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First Diastereoselective Intramolecular Baylis−Hillman Reaction: An Easy Access to Chiral α-Methylene-β-hydroxylactones†

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Abstract: The first diastereoselective intramolecular Baylis−Hillman reaction of chiral substrates is reported wherein both aldehyde and activated olefin coexist as substituents to afford α-methylene-β-hydroxylactones in good yields exclusively as single isomers under the standard base-catalyzed reaction conditions in CH_2Cl_2. Formation of alkoxylactones by an in situ derivatization of adducts was also observed.

The asymmetric Baylis−Hillman reaction[1] has attracted much attention in recent times as it provides multifunctional products with newly created stereogenic centers, and such adducts proved to be versatile synthetic intermediates in organic synthesis.[2] Although the Baylis−Hillman reaction is well documented in the literature, its intramolecular version is of much recent origin. Frater[3] reported the first intramolecular Baylis−Hillman reaction (IBHR) followed by Drewes,[4] Murphy,[5] and Keck[6] independently. More recently, Krishche[7] and Roush[8] have disclosed a vinylogous intramolecular Baylis−Hillman reaction of 1,5-hexadienes and 1,6-heptadienes as a protocol, catalyzed by trialkylphosphines, for the synthesis of substituted cyclopentenes and cyclohexenes in good yields. The only known chiral catalyst (−)-CAMP[3] for the intramolecular Baylis−Hillman cyclization of α,β-unsaturated-ϵ-ester provided the corresponding adduct in 14% ee. To the best of our knowledge, a diastereoselective intramolecular Baylis−Hillman reaction using a chiral substrate wherein both the aldehyde and activated olefin coexist has not been reported so far. In continuation of our work on the asymmetric Baylis−Hillman reaction,[9] we report herein the first examples of the diastereoselective intramolecular Baylis−Hillman reaction for the synthesis of α-methylene-β-hydroxylactones which constitute important structural features of many bio-active natural products.[10]

Initially, **2** was elected as the substrate for the study (Scheme 1). Accordingly, the known[11] carbinol **1** on acryloylation (acryloyl chloride, Et_3N, CH_2Cl_2), deacetonation ($BiCl_3$,[12] CH_2Cl_2), and oxidative cleavage ($NaIO_4$) of the diol in CH_2Cl_2 gave **2**. The intramolecular Baylis−Hillman reaction of **2** in the presence of DABCO (50 mol %) in THF afforded **3**, albeit in poor yields (39%, 15 h). However, the same reaction when conducted in CH_2Cl_2 furnished **3** in 62% yield in 10 h. Interestingly, the chiral α-methylene-β-hydroxy-γ-butyrolactone skeletal framework obtained in the present study is ubiquitous to many natural products such as blastomycinone[13] and sesquiterpene lactone,[14] and this protocol offers an alternate access to similar systems. The variation of base for this reaction was examined in CH_2Cl_2. For instance, DMAP (50 mol %)-catalyzed intramolecular Baylis−Hillman reaction of **2** gave **3** in 38% yield while the other catalysts such as DBU (50 mol %) and Bu_3P (50 mol %) were ineffective. Thus, DABCO was established as the standard catalyst.

Further, the study was extended to sugar-derived chiral substrate **5**. Accordingly, 1,2-*O*-isopropylidine-3-*O*-acrylate-α-D-*xylo*-pentadialdo-1,4-furanose **5** was prepared from known[9a] 1,2:5, 6-di-*O*-ispropylidine-α-D-glucofuranose-3-*O*-acrylate **4** by selective hydrolysis of primary acetonide and oxidative cleavage of the thus-obtained diol in methanol.

Compound **5** was then subjected to intramolecular Baylis−Hillman reaction in CH_2Cl_2 in the presence of DABCO at room temperature for 10 h to afford lactone **6** (71%) exclusively as a single isomer (route I). The cis-fused tetrahydrofurano-2-pyrone structure of lactone **6** constitutes an important partial structure of biologically active altholactones.[15] Interestingly, this reaction also furnished the 5-*O*-methyllactone **7a** in 8% yield. As no additive was used, the source of the methyl group was

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(1) (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Ciganek, E. The Morita-Baylis-Hillman reaction. In *Organic Reactions* Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, p 201. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(2) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317.

(3) Roth, F.; Gygax, P.; Frater, G. *Tetrahedron Lett.* **1992**, *33*, 1045.

(4) Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun.* **1993**, *23*, 2807.

(5) (a) Black, G. P.; Dinon, F.; Fratucello, S.; Murphy, P. J.; Nielsen, M.; Williams, H. L. *Tetrahedron Lett.* **1997**, *38*, 8561. (b) Dinon, F.; Richards, E. L.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1999**, *40*, 3279. (c) Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, *57*, 7771.

(6) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687.

(7) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402.

(8) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.

(9) (a) Radha Krishna, P.; Kannan, V.; Ilangovan, A.; Sharma, G. V. M. *Tetrahedron: Asymmetry* **2001**, *12*, 829. (b) Radha Krishna, P.; Kannan, V.; Sharma, G. V. M.; Ramana Rao, M. H. V. *Synlett* **2003**, 888. (c) Radha Krishna, P.; Narasingam, M.; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 4773. (d) Radha Krishna, P.; Kannan, V.; Narasimha Reddy, P. V. *Adv. Synth. Catal.* **2004**, *346*, 603.

(10) (a) Grieco, P. A. *Synthesis* **1975**, 67. (b) Hoffman, H. M. R.; Rabe, J. *Angew Chem., Int. Ed. Engl.* **1985**, *24*, 94.

(11) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104.

(12) Raghavendra Swamy, N.; Venkateswarlu, Y. *Tetrahedron Lett.* **2002**, *43*, 7549.

(13) (a) Chen, M.-J.; Lo, C.-Y.; Chin, C.-C.; Liu, R.-S. *J. Org. Chem.* **2000**, *65*, 6362. (b) Radha Krishna, P.; Ramana Reddy, V. V.; Sharma, G. V. M. *Synthesis* **2004**, in press.

(14) Schmidt, T. J.; Lyb, G.; Pahl, H. L.; Merfort, I. *Bioorg. Med. Chem.* **1999**, *7*, 2849.

(15) (a) Tadano, K.-I.; Ueno, Y.; Ogawa, S. *Chem. Lett.* **1988**, 111. (b) Bessodes, M.; Benamghar, R.; Antonakis, K. *Carbohydr. Res.* **1990**, *200*, 493. (c) Gesson, J.-P.; Jacquessy, J.-C.; Mondon, M. *Tetrahedron Lett.* **1987**, *28*, 3945.

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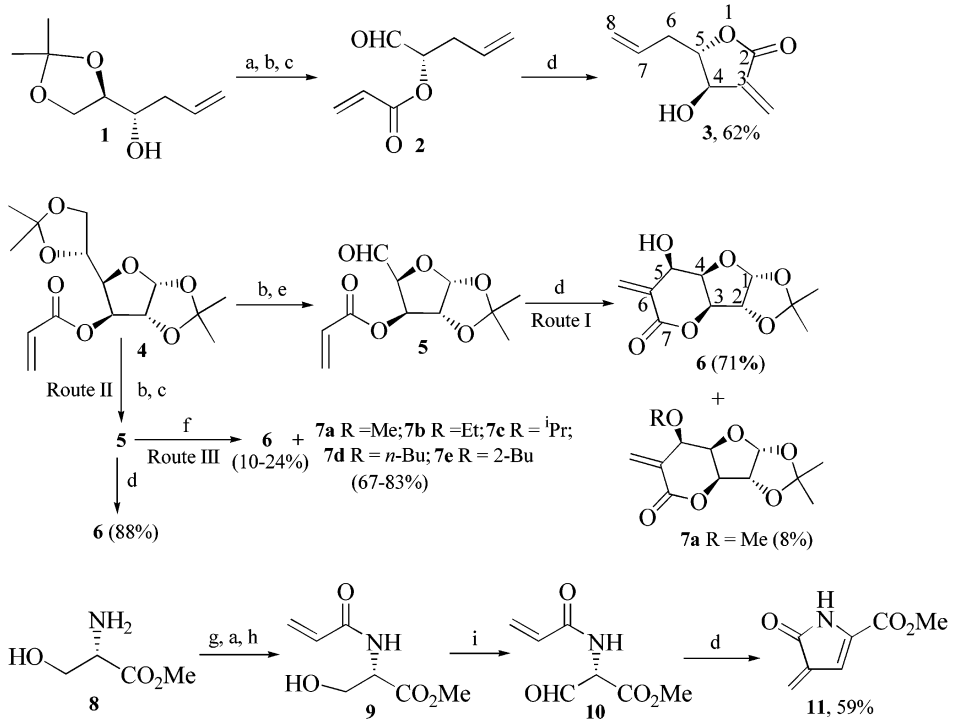
SCHEME 1[a]



[a] Reaction conditions: (a) acyloyl chloride, Et_3N, CH_2Cl_2, rt, 10 h; (b) $BiCl_3$, CH_3CN/H_2O, rt, 4 h; (c) $NaIO_4$, CH_2Cl_2, 6 h; (d) DABCO, CH_2Cl_2, rt, 10 h; (e) $NaIO_4$, MeOH, 1 h; (f) DABCO, CH_2Cl_2/ROH, rt, 10 h; (g) TBSCl, imidazole, DMF, 6 h; (h) TBAF, CH_2Cl_2, 24 h; (i) Swern oxidation.

assumed to be from the reaction medium itself. However, the initial presumption that solvent could be the source was ruled out when the intramolecular cyclization of **5** was carried out independently in $ClCH_2CH_2Cl$ and THF, which continued to afford **7a** along with the major product **6**. Intrigued, a thorough investigation was undertaken. Consequently, a repeat Baylis−Hillman reaction of **5** obtained by a $NaIO_4$ cleavage in CH_2Cl_2 afforded **6** (88%) as an exclusive product (route II). This result clearly demonstrated that the formation of **7a** was due to entrapped methanol.

Having set the reaction conditions for obtaining **6** as the exclusive product, the next task was to tune the reaction conditions to obtain **7a** as the major product. Thus, when the intramolecular Baylis−Hillman reaction of **5** was conducted in a mixture of CH_2Cl_2 and MeOH (8.5:1.5), **7a** was obtained in an optimum yield of 83%[16] along with **6** in 10% yield (route III). The formation of alkoxylactone **7a** may be attributed to the in situ derivatization of the hydroxy lactone **6** due to the presence of protic additive (MeOH). The generality of this in situ derivatization was further demonstrated with other alcohols such as ethanol, isopropyl alcohol, *n*-butanol, and 2-butanol to afford the ethers **7b**, **7c**, **7d**, and **7e**, respectively (Table 1) as major products (67−77%) with the normal adduct **6** as a minor product (10−24%).

Subsequently, the study was extended to chiral acrylamide aldehyde **10** in an effort to obtain α-methylene-β-hydroxylactam. Accordingly, **10** was prepared from L-serine derivative **8** in four steps, viz. (a) silylation, (b) acryloylation, (c) desilylation, and (d) Swern oxidation and subjected to intramolecular Baylis−Hillman reaction with DABCO in CH_2Cl_2. However, the Baylis−Hillman reaction of acrylamide **10** resulted in the lactam **11** (59%) as the product instead of the normal adduct.

TABLE 1. Asymmetric Intramolecular Baylis−Hillman Reaction of Chiral Substrates and Its in Situ Derivatization in the Presence of Different Alcohols

entry	substrate	solvent	yield[a] (%)	de[b] (%)	config[c]
1	**2**	CH_2Cl_2	**3**, 62	>95	*R*
2	**3**	CH_2Cl_2	**6**, 88	>95	*R*
3	**5**	CH_2Cl_2/MeOH	**6**, 10	>95	*R*
		8.5:1.5	**7a**, 83	>95	*R*
4	**5**	CH_2Cl_2/EtOH	**6**, 16	>95	*R*
		8.5:1.5	**7b**, 77	>95	*R*
5	**5**	CH_2Cl_2/IPA	**6**, 19	>95	*R*
		8.5:1.5	**7c**, 74	>95	*R*
6	**5**	CH_2Cl_2/*n*-BuOH	**6**, 20	>95	*R*
		8.5:1.5	**7d**, 72	>95	*R*
7	**5**	CH_2Cl_2/2-BuOH	**6**, 24	>95	*R*
		8.5:1.5	**7e**, 67	>95	*R*
8	**10**	CH_2Cl_2	**11**, 59		

[a] Yields of isolated product. [b] NMR studies show the presence of single isomer only. [c] Determined by *J* values and 1D-NOE studies.

The de and absolute stereochemistry at the newly created center of **3**, **6**, and **7a** were determined by NMR studies. For instance, H-4 of **3** was observed at δ 4.58 as a doublet with large coupling constant value (J = 7.8 Hz) suggesting the anti relationship with H-5, and 1D-NOE studies unequivocally assigned the configuration as *R* (see the Supporting Information). Similarly, ^{1}H NMR spectra of **6** and **7a** revealed H-5 proton at δ 4.76 and

(16) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692. Though recently Aggarwal group isolated the methyl ether product for the Baylis−Hillman reaction of acetylenic aldehydes in the presence of methanol and quinuclidine, its scope and generality has not been defined.

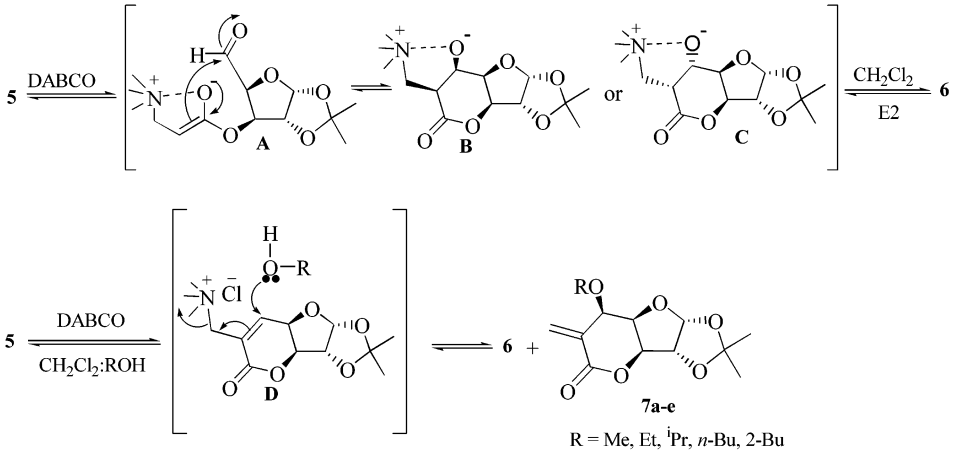


FIGURE 1. Proposed reaction mechanism.

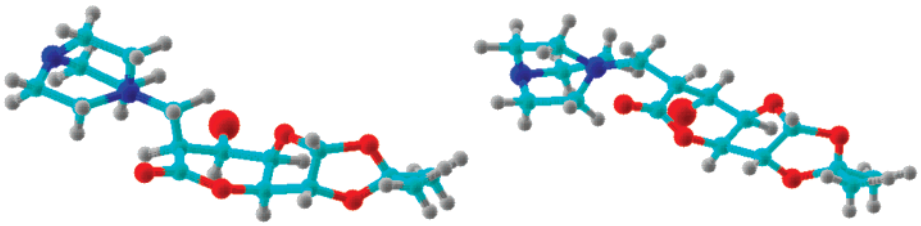


FIGURE 2. Energy-minimized structures.

4.14 as doublets with vicinal coupling constants[17] $J_{5,4}$ = 3.8 Hz and $J_{5,4}$ = 4.3 Hz, respectively. These smaller coupling constant values confirm the D-*gluco* configuration (*erythro* relationship between H-4 and H-5), which was further confirmed by 1D-NOE experiments while the stereochemistry at C-5 was assigned as *R* for both **6** and **7a** (see the Supporting Information). Thus, the stereochemical outcome of the intramolecular Baylis−Hillman reaction in **3** and **6** is complimentary to the results reported for 5-hexenyl[18a] and 6-heptnyl[18b] radical cyclization reactions[18c] onto aldehydes.[18d]

The plausible mechanism of intramolecular Baylis−Hillman reaction is depicted in Figure 1. The first step involves a Michael addition of DABCO onto the acrylate **5** to result in the formation of *Z* enolate **A**. The intramolecular nucleophilic attack of the enolate **A** on the aldehyde either by a *Re* or *Si* attack results in two possible *syn* zwitterions **B** and **C,** respectively. Energy minimization studies on intermediates **B** and **C** revealed that the newly created pyranone ring takes a near-$^4C_1$ conformation wherein the bulky alkylammonium ion occupies a favorable pseudoequatorial orientation (for energy-minimized structures[19] see Figure 2). A comparatively shorter interatomic distance between the charged species in **B** establishes it to be the preferred intermediate. The *trans* dispositioned zwitterionic intermediates were ruled out since there cannot be charge stabilization between the ions. The usual proton transfer followed by the E2 elimination of the tertiary amine from **B** affords **6** in CH_2Cl_2. Similarly, formation of alkyl ether adducts **7a**−**e** could be rationalized by the preferential *β*-facial Michael addition of ROH on **D**[4] and subsequent elimination of DABCO by a preferred E2 mode.

In conclusion, a novel intramolecular diastereoselective Baylis−Hillman reaction (de >95%) is reported for the first time. This is an alternate route to the synthesis of α-methylene-*β*-hydroxylactones. The absolute stereochemistry at the newly created stereogenic center was assigned as *R* for all adducts. Precise reaction conditions are set for the in situ derivatization of the hydroxy lactones. Further work is currently in progress to explore the scope of this methodology to other chiral substrates and application in natural product synthesis.

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Supporting Information Available: General experimental procedure, $[\alpha]_D$, mp, ^{1}H NMR, ^{13}C NMR, IR, Mass spectral data for compounds **3**, **6**, **7a**−**e** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Cornia, M.; Casiraghi, G. *Tetrahedron* **1989**, *45*, 2869. (b) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065.

(18) (a) Rama Rao, A. V.; Bhanu, M. N.; Sharma, G. V. M. *Tetrahedron Lett.* **1991**, *32*, 3907. (b) Rama Rao, A. V.; Sharma, G. V. M.; Bhanu, M. N. *Tetrahedron Lett.* **1993**, *34*, 707. (c) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1996; Vol. 48, p 301. (d) Sharma, G. V. M.; Subhash Chander, A.; Goverdhan Reddy, V.; Krishnudu, K.; Ramana Rao, M. H. V.; Kunwar, A. C. *Tetrahedron Lett.* **2002**, *41*, 1997.

(19) The energy minimization was carried out using Sybyl 6.8 with default Tripose force field Parameters. Minimization was done first with steepest discent followed by conjugate gradient methods for a maximum of 2000 iterations each or rms deviation of 0.005 kcal/mol, whichever was earlier.