CHEMISTRY LETTERS, pp. 1257-1258, 1980.

SYNTHESIS OF (±)-α-AMBRINOL

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Synthesis of α-ambrinol was successfully accomplished by cyclization of dihydro-γ-ionone ethylene acetal which was prepared by the titanium(IV)-promoted reaction of 3,3-dimethyl-1-trimethylsiloxycyclohexene with methyl vinyl ketone ethylene acetal followed by exo-methylenation with triphenylphosphonium methylide.

In this communication, we wish to report a convenient synthesis of α-ambrinol(V) starting from readily available 3-methyl-2-cyclohexenone.

α-Ambrinol(V) has been isolated from extracts of ambergris which are highly appreciated in perfumery for their peculiar smell and fixative power and is known to contribute much to ambergris odour by its characteristic strong earthy and musty odour.[1] Therefore, α-ambrinol seems to be a potent perfume. Concerning the synthesis of α-ambrinol, so far three methods are known. Stoll's method involves cyclization of dihydro-γ-ionone as a key step.[2] However, it is difficult to obtain a large quantity of pure dihydro-γ-ionone and its preparation requires many steps starting from α-ionone.[3] In the other two methods,[4] an epimer of α-ambrinol was accompanied by α-ambrinol.

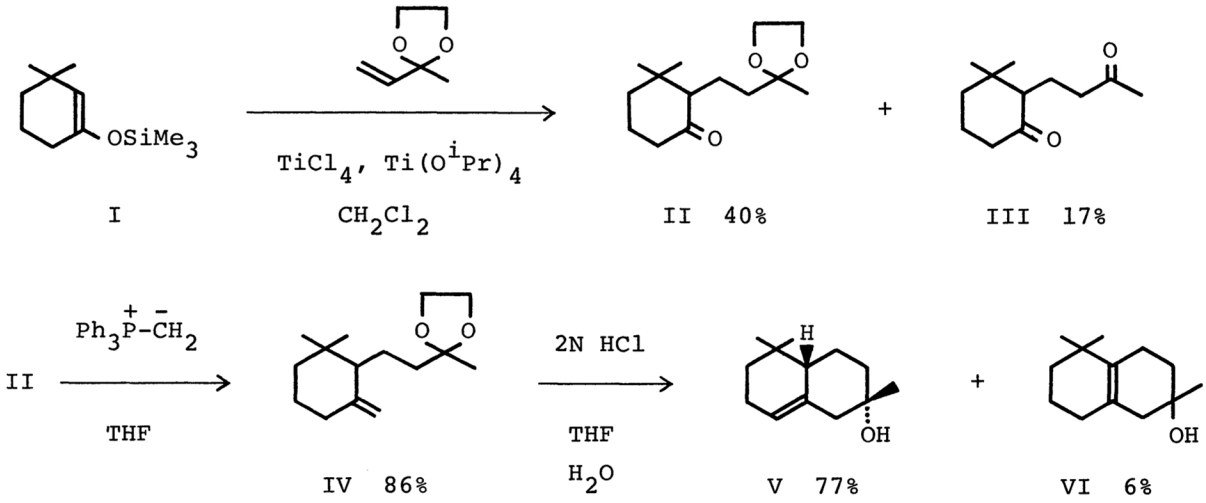
Recently, Mukaiyama et al. have reported that the reaction of acetals of α,β-unsaturated carbonyl compounds with silyl enol ethers in the coexistence of $TiCl_4$ and $Ti(O^iPr)_4$ gives the adducts, 1,5-dicarbonyl derivatives.[5] According to the reaction, regioselective alkylation is achieved and the acetal function is kept intact so that one of two carbonyl groups can be selectively transformed to other functions. These features fulfill our synthetic project of α-ambrinol. Thus, the titanium(IV)-promoted C-C bond formation followed by selective Wittig reaction would afford a key intermediate IV which has all carbon atoms required for building α-ambrinol.

Starting from 3-methyl-2-cyclohexenone silyl enol ether I was prepared by 1,4-addition of methylmagnesium iodide in the presence of copper(I) iodide and subsequent quenching with trimethylchlorosilane.[6] Treatment of I with methyl vinyl ketone ethylene acetal in dichloromethane at -78°C for 1 h in the coexistence of $TiCl_4$ and $Ti(O^iPr)_4$ gave 3,3-dimethyl-2-(3,3-ethylenedioxybutyl)cyclohexanone(II)[7] and its deacetalized 1,5-diketone III[8] in 40% and 17% yields, respectively. The former II permits selective exo-methylenation. Thus, II was allowed to react with triphenylphosphonium methylide, derived from methyltriphenylphosphonium bromide by the action of butyllithium, in THF at room temperature for 48 h to give dihydro-γ-ionone ethylene acetal(IV)[9] in 86% yield. The acetal IV in THF was then treated with 2N HCl at

room temperature for 24 h to afford α-ambrinol(V)[10] in 77% yield along with 6% of β-ambrinol(VI).[11]

As described above (±)-α-ambrinol was successfully prepared in a short pathway.

The authors wish to express their thanks to Professor Teruaki Mukaiyama, The University of Tokyo, for his helpful discussion.



References and Notes

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7) II: IR (film) 1700, 1050 cm^{-1}; NMR (CCl_4) δ=0.75 (s,3H), 1.03 (s,3H), 1.21 (s,3H), 1.0-2.4 (m,11H), 3.80 (s,4H).

8) III: IR (film) 1715 cm^{-1}; NMR (CCl_4) δ=0.76 (s,3H), 1.08 (s,3H), 2.03 (s,3H), 1.4-2.6 (m,11H).

9) IV: IR (film) 1050, 880 cm^{-1}; NMR (CCl_4) δ=0.85 (s,3H), 0.92 (s,3H), 1.21 (s,3H), 1.0-2.3 (m,11H), 3.80 (s,4H), 4.65 (m,2H).

10) V: IR (film) 3450 cm^{-1}; NMR ($CDCl_3$) δ=0.88 (s,3H), 0.92 (s,3H), 1.22 (s,3H), 1.65 (s,1H), 1.1-2.3 (m,11H), 5.44 (t,J=3.0 Hz,1H),: Spectral data of V were consistent with those of the authentic sample, prepared by the method of A.G.Armour et al.[4]

11) VI: IR (film) 3250 cm^{-1}; NMR ($CDCl_3$) δ=1.00 (s,6H), 1.20 (s,3H), 1.71 (s,1H), 1.3-2.3 (m,12H).

(Received August 6, 1980)