

Reproductive Regulating Pheromones of Queen Ant: A Short and Versatile Synthesis of 3,11-Dimethylheptacosane

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Received August 12, 2011, Accepted August 14, 2011

Key Words : Pheromone, Communication, Metathesis, Cuticular hydrocarbon

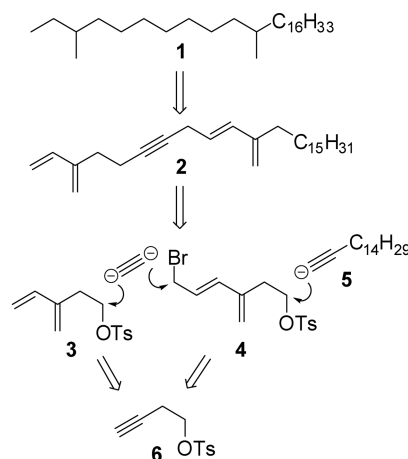
Social behavior of insects always fascinates human beings as they appear to maintain good order and communication in the society.¹ Insects have developed sophisticated chemical communication systems using their pheromones for the purpose.² Among the pheromones, cuticular wax is used to recognize group members from non-members.³ In ants, there have been identified close to 1,000 cuticular hydrocarbons (CHCs)⁴ and the composition of CHCs of cuticles works for the discrimination between their friends and foes.³ Some species of ants are known to use cuticular wax of the dead ants in other colonies to disguise their identity when they invade other colonies.^{1b} It was known that the antennae of ants recognize the composition of the CHCs but the exact mechanism of this recognition has not been well studied.⁵ The CHCs on the cuticles are also used to distinguish the queen ant from other fertile ants.⁶ Queen ants produce 3,11-dimethylated linear hydrocarbons longer than C₂₆ (Figure 1). Interestingly, only the odd numbered carbon chains ranging from 27 to 33 are found in insect society.³ These CHCs are also coated on the eggs of the queen but do not exist on those of other ants, which allow ants to distinguish those eggs and destroy the latter by eating to control their social hierarchy.⁷

We became interested in the recognition mechanism of the different composition of CHCs and the effect of the disruption of CHC composition on the social behavior of ants. For these studies, we need to devise a versatile synthetic route to these branched hydrocarbons.⁸ Herein, we report the first synthesis of 3,11-dimethylheptacosane (**1**) through a short and versatile synthetic route.

The synthetic analysis of 3,11-dimethylheptacosane (**1**) shows that intermolecular enyne metathesis⁹ can allow to

introduce two methyl group on the chain and the overall chain length could be controlled by using an alkyne with proper chain length (Scheme 1). Two methyl groups of **1** can be obtained from two conjugated dienes of **2**. These two diene fragments, **3** and **4**, can be prepared through enyne metathesis of tosylated butynol **6** with proper olefin. This synthesis would not require any protecting group and allows that alkyne **5** could be replaced by other alkynes with different chain length for the synthesis of all possible CHC pheromones.

The synthesis started from 3-butynol to produce the corresponding tosylate **6**. The alkyne **6** was treated with the second generation Grubbs catalyst (Grubbs II) under ethylene atmosphere¹⁰ to produce diene **3**. Since allyl bromide was not



Scheme 1. Synthetic analysis of 3,11-dimethylheptacosane.

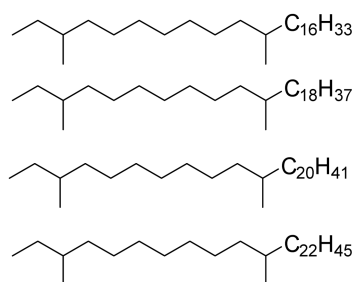
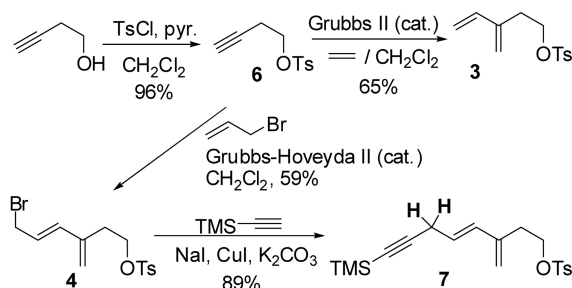
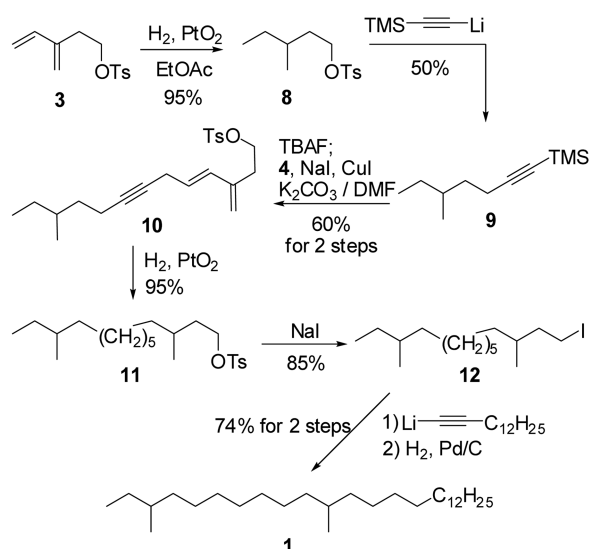


Figure 1. CHCs that regulate fertility of ants.



Scheme 2. Preparation of diene intermediates.



Scheme 3. Total synthesis of 3,11-dimethylheptacosane.

reactive with Grubbs II catalyst in the enyne metathesis reaction, **6** was reacted with allyl bromide in presence of the second generation Grubbs-Hoveyda catalyst (Grubbs-Hoveyda II)¹¹ to produce **4** in good yield (Scheme 2). The next stage of the synthesis was to combine **4** with acetylide anion first and then to attach **5** on to the resulting product **7** by utilizing the different reactivity of halide and tosylate. The first alkylation reaction to afford **7** by selective substitution of bromide worked well, but unfortunately, the reaction of **7** with **5** was not successful presumably due to the high acidity of the C-H positioned between triple and double bond in **7**.

To circumvent the competing deprotonation reaction, the order of the reaction sequence was altered to connect **3** with acetylide anion before the reaction of **4**. However, when **3** was reacted with the acetylide anion **5** the desired product could not be obtained. Still the acidic allylic site of **3** appeared to be problematic. To eliminate possible competing reactions, **3** was hydrogenated before the reaction of **3** with the acetylide anion **5** (Scheme 3). Saturated tosylate **8** was obtained from the PtO₂ catalyzed hydrogenation while catalytic hydrogenation with Pd/C catalyst destroyed tosylate. The reaction of the acetylide anion **5** with the tosylate **8** produced **9**. Since desilylation of **9** produce volatile 5-methylheptyne, one pot process of generating the acetylide nucleophile of **9** was devised. TBAF mediated desilylation of **9** in DMF solution¹² followed by *in situ* Cu mediated alkylation¹³ with **4** produced **10**. Hydrogenation of **10** produced dimethyl intermediate **11** that can serve as the common intermediate for various CHCs. However, as tosyl-

ate **11** was not reactive enough to undergo substitution reaction with alkylacetylide anions, it was converted into the corresponding iodide **12**. Finally, the target CHC, 3,11-dimethylheptacosane (**1**)¹⁴ was obtained by treatment of **12** with 1-tetradecyne, followed by hydrogenation reaction.

In summary, we have devised a versatile and divergent synthetic route to dimethylated saturated hydrocarbons by demonstrating the synthesis of 3,11-dimethylheptacosane (**1**). The current route offers an opportunity to control the stereochemistry of two methyl groups independently if an enantioselective hydrogenation of diene could be available in the future. With the CHC in hand, SEM study of the surface structure of cuticle with **1** in combination with other available linear hydrocarbons will be reported in due course.

Acknowledgments. This work was supported by the NRF grant (No.2011-0013842) funded by Korean Ministry of Education, Science and Technology (MEST).

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- ¹H NMR (400 MHz, CDCl₃) δ 1.35-1.18 (brs, 44H), 1.15-1.02 (m, 4H), 0.88-0.81 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 37.1, 36.7, 34.4, 32.8, 31.9, 30.1, 29.78, 29.74, 29.71, 29.67, 29.5, 29.4, 27.13, 27.10, 22.7, 19.7, 19.2, 14.1, 11.4.