Preparation of (Z)-3-acetoxy-5-carbomethoxy-l-cyclohexene

Preparation of (*Z*)-3-acetoxy-5-carbomethoxy-1-cyclohexene

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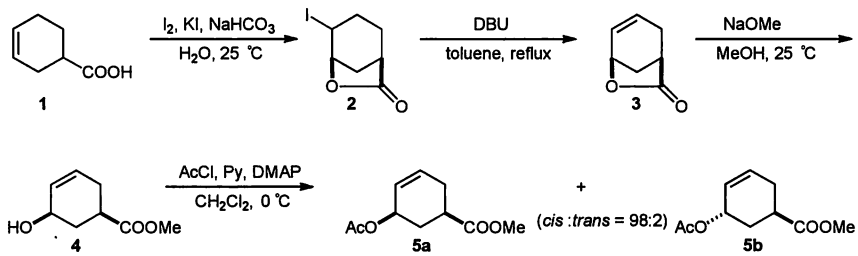
Abstract

(*Z*)-3-Acetoxy-5-carbomethoxy-1-cyclohexene was prepared via according to the reported procedures. Thus, iodolactonization of (*rac*)-3-cyclohexene-1-carboxylic acid followed by elimination of iodide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the unsaturated lactone in 86% yield for 2 steps. Alcoholysis of the obtained lactone with sodium methoxide in methanol afforded (*Z*)-5-carbomethoxy-3-hydroxy-1-cyclohexene in 95% yield with sole isomer. Acetylation of the alcohol **4** was carried out with AcCl and pyridine in CH_2Cl_2 at 0 ℃ for 40 min to give (*Z*)-3-acetoxyl-5-carbomethoxy-1-cyclohexene in 22% yield with a mixture of 88% *Z*-isomer and 12% *E*-isomer.

Introduction

(*Z*)-3-Acetoxy-5-carbomethoxy-1-cyclohexene is of considerable interest for organic chemistry because of the *cis*-allyl ester **5a** is used for determination of reaction pathway during the π -allylic palladium intermediate reactions[1] and found widespread utility as synthetic precursors of various bioactive compounds.[2] *cis*-Allyl ester **5a** was synthesized by B. M. Trost et. al. in 1980 as shown in scheme 1.[3] These results led us to examine the preparation of (*Z*)-3-acetoxy-5-carbomethoxy-1-cyclohexene (**5a**).



Scheme 1. Preparation of (*Z*)-3-acetoxy-5-carbomethoxy-1-cyclohexene (reported by B. M. Trost)

Results and Discussion

We examined to prepare the (*Z*)-3-acetoxy-5-carbomethoxy-1-cyclohexene via according to the reported procedures. Thus, iodolactonization of (*rac*)-3-cyclohexene-1-carboxylic acid followed by elimination of iodide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the unsaturated lactone in 86% yield for 2 steps.

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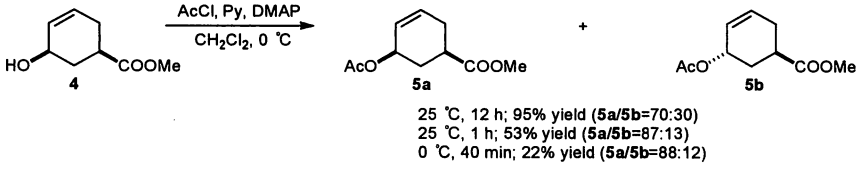
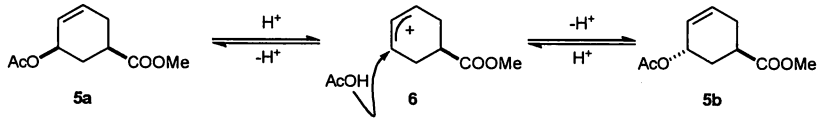
Alcoholysis of the obtained lactone with sodium methoxide in methanol gave (*Z*)-5-carbomethoxy-3-hydroxy-1-cyclohexene in 95% yield with sole isomer. Acetylation of the alcohol **4** was carried out with AcCl and pyridine in CH_2Cl_2 at 25°C for 1 h to give (*Z*)-5-carbomethoxy-3-hydroxy-1-cyclohexene in 53% yield with a mixture of 87% *Z*-isomer and 13% *E*-isomer as shown in scheme 2.



Scheme 2. Acetylation of (*Z*)-5-carbomethoxy-3-hydroxy-1-cyclohexene (**4**)

The diastereomeric purity of the *cis*-allyl ester **5a** decreased as the reaction time was prolonged. Thus, the acetylation of **4** for 12 hours gave 40% diastereomeric excess (de) of the ally esters **5** under otherwise similar reaction conditions, whereas 74% de of **5** was obtained in one hour. We considered that *cis*-allyl esters **5** can react with internal acetoxy group under acidic conditions by way of the ally cation intermediate **6** as shown in scheme 3. During the acetylation of the diastereomeric pure compound **4**, the diasteromerically enriched **5a** generated in situ should undergo the allyl cation formation and subsequent acetoxylation to result in the epimerization of **5a**. The highly diasteromerically enriched **5a** of 76% de was obtained when the acetylation of the (*Z*)-5-carbomethoxy-3-hydroxy-1-cyclohexene **4** was carried out at 0 °C for 40 minutes.



Scheme 3. Proposal reaction pathway of epimerization of (*Z*)-ally ester between (*E*)-allyl ester

Conclusions

Preparation of (*Z*)-3-acetoxy-5-carbomethoxy-1-cyclohexene was achieved in 4 steps (iodolactonization; elimination; alcoholysis; acetylation). During the acetylation reaction of diastereomerically pure alcohol **4**, epimerization of (*Z*)-3-acetoxy-5-carbomethoxy-1-cyclohexene underwent to afford (*E*)-3-acetoxy-5-carbomethoxy-1-cyclohexene under reaction conditions (AcCl, Py, CH_2Cl_2, DMAP).

Experimental Section

Preparation of (±)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one (2). To a solution of $NaHCO_3$ (10.2 g, 121 mmol) in water (100 mL) was added 3-cyclohexene-1-carboxylic acid (5.08 g, 40.3 mmol). The resulting mixture was stirred until it became homogeneous. The flask was protected from light, and the mixture was treated in one portion with a solution of KI (40.1 g, 241.3 mmol) and iodine (10.7 g, 42.3 mmol) in water (101 mL). The reaction mixture was stirred at 25 °C for overnight and extracted with $CHCl_3$. The organic extracts

were combined, washed with 10% aqueous $Na_2S_2O_3$, 10% aqueous $NaHCO_3$, and water, and then dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo gave **2** in 95% yield (9.63 g, 38.2 mmol). **(±)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one (2):** ^{1}H NMR ($CDCl_3$); δ 4.83 (s,1 H), 4.51 (s, 1 H), 2.80 (d, J = 12.2 Hz, 1 H), 2.68 (s, 1 H), 2.47-2.40 (m, 2 H), 2.12 (d, J = 16.3 Hz, 1 H), 1.84-1.71 (m, 2 H).

Preparation of (±)-6-oxabicyclo[3.2.1]oct-3-en-7-one (3). Iodolactone **2** (9.63 g, 38.2 mmol) was dissolved in dry toluene (110 mL) containing 1,8-dazabicyclo[5.4.0]undec-7-ene (DBU) (8.88 g, 57.8 mmol), the mixture was heated at reflux for overnight, cooled, and filtered, and the filtrate was concentrated under reduced pressure to give an oil. This crude oil was directly used in the next step.

Preparation of (*Z*)-5-carbomethoxy-3-hydroxy-1-cyclohexene (4). Lactone **3** (4.73 mg, 38.2 mmol) and sodium methoxide (286 mg, 5.2 mmol) were stirred in 220 mL of anhydrous methanol at 25 ℃ for overnight. The solvent was removed in vacuo and the residue partitioned between ether and water. The aqueous phase was extracted with ether and dried over anhydrous magnesium sulfate, and the organic solvent removed in vacuo to give **4** in 53% yield (2.85 g, 20.3 mmol). **(*Z*)-5-carbomethoxy-3-hydroxy-1-cyclohexene (4):** ^{1}H NMR ($CDCl_3$); δ 5.79 (s, 2 H), 4.29 (s, 1 H), 3.70 (s, 3 H), 2.75-2.69 (m, 1 H), 2.38-2.28 (m, 3 H), 1.85-1.72 (m, 1 H), 1.62 (br 1 H).

Preparation of (*Z*)-3-acetoxy-5-carbomethoxy-1-cyclohexene (5a). Acetyl chloride (0.7 mL, 8.9 mmol) was added over 10 min to a cooled (0 ℃) solution of **4** (1.05 g, 7.5 mmol) in 15 mL of dichloromethane and 5 mL of pyridine. The resulting white slurry was stirred for 40 min, neutralized with aqueous Na_2CO_3, and diluted with ether. The organic phase was washed for three times successively with saturated aqueous Na_2CO_3, saturated cupper (II) sulfate. Subsequently, the organic phase was washed with water, aqueous Na_2CO_3, and saturated aqueous NaCl and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give a yellow liquid, which was purified via distillation (60-70 ℃, 0.2 mmHg) to give 22% yield (1.48 g, 7.50 mmol) of a mixture of **5a** and **5b** in a ratio of 88:12. **(*Z*)-3-Acetoxy-5-carbomethoxy-1-cyclohexene (5a):** ^{1}H NMR ($CDCl_3$); δ 5.88 (tdd, J = 3.5, 11.0, 1.7 Hz, 1 H), 5.64 (d, J = 10.2 Hz, 1 H), 5.37-5.41 (m, 1 H), 3.70 (s, 3 H), 2.81-2.70 (m, 1 H), 2.42-2.29 (m, 3 H), 2.06 (s, 3 H), 1.76 (td, J = 12.4, 9.0 Hz, 1 H).

Acknowledgment

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