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Baylis–Hillman chemistry: synthesis of *cis*- and *trans*-α-methylene-γ-lactones

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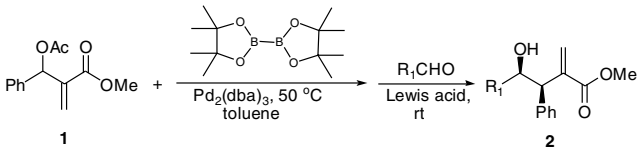
Abstract—*syn*-Homoallylic alcohols prepared from Baylis–Hillman adducts react with CBr_4/PPh_3 to give *trans*-α-methylene-γ-lactones. Notably, the same alcohols yield the *cis*-α-methylene-γ-lactones in the presence of traces of *p*-toluenesulfonic acid.

α-Methylene-γ-lactone derivatives have attracted attention over the years, since they are important functional components in a wide range of natural products.[1] The α-methylene-γ-lactone moiety, due to its propensity for Michael-type addition reactions, may play an important role in the biological activity on many naturally occurring products.[2] A variety of methodologies have been developed to synthesize α-methylene-γ-lactones; the most common method involves the reaction of allylic derivatives with carbonyl compounds.[3] This chemistry has been used successfully by employing allyl derivatives of zinc,[3a] tin,[3b] chromium,[3c] and indium.[3d] Recently, substituted allylborates were also used for the synthesis of α-methylene-γ-lactones.[4] However, the reported procedures generally result in the generation of *cis*-α-methylene-γ-lactones. Paquette and Andino used organoindium chemistry to produce 3:2 ratio of cis and trans substituted α-methylene-γ-lactones.[3d] Liu utilized a tungsten-promoted, intramolecular alkoxycarbonylation to prepare a *trans*-α-methylene-γ-lactone.[5] However, available syntheses of *trans*-α-methylene-γ-lactones remain limited. We wish to report new, straightforward methods for preparing both *trans*- and *cis*-α-methylene-γ-lactones using Baylis–Hillman adducts as precursors.

The Baylis–Hillman reaction is one of the most versatile carbon–carbon bond-forming reactions in modern organic synthesis. It has drawn considerable attention in the past few decades due to its atom economy, mild reaction conditions, and functional group compatability.[6] As part of our general interest in Baylis–Hillman chemistry, we recently developed a cross-coupling reaction of Baylis–Hillman adducts with bis(pinacolato)-diboron that produces 3-substituted-2-alkoxycarbonyl allylboronates; these boronates readily react with aldehydes in the presence of a silica supported BF_3 catalyst to form highly functionalized homoallylic alcohols in excellent yields (Scheme 1).[7]

The homoallylic alcohols **2** obtained in this reaction are useful due to the presence of multiple functionalities in close proximity. We felt that these alcohols would be excellent precursors to certain biologically important heterocycles. As part of our investigation, we attempted to brominate the *syn*-homoallylic alcohol with carbon tetrabromide and triphenylphospene. The reaction did not produce the expected brominated intermediate, but yielded the corresponding *trans*-α-methylene-γ-lactone (Scheme 2). The trans stereochemistry was somewhat surprising in light of the earlier studies.[3,7] Several homoallylic alcohols were synthesized using the one pot cross-coupling/allylboration reaction (Scheme 1), and then treated with CBr_4 and PPh_3 at room temperature.[8] *trans*-α-Methylene-γ-lactones were produced in moderate



Scheme 1. Synthesis of homoallylic alcohols.

Keywords: Lactone; Baylis–Hillman; Allylboronate; Homoallylic alcohol; Cross-coupling.
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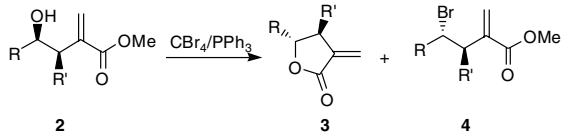
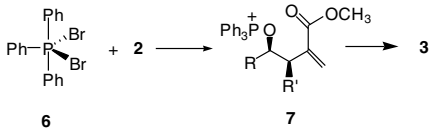


Scheme 2. Formation of *trans*-α-methylene-γ-lactones.



Scheme 4. Formation of a phosphonium intermediate.

to good yields (Table 1). The reaction yields were quite good when electron withdrawing groups were present on the aromatic ring. The presence of electron donating groups inhibited the formation of the lactone, and bromination products were isolated (Table 1, entry 10). Homoallylic alcohol derived from an aliphatic Baylis–Hillman adduct also gave the corresponding *trans*-α-methylene-γ-lactones along with a small quantity of the brominated byproduct (Table 1, entry 2).

The reaction does not appear to be limited to CBr_4/PPh_3 bromination reagent. Indeed, a good yield of the lactone was obtained utilizing NBS (Table 1, entry 5). In contrast, lactonization of **2** using *p*-toluenesulfonic acid produced the expected *cis*-α-methylene-γ-lactones **5** in isolated yields ranging from 94% to 99% in all cases (Scheme 3).[9,10]

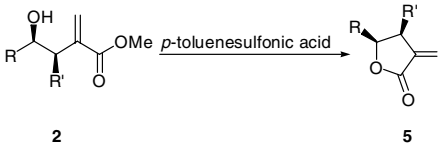
Although a detailed mechanistic study has not been undertaken for the formation of *trans*-α-methylene-γ-lactones, we believe that the reaction does not proceed via a brominated intermediate. We base this conclusion on a series of experiments in which the brominated product isolated from the reaction of methyl 4-hydroxy-3-methyl-2-methylene-4-phenylbutanoate (see entry 2, Table 1) was allowed to react with CBr_4/PPh_3 under the same reaction conditions used for lactone formation. None of the expected α-methylene-γ-lactone formed. Additional experiments were carried out in which the same butanoate was allowed to react separately with CBr_4 and PPh_3. Again, none of the lactone formed. It is possible that triphenylphoshpine reacts with the brominating agent to form dibromotriphenylphosphorane **6**, which would then be expected to react with the 4-hydroxy substituent in **2** to form a benzylic phosphonium intermediate **7** (Scheme 4). An intramolecular cyclization of **7** via a Mitsunobu-like substitution (or via a benzylic cation[9]) would result in the formation of the thermodynamically more stable *trans* lactone **3**. Further mechanistic studies are currently underway.

In conclusion, we have utilized *syn*-homoallylic alcohols, prepared via a one pot cross-coupling/allylboration reaction, to synthesize *cis*- and *trans*-α-methylene-γ-lactones. The methods are quite straightforward; by simply changing the ring closing reagent one can stereoselectively obtain either the cis or trans, bio-active α-methylene-γ-lactones.

Table 1. Synthesis of *trans*-α-methylene-γ-lactones[a,b]

Entry	R	R′	3	4
1	Phenyl	Phenyl	56	0
2	Phenyl	Methyl	49	17
3	*p*-Nitrophenyl	Phenyl	68	0
4	*p*-Nitrophenyl	*p*-Tolyl	71	0
5[c]	*p*-Nitrophenyl[c]	*p*-Tolyl	66	0
6	*p*-Nitrophenyl	*p*-Methoxyphenyl	70	0
7	*p*-Nitrophenyl	1-Napthyl	52	0
8	*p*-Nitrophenyl	*p*-Chlorophenyl	63	0
9	*p*-Trifluoromethylphenyl	Phenyl	67	0
10	*p*-Methoxyphenyl	Tolyl	0	59

[a] Unless otherwise noted, reactions carried out at rt for 15 h in the presence of 1.5 equiv of CBr_4 and PPh_3 in CH_2Cl_2.
[b] Isolated yields.
[c] Reaction carried out in the presence of 1.5 equiv of NBS in CH_2Cl_2 for 12 h.



Scheme 3. Synthesis of *cis*-α-methylene-γ-lactones.

Acknowledgements

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8. General experimental procedure for *trans*-α-methylene-lactones: The homoallylic alcohol (1 mmol) was dissolved in dichloromethane (5 mL) and the solution cooled to 0 °C. Carbon tetrabromide (1.5 mmol) and triphenylphosphene (1.5 mmol) were added sequentially, and the reaction mixture allowed to stir at room temperature overnight under a nitrogen atmosphere (reaction monitored by TLC). After completion of the reaction, the solvent was removed and the product was isolated by column chromatography.
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