CHEMISTRY LETTERS, pp. 649-652, 1979. Published by the Chemical Society of Japan

PHOTOCHEMICAL CONSTRUCTION OF THE PROTOILLUDANE SKELETON: A TOTAL SYNTHESIS OF PROTOILLUD-7-ENE AND SOME OXYGENATED DERIVATIVES

Hitoshi TAKESHITA*, Hisakatsu IWABUCHI**, Isao KOUNO,
Mitsuaki IINO, and Danji NOMURA**
Research Institute of Industrial Science, 86, and Faculty of Agriculture,
46**, Kyushu University, Hakozaki, Fukuoka 812

Starting from 4,4-dimethylcyclopentene, the protoilludane skeleton was prepared by two steps of photocycloadditions and methylation with a Grignard reagent. A series of transformations on these products led to protoillud-7-ene and some derivatives.

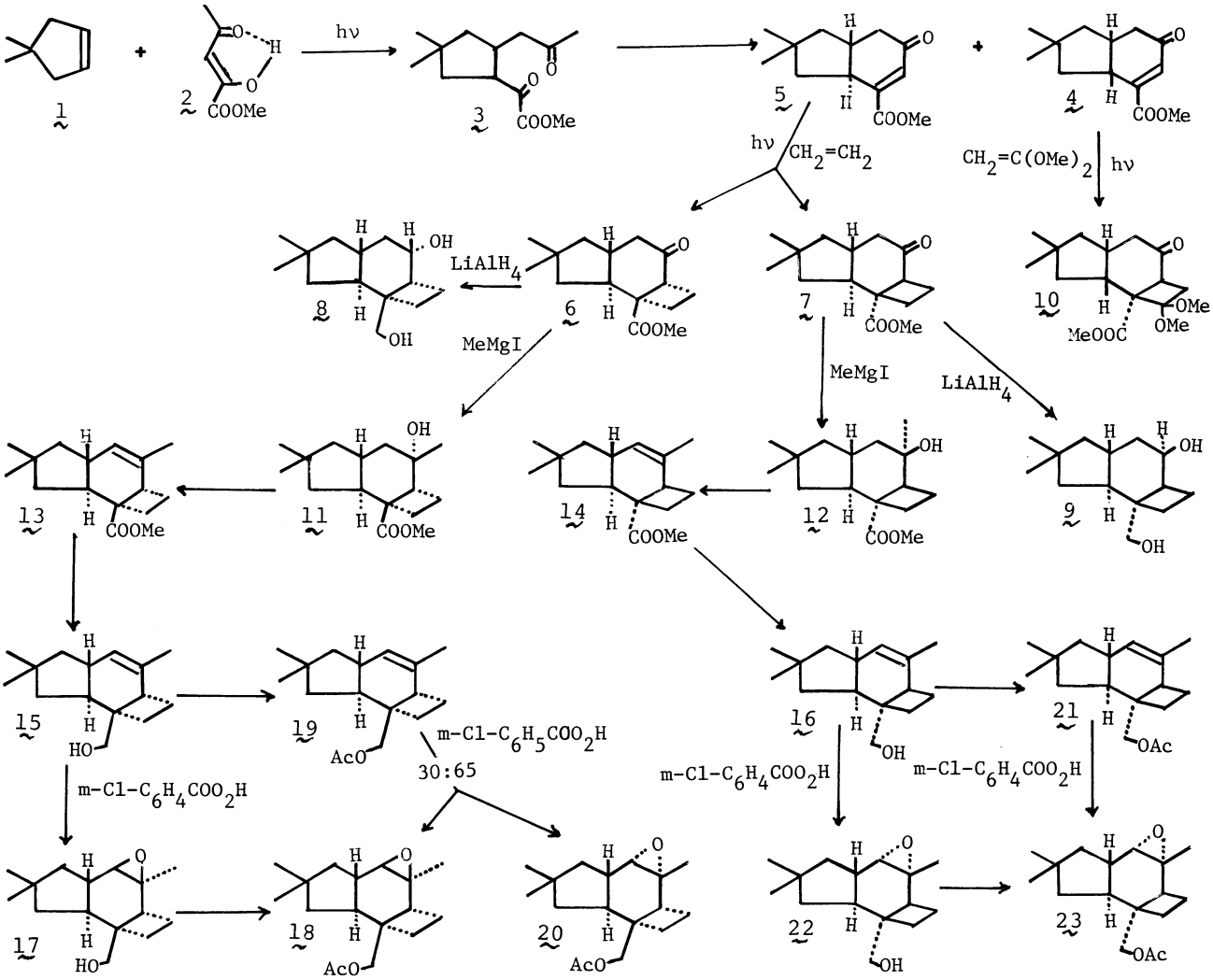
It is accepted that protoilludyl cation, an immediate cyclization product of humulene, is a common precursor for various cyclopentane sesquiterpenoids from fungi and ferns.[1,2] The stereochemistry of illudol, a metabolite of Clitocybe illudens,[3] confirmed additionally by the total synthesis,[4] provided a strong support for this biogenetic concept. Since a number of these sesquiterpenoids are highly oxygenated, it will be worth-while to synthesize a series of oxygenated protoilludanes for in vivo and in vitro transformation studies. We will herein describe a facile construction of the framework by two steps of photocycloadditions followed by methylation.

When a neat mixture of 4,4-dimethylcyclopentene(1)[5] and methyl 2,4-diketopentanoate(2)[6] was irradiated by means of a 450 W high-pressure mercury lamp at below 10°C for 16 h, an oily sole product(3) was formed in an 85 % yield. The structure of 3 was evident on the NMR and IR spectral data together with the known mode of the reaction.[7] An acid-induced cyclization of 3 by p-toluenesulfonic acid in benzene gave cis- and trans-5-methoxycarbonyl-2,2-dimethyl-4,7,8,9-tetrahydroindan-7-ones(4 and 5), both colorless oils, which were separated by silica gel chromatography. The trans-isomer(5) was isomerized into more stable cis-isomer (4). To construct the protoilludanes, a photoaddition of 4 or 5 with ethylene seems to be an attractive route. However, with ethylene, 4 was unreactive and only 5 gave the isomeric pair of α- and β-(2+2)π adducts(6 and 7), colorless oils.[8] This difference in the photoreactivity enabled us to use a mixture of 4 and 5 without fractionation. The lithium aluminum hydride(LAH) reduction of the mixture (6:7=2:1) gave two crystalline diols(8, mp 162-163°C, and 9, mp 120-121°C), in quantitative yields.

In contrary, the photocycloaddition of 4 did occur with 1,1-dimethoxyethylene to give an oily product(10), 95 %. The difference in stereostructure should have influenced the selectivity of the product formation, i.e., the α-side of the cis-hydroindenone(4) must be hindered from the approach of olefins. Clearly, an inertness of 4 to ethylene can not be due to a sterical reason, and a change of the

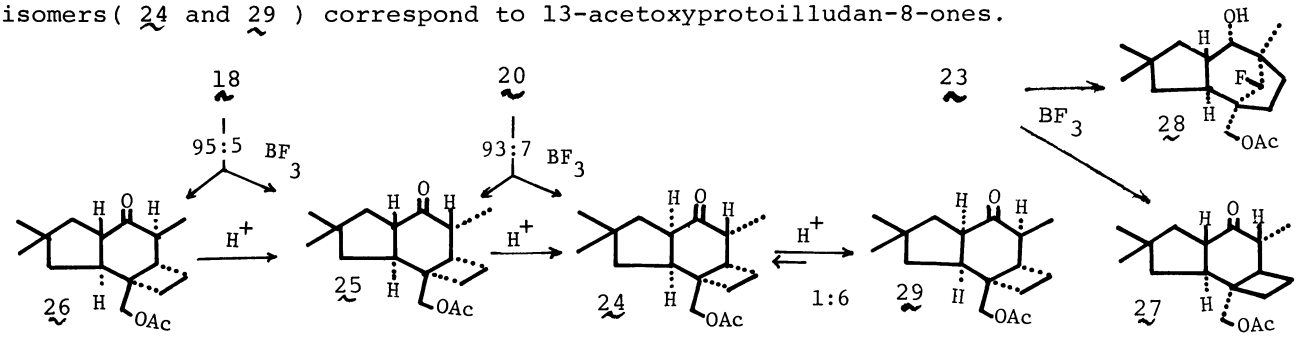
coformation of an excited 4 should result in a deactivation.

By the reaction of methylmagnesium iodide, the mixture of 6 and 7 selectively produced 11 and 12, 88 %, which were separable on a silica gel column. The iodine-catalyzed dehydration of the alcohols yielded unsaturated esters(13, 96 %, and 14, 95 %), colorless oils. These esters were subsequently reduced by LAH to give alcohols(15, 95 %, and 16, 97 %), colorless oils, respectively. The epoxidation of 15 by m-chloroperbenzoic acid gave a single product(17), a colorless oil, 90 %, which gave an oily acetate(18). However, 19, the acetate of 15, yielded two epoxides(18, 30 %, and 20, 65 %, a colorless oil), while the epoxidation of 16 or its acetate(21) produced 22, 97 %, a colorless oil, or its acetate(23), 95 %, in a stereospecific fashion. This contrast may be due to the orientation of the cyclobutane ring: An inspection using a molecular model suggested the cyclobutane ring of trans-anti-cis compounds is quasi-equatorial, but that of trans-syn-cis compounds is quasi-axial, and this leads to a conclusion that 15 and 19 must fall into the former series, while 16 and 21 into the latter series. The specific formation of 17 and 22 indicated that the orientation of the epoxide rings is syn to their hydroxymethyl groups.[9] This relationship is expressed in the following chart.



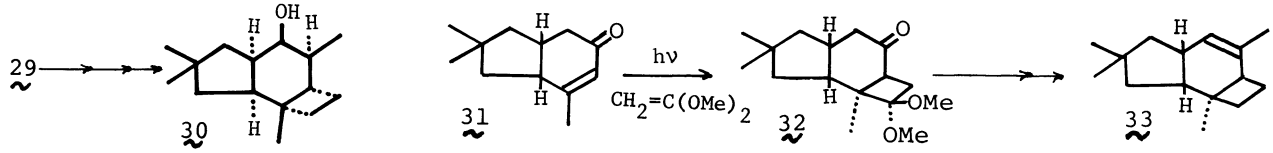
When 20 was treated with boron trifluoride etherate in benzene, a kinetically controlled rearrangement occurred to give 24 and 25 (3:97), colorless oils, in 95 %. On the other hand, 18 gave 25 and 26 (5:95), colorless oils, 98 %. However, 23 gave two products, 27, 34 %, a colorless oil, and 28, 53 %, a colorless oil. 28 was shown to be a fluoroalcohol on the basis of NMR analysis. This rearrangement is also in accord with the stereochemistry of the epoxy group as shown.

When a chloroform solution of 25 containing a small amount of trifluoroacetic acid was kept at room temperature for a week, a neat epimerization took place to form 29 and 24, in a ratio of 6:1. Under the same conditions, 26 produced the same mixture of 29 and 24 via 25, which was confirmed by the NMR spectroscopy. Hence, the sequence of isomerization is shown to be 26 ⟶ 25 ⟶ 24 ⟶ 29. The latter two isomers(24 and 29) correspond to 13-acetoxyprotoilludan-8-ones.



To check the generality of this method, we have then tried some deoxygenation reactions: By a sequence of reactions(the LAH reduction, the Collins oxidation, acetalization by 1,3-dithiopropane with BF_3, the Raney Nickel-desulfurization, and the LAH reduction), 29 was converted into 8β-hydroxyprotoilludane(30). Every attempt to remove the oxygen function of 30 has failed, and according to a model consideration, the oxygen functions at C-8 suffer a large steric hindrance, and the observed inertness during the transformations supported the assigned structures.

Finally, the cis-hydroindenone(31) obtained from 1 and acetylacetone was further irradiated with 1,1-dimethoxyethylene to give a cis-anti-cis-adduct(32). 32 yielded protoillud-7-ene(33) by the methylation with Grignard reagent, an acetalization with 1,2-ethanedithiol and BF_3 in benzene, and the Raney Nickel-desulfurization. 33 was identical with the previously obtained sample[10,11] in respects of comparisons with the recorded physical data.



In conclusion, the present results provided a sufficiently effective new entry to an increasingly important member of sesquiterpenoids, oxygenated protoilludanes, some of which are physiologically active. Further works on the related aspects are in progress, and will be a subject of an independent paper.

The NMR Spectra of New Compounds (in $CDCl_3$ Solutions).

6. 1.08(3H, s), 1.10(3H, s), 1.2-3.0(13H, m), and 3.72(3H, s).
7. 1.00(3H, s), 1.09(3H, s), 1.2-2.9(13H, m), and 3.68(3H, m).
8. 1.01(3H, s), 1.03(3H, s), 1.1-2.1(14H, m), 2.60(1H, m), 3.45(2H, s), and 3.72(1H, m).

9. 1.02(3H, s), 1.06(3H, s), 0.8-2.3(15H, m), 3.46(2H, s), and 3.86(1H, m).
10. 1.04(3H, s), 1.10(3H, s), 1.2-3.2(11H, m), 3.20(3H, s), 3.27(3H, s), and 3.77(3H, s).
11. 1.00(3H, s), 1.05(3H, s), 1.07(3H, s), 1.1-2.6(13H, m), and 3.68(3H, s).
12. 1.02(3H, s), 1.05(3H, s), 1.09(3H, s), 1.1-2.6(12H, m), 2.66(1H, tm, J=8 Hz), and 3.69(3H, s).
13. 1.01(3H, s), 1.05(3H, s), 1.56(3H, br. s), 1.1-2.5(10H, m), 3.70(3H, s), and 5.52(1H, br. s).
14. 1.04(6H, s), 1.61(3H, m), 1.1-2.9(11H, m), 3.70(3H, s), and 5.52(1H, br. s).
15. 1.05(6H, s), 1.52(3H, br. s), 1.1-2.2(10H, m), 2.51(1H, OH), 3.41(1H, d, J=11 Hz), 3.55(1H, d, J=11 Hz), and 5.39(1H, br. s).
16. 1.03(6H, s), 1.58(3H, m), 1.2-1.9(9H, m), 2.25-2.47(2H, m), 3.45(1H, d, J=12 Hz), 3.57(1H, d, J=12 Hz), and 5.45(1H, br. s).
17. 1.06(3H, s), 1.09(3H, s), 1.22(3H, s), 1.3-2.1(10H, m), 1.66(1H, m), 3.00(1H, br. s), 3.35(1H, d, J=11 Hz), and 3.55(1H, d, J=11 Hz).
18. 1.03(3H, s), 1.08(3H, s), 1.18(3H, s), 1.2-2.0(10H, m), 2.06(3H, s)2.91(1H, s), 3.75(1H, d, J=11 Hz), and 3.97(1H, d, J=11 Hz).
19. 1.04(6H, s), 1.60(3H, m), 1.2-2.0(9H, m), 2.07(3H, s), 2.2-2.5(2H, m), 4.06(2H, s), and 5.50 (1H, br. s).
20. 1.02(3H, s), 1.05(3H, s), 1.21(3H, s), 1.2-2.2(10H, m), 2.08(3H, s), 2.43(1H, m), 2.99(1H, s), and 3.86(3H, s).
21. 1.04(6H, s), 1.60(3H, m), 1.2-2.0(9H, m), 2.07(3H, s), 2.2-2.5(2H, m), 4.06(2H, s), and 5.50 (1H, br. s).
22. 0.86(1H, t, J=12 Hz), 1.04(3H, s), 1.05(3H, s), 1.20(3H, s), 1.2-2.5(10H, m), 2.73(1H, OH), 3.04(1H, s), 2.34(1H, d, J=11 Hz), and 3.47(1H, d, J=11 Hz).
23. 0.88(1H, t, J=12 Hz), 1.04(6H, s), 1.19(3H, s), 1.2-2.6(10H, m), 2.07(3H, s), 3.00(1H, s), 3.84 (1H, d, J=12 Hz), and 3.94(1H, d, J=12 Hz).
24. 1.04(3H, s), 1.05(3H, s), 1.06(3H, d, J=8 Hz), 1.2-2.0(9H, m), 2.09(3H, s), 2.2-2.6(3H, m), and 4.08(2H, s).
25. 0.89(3H, d, J=7 Hz), 1.06(6H, s), 1.2-1.9(10H, m), 2.12(3H, s), 2.45(1H, m), 2.82(1H, m), 4.05 (1H, d, J=11 Hz), and 4.21(1H, d, J=11 Hz).
26. 1.07(3H, d, J=6 Hz), 1.10(6H, s), 1.2-2.1(10H, m), 2.07(3H, s), 2.5-3.1(2H, m), and 3.99(2H, s).
27. 1.07(6H, s), 1.29(3H, s), 1.2-2.0(11H, m), 2.05(3H, s), 3.36(1H, m),3.86(1H, d, J=11 Hz), 4.01 (1H, d, J=11 Hz), and 4.44(1H, d, J=56 Hz).
28. 1.06(6H, s), 1.10(3H, s), 1.2-2.4(12H, m), 2.04(3H, s), 3.92(1H, d, J=11 Hz), and 4.09(1H, d, J=11 Hz).
29. 0.90(3H, d, J=6 Hz), 0.96(3H, s), 1.09(3H, s), 1.1-2.0(10H, m), 2.09(3H, s), 3.98(1H, d, J=12 Hz), and 4.19(1H, d, J=12 Hz).
30. 0.93(3H, s), 0.97(3H, d, J=7 Hz), 1.01(3H, s), 1.08(3H, s), 1.2-2.5(12H, m), and 3.47(1H, br. s).
32. 1.01(3H, s), 1.11(3H, s), 1.28(3H, s), 1.5-2.0(4H, m), 2.1-2.9(7H, m), 3.08(3H, s), and 3.19 (3H, s).
33. 0.98(6H, s), 1.17(3H, s), 1.59(3H, br. s), 0.9-2.0(11H, m), and 5.11(1H, br. s).

References and Note

1) T. C. McMorris and M. Anchel, J. Am. Chem. Soc., 87, 1597 (1965). Also see a Review, W. Parker, J. C. Roberts, and R. Ramage, Quart. Rev., 21, 331 (1967).

2) M. Fukuoka, M. Kuroyanagi, M. Toyama, K. Yoshihira, and S. Natori, Chem. Pharm. Bull, 20, 2282(1972).

3) T. C. McMorris, M. S. R. Nair, P. Singh, and M. Anchel, Phytochemistry, 10, 1611 (1971).

4) T. Matsumoto, K. Miyano, S. Kagawa, S. Yu, T. Ogawa, and A. Ichihara, Tetrahedron Lett., 1971, 3521.

5) E. J. Corey and S. Nozoe, J. Am. Chem. Soc., 86, 1652 (1964).

6) H. Takeshita and S. Tanno, Bull. Chem. Soc. Jpn., 46, 880 (1973).

7) P. de Mayo, Accounts of Chem. Research, 4, 41 (1971).

8) Separation of 6 and 7 was rather difficult. Although 6 was isolable on a silica gel column, the analytical specimen of 7 was obtained by derivation from 9.

9) P. Chamberlain, M. L. Roberts, and G. H. Whitham, J. Chem. Soc., B, 1970, 1374. Also see a text, H. O. House, "Modern Synthetic Reactions(2nd Ed.)", W. A. Benjamin, Inc., N. Y. and Amsterdam, 1972, p. 303.

10) Y. Ohfune, H. Shirahama, and T. Matsumoto, Tetrahedron Lett., 1975, 4377.

11) S. Nozoe, H. Kobayashi, S. Urano, and J. Furukawa, Tetrahedron Lett., 1977, 1381.

(Received January 22, 1979)