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Concise asymmetric synthesis of the sex pheromone of the tea tussock moth

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ABSTRACT

A concise asymmetric total synthesis of the sex pheromone of the tea tussock moth has been achieved from commercially available starting materials. The chiral moiety was introduced by Evans' template and the key C—C bond construction was accomplished through Julia-Kocienski coupling and Wittig olefination. The salient characteristic of our synthetic route is that it is protecting a group free.

1. Introduction

Nowadays, high standard agricultural requirements demand that farming products are provided in a greener way than before. In this context, sex pheromone traps as low-cost, physical killing and ecological tolerance have appealed to many scientists.[1] Sex pheromones of insects are usually volatiles with unique stereochemical properties, and are derived from simple metabolic substances such as terpenes or fatty acids under enzyme modification.[2] In China, there is a type of pest, the tea tussock moth: *Euproctis pseudoconspersa* which brings about huge destruction in the tea-leaves industry. The structural elucidation of the main component of the sex attractant pheromone was first reported by Wakamura et al. as 10,14-dimethyl-l-pentadecyl isobutyrate **1** (Scheme 1).[3] Although the natural pheromone was established as having an (*R*)-configuration at the C-10 methyl group,[4] further studies showed that both the (*R*)-enantiomer and the (*S*)-enantiomer were attractive in field trials.[5]

There have been two reports on the total synthesis of the sex pheromone of the tea tussock moth **1**. The first asymmetric total synthesis of (*R*)-**1** was reported by Ichikawa et al. using a Wittig reaction strategy from commercially available (*S*)-citronellol.[4] Soon afterwards, Zhao et al. reported another asymmetric total synthesis of (*R*)-**1** using an alkynylation coupling strategy from a similar chiral moiety, (*S*)-citronellyl bromide.[5] There are two main issues involving the construction of a carbon skeleton and the enantioselective introduction of a methyl group at C-10.

First, we envisioned that the Wittig coupling strategy offers a greater operability and compatibility in C—C bond formation with less side reactions.[6] There are many other olefination methods including Julia coupling[7] that could be applied to improve the reaction yield. Thus, an improved Ichikawa synthesis based on Julia olefination was developed.

Next, the development of more efficient and economical methods for obtaining enantiomerically pure organic compounds turned our attention to stereoselective synthesis. Stereoselective synthesis, in which chiral auxiliaries, organocatalysts or metal complex are used, has become a valuable methodology in modern organic chemistry. Asymmetric Evans alkylation is one of the most common methods to synthesize a stereogenic carbon center.[8] In continuation of studies of systematic methodologies for the preparation of methyl-branched chiral pheromone,[9] we wished to develop an efficient stereoselective synthetic route to the sex attractant pheromone of the tea tussock moth **1**. Herein, we report a protecting-group-free asymmetric total synthesis of **1** based on a Julia olefination and Evans chiral auxiliary strategy.

2. Results and discussion

As outlined in Scheme 2, an improved Ichikawa's synthetic route based on a Julia-Kocienski coupling strategy was completed in 37% yield over 4 steps (Scheme 3). (*S*)-Citronellol (97% *ee*) was first converted into sulfone **7** via conventional Mitsunobu reaction[10] and further H_2O_2/sodium tungstate oxidation.[11] Julia-Kocienski coupling between BT-sulfone **7** and aldehyde **8** was then conducted to give the olefination product **11**. Aldehyde **8** was synthesized via two chemical steps with ease, monoesterification of 1,7-heptanediol by isobutyric acid and further oxidation

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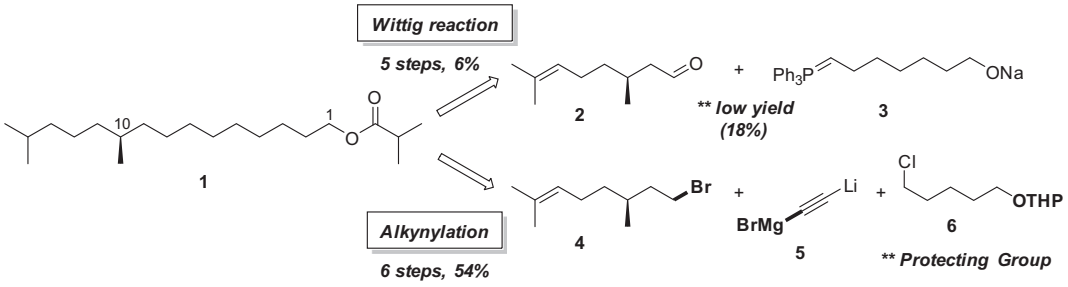
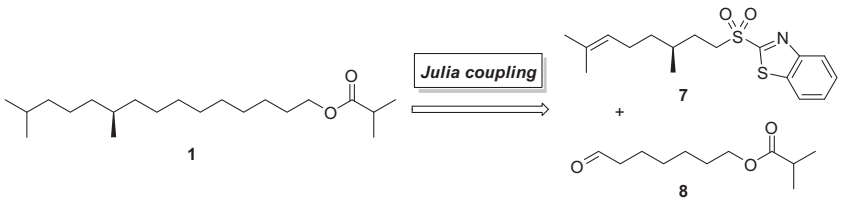
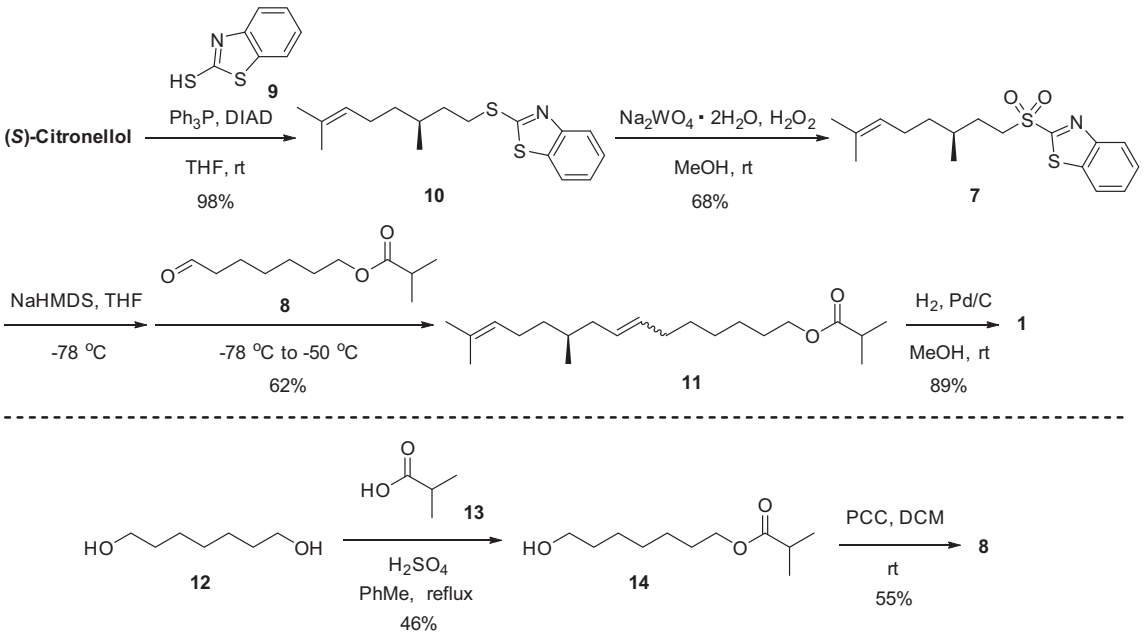


Scheme 1. Structure and asymmetric total syntheses of **1**.



Scheme 2. Improved Julia coupling strategy to **1** from (*S*)-citronellol.



Scheme 3. Total synthesis of **1** based on a Julia strategy route.

of the residual hydroxyl group by PCC. Hydrogenation of diene **11** to give the target molecule **1** in high yield.

In order to introduce the C-10 methyl group via asymmetric Evans methylation, a new retrosynthetic analysis is shown in Scheme 4. The target molecule **1** could be transformed into intermediate **15** via a catalytic hydrogenation process. The key Julia-Kocienski coupling between BT-sulfone **16** and aldehyde **17** could then be adopted in the synthesis of intermediate **15**. BT-sulfone **16** could be obtained from phosphonium bromide **19** in 6 steps, while the intermediate **17** could be prepared from 1,8-octanediol **20** in 2 steps.

As shown in Scheme 5, the total synthesis of **1** was realized according to the new retrosynthetic analysis. (*Z*)-6-Methylhept-4-enoic acid **23** was synthesized by a Wittig reaction as a mixture of *Z*/*E* (12:1, determined from ^{1}H NMR) isomers between isobutyraldehyde **22** and commercially available phosphonium bromide **21** in 72% yield.[12] After activation by pivaloyl chloride, acid **23** was connected quantitatively with Evans auxiliary **24**.[13] Enantioselective methylation of **18** at low temperature gave compound **25** in 79% yield. Reduction of **25** afforded **26** in 82% yield. Next, alcohol **26** was converted into sulfone **16** via Mitsunobu reaction and further H_2O_2/sodium tungstate oxidation in high yield. The stereoselectivity of the Evans methylation was measured to be 95% *ee* value for the derivative **27** by HPLC on chiral OD-H column. Aldehyde **17** was prepared using the same procedure as compound **8** from 1,8-octanediol in 2 steps (42% yield).

Finally, the total synthesis of **1** was accomplished by a Julia-Kocienski coupling between sulfone **16** and aldehyde **17**, followed by hydrogenation using Pt/C catalyst to avoid racemization of the allylic methyl group (Scheme 6).[14] All of the data are consistent with the literature values.[4,5]