

Practical chemical syntheses of high-grade musk and jasmine perfumes utilizing original titanium mediated reactions

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We engage in the exploitation of new practical organic reactions directed toward the process chemistry utilizing our original reactions. Especially, we focused our attention on the Ti-Claisen condensation and aldol additions from a recent standpoint of the environmentally benign organic synthesis for the valuable perfumes such as macrocyclic musks (civetone and muscone), jasmine (furanone analogs of jasmone), and mints, and for 1 β -methylcarbapenem antibiotics (meropenem).

- (1) Practical synthesis of natural macrocyclic musks, especially civetone and muscone, is one of the most important topics in perfume chemistry. An efficient, practical, and stereocontrolled synthesis of natural *Z*-civetone, a representative musk perfume, was performed utilizing a Ti-Dieckmann (intramolecular Ti-Claisen) condensation of dimethyl *Z*-9-octadecanedioate as the key step. This cyclization reaction to afford the 17-membered β -keto ester has some advantages compared with the traditional basic Dieckmann condensation such as higher concentration (100–300 mM), lower reaction temperature (0–5°C), shorter reaction time (1–3 h), use of environmentally benign (low toxicity and safe) reagents (TiCl₄ and Et₃N or Bu₃N), and economical reagents and solvents.
- (2) A laboratory scale synthesis was also performed utilizing intermolecular the Ti-Claisen condensation of methyl 10-decenoate followed by an intramolecular olefin metathesis using the Grubbs' reagent afforded the 17-membered β -keto ester. Characteristic features of this synthesis are as follows; simplest synthesis ever reported, highest overall yields, not only a stepwise but also a one-pot procedures.
- (3) A formal synthesis of *R*-muscone was achieved utilizing the intramolecular powerful Ti-aldol addition of available 2,15-hexadecanedione to afford the 15-membered aldol. Salient features are as follows. Aldol adduct was obtained for the first time. The reaction proceeded with a higher concentration (10–50 mM) compared with ring closing metathesis. Stereoselective dehydration of aldol adduct using Ti (Oi-R)₄ afforded *E*-3-methylcyclopentadecenone, which is a key precursor of the Noyori asymmetric hydrogenation using Ru-BINAP.
- (4) TiCl₄-Bu₃N-mediated condensation of ketones with α,α -dimethoxyketones afforded trialkylsubstituted 2(5*H*)-furanones in a one-pot manner, wherein aldol addition and furanone formation occurred sequentially. Its application to straightforward synthesis of (*R*)-mintlactone and (*R*)-menthofuran, two representative natural mint perfumes, was demonstrated. Because of their interesting structure and usefulness, these compounds have been challenging synthetic targets. Our present method of (*R*)-mintlactone seems to be the simplest of the reported methods, because of the one-step synthesis.
- (5) We developed the present protocol for the aldol-type addition using simple phenyl esters and its application to a short step synthesis of the lactone analogs of dihydrojasmone and jasmone, which are representative perfumes with jasmine odor. The analogs were found to possess unique odor for fragrance.
- (6) As a notable recent application of the present reagent (TiCl₄ - Bu₃N), the Merck process group demonstrated a multi-kilogram scale practical synthesis of the anti-MRSA carbapenem intermediate utilizing the TiCl₄ - Bu₃N reagent as its key step. We found that Ti-reaction successfully applied to a couple of key reactions to construct 1 β -carbapenem skeleton. In particular, a short step synthesis of 1 β -methylcarbapenem, ex. Meropenem® was performed utilizing a new dehydration Ti-Claisen condensation.