Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3176–3182

A simplified synthesis of (*R*)-(−)-muscone using a ring-opening reaction of (*R*)-(+)-β-methyl-β-propiolactone

Motoaki Morita, Nobuyuki Mase, Hidemi Yoda and Kunihiko Takabe*

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan

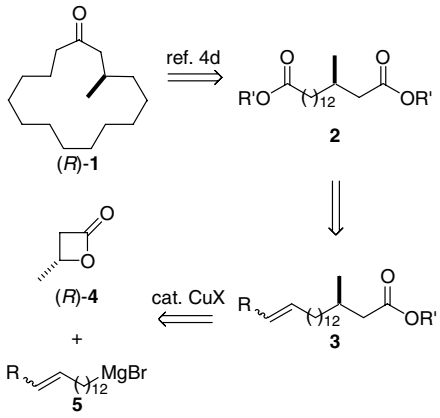
Received 6 July 2005; revised 12 August 2005; accepted 17 August 2005

Abstract—A chiral macrocyclic precursor can be constructed via a ring-opening reaction of (*R*)-(+)-β-methyl-β-propiolactone with a functionalized organocuprate with no loss of enantiomeric excess. The carboxylic acid precursor was used as a chiral building block for the synthesis of chiral muscone and musky macrolactones.

1. Introduction

Musk is a fatty excretion produced by the male musk deer during the mating season to attract females. Dried musk glands have been sold at high prices for thousands of years. (*R*)-(−)-3-Methylcyclopentadecanone [(*R*)-muscone] (*R*)-**1** is the most important classical source of musk odors for perfumes and colognes. (*R*)-Muscone has a very nice musky, rich powerful fragrance, its odor threshold being 61 ppb. On the other hand, (*S*)-muscone is less fragrant, with its odor threshold only being 223 ppb. Due to overhunting, the musk deer is now a protected species, therefore a conventional chemical synthesis of homochiral (*R*)-**1** is needed. There are four main types of synthetic approaches to (*R*)-**1**; asymmetric Michael reaction,[1] asymmetric hydrogenation,[2] ring expansion,[3] and macrocyclization.[4,5] Dieckmann condensation of diester **2** is a promising macrocyclization.[4d,5b] However, diester **2** was previously prepared from ethyl cyanoacetate in 15 steps including a resolution using (+)-α-methylbenzylamine.[4d] A shortened synthesis of diester **2** might be the key to providing a practical and cheaper synthetic muscone (*R*)-**1**. In the early 1980s, Fujisawa et al. reported a regiospecific and stereoselective ring-opening reaction of β-methyl-β-propiolactone **4** with various organocuprates to give β-methylpropionic acid derivatives in high yields with high enantiomeric excesses, and synthesized optically active compounds such as (*R*)-(+)-citronellol, (*R*)-(+)-pulegone, (*S*)-(+)-ar-turmerone, and (*R*,*R*)-phytol.[6]

The key intermediate diester **2** can be prepared from β-methylcarboxylic acid derivative **3**, which was obtained by Fujisawa's ring-opening reaction of (*R*)-**4** with Grignard reagent **5** (Scheme 1). Herein, we report a greatly simplified asymmetric synthesis of chiral muscone (*R*)-**1** using Fujiwasa's ring-opening reaction as the key step.



Scheme 1. Retrosynthesis of (*R*)-(−)-muscone.

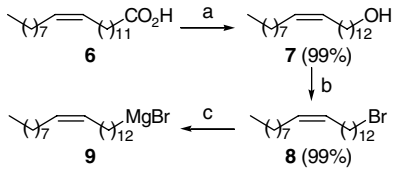
2. Results and discussions

The functionalized Grignard reagent **9** was prepared in three steps from readily available erucic acid [(*Z*)-13-docosenoic acid] **6**, which is a fatty acid found in rapeseed, wallflower seed, and mustard seed. Reduction of

* Corresponding author. Tel./fax: +81 53 478 1148; e-mail: tcktaka@ipc.shizuoka.ac.jp

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.08.042

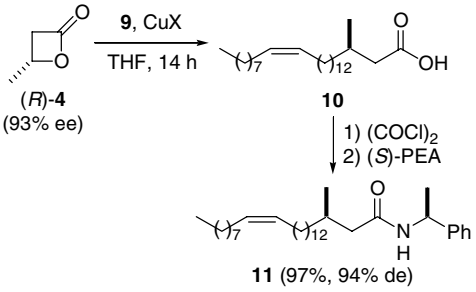
6 with lithium aluminum hydride (LAH) gave (*Z*)-13-docosen-1-ol **7** in 99% yield. Alcohol **7** was subsequently brominated with PPh_3–CBr_4 in 99% yield, and then Grignard reagent **9** was prepared in an approximately 0.5 M solution of THF (Scheme 2).



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 3 h; (b) PPh_3, CBr_4, CH_2Cl_2, rt, 3 h; (c) Mg, I_2, THF, reflux, 1 h.

Ring-opening reactions of (*R*)-(+)-β-methyl-β-propiolactone (*R*)-**4** with organocuprates were examined (Table 1). In the presence of copper(I) chloride (0.02 equiv), carboxylic acid **10** was obtained in moderate yield at room temperature, while lowering temperature improved the chemical yield up to 94% yield (entries 1 and 2). When the catalyst loading was decreased to 0.01 equiv, the yield after 14 h was 92% (entry 3). Copper(I) iodide was also an efficient catalyst, and gave the desired product **10** in 98% yield (entry 4). No loss of enantiomeric excess was observed after the transformation of carboxylic acid **10** with (*S*)-1-phenylethylamine (PEA) to give amide **11** in 97% yield with 94% de. Carboxylic acid **10** had an (*R*)-configuration, which was determined by transformation of **10** to muscone **1** (vide infra), thereby, this ring-opening reaction proceeded in S_N2 mechanism.[6d]

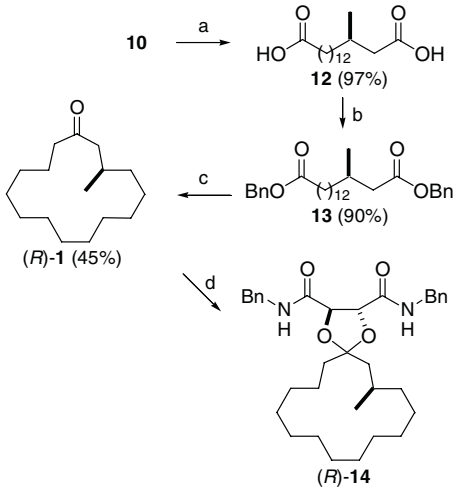
Table 1. Ring-opening reactions of (*R*)-(+)-β-methyl-β-propiolactone (*R*)-**4** with organocuprate[a]



Entry	CuX (equiv)	Temperature (°C)	Yield (%)
1	CuCl (0.02)	rt	59
2	CuCl (0.02)	0	94
3	CuCl (0.01)	0	92
4	CuI (0.02)	0	98

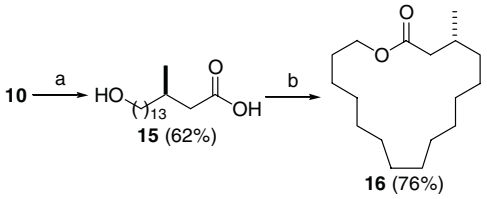
[a] Reactions were carried out using 2 equiv of Grignard reagent **9**.

The synthesis of chiral (*R*)-(−)-muscone (*R*)-**1** was carried out as shown in Scheme 3. Oxidation of olefin **10** to carboxylic acid **12**, following esterification gave dibenzylester **13** in high yield. This key intermediate diester **13** was prepared from (*R*)-**4** (93% ee) in overall 86% yield in three steps. Dieckmann cyclization followed by decarboxylation of diester **13** according to Nohira's procedure[4d] afforded (*R*)-**1** in 45% yield.[7] The spectral data and the sign of rotation of (*R*)-**1** were in agreement with reported values.[4d] The enantiomeric excess was determined by HPLC analysis of acetal **14**, which was prepared by the acetalization of **1** with *N*,*N*′-dibenzyl-L-tartaramide. Previously, the enantiomers of muscone **1** have been extremely difficult to separate by chiral chromatographic technique due to the lack of steric and electronic differences between (*S*)- and (*R*)-isomers; however, recently we have found that a diastereomeric mixture of acetal **14** can be separated by chiral HPLC.[8] Furthermore, simple recrystallization of acetal **14** gave chiral acetal (*R*)-**14**. The acetalization of (*R*)-**1** afforded the corresponding acetal **14** with almost no loss of enantiomeric purity (91% de).



Scheme 3. Reagents and conditions: (a) $KMnO_4$, $NaIO_4$, K_2CO_3, H_2O/acetone, rt, 3 days; (b) BnOH, *p*-TsOH·H_2O, reflux, 6 h; (c) $(Me_3Si)_2NLi$, THF, rt, 14 h, then decarboxylation; see Ref. 4d; (d) see Ref. 8.

Encouraged by these results, we next investigated the synthesis of chiral macrolactones from carboxylic acid **10**. One-pot ozone-oxidation following the reduction gave ω-hydroxycarboxylic acid **15** in 62% yield. Macrolactonization of **15** was initially performed by using 2,2′-dipyridyl disulfide and triphenylphosphine,[9] in which many spots were observed by TLC analysis. We found that 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-(dimethylamino)pyridine (DMAP) reagents reported by Shiina et al.[10] gave the powdery and musky macrolactone **16**[11] in 76% yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) O_3, $CHCl_3$, −20 °C, $NaBH_4$; (b) MNBA, DMAP, CH_2Cl_2, rt, 24 h.