

SYNTHESIS OF THE OPTICALLY ACTIVE GRASSHOPPER KETONE

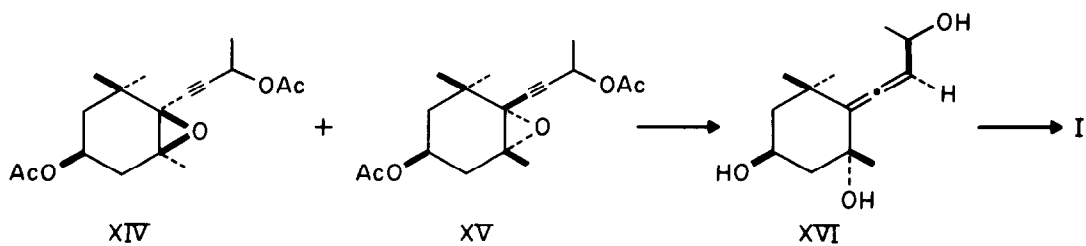
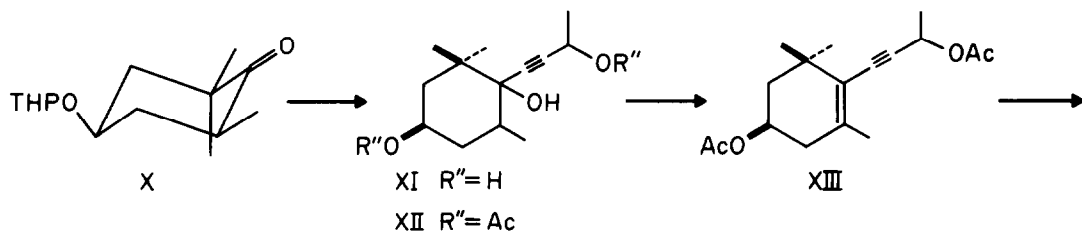
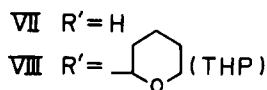
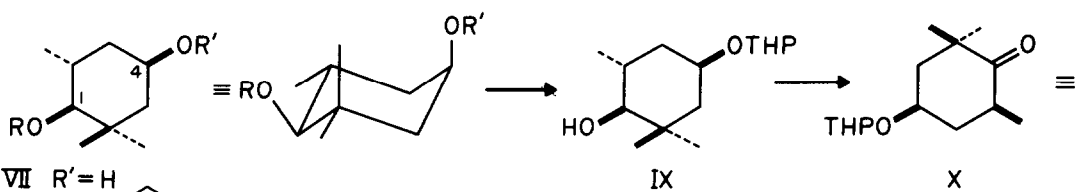
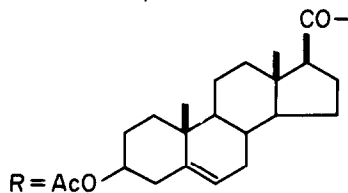
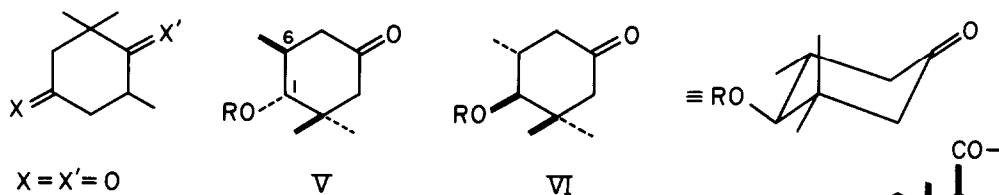
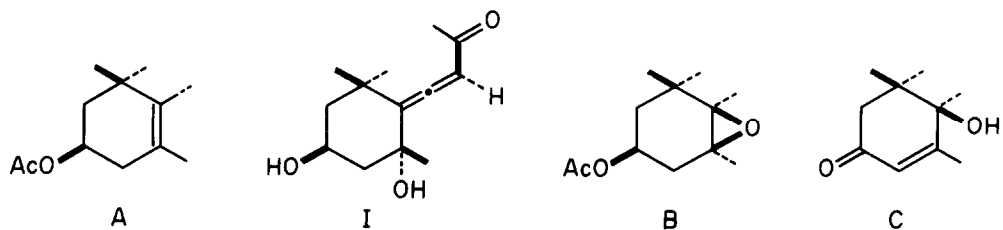
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Recently Taylor and Burden provided an evidence that the absolute configuration of either violaxanthin or (+)-abscisic acid had been incorrectly assigned (1). This aroused our interest to attempt syntheses of degraded carotenoids related to abscisic acid in their natural configuration. Our strategy was to secure a common intermediate A which would readily be convertible to the grasshopper ketone (I)(2) or to compounds with an unsaturated ketol moiety C via an epoxide B. Here we describe a synthesis of the grasshopper ketone (I) in its natural configuration, although the optical purity is not satisfactory at present.

The known diketone (II)(3) was reported to give a ketol (III) upon hydrogenation (PtO₂/MeOH)(4). However, the product, mp 75-76° (lit.⁴ 56°), δ 0.86 (3H, s), 1.08 (3H, s), 1.09 (3H, d, J=6Hz), 3.37 (1H, d, J=10Hz), was found to be IV by its conversion to 2,2,6-trimethylcyclohexanone by means of the Huang-Minlon reduction followed by the Jones oxidation. This selective hydrogenation of the more hindered CO of II is an interesting phenomenon (5). The optical resolution of the ketol (IV) was achieved by the use of 3 β -acetoxyetienic acid (6,7). A mixture of two diastereomers (V and VI) was separated by fractional crystallization to give the more soluble etienate (V), mp 184.5-186.0°, $[\alpha]_D^{24}$ -13° (c 0.037 in dioxan), and the less soluble etienate (VI), mp 243-244°, $[\alpha]_D^{24}$ -31° (c 0.037 in dioxan). The 1,6-trans stereochemistry of V and VI was based on the magnitude of J_{1,6} (10Hz). The absolute configurations as shown in V and VI were deduced from the ORD data of V, negative Cotton effect (c 0.002 in MeOH), $[\phi]_{308}$ -500° (trough), $[\phi]_{233}$ +2500° (peak), and VI, positive Cotton effect (c 0.002 in MeOH), $[\phi]_{308}$ -100° (peak), $[\phi]_{270}$ -500° (trough), $[\phi]_{233}$ +2000° (second peak). The peak at 233 nm was due to the steroidal ester portion (8).



The less soluble ketone (VI), $[\alpha]_D^{24} -28.0^\circ$, (c 0.01 in dioxan, 83% purity with 17% of V) was reduced with LiAlH_4 (OMe^t)₃ to give, after chromatography over Al_2O_3 , an axial alcohol (VII), mp 205-206°, $[\alpha]_D^{24} -39.4^\circ$ (c 0.01 in dioxan). Its C-4 proton absorbed at δ 3.99 (1H, t) with J=6Hz, indicating the β -axial configuration of the OH group. After protecting the OH group as a THP ether (VIII), mp 195-200°, $[\alpha]_D^{24} -20.2^\circ$ (c 0.01 in dioxan), the steroidal ester (VIII) was treated with LiAlH_4 to give an alcohol (IX)(9). The Sarett oxidation of IX followed by equilibration with NaOMe/MeOH afforded the key intermediate (X) after chromatography over Al_2O_3 . This ketone (X) exhibited a positive Cotton effect curve (c 0.0013 in MeOH), $[\phi]_{315} +2900^\circ$ (peak), $[\phi]_{285} +2400^\circ$ (trough) in accord with the assigned stereochemistry (10). The equatorial configuration of the THPO-group was manifested in the large $\frac{W_1}{2}$ value ($\sim 15\text{Hz}$) of THPO-CH-proton.

Treatment of the ketone (X) with a Grignard reagent prepared from EtMgBr and but-3-yn-2-ol THP ether gave XI as di-THP ether. The crude product was treated with 0.14% *p*-TsOH/MeOH to give a triol (XI). Further transformation to the grasshopper ketone (I) was carried out in the same manner as described by Weedon and Russell (11) for the synthesis of the racemic ketone (I). The triol (XI) was converted to a diacetate (XII) which in turn was dehydrated to give an enyne diacetate (XIII), δ 1.15 (6H, s), 1.53 (4H, a, J=7.2), 1.86 (3H, s), 2.01 (3H, s), 2.05 (3H, s), 4.95 (1H, m), 5.56 (1H, q). Epoxidation of XIII with *m*-chloroperbenzoic acid in CHCl_3 gave a mixture of two epoxides XIV and XV which was partly separated by chromatography over Al_2O_3 . The fractions rich in the more strongly absorbed XV were combined and reduced with $\text{LiAlH}_4/\text{THF}$ to give a crude allenic triol (XVI), $\nu_{\text{max}} \sim 3300$, 1950 (weak), 1050 cm^{-1} . This was oxidized with MnO_2 in acetone and purified by preparative TLC (silica gel GF₂₅₄, EtOAc C_6H_6 7:3) to give the grasshopper ketone (I, R_f 0.24, 4mg). Although the product could not be crystallized because of its unsatisfactory optical purity, its spectral properties were in good agreement with those of the natural product (2,11): $\nu_{\text{max}} \sim 3300$, 1955, 1660 cm^{-1} , δ 1.17 (3H, s), 1.40 (3H, s), 1.45 (3H, s), 2.19 (3H, s), 4.30 (1H, m), 5.87 (1H, s). Moreover, the CD curve of our totally synthetic material (c 0.0004 in dioxan), $[\theta]_{300} 0$, $[\theta]_{255} -7600$, $[\theta]_{239} 0$, $[\theta]_{228} +8400$, $[\theta]_{214} 0$, $[\theta]_{211} -3800$, was qualitatively in good agreement with that of the semi-synthetic grasshopper ketone (I) prepared from fucoxanthin (12). The data kindly supplied by Prof. Weedon were $[\theta]_{255} -11300$, $[\theta]_{210} 0$, $[\theta]_{229} +9830$, $[\theta]_{216} 0$, $[\theta]_{211} -6040$. The optical purity of the synthetic product was more than 65% as judged by these values.

In view of the established stereochemistry (I) of the fucoxanthin degradation product by X-ray crystallographic analysis (12), the present synthesis confirmed the absolute configuration of our key intermediate (X) determined by ORD method. Conversion of X into other terpenes will be reported in due course.

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REFERENCES AND FOOTNOTES

1. R.S. Burden and H.F. Taylor, Tetrahedron Lett., 4071 (1970); H.F. Taylor and R.S. Burden, Proc. Royal Soc., B 180, 317 (1972).
2. J. Meinwald, K. Erickson, M. Hartshorn, Y.C. Meinwald and T. Eisner, Tetrahedron Lett. 2959 (1968).
3. J.N. Marx and F. Sondheimer, Tetrahedron Suppl. 8, Part I 1 (1966).
4. F. Hoffmann-La Roche & Co., A.G., Brit. Pat., 790, 607. see C.A. 52, 15575d (1958).
5. Further studies on this problem will be published elsewhere by K. Mori, S. Saito and M. Matsui.
6. R.B. Woodward and T.J. Katz, Tetrahedron, 5, 70 (1959).
7. J. Staunton and E.J. Eisenbraun, Org. Synth., 42, 4 (1962).
8. An attempt to resolve III was unsuccessful.
9. The purity of oily products was checked by TLC and/or GLC.
10. The optical purity of this ketone (X) could not be determined, since the $[\alpha]_D$ value of pure X was not known. However, it might be assumed to be 66% reflecting the purity of the starting steroidal ester (VI).
11. S.W. Russell and B.C.L. Weedon, Chem. Commun., 85 (1969); see also D.E. Loeber, S.W. Russell, T.P. Toube, B.C.L. Weedon and J. Diment, J. Chem. Soc. (C), 404 (1971).
12. T.E. DeVille, M.B. Hursthouse, S.W. Russell and B.C.L. Weedon, Chem. Commun., 1311 (1969).