Recent progress in the synthesis of butenolide carotenoids and retinoids

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Abstract- Two kinds of method (the Wittig and sulphone methods) to prepare 4-alkylidenebutenolides are described. An empirical rule regarding the NMR chemical shifts of H-3 in 4-alkylidenebutenolides displaying an extended conjuga- ed system at the C-2 position is shown. Total synthesis of racemic peridinin and pyrrhoxanthin has been accomplished by means of the sulphone method and optically active peridinin has been synthesised. Recent work on the synthesis of butenolide retinoids is also described.

INTRODUCTION

Of ca. 600 naturally occurring carotenoids of known structure (ref. 1), butenolide carotenoids, peridinin (1), peridininol (2), anhydroperidinin (3), pyrrhoxanthin (4), and pyrrhoxanthinol (5) are unusual C_{37}-skeletal nor-carotenoids because of the presence of a 4-alkylidenebutenolide system (6) carrying an allene or an acetylene function in the main polyene chain. They are found in the photosynthetic dinoflagellates. The principal carotenoid of the planktonic algae causing "red tide", peridinin, was first isolated in 1890 (ref. 2) and its unique C_{37}-tricyclic formulation was published in 1971 by the Jensen group (refs. 3,4). The stereostructure was determined in 1977 by the same group (refs. 5,6).

C_{37}-

1 : R=OAc

2 : R=OH

3

4 : R=OAc

5 : R=OH

C_{40}-

7

6

R^1: alkyl or polyene chain

R^2: polyene chain
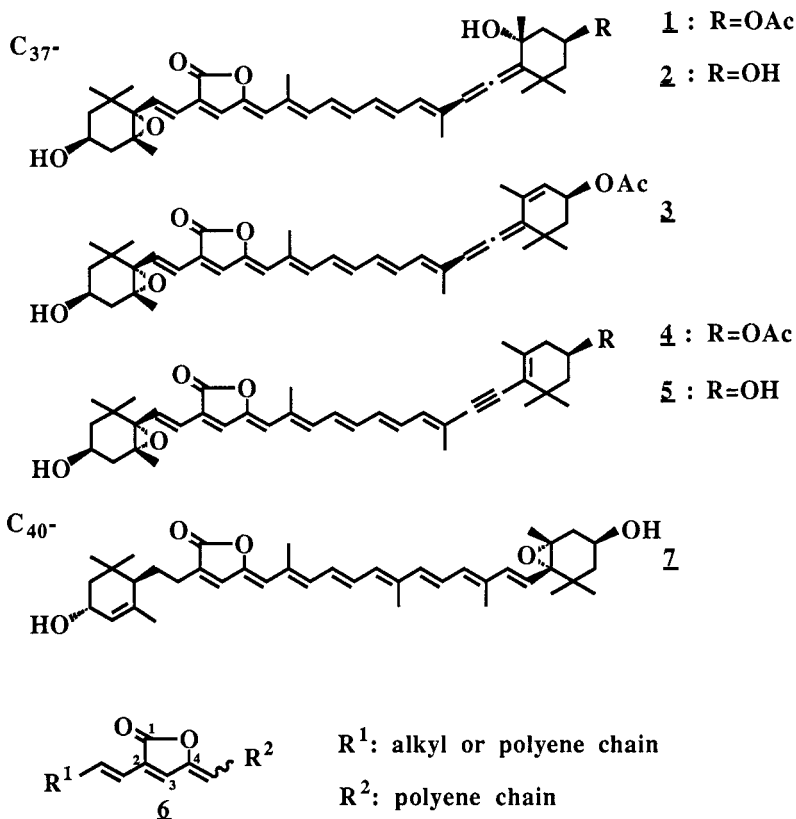
On the other hand, from the point of carotenoid function, peridinin is known as an auxiliary light-harvesting pigment for photosynthesis. Because of the importance of peridinin in photosynthesis in the sea, total synthesis of peridinin has been an important goal. The synthesis of peridinin is difficult because of its complicated structure and instability. Therefore, total synthesis of peridinin presents an interesting challenge to synthetic chemists in the carotenoid field. In addition, a new C_{40}-butenolide carotenoid, uriolide (7), was recently found in a prasinophyte (ref. 7).

SYNTHESIS OF 4-ALKYLIDENEBUTENOLIDES

Two procedures, a Wittig method (refs. 8,9,10) and a sulphone method (ref. 11), were developed to prepare the 4-alkylidenebutenolides (6) which display extended conjugation at the C-2 position. The numbering system used throughout this section is that for the butenolides and illustrated in 6.

i) Wittig method (Schemes 1 and 2)
(a) Treatment of the retinoidal acid anhydride (8) with acetyl phosphorane (9) gave the ylidenebutenolide (10) which was converted into the retinoidal ylidenebutenolide (11). In this Wittig reaction, regioselectivity at the carbonyl groups of the acid anhydride (8) was not high. Attempts to extend the conjugation by use of compounds (10) or (11) were frustrated by the instability of the intermediates. In addition, the ketone group in (10) was unreactive towards the conjugated polyene ylide.
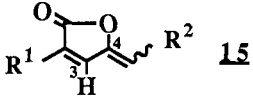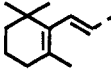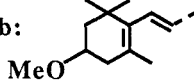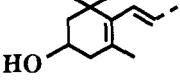
Scheme 1

R=H, OMe
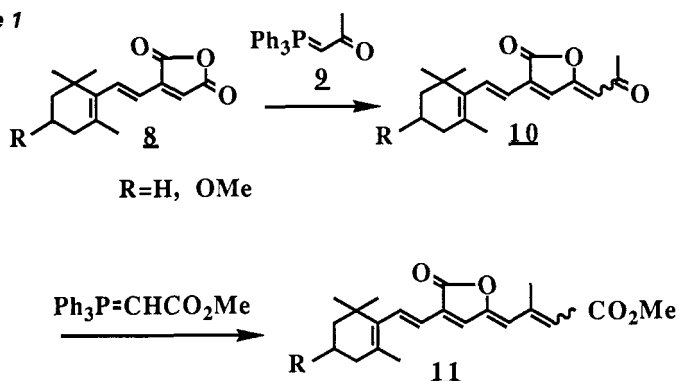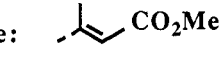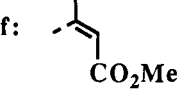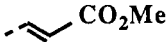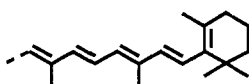
(b) The lactone-Wittig salt, derived from the corresponding hydroxy-butenolide (12) and triphenylphosphonium bromide, was condensed with conjugated aldehydes in the presence of NaH to give carotenoidal ylidenebutenolides (13) in low yield together with many by-products. This reaction is presumed to proceed via the lactone-ylide intermediate (14).

Scheme 2
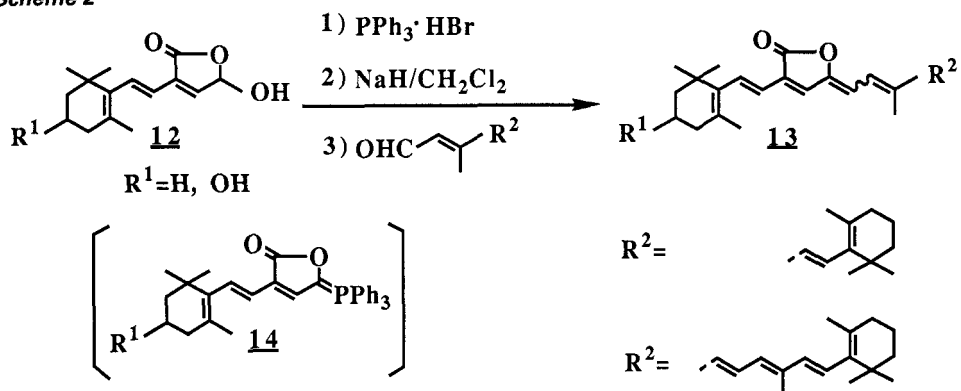
Both Wittig methods were found to be inappropriate for the preparation of alkylidene-butenolides with longer conjugated chains because of the drastic reaction condition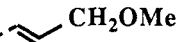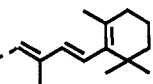s. However, by combination of two Wittig methods, E and Z isomers of 4-alkylidenebutenolides having the common structure (15) were prepared. Consequently, we found an empirical rule that in compounds of this type, the NMR signal for H-3 in the 4Z isomer was observed at δ7.00 to 7.20, whereas the corresponding signal for the 4E isomer was found downfield below δ7.40 (Table 1). These values can be used to determine the stereochemistry of the ylidene part of the conjugated double bond chromophore.

TABLE 1. Chemical shifts (δ ppm) of H-3 in 4-alkylidenebutenolides (ref. 12)

	4Z-series	4E-series
R^1=a, R^2=d	7.08	7.93
R^1=b, R^2=d	7.08	7.95
R^1=a, R^2=l	7.02	7.42
R^1=c, R^2=l	7.07	7.44
R^1=a, R^2=m	7.04	7.42
R^1=g, R^2=l	7.05	7.44
R^1=g, R^2=d	7.16	7.96
R^1=g, R^2=h	7.0	8.01
R^1=g, R^2=i	7.08	7.51
R^1=g, R^2=f	7.13	7.46
R^1=g, R^2=j	7.05	7.42
R^1=g, R^2=k	7.11	7.49
R^1=a, R^2=e	7.00	
R^1=b, R^2=e	7.03	
R^1=a, R^2=f	7.09	
R^1=b, R^2=f	7.11	
R^1=g, R^2=e		7.50

ii) Sulphone method (Scheme 3)

The reaction of the conjugated formyl ester (16) with various allylic sulphones (17) in the presence of lithium di-isopropylamide (LDA) at -78 °C gave conjugated alkylidenebutenolides (18) in moderate yields as a mixture (ca. 1:1) of Z and E isomers about the ylidene double bond (Table 2). In this reaction, addition of sulphone-anion to the aldehyde, cyclisation of the resulting hydroxy ester, and elimination of the sulphone group took place successively in one pot to give the expected products (18).

Scheme 3
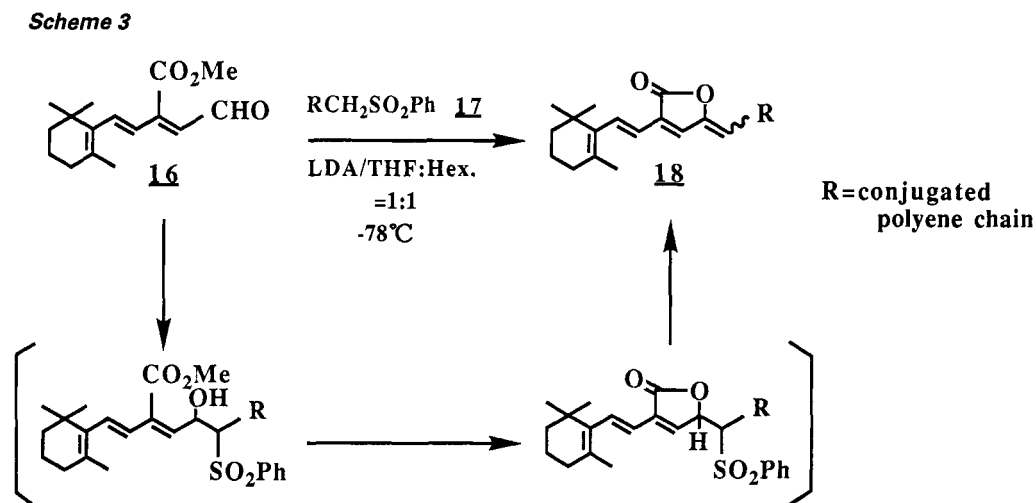
TABLE 2. Synthesis of conjugated alkylidenebutenolides

Entry	Sulphone (17)	Product (18)	Total yield of E and Z
1			56%
2			46%
3			46%
4			33%
5			37%*

* This was improved to 49% yield by use of *n*-BuLi in THF containing HMPA.

By use of the sulphone method, the first synthesis of peridinin and pyrrhoxanthin was achieved by the reaction of the C_{15}-epoxy formyl ester (19) with the conjugated C_{22}-allenic sulphone (20) or C_{22}-acetylenic sulphone (21), respectively, (Scheme 4).

Scheme 4
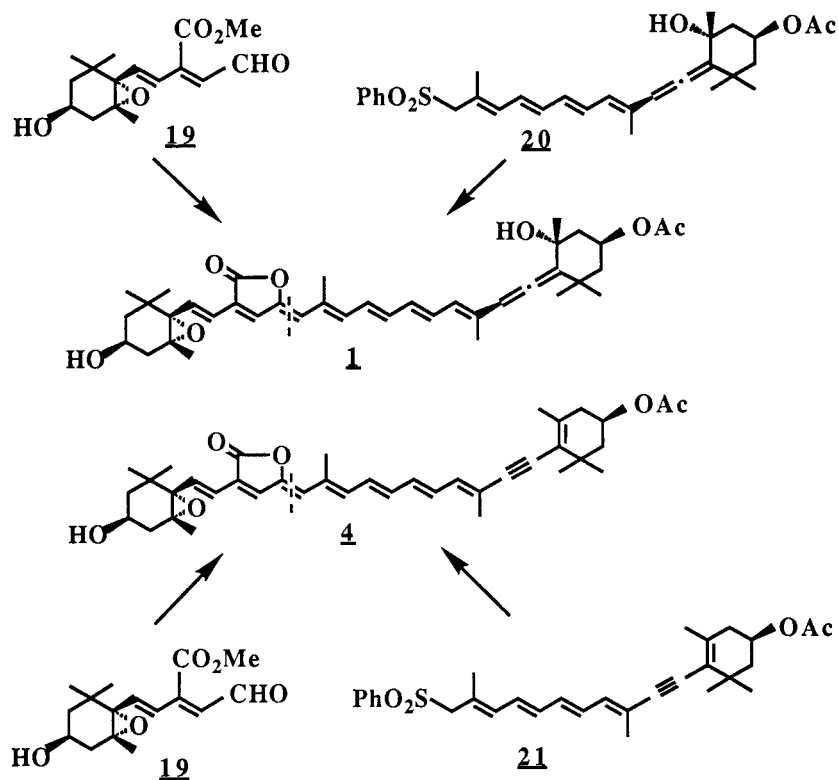
SYNTHESIS OF C$_{15}$-EPOXY FORMYL ESTER

The t-butyl-dimethylsilyl(TBDMS) ether (23) of 4-hydroxy-2,2,6-trimethylcyclohexanone (22)
(ref. 13) was converted into the enol triflate (24) in 89% yield by the reaction with
N-phenyltrifluoromethanesulphonimide(Tf$_2$NPh)(ref. 14) in the presence of LDA (Scheme 5).
A coupling reaction (ref. 15) of the triflate (24) with methyl acrylate, in the presence of
a palladium (II) catalyst, afforded in 93% yield the diene-ester (25) which was reduced with
lithium aluminium hydride (LAH) and acetylated to give the allylic acetate (26, 80%). The
allylic sulphone (27) was prepared in high yield by the reaction with sodium sulphinate
catalysed by Pd(PPh$_3$)$_4$ (ref. 16). Functionalisation (introduction of carbomethoxyl and al-
lyl groups) of the sulphone (27) and deprotection gave the compound (28) which was oxidised
regioselectively at the terminal vinyl group and the sulphone group eliminated to afford a
mixture of the formyl ester isomers (29, 21%) and (30, 17%), which were each obtained pure
by preparative h.p.l.c.. Iodine-catalysed isomerisation of the isomer (29) provided a mix-
ture (3:4) of 29 and 30. Epoxidation of compound (30) with m-chloroperbenzoic acid (MCPBA)
gave a mixture of the cis(β)-epoxide (31, 56%) and trans(α)-epoxide (32, 19%). The stereo-
structures of both isomers were confirmed by ^{1}H NMR data (ref. 11).

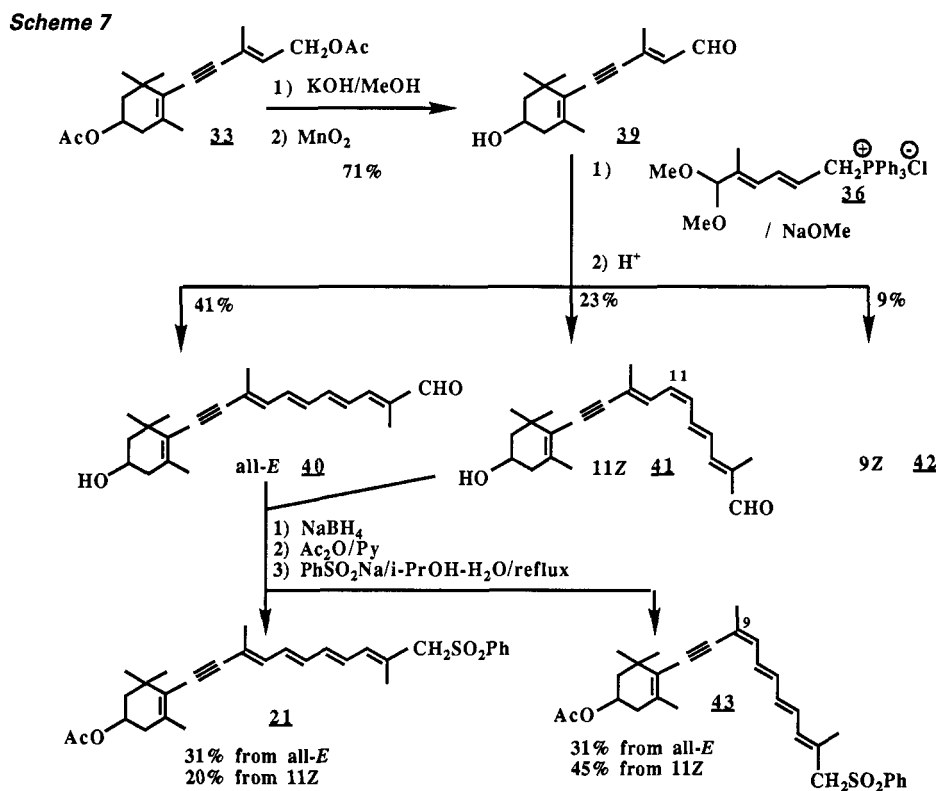**Scheme 5**
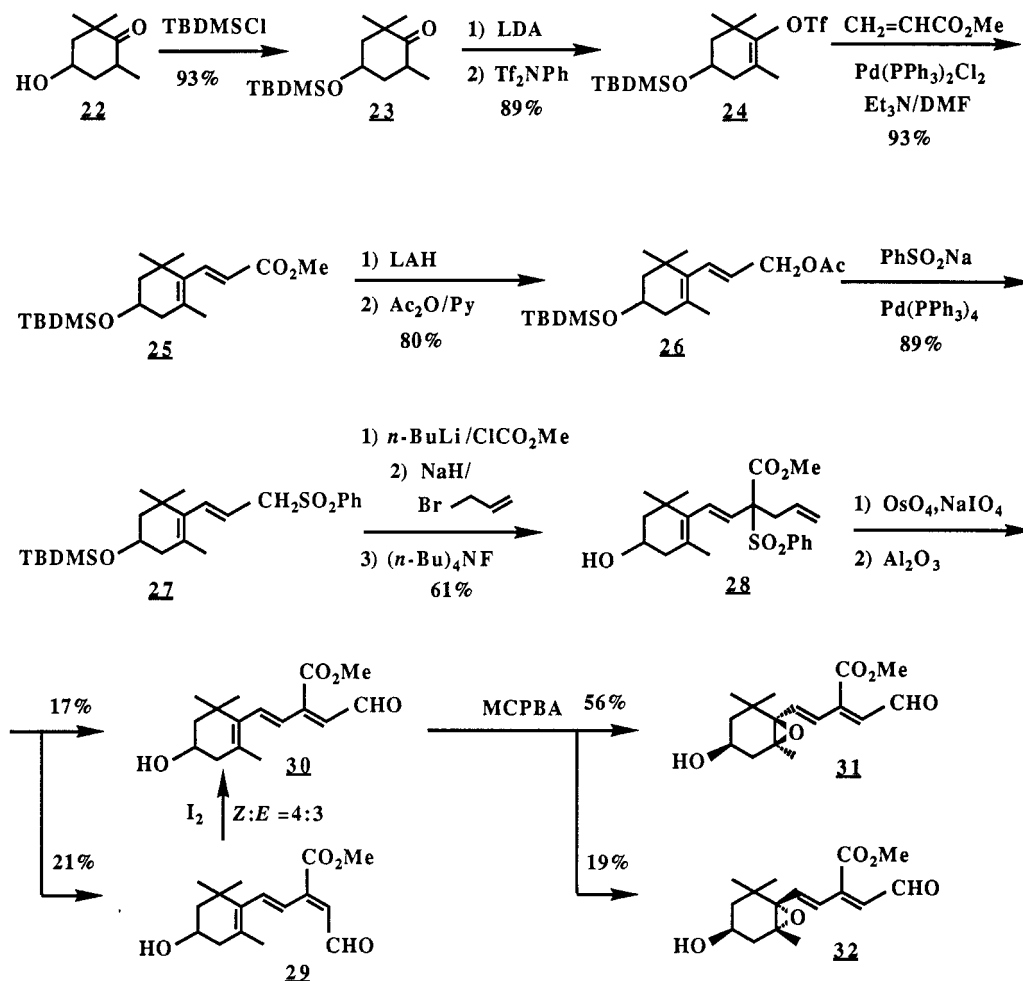
SYNTHESIS OF C$_{22}$-ALLENIC AND C$_{22}$-ACETYLENIC SULPHONES

The known C$_{15}$-acetylenic diacetate (33, ref. 17) was transformed through the epoxide (34,
ref. 13) to the allenic aldehyde (35, ref. 18) which possesses the required three chiral
centres in the C$_{22}$-allenic component (Scheme 6). Wittig condensation of the C$_{15}$-allenic
aldehyde (35) with the C$_7$-phosphonium salt (36) and deprotection of the product gave a mix-
ture of two C$_{22}$-allenic aldehydes (37) and (38) which were cleanly separated by preparative
h.p.l.c. in the dark. Each isomer (37) or (38) was independently transformed to the (all-
E)-allenic sulphone (20) in three steps (Scheme 6). The formation of the (all-E)-sulphone
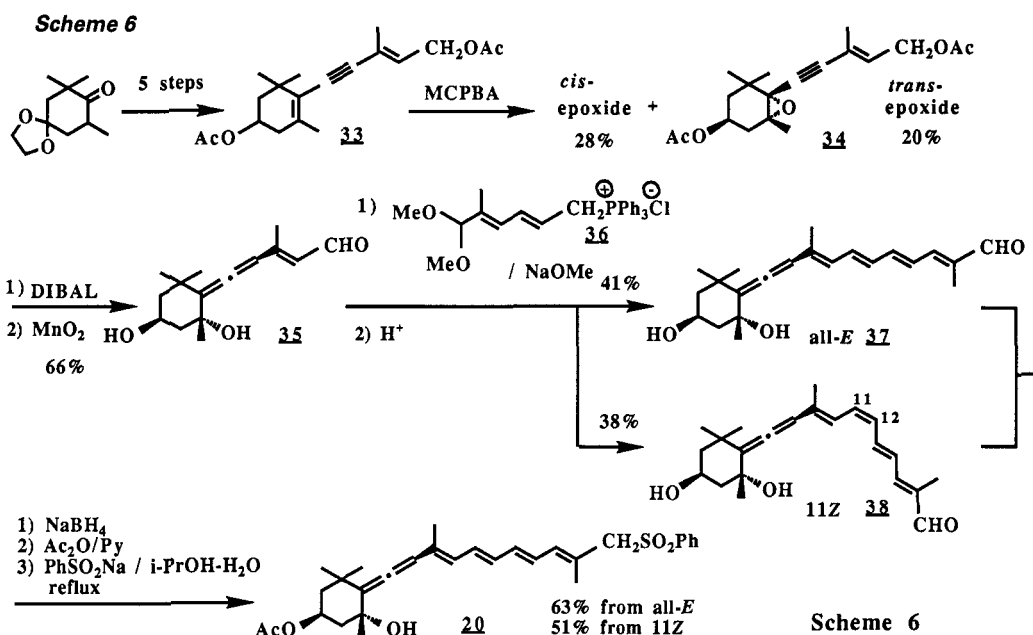
Scheme 6

Scheme 6

(20) from the (11Z)-aldehyde (38) is presumed to result from isomerisation in the refluxing conditions. The C_{22}-acetylenic component was prepared similarly as shown in Scheme 7. The C_{15}-acetylenic diacetate (33) was converted into the hydroxyaldehyde (39) which was condensed with the C_7-Wittig salt (36). After deprotection and purification by preparative h.p.l.c. this gave the (all-E)-C_{22}-aldehyde (40, 41%), the (11Z)-isomer (41, 23%), and the (9Z)-isomer (42, 9%), respectively. The (all-E)-acetylenic sulphone (21) was synthesised independently from the two aldehydes (40 and 41), but the (9Z)-isomer (43) was always produced in ca. equal or greater amount than the (all-E)-isomer (21).

Scheme 7

TOTAL SYNTHESIS OF PERIDININ AND PYRRHOXANTHIN

The trans-epoxide (32) was condensed with the (all-E)-allenic sulphone (20) in the presence of LDA at -78 °C to afford, in 9% yield, the expected products (Scheme 8); preparative h.p.l.c. in the dark gave peridinin (1) and its (11'E)-isomer in pure form in ca. equal yield. The spectral properties and h.p.l.c. behaviour of the synthetic peridinin were in good agreement with those of the natural specimen (ref. 19). Condensation between the trans-epoxide (32) and the (all-E)-acetylenic sulphone (21) in the presence of LDA at -78 °C produced a mixture (1:1) of pyrrhoxanthin (4) and its (11'E)-isomer in 13% yield; these were cleanly separated by preparative h.p.l.c. in the dark. The ^{1}H NMR data of synthetic pyrrhoxanthin were in accordance with those of natural pigment (ref. 20).

Scheme 8
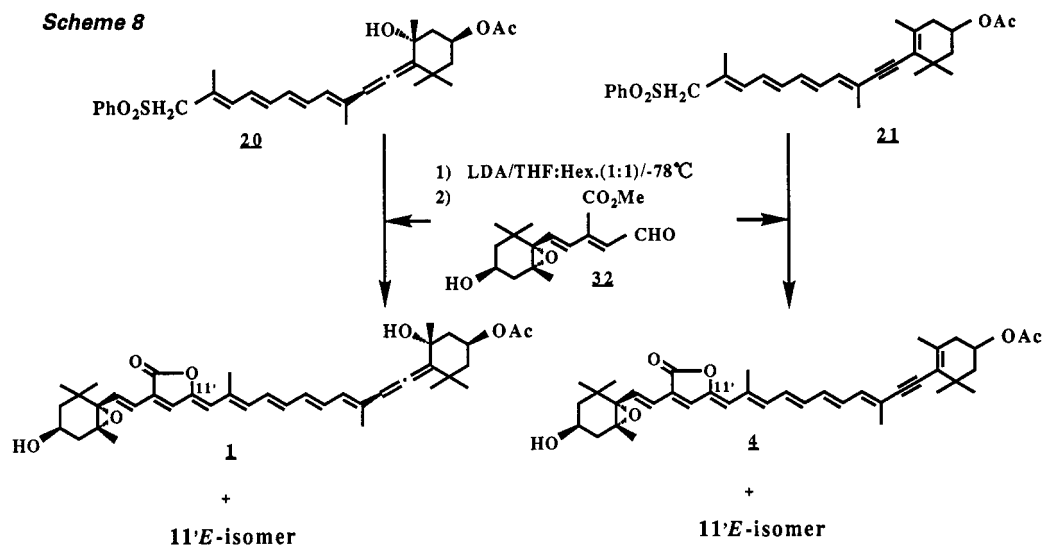
SYNTHESIS OF OPTICALLY ACTIVE PERIDININ

The synthetic peridinin was a mixture of diastereoisomers from which optically active isomers could not be isolated by h.p.l.c.. Thus, with the readily available (4R,6R)-4-hydroxy-2,2,6-trimethylcyclohexanone (44, ref. 21) as starting material, the same pathway as described in the synthesis of the racemic peridinin was used for the synthesis of the optically active form. The optically active C_{15}-epoxy formyl ester was prepared in 12 steps and the C_{22}-allenic sulphone in an optically active form was prepared in 13 steps. Condensation of the two components produced optically active peridinin (Scheme 9) whose spectral data (UV-VIS, IR, NMR, and MS) were identical with those of the natural specimen. In addition, its circular dichroism (CD) spectrum (Fig. 1) was nearly superimposable on that reported by the Jensen group (ref. 6). This is the first total synthesis of optically active peridinin.
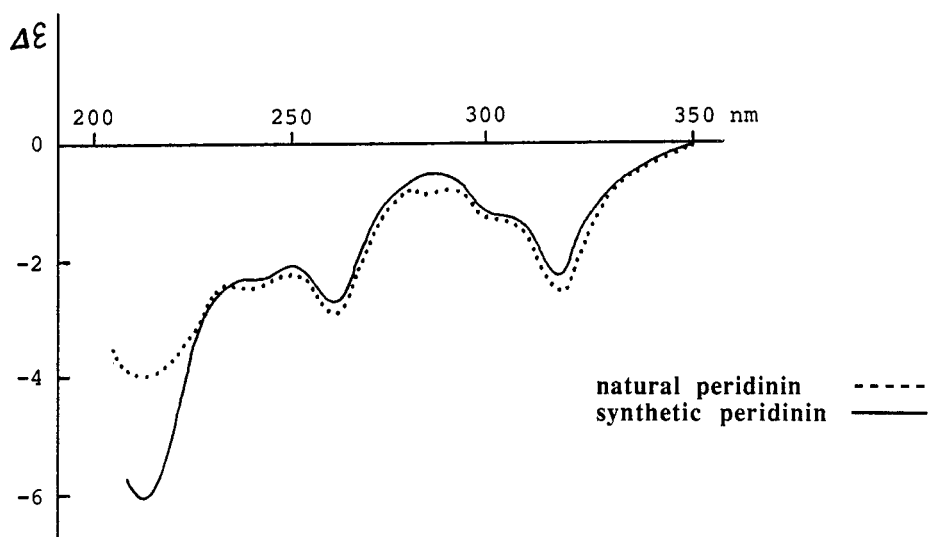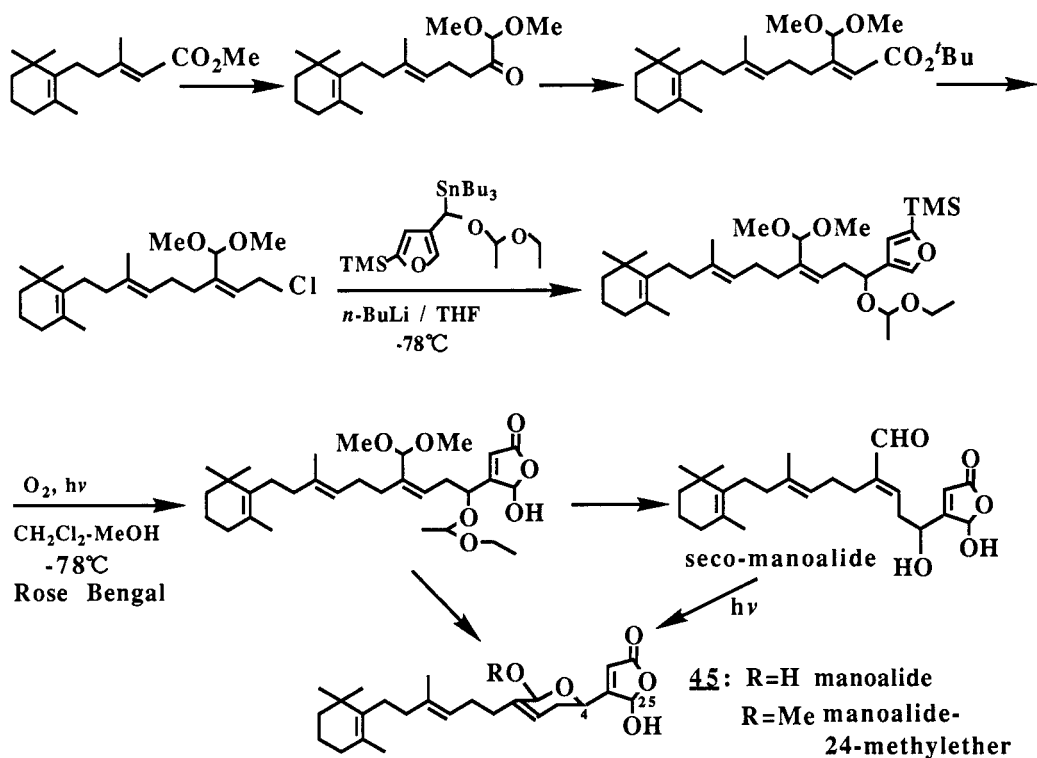
Scheme 9
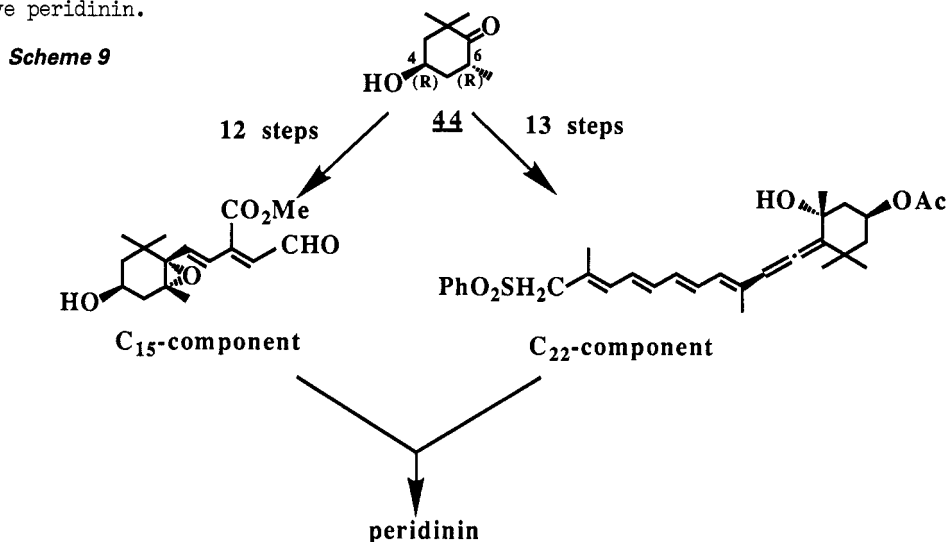
Fig. 1. CD spectra of natural peridinin and
   optically active synthetic peridinin (in EPA solution)

SYNTHESIS OF BUTENOLIDE RETINOIDS

The most attractive compound among the recently described retinoidal butenolides is
manoalide (45, ref. 22) which inhibits phospholipase A_2 and possesses topical anti-
inflammatory activity. Manoalide contains a β-substituted γ-hydroxybutenolide moiety whose
efficient synthesis was described recently by Isoe et al.(ref. 23). This provides a general
synthetic method for γ-hydroxybutenolides with various substituents, and employs photosen-
sitized oxygenation of substituted α-trimethylsilylfuran, and chemoselective oxidation of a
furan ring possessing tri- and tetra-substituted olefins in the side chain. This method
was applied to the total synthesis of manoalide (45) which was achieved by two groups
(refs. 24,25), by the approaches shown in Schemes 10 and 11.

Scheme 10

Scheme 11
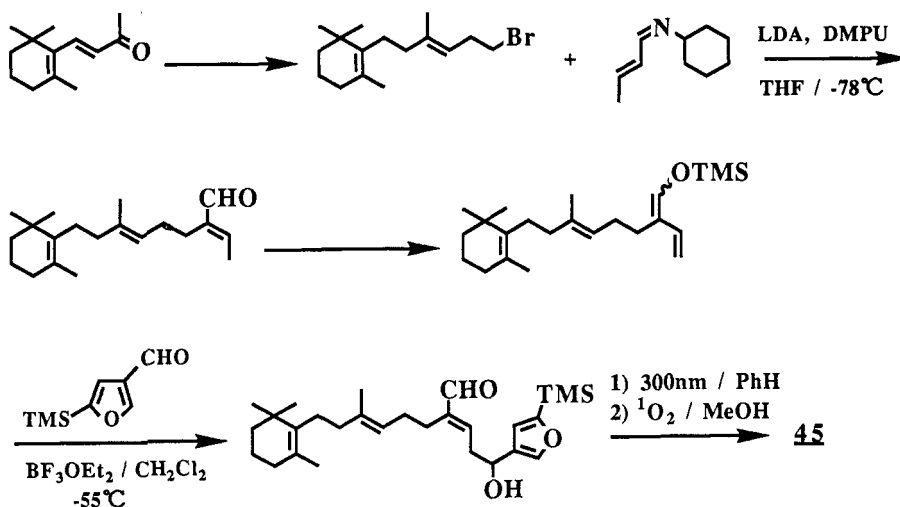
The precursor (46) of the retinoidal acid anhydride (8) possesses a γ-hydroxybutenolide moiety with a conjugated substituent at the β-position. Cytotoxic activity of the retinoidal butenolide (46) on mouse neuro cancer cells has been examined. Compound (46) was found to be about 90 times more potent than retinoic acid (refs. 26,27). In addition, 46 and related compounds (47) showed anti-ulcer activity against ulcer models induced by HCl-ethanol, though compound (12) exhibited no activity (ref. 28).

Acknowledgements

REFERENCES

1. H. Pfander, Key to Carotenoids, 2nd Ed., Birkhäuser, Basel, 1987.
2. F. Schütt, Ber. Deut. Bot. Ges., 8, 9-32 (1890).
3. 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., 93, 1823-1825 (1971).
4. H.H. Strain, W.A. Svec, P. Wegfahrt, H. Rapoport, F.T. Haxo, S. Norgård, H. Kjøsen and S. Liaaen-Jensen, Acta Chem. Scand., B, 30, 109-120 (1976).
5. J.E. Johansen, S. Liaaen-Jensen and G. Borch, in Marine Natural Products Chemistry, (D.J. Faulkner and W.H. Fenical eds.), Plenum Press, pp. 225-237 (1977).
6. J.E. Johansen, G. Borch and S. Liaaen-Jensen, Phytochemistry, 19, 441-444 (1980).
7. P. Foss, R.R.L. Guillard and S. Liaaen-Jensen, Phytochemistry, 25, 119-124 (1986).
8. M. Ito, T. Iwata and K. Tsukida, Heterocycle, 19, 1385-1389 (1982).
9. M. Ito, T. Iwata and K. Tsukida, Chem. Pharm. Bull., 32, 1709-1716 (1984).
10. M. Ito, Y. Hirata, Y. Shibata, A. Sato and K. Tsukida, J. Nutr. Sci. Vitaminol., 33, 313-318 (1987).
11. M. Ito, Y. Hirata, Y. Shibata and K. Tsukida, J. Chem. Soc., Perkin Trans. I, 197-199 (1990).
12. M. Ito, in Chemistry and Biology of Synthetic Retinoids, (M.I. Dawson and W.H. Okamura eds.), CRC Press, pp. 77-97 (1990).
13. E. Widmer, Pure Appl. Chem., 57, 741-752 (1985).
14. J.E. McMurry and W.J. Scott, Tetrahedron Lett., 24, 979-982 (1983).

15. W.J. Scott, M.R. Peña, K. Swärd, S.J. Stoessel and J.K. Stille, <u>J. Org. Chem.</u>, <u>50</u>, 2302-2308 (1985).
16. K. Inomata, T. Yamamoto and H. Kotake, <u>Chemistry Lett.</u>, <u>1981</u>, 1357-1360.
17. A.J. Davies, A. Khare, A.K. Mallams, R.A. Massy-Westropp, G.P. Moss and B.C.L. Weedon, <u>J. Chem. Soc., Perkin Trans. I</u>, 2147-2157 (1984).
18. M. Ito, Y. Hirata, K. Tsukida, N. Tanaka, K. Hamada, R. Hino and T. Fujiwara, <u>Chem. Pharm. Bull.</u>, <u>36</u>, 3328-3340 (1988).
19. This was kindly supplied by Dr. Y. Tanaka, Kagoshima University, Japan.
20. ^{1}H NMR data of natural pyrrhoxanthin were kindly provided by Prof. S. Liaaen-Jensen, The Norwegian Institute of Technology, University of Trondheim, Norway.
21. H.G.W. Leuenberger, W. Boguth, E. Widmer and R. Zell, <u>Helv. Chim. Acta</u>, <u>59</u>, 1832-1849 (1976).
22. E.D. de Silva and P.J. Scheuer, <u>Tetrahedron Lett.</u>, <u>21</u>, 1611-1614 (1980).
23. S. Katsumura, K. Hori, S. Fujiwara and S. Isoe, <u>Tetrahedron Lett.</u>, <u>26</u>, 4625-4628 (1985).
24. S. Katsumura, S. Fujiwara and S. Isoe, <u>Tetrahedron Lett.</u>, <u>26</u>, 5827-5830 (1985).
25. M.E. Garst, E.A. Tallman, J.N. Bonfiglio, D. Harcourt, E.B. Ljungwe and A. Tran, <u>Tetrahedron Lett.</u>, <u>27</u>, 4533-4536 (1986).
26. H. Higashida, N. Miki, M. Ito, T. Iwata and K. Tsukida, <u>Int. J. Cancer</u>, <u>33</u>, 677-681 (1984).
27. M. Ito, T. Iwata and K. Tsukida, <u>Chem. Pharm. Bull.</u>, <u>34</u>, 4346-4351 (1986).
28. M. Ito, to be published.