JOC*Note*

Morita−Baylis−Hillman Reaction of Masked 5-Alkylidene-2-cyclopentenones: General Entry to 5-Alkylidene-2-(hydroxyalkyl)-2-cyclopentenones

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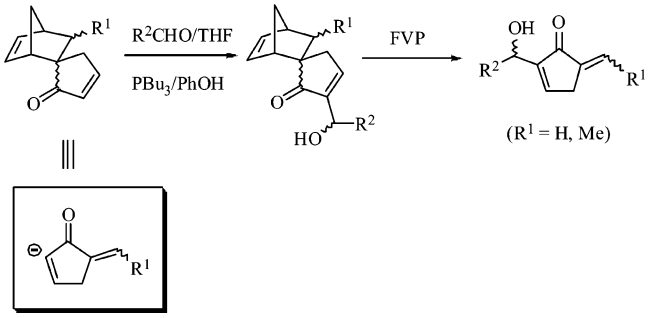
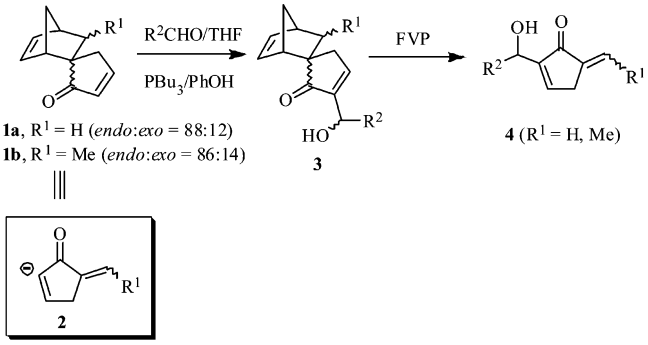


The reaction of masked 5-alkylidene-2-cyclopentenones with aldehydes catalyzed by tributylphosphine in the presence of phenol provided the corresponding Morita−Baylis−Hillman adducts, which were subjected to flash vacuum pyrolysis to afford 5-alkylidene-2-(hydroxyalkyl)-2-cyclopentenones.

The Morita−Baylis−Hillman (MBH) reaction is one of the most versatile carbon−carbon bond forming reactions at the α-carbon of activated alkenes with various types of electrophiles, providing a convenient method for the synthesis of α-functionalized activated alkenes.[1] A considerable amount of effort has been devoted to the improvement of reaction conditions, employing a wide range of organocatalysts such as DABCO, DBU, phosphines, and Lewis acids, which allow the MBH reaction to be applied with a broad range of activated alkenes and electrophiles.[2] Moreover, the MBH reaction has been applied to catalytic asymmetric synthesis using a chiral catalyst.[3] The MBH adducts have also proven to be versatile precursors for further synthetic transformation.[4]

It is anticipated that a general entry to 5-alkylidene-2-(hydroxyalkyl)-2-cyclopentenones of the type **4** could be achieved by utilizing the spiro-cyclopentenone **1**[5] as a carbanion synthon **2**. The reaction of **1** with aldehydes, using MBH-type reaction conditions followed by pyrolysis, would give the highly functionalized cyclopentenones **4** (Scheme 1), which may be used as useful precursors for further synthetic manipulation leading to highly substituted cyclopentanoid natural products.

SCHEME 1. Preparation of 5-Alkylidene-2-(hydroxyalkyl)-2-cyclopentenones 4 by the MBH Reactions of 1a and 1b with Aldehydes Followed by FVP



To the best of our knowledge, there have been no reports on utilizing such a synthon for the preparation of this type of compound previously. The use of tertiary phosphines as Lewis bases has been described previously.[2a,b,e,m,6] In general, the reactions proceed completely in a short period of time. Initially,

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(3) For a review, see: Langer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049−3052.

(4) For some recent synthetic applications of MBH adducts, see: (a) Lee, K. Y.; Seo, J.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3913−3917. (b) Singh, V.; Pathak, R.; Kanojiya, S.; Batra, S. *Synlett* **2006**, 2465−2468. (c) Liu, Y.; Xu, X.; Zheng, H.; Xu, D.; Xu, Z.; Zhang, Y. *Synlett* **2006**, 571−574. (d) Horn, C. R.; Perez, M. *Synlett* **2006**, 1480−1482. (e) Wasnaire, P.; Wiaux, M.; Touillaux, R.; Markó, I. E. *Tetrahedron Lett.* **2006**, *47*, 985−989. (f) Coelho, F.; Veronese, D.; Pavam, C. H.; de Paula, V. I. *Tetrahedron* **2006**, *62*, 4563−4572. (g) Kabalka, G. W.; Venkataiah, B.; Chen, C. *Tetrahedron Lett.* **2006**, *47*, 4187−4189. (h) Das, B.; Banerjee, J.; Chowdhury, N.; Majhi, A.; Mahender, G. *Helv. Chim. Acta* **2006**, *89*, 876−883. (i) Singh, V.; Batra, S. *Synthesis* **2006**, 63−72. (j) Gowrisankar, S.; Lee, K. Y.; Kim, J. N.; *Tetrahedron Lett.* **2005**, *46*, 4859−4863. (k) Aggarwal, V. K.; Patin, A.; Tisserand, S. *Org. Lett.* **2005**, *7*, 2555−2557. (l) Batra, S.; Singh, V.; Saxena, R. *J. Org. Chem.* **2005**, *70*, 353−356. (m) Kabalka, G. W.; Dong, G.; Venkataiah, B.; Chen, C. *J. Org. Chem.* **2005**, *70*, 9207−9210. (n) Krische, M. J.; Cho, C. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689−6691. (o) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379−7382. (p) Das, B.; Banerjee, J.; Majhi, A.; Mahender, G. *Tetrahedron Lett.* **2004**, *45*, 9225−9227.

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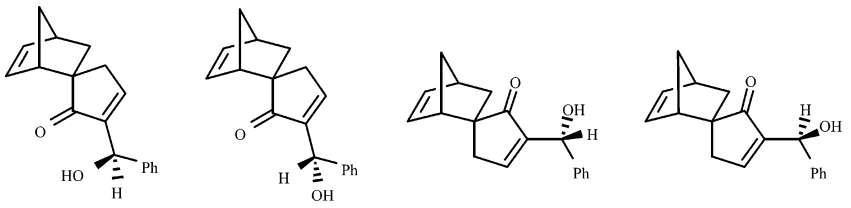
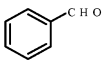
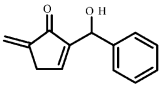
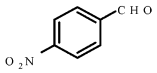
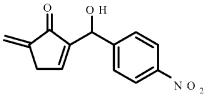
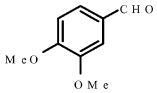
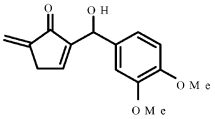
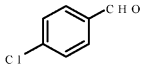
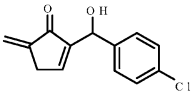
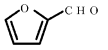
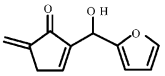
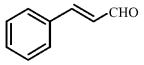
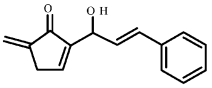
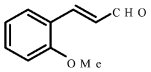
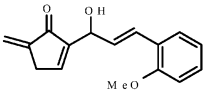
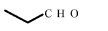
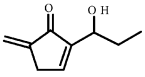
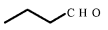
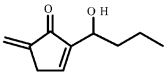
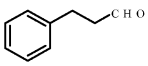
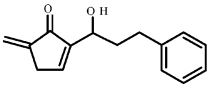


FIGURE 1. Diastereomers of *endo*-**3a** (A and B) and *exo*-**3a** (C and D) obtained from the MBH reaction of **1a** (*endo*:*exo* = 88:12) with benzaldehyde.

TABLE 1. Preparation of Compounds 3 by the MBH Reaction of 1a with Aldehydes Catalyzed by PBu_3 in the Presence of Phenol in THF and Their FVP to Highly Functionalized Cyclopentenones 4

Entry	RCHO	**3** (% yield)[a,b]		**4** (% yield)[a]
1		**3a** (82)		**4a** (86)[c]
2		**3b** (60)		**4b** (68)[c]
3		**3c** (80)		**4c** (70)
4		**3d** (78)		**4d** (75)[c]
5		**3e** (75)		**4e** (80)[c]
6		**3f** (74)		**4f** (49)
7		**3g** (73)		**4g** (45)
8		**3h** (74)		**4h** (76)[c]
9		**3i** (80)		**4i** (85)[c]
10		**3j** (74)		**4j** (82)[c]

[a] Yields refer to the purified products. [b] Obtained as mixtures of diastereomers of endo- and exo-isomers. [c] Quantitative yield of the crude product was obtained.

the reaction of **1a** (endo/exo isomers = 88:12) with benzaldehyde (1.5 equiv) in the presence of 20 mol % PBu_3[6] as an organocatalyst and 20 mol % phenol[7] at room temperature for 1 h gave mainly the starting materials and a small amount of the expected MBH adduct. Fortunately, the reaction performed at the same temperature overnight (15 h) afforded the expected MBH adduct **3a** (R^2 = Ph) in 82% yield after chromatography as a 46:42:12:trace mixture of diastereomers, presumably *endo*-**3a** (Figure 1A), *endo*-**3a** (Figure 1B), *exo*-**3a** (Figure 1C), and *exo*-**3a** (Figure 1D), respectively (Figure 1). To further probe the scope of the reaction, **1** was reacted with various aliphatic and aromatic aldehydes including unsaturated aldehydes. Thus, the MBH adducts **3b**−**j** were prepared in good yield by employing standard conditions. The results are summarized in Table 1. In all cases, the reactions provided mixtures of four diastereomers as indicated in Figure 1. Separation of these diastereomers was not attempted because they were expected to lead to the same 2-(hydroxyalkyl)-5-methylene-2-cyclopentenones **4** after flash vacuum pyrolysis. However, *endo*-**3b** (Figure 2A) and *endo*-**3b** (Figure 2B) (Figure 2) obtained from

(7) Phenol acts as an intramolecular H-bonding donor (a Brønsted acid) to accelerate the reaction; see ref 2m.

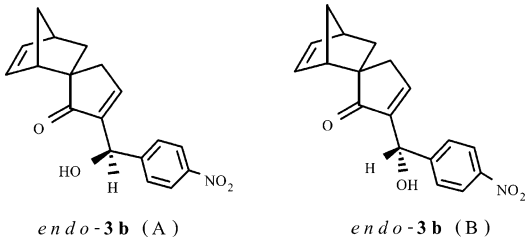
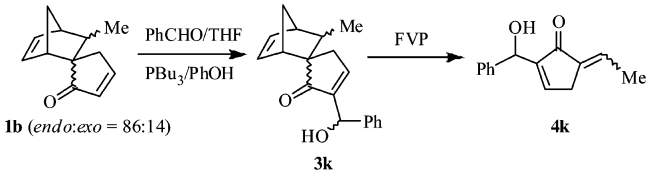


FIGURE 2. Diastereomers *endo*-**3b** (A) and *endo*-**3b** (B) obtained from the reaction of **1a** (*endo:exo* = 88:12) with *p*-nitrobenzaldehyde of which the stereochemistries were confirmed by X-ray crystallography.

SCHEME 2. Preparation of 5-Alkylidenecyclopentenone 4k



the reaction of **1a** with 4-nitrobenzaldehyde were successfully separated by chromatography. Their structures and relative stereochemistry were established by X-ray crystallography (see Supporting Information). It should be noted that the reaction of **1a** with cyclopentanone or cyclohexanone, instead of an aldehyde, gave no MBH adducts, presumably due to the steric effect and the low electrophilicity of the carbonyl carbons.

Having succeeded in preparing the MBH adducts **3a**−**j,** we then turned our attention to the generation of the required 2-(hydroxyalkyl)-5-methylene-2-cyclopentenones **4**. Thus, flash vacuum pyrolysis of **3a**−**j** at 375 °C/0.05 mmHg afforded the corresponding cyclopentenones **4a**−**j** in moderate to good yields after chromatography. Low yields of cyclopentenones **4f**,**g** (Table 1, entries 6 and 7) were obtained due to their decomposition during purification as monitored by ^{1}H NMR analyses.

To demonstrate the generality of this method, the MBH reaction of **1b** (endo/exo isomers = 86:14) was investigated. A crude MBH adduct **3k** was obtained in good yield as a 43:37:20:trace mixture of diastereomers, when **1b** was treated with benzaldehyde under standard conditions. Further flash vacuum pyrolysis of **3k** afforded the required cyclopentenone **4k** as a mixture of *E* and *Z* isomers (88:12). Purification of the crude pyrolysate provided a colorless liquid of a 98:2 mixture of *E* and *Z* isomers of **4k** in 68% yield (Scheme 2).

In summary, we have successfully developed a general and convenient method for the synthesis of 2-(hydroxyalkyl)-5-methylenecyclopentenones via the MBH reaction of a masked 5-alkylidene-2-cyclopentenone **1**, followed by the FVP of the resulting adducts. These highly functionalized cyclopentenones appear to be versatile precursors for further synthetic manipulations, and efforts in this area are in progress.

Experimental Section

General Procedure for the Preparation of MBH Adducts 3. 2′-Oxo-3′-hydroxy(phenyl)methylcyclopent-3′-ene-1′-spiro-2-bicyclo[2.2.1]hept-5-ene (3a). To a solution of **1a** (1.30 g, 1.875 mmol), benzaldehyde (0.298 g, 2.81 mmol), and phenol (0.035 g, 0.375 mmol) was added PBu_3 (0.093 mL, 0.375 mmol) at 15 °C under an argon atmosphere. After stirring at room temperature overnight (15 h), the organic solution was concentrated to give a crude liquid, which was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give a 46:42:12:trace mixture of diastereomers. The ratio was determined by ^{1}H NMR of the olefinic protons. Attempted separation of diastereomers was made by chromatotron (silica gel, 10% EtOAc in hexanes) to give two fractions of **3a** (0.412 g, 82% combined yield).

The first fraction (less polar) was obtained as a pale yellow solid containing a 77:18:5 mixture of three isomers (0.2197 g, 44% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−7.16 (m, 15H), 7.06 (m, 3H), 6.32−6.18 (m, 3H), 6.06 (dd, J = 5.5, 2.9 Hz, 1H), 5.90 (dd, J = 5.5, 2.9 Hz, 1H), 5.58 (dd, J = 5.6, 3.0 Hz, 1H), 5.49 (s, 1H), 5.44 (s, 2H), 3.60 (br s, OH), 2.95−2.78 (m, 3H), 2.71 (dt, J = 17.5, 2.0 Hz, 1H), 2.55 (app. d, J = 17.5 Hz, 1H), 2.50−2.10 (m, 9H), 2.09−1.98 (m, 2H), 1.60 (dd, J = 11.9, 3.7 Hz, 1H), 1.47−1.06 (m, 5H), 1.02 (m, 2H); MS: *m*/*z* (%) relative intensity 266 (M^+, 2), 248 (9), 183 (100).

The second fraction (more polar) was obtained as a pale yellow viscous liquid of pure *endo*-**3a** (0.1915 g, 38% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.15 (m, 5H), 7.05 (s, 1H), 6.25 (dd, J = 5.4, 3.1 Hz, 1H), 5.84 (dd, J = 5.4, 2.9 Hz, 1H), 5.46 (s, 1H), 3.65 (br s, OH), 2.90 (br s, 1H), 2.71 (dt, J = 18.9, 2.0 Hz, 1H), 2.54 (dt, J = 18.9, 2.2 Hz, 1H), 2.42 (br s, 1H), 1.62 (dd, J = 11.7, 3.7 Hz, 1H), 1.48−1.33 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.3, 155.4, 146.5, 141.3, 138.1, 132.5, 128.4, 127.7, 126.3, 70.2, 54.8, 54.0, 50.0, 45.0, 43.6, 39.6; IR ($CHCl_3$): ν_{max} 3474 m, 1687s, 1635 m, 1494 m, 1456 m cm^{-1}; MS: *m*/*z* (%) relative intensity 266 (M^+, 2), 248 (11), 183 (100). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.15; H, 6.75.

Preparation of Cyclopentenones 4 from MBH Adducts 3 by Flash Vacuum Pyrolysis 2-(Hydroxy(phenyl)methyl)-5-methylene-2-cyclopentenone (4a). General Procedure. Flash vacuum pyrolysis of **3a** (50 mg, 0.19 mmol) (conditions: oven temperature 240 °C, column temperature 375 °C, pressure 0.07 mmHg) gave a crude pyrolysate, which was purified by chromatotron (silica gel, 15% ethyl acetate in hexanes) to give a pale yellow solid of **4a** (33 mg, 86% yield, mp 116−118 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.25 (m, 5H), 7.20 (app. sept., J = 1.3 Hz, 1H), 6.14 (m, 1H), 5.62 (d, J = 1.3 Hz, 1H), 5.49 (s, 1H), 3.18 (app. quint., J = 1.9 Hz, 2H), 3.10 (br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 152.6, 149.3, 141.7, 141.1, 128.5, 127.9, 126.4, 118.3, 70.2, 32.1; IR ($CHCl_3$): ν_{max} 3487 m, 1696 s, 1649 m, 1622 w, 1493 w cm^{-1}; MS: *m*/*z* (%) relative intensity 201 (M^+ + 1, 10), 200 (M^+, 58), 199 (100). HRMS (ESI-TOF) for $C_{13}H_{12}O_2Na$: calcd, 223.0735; found, 223.0735.

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Supporting Information Available: Complete experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, IR, MS, HRMS, X-ray, and/or elemental analysis) for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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