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Dienolether condensations—a powerful tool in carotenoid synthesis*

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Abstract: The catalytic dienolether condensation reactions, discovered by Nazarov and Makin in 1958, are of special interest in the carotenoid field for chain extension by five carbon atoms. In this paper, new developments in the synthesis of apoesters and apocarotenals using vinyl ketene acetals and dienolethers, respectively, as C_5-building blocks are discussed. New 'Wittig-free' routes to astaxanthin and canthaxanthin applying these Lewis acid-catalysed dienolether condensation reactions are described.

INTRODUCTION

The coupling of alkyl enolethers with acetals to give 3-alkoxyacetals, promoted by Lewis acids, was discovered in 1939 [1] and later found widespread application as an alternative to the aldol condensation. It has found use in the large-scale production of 8′-apo-β-caroten-8′-al [2] and β,β-carotene [3]. The reaction is not restricted to C_2- or C_3-enolethers as building units. 1-Alkoxydienes were also introduced as coupling reagents for chain extension by four or five carbon atoms in 1958 (Fig. 1) [4,5].

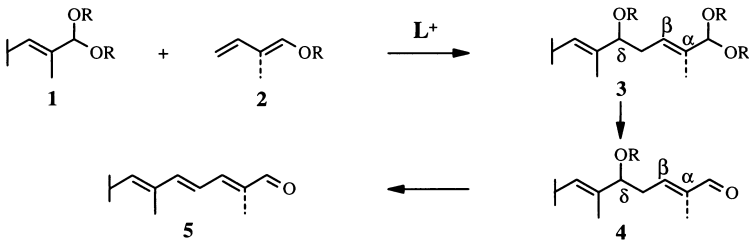

Fig. 1 Reaction of α,β-unsaturated acetals **1** with dienolethers **2**.

The reaction is described as a Lewis acid-promoted addition of a dienolether **2** to an α,β-unsaturated acetal **1** to yield an intermediary δ-alkoxy-α,β-unsaturated acetal **3** which subsequently, if required, is converted via a δ-alkoxy-α,β-unsaturated aldehyde **4** into the C_5 (or C_4)-elongated aldehyde **5**. The acetal group, in contrast to its customary role as a protective group, functions here as an activated form of the carbonyl group. The Lewis acids generally used as promoters are BF_3-etherate, $ZnCl_2$, $FeCl_3$ and others. (For a general review and a detailed discussion of the reaction mechanism, see [6].)

This reaction seemed to us a very attractive method to construct carbon–carbon double bonds, as it requires only inexpensive reagents in catalytic amounts and produces no environmentally undesirable or hazardous waste products. However, the reaction of acetal **1** with dienolether **2** yields an α,β-unsaturated acetal **3** which reacts in competition with the starting acetal **1** with an additional enolether molecule to form a C_5 (or C_4)-elongated acetal. This side reaction (telomer formation) is a severe problem and yields mixtures of acetals which are difficult to separate [4,5,7]. Despite these discouraging facts, we tried to

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utilize these dienolether condensation reactions in elongations of apoaldehydes by suitable C_5-units yielding apoester and apocarotenal homologues.

APOESTERS

Ethyl-8′-apo-β-carotenoate (**9**), produced on a commercial scale, is used for egg yolk and broiler pigmentation [8]. It is synthesized via Horner–Emmons olefination [9], Wittig reaction [10] or sulfone coupling [11] of suitable precursors. In these syntheses, stoichiometric amounts of triphenyl phosphine, triethyl phosphite or sodium benzenesulfinate (or a derivative of it) are required. On a large scale, these auxiliaries have to be recycled for economical and ecological reasons. We were interested to perform such C_5-elongations by a Lewis acid-catalysed reaction of an apocarotenal dialkyl acetal (e.g. 12′-apo-β-carotenal dimethylacetal (**7**)) with vinyl ketene acetal **11** or **15**. From the work of Fleming *et al*. [12], it is known that compound **11** reacts with electrophiles, such as chloromethyl phenyl sulfide or trimethyl orthoformate, in the presence of a Lewis acid catalyst (e.g. $ZnCl_2$). But, reaction occurs not only at the γ-position of the diene **11**, but also at the α-position (ratio γ:α = 1:1–4:1, depending on the electrophile) leading to branched products, which cannot be used for polyene syntheses.

Despite this bad omen, we tried to react 12′-apo-β-carotenal dimethylacetal (**7**) with the silylated vinyl ketene acetal **11** (Fig. 2).

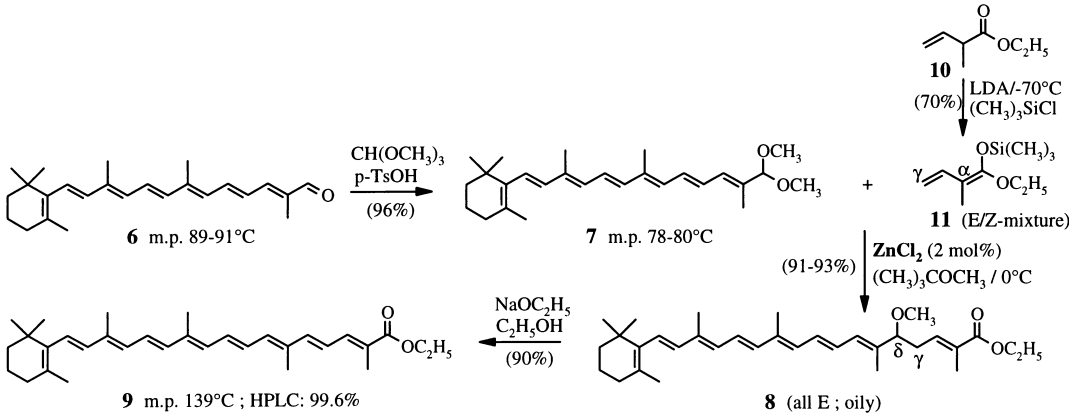


Fig. 2 Synthesis of ethyl-8′-apo-β-carotenoate (**9**).

The crystalline dimethylacetal **7** (m.p. 78–80 °C), which we prepared from 12′-apo-β-carotenal (**6**) [13] by reaction with trimethyl orthoformate in the presence of a catalytic amount of *p*-TsOH (yield up to 96%), reacted with silylated vinyl ketene acetal **11** [12] in *tert*-butyl methyl ether at 0 °C. By using $ZnCl_2$ (2 mol.%) as catalyst, the coupling product **8** (γ-addition!) could be isolated in 91–93% yield, based on the acetal **7**. To our surprise, no traces of a (branched) α-addition product could be detected by high performance liquid chromatography (HPLC) or proton nuclear magnetic resonance (^{1}H-NMR) analysis. The elimination of methanol was effected with a catalytic amount of a mineral acid or with a strong base. The method of choice was treatment of a solution of δ-methoxy ester **8** in ethanol with 2 equivalents of sodium ethylate at 40 °C. Ethyl-8′-apo-β-carotenoate (**9**) thus crystallized directly from the reaction mixture and was isolated in approximately 90% yield. In a through process **7** → **9** (without purification of intermediate **8**), C_{30}-apoester **9** was isolated in a yield of 80% (based on **7**); HPLC purity: 99.6% (wt.%).

As compound **11** is not easily available (on a technical scale) from ester **10** (use of LDA at −70 °C), and as we wanted to displace all heteroatoms other than oxygen in our reactions (including S, P and Si), we tried to prepare the corresponding dimethyl vinyl ketene acetal **15** (Fig. 3). As cheap and readily available starting material, we employed 2-methyl-3-butene nitrile (**12**), a by-product in the adiponitrile synthesis (nylon industry). Reaction of **12** with one equivalent of methanol in the presence of HCl (g) gave crystalline iminoester salt **13**, which was reacted with excess methanol in a two-phase system methanol/pentane at room temperature to give orthoester **14**. Successful elimination of methanol was effected with a strong base such as sodium amide in liquid ammonia to yield the desired pure vinyl

dimethyl ketene acetal **15** as a colourless, distillable liquid. Successful reaction of ketene acetal **15** with the acetal **7** was achieved using a strong Lewis acid, such as $BF_3O(C_2H_5)_2$ or $Fe(III)Cl_3$. Then the coupling product **16** was obtained in high yield.

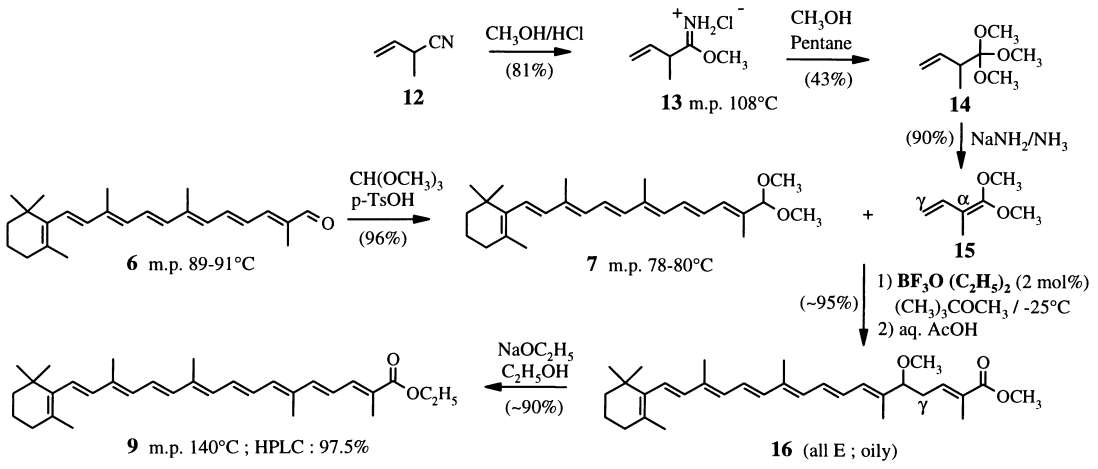


Fig. 3 Synthesis of ethyl-8′-apo-β-carotenoate (**9**).

Also here only γ-addition was always observed. The elimination of methanol in the next step was performed as usual with sodium ethylate in ethanol. Then, at the same time, a transesterification of the methylester **16** to ethyl apoester **9** occurs. The yield of **9** (86%; HPLC: 97.5%, wt.%) based on the starting acetal **7** is slightly higher in this sequence than in the process described in Fig. 2. By this general method, other apoesters, such as neurosporaxanthin-, torularhodin- or crocetin-esters, were synthesized.

APOALDEHYDES

8′-Apo-β-carotenal (**21**) is produced industrially for food colouring [14]. It can be synthesized by Wittig [10], sulfone [11] or enolether [2] technology.

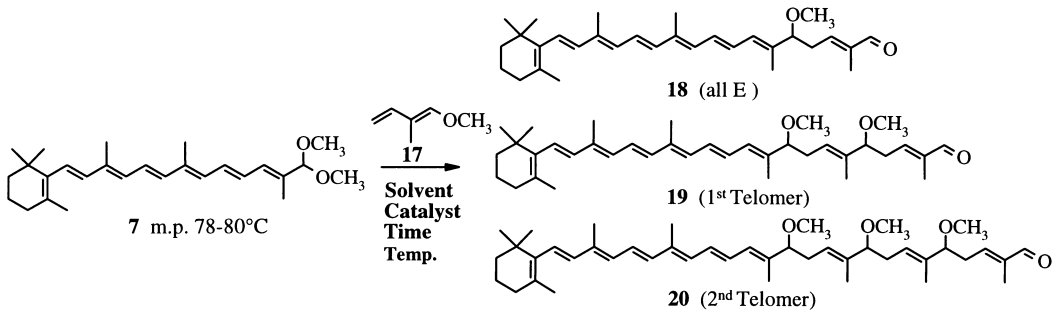
We intended to prepare apoaldehydes following a similar scheme to that illustrated in Fig. 3 for apoesters. In contrast to the synthesis of unsaturated esters with vinyl ketene acetals which is new, the reaction of C_5-dienolethers with simple α,β-unsaturated acetals is known. But, it is also known that this is a very bad reaction [4,5,7]. The formation of considerable amounts of telomers in this reaction could be a serious obstacle for us, as discussed in the introduction. However, apocarotenal acetals (e.g. compound **7**), which we would use in our investigation as substrates, are more reactive than simple α,β-unsaturated acetals, which Nazarov and Krasnaia [4] and others [5,7] have used in their studies. In addition, they have tested only $ZnCl_2$ as catalyst in ethylacetate as solvent. Therefore, we were optimistic of finding improved reaction conditions which would allow us to suppress the undesired telomer formation.

In our optimization study, 12′-apo-β-carotenal dimethylacetal (**7**) was reacted with methoxy isoprene **17** in the presence of various catalysts in several solvents (Fig. 4). The product mixture (**18**, **19** and **20**) was then isolated by a short flash chromatography and analysed by HPLC.

Methoxy isoprene **17** was synthesized from acetaldehyde dimethylacetal (**22**) and propenyl methylether (**23**). In an enolether condensation reaction catalysed by $BF_3O(C_2H_5)_2$, the intermediate 2-methyl-3-methoxy-butanal dimethylacetal (**24**) was prepared. A subsequent double elimination of methanol on aluminum silicate at 300 °C yielded the desired 1-methoxy-2-methyl-1,3-butadiene (**17**) (= methoxy isoprene).

Some of our optimization experiments in the condensation reaction are listed in Fig. 4.

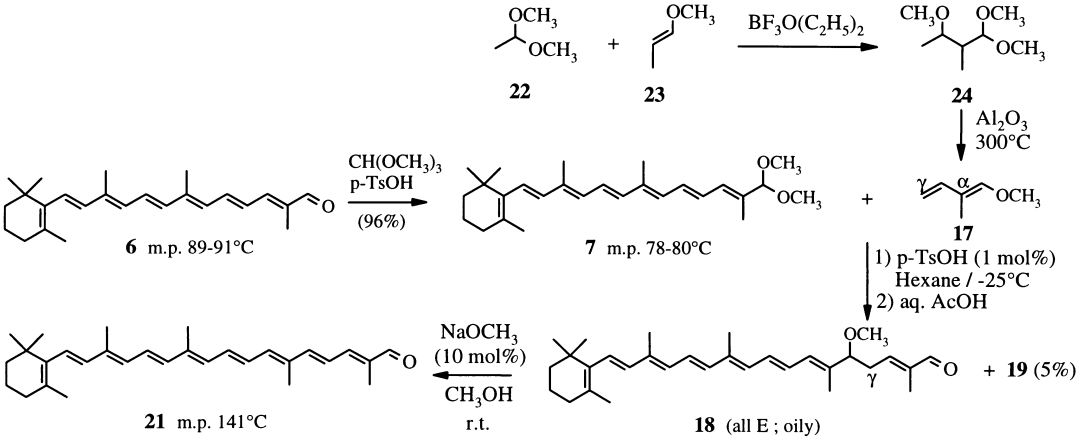
The reaction is strongly dependent on the catalyst and the solvent used. Lewis acids, such as $ZnCl_2$, $ZnBr_2$, $BF_3O(C_2H_5)_2$, in ethylacetate, ether or hexane gave considerable amounts (up to 10%) of the first telomer **19** (Fig. 4, entries 1–4). Better results were obtained with Brönsted acids, such as *p*-TsOH, H_2SO_4 (conc.) or CH_3SO_3H, in hexane (Fig. 4, entries 5–9).



No.	Solvent	Catalyst (mol %)	Time (h)	Temp. (°C)	Chem. yield (corr. HPLC)*1)			Remarks
					18	19	20	
1	AcOEt	$ZnCl_2$ (10%)	20	+25	70%	10%	1%	**18** (isolated) : 51%
2	AcOEt	$BF_3O(C_2H_5)_2$ (2%)	2	-25	78%	11%	1%	
3	Ether	$BF_3O(C_2H_5)_2$ (3%)	3	-25	82%	8%	---	
4	Hexane	$BF_3O(C_2H_5)_2$ (2%)	2	-25	88%	10%	1%	
5	AcOEt	p-TsOH (3%)	3	-25	82%	1%	---	
6	Ether	p-TsOH (3%)	3	-25	71%	1%	---	
7	Hexane	p-TsOH (4%)	2.5	-25	95%	5%	---	**18** (isolated) : 86%
8	Hexane	H_2SO_4 (4%)	1	-25	86%	2%	---	
9	Hexane	CH_3SO_3H (4%)	3	-25	94%	2%	---	

Fig. 4 Optimization of the reaction of 12′-apo-β-carotenal dimethylacetal (**7**) with methoxy isoprene **17**.

In a preparative run, 12′-apo-β-carotenal dimethylacetal (**7**) was caused to react with 2.5 equivalents of methoxy isoprene **17** in the presence of *p*-TsOH (1 mol%) in hexane at −25 °C/2 h (Fig. 5). After hydrolysis with aqueous acetic acid and work-up, crude δ-methoxy-α,β-unsaturated aldehyde **18** was isolated as an orange oil.



Yield of **21** : **81%** based on **7** ; HPLC-content : 99.5% (weight-%)

Fig. 5 Synthesis of 8′-apo-β-carotenal (**21**).

According to HPLC analysis, it contained besides the aldehyde **18** approximately 5% of the first telomer **19**. A solution of this crude orange oil in methanol was treated at room temperature with 10 mol.% of sodium methylate. After a few seconds, the orange solution turned dark and, after some minutes, the aldehyde **21** began to crystallize from the reaction mixture. After filtration and recrystallization, we obtained (all *E*)-8′-apo-β-carotenal (**21**) as dark shiny crystals in 81% yield (based on **7**) with an HPLC purity of 99.5% (wt.% compared to a standard).

The absence of any trace of 4′-apo-β-carotenal (**26**) in the final product gave rise to the question of

what had happened to the small amount (5%) of telomer **19** present in the reaction mixture under the basic elimination conditions. By a twofold elimination of methanol, C_{35}-apoaldehyde **26** could have been formed. To answer this question, we reacted 12′-apo-β-carotenal dimethylacetal (**7**) with an excess of methoxy isoprene **17** in the presence of $BF_3O(C_2H_5)_2$ as catalyst (Fig. 6). Besides 25% of aldehyde **18** we were able to isolate, after silica gel chromatography, 21% of pure telomer **19** (mixture of stereoisomers). Treatment of dimethoxy aldehyde **19** with 10 mol.% sodium methylate in ethanol at room temperature furnished the mono-elimination product **25**. No trace of bis-elimination product **26** (= C_{35}-apoaldehyde) was formed at room temperature. As compound **25** is easily soluble in ethanol or methanol, it remains in our process after filtration of the main product **21** in the mother liquor. The second methoxy group of **25** can be eliminated at elevated temperature (e.g. at 60 °C); then 4′-apo-β-carotenal (**26**) is formed.

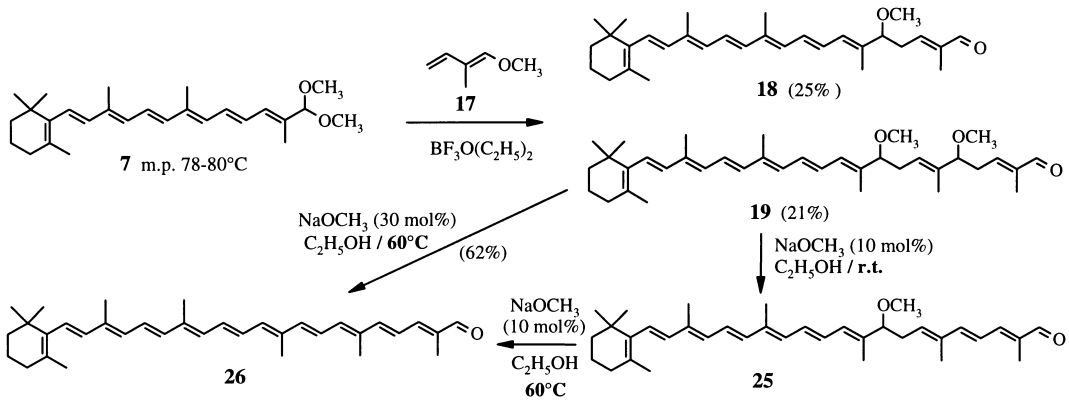


Fig. 6 Synthesis and reaction of first telomer **19**.

Other apo- and bis-apoaldehydes (e.g. neurosporaxanthinal (**26**) (= 4′-apo-β-carotenal), torularhodinaldehyde (= 3′,4′-didehydro-β,ψ-caroten-16′-al), crocetindialdehyde (**40**) (= 8,8′-diapocarotene-8,8′-dial) and 4,4′-diapo-carotene-4,4′-dial) were synthesized using the same technique.

ASTAXANTHIN

Astaxanthin (**27**) has been synthesized industrially by Roche since 1984. A key step is a Wittig reaction of 2 equivalents of a C_{15}-phosphonium salt with C_{10}-dialdehyde as central component [15]. This red pigment is used as feed additive in aquaculture (Salmonidae, Crustacea).

Our plan to synthesize astaxanthin (**27**) by a dienolether condensation strategy is illustrated in Fig. 7. The synthesis is based on a $C_{10} + C_{20} + C_{10} = C_{40}$ scheme. A double condensation of a specifically substituted dienolether **30** with crocetindialdehyde dialkylacetal (e.g. **29**) as central C_{20}-component could give intermediate **28** comprising already the end group functionality of astaxanthin in protected form.

Hydrolysis with a mineral acid should liberate the free α-hydroxy keto group and, perhaps, methanol will be eliminated under these conditions to yield directly astaxanthin (**27**).

Our first attempts to condense dienolether **31** (2.5 equivalents) with crocetindialdehyde dimethylacetal **29** in the presence of a Lewis acid (e.g. $ZnBr_2$) were not very successful (Fig. 8). However, at least we showed that the idea works and isolated after work-up and chromatography on silica gel the expected (hydrolysed) coupling product **32** as yellow crystals (m.p. 171 °C) in up to 30% yield. On the other hand, it was not possible to improve the poor yield of this reaction using other catalysts and solvents.

After a careful consideration of the mechanism of this reaction, we came to the following conclusion. In the first step of this condensation, an alkoxy (methoxy) group is removed from the acetal **29** by the Lewis acid to generate a carbenium ion which then reacts with the nucleophilic dienolether (e.g. **30** or **31**) as outlined in Fig. 1 and Fig. 7. Compound **31** itself consists of a dienolether and an acetal part. A Lewis acid (e.g. ZnB_2) can complex with one of the oxygen atoms and open the acetal group to form a tertiary carbenium ion (**33**/**34**), which is stabilized by the neighbouring oxygen atom (Fig. 9). A further reaction of this intermediate with itself or with another dienolether **31** leads to oligomeric products. Such a side

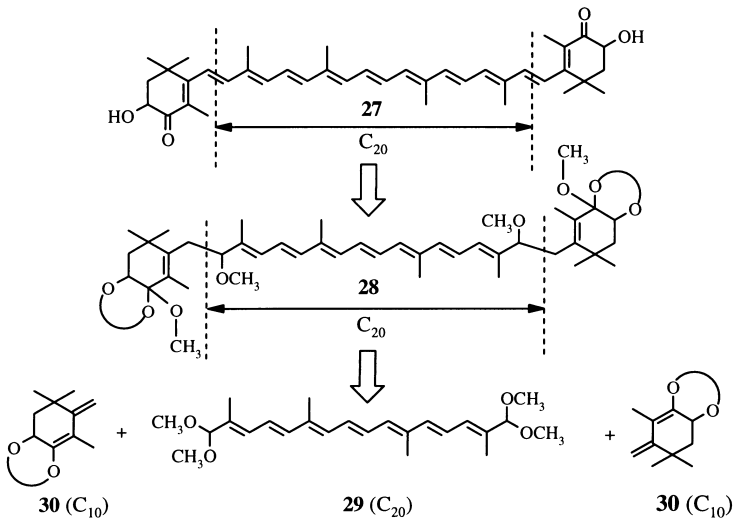


Fig. 7 Retrosynthetic analysis of astaxanthin (**27**).

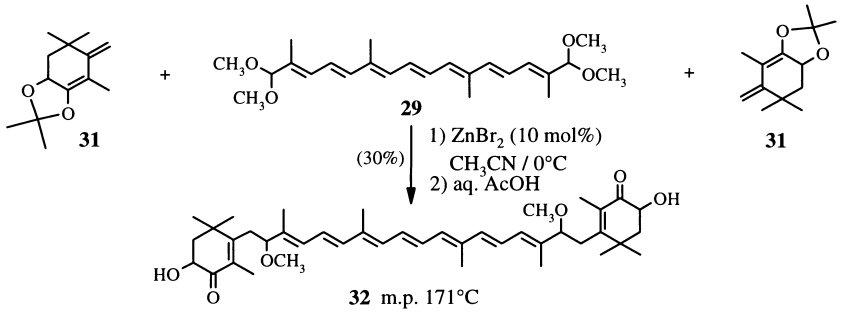


Fig. 8 Reaction of crocetindialdehyde dimethylacetal (**29**) with dienolether **31**.

reaction could be perhaps suppressed (or even prevented) by replacing the geminal methyl groups in **31** by two hydrogen atoms. Then the corresponding charged intermediates **33/34** would be less stable and therefore also less favoured.

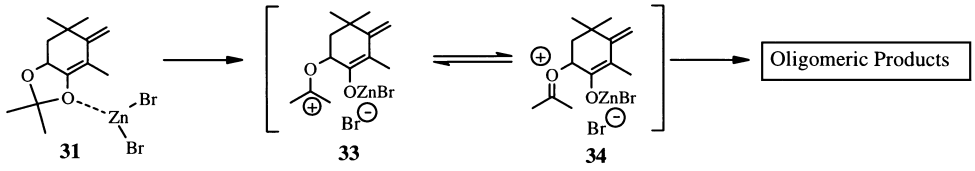


Fig. 9 Rationale of reaction of dienolether **31** with Lewis acids.

The desired dienolether **38** was synthesized as shown in Fig. 10. 2,2,6-Trimethyl-4,5-dihydroxy-cyclohex-5-en-1-one (**35**) [15] reacted with *p*-formaldehyde in ethylacetate at reflux temperature in the presence of *p*-TsOH to give crystalline protected ketone **36** in 93% yield. A subsequent Peterson olefination [16] with trimethyl-silylmethyllithium in pentane furnished, via intermediate **37**, C_{10}-dienolether **38** as a colourless distillable liquid.

Crocetindialdehyde dimethylacetal (**29**) was prepared by applying the technique discussed in the section on apocarotenals. C_{10}-Dialdehyde dimethylacetal **39** [17] reacted with 2 equivalents of 1-methoxy-2-methyl-1,3-butadiene (**17**) (= methoxy isoprene) in the presence of *p*-TsOH (1 mol.%) in toluene at −25 °C. After hydrolysis (aq. AcOH) and elimination of 2 equivalents of methanol (15 mol.% $NaOCH_3$), crocetindialdehyde (**40**) was obtained in 73% yield (HPLC purity: 99.3%) as violet small plates, m.p. 194 °C. Acid-catalysed acetalization with trimethyl orthoformate furnished the corresponding crystalline diacetal **29** as orange needles (m.p. 139 °C) in 91% yield (Fig. 11).

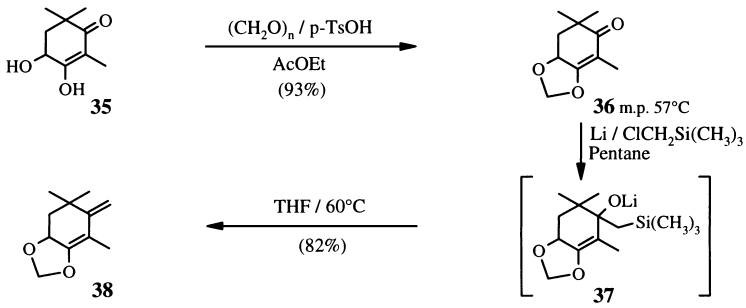


Fig. 10 Synthesis of dienolether **38**.

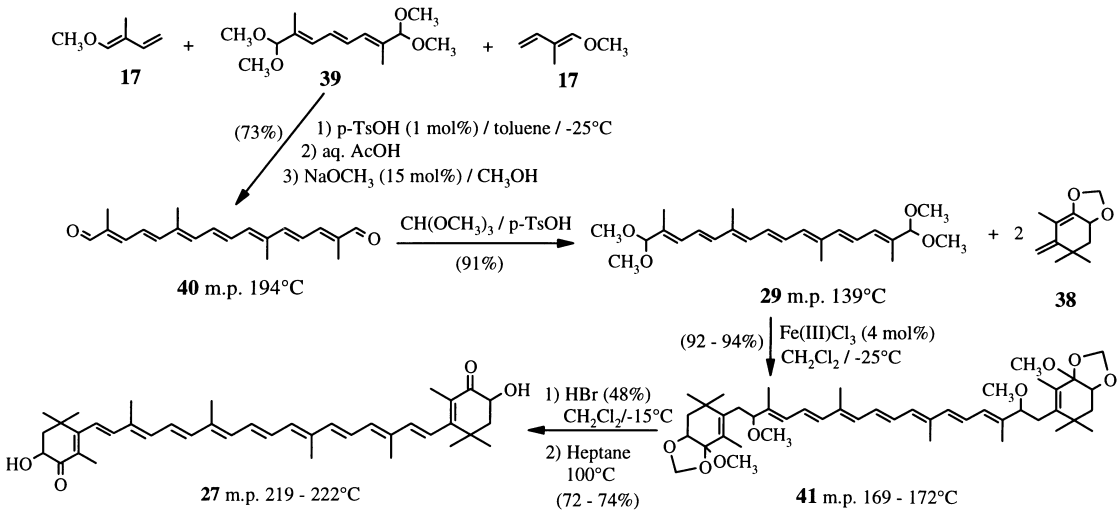


Fig. 11 Synthesis of astaxanthin (**27**).

A reaction of modified C_{10}-dienolether **38** with crocetindialdehyde dimethylacetal (**29**) in dichloromethane at −25 °C yielded the expected condensation product **41**, now in up to 94% yield, based on the acetal **29**. The isolation of this crystalline intermediate (m.p. 169–172 °C) proved to be very simple: direct solvent exchange (CH_2Cl_2 to CH_3OH) after the reaction resulted in the precipitation of the product **41**. The best catalysts found for this reaction were Fe(III)Cl_3 or $BF_3O(C_2H_5)_2$.

When compound **41** (mixture of stereoisomers) was treated with aq. HBr (48%) in dichloromethane at −15 °C, hydrolysis of the acetal groups and elimination of methanol occurred immediately. Astaxanthin (**27**), which was formed as a mixture of (all *E*)-, (9*Z*)- and (13*Z*)-isomers (approximately 15–20% of (9*Z* + 13*Z*)-**27** were formed) was then isomerized to (all *E*)-**27** in refluxing heptane.

After crystallization from dichloromethane/acetone, (all *E*)-astaxanthin (**27**) was isolated as violet shiny crystals with m.p. 219–222 °C. HPLC content (wt.%; crystals enclose approximately 1% CH_2Cl_2): 95–96% (all *E*)-**27**, 0.5% (9*Z* + 13*Z*)-**27**, 1% 8′-apo-β-astaxanthinal (C_{30}), 1.5% mono-(methoxymethoxy)-astaxanthin and 0.3% 'semi-astacene'.

CANTHAXANTHIN

Canthaxanthin (**47**) is synthesized on an industrial scale for egg yolk and broiler pigmentation. A wide range of synthetic approaches have been reported [18].

In analogy to the astaxanthin synthesis discussed in the section above, we prepared canthaxanthin (**47**) following a similar $C_{10} + C_{20} + C_{10} = C_{40}$ scheme (Fig. 12). Reaction of dienolether **43**, prepared from known ketone **42** [19] via Peterson olefination [15], with C_{20}-diacetal **29** in the presence of Fe(III)Cl_3 (5 mol.%) provided, in up to 95% yield, the condensation product **45** as a yellow ochre powder, m.p. 166–173 °C. The surprising cyclic dienolether structure of compound **45** was proven by spectroscopic

methods. Its formation may be explained in the following way. The methoxide group—after dissociation from the acetal **29** complexed probably to the iron atom—presumably acts here as a base and removes a hydrogen atom at C-3 instead of nucleophilic addition to the positively charged carbonyl group at C-4 of intermediate **44**. A mild hydrolysis of **45** with *p*-TsOH in aq. AcOH at 40 °C provided 7,8,7′,8′-tetrahydro-8,8′-dimethoxy-canthaxanthin (**46**) as orange crystals, m.p. 200–203 °C, in 68% yield. The double elimination of methanol was achieved using a strong base (e.g. $NaOC_2H_5$ in refluxing ethanol) or a mineral acid (e.g. HBr (48%) or HCl (37%)) in acetonitrile or dichloromethane at −15 °C. Then, canthaxanthin (**47**) was obtained as an *E*/*Z*-mixture ((all *E*): 77%, (9*Z* + 13*Z*): 13%). After isomerization in heptane at 100 °C and crystallization (CH_2Cl_2/acetone), canthaxanthin (**47**) was isolated in 76% yield as deep violet crystals, m.p. 207–208 °C. HPLC content (area %): 96% (all *E*)-**47**, 1.6% (9*Z* + 13*Z*)-**47** and 2.1% 8′-apo-β-canthaxanthinal (C_{30}).

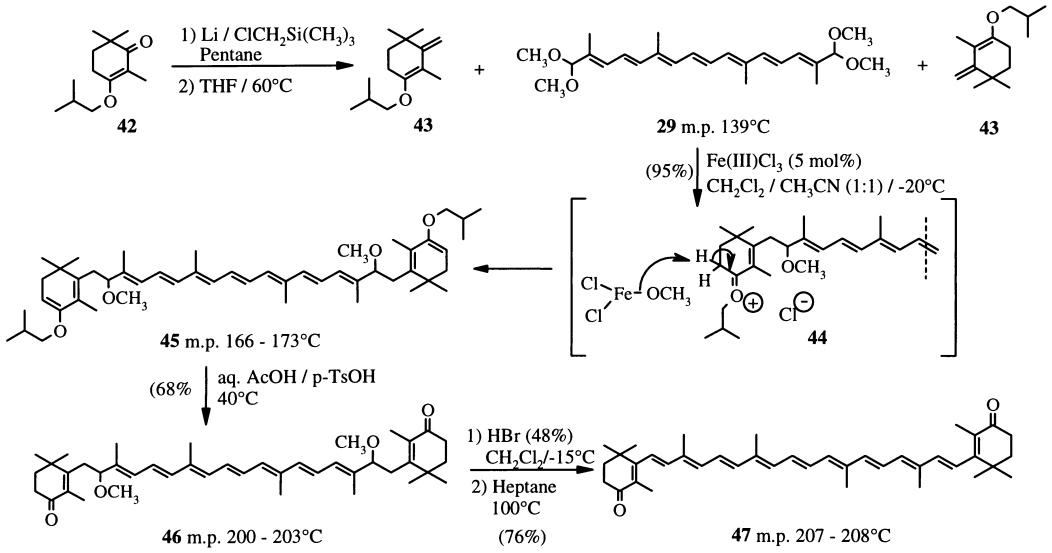


Fig. 12 Synthesis of canthaxanthin (**47**).

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