Synthesis of the 4-Alkylidenebutenolide Carotenoids, Peridinin and Pyrrhoxanthin

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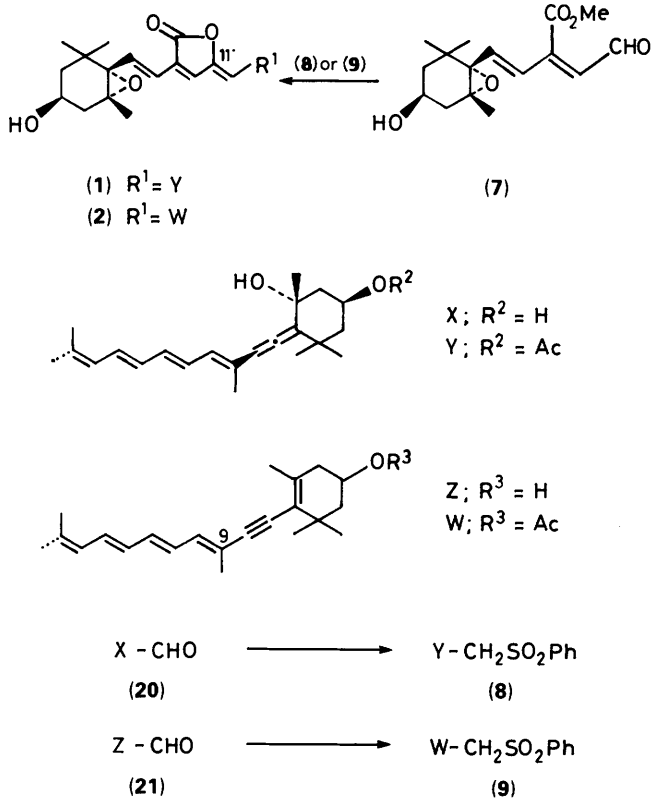
A novel synthetic method of carotenoidal alkylidenebutenolides has been developed, and applied to the first synthesis of peridinin (**1**) and pyrrhoxanthin (**2**).

Peridinin (**1**) and pyrrhoxanthin (**2**) (Scheme 1) are unique C_{37}-skeletal nor-carotenoids owing to the presence of a 4-alkylidenebutenolide system carrying an allene or an acetylene function in the main polyene chain. Both pigments were isolated[1] from the planktonic algae, dinoflagellates causing 'red tide'. Their absolute stereostructures were determined by Jensen *et al.*[2] The main pigment peridinin is known as an auxiliary light-harvesting pigment for photosynthesis.[3] In previous papers,[4,5] Wittig methods were reported toward the synthesis of carotenoidal alkylidenebutenolides, but they were found to be inappropriate for the preparation of alkylidenebutenolides with longer conjugated chain due to drastic reaction conditions.

Here, we describe the total synthesis of both carotenoids (**1**) and (**2**). In order to accomplish this, a novel synthetic method for carotenoidal alkylidenebutenolides was developed *via* reaction of the conjugated formyl ester (**3**)[6] with various allylic sulphones (**5**)[7] in the presence of lithium di-isopropylamide (LDA) at −78 °C (Table). In this reaction, addition, cyclisation, and elimination took place successively in one pot to give the expected products (**6**) in moderate yields (Table) as a mixture (*ca.* 1:1) of *Z* and *E* isomers in the ylidene double bond.

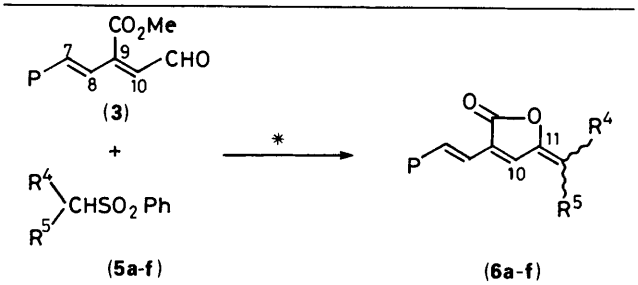


Scheme 1.

Separated and purified isomers were characterised[4,5] respectively by UV, IR, ^{1}H NMR, and mass analyses. Using this method, the first synthesis of peridinin (**1**) and pyrrhoxanthin (**2**) was achieved by reaction of the C_{15}-epoxy formyl ester (**7**) with the conjugated C_{22}-allenic sulphone (**8**) or C_{22}-acetylenic sulphone (**9**) (Scheme 1).

The C_{15}-epoxy formyl ester (**7**) was prepared as follows (Scheme 2). Treatment of the t-butyldimethylsilyl (TBDMS) ether (**11**) of the 4-hydroxy-2,6,6-trimethylcyclohexanone (**10**)[8] with *N*-phenyltrifluoromethanesulphonimide (Tf_2NPh)[9] in the presence of LDA gave the enol triflate (**12**), (89%) which underwent a coupling reaction[10] with methyl acrylate in the presence of a palladium(II) catalyst to afford the diene ester (**13**), (93%). Reduction of the ester group in (**13**) followed by acetylation gave the allyl acetate (**14**), (80%) which was treated with sodium sulphinate catalysed by $Pd(PPh_3)_4$[11] to provide the allylic sulphone (**15**), (89%). Introduction[4] of a methoxycarbonyl group in the sulphone (**15**) and subsequent alkylation with allyl bromide gave the compound (**16**), (72%) which, after deprotection (84%), was oxidised regioselectively at the terminal vinyl group followed by elimination of the sulphone group to afford a mixture of the formyl ester isomers (**17**), (21%) and (**18**), (17%), preparative HPLC of which gave each pure isomer. Treatment of the former isomer (**17**) with a catalytic amount of I_2 provided a mixture (3:4) of (**17**) and (**18**). Compound (**17**): δ[12] 6.67 (1 H, d, *J* 16 Hz, 8-H), 6.66 (1 H, d, *J* 7.5 Hz, 10-H), and 6.59 (1 H, br d, *J* 16 Hz, 7-H). Compound (**18**): δ 6.65 (1 H, br d, *J* 16 Hz, 7-H), 6.22 (1 H, d, *J* 16 Hz, 8-H), and 6.09 (1 H, d, *J* 7.5 Hz, 10-H). Epoxidation of (**18**) with *m*-chloroperbenzoic acid (MCPBA) gave a mixture of the *syn*-(β)-epoxide (**19**), (56%) and the *anti*-(α)-epoxide (**7**), (19%). Stereostructures of both isomers were confirmed by ^{1}H NMR data. Compound (**19**): δ 6.46 (1 H, d, *J* 16 Hz, 7-H), 6.37 (1 H, d, *J* 16 Hz, 8-H), 6.15 (1 H, d, *J* 7.5 Hz, 10-H), 1.57 (1 H, dd, *J* 12, 11 Hz, 2_{ax}-H), and 1.34 (1 H, ddd, *J* 12, 4, 1 Hz, 2_{eq}-H). Compound (**7**): δ 6.52 (1 H, d, *J* 16 Hz, 7-H), 6.38 (1 H, d, *J* 16 Hz, 8-H), 6.14 (1 H, d, *J* 7.5 Hz, 10-H), 1.63 (1 H, ddd, *J* 12.5, 3.5, 1.5 Hz, 2_{eq}-H), and 1.26 (1 H, dd, *J* 12.5, 11 Hz, 2_{ax}-H).

Table Conjugated alkylidenebutenolide synthesis.

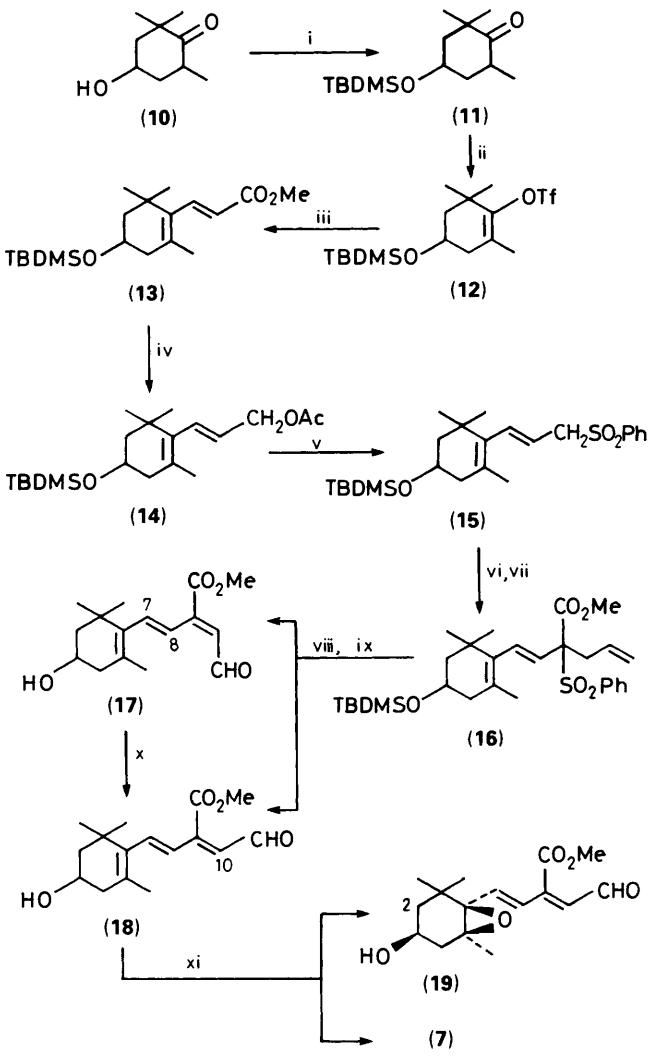


Entry	(5a-f), (6a-f)	Yield (%)
1	**a**; R^4 = H, R^5 =	56
2	**b**; R^4 = H, R^5 =	46
3	**c**; R^4 = H, R^5 =	46
4	**d**; R^4 = H, R^5 =	33
5	**e**; R^4 = Me, R^5 =	49†
6	**f**; R^4 = H, R^5 =	32

* LDA, THF–hexane = 1:1, −78 °C to −50 °C † Addition of hexamethylphosphoric triamide.

The all-*E*-C_{22}-allenic sulphone (**8**) was prepared in three steps from the known aldehyde (**20**)[13] by first converting (**20**) into the corresponding alcohol followed by acetylation and subsequent treatment of the acetate with sodium sulphinate [63% yield from (**20**)] (Scheme 1). Similar treatment of the known acetylenic aldehyde (**21**)[13] gave a mixture (1:1) of the all-*E*-C_{22}-acetylenic sulphone (**9**) and its 9*Z*-isomer in 62% yield from which (**9**), (31%) was obtained in a pure state by preparative HPLC in the dark.

The carbanion prepared from the allenic sulphone (**8**) and LDA in a mixture (1:1) of tetrahydrofuran (THF) and hexane was treated with the *anti*-epoxide (**7**) at −78 °C to afford the condensed products (9%), repeated purification of which by preparative HPLC in the dark led to peridinin (**1**) and its 11′*E*-isomer in a pure form, respectively. Spectral properties (UV.-visible, IR, NMR, and mass) of the synthetic peridinin[14] were in good agreement with those of the natural specimen.[15] The same condensation between the acetylenic sulphone (**9**) and the *anti*-epoxide (**7**) produced a mixture (1:1) of pyrrhoxanthin (**2**) and its 11′*E*-isomer in 13% yield which was cleanly separated by preparative HPLC in the dark. Spectral properties of the synthetic pyrrhoxanthin acetate[14] agreed with those reported previously.[1,16] Work is in progress on the synthesis of optically active (**1**) and (**2**).



Scheme 2. All compounds are racemic. *Reagents:* i, TBDMSCl, Et_3N, dimethylaminopyridine, CH_2Cl_2, 93%; ii, LDA, Tf_2NPh, THF, 89%; iii, CH_2=$CHCO_2Me$, $PdCl_2(PPh_3)_2$, Et_3N, dimethylformamide (DMF), 93%; iv, $LiAlH_4$, Et_2O, then Ac_2O–pyridine, 80%; v, $PhSO_2Na$, $Pd(PPh_3)_4$, THF–MeOH, 89%; vi, BuLi, $ClCO_2Me$, THF, 74%; vii, NaH, $BrCH_2CH$=CH_2, DMF, 98%; viii, Bu_4NF, THF, 84%; ix, OsO_4–$NaIO_4$, dioxane–H_2O, then Al_2O_3, 38%; x, I_2, Et_2O–hexane, 79%; xi, MCPBA, CH_2Cl_2, 75%.

Experimental

Preparation of the Alkylidenebutenolide (**6a**): *General Procedure for the Conjugated Alkylidenebutenolide Synthesis*—A solution (0.36 ml, 0.57 mmol) of butyl-lithium (1.59M in hexane) was added to a stirred solution of di-isopropylamine (58 mg, 0.57 mmol) in dry THF (1.5 ml) and hexane (1.5 ml) at −78 °C under N_2 and the mixture was stirred for a further 30 min. To this LDA solution was added a solution of the sulphone (**5a**) (143 mg, 0.57 mmol) in a mixture (4 ml) of dry THF and hexane (1:1). After the addition was complete, the mixture was stirred for 30 min, after which a solution of the formyl ester (**3**) (100 mg, 0.38 mmol) in dry THF (2 ml) and hexane (2 ml) was added dropwise at −78 °C. The reaction mixture was then stirred at −78 °C for 10 min before being allowed to warm to room temperature over *ca.* 20 min with stirring. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and evaporated to give an oil which was purified by silica gel short column chromatography (ether–hexane, 1:9) under reduced pressure to afford (**6a**) (72 mg, 56%). Isomers (*Z*:*E*=*ca.* 1:1) were separated by preparative TLC (silica gel/benzene–hexane, 2:3) to give each pure specimen. (11*Z*)-Isomer, mp 127–130 °C; (11*E*)-isomer mp 123–126 °C.

Acknowledgements

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References

1 H. H. Strain, W. A. Svec, K. Aitzetmüller, M. C. Grandolfo, J. J. Katz, H. Kjøsen, S. Norgård, S. Liaaen-Jensen, F. T. Haxo, P. Wegfahrt, and H. Rapoport, *J. Am. Chem. Soc.*, 1971, **93**, 1823; H. H. Strain, W. A. Svec, P. Wegfahrt, H. Rapoport, F. T. Haxo, S. Norgård, H. Kjøsen, and S. Liaaen-Jensen, *Acta Chem. Scand., Sect. B*, 1976, **30**, 109; J. E. Johansen, W. A. Svec, S. Liaaen-Jensen, and F. T. Haxo, *Phytochemistry*, 1974, **13**, 2261.

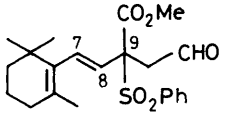
2 J. E. Johansen, G. Borch, and S. Liaaen-Jensen, *Phytochemistry*, 1980, **19**, 441; V. Partali, B. Bowden, and S. Liaaen-Jensen, in 'Abstracts of 8th Int. Symp. on Carotenoids,' 1987 (Boston), P58.

3 F. T. Haxo, in 'Comparative Biochemistry of Photoreactive Systems,' ed. by M. B. Allen, 1960, Academic Press, New York, p 339.

4 M. Ito, T. Iwata, and K. Tsukida, *Chem. Pharm. Bull.*, 1984, **32**, 1709.

5 M. Ito, Y. Hirata, Y. Shibata, A. Sato, and K. Tsukida, *J. Nutr. Sci. Vitaminol.*, 1987, **33**, 313.

6 Treatment of the known formyl sulphone (**4**)[5] with alumina gave a mixture (4:5) of (**3**) and its 9*E*-isomer in 69% yield. The purified latter isomer was converted into (**3**) by treatment with I_2.



(**4**)

7 The sulphones (**5a–f**) were prepared from corresponding allylic alcohols by the standard method.

8 E. Widmer, *Pure Appl. Chem.*, 1985, **57**, 741.

9 J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1983, **24**, 979.

10 W. J. Scott, M. R. Peña, K. Swärd, S. J. Stoessel, and J. K. Stille, *J. Org. Chem.*, 1985, **50**, 2302.

11 K. Inomata, T. Yamamoto, and H. Kotake, *Chem. Lett.*, 1981, 1357.

12 ^1H NMR was determined with 200 or 500 MHz FT NMR instrument.

13 M. Ito, Y. Hirata, K. Tsukida, N. Tanaka, K. Hamada, R. Hino, and T. Fujiwara, *Chem. Pharm. Bull.*, 1988, **36**, 3328.

14 This seems to be a mixture of diastereoisomers.

15 This was kindly supplied by Dr. Y. Tanaka, Kagoshima University, Japan. A mixed HPLC of the synthetic and the natural pigment showed no separation.

16 Natural pyrrhoxathin acetate was kindly supplied by Prof. S. Liaaen-Jensen, The Norwegian Institute of Technology, University of Trondheim, Norway. Co-injection of the synthtic acetate and the natural specimen on HPLC resulted in no separation. According to a personal communication, Prof. Jensen recently isolated natural pyrrhoxanthin from dinoflagellate blooms whose ^1H NMR data (500 MHz) were in accordance with those of our synthetic sample.

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