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SYNTHESIS OF (2S)-β,β-CAROTEN-2-OL

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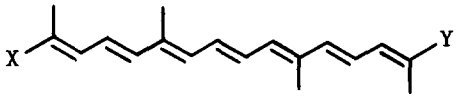
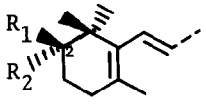
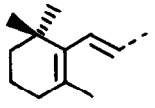
The carotenoids with 2-hydroxylated β-ring [(1),(2),(3),(4),(5) and (6)] [Fig.1][1] are new series of naturally occurring xanthophylls. From the biosynthetic aspects, they are believed to be closely related to the aromatic carotenoids (eg. isorenieratene) or the C_{50}-carotenoids bearing C_5-alkyl chains at C-2 and C-2' positions.





a : R_1=OH, R_2=H

a': R_1=H , R_2=OH



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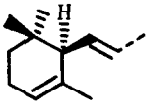

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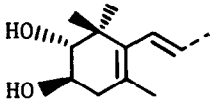

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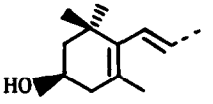

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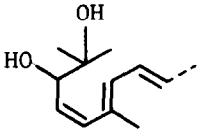
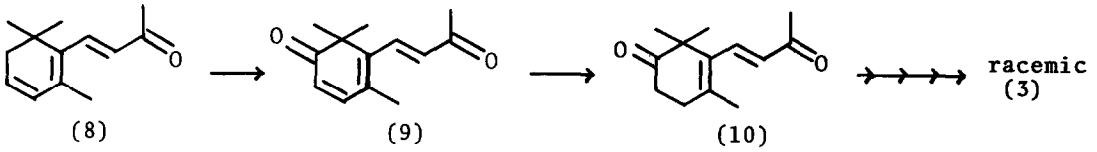


f

(1) X=a, Y=b
(2) X=a, Y=c
(3) X=Y=a
(4) X=d, Y=e
(5) X=Y=d
(6) X=a or a', Y=f
(7) X=a', Y=b

Fig.1



(8) (9) (10)

Fig.2

This communication deals with the first synthesis of an optically active carotenoid with 2-hydroxylated β-ring which illustrates a flexible new route to 2-hydroxylated carotenoids. Although we had already accomplished the synthesis of racemic β,β-carotene-2,2'-diol (3) having a symmetrical structure [Fig.2][2], several disadvantages had been pointed out: 1. Selenium dioxide oxidation of (8) afforded various kinds of compounds other than the expected product (9). 2. Catalytic reduction [(9)→(10)] had the lack of regiospecificity, and so on. Therefore, an alternative route to a key intermediate, 2-oxo-β-ionone (10) has been developed as follows [Fig.3].

Selective ketalisation of 2,2,4-trimethyl-cyclohexane-1,3-dione (11)[3] gave the monoketal-ketone (12)[4] which was treated with the lithium derivative prepared from n-butyl lithium and but-3-yn-2-ol THP ether to afford the hydroxy compound (13) in almost quantitative yield. The latter (13) was transformed by treatment with p-TsOH in MeOH followed by acetylation and reketalisation into the hydroxy acetate (14) which on dehydration with $POCl_3$ in pyridine and on subsequent purification by chromatography (Al_2O_3) provided the eneyne acetate (15) in ca.50% yield. The triple bond of (15) was stereospecifically reduced with sodium bis-(2-methoxyethoxy-)-aluminium hydride (SMEAH) to yield the *trans* diene alcohol (16) [δ:5.49(dd,J=15.9 and 6Hz, C-8-H);6.04(d,J=15.9Hz, C-7-H)]. The allylic hydroxyl group in the compound (16) was oxidized with DDQ in dioxane followed by deketalisation and subsequent chromatography over Al_2O_3 to give 2-oxo-β-ionone (10). Spectral data of (10) were consist with those reported by us.

Chirality was introduced at C-2 by a regiospecific and stereospecific fermentative reduction of 2-oxo-β-ionone (10) using baker's yeast as the biocatalyst. Fermentation of (10) by active dried yeast for baking for 70 hr at 28° followed by acetylation produced an optically active 2-acetoxy-β-ionone (17), $[\alpha]_D^{23}$ +8° (c=1.06,EtOH), in 60% yield along with 10% of the starting material (10). Its light absorption resembled that of β-ionone. The structure of this product was confirmed by its n.m.r. spectrum [δ(90MHz) 1.07(s,6H, gem-CH_3), 1.79(s,3H,C-5-CH_3), 2.09(s,3H,$COCH_3$), 2.32(s,3H,C-9-CH_3), 4.84(dd, 1H,J=7 and 4Hz,C-2-H_{ax}), 6.16(d,1H,J=17Hz), 7.27(d,1H,J=17Hz)]: in particular, the coupling constant of the hydrogen at C-2 established that the configuration of acetoxyl group was equatorial. Absolute configuration of (17) was qualitatively assumed to be 2S from the comparison with the CD spectrum of (2R)-2-acetoxy-β-ionone (18)[5], the degradation product of natural (2R)-2-hydroxylated carotenoid.

Horner reaction between (17) and diethyl methoxycarbonylmethylphosphonate led to the 2-acetoxy-β-ionylidene ester (19). This on reduction with SMEAH followed by treatment with triphenylphosphonium bromide furnished the Wittig salt (20) which, without purification, was condensed in the presence of NaOMe

in DMF with β-apo-12'-carotenal (21)[6] prepared from 2,7-dimethylocta-2,4,6-triene-1,8-dial and (β-ionylideneethyl)triphenylphosphonium bromide gave an optically active β,β-caroten-2-ol (7) having an unsymmetrical structure. Its spectral properties (visible light absorption, n.m.r. and m.s.) were in good agreement with those[7] reported for (2R)-β,β-caroten-2-ol (1). The CD curve of our synthetic material was opposite to that of natural (2R)-β,β-caroten-2-ol (1)[5] kindly supplied by Prof. S.Liaaen-Jensen. Therefore, the absolute configurations of both (7) and (17) were deduced to be 2S.

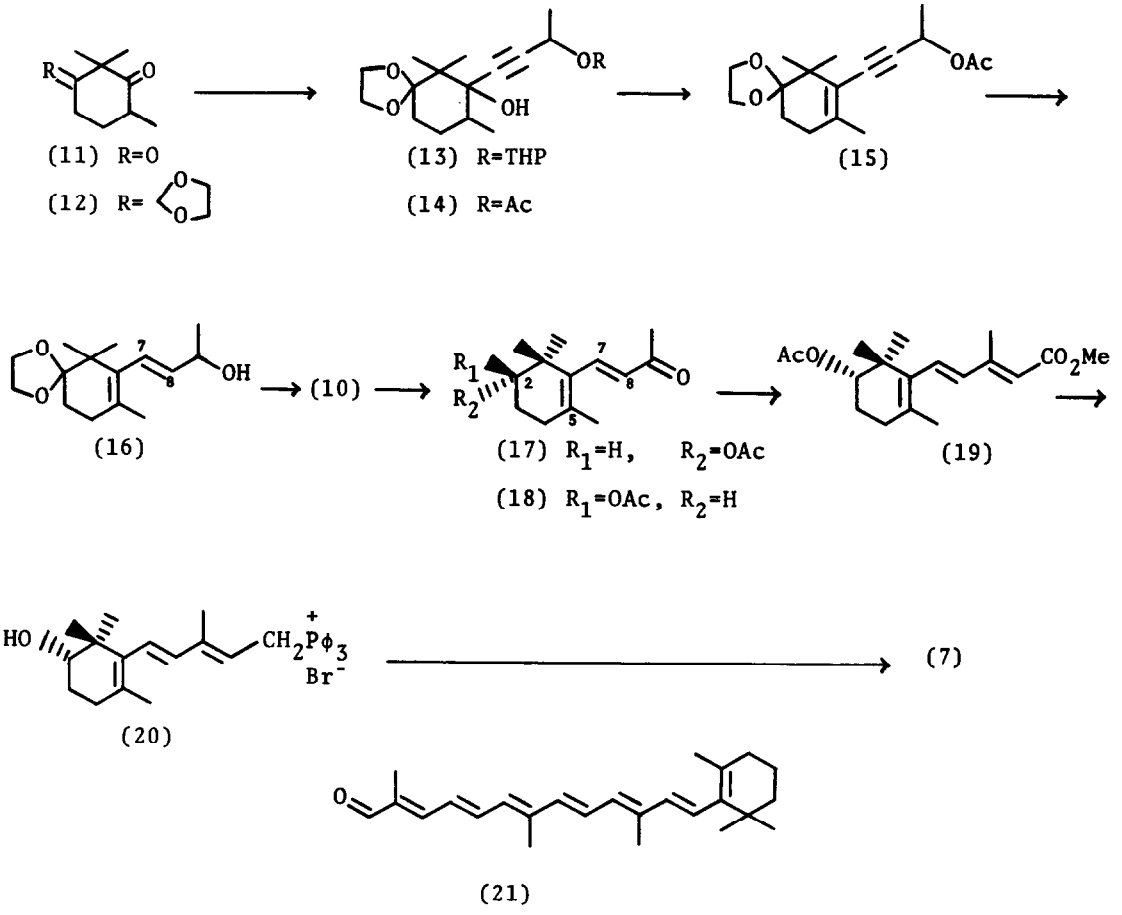


Fig.3

Of 2-hydroxylated carotenoids, both caloxanthin (4)[8] and nostoxanthin (5)[8] have the same absolute configuration at C-2 or C-2' as (7) prepared by us. It might be thought that (10) or (17) is the valuable intermediate for synthesis of optically active (4) or (5). Our fermentative result of (10) is

quite interesting in view of the fact that 2-OH-plectaniaxanthin (6) was isolated from red yeast[9].

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