonyl source in the cyclocarbonylation reactions of enyne **1a** to produce the carbonylated product **3a**, although the yields were slightly lower (**2c** 39%; **2d** 29%; **2e** 43%; **2f** 39%) than that for the masked D-glucose **2b** (Chart 1).

The cyclocarbonylation reactions of various enynes were explored using aldose derivatives. Some selected results are shown in Table 1. Some enynes preferred the use of the masked xylose **2e** to the glucose analogue **2b** as a carbonyl source and/or xylene to the mixed solvent (1,4-dioxane/DMA). Replacement of the phenyl group in **1a** with a butyl substituent (**1b**) gave the carbonylated product **3b** in 67% yield (entry 4). When various substituents with different electronic properties were introduced into the aromatic ring of **1a**, the corresponding bicyclic cyclopentenones **3c**−**h** were obtained in moderate to high yields (entries 5, 7, 9, 11, 13, and 15). For enynes **1e**−**h** having an electron-withdrawing group, a less polar solvent, xylene, was more suitable for this reaction than a polar mixed solvent, 1,4-dioxane/DMA, because the latter solvent accelerated the dimerization of enynes.[7] Enyne **1i**, containing a 1,1-disubstituted alkene unit, reacted slowly to give **3i** in 23% yield, along with 53% of the starting material (entry 17). The reaction of enyne **1j**, which is easily prepared from malonic acid ester, also proceeded slowly to yield 23% of **3j** with 56% of unreacted **1j** after 40 h (entry 19). The *N*-tosylamide-tethered enyne **1k** reacted relatively smoothly to afford **3k** in 54% yield (entry 21).

We further studied an enantioselective reaction using aldose derivatives as a carbonyl source. For the former

(7) (a) Oh, C. H.; Sung, H. R.; Jung, S. H.; Lim, Y. M. *Tetrahedron Lett.* **2001**, *42*, 5493–5495. (b) Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 6697–6705. (c) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307–2327. (d) Shibata, T.; Otomo, M.; Tahara, Y.; Endo, K. *Org. Biomol. Chem.* **2008**, *6*, 4296–4298.

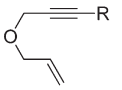
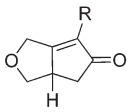
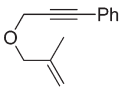
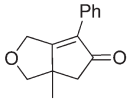
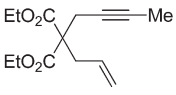
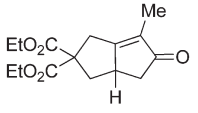
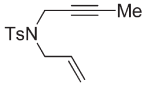
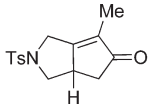
(8) The use of H_2O or 1-butanol as a solvent, which can dissolve at the reaction temperature, afforded no carbonylated product.

(9) For the first step, see: (a) Robert, S. W.; Rainier, J. D. *Org. Lett.* **2007**, *9*, 2227–2230. For the second step, see: (b) Sim, M. M.; Kondo, H.; Wong, C. H. *J. Am. Chem. Soc.* **1993**, *115*, 2260–2267.

(10) Kim, D. E.; Kim, I. S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Jeong, N. *J. Org. Chem.* **2008**, *73*, 7985−7989.

(11) For the synthesis of **2c** and **2d**, see ref 9. For the synthesis of **2e** and **2f**, see: Itoh, T.; Takamura, H.; Watanabe, K.; Araki, Y.; Ishido, Y. *Carbohydr. Res.* **1986**, *156*, 241–246.

TABLE 1. Rh(I)-Catalyzed Cyclocarbonylation of Various Enynes Using Aldose Derivatives[a]

Entry	Enyne	Aldose	Solvent	Product	Yield[c]	Ee[d]
1	 **1a** R = Ph	**2b**	dioxane/DMA (1/1)	 **3a**	55%	–
2[b]					44% (8%)	59%ee (*S*)
3	**1b** R = Bu	**2b**	dioxane/DMA (1/1)	**3b**	67%	–
4[b]					57%	92%ee (*S*)
5	**1c** R = 4-MeOC$_6$H$_4$	**2e**	xylene	**3c**	63%	–
6[b]					54%	80%ee (*S*)
7	**1d** R = 3-MeOC$_6$H$_4$	**2b**	dioxane/DMA (1/1)	**3d**	40%	–
8[b]					33% (11%)	57%ee (*S*)
9	**1e** R = 4-MeC$_6$H$_4$	**2b**	dioxane/DMA (1/1)	**3e**	37% (28%)	–
10[b]					30% (23%)	59%ee (*S*)
11	**1f** R = 4-CF$_3$C$_6$H$_4$	**2e**	xylene	**3f**	58% (38%)	–
12[b]					46% (33%)	81%ee (*S*)
13	**1g** R = 4-ClC$_6$H$_4$	**2e**	xylene	**3g**	39% (30%)	–
14[b]					37% (26%)	63%ee (*S*)
15	**1h** R = 4-FC$_6$H$_4$	**2e**	xylene	**3h**	37% (31%)	–
16[b]					27%	67%ee (*S*)
17	 **1i**	**2e**	DMA	 **3i**	23% (53%)	–
18[b]					22% (47%)	84%ee (*S*)
19	 **1j**	**2e**	xylene	 **3j**	25% (56%)	–
20[b]					24% (40%)	68%ee (*R*)
21	 **1k**	**2e**	xylene	 **3k**	54%	–
22[b]					51%	61%ee (*S*)

[a]Conditions: enyne (0.50 mmol), acetyl-masked aldose (1.0 mmol), [RhCl(cod)]$_2$ (0.025 mmol), *rac*-BINAP (0.050 mmol), and solvent (2 mL) at 130 °C for 40 h in a sealed tube. [b](*S*)-BINAP was used as a ligand. [c]Isolated yield. The value in parentheses is the yield of the recovered enyne. [d]Enantiomeric excess and absolute configuration were determined by HPLC using chiral stationary columns and specific optical rotation using a polarimeter, respectively.

reaction using racemic BINAP as a ligand, no enantioselectivity was observed in the formation of **3a**. Thus, the chiralities of **2b** and the decarbonylated residue do not affect the enantioselectivity of the reaction. In the reaction of **1a** with **2b**, the use of either (*S*)- or (*R*)-BINAP led to enantioselective cyclocarbonylation to afford **3a** in the same chemical yields and moderate enantiomeric excesses: for (*S*)-BINAP, 44 and 59% ee (*S*); for (*R*)-BINAP, 44 and 56% ee (*R*). The reaction of **1a** with 0.2 or 2.0 equiv of D-glucose in the presence of 8 mol % of RhCl(CO)((*S*)-BINAP)[12] in diglyme at 160 °C for 12 h resulted in a complete consumption of **1a** to give a messy mixture, including less than 10% yield of the cyclocarbonylated product **3a** without enantioselectivity. In all of the reactions examined using (*S*)-BINAP, the cyclocarbonylation proceeded slightly less efficiently than when racemic BINAP was used, although with moderate to high enantioselectivity, to give the corresponding bicyclic cyclopentenones (entries 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22). For the reactions of less reactive enynes, such as entries 18 and 20, higher catalyst loading (10 mol % of [RhCl(cod)]$_2$ and 20 mol % of (*S*)-BINAP) had almost no remarkable effect on the reactivities and selectivities.[13] It would be caused by the deactivation of the catalysts by the high reducing ability of the aldose.[14]

A reaction pathway for the present cyclocarbonylation is proposed, which consists of two rhodium-catalyzed processes, as follows: the decarbonylation of the masked aldose in the acyclic aldehyde form leading to the formation of a rhodium−carbonyl species,[15] and the subsequent carbonylation of the enyne utilizing the resulting carbonyl moiety (Scheme 3). Although, in general, the acyclic aldehyde form is present at extremely low concentrations in an equilibrium mixture of the dissolved aldoses,[16] the rhodium catalyst is able to capture it efficiently and to consequently donate the carbonyl moiety in the formyl group to the enyne. On the basis of our previous studies,[2a,k] we postulate that the

(12) Bunten, K. A.; Farrer, D. H.; Poë, A. J.; Lough, A. *Organometallics* **2002**, *21*, 3344–3350. synthesis of RhCl(CO((*S*)-BINAP.

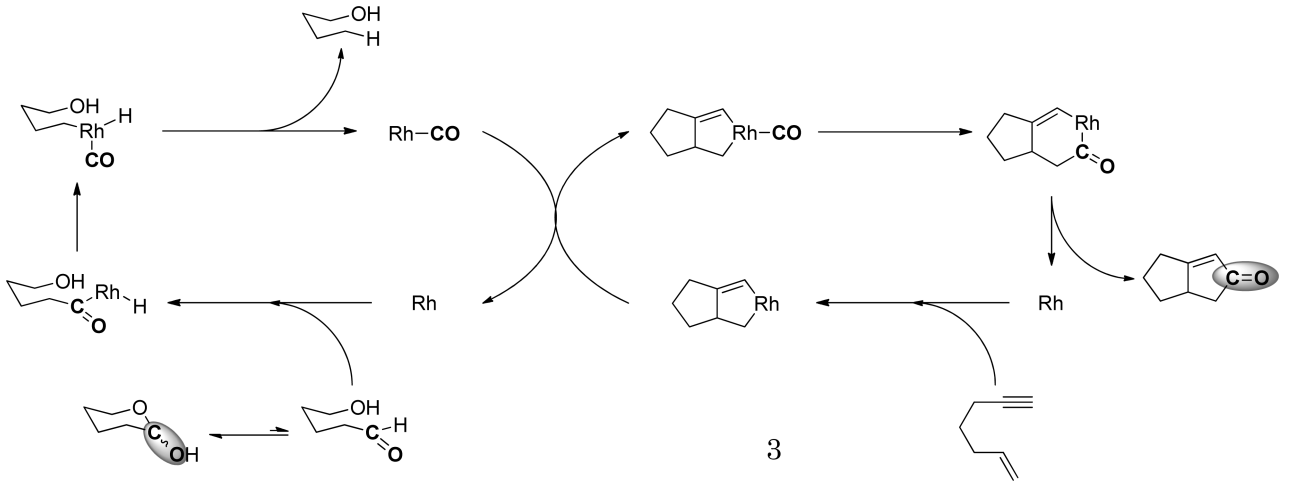
(13) For entry 18, 29% yield (32% recovery) and 86% ee; for entry 20, 31% yield (29% recovery) and 71% ee.

(14) Madsen has described the similar discussion on the rhodium-catalyzed decarbonylation of aldoses in the previous report. See ref 6e.

(15) At present, we have failed unfortunately to recover the decarbonylated residue.

(16) For example, the acyclic aldehyde form of D-glucose exists only 0.019% in aqueous solution. See: Maple, R. R.; Allerhand, A. *J. Am. Chem. Soc.* **1987**, *109*, 3168–3169.

SCHEME 3. Plausible Reaction Pathway



carbonyl moiety is transferred directly from the decarbonylation process to the cyclocarbonylation process, resulting in a CO gas-free cyclocarbonylation of the enyne.

In conclusion, we report on the development of a new method for the cyclocarbonylation of enynes using readily available aldose derivatives. This represents a novel utilization of aldoses as a carbon monoxide equivalent.[2l] Various aldoses, such as D-glucose, D-galactose, D-mannose, D-xylose, and D-ribose, can be used in the present method. The ^{13}C labeling experiment verifies that the anomeric carbon of aldoses is exclusively introduced into products under the conditions of the rhodium catalysis. Thus, the reaction involves the catalytic decarbonylation of the acyclic aldehyde forms of aldoses as a key step. The use of chiral BINAP as a ligand to the rhodium catalyst led to the asymmetric formation of various bicyclic cyclopentenones.

Experimental Section

Typical Procedure. In a 7 mL screw-capped tube were placed $[RhCl(cod)]_2$ (12.3 mg, 0.025 mmol), BINAP (31.8 mg, 0.050 mmol), 2,3,4,6-tetraacetyl-D-glucose (**2b**) (348.3 mg, 1.0 mmol), enyne **1a** (86.1 mg, 0.50 mmol), and 1,4-dioxane/*N*,*N*-dimethylacetamide (2.0 mL, v/v = 1/1). The tube was degassed using freeze−pump−thaw method and sealed under N_2, and the mixture was stirred at room temperature for 20 min and then at 130 °C for 40 h. The reaction was analyzed by GC. The reaction mixture was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (eluent; hexane/AcOEt = 4/1) to give bicyclic cyclopentenone **2a** (R_f 0.31, 55.0 mg, 0.28 mmol) in 55% yield as colorless oil:[2a] ^1H NMR ($CDCl_3$) δ 2.34 (dd, J = 3.7 Hz, J = 18 Hz, 1H), 2.85 (dd, J = 6.1 Hz, J = 18 Hz, 1H), 3.24 (dd, J = 7.9 Hz, J = 12 Hz, 1H), 3.29−3.37 (m, 1H), 4.37 (t, J = 7.9 Hz, 1H), 4.59 (d, J = 17 Hz, 1H), 4.94 (d, J = 17 Hz, 1H), 7.33−7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 40.3, 43.3, 66.3, 71.3, 128.0, 128.0, 128.5, 128.6, 130.6, 134.7, 177.4, 206.8.

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Supporting Information Available: General experimental methods, additional experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.