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Practical Preparation of (4*R*,5*R*,*E*)-methyl 5-(*tert*-butyldimethyl-silyloxy)-4-hydroxyhepta-2,6-dienoate

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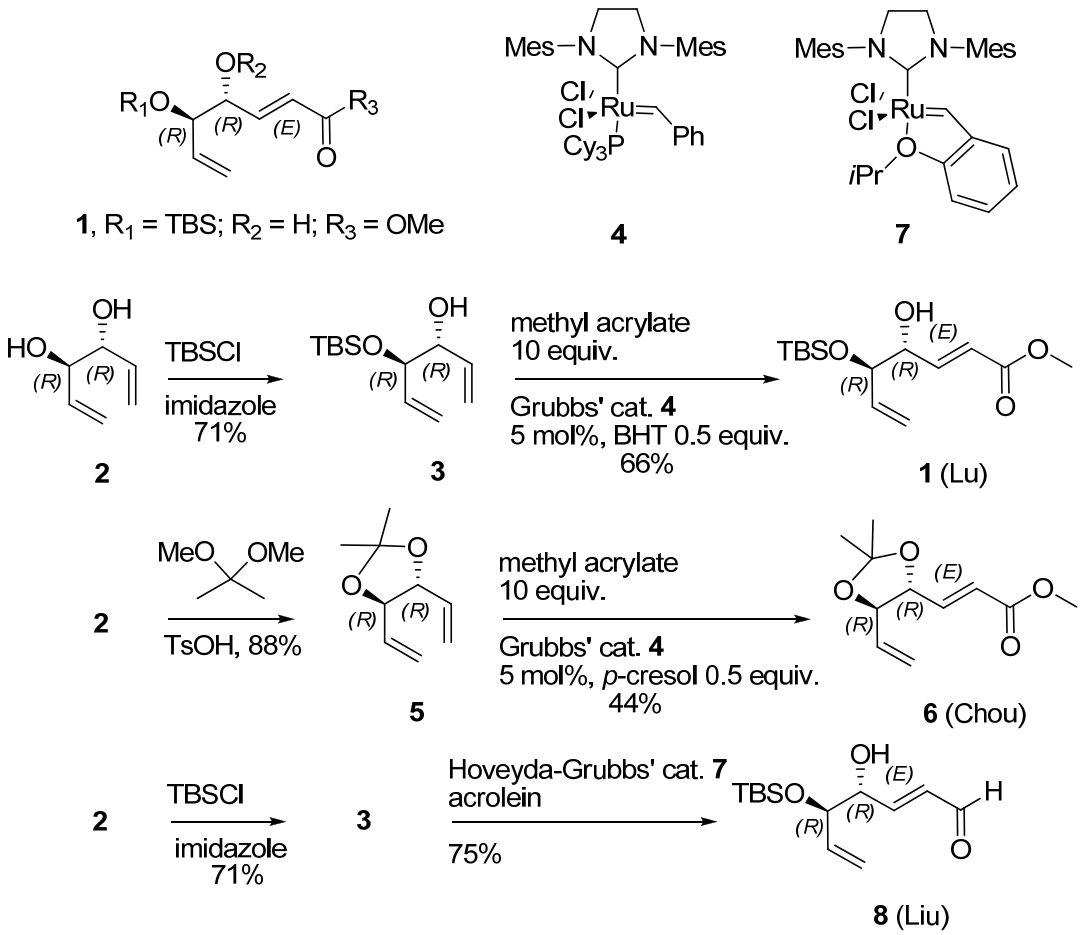
ABSTRACT

This study is aimed to improve the preparation of uselful synthetic block (4*R*,5*R*,*E*)-methyl 5-(*tert*-butyldimethylsilyloxy)-4-hydroxyhepta-2,6-dienoate (**1**). This intermediate was used in the synthesis of (+)-Cladospolide D. The strategy developed by Voigtritter et al. was adopted to exploit the acceleration effect of copper (I) iodide. This compound was prepared from D-mannitol-derived dienediol (**2**) coupled with methyl acrylate through olefin cross-metathesis reaction in various conditions. It was found that performing the reaction in the presence of 3 mol% of CuI in refluxing diethyl ether gave the product up to 75% of yield with lower catalyst loading, i.e.: 2 mol%.

Key word: acrylate, olefin cross-metathesis, Grubbs' catalyst, copper iodide

INTRODUCTION

Highly functionalized olefins prepared from unsaturated alcohols and acrylate derivatives, such as (4*R*,5*R*,*E*)-methyl 5-(*tert*-butyldimethylsilyloxy)-4-hydroxyhepta-2,6-dienoate (**1**), are useful synthetic building blocks [1]. They have been applied in natural product synthesis such as (+)-Cladospolide C [2], (+)-Cladospolide D [3], and (−)-Lentiginosine [4]. Previously reported methods to prepare this type of olefin applied cross-metathesis reaction by the addition of phenolic compounds and avoiding the less reactivity of olefins with electron-withdrawing functionality [5]. As the key intermediate in their research, Lu et al. [3] prepared this compound *via* the metathesis reaction using 5 mol% of the second generation Grubbs' catalyst in the presence of 0.5 equiv of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 1). Chou et al. [2] applied the same strategy to prepare similar compound **6** using *p*-cresol as the additive. Liu et al. [4] prepared the aldehyde **8** using the more reactive Hoveyda-Grubbs' catalyst. These existing procedures still required high catalyst loading, excess amount of reactant, and only relatively moderate yields of product were provided. However, chemists' efforts to circumvent this problem have shown in recent literatures. For example, shorter reaction time and better yields were achieved by applying microwave irradiation [6,7,8]. One interesting approach was reported by Lipshutz's group: they found that copper (I) iodide is an effective additive for olefin cross-metathesis reactions [9]. Thus, a variety of Michael acceptors or electron deficient olefins can be cross-coupled under mild reaction conditions and environmentally benign solvents, such as ethers, can be used, rather than chlorinated solvents. Therefore, we would like to adopt the strategy for our research and report our results here.



Scheme 1 Preparation of protected carbonyl derivatives of (4*R*,5*R*,*E*)-4,5-dihydroxyhepta-2,6-dienes

EXPERIMENT

Chemicals and instrumentations

Chemicals used were analytical grade; D-mannitol (Acros), acetyl bromide (Lancaster), acetic anhydride (Echo), 1,4-dioxane (Tedia), pyridine (Showa), zinc dust (Panreac), glacial acetic acid (Scharlan), sodium hydroxide (Showa), methanol (Acros), hydrochloric acid (Fisher Scientific), ethyl acetate (Echo), sodium sulfate (Showa), diethyl ether (Echo), *tert*-butyldimetylsilyl chloride (TBSCl) (China), imidazole (Acros), dichloromethane (Echo), hexane (Echo), copper iodide (Fluka), methyl acrylate (Fluka), Grubbs' catalyst second generation (Aldrich). The instrumentations used were NMR spectrometer 300 MHz (Bruker) and microwave instrument (Monowave 300).

Preparation of (3*R*,4*R*)-hexa-1,5-diene-3,4-diol (2)

To a suspension of 20.00 g (0.11 mol) of D-mannitol in 1,4-dioxane (157 mL) was added with AcBr (20 mL, 0.27 mol) and then allowed to room temperature for 2 days. Removal of the solvent gave a syrup which was treated 24 hours with an excess of Ac_2O (47 mL, 0.50 mol) in pyridine (27 mL, 0.34 mol). The pyridine was removed by applying vacuum distillation and trapped by liquid nitrogen. The residue was diluted by ethyl acetate (100 mL),

1*N* hydrochloric acid (25 mL) and deionized water (50 mL). The two layers were separated and the water layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated. The obtained orange syrup was then added with NaOH (6.59 g, 0.16 mol), glacial acetic acid (28 mL, 0.49 mol), zinc dust (32.31 g, 0.49 mol) and water (220 mL) and allowed to reflux (100°C) for 3 h. Extraction of this mixture (3 x 50 mL of ethyl acetate) and concentration gave a syrup which was treated 3 hours with NaOH (6.59 g, 0.16 mol) in methanol (110 mL) at 80°C. The mixture was concentrated, neutralized (pH 6-8 by 1*N* $HCl_{(aq)}$), diluted with H_2O (35 mL) and extracted by diethyl ether (3 x 50 mL). After concentration, the crude product was vacuum distilled at 110°C (oil bath temperature) to give **2** (4.96 g, 43.46 mmol, 40%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 5.92-5.80 (m, 2H), 5.42-5.37 (d, J_{trans}= 17.22 Hz, 2H), 5.30-5.26 (d, J_{cis}=10.56 Hz, 2H), 4.05-4.03 (d, *J* = 4.77 Hz, 2H), 2.45 (s, 2H) ppm. ^{13}C NMR (75 MHz, CDCl3, 25°C): δ = 136.57, 117.42, 75.65 ppm.

Preparation of (3*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-ol (3)

tert-Butyldimethylsilyl chloride (TBSCl, 1.3205 g, 8.8 mmol) was added to a solution of dienediol **2** (1.0000 g, 8.8 mmol), imidazole (894.7 mg, 13.14 mmol), and dry dichloromethane (50 mL) in a sealable tube at 0°C. The solution was allowed to room temperature for 16 h, quenched with water (30 mL), and diluted with ether (60 mL). The aqueous layer was further extracted with ether (20 mL x 3), and the combined organic layer was washed with $HCl_{(aq)}$ (0.1 *N*, 50 mL), satd $NaCl_{(aq)}$ (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:10; Rf 0.36) to give **3** (1.4719 g, 6.44 mmol, 74%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 5.87-5.74 (m, 2H), 5.33-5.15 (m, 4H), 3.97-3.90 (m, 2H), 2.56-2.55 (d, *J* = 4.56 Hz, 1H), 0.89 (s, 9H), 0.10-0.08 (d, *J* = 8.4 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 137.76, 136.91, 117.06, 116.47, 75.68, 25.82, 18.18, -4.15, -4.87 ppm.

Preparation of (3*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-ol (1)
Without copper (I) iodide

Grubbs' catalyst second generation **4** (18.6 mg, 0.02 mmol) was added to the solution of diene **3** (100.0 mg, 0.44 mmol), 2,6-di-*tert*-butyl-4-methylphenol (BHT, 48.2 mg, 0.22 mmol), and methyl acrylate (376.9 mg, 4.4 mmol) in toluene (1 mL). After being heated at reflux for 6 h, the reaction mixture was concentrated and the crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; Rf 0.40) to give **1** (24.9 mg, 0.09 mmol, 20%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.94-6.87 (dd, *J* = 15.6, 4.2 Hz, 1H), 6.14-6.09 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.86-5.74 (ddd, *J* = 17.4, 6.9, 6.6 Hz, 1H), 5.30-5.21 (m, 2H), 4.14-4.09 (m, 1H), 4.02-3.98 (m, 1H), 3.72 (s, 3H), 2.60-2.58 (d, *J* = 5.1 Hz, 1H), 0.88 (s, 9H), 0.05-0.03 (d, *J* = 5.1 Hz, 6 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 166.74, 146.57, 137.13, 121.54, 117.99, 76.89, 51.57, 25.75, 18.14, -4.22, -4.94 ppm.

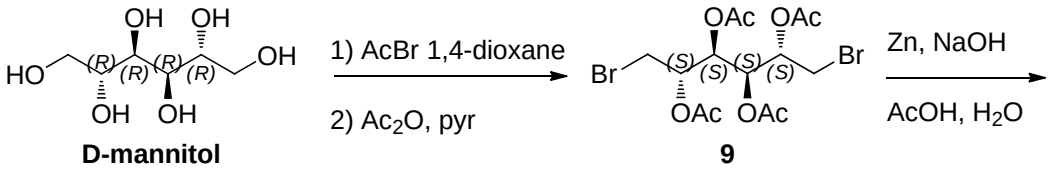
Preparation of (3*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)hexa-1,5-dien-3-ol (1)
With copper (I) iodide

A flame-dried pear-shaped flask with a rubber septum containing a stir bar was charged with **3** (100 mg, 0.44 mmol) and equipped by nitrogen baloon. Freshly distilled ethyl ether (4.4 mL) was added. To this mixture was then added with CuI (2.5 mg, 0.01 mmol),

methyl acrylate (188.5 mg, 2.2 mmol) and Grubbs' catalyst second generation **4** (7.4 mg, 0.009 mmol). The rubber septum was then replaced with a reflux condenser. The solution was heated at reflux for 4.3 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; Rf 0.40) to give **1** (93.9 mg, 0.09 mmol, 75%) as a light yellow oil.

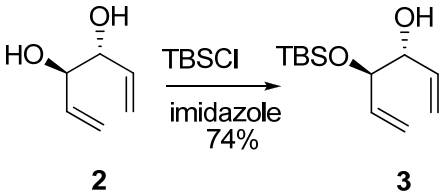
RESULT AND DISCUSSION

The starting material in our research, dienediol **2**, was prepared in four steps from commercially available D-mannitol [10-12], where the purification by column chromatography was not required for the first three steps. According to a literature procedure, dibromide **9** was easily prepared from D-mannitol by regioselective bromination with acetyl bromide, followed by acetylation of the remaining hydroxyl groups [10,11]. Coumpound **9** underwent reductive elimination of bromide and acetate with zinc to give diacetate **10**, as described by Burke et al. [12],. Deacetylation of **10** was achieved by methanolysis in the presence of NaOH. Thus, **2** was prepared from D-mannitol in four steps with multi-gram quantities and a 40% overall yield (Scheme 2).



Scheme 2 Preparation of dienediol **2**

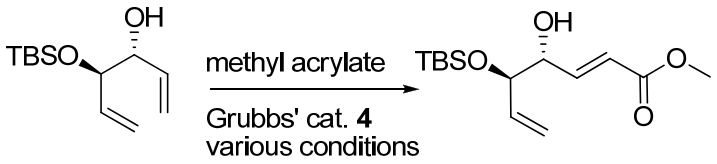
Before attempting the cross-couple reaction with methyl acrylate to afford compound **1**, dienediol **2** was first subjected to the hydroxyl group protection reaction (Scheme 3). The protection on one of the two hydroxyl groups of **2** has some beneficial effects to the subsequent cross metathesis reaction. Previous studies showed that the substituent at the allylic position influences the reactivity of metathesis significantly. An alkyl substitution at the allylic position retards the metathesis reaction of the alkene with metal carbenes. In contrast, a hydroxyl group at the allylic position accelerates this reaction. This effect of the hydroxyl group may arise through pre-association of the diene with the catalyst. Hydrogen bonding between the hydroxyl group and one of the chloride ligands may also favour the reaction between the alkene and the carbene centre [13]. To facilitate the metathesis reaction at one side of the olefin **2** only, bulky *tert*-butyldimethylsilyl chloride was used as the protecting agent. Mono-protected dienediol **3** was achieved in 74% yield.



Scheme 3 Mono-protection of **2**

Starting from mono-protected dienediol **3**, a set of cross-metathesis reaction with methyl acrylate was performed in different conditions, i.e. by applying microwave irradiation and strategy developed by Voigtritter et al. [9]. The conventional procedure [3] was also included for comparison. The experimental results are summarized in Table 1. Performing this reaction under the conventional condition (0.5 equiv. of BHT as the additive) afforded the product in 20% yield (entry 1), and the yield increased to 55% when microwave irradiation was applied to raise the reaction temperature to 100 ^{o}C (entry 2). In the addition of copper (I) iodide, the yield increased to 61%. Further increase in the yield, i.e. 75%, was observed at longer reaction time and more methyl acrylate (entry 4). Under this condition, the reaction was performed in refluxing diethyl ether, lower amount of methyl acrylate and catalyst, compared to the conventional procedures.

Table 1. Cross-metathesis reaction of **3**

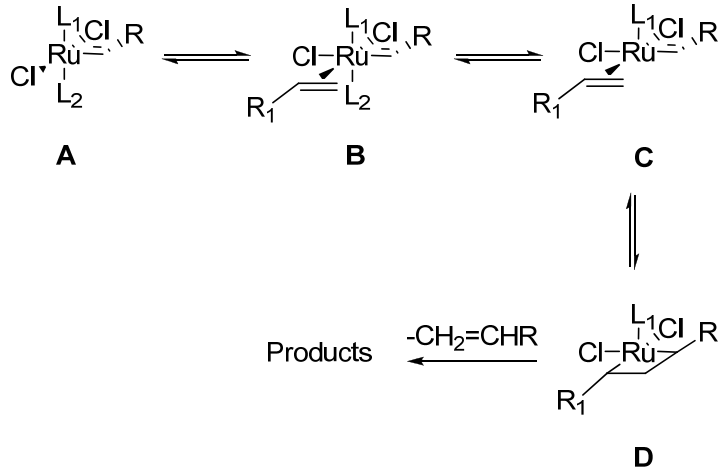


3 **1**

Entry	equiv[a]	equiv of G-2	additive (equiv)	time (h)	yield (%)[e]
1	10[b]	0.05	BHT (0.5)	6	20
2	10[c]	0.05	BHT (0.5)	0.25	55
3	3[d]	0.02	CuI (0.03)	3	61
4	5[d]	0.02	CuI (0.03)	4.3	75

[a]dienediol **3** was considered as 1 equiv. [b]the reaction was performed in refluxing toluene (0.44M). [c]the reaction was performed at 100^{o}C under microwave irradiation in 1,2-dichloroethane (0.44M). [d]the reaction was performed in refluxing diethyl ether (0.1M). [e]isolated yield

To understand the effect of copper (I) iodide, it is necessary to consider the mechanism of metathesis reaction in detail. Grubbs proposed a three-step sequence for metathesis (Scheme 4): first, the olefin coordination to the metal center to form the species **B**, then the dissociation of one of the ligands (L_2) to form **C**, and the formation of the metallacyclobutane **D** followed by the conversion to the product [13]. To have a productive metathesis reaction, the key step is the dissociation of the ligands. Thus, variation at the ligands or the substituent R, which are assisting the ligand dissociation process, make **A** a more active catalyst [13]. Copper (I) iodide has shown to be an effective co-catalyst for the olefin cross-metathesis reaction because it has the catalyst stabilizing effect due to the iodide ion stabilizing the matal center, and the phosphine-scavenging properties by copper (I). Both of these phenomena responsible to acceleration effect of copper (I) iodide.



Scheme 4 Three-steps sequence for metathesis proposed by Grubbs

CONCLUSION

In conclusion, we report here an improved, practical route to prepare (4*R*,5*R*,*E*)-methyl 5-(*tert*-butyldimethylsilyloxy)-4-hydroxyhepta-2,6-dienoate (**1**). The merits of this synthesis include inexpensive co-catalyst and avoid the use of chlorinated solvents, which provides a more efficient access to these useful compounds.

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