CHEMISTRY LETTERS, pp. 991-992, 1976. Published by the Chemical Society of Japan

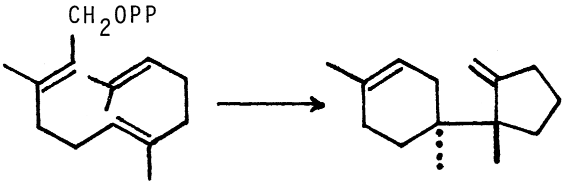
TOTAL SYNTHESIS OF (±)-NORKETOTRICHODIENE[1]

Koji YAMAKAWA,* Reiji SAKAGUCHI, Tadaharu NAKAMURA, and Kensuke WATANABE

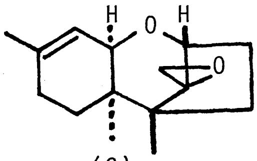
Faculty of Pharmaceutical Sciences, Science University of Tokyo
Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162

The total synthesis of (±)-norketotrichodiene (14) is described. The photocycloaddition reaction of 3,6-dimethylcyclohexenone and cyclotene afforded the tricyclo$[4.3.2^{3,5}.0^{1,6}]$undecane derivatives (4 and 5). The retro-aldol reaction of (4) with alkali gave triketone (6a), which was converted to the tosylate (6b). Catalytic hydrogenolysis of (6b) yielded the ketol (10). Treatment of (10) with $POCl_3$-pyridine gave (±)-norketotrichodiene (14) which was identical with the norketone (14) derived from (+)-trichodiene (1).

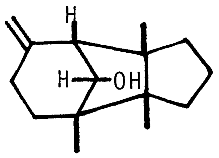
Trichodiene (1) is a biogenetically significant precursor of trichothecane (2)[2,3] and gymnomitrene (3)[4] type sesquiterpenes. Recently, Evans and Hanson[5] reported that the isomerization and cyclization of *trans*-farnesylpyrophosphate to trichodiene (1) by a cell free system obtained from *Trichotecium roseum*.



(1)



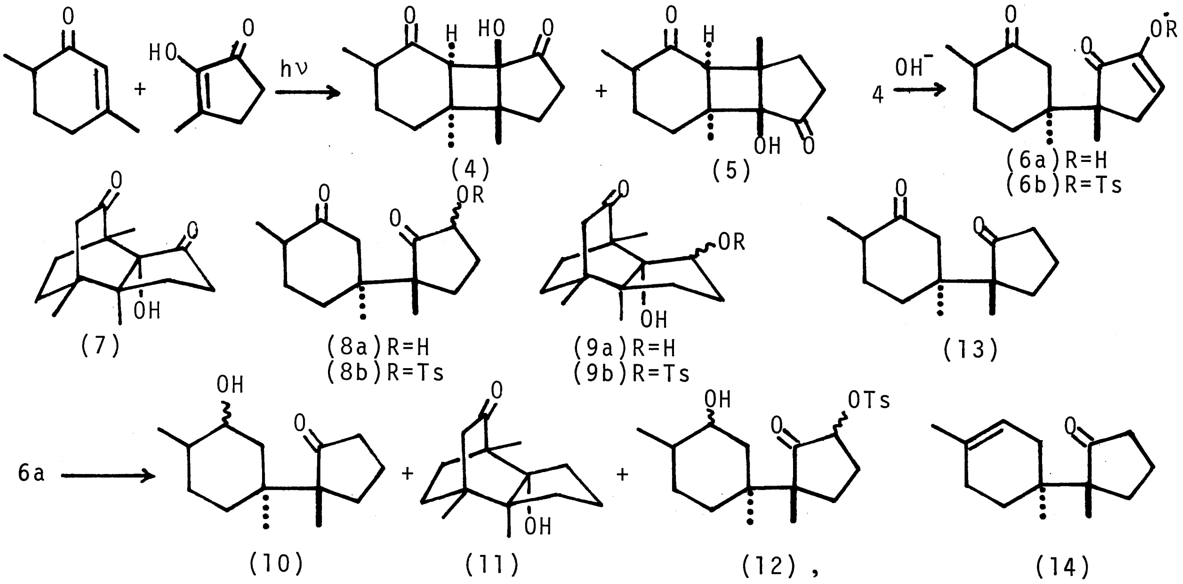
(2)



(3)

In a previous paper we reported[6] the photocycloaddition of 3-methylcyclohexenone and 2-hydroxy-3-methylcyclopent-2-ene (cyclotene) as a synthetic approach toward the fungal isoprenoids. Very recently, Kamikawa *et al.*[7] reported biomimetic synthesis of 12,13-epoxytrichothec-9-ene from a photocycloaddition product.

We now wish to report the total synthesis of (±)-norketotrichodiene (14). Irradiation of a solution of 3,6-dimethylcyclohex-2-ene and cyclotene in n-hexane with a 400 W high-pressure mercury lamp (Ushio UM-400) using a Pyrex filter at room temperature for 10 hr gave head-to-head *cis-anti-cis* adduct (4), mp 188-189° (decomp) [MS m/e 236, M^+; IR cm^{-1}: 3400 (OH), 1740, 1720 (CO); NMR δ: 0.96 (3H, s), 1.05 (3H, s), 1.08 (3H, d, J=7.5 Hz), 2.57 (1H, bs), 2.78 (1H, s)] and head-to-tail *cis-anti-cis* adduct (5), mp 190-193° [MS m/e: 236, M^+; IR cm^{-1}: 3400 (OH), 1780, 1700 (CO); NMR δ: 0.93 (3H, s), 1.04 (3H, d, J=7 Hz), 1.18 (3H, s), 2.45 (1H s), 3.49 (1H, s)], and a complex mixture of at least four products. The structure of the adducts (4 and 5) was confirmed by the NMR spectra using $Eu(DMP)_3$ as shift reagent in the manner described by us.[6] Treatment of (4) with 10% KOH gave triketone (6a), mp 113-114° [MS m/e 236, M^+; UV λ_{max}^{EtOH} 257 nm (ε 4,000); IR cm^{-1}: 1700 (CO), 1660 (C=C), 3270 (OH); NMR δ: 0.92 (3H, s), 0.99 (3H, d, J=7 Hz), 1.16 (3H, s), 5.75 (1H, s), 6.47 (1H, t, J=3 Hz)]. Triketone (6a)was converted to tricyclic ketol (7), mp 174-176°, on standing for several months at room temperature. Catalytic hydrogenation of (6a) with PtO$_2$ in acetic acid gave ketol (8a), mp 97-98.5°. The intramolecular cyclization of ketol (8a) and its tosylate (8b), mp 141-143°, easily occured to give tricyclic ketol (9a), mp 162-163°, and its tosylate (9b), mp 157-158°, respectively. Hydrogenolysis of tosylate (6b), mp 119-121°, with PtO$_2$ afforded ketol (10; 41%)[MS m/e: 222, M$^+$; IR cm^{-1}: 3450 (OH), 1720 (CO)], tricyclic ketol(11; 49%)[MS m/e: 222, M$^+$; IR cm^{-1}: 3510 (OH), 1710 (CO); NMR δ: 0.89 (3H, s), 0.96 (3H, s), 1.06 (3H, s)] and ketol tosylate (12; 5.8%). Oxidation of ketol (10) with CrO$_3$-pyridine complex afforded diketone (13)[MS m/e: 222, M$^+$; IR cm^{-1}: 1720, 1710 (CO); NMR δ: 0.92 (3H, s), 1.05 (3H, d, J=7 Hz), 1.10 (3H, s)] which was converted with alkai into tricyclic ketol (11) quantitatively.



Treatment of ketol (10) with POCl$_3$-pyridine at room temperature afforded a keto-olefin, (±)-norketotrichodiene (14), as oily product [MS m/e: 108 [M-98]$^+$, 98, 93, 65; IR cm^{-1}: 1725 (CO); NMR δ: 0.87 (3H, s), 0.97 (3H, s), 1.60 (3H, bs), 5.20 (1H, m)] which was identified by comparing its IR and NMR spectra with those of the norketone (14) derived from (+)-trichodiene (1) by Nozoe *et al.*$^{2)}$ Attempted conversion of (14) into trichodiene (1) is still unsuccessful.

Acknowledgment We thank Professor S. Nozoe, the University of Tokyo, for IR and NMR spectra of natural norketotrichodiene.

References

1) Studies on the Terpenoids and Related Alicyclic Compounds IX. Part VIII. K. Yamakawa and K. Nishitani, *Chem. Pharm. Bull.(Tokyo)*, in press.
2) S. Nozoe and Y. Machida, *Tetrahedron* , 28, 5105, 5113 (1972).
3) R. Evans, A.M. Holton, and J.R. Hanson, *J. Chem. Soc. Chem. Comm.*, 465(1973).
4) J.D. Conolly, A.E. Harding, and I.M.S. Thornton, *J. Chem. Soc. Perkin* I, 2487(1974).
5) R. Evans and J.R. Hanson, *J. Chem. Soc. Perkin* I, 326 (1976).
6) K. Yamakawa, J. Kurita, and R. Sakaguchi, *Tetrahedron Lett.*, 3877 (1973).
7) N. Masuoka and T. Kamikawa, *Tetrahedron Lett.*,1691 (1976); *Chem. Lett.*, 751 (1974).

(Received July 23, 1976)