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A Highly Efficient Synthesis of Civetone

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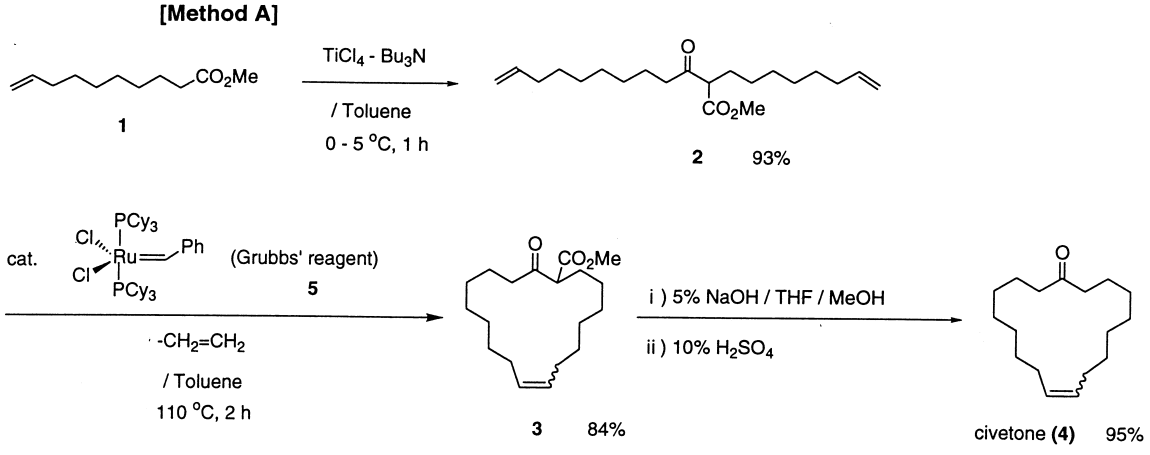
Abstract—A highly efficient synthesis of civetone has been performed by joining two crucial reactions; (a) Ti-Claisen condensation and (b) intramolecular olefin metathesis using Grubbs' reagent. This synthesis includes not only a stepwise method (A) but also a one-pot method (B).

Civetone (**4**) is a representative and attractive ingredient in musk perfumes,[1] and has been one of the most challenging synthetic target in macrocyclic musk due to its unique 17-membered structure.[2] Several reported methods for the synthesis are still now limited to the laboratory scale because of their low yields and/or multistep procedure, therefore, a glandular secretion of African civet cat is virtually the main commercial source. The Washington treaty, namely, CITES (Convention on International Trade in Endangered Species of Wild Fauna and Flora) claims such an ill treatment of the wild animals. Accordingly, the practical synthesis of civetone (**4**) has been desired. Among hitherto reported syntheses, Tsuji's protocol[3] is considered to be elegant wherein an intermolecular olefin metathesis of methyl oleate (methyl 9-octadecenoate) using $WOCl_4$–Cp_2TiMe_2 or WCl_6–Me_4Sn as a catalyst, followed by an intramolecular Dieckmann condensation using KH as a base. Later, Choo and his co-workers improved this method and achieved the best 47–58% overall *conversion* yield.[4]

Meanwhile, the recent remarkable development of the intramolecular olefin metathesis[5] would be a promising candidate for the synthesis of civetone (**4**). This ring-closing metathesis (RCM) approach was actually tried by Plugge and Mol using methyl oleate catalyzed by Re_2O_7–$SiO_2{\cdot}Al_2O_3$–Bu_4Sn, however, the total overall *isolated* yield is only 12%.[6] We describe herein a short-step and efficient method for the synthesis of civetone (**4**) by joining two crucial reactions; (a) the Ti-Claisen condensation[7] and (b) the RCM using the Grubbs' reagent **5**[8] as shown in Scheme 1. Thus, the simple and practical method with high *isolated* yield (max. 74% overall) has been performed.

First, the method A is described (Scheme 1). The Ti-Claisen condensation of methyl 9-decenoate (**1**) successfully



Scheme 1.

Keywords: civetone; Ti-Claisen condensation; metathesis.

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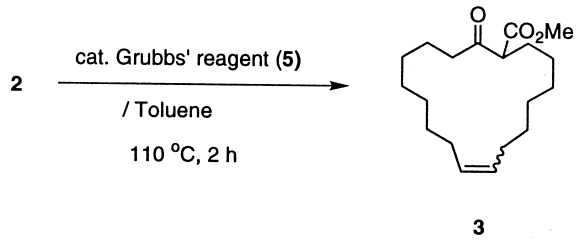
Table 1. Optimization of RCM (ring closing metathesis)



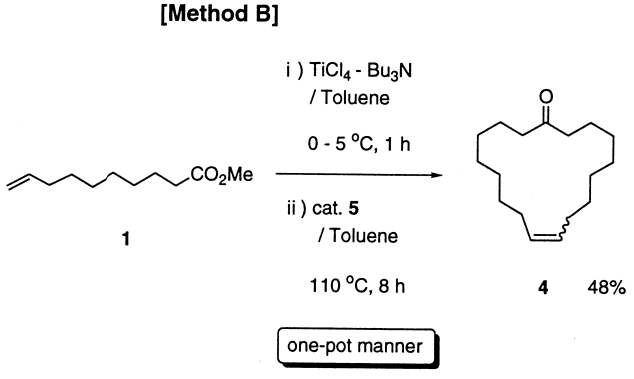
Entry	Concentration (mN)	Catalyst (mol %)	Yield (%)
1	16	10	57
2	7.5	10	70
3	3.75	10	84
4	3.75	5	79
5	3.75	10	70[a]

[a] Substrate **2** and the **5** were simultaneously added dropwise over 1 h.

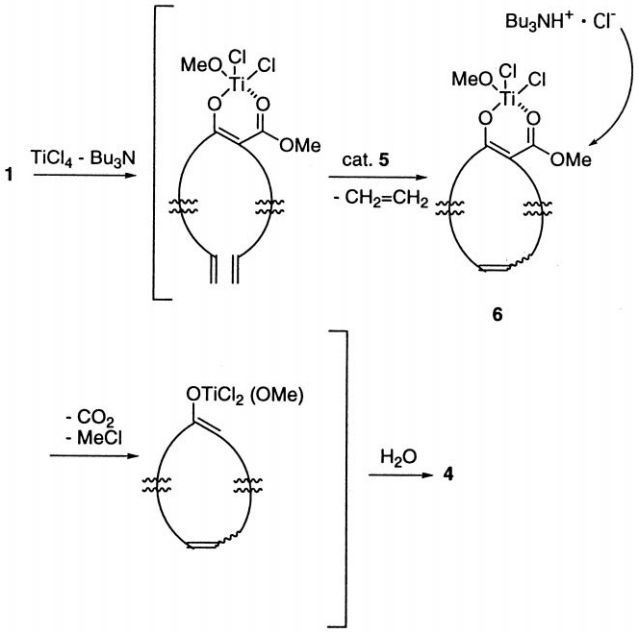
afforded β-ketoester **2** in 93% yield, whose result overcame a traditional basic Claisen condensation (ca. 80%) using NaH as the promoter.[9] Some experiments of the NaH-mediated method in our hands revealed that a considerable amount (~24%) of the hydrolytic product of methyl ester **1**, 9-decenoic acid, was produced during the reaction despite its strict reaction conditions (dryness of a solvent, reagents and an atmosphere). Accordingly, the Ti-Claisen condensation clearly has the advantage of a high yield, mild conditions, a shorter reaction time.

Subsequent RCM of **2** was performed using the Grubbs' reagent (**5**) to afford the desired 17-membered β-ketoester **3** (Table 1). With decreasing concentration of the reaction solution the yields apparently increased; considerable amounts of intramolecular by-products emerged (entries 1 and 2). Highest yield (84%) was obtained under optimized conditions (entry 3). A similar RCM of methyl oleate[6] under identical conditions, however, resulted in low conversion yield of **3** (~20%), probably because the reversible equilibrium did not sufficiently shift to the favorable production of **3**.[5]

Finally, aqueous NaOH hydrolysis of **3**, followed by acidic decarboxylation gave the desired civetone (**4**) in 95% yield according to the reported method.[4] The overall *isolated* yield is 74%, which is considerably high compared with hitherto reported syntheses.



Scheme 2.



Scheme 3.

As a further notable extension, we tried a *one-pot reaction sequence* which is the method B as shown in Scheme 2. Eventually, methyl 9-decenoate (**1**) was straightforwardly transformed into civetone (**4**) *in a one-pot manner* in 48% yield. It is worth noting that (a) the present RCM proceeded using even the titanium-intermediate of β-ketoester **2**, and that (b) interestingly, the elimination of methoxycarbonyl group spontaneously took place without any special procedure and/or any addition of reagents. As illustrated in Scheme 3, Cl^- of $Bu_3N{\cdot}HCl$ salt would attack the MeO — function of intermediate **6** during the sequential reactions. The elimination of methoxycarbonyl group did not occur in the case of the Ti-Claisen condensation of under identical conditions (0–5°C, 1 h; 110°C, 2 h). Accordingly, this elimination is not general for the present Ti-Claisen condensation and probably limited to the specific case of the 17-membered ring β-ketoester.

In conclusion, we achieved a simple, highly efficient and practical synthesis of civetone (**4**) (methods A and B) in high isolated yields using readily available materials and reagents.

Experimental

Methyl 2-(7-octenyl)-3-oxo-11-dodecenoate (2) [Method A]

(Ti-Claisen method) $TiCl_4$ (1.65 ml, 15.0 mmol) in toluene (4.0 ml) was added to a stirred solution of methyl 9-decenoate (**1**; 1.84 g, 10.0 mmol) and Bu_3N (3.34 g, 18.0 mmol) in toluene (16.0 ml) at 0–5°C. After stirring at the same temperature for 1 h, the mixture was quenched with water (20 ml) and extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane:

ether=40:1) to give the desired β-ketoester (**2**; 1.43 g, 93%). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–1.43 (16H, m), 1.51–1.63 (2H, m), 1.78–1.89 (2H, m), 1.99–2.07 (4H, m), 2.39–2.60, (2H, m), 3.43 (0.97H, t, J=7.4 Hz; keto form), 3.71 (2.91H, s; keto form), 3.75 (0.09H, s; enol form), 4.90–5.03 (4H, m), 5.72–5.87 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.37, 27.37, 28.19, 28.70, 28.78, 28.83, 28.91, 29.11, 29.13, 33.62, 33.67, 41.77, 52.14, 58.94, 114.14, 114.18, 138.89, 138.96, 170.34, 205.27. IR (neat) 2928, 2857, 1748, 1717 cm^{-1}. Anal. Calcd for $C_{21}H_{36}O_3$: C, 75.0; H, 10.8. Found: C, 74.7; H, 10.6.

(NaH-Claisen method) **1** (369 mg, 2.00 mmol) in strictly dried (benzophenone-ketyl) DME (3.6 ml) was added to a stirred powder of NaH (82 mg, 3.40 mmol) at 20–25°C for 5 min. The mixture was refluxed for 20 h and cooled down. A small amount of water and 1 M aqueous HCl (20 ml) were successively added to this mixture. The organic phase was extracted twice with ether, which was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane: ether=20:1) to give the desired β-ketoester (**2**; 254 mg, 75%) along with 9-decenoic acid (81 mg, 24%).

2-Methoxycarbonyl-9-cycloheptadecenone (3) [Method A]

The Grubbs' reagent, bis(tricyclohexylphosphine)benzilidene ruthenium dichloride (**5**; 25 mg, 0.03 mmol) in toluene (1.0 ml) was added dropwise to a stirred solution of **2** (101 mg, 0.3 mmol) in toluene (79 ml) at 110°C for a few minutes. The mixture was stirred at that temperature for 2 h, then the solvent was removed in vacuum. The residue was purified by SiO_2-column chromatography (hexane: EtOAc=40:1→20:1) to give the desired β-ketoester **3** (78 mg, 84%; *E*:*Z*=ca. 3:1). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.45 (16H, m), 1.51–1.71 (2H, m), 1.73–2.11 (6H, m), 2.45–2.56 (2H, m), 3.49 (0.25H, dd, J=9.0 Hz, J=5.4 Hz; *Z* form), 3.51 (0.75H, dd, J=8.7 Hz, J=6.2 Hz; *E* form), 3.70 (3H, s), 5.25–5.39 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) *E*-form; δ 23.40, 27.19, 27.37, 27.41, 27.84, 28.30, 28.40, 28.60, 28.70, 28.84, 31.84, 41.43, 52.20, 58.35, 130.85, 131.08, 170.16, 206.73. *Z* form; δ 23.35, 26.58, 26.79, 27.05, 27.96, 28.00, 28.08, 28.15, 28.35, 28.45, 28.98, 29.01, 41.54, 52.24, 58.42, 130.07, 130.15, 170.24, 206.36. IR (neat) 2928, 2855, 1750, 1715 cm^{-1}.

Civetone (4; 9-cycloheptadecenone) [Method A]

According to the reported procedure,[4] a mixture of β-ketoester (**3**; 247 mg, 0.8 mmol) in 5% aqueous NaOH–MeOH–THF (6.5 ml:13 ml:6.5 ml) was stirred at 70°C for 5 h. After cooling to 0°C, 10% aqueous H_2SO_4 was added to the mixture (slightly acidic), which was refluxed for 10 min. After evaporation of the solvent, the residue was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane: ether=30:1→20:1) to give civetone (**4**; 9-cycloheptadecenone; 190 mg, 95%; *E*:*Z*=ca. 3:1). Colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16–1.41 (16H, m), 1.53–1.67 (4H, m), 1.95–2.07 (4H, m), 2.37 (1.5H, t, J=7.1 Hz; *E* form), 2.40 (0.5H, t, J=6.7 Hz; *Z* form), 5.25–5.39 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) *E*-form; δ 23.98, 27.38, 28.32, 28.74, 28.79, 31.91, 42.45, 130.93, 213.13. *Z*-form; δ 23.83, 26.66, 28.10, 28.18, 28.57, 29.00, 42.41, 130.12, 212.50. IR (neat) 2928, 2855, 1713 cm^{-1}.

[Method B]

$TiCl_4$ (1.0 M solution in toluene; 0.90 ml) was added to a stirred solution of **1** (111 mg, 0.6 mmol) and Bu_3N (200 mg, 1.08 mmol) in toluene (2.6 ml) at 0–5°C. The mixture was stirred for 1 h followed by addition of toluene (76 ml). Then, Grubbs' reagent (**5**; 49 mg, 0.06 mmol) in toluene (0.5 ml) was added to the reaction mixture at 110°C for a few min. The mixture was stirred for 8 h by monitoring with TLC, and then was quenched with water (20 ml). After evaporation of toluene, the residue was extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (30:1→20:1) to give civetone (**4**; 36 mg, 48%).

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