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METHODOLOGY FOR THE POLYENE AND RELATED ANTIBIOTICS—VERSATILE AND PRACTICAL ACCESS TO BIFUNCTIONAL ALL-TRANS POLYOLEFINIC SYSTEMS

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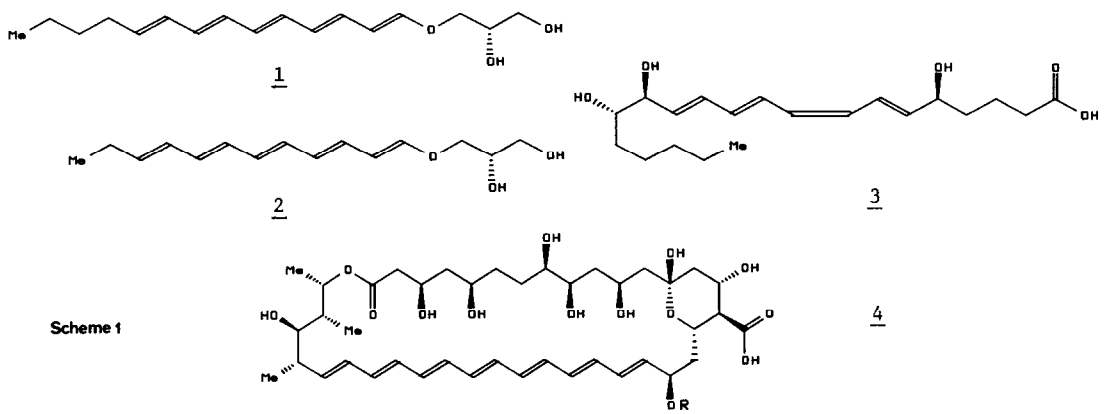
Abstract - A method is described to assemble all-trans bifunctional polyolefinic chains based on the reaction of aldehydes with a trienic phosphorane developed by Vedejs and coworkers.

Polyolefinic units of different geometric configurations and lengths are found in a number of biologically relevant molecules.[1] In several instances, the polyene system may be the dominant feature of the molecule, while in others it may be part of a more complex polyfunctional structure. The potent mutagens, fecapentaenes 1 and 2[2,3], the biologically relevant eicosanoid, lipoxin B 3[4], and the fungicidal antibiotic amphotericin B[5,6] 4 are four representative compounds of naturally occurring polyenes, that encompass such features (Scheme 1). Although much effort has been devoted to the synthesis of polyenes over the years, problems concerned with stereoselectivity, stability, accessibility to geometrically

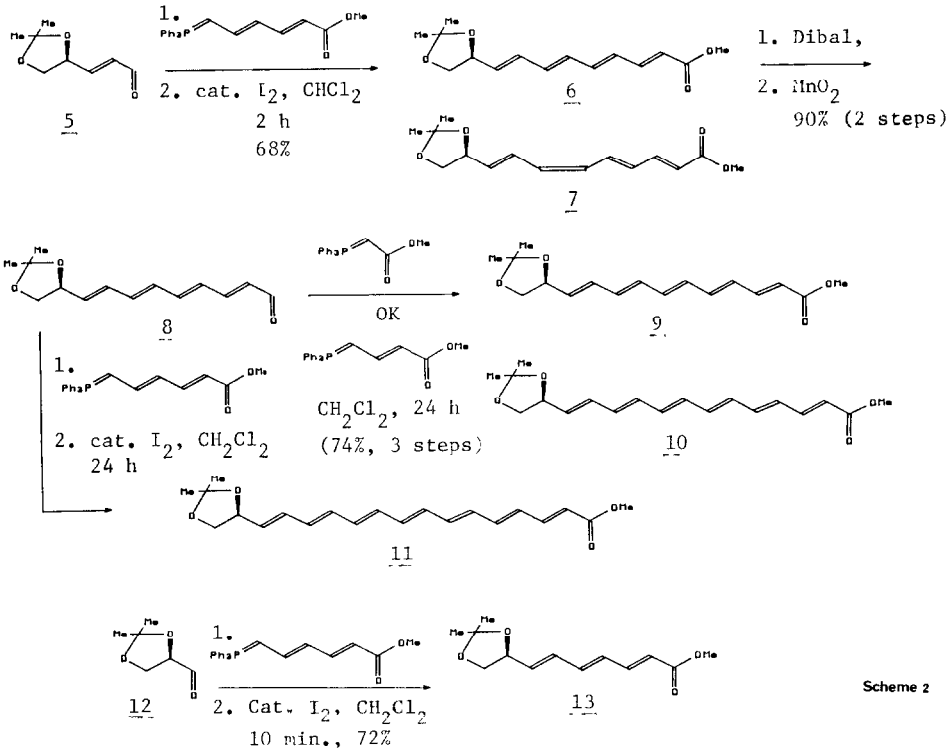


Scheme 1

uniform long chain units, and incorporating diverse functionality have fostered a number of recent studies in this area.[6,7] Nevertheless, improved methodology is much in demand.

We report a versatile and practical approach to the synthesis of bifunctional all-trans polyenes of varying lengths. Moreover, these compounds contain different functional groups at both ends which would allow their chemical manipulation individually. The method consists in an adaptation of a Wittig reagent developed by Vedejs and Bershas[8] for trienic esters.[9] This seldom used method provides an excellent source of a five-carbon trienic unit which is admirably suited for the synthesis of higher polyenes in a single-stage or reiterative process as demonstrated in this paper.

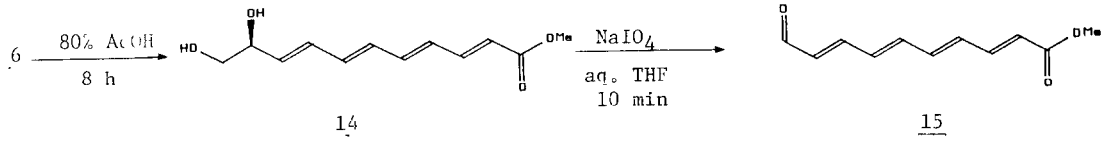
Scheme 2 illustrates easy access to a number of bifunctional polyenes that can be obtained by reaction of the readily available enal 5[10] with the Vedejs reagent. The 1:1.75 mixture of tetraenes 6 and 7, mp 63-65°, $[\alpha]_D$-16° (c 0.8, $CHCl_3$) can be quantitatively converted to the all-trans tetraene 6, m.p. 79-80°; $[\alpha]_D$ + 7.9° (c, 1.4, $CHCl_3$) with a catalytic quantity of iodine in dichloromethane.[11] It should be noted that the addition of 10% 2,6-di-t-butylphenol as a radical scavenger (and a proton source) gave consistently cleaner reactions. Compound 7 which can be considered as a versatile synthetic precursor to lipoxin B could be easily distinguished from the all-trans isomer by HPLC. It was found to isomerize only slowly in ethyl acetate-hexanes (~10% in 48h at 25°). Mixtures of 6 and 7 could be chromatographed over silica gel in the same solvent system without noticeable isomerization. Treatment of 6 with Dibal-H followed by MnO_2 oxidation afforded the aldehyde 8, mp 108-109°; $[\alpha]_D$ +22.2° (c 0.75, $CHCl_3$). Wittig olefination with the appropriate reagent gave the corresponding pentaene 9, m.p. 93-95°, $[\alpha]_D$ + 6.4° (c, 0.5 $CHCl_3$), hexaene 10, $[\alpha]_D$ +3.8° (c 0.5, $CHCl_3$), and heptaene 11, m.p. 166-68°, $[\alpha]_D$ +11 (c 1.63 $CHCl_3$) esters in over 74% in each case.[12]



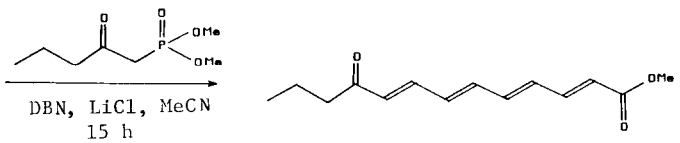
Scheme 2

Reaction of 2,3-O-isopropylidene-D-glyceraldehyde 12[13] with the Vedejs reagent gave initially a 1:1.8 mixture of E and Z olefins $[\alpha]_D$ - 46° (c 1.1, $CHCl_3$). Treatment with iodine afforded the all-trans bifunctional triene ester 13, $[\alpha]_D$ + 12.3° (c 1.6, $CHCl_3$).

Aldehydes 5 and 12 were chosen as substrates in order to have access to chiral polyenic diol esters in which either extremity of the chain could be independently modified. The versatility and chemical compatibility of these bifunctional polyenes can be demonstrated by effecting transformations at the diol end (Scheme 3). Thus, acid hydrolysis of 6 gave the



Scheme 3



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crystalline diol 14, m.p. 89-90°; $[\alpha]_D$ -33.3° (c 0.95, $CHCl_3$), which was oxidatively cleaved to the crystalline aldehyde 15, m.p. 167-169°, in high overall yield. Treatment of 15 with a model phosphonate reagent[14] gave the polyene keto ester 16, m.p. 151-153°. It is of interest that the trans-polyenes described herein were stable for prolonged periods of time particularly if kept below -20°C (n.m.r. monitoring).[15]

The adaptation of the Vedejs reagent[8] to the synthesis of bifunctional tri-, tetra, penta, hexa, and heptaenes as demonstrated in this paper, offers the merits of simplicity of operation, flexibility, and functional maneuvrability. A number of difficulties encountered in polyene synthesis[6] can be effectively addressed and reliably circumvented by adopting this methodology. It is also evident that by virtue of the bifunctional nature of our polyenes, a number of synthetic applications that are particularly directed towards challenging targets such as 1-4 can be readily envisaged.

Synthesis of the tetraene 6: Allyltriphenylphosphonium bromide (0.19 g, 0.5 mmole) in dry THF (10 ml) was treated with a solution of LDA [from 0.08 ml, (0.5 mmol) of diisopropylamine and 0.4 ml of 1.23 N n-butyl lithium in hexanes, 0°]. After 30 min. at room temperature, trans-methyl 3-chloroacrylate (0.06 g, 0.5 mmole) in 1 ml THF was added. The mixture was allowed to stir for 2 h after which the aldehyde 5 (0.156 g., 1 mmole) was added, immediately followed by the addition of 2,6-di-t-butylphenol (15 mg). After being stirred for 1h, the mixture was diluted with satd. aq. ammonium chloride, then with ether, and the organic layer was processed as usual. The resulting product was chromatographed (flash column, silica gel, EtOAc-hexane, 1:9) to give the polyenes 6 and 7 (1:1.75 ratio, HPLC) (0.09 g, 67%, based on the acrylate), m.p. 63-65°; $[\alpha]_D$ - 16° (c 0.8, $CHCl_3$). The mixture (60 mg) in 4 ml dichloromethane was treated with 100 µl of a 2.5 mmolar solution of iodine in the same solvent (2 h, HPLC monitoring). Dilution with ether, washing successively with sodium thiosulfate, water and usual processing of the organic phase gave the crystalline E-polyene 6 (60 mg, quant.), mp 79-80°; $[\alpha]_D$ +7.9° (c. 1.4, $CHCl_3$)

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9. The original method called for the use of excess aldehyde as a reactant and a quenching substrate (benzaldehyde, 2-propanal were used).

10. Obtained by treatment of 2,3-O-isopropylidene-D-glyceraldehyde (see ref. 13) with formylmethylene triphenylphosphorane (Aldrich); CH_2Cl_2, 48h, 80%; $[\alpha]_D$ +27.4° (c 1.5, $CHCl_3$). See also T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham and F.J. Walker, J. Org. Chem., 47, 1373 (1982).

11. The identity of the polyenes was rigorously established by ^1H NMR studies at 400 MHz (decoupling) and other spectroscopic means. Purity was checked by HPLC and MS. Polyenes containing four double bonds or more ranged in color from pale yellow to light orange. Their color darkened with time although the ^1H n.m.r. spectra remained essentially unchanged.

12. The initial reaction mixture in the case of the heptaene 11 consisted of a 1:1.4 ratio of E and Z olefins respectively which was quantitatively transformed into the E isomer (contaminated with ~15% of the Z isomer) by treatment with cat. iodine (24 h, CH_2Cl_2). Polyenes 9 and 10 consisted of all-trans products directly after the Wittig reactions.

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15. Samples of 15 remain practically unchanged after 2 months at 0°, or at room temperature

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