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# A concise synthesis of γ-carboxy-γ-lactones

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## ABSTRACT

A short protocol for the synthesis of γ-carboxy-γ-lactones has been developed via hydroboration followed by oxidation of α-hydroxy-4-pentenoates.



## KEYWORDS

α-Hydroxy-4-pentenoate;
α,δ-Dihydroxyesters;
γ-Carboxy-γ-lactone;
Hydroboration;
Oxidation.

## INTRODUCTION

γ-Carboxy-γ-lactone moiety is an extremely important motif found in several natural products[1]. As a part of our ongoing project involving the synthesis of biologically active small molecules, we undertook the synthesis of γ-carboxy-γ-lactones via the allylboration of α-ketoesters[1]. Asymmetric allylboration of carbonyl compounds with several chiral auxiliaries has been extensively studied for stereoselective formation of homoallylic alcohols and of all these reagents, B-allyldiisopinocampheylborane ($Ipc_2BAllyl$, 1) has proven to be one of the practical and widely used reagents in terms of the cost and level of stereoselectivity observed[1].

## EXPERIMENTAL

### Preparation of ethyl 2-oxo-2-phenylacetate, (2a)

Thionyl chloride (8 mL, 8 mmol, 1M solution in ether) was added to a solution of benzoylformic acid (1.0 g, 6.66 mmol) and pyridine (0.5 g) in anhydrous ether (10 mL) at room temperature and stirred for 1.5 h. Ethereal solution was decanted and concentrated. Hexane (8 mL) was added to resulting solution and concentrated again. The remaining thionyl chloride was removed under reduced pressure to yield phenylglyoxylyl chloride (1.06 g). To a solution of the crude phenyl glyoxylyl chloride (1 g, 5.95 mmol) in 12 mL of toluene, was added pyridine (0.94 g, 8 mmol) and ethanol (0.36 g, 7.1 mmol) and stirred overnight. The resulting solution was decanted, concentrated under reduced pressure and purified by column chromatography (ethyl acetate: hexane 1:19 ratio) to yield ethyl 2-oxo-2-phenylacetate **(2a)** (0.9 g, 79% yield). $^1$H NMR ($CDCl_3$, 500 MHz): δ7.98-8.00 (m, 2H), 7.47-7.64 (m, 3H), 4.43 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 186.7, 164.1, 135.1, 132.8, 130.0, 129.1, 62.4, 14.2.

### Preparation of isopropyl 2-oxo-2-phenylacetate, (2b)

Procedure similar to that of **(2a)**. (76% yield) $^1$H NMR ($CDCl_3$, 500MHz) δ 7.88 (d, J = 7.5 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.40 (m, 2H), 5.25 (m, 1H), 1.30 (d, J = 6.0 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 187.0,

163.9, 135.1, 132.8, 130.2, 129.1, 70.9, 21.9.

**Preparation of benzyl 2-oxo-2-phenylacetate, (2c)**

Procedure similar to that of **(2a)**. (72% yield) $^1$H NMR ($CDCl_3$, 500MHz) δ 7.99-8.01 (m, 2H), 7.65-7.68 (m, 1H), 7.39-7.53 (m, 7H), 5.45 (s, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 186.4, 163.9, 135.2, 134.8, 132.7, 130.3, 129.2, 129.1, 129.0, 128.9, 68.0.

**Preparation of methyl (R)-2-hydroxy-2-phenyl-4-pentenoate, (3a)**

To a solution of (-) $Ipc_2$Ballyl 1 (9 mL, 9 mmol, 1M solution in pentane) in ether (9 mL) was added a solution of methyl benzoylformate 2a (0.98 g, 6 mmol) in ether (2 mL) at -78$^0$C under inert atmosphere and stirred for 8 h. The reaction was monitored for completion by $^{11}$B NMR (δ 50) and oxidized with 3M sodium bicarbonate (0.3 mL) and 30% hydrogen peroxide (2 mL). After stirring for 4 h at room temperature, the reaction mixture was extracted with $Et_2O$. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane:ethyl acetate (1:19)) to obtain 0.98g (79%) of the pure alcohol **(3a)**. $^1$H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.49 (m, 2H), 7.15-7.24 (m, 3H), 5.65-5.73 (m, 1H), 4.99-5.06 (m, 2H), 3.82 (bs, 1H), 3.61 (s, 3H), 2.86 (dd, J = 7.5, 14.0 Hz, 1H), 2.63-2.68 (m, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ175.3, 141.6, 135.2, 132.7, 129.2, 128.1, 125.8, 78.5, 53.4, 44.4.

**Preparation of isopropyl (R)-2-hydroxy-2-phenyl-4-pentenoate (3b)**

Procedure similar to that of **(3a)**. (79% yield) $^1$H NMR ($CDCl_3$, 500MHz) δ 7.65-7.67 (m, 2H), 7.36-7.40 (m, 2H), 7.28-7.32 (m, 1H), 5.82-5.90 (m, 1H), 5.16-5.23 (m, 2H), 5.07-5.10 (m, 1H), 3.90 (bs, 1H), 3.00 (dd, J = 7.5, 14.0 Hz, 1H), 2.80 (dd, J = 6.5, 13.5 Hz, 1H), 1.32 (d, J = 6.0 Hz, 3H), 1.22 (d, J = 6.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 174.4, 141.9, 132.7, 130.2, 129.0, 128.7, 128.6, 78.0, 70.7, 44.5, 21.9, 21.8.

**Preparation of benzyl (R)-2-hydroxy-2-phenyl-4-pentenoate, (3c)**

Procedure similar to that of **(3a)**. (78% yield) $^1$H NMR ($CDCl_3$, 500MHz) δ 7.64-7.66 (m, 2H), 7.30-7.41 (m, 8H), 5.77-5.86 (m, 1H), 5.13 -5.28 (m, 4H), 3.81 (bs, 1H), 3.04 (dd, J = 7.5, 14.0Hz, 1H), 2.80-2.85 (m, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 174.8, 141.4, 135.2, 132.4, 128.9, 128.8, 128.6, 128.5, 128.1, 125.9, 119.7, 78.2, 68.4, 44.3.

**Preparation of (R)-2-hydroxy-2-phenyl-4-pentenoic Acid, (6a)**

Methyl (R)-2-Hydroxy-2-phenyl-4-propeonate **(3a)** (0.9 g, 4.36 mmol) was added at room temperature to a solution of LiOH (0.31 g, 13 mmol) in $CH_3OH$ (9 mL). After stirring overnight, the solvent was removed *in vacuo*. The residue was suspended in ether and acidified with 3M HCl to pH 1 and extracted with ether and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and purified by column chromatography (silica gel, hexane: ethyl acetate (2:5)) to obtain (0.59 g) 70% of product **(6a)**. $^1$H NMR ($CDCl_3$, 500MHz) δ 7.63-7.65 (m, 2H), 7.28-7.40 (m, 3H), 5.76-5.84 (m, 1H), 5.20-5.26 (m, 2H), 3.04 (dd, J = 7.5, 14.0 Hz, 1H), 2.82 (dd, J = 7.0, 14.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ178.5, 140.4, 132.0, 128.7, 128.4, 125.7, 120.7, 78.1, 44.4.

**Preparation of (R)-2-Hydroxy-2-methyl-4-pentenoic Acid, (6b)**

Procedure similar to that of **(6a)**. (71% yield) $^1$H NMR ($CDCl_3$, 500 MHz) δ 5.78-5.86 (m, 1H), 5.18-5.21 (m, 2H), 2.61 (dd, J = 7.0, 13.5 Hz, 1H), 2.46 (dd, J = 7.5, 14.0 Hz, 1H), 1.51 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 181.0, 132.0, 120.2, 74.6, 44.6, 25.6.

**Preparation of 2-((1-methoxy-1-oxo-2-phenyl-pent-4-ene-2-yloxy)carbonylbenzoic acid, (5a)**

To a solution of the alcohol **(3a)** (0.1 g, 0.48 mmol) in dichloromethane (2 mL) were added triethylamine (0.67 mL, 4.8 mmol), phthalic anhydride (0.35 g, 2.4 mmol) and DMAP (7 mg, 0.05 mmol) and the reaction was refluxed for 24 h. Upon completion (TLC), the solvent was removed in vacuo and suspended in 5 mL of ether. After stirring for 20 minutes, the solution was decanted and concentrated. The crude product thus obtained, was purified by column chromatography (silica gel, hexane: ethyl acetate (2:5)) to obtain 50 mg, (29% yield) of the phthalate ester **(5a)**. $^1$H NMR ($CDCl_3$, 500 MHz): δ 10.7 (bs, 1H), 7.86-7.92 (m, 2H), 7.56-7.67 (m, 4H), 7.32-7.42 (m, 3H), 5.52-



SCHEME 1

5.60 (m, 1H), 5.00-5.08 (m, 2H), 3.74 (s, 3H), 3.61 (dd, J = 8.0, 15.5 Hz, 1H), 3.30 (dd, J = 6.5, 13.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 172.8, 171.1, 165.9, 137.5, 132.4, 132.1, 131.7, 131.6, 131.4, 130.0, 129.7, 128.8, 128.5, 125.4, 119.8, 84.9, 53.1, 40.3.

**Preparation of 2-((1-methoxy-1-oxo-2-methyl-pent-4-ene-2-yloxy)carbonylbenzoic acid, (5d)**

Procedure similar to that of **(5a)**. (30% yield) $^1$H NMR ($CDCl_3$, 500MHz): δ 7.71-7.78 (m, 1H), 7.61-7.68 (m, 1H), 7.44-7.54 (m, 2H), 5.75-5.83 (m, 1H), 5.08-5.12 (m, 2H), 3.72 (s, 3H), 2.75 (dd, J = 6.5, 13.5 Hz, 1H), 2.59 (dd, J =7.5, 14.0 Hz, 1H), 1.66 (s, 3H). Preparation of Methyl-2,5-dihydroxy-2-phenyl-pentanoate, 7: $BH_3.Me_2S$ (2.0 mmol, 0.2 mL, 10M solution) was added to cooled solution of the olefin 3a (0.2 g, 0.97 mmol) in THF (2 mL) at 0$^0$C and stirred for 15 min. Excess borane was quenched slowly by adding methanol (1 mL) at the same temperature. The reaction mixture was oxidized with 1 mL of 3M NaOH and 1 mL of 30% hydrogen peroxide and stirred for 6h at room temperature. The product was extracted with $Et_2O$ and dried over $MgSO_4$. The solvent was removed under aspirator vacuum. The crude product was purified by column chromatography (silica gel, hexane: ethyl acetate (4:1)) to yield 73% (0.16 g) of diol 7. $^1$H NMR ($CDCl_3$, 500MHz): δ 7.57-7.59 (m, 2H), 7.27-7.36 (m, 3H), 4.41 (br s, 1H), 3.76 (s, 3H), 3.61 (t, J = 6.2 Hz, 2H), 2.82 (br s, 1H), 2.30 (ddd, J = 5.5, 9.0, 14.0 Hz, 1H), 2.15 (ddd, J = 5.5, 9.5, 14.5 Hz, 1H), 1.52-1.69(m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ175.8, 141.8, 128.5, 128.0, 125.7, 78.6, 62.7, 53.5, 36.7, 27.2.

**Preparation of tetrahydro-5-oxo-2-phenyl-2-furancarboxylic acid methyl ester, (9)**

Tetrapropylammonium perruthenate (TPAP) (10 mg, 0.03 mmol) was added to a stirred solution of the diol 7 (100 mg, 0.45 mmol), and NMO (192 mg, 1.64 mmol) in dicholoromethane (2 mL) at rt for 24h. After completion of the reaction (TLC), $CH_2Cl_2$ was evaporated and the black residue was purified by column chromatography (silica gel, hexane: ethyl acetate (4:1)) to afford (88 mg) 89% of the lactone 9. $^1$H NMR ($CDCl_3$, 500 MHz): δ7.38-7.40 (m, 2H), 7.22-7.29 (m, 3H), 3.61 (s, 3H), 2.93-2.98 (m, 1H), 2.40-2.59 (m, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 175.3, 171.0, 138.3, 129.0, 128.9, 125.3, 87.0, 53.5, 33.6, 28.3.

## RESULTS AND DISCUSSION

Owing to the importance of allylboration reaction in synthetic organic and medicinal chemistry, we wanted to further expand the scope of 1. α-Ketoesters are reactive prochiral ketones that upon asymmetric nucleophilic additions provide quaternary chiral centers and are highly useful for the synthesis of variety of structurally intriguing natural products. Allylation of α-ketoesters provides tertiary α-carboxyhomoallylic alcohols, however, stereoselective allylmetallation of α-ketoesters has not been a well studied protocol[1]. Asymmetric allylboration of $Ipc_2$Ballyl 1 with aldehydes provides the homoallylic alcohols in very high ee[3]. However, asymmetric allylboration of ketones with 1 gives very low to moderate enantiomeric excess[3]. α-Ketoesters are stereo-electronically different from normal ketones due to the presence of an electron withdrawing carboxy ester moiety. It is known in the literature that α-ketoesters are more reactive than normal ketones with a reactivity pattern almost similar to that of aldehydes. Reactions such as Baylis Hillman reaction[1], Barbier allylation[1], etc. that are facile with aldehydes and sluggish with ketones, take place very readily with α-ketoesters/α-iminoesters. Based on this general observation, we hypothesize that α-ketoesters could undergo facile allylboration with $Ipc_2$BAllyl 1 with the reactivity very similar to that of aldehydes.

We hypothesize that the product homoallylic alcohols upon hydroboration followed by oxidation of the resulting primary alcohols should provide γ-carboxy-γ-lactone moiety. With the above hypothesis in mind, we initiated the project with stereoselective asymmetric allylboration of methyl benzoylformate **(2)** with $Ipc_2$BAllyl 1. The reagent 1 was prepared by treating commercially available *B*-methoxydiisopinocampheyl borane with allyl magnesium bromide at 0$^0$C followed by filtration of the resulting solid methoxymagnesium bromide (Mg(OMe)Br). The filtrate thus obtained was concentrated under inert atmosphere and stored at 4$^0$C as a 1 M stock solution in pentane. The reagent was essentially pure as analyzed by $^{11}$B NMR spectroscopy (with a broad single peak at δ 78 ppm). The initial re-

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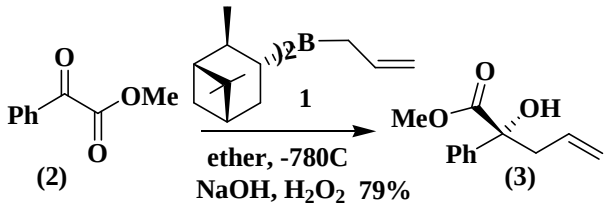
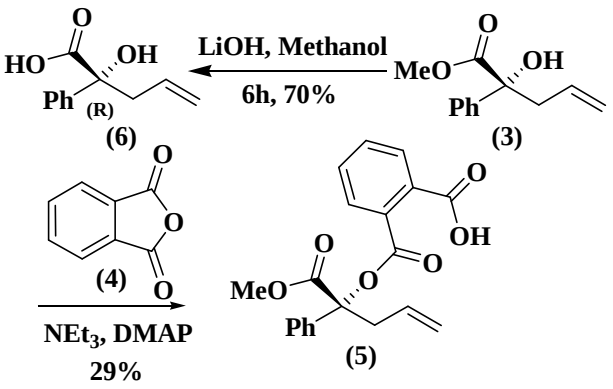
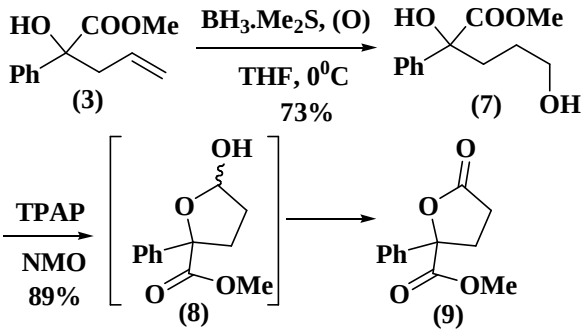



**SCHEME 1: Allylboration of methyl benzoylformate**




**SCHEME 2: Determination of optical purity and absolute configuration**




**SCHEME 3: Synthesis of γ-carboxy-γ-lactone**

action of $Ipc_2B$Allyl 1 with methyl benzoylformate **(2)** was carried out at -78$^0$C at 0.5M concentration of the reagent in 1:1 (ether:pentane). The reaction was monitored for completion by $^{11}$B NMR and oxidized with sat $NaHCO_3$, and $H_2O_2$ to obtain the product homoallylic alcohol **(3)** along with the byproduct isopinocampheol. The crude homoallylic alcohol **(3)** was purified by silica gel chromatography to obtain 79% of the pure product (SCHEME 1).

The enantioselectivity of the homoallylic alcohol **(3)** was determined based on Chiral HPLC analysis. The alcohol was derivatized as its monophthalate ester **(5)** by treatment with phthallic anhydride 4 and $NEt_3$/ DMAP and analyzed on CHIRALPAK AD-H column using Shimadzu HPLC with hexane and isopropanol as the eluting system and the ee was determined to be 60% (SCHEME 2).

In order to confirm the absolute configuration of the homoallylic alcohol **(3)**, it was hydrolyzed to the known α-hydroxycarboxylic acid 6 via treatment with LiOH in MeOH (SCHEME 2). The acid was obtained in 70% yield upon silica gel column chromatography. The absolute configuration was determined to be *R* by comparing the specific rotation with the literature value[1].

Encouraged by this result, we have also carried out the reaction with few other α-ketoesters isopropyl benzoyl formate **(2b)**, benzyl benzoylformate **(2c)**, and methyl pyruvate **(2d)**. We prepared them in two steps starting from α-ketoacids via thionyl chloride treatment followed by alcoholysis of the resulting acid chlorides. In all the cases, the products were obtained in good yields and were characterized by $^1$H and $^{13}$C NMR spectroscopy.

We then carried out allylboration of the above synthesized α-ketoesters **(2a-d)**with *B*-allyldiisopino campheylborane 1. In each case, the α-ketoester was reacted with 1 at -78$^0$C, and the crude homoallylic alcohols were obtained by alkaline hydroperoxide oxidation (with saturated $NaHCO_3$ and $H_2O_2$). The homoallyl esters **(3a-d)** were hydrolyzed using alkaline conditions (LiOH/MeOH) to afford the α-hydroxy acid 6. In each case, the optical rotation was measured and compared to the literature value to calculate the ee as well as to confirm the absolute stereochemistry of the product. For the confirmation of the % ee values, the acids were further converted to the methyl ester by refluxing in methanol in the presence of catalytic pTSA. The α-hydroxy ester thus obtained was converted to its monophthalate ester and analyzed on the HPLC. In the case of methyl, isopropyl, and benzyl esters, the ee's were in the range of 59-73% with absolute configuration (R) in all the cases.

After obtaining the homoallylic alcohols, we applied the above methodology for the synthesis of γ-carboxy-γ-lactone **(9)**. The homoallylic alcohol 3 obtained by the allylation of methyl benzoylformate 2, was subjected to hydroboration with $BH_3.Me_2S$ followed by oxidation with sodium hydroxide and hydrogen peroxide to afford the diol 7 in 73% yield after purification. Further oxidation of the diol with tetrapropylammonium

perruthenate (TPAP) and N-methylmorpholine-N-oxide (NMO) led to the formation of the γ-lactone 9 via the intermediate γ-lactol 8 (SCHEME 3).

## CONCLUSIONS

In conclusion, we have developed a simple chemical methodology for the synthesis of γ-carboxy substituted γ-lactone via the hydroboration and lactonization of homoallylic alcohols obtained from allylboration of α-ketoesters. Further studies are underway for the extension of this protocol for the synthesis of the γ-lactone based natural products.

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