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Metal-mediated allylation of mucohalic acids: facile formation of γ-allylic α,β-unsaturated γ-butyrolactones☆

Ji Zhang,* Peter G. Blazecka, Heidi Berven and Daniel Belmont

Chemical Research and Development, Pfizer Global Research & Development, Ann Arbor Laboratories, Pfizer, Inc.,
2800 Plymouth Road, Ann Arbor, MI 48105, USA

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Abstract—Mucohalic acids {mucochloric acid (**1**, 3,4-dichloro-5-hydroxy-5*H*-furan-2-one and mucobromic acid (**2**, 3,4-dibromo-5-hydroxy-5*H*-furan-2-one)} were employed as aldehydes in the indium- and tin-mediated Barbier-type allylation reactions and afforded γ-allylic α,β-unsaturated γ-butyrolactones in good to excellent yield.

In a further effort to fully exploit the potential of mucohalic acids **1** and **2** as useful building blocks in organic synthesis, selective manipulation of one of the carbonyl groups was examined recently in our laboratory.[1] Allylation of aldehydes is known to be one of the most important and fundamental transformations in organic synthesis,[2] and the metal-mediated Barbier-type allylation reaction is considered to be a useful and effective approach.[3] A vast number of bioactive natural products contain a substituted γ-allylic γ-butyrolactone, such as antifungal metabolites from the marine sponge *Pachastrissa* sp.,[4] bipinnatin J isolated from *Pseudopterogorgia bipinnata*,[5] palinurin and palinurine A and B,[6a] novel cytotoxic sesterterpenes from the sponge *Sarcotragus* sp.,[6b] and others[7] (Fig. 1). Furthermore, these substituted lactone species have been used in the construction of complex natural products, such as securinine,[8] okinonellin B,[9] (+)-aspicilin,[10] (−)-roccellaric acid[11] and (11*R*,12*S*)-oxidoarachidonic acid,[12] in leading academic and pharmaceutical laboratories (Scheme 1). These literature reports were the impetus to investigate the metal-mediated allylation reaction as applied to the aldehyde functional groups of **1** and **2**.

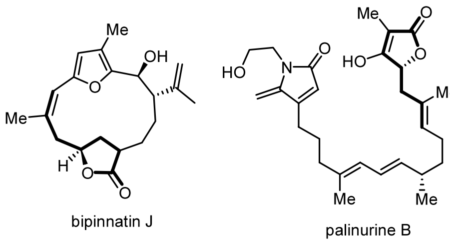
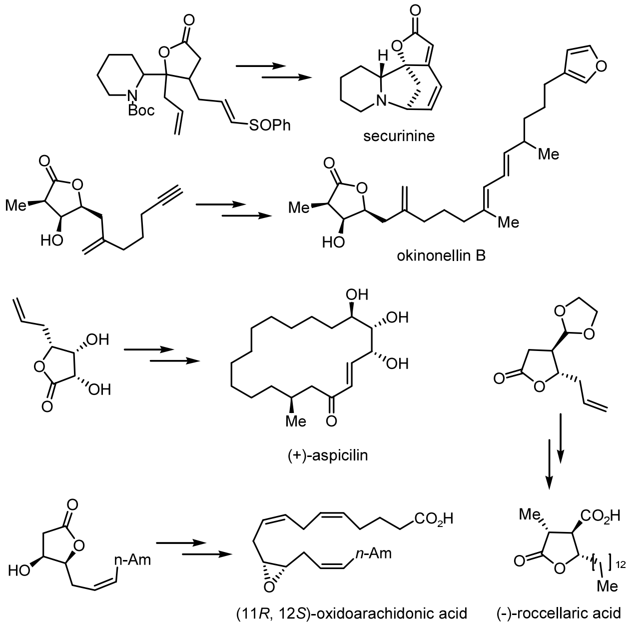


Figure 1. Examples of natural products containing a substituted γ-allylic γ-butyrolactone.

Although mucohalic acids **1** and **2** exist predominantly in the lactone form, the open form is responsible for



Scheme 1. Examples of some substituted γ-allylic γ-butyrolactones used in complex syntheses.

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* Corresponding author. Tel.: +1-734-622-3940; fax: +1-734-622-3294; e-mail: ji.zhang@pfizer.com

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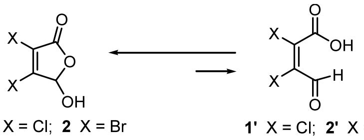
their activity as an aldehyde (Fig. 2). We initially considered water as the best solvent for the allylation of **1** and **2** for several reasons: (1) water is an environmentally benign solvent and fits in well with the theory of Green Chemistry;[13] (2) metal, especially indium-mediated Barbier-type reactions in water, have been reported and widely used for over a decade; (3) a greater proportion of the open forms of **1** and **2** exists in aqueous media, thus enhancing the reactivity of mucohalic acid as an aldehyde; (4) unlike Grignard or lithium reagents, the indium-mediated allylation reaction proceeds in neutral to slightly acidic aqueous conditions, environments well tolerated by the two vinylic halogen atoms and carboxylic acid function.

The indium-mediated Barbier-type allylation reaction of mucohalic acids proceeds extremely well using a modified version of Li and Chan's conditions.[14] Typically, a mixture of mucohalic acid (10 mmol), allylic bromide (12 mmol), indium (12 mmol) and NH_4Cl (10%) in a 1:1 mixture (30 mL) of THF/H_2O or MeOH/H_2O at 0°C to room temperature for 16–24 h afforded γ-allylic γ-butyrolactones in good to excellent yield (Table 1). The use of THF or MeOH as co-solvent was necessary to increase the solubility of both starting material and product; the product not simply being the homoallylic alcohol, but rather the lactone.[15,16] The role NH_4Cl plays is perhaps twofold: (1) to activate the carbonyl group, and (2) to polish the metal surface. We also deemed it prudent to cool the reaction mixture to 0°C when adding the metal, since the resulting exotherm may change the physical characteristics of the metal, thus affecting its reactivity.

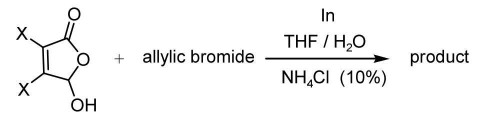
Nokami and co-workers[17] reported the first successful tin-mediated Barbier reaction of allyl bromide with carbonyl compounds. The HBr catalyzed reaction was carried out in water and yielded the desired homoallylic alcohols. Later, Luche[18] found that, without adding HBr, employing ultrasonic irradiation together with saturated aqueous NH_4Cl/THF solution gave the desired products. More recently, Chan and Li[19] demonstrated that allyltin(II) and diallyltin were involved in the mechanism. Since the ability to replace indium with much less expensive tin metal would translate into a significant cost-savings, we investigated the use of tin in the Barbier allylation reaction under similar conditions (THF/H_2O, NH_4Cl (10%), 0°C to rt for 16–24 h) (Table 2). Indium was successfully replaced with much less expensive tin at no cost to yield.[20] However, the success was limited to allylations involving allyl bromide (Table 2, entries 1, 2 and 5). Reactions with more highly substituted allylic bromides gave modest yields of the desired products or exhibited no reaction (Table 2, entries 3, 4, 6 and 7).



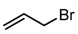
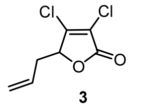
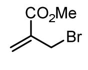
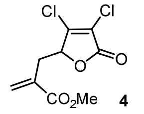
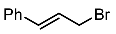
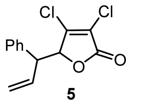
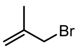
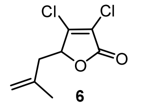
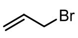
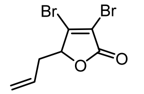
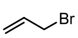
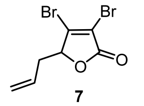
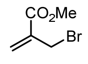
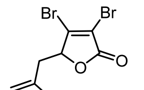
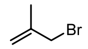
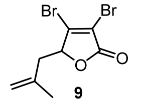
1 X = Cl; **2** X = Br **1'** X = Cl; **2'** X = Br

Figure 2. Equilibria of mucochloric and mucobromic acids.

Table 1. Indium-mediated allylation of mucohalic acids[a]



1 X = Cl; **2** X = Br

Entry	S.M.	Allylic bromide	Product	Yield (%)[b]
1	**1**		 **3**	90
2	**1**		 **4**	76
3	**1**		 **5**	46[c]
4	**1**		 **6**	82
5	**2**		 **7**	70
6	**2**		 **7**	86[d]
7	**2**		 **8**	74
8	**2**		 **9**	61

[a] Reaction conditions: 1 equiv (10 mmol) of **1** or **2**, 1.2 equiv of indium metal, 1.2 equiv of desired allylic bromide, 0.1 equiv of NH_4Cl, 1:1 v/v H_2O/THF, 16-24 h at 0 °C to room temperature. The reaction time was not optimized.

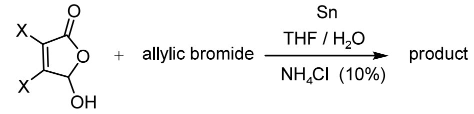
[b] Products were isolated and purified by silica gel chromatography. Products are estimated to be >95% pure by ^1H NMR and elemental analysis. All compounds gave satisfactory elemental analysis data.

[c] Mixture of α- and γ-isomers.

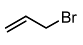
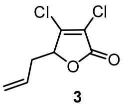
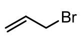
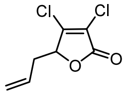
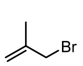
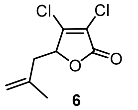
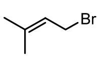
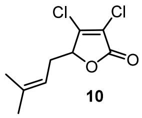
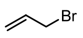
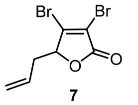
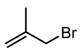
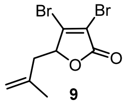
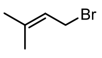
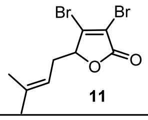
[d] H_2O/THF was replaced by 1:1 v/v H_2O/MeOH.

With the γ-allylic α,β-unsaturated γ-butyrolactones in hand, we began to consider the use of mucohalic acid

Table 2. Tin-mediated allylation of mucohalic acids[a]



1 X = Cl; **2** X = Br

Entry	S.M.	Allylic bromide	Product	Yield (%)[b]
1	**1**		 **3**	84
2	**1**		 **3**	77[c]
3	**1**		 **6**	50
4	**1**		 **10**	NR[d]
5	**2**		 **7**	75[c]
6	**2**		 **9**	41
7	**2**		 **11**	NR[d]

[a] Reaction conditions: 1 equiv (10 mmol) of **1** or **2**, 1.2 equiv of tin metal, 1.2 equiv of desired allyl bromide, 0.1 equiv of NH_4Cl, 1:1 v/v H_2O/THF, 24-48 h at 0 °C to room temperature. The reaction time was not optimized.

[b] Products were isolated and purified by silica gel chromatography. Products are estimated to be >95% pure by ^1H NMR and elemental analysis. All compounds gave satisfactory elemental analysis data.

[c] Reaction scaled up to 100 mmol.

[d] No reaction observed.

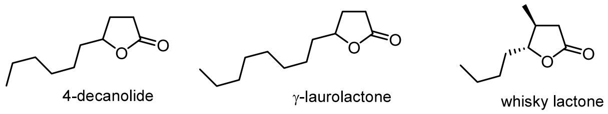
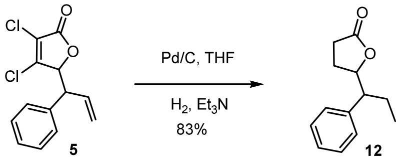


Figure 3. Naturally occurring γ-butyrolactones.

as a building block for other complex molecules.[21] Saturated butyrolactones, such as 4-decanolide,[22] γ-dodecanolactone[23] (a fruit flavor principle, γ-dodecalactone or γ-laurolactone) and whisky lactone,[24] are widely found in flavors and fragrances[25] (Fig. 3). Therefore preparation of saturated γ-butyrolactones was studied under hydrogenation conditions using 20% Pd/C and Et_3N in THF (Scheme 2). Both Cl atoms were easily removed by hydrogenation, and product **12** was isolated in good yield.



Scheme 2. Hydrogenation of allylation product.

In summary, we have developed a simple, efficient and green method for preparing γ-allylic α,β-unsaturated γ-butyrolactones in good to excellent yield. Further utilization of these functionalized lactones in organic synthesis will be reported in due course.

Acknowledgements

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