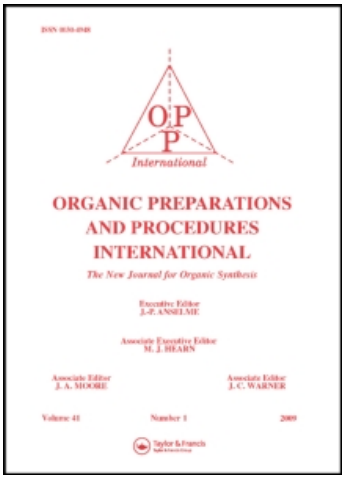

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RECENT ADVANCES IN THE SYNTHESIS OF RETINOIDS

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I. STRUCTURE AND BIOLOGICAL ACTIVITIES OF RETINOIDS. AN OVERVIEW

The term retinoids[1] collectively describes a group of natural and synthetic analogues of retinol (vitamin A, **1**, see *Fig. 1*)[2] with important biological activities and potential therapeutic applications. Native retinoids play key biological roles during the development of the embryo and postnatal life. Selected natural and synthetic retinoids have found application in the treatment of dermatological diseases and some types of cancer. Interestingly, from the perspective of synthetic chemists, those biological activities are structurally dependent upon the nature of the end group and the geometry of the polyene side-chain. Vitamin A (**1**) is responsible for the normal development of many cell types.[3] Retinaldehydes act as chromophores of photoreceptor proteins, to which they are bound as protonated Schiff bases with lysine residues in the binding pocket. It is known from the pioneering studies of Wald that 11-*cis*-retinal (**2**) is the chromophore of rhodopsin and cone opsins, the light-capturing membrane proteins in the retina involved in vision. Rhodopsin is a representative member of the G protein coupled receptors superfamily (GPCRs). Upon light-induced isomerization of the 11-*cis* to *trans* double bond of the polyene chromophore, a series of intermediates are generated that can be characterized spectrometrically. The protein intermediate state known as Meta II then interacts with a G protein, transducin, triggering the neural signal that provides the sensation of vision.[4] The free *trans*-retinal (**3**) detached from the protein isomerizes back to its 11-*cis* isomer in a complex sequence of biochemical events.[4g-h] On the other hand, *trans*-retinal (**3**) functions as the chromophore of the light-harvesting device coupled to the ion-pumps of Halobacteria.[5] The photochemical cycle is initiated by the light-induced isomerization of the chromophore to 13-*cis*-retinal, which triggers a sequence of protonation and deprotonation reactions of the protein and the Schiff base, linked to the bacterial proton pumping action. Most recently, retinoic acid (**4**) and 9-*cis*-retinoic acid (**5**) have been identified as the natural ligands for the retinoid families of nuclear receptors (retinoic acid receptors RAR's, isotypes α, β and γ; and retinoid X receptors, RXR's, isotypes α, β and γ), which function as transcription factors.[6] These proteins, upon ligand activation, are

capable of influencing cell proliferation and cell differentiation processes under the control of the responsive genes, thus transducing the pleiotropic effects of retinoids on morphogenesis, differentiation and homeostasis. Other native retinoids have been isolated more recently. (14*R*)-14-Hydroxy-4,14-*retro*retinol (14-HRR, **6**)[7a] is the first vitamin A metabolite with a *retro*-retinoid structure[2] and has shown a potent intracellular agonist activity of retinol-dependent events in the immune system. Anhydroretinol (AR, **7**) is another metabolite of retinol that reversibly inhibits physiological effects in immunity regulated by **1** and by its messenger **6**.[7b] Accordingly, 14-HRR **6** and AR **7** are considered to be the first agonist/antagonist pair of lipid-signaling molecules yet discovered. In addition, it has been found that the 13,14-dihydroxyretinol stereoisomers **8a** and **8b** can induce cell proliferation.[7c,8a]

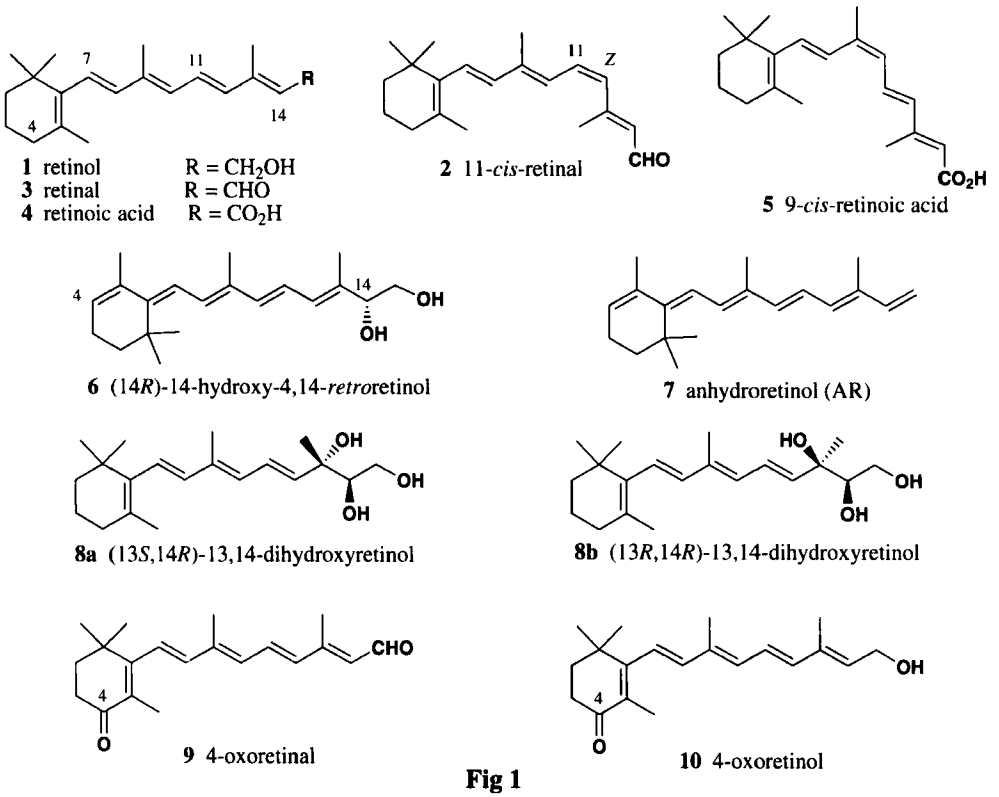
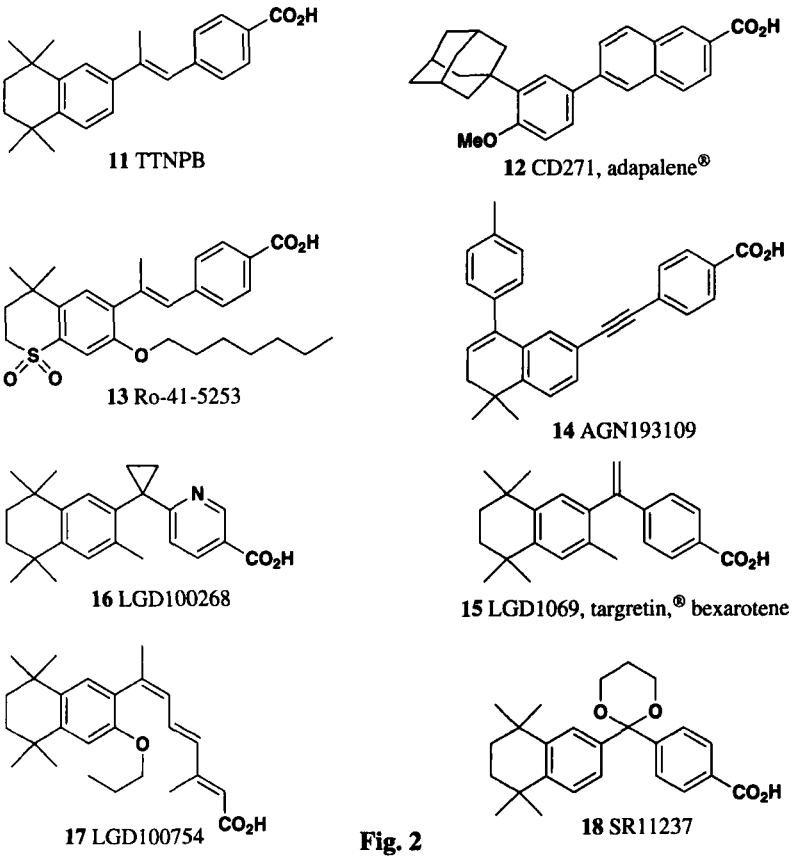


Fig 1

Interestingly, other retinoid metabolites, lacking the carboxylic acid, have been found to bind to and transactivate RARs in embryos and cell lines. 4-Oxoretinal (**9**) has been identified as the major bioactive retinoid in *Xenopus* embryos, and was considered to serve as metabolic precursor of both the corresponding carboxylic acid, and of 4-oxoretinol (**10**). The latter is also a RARs (but not RXRs) agonist, regulating cell differentiation. It is reasonable to expect that other yet unknown members of this group of retinoids will be discovered as a result of developments

on biochemical and molecular biology techniques, as well as improvements on separation and identification methods. Retinoid receptors are a particularly attractive source for ligand design. From a pharmacological perspective, the signaling capacity of these receptors can be modulated by appropriate choice of ligands. Great effort is being carried out to discover ligands that activate (agonists **11**,[9a] **12**,[9b] **15**,[9e] **16**,[9f] **18**[9h]), deactivate (antagonists **13**,[9c] **14**[9d], **17**[9g]), or inhibit (inverse agonists, **14**) individual retinoid receptors (RARs, **11-14**, RXRs, **15-18**) and their isotypes (α,β,γ). A representative number of these synthetic modulators of retinoid receptors is depicted in *Fig. 2*, which serves to illustrate structural diversity.[9] Other receptor-selective gene modulators will be described along this review.



11 TTNPB

12 CD271, adapalene®

13 Ro-41-5253

14 AGN193109

16 LGD100268

15 LGD1069, targretin,® bexarotene

17 LGD100754

18 SR11237

Fig. 2

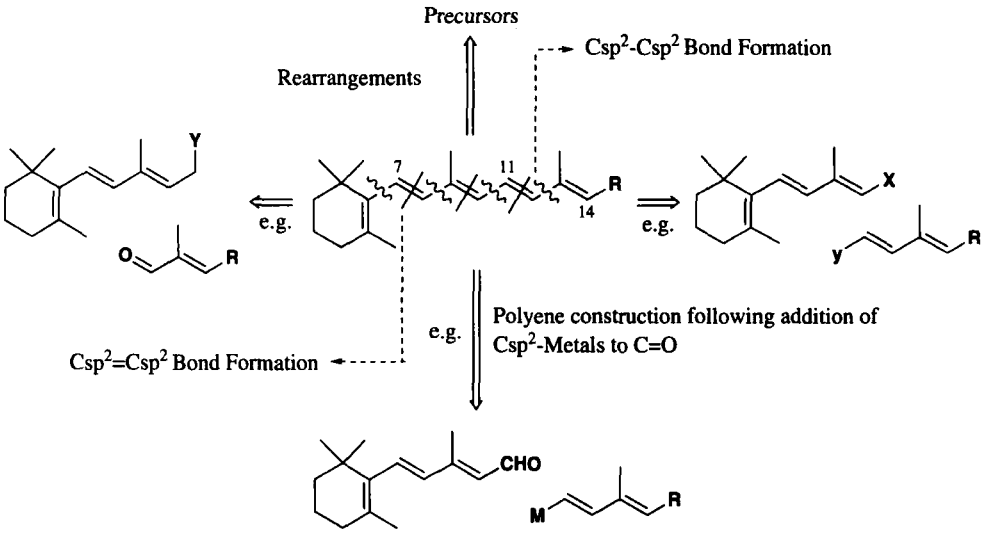
II. SCOPE AND ORGANIZATION OF THE REVIEW

The consideration of retinol as a vitamin spurred the interest of the chemical industry to develop efficient industrial synthesis of this important chemical, mainly for use as a food additive. The industrial production of vitamin A is close to 10,000 Tm/year. Industrial-scale

syntheses were also developed for the preparation of retinoic acid (**4**), its 13-*cis*-isomer and other selected analogues following the discovery of their potency as therapeutic agents for the treatment of dermatological disorders. Until the discovery of the nuclear receptor superfamily and identification of the retinoid ligands for the retinoid family of receptors fifteen years ago, most of the retinoid research was devoted to gaining further understanding of the biological processes mediated by retinaldehydes in phototransduction, and retinoic acid (**4**) in dermatology. These early synthetic efforts were reviewed by Frickel in 1984.[10a] The synthetic approaches to retinaldehydes, their chemical properties and spectroscopic characterization, together with the discussion on the photochemical interconversion of polyenes related to vitamin A was reviewed in 1984 by Liu and Asato.[10b] In 1994 Dawson and Hobbs wrote a more comprehensive review collecting all synthetic efforts in the field.[10c] It included the preparation of retinoids modified at the polar terminus, and also of derivatives designed to prove particular biological mechanisms of these compounds, such as isotopomers, and probes with fluorescent and photoaffinity labels. The review covered in depth the preparation of retinoid structures that, although retaining the carboxylic polar end group and a hydrophobic moiety, restrict the conformational freedom of the polyene chain into a variety of carbocyclic and aromatic rings, thus increasing its stability. These so-called arotinoids[11] have shown promising therapeutical applications, particularly as ligands of the retinoid families of nuclear receptors.

The exciting recent discoveries on the complex biological networks governed by retinoids served as a stimulus to further develop efficient approaches to these natural polyenes and their synthetic analogues. This research has been developed at the same time as the development of new synthetic procedures for C-C bond formation, particularly those involving transition metals. It is the purpose of this review to collect representative classical approaches to retinoids as well as to comprehensively treat the construction of polyenes using transition metal catalyzed processes. In this way, we wish to put into perspective the new synthetic trends as applied to a demanding synthetic challenge, since the known instability of the target compounds to a variety of conditions poses a limitation to certain methodologies.

A general classification of synthetic routes to the retinoid polyene skeleton distinguishes two distinct methodologies, double and single bond forming reactions.[10] Within the former group, Wittig and Julia condensation deserve most attention, due to their extensive use in polyene construction. The palladium-catalyzed cross-coupling reactions employing a number of organometallic partners (B, Sn, Zn, Zr...) and electrophiles form the second group (*Scheme 1*). A group of reactions, including aldol and its vinylogous counterpart, generates the polyene by dehydration following the addition of organometallic reagents to carbonyl groups. Finally, other unusual approaches to retinoids, mainly based on rearrangement reactions, will be presented. It is common practice in this field to label the building blocks of the synthetic scheme with the number of carbons ($C_i + C_j$; $i + j = 20$) they contribute to the final diterpene skeleton. This terminology will be used where appropriate.



Scheme 1

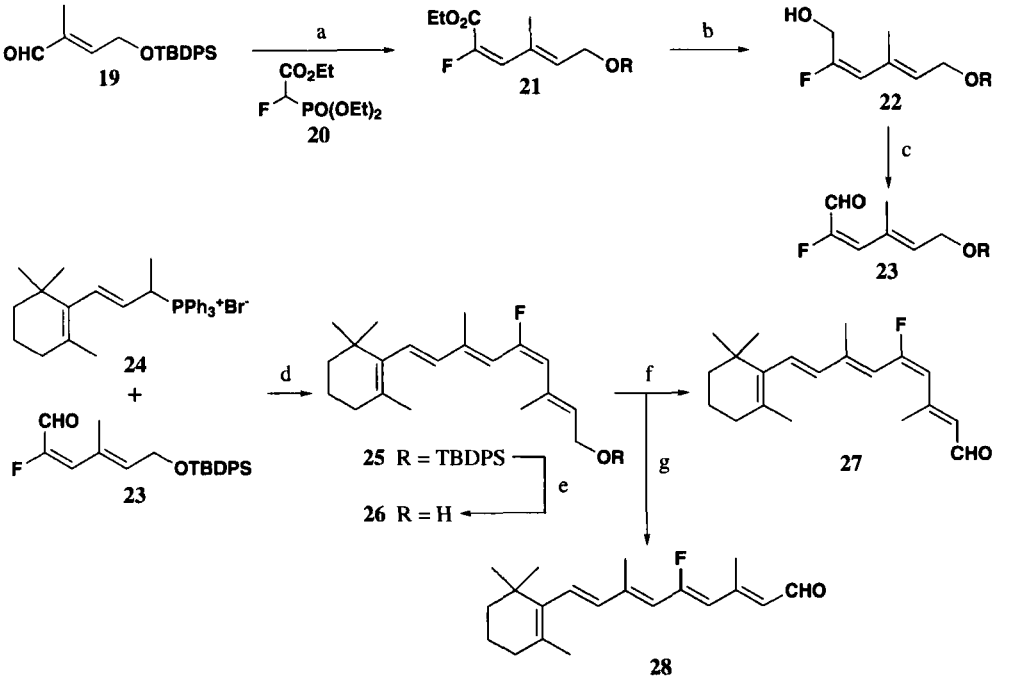
III. Csp^2=Csp^2 BOND FORMATION BY CONDENSATION REACTIONS

1. Wittig and Horner-Wadsworth-Emmons (HWE) Condensations

Soon after its discovery the venerable Wittig reaction[12] found an obvious application to retinoid synthesis, becoming the key step in the C_{11}-C_{12} bond formation in BASF's industrial synthesis of vitamin A using the C_{15} + C_5 approach.[13] The position-selectivity of the formed double bond, the alkaline or virtually neutral reaction conditions compatible with acid-sensitive functional groups, and the *in situ* generation of the ylide are advantages of this powerful synthetic method. As drawbacks, besides the sensitivity of phosphoranes to the steric hindrance of the carbonyl compounds, stands the difficulty in predicting the *E/Z* ratios for trisubstituted olefin formation. For retinoids, the main limitation of these condensation reactions is the control of the geometries of trisubstituted double bonds (C_9-C_{10} and C_{13}-C_{14}), since their formation requires the combination of either a ketone or a substituted-allylic phosphorane as one of the reaction partners. It is known that poor stereocontrol is exerted when using those components in Wittig reactions. More reliable is the prediction of stereocontrol on condensation approaches to disubstituted olefins of the retinoid side-chain (C_7-C_8 and C_{11}-C_{12} bonds), the usual outcome of Wittig and related condensations being the stereoselective formation of the *E*-double bonds in polyenes. This prediction is particularly reliable for the C_7-C_8 bond, due to the hindered nature of the component attached to the trimethylcyclohexenyl fragment. Nevertheless, the relevance of 11-*cis*-retinal (**2**) as a chromophore of the visual pigments, has in turn led to the development of a highly *cis*-selective variant of the Wittig reaction, employing dianions of hydroxyphosphonium salts within the classical C_{15} + C_5 route.[14a]

The Horner-Wadsworth-Emmons (HWE) reaction uses phosphonates with a carbanion stabilizing substituent, which are better nucleophiles than phosphoranes, being suitable for the preparation of trisubstituted olefins with high *E* selectivity.[12] Conditions have been developed, however, for the preparation of *Z* olefins, using modified phosphonate esters.[14b,c] The complementary outcome of modified Wittig and HWE condensations has placed this process at the forefront of the few general methods available for the preparation of site-selective and stereodefined olefins, and retinoids in particular. Not unexpectedly, numerous examples are known on the use of Wittig and HWE reactions in the synthesis of retinoid building blocks or the entire retinoid side chain.[10] Most of them have been described in previous reviews, and recent examples will be mentioned in other chapters of this review when used in combination with other strategies. We have selected recent applications of HWE and Wittig reactions to the synthesis of retinoids that, contrary to the principles outlined above, afford unusual stereochemical outcome, thus complementing classical approaches.

A combination of HWE and Wittig condensation reactions allowed the preparation of retinal analogues with fluorine atoms at the odd-numbered position of the side chain (*Scheme* 2).[15] The synthesis of (11*E*)-11-fluororetinal (**27**) (the 11-*cis* isomer of the polyene chain) and (11*Z*)-11-fluororetinal (**28**) (the *trans* isomer) is illustrative. The initial HWE condensation employing



a) Diethyl (fluorocarbethoxymethyl)phosphonate (**20**), *n*-BuLi, THF, -78 to 25°C (92%); b) DIBAL-H, THF, -78 to 0°C (90%); c) $BaMnO_4$, CH_2Cl_2, 25°C (90%); d) *n*-BuLi, THF, -78 to 25°C (57%); e) *n*-Bu_4NF, Et_2O, 25°C (74%); f) MnO_2, Na_2CO_3, CH_2Cl_2, 25°C (80%); g) $BaMnO_4$, CH_2Cl_2, 25°C (94%)

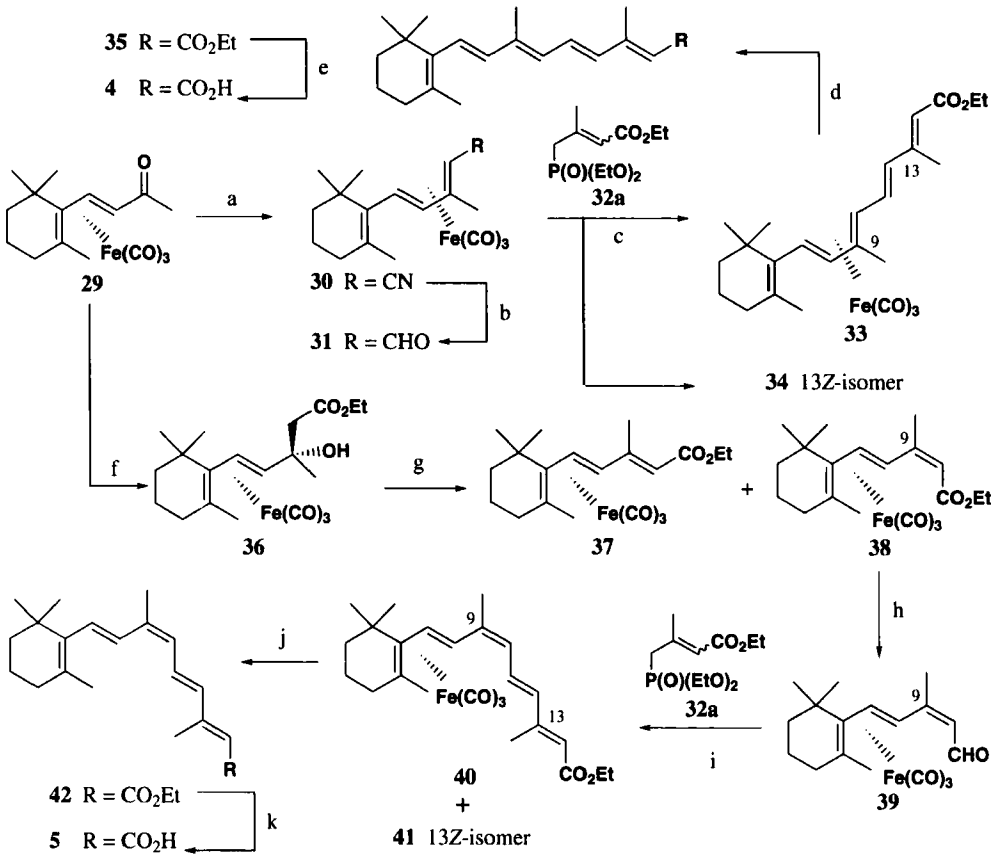
Scheme 2

diethyl(fluorocarbethoxymethyl)phosphonate (**20**) and aldehyde **19** is highly stereoselective, and leads to the *E*-geometry (CIP descriptor), but builds the polyene chain with a *cis* arrangement of the formed Csp^2 atoms, thus opening the way to the preparation of 11-*cis*-retinal analogues with fluorine atoms on the side chain. Reduction of the ester moiety and subsequent oxidation of **22** to the corresponding aldehyde followed the HWE condensation. The second Wittig condensation, representative of a $C_{13} + C_7$ approach, involving the anion derived from allylic phosphonium salt **24** and fluorinated aldehyde **23** is also unusual, since only the *trans*-trisubstituted olefin double-bond isomer was obtained. Addition of fluoroaldehyde **23** to the phosphorane derived from **24** and *n*-BuLi at –78°C, afforded (9*E*)-TBDPS-protected 11-fluororetinol **25** as the only isomer in 57% yield. Most likely, this is the result of the electronic effect of the fluorine atom geminal to the aldehyde (*c.f.*, with H instead of F, the $C_{13} + C_7$ Wittig condensation leads to a *ca.* 1.4:1 *E/Z* isomer ratio). Deprotection of **25** with *n*-Bu_4NF followed by oxidation of **26** with MnO_2, in the presence of Na_2CO_3, provided the stereochemically labile (11*E*)-11-fluororetinal (**27**). Its facile transformation into the more stable *trans*-11-fluororetinal (**28**) can be achieved in 94% yield by treating alcohol **26** with $BaMnO_4$ attesting to the lability of these fluorinated 11-*cis* retinals to isomerization (*Scheme 2*).

The use of diene-tricarbonyliron complexes in HWE reactions has revealed other subtle factors affecting stereoselectivity in condensation reactions involving organometallic compounds. $Fe(CO)_3$-diene complexes are finding increasing applications in organic synthesis due to their easy preparation, intrinsic chirality allowing for resolution, and potential diastereoselectivy in their reactions.[16] The synthesis of all-*E*- (**4**) and (9*Z*)-retinoic acid (**5**) illustrate the use of $Fe(CO)_3$-diene complexes in stereoselective organic synthesis (*Scheme 3*).[17] The synthesis of both isomers was achieved by stereocontrolled preparation of trienals with the desired double-bond geometry, **31** and **39**, respectively, differing in the C_9-C_{10} configuration. This novel and highly stereoselective route to these C_{15}-aldehydes took advantage of the effect of the complexed tricarbonyl-iron moiety. β-Ionone-$Fe(CO)_3$ complex **29** was treated with the lithium salt of acetonitrile at –70°C to afford **30** in 91% yield. Dehydration and migration of the metal carbonyl took place under these conditions. Reduction of the nitrile moiety with DIBAL-H afforded aldehyde **31** quantitatively. The resulting complexed trienal then underwent HWE condensation with the C_5-phosphonate **32a** (4:1 isomer mixture) in the presence of *n*-BuLi at 0°C, to afford ester **33** in 89% yield and its 13*Z* isomer **34** in 7% yield. After oxidative decomplexation of **33** using $CuCl_2$ in EtOH, the ester moiety was saponified to afford retinoic acid (**4**) in 98% yield.

Alternatively, the reaction of **29** with the lithium enolate of ethyl acetate in THF at –70°C gave the adduct **36** as a single product in 89% yield. In stark contrast with the usual *E*-selective dehydration in the uncomplexed adduct (*via* E1 mechanism), the dehydration of **36** with thionyl chloride afforded predominantly the (9*Z*)-ester **38** (65%) together with its (9*E*)-isomer **37** (10%). This outcome was rationalized by invoking a transition state in which iron chelates the ester group, favouring a presumably *anti*-elimination from a carbenium ion interme-

diate. (9Z)-Ester **38** was subsequently converted to aldehyde **39** (71%) without decomplexation by mild oxidation of the intermediate alcohol using Mukaiyama's method. Following an identical synthetic route to the one described above, aldehyde **39** was converted to (9Z)-retinoic acid



a) LDA, CH_3CN, THF, -70°C (91%); b) DIBAL-H, CH_2Cl_2, 0°C (quant.); c) *n*-BuLi, THF, 0°C (89% for **33**, 7% for **34**); d) $CuCl_2$, EtOH, 25°C (56%); e) NaOH, MeOH, 50°C (98%); f) LDA, CH_3CO_2Et, THF, -70°C (89%); g) $SOCl_2$, pyridine, 0°C (10% for **37**, 65% for **38**); h) *i.* DIBAL-H, Et_2O, -45°C; *ii.* *i*-PrMgBr, THF, 0°C; *iii.* Azodicarbonyldipiperidine, THF, 0°C (71%); i) *n*-BuLi, THF, 0°C (92% for **40**, 8% for **41**); j) $CuCl_2$, EtOH, 25°C (98%); k) NaOH, MeOH, 50°C (74%)

Scheme 3

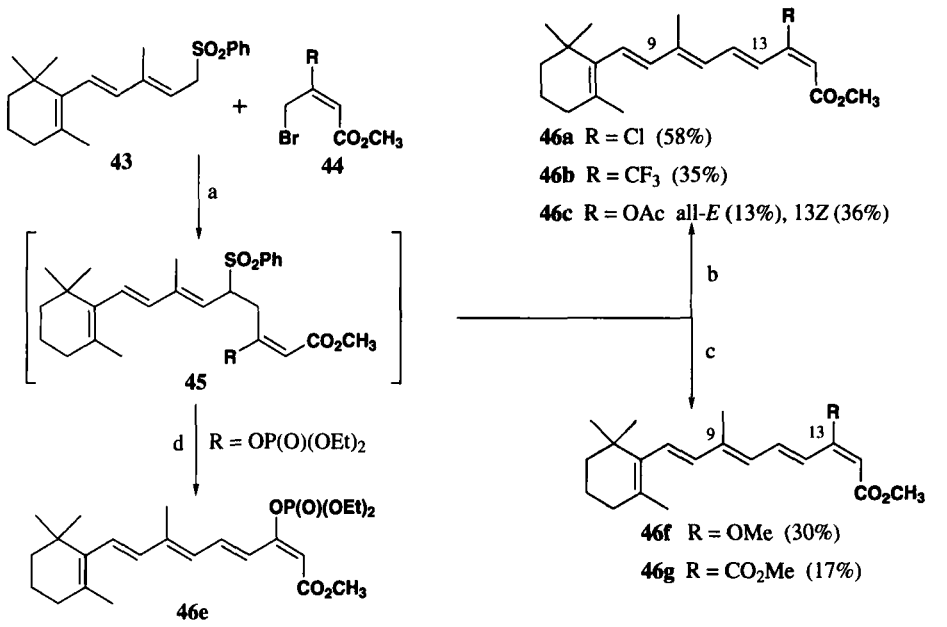
(**5**) by quantitative and highly stereoselective (12:1 11*E*/13*E* to 11*E* /13*Z* ratio) HWE condensation with phosphonate **32a**, followed by decomplexation of **40** with $CuCl_2$ (98% yield) and hydrolysis of the ester **42** in 74% yield.

2. Julia and Related Olefinations

This section collects condensation reactions involving anions derived from sulfones, the so-called Julia and related condensations for the synthesis of polyenes.[18] Julia *et al.* first discovered that carbanions stabilised by sulfones could be alkylated with alkyl halides, and the resulting

alkylated sulfones, upon base-promoted elimination of sulfinic acid, afforded olefins. An extension of this process was the preparation of methyl retinoate ($C_{15} + C_5$ route).[19] These pioneering studies were soon followed by similar approaches to achieve the formation of other double bonds of the retinoid side-chain, thus demonstrating a general application of the Julia reaction in the creation of both di- and trisubstituted retinoid double bonds. As occurs with the Wittig condensation, the stereocontrol of this reaction for trisubstituted olefins is not yet satisfactory. Nevertheless, the Julia condensation constitutes the base of Rhone-Poulenc's industrial syntheses of vitamin A.[19b]

The preparation of native retinoids was further extended to the synthesis of side-chain modified analogues. Welch and Gruber reported the first approach to C_{13}-modified retinoids based on a modification of Julia and Arnould's original $C_{15} + C_5$ procedure.[20] This involves alkylation of the C_{15} phenyl sulfone **43** with a series of allyl bromides **44**, prepared by radical bromination of the parent esters, followed by elimination of benzenesulfinic acid in basic media (*Scheme 4*). Deprotonation of sulfone **43** with *n*-BuLi in THF at –78°C, followed by addition of



a) *n*-BuLi, THF, -78°C; b) DBU, Et_2O, 25°C; c) MeONa, THF, -78°C to 25°C; d) pyrrolidine, Et_2O, 25°C

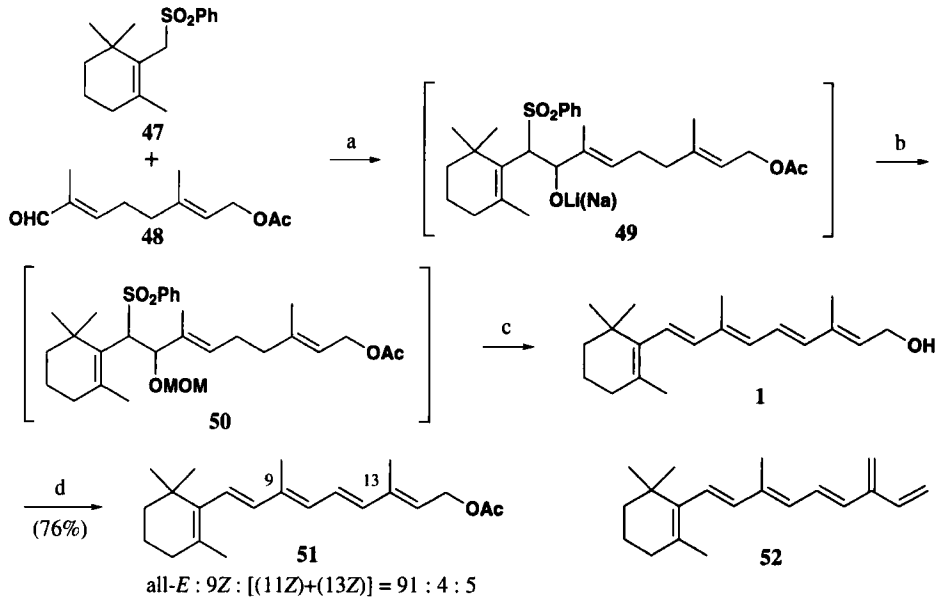
Scheme 4

the substituted bromide **44** afforded intermediate **45** that in some cases (R = OAc) was isolated and fully characterized. Elimination of benzenesulfinic acid to afford the corresponding methyl retinoate analogues **46a-c** took place in moderate yields by treatment with DBU in Et_2O (R = Cl, CF_3, OAc). Alternatively, pyrrolidine [R = $OP(O)(OEt)_2$] or sodium methoxide (R = OMe,

CO_2Me) have also been employed to effect the elimination in other substrates (**46e-g**). Stereoselective formation of the *E*-C_{11}-C_{12} double bond results under these conditions, although the overall transformation proceeds in only moderate yield.

Otera and co-workers reported a most significant advance in this process by coupling the sulfone anion with α,β-unsaturated aldehydes with Csp^3 carbons at the γ and δ positions, followed by desulfonylation of the acetoxy or tetrahydropyranyloxy derivative with a metal alkoxide. From these intermediates, a double elimination is induced by consecutive abstraction of the γ and δ allylic hydrogens. The double elimination reaction for the preparation of trienes is highly *E*-selective. A highly stereocontrolled synthesis of different analogues of retinol was developed by judicious choice of the starting components.[21] The first step of this method (C_{10} + C_{10} approach) involves the nucleophilic attack of the anion derived from sulfone **47** on to the appropriate dienal **48**, followed by protection of the newly formed hydroxyl group. Exposure of the β-alkoxysulfones to an excess of base in a polar solvent results in elimination of both functional groups in a one-pot reaction. The stereoselectivity was very high, and only minor amounts of the 9*Z* (4%) and 11*Z*+13*Z* (5%) isomers were isolated as side products together with the all-*E*-**51** (91%). Whereas methyl retinoate could be efficiently prepared using the general procedure, unstable vitamin A (**1**) and its 13*Z*-isomer (available from the double bond isomer of enal **48**) were only obtained in good yield when the double-elimination reaction was performed in a hydrocarbon solvent.[21b] The advantage of this highly efficient and practical method for polyene construction is that the desired skeleton and labile double bond system are generated in a single elimination step, thus unravelling the triene system of the retinoid C_7-C_{12} fragment. Nevertheless, no *Z*-selective variant of the Julia olefination has been found for that retinoid triene fragment formed by double elimination reaction.

More recently, this methodology has been successfully applied to the one-pot synthesis of retinol acetate (**51**), in what has been termed an "integrated chemical process".[21d] The one-pot procedure starts with the preparation of the lithium salt of cyclogeranylsulfone **47** with *n*-BuLi at –78°C, in the presence of NaI, followed by addition of aldehyde **48** to give the adduct **49**, which was immediately trapped with MOMCl. The MOM ether **50** underwent double elimination upon treatment with KOMe to afford retinol (**1**) that was protected as the corresponding acetate **51** by treatment with Ac_2O, DMAP, and pyridine in hexane at room temperature (*Scheme 5*). Addition of NaI at the beginning of the reaction helped to prevent the formation of polymeric material derived from the diene by-product **52**, and allowed the alkylation of the alkoxide with the cheaper MOMCl (Finkelstein reaction). The yield of vitamin A acetate **51** was determined by HPLC to be about 76%, which is higher than the 67% obtained in the corresponding stepwise procedure. In this way, optimising a multi-step process in which the experimental conditions are shared by all individual steps, an increase in the overall yield can be achieved, with clear economic and environmental implications.



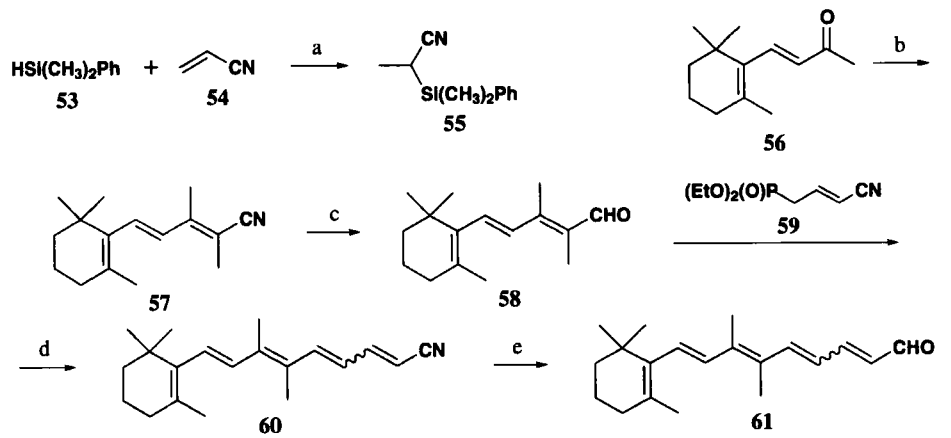
a) *n*-BuLi, NaI, THF, -78°C; b) MOMCl, -78°C to 25°C; c) KOMe, cyclohexane, 25°C to 40°C; d) Ac_2O, DMAP, pyridine, hexane, 25°C

Scheme 5

3. Peterson Olefinations

The Peterson olefination has shown some advantages over the Wittig reaction due to the greater reactivity and reduced sensitivity to steric hindrance of the silyl-stabilized carbanions compared to the phosphoranes.[22] For simple alkenes, the choice of the elimination reaction conditions (acid or base) can provide stereocomplementary results. The advantages imparted by these properties can be exploited in syntheses employing ketones or highly hindered aldehydes. Again we will highlight recent applications expanding the synthetic utility of the Peterson olefination in route to retinoids.

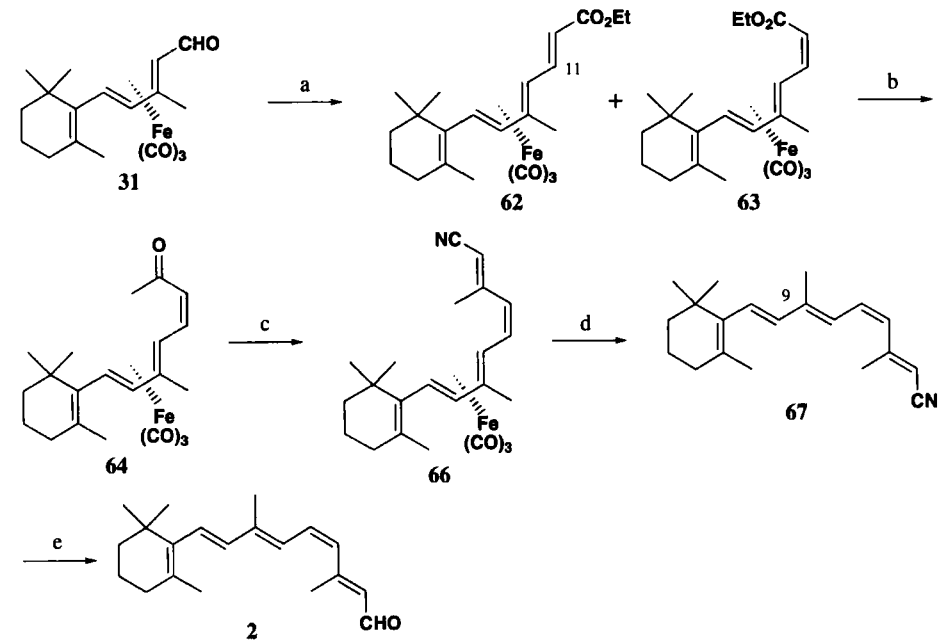
13-Demethyl-10-methylretinal (**61**) has recently been synthesized from β-ionone (**56**) in an overall yield of *ca.* 5% (see *Scheme 6*).[23] The critical step of this synthetic route is the application of the Peterson olefination to the formation of the tetrasubstituted C_9-C_{10} bond. The required dimethylphenyl-silyl-2-propionitrile (**55**) was prepared by addition of dimethyl-phenyl-silane (**53**) to acrylonitrile (**54**) in the presence of Wilkinson's catalyst. Subsequent Peterson condensation of **55** and β-ionone (**56**) yielded β-ionylidene propionitrile (**57**) which was reduced with DIBAL-H to the corresponding aldehyde **58**. Trienal **58** underwent HWE condensation with 4-phosphono-crotonitrile **59** and NaH at –20°C. Finally, reduction of **60** with DIBAL-H afforded 13-demethyl-10-methylretinal (**61**) as a mixture of isomers. The mixture was enriched in the desired isomer by photochemical irradiation, and then purified by preparative HPLC.



a) $RhCl(PPh_3)_3$, 100°C; b) **55**, LDA, -70°C; c) DIBAL-H; d) NaH, THF, -20°C; e) DIBAL-H (*ca.* 5% overall yield)

Scheme 6

In yet another application of the diene-$Fe(CO)_3$ complexes, Ito and co-workers reported the stereoselective synthesis of (11Z)-retinal (**2**) and some 9-substituted analogues (*Scheme 7*).[24] The synthesis starts with the formation of the C_{11}-C_{12} bond with Z geometry in compound **63**.



a) $Me_3SiCH_2CO_2Et$, LDA, THF, -78°C (15% **62**, 77% **63**); b) Ph_3SnCH_2I, *n*-BuLi, THF (79%); c) $(i\text{-PrO})_2P(O)CH_2CN$ **65**, NaH, THF (73%); d) $CuCl_2$, EtOH (72%); e) DIBAL-H, PhMe (98%)

Scheme 7

This bond is obtained in highly stereoselective fashion and in 77% yield by Peterson condensation of β-ionylideneacetaldehyde-tricarbonyliron complex (**31**) and the lithium enolate of ethyl

trimethylsilylacetate in THF at –70°C. Although the corresponding 11*E*-isomer **62** was obtained in 15% yield, it became the sole product when a HWE reaction was attempted on the same substrate, revealing a more subtle effect of metal complexation. The mechanism of the highly Z-stereoselective elimination to afford **63** is not clear yet, but preliminary studies suggest that both the tricarbonyliron moiety and the substituent at C_9 are essential for achieving stereocontrol. Ester **63** was converted in good yield (79%) into the C_{18}-ketone tricarbonyliron complex **64** using triphenylstannylmethyl lithium. The HWE condensation of **64** with diisopropyl cyanomethylphosphonate (**65**) and NaH afforded nitrile **66** as a single product in 73% yield. After decomplexation of **66** with $CuCl_2$, the resulting nitrile **67** was reduced in excellent yield (98%) to the desired (11Z)-retinal (**2**) using DIBAL-H in toluene.

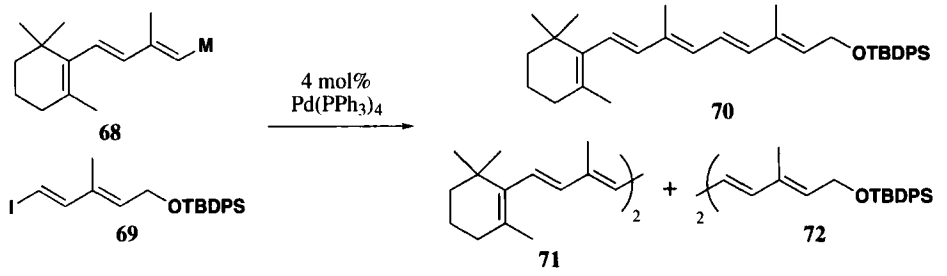
IV. Csp^2-Csp^2 AND Csp^2-Csp BOND FORMATION BY METAL CATALYZED CROSS-COUPLING REACTIONS

1. Introduction

The palladium and nickel-catalyzed cross-coupling reaction of organometallic reagents with electrophiles has emerged as a highly versatile method for C-C bond formation.[25] Its development has complemented the more traditional C-C coupling processes between Csp^3 carbons using alkali organometal derivatives, since they promote the otherwise difficult bond formation between unsaturated Csp and Csp^2 atom centers. Starting in the late 1970s, these reactions have evolved to become the most powerful and general methodology for C-C bond formation between vinyl, aryl and alkynyl species and nowadays it is undoubtedly the synthetic method of choice for the described transformation. Recent developments in reaction conditions, in particular the advent of new metal ligands and additives allow the coupling reactions to be performed, in most cases, at ambient temperature. The mild reaction conditions are very appealing for extending this methodology to the preparation of natural products with complex structure, as well as new materials and supramolecular devices.

It has been proposed that most of the metal-mediated cross-coupling reactions follow a similar mechanistic scheme, involving three basic steps: oxidative addition, transmetalation and reductive elimination, sequentially describing the events occurring at the metal centre.[25] The reaction starts by oxidative addition of the electrophile to the metal, usually Pd(0) or Ni(0). Recent advances in catalysis have allowed the use of aryl and vinyl chlorides as electrophile partners of the coupling in addition to organic iodides, bromides and triflates, thus expanding the range of halides to those more widely available. For the transmetalation step, a wide range of organometallic compounds are at hand, but the most widely used are derivatives of boron, tin, zinc, silicon, zirconium and aluminium. In most cases the transmetalation step is considered to be rate-determining, although the particular details are not fully understood,[26] and are highly dependent upon the organometallic reagent and the reaction conditions. The reductive elimination is usually fast, leading to the coupled product. [25]

Conceptually, the application of transition metal catalysed processes to retinoids could readily complement the general condensation approaches described in Section 3. The synthetic alternative would provide polyenes by single bond construction between unsaturated centres, instead of by double-bond formation. Negishi and Owczarczyk[27] pioneered this field by carrying out a comprehensive study of the performance of different metals in the palladium-catalyzed [$Pd(PPh_3)_4$] cross-coupling of trienylmetal derivatives and dienyliodides using a $C_{14} + C_6$ approach (*Scheme 8*). In this study C_{14}-alkenyldiorganozinc reagents were found to be superior to other metals (Al, Mg, Sn, Cu, B, and Zr, see *Scheme 8* and Table 1). Almost simultaneously it was also, discovered that alkenylboron reagents were equally effective.[28] Following these studies significant developments have been achieved during the last decade, and they have been classified according to the nature of the organometal component of the coupling reaction.



Scheme 8

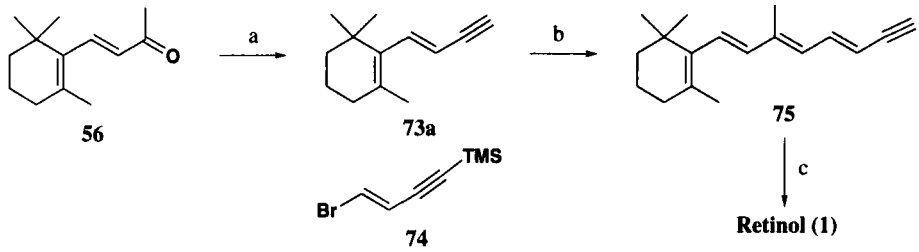
Table 1. Preparation of Retinol-TBDPS-ether **70** using $Pd(PPh_3)_4$-catalyzed Alkenyl-alkenyl Cross-coupling Reactions

M	Solvent	T (°C)	t (h)	70	71	72	69
$Zn_{1/2}$	THF	25	1	87	4	traces	0
$AlMe_2$	THF	25	3	41	5	3	33
$Mg_{1/2}$	THF	25	3	57	2	1	35
$SnMe_3$	THF or HMPA	25	3	traces	traces	traces	>90
$SnMe_3$	HMPA	65	3	39	18	19	traces
$Cu{\bullet}MgX_2$	THF	-20 to 25	3	11	10	8	64
$BO_2C_6H_4$	benzene, MeOH	90	3	traces	0	0	14
$ZrCp_2Cl$	THF	25	6	traces	33	17	67

2. Negishi Coupling

Organozinc derivatives can be prepared as organozinc halides by direct insertion of activated zinc dust into alkylhalides, or as the more reactive diorganozincs by iodine-Zn exchange reaction (mediated by Cu) or by boron-zinc exchange reaction after hydroboration of alkenes.[29] Although organozincs are generally less reactive with organic electrophiles than other main-group organometallics, they undergo transmetalation in the presence of transition metals, thus becoming alternative partners for C-C bond formation. Their increasing popularity in organic

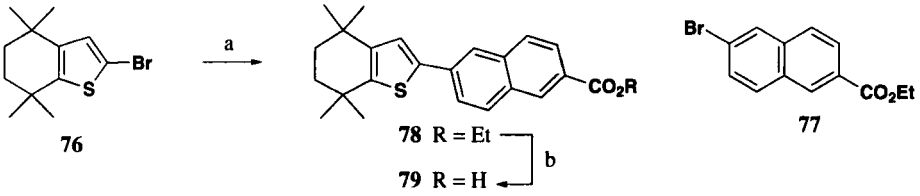
synthesis is mainly due to their broad tolerance to functional groups and the recent development of ligands and additives for accelerating even Csp^3-Csp^3 bond forming reactions, without complications due to β-elimination. Transmetalation to copper allows polyfunctionalized organozinc reagents to cross couple with alkenyl, alkynyl and aryl halides. Transmetalation to palladium and nickel promotes the same coupling reactions also with polyfunctional unsaturated substrates. The superiority of dialkylzinc reagent **68** (M = $Zn_{1/2}$) on coupling to alkenylhalide **69** on the synthesis of protected retinol **70** has already been highlighted (*Scheme 8*).[27a] A more recent preparation of retinol (**1**) in 40% overall isolated yield in three linear steps from β-ionone (**56**) *via* alkyne **73a** is a shorter stereoselective approach.[27b] It uses a sequence of alkyne methylalumination,[30] transformation into the alkenylaluminate complex, exchange to zinc, and Pd-catalyzed cross coupling of the organozinc with electrophile **74**. This bromoenyne serves as a lynchpin to finally complete the retinoid side chain by means of another methylalumination of **75** and trapping the alkenylaluminate complex with formaldehyde (*Scheme 9*).



a) *i.* LDA, THF; *ii.* $ClPO(OEt)_2$; *iii.* LDA (2 equiv.) (85%); b) *i.* Me_3Al, Cp_2ZrCl_2, $(CH_2Cl)_2$, 23°C; *ii.* evaporation at 50°C and 0.5 mmHg; *iii.* **74**, $ZnCl_2$, THF, $Pd_2(dba)_3$ (2.5 mol%), tri(2-furyl)phosphine (10 mol%), DMF, 23°C; *iv.* K_2CO_3, MeOH, 23°C; c) *i.* Me_3Al, Cp_2ZrCl_2, $(CH_2Cl)_2$, 23°C; *ii.* evaporation at 50°C and 0.5 mmHg; *iii.* *n*-BuLi, THF, 23°C; *iv.* $(CH_2O)_n$, 23°C (67% from **73a**)

Scheme 9

The Ni and Pd-catalyzed cross-coupling of arylorganozinc reagents and arylhalides now constitutes a general synthetic method for the preparation of biaryl bonds, and as such it has found extended application for the preparation of certain arotinoids and heteroarotinoids. As an example,[31] the central single bond of arotinoid **79** was constructed by Ni-catalyzed cross-coupling involving the organozinc derived from the bromothiophene **76** and ethyl 6-bromo-2-naphthoate (**77**), followed by hydrolysis (*Scheme 10*). It was necessary to prepare the highly active Ni catalyst by DIBAL-H reduction of the Ni(II) pre-catalyst.



a) *i.* *n*-BuLi, THF; *ii.* $ZnCl_2$, THF; *iii.* bromide **77**, $NiCl_2(PPh_3)_2$, PPh_3, DIBAL-H, THF; *iv.* aq. HCl; b) *i.* aq. KOH, MeOH; *ii.* aq. AcOH (40% from **76**)

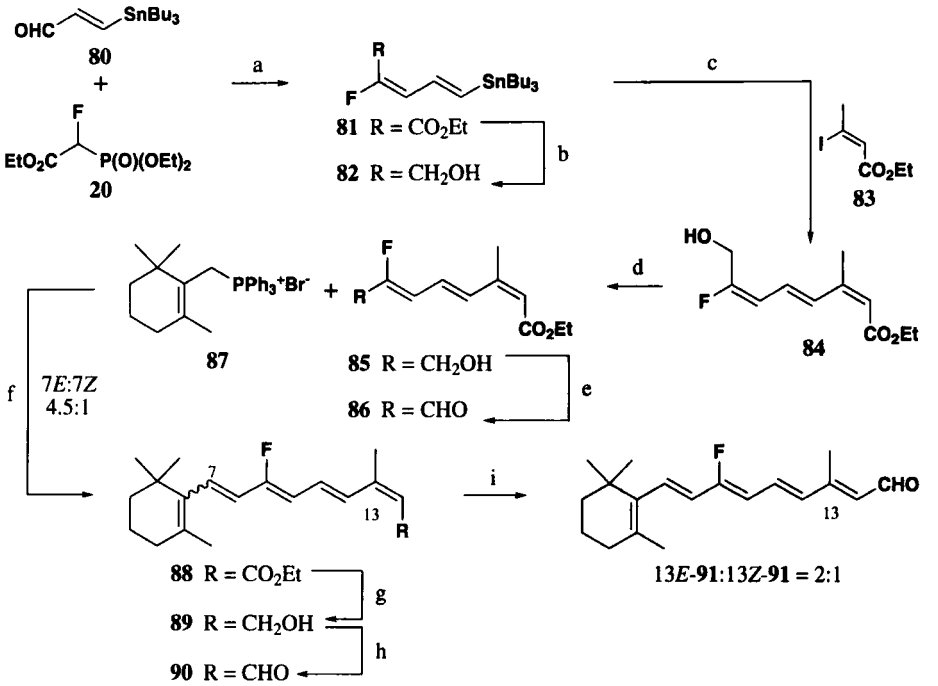
Scheme 10

3. Stille Reaction

The Pd-catalyzed cross coupling of organostannanes and electrophiles, known as Stille coupling, is the most widely used variant of the metal-catalyzed cross-coupling processes.[32] Its popularity can be explained by the fact that organostannanes are easily available from alkynes using hydrostannation or stannylcupration, or from unsaturated bromides by trapping the carbanion obtained by halogen-lithium exchange with a trialkyltin halide. The cross-coupling reaction conditions are compatible with a variety of functional groups on both components. Although the early reaction conditions limited its application to thermally stable polyenes (since high coupling temperatures were not unusual), recent discoveries on the rate acceleration effect of bulky phosphines and/or additives on the coupling process, extended its application to a plethora of natural products of great complexity and instability, such as retinoids. However the high toxicity associated with tin compounds remains to be the main limitation of this methodology. Despite the development of work-up protocols for minimising the presence of tin in organic solvents, their disposal is a concern. This has been partially alleviated by the recent discovery of Stille coupling reactions catalytic in tin.

The preparation of 9-*trans*-9-fluororetinal (**91**) became one of the first reported applications of the Stille reaction to the synthesis of side-chain modified retinoids.[33] Fluorinated retinals have been used in bioorganic studies of retinal proteins through the analysis of ligand-receptor interactions by ^{19}F NMR.[34] The construction of the polyene chain commenced with the Stille cross coupling of fluorostannane **82** and ethyl *Z*-iodobut-2-enoate (**83**). Highly functionalized diene **81** was in turn prepared by HWE condensation of aldehyde **80** and fluorophosphonate **20**. The high *E*-stereoselectivity of condensation reactions using this phosphonate has already been noted (*Scheme 2*). The condensation was followed by reduction of ester **81** with DIBAL-H. The key Pd-catalysed cross coupling proceeded with retention of configuration of both coupling fragments **82** and **83**, providing geometrically homogeneous (2*Z*,4*E*,6*E*)-triene **84** in 74% yield. Treatment of **84** with a substoichiometric amount of iodine led to a regioselective isomerization at the C_6-C_7 bond, yielding **85** as a single geometric isomer. Oxidation of **85** with MnO_2, followed by Wittig condensation with phosphonium salt **87** afforded a 4.5:1 mixture of 7*E*- and 7*Z*-9-fluororetinoids **88**. In stark contrast to the high *E*-selectivity of similar non-fluorinated trienals, the Wittig reaction of **86** showed decrease in the stereocontrol previously observed (*Scheme 2*). Subsequent reduction of **88** and oxidation of **89**, followed by acid-catalysed isomerization of aldehyde **90** afforded a 2:1 mixture of 13-*E* and 13*Z*-**91** (*Scheme 11*). Despite the use of Pd-catalyzed cross coupling to ensure a highly stereoselective preparation of triene **84**, the four-components coupling approach subsequently requires two double-bond isomerization steps to partially correct the low stereoselectivity of the Wittig product **88**, and the undesired geometry of the HWE product **81**.

An application of the Stille cross coupling to the synthesis of arotinoids with a substituted imidazole-stilbene structure was reported by Chandraratna *et al.*[35] The key step features

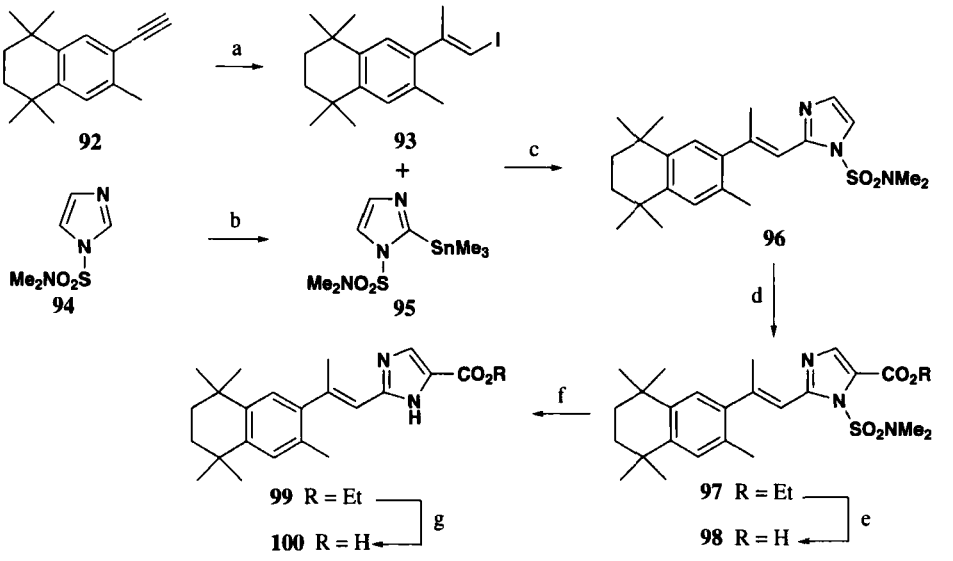


a) *n*-BuLi, THF, -78 to 0°C (95%); b) DIBAL-H, CH_2Cl_2, -78°C (74%); c) $PdCl_2(MeCN)_2$, DMF (74%); d) I_2, hexane (87%); e) MnO_2, hexane, CH_2Cl_2 (75%); f) *n*-BuLi, THF, -78°C (75%); g) DIBAL-H, CH_2Cl_2, -78°C; h) MnO_2, hexane (40%); i) TFA, CH_2Cl_2 (90%)

Scheme 11

cross coupling of protected 2-trimethylstannyl imidazole (**95**), prepared *in situ* from imidazole (**94**), with alkenyliodide **93**, obtained by carboalumination of alkyne **92**, and iodination of the alkenylalane intermediate (*Scheme 12*). Lithiation of the heterocycle and trapping of the organolithium with ethyl chloroformate attached the terminal carboxylate. Saponification of **97** produced the *N*-sulfamoyl carboxylic acid **98**. Removal of the *N*-sulfamoyl group in acidic media followed by saponification led to arotinoid **100**.

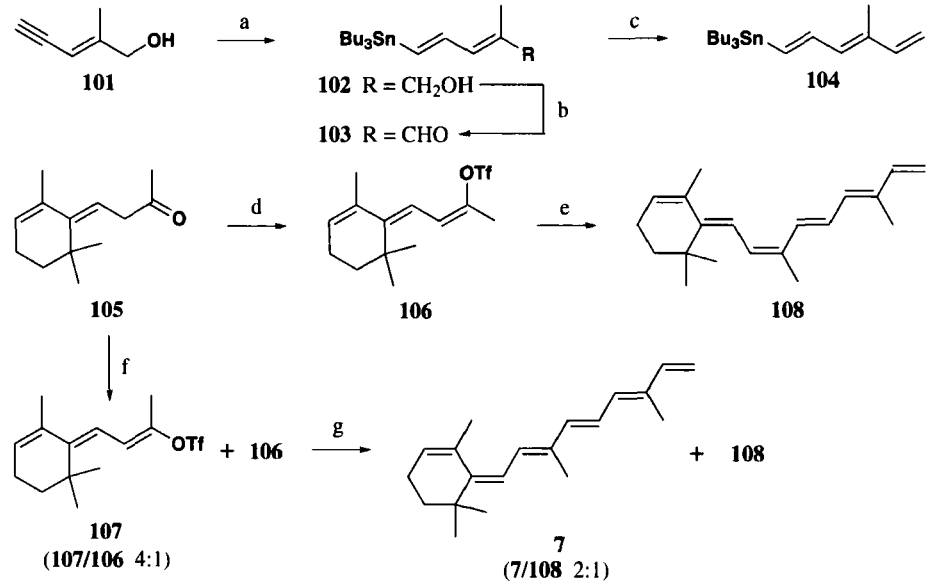
The Stille cross-coupling reaction has also been successfully applied to the preparation of highly unstable retinoids such as the hexaenes anhydroretinol (**7**) and its (8*Z*)-isomer (**108**) (*Scheme 13*).[36] It was envisaged that these hexaenes might be acquired by a convergent approach using triene fragments of comparable complexity. Trienylstannane **104** was regio and stereoselectively prepared by stannylcupration[37] of enynol **101** to give **102**, followed by oxidation to the corresponding aldehyde **103** and Wittig olefination of the latter under the mild conditions reported by Stork for related iodoolefinations. The preparation of trienyl triflates **106** and **107** proved to be more challenging. After extensive experimentation using different starting materials, bases and trapping agents, appropriate reaction conditions were found to access these compounds from *retro*-ionone (**105**), prepared by allylic deprotonation and deconjugation of β-ionone (**56**). The stereoselective preparation of (*Z,E*)-triflate **106** was achieved in 94% yield by



a) *i.* $AlMe_3$, Cl_2ZrCp_2; *ii.* I_2 (49%); b) *i.* *n*-BuLi; *ii.* Me_3SnCl; c) $Pd(PPh_3)_4$ (55%); d) *i.* *n*-BuLi; *ii.* $ClCO_2Et$ (70%); e) KOH (71%); f) HCl (91%); g) KOH (80%)

Scheme 12

deprotonation of **105** with LHMDS in THF at 0°C in the presence of HMPA, followed by trapping the enolate with *N*-phenyltriflimide. The optimized conditions for the preparation of isomeric (*E,E*)-triflate **107** also involve lithium enolate formation by treatment with $LiNEt_2$,



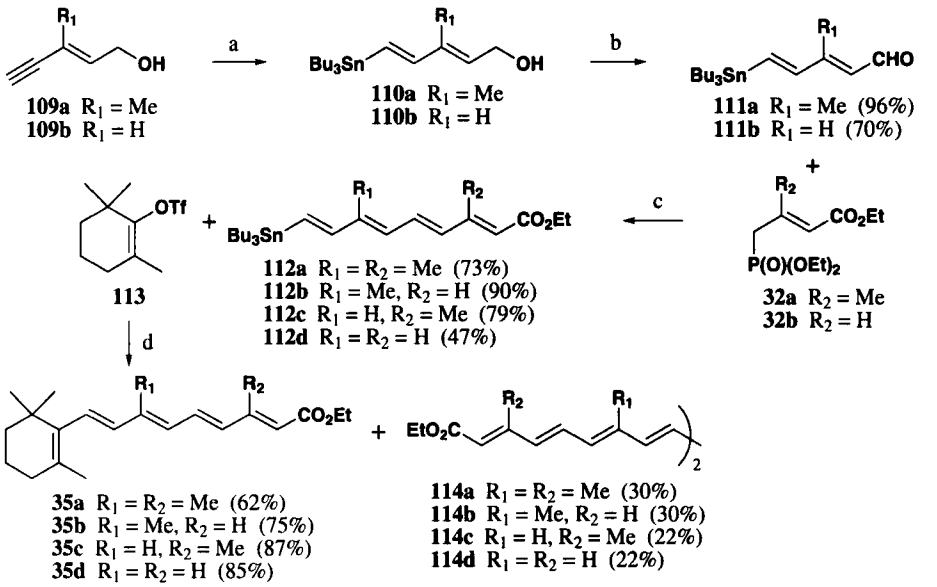
a) CuCN, *n*-BuLi, *n*-Bu_3SnH, THF, -30°C (94%); b) MnO_2, CH_2Cl_2, 25°C (89%); c) CH_3PPh_3Br, $NaN(TMS)_2$, HMPA, -78 to 25°C (80%); d) *i.* LiHMDS, THF, HMPA, 0°C. *ii.* Tf_2NPh (94%); e) **104**, $Pd_2(dba)_3$, $AsPh_3$, NMP, 25°C (70%); f) *i.* $LiNEt_2$, THF, -78°C. *ii.* HMPA. *iii.* Tf_2NPh (83%); g) **104**, $Pd_2(dba)_3$, $AsPh_3$, NMP, 25°C (75%)

Scheme 13

followed by the sequential addition of HMPA and *N*-phenyltriflimide. A mixture of the terminal double bond triflate isomers **107** and **106** was isolated in a 4:1 ratio, in a satisfactory 83% yield. The critical coupling step was performed using the conditions developed by Farina[38] that involve "ligandless" Pd in combination with ligands of low donor ability in a polar aprotic solvent [$Pd_2(dba)_3$, $AsPh_3$, *N*-methylpyrrolidinone]. Under these conditions fragments **104** and **106** coupled at ambient temperature, affording (8*Z*)-anhydroretinol **108** in 70% yield with retention of the stereochemical integrity of both partners. The use of identical reaction conditions in the coupling of the inseparable 4:1 mixture of triflates **107** and **106** and stannane **104**, led in 75% yield to the desired anhydroretinol (**7**) together with its (8*Z*)-isomer **108** in *ca.* 2:1 ratio. Control experiments showed that isomerization took place at the product stage, since 3:2 and 2:1 *E/Z* (**7/108**) ratios were obtained by stirring pure anhydroretinol (**7**) in NMP for two hours, in the absence or in the presence of Pd, respectively. Although it is unknown whether the isomerization is catalyzed by Pd, the instability of highly conjugated polyenes might become a limitation for the synthesis of the thermodynamically less stable isomers of these compounds.

The rate-acceleration reaction conditions for Stille coupling developed by Farina [$Pd_2(dba)_3$, $AsPh_3$, NMP] were also selected in an effort to carry out an exhaustive study of the application of this process to the formation of every retinoid side-chain single bond.[39]

The method of choice for the C_6-C_7 bond construction (C_9 + C_{11} pattern) was the coupling of cyclohexenyl triflates (regioselectively obtained from commercially available ketones) and tetraenylstannanes **112** (synthesis depicted in *Scheme 14*). This selection stems



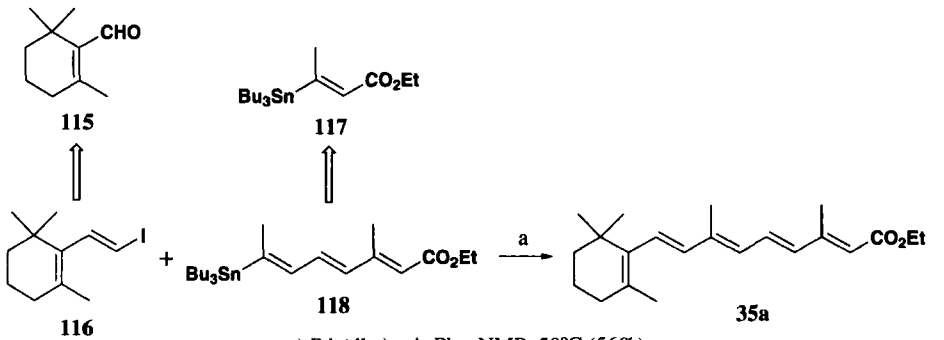
a) (*n*-Bu_3Sn)(Bu)CuLi•LiCN, THF –78°C; b) SO_3•Py, Et_3N, CH_2Cl_2, DMSO, 0°C; c) *i.* *n*-BuLi, DMPU, THF, 0°C for **112a** and **112c**; or LiHMDS, HMPA, -78°C for **112b** and **112d**; *ii.* aldehyde **111**, -78 to 20°C; d) $Pd_2(dba)_3$, $AsPh_3$, NMP, 70°C for **35a** and **35b**, 50°C for **35c** and **35d**

Scheme 14

from the easy and well-documented preparation of methyl-substituted cyclohexenyl triflates from the corresponding cyclohexanones, and allowed the preparation of the entire series of ring-demethylated retinoic acid analogues.[38a] Since the Stille reaction is sensitive to steric hindrance, the reaction temperatures required for the coupling of cyclohexenyltriflates and tetraenylstannanes showed an inverse correlation with the number and position of the methyl substituents, in particular in the hydrophobic ring.[38a] As a consequence, and despite careful deoxygenation of reaction flasks and solvents, octaenes were obtained by dimerization of tetraenylstannanes and isolated as secondary products in quantities related to the reaction temperatures employed. Dimerization of the stannane counterpart is perhaps the most common side-reaction in Stille couplings.[40] Despite this shortcoming, the approach is highly reliable in providing good to excellent yields of retinoids with *trans* geometries. The study was also extended to the preparation of side-chain demethylated retinoids **35b-d** (*Scheme 14*). Functionalized tetraenylstannanes **112a-d** were stereoselectively prepared in good yield by HWE condensation of phosphonates **32a** and **32b** with stannyldienals **111a** and **111b**. Stille coupling reaction of stannanes **112a-d** and trimethylcyclohexenyl triflate **113** required heating at 50-70°C and provided retinoates **35a-d**, together with variable amounts of the octaenes **114a-d**. In spite of the formation of these undesired by-products, this route has proven remarkably versatile since both coupling components are easily prepared, and the tetraenylstannanes were found to be moderately stable.

The temperatures required for coupling highly substituted triflates appear to be incompatible with the more sensitive *cis*-geometries of the side chain. This limitation was overcome by employing the Suzuki cross-coupling of components of similar complexity (*vide infra*).

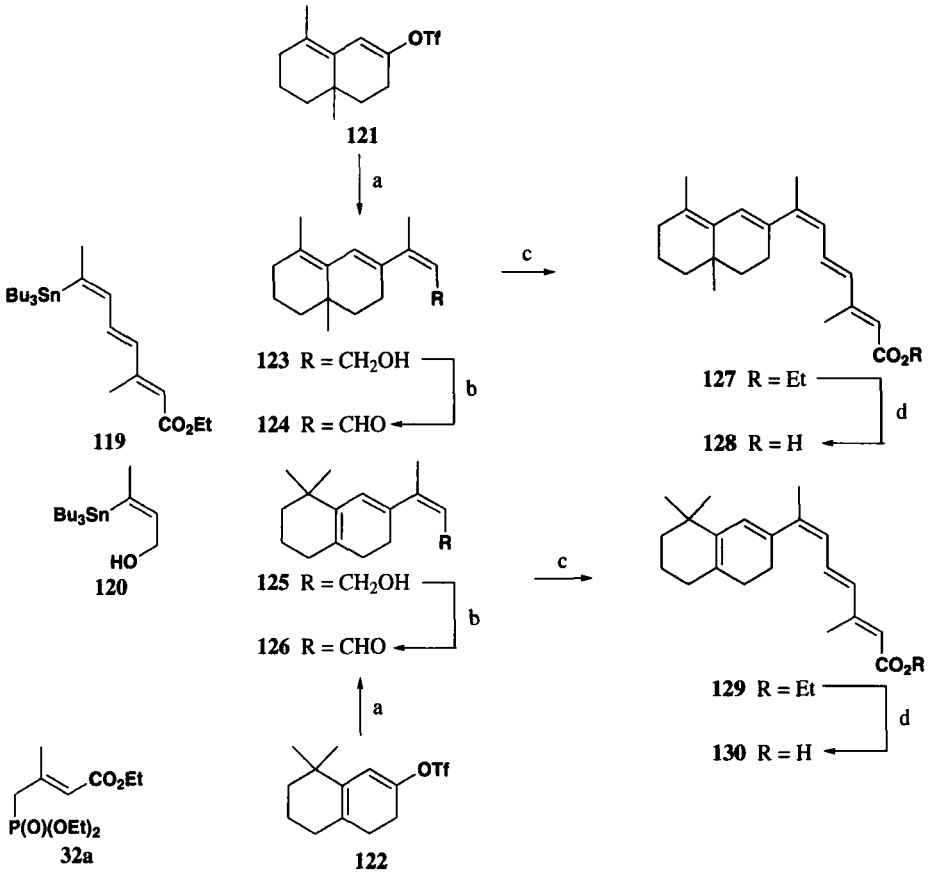
The Stille reaction leading to ethylretinoate (**35a**) by formation of the C_8-C_9 bond through condensation of dienyliodide **116** and trienylstannane **118** took place at moderate temperatures (50°C), which might be advantageous for the preparation of certain labile *cis* retinoids. However, difficulties were encountered in the preparation of dienyl iodide **116** from β-cyclocitral (**115**) (*Scheme 15*), which constitutes the main limitation of this variant.



a) $Pd_2(dba)_3$, $AsPh_3$, NMP, 50°C (56%)

Scheme 15

However, for dienyl electrophiles that are easier to synthesize, such as triflates **121** and **122**, the condensation with stannanes proved to be high yielding, as demonstrated for the preparation of 9-*cis*-retinoic acid analogues with locked 6-*s*-*trans* and 6-*s*-*cis* conformations (**128** and **130**).[41] Although the convergent route involving the Stille coupling of dienyltriflate **121** and trienylstannane **119** at 40°C led to partial isomerization of the labile *cis* double bond, the stepwise approach to the polyene chain was successful, as shown in *Scheme 16*. (*Z*)-3-Tributylstannylbuten-1-ol (**120**) coupled to triflates **121** and **122** at room temperature providing trienes **123**



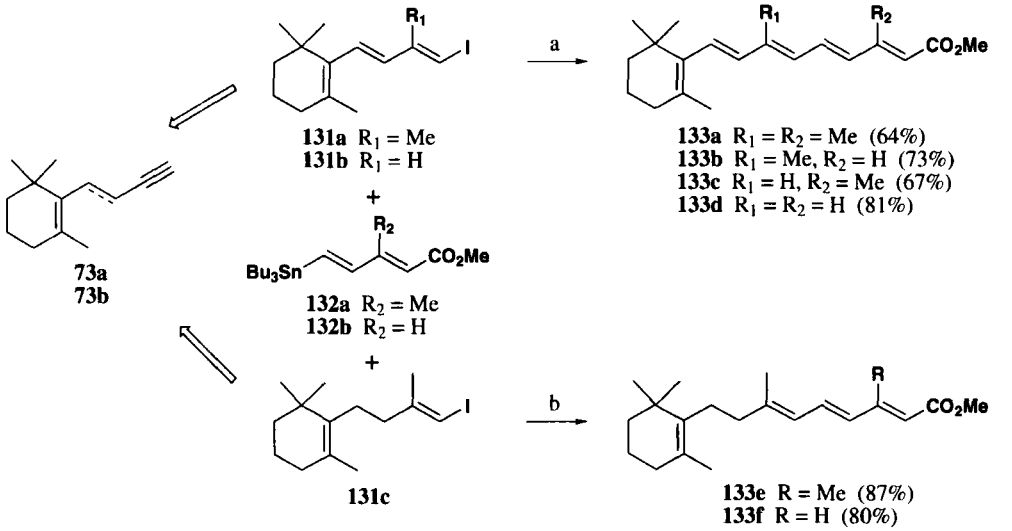
a) **120**, $Pd_2(dba)_3$, $AsPh_3$, NMP, 25°C (95% for **123**, 95% for **125**); b) Dess-Martin periodinane, pyridine, CH_2Cl_2, 0°C (95% for **124**, 95% for **126**); c) **32a**, *n*-BuLi, DMPU, THF, -78°C (70% for **127**, 77% for **129**); d) 5N KOH, EtOH, 80°C (77% for **128**, 95% for **130**)

Scheme 16

and **125** in excellent yield. Interestingly, a comprehensive study of the reactivity of **120** and a series of highly hindered triflates revealed that the alcohol group of **120** induced a rate-acceleration effect, allowing room-temperature Stille coupling reactions, perhaps through coordination of the heteroatom to Pd in the rate-limiting transmetalation step. Oxidation of trienols **123** and **125** to the corresponding aldehydes **124** and **126** with the Dess-Martin reagent, followed by HWE condensation of the carbonyl compounds using the lithium anion of phosphonate **32a**, in

THF/DMPU, led to pentaenes **127** and **129** in good yield and with excellent stereocontrol. Finally, esters **127** and **129** were saponified to afford the desired retinoic acid analogues **128** and **130** without compromising the stereochemical integrity of the polyene chain.

The most convenient of the convergent approaches to the retinoid skeleton, in terms of the straightforward preparation of the required fragments, is that based on the formation of the C_{10}-C_{11} bond ($C_{14} + C_6$ construction tactic). Alkenyl iodide **131a** and its analogue **131c** can easily be obtained by zirconium-assisted carboalumination of the appropriate alkyne followed by iodination of the alkenylalane intermediate (*Scheme 17*).[42] Alternatively, the boron-iodine exchange

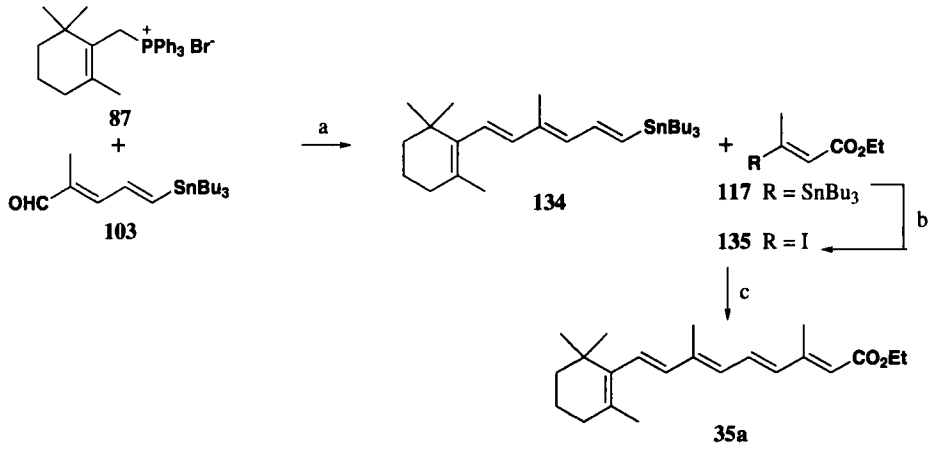


a) $Pd_2(dba)_3$, $AsPh_3$, NMP, 60°C for **133a**; 50°C for **133b**, **133c** and **133d**; b) $Pd_2(dba)_3$, $AsPh_3$, NMP, 80°C

Scheme 17

was employed for the preparation of the demethylated analogue **131b** starting from the corresponding pinacol boronate.[43] This stable compound results from hydroboration of the alkyne with pinacol borane.[44] These trienyl iodides **131a** and **131b**, and dienyl stannanes **132a** and **132b** were subjected to the standard conditions described above within the temperature range 50 to 80°C depending upon structural variations. They afford parent methylretinoate (**133a**), its side-chain demethylated analogues (**133b-d**) and some 7,8-dihydroderivatives (**133e-f**) in good to excellent yields.

The terminal alkenyl-alkenyl disconnection (C_{12}-C_{13} bond construction) requires the preparation of the complementary functionalized fragments with tetraenyl and vinyl structures **134** and **135**. The C_{16}-tetraenyl stannane **134** was prepared in 77% yield by Wittig condensation of phosphonium salt **87** and stannyl aldehyde **103** (*Scheme 18*). In addition, C_4-alkenylstannane **117**, derived from methyl tetrolate, was treated with I_2 in CH_2Cl_2 to provide vinyl iodide **135**. Coupling of both fragments under standard conditions took place at room temperature to afford ethyl retinoate (**35a**) in 97% yield.



a) *i.* *n*-BuLi, THF, 0°C; *ii.* aldehyde **103**, THF, 0 to 25°C (77%); b) I_2, CH_2Cl_2, 25°C (67%); c) $Pd_2(dba)_3$, $AsPh_3$, NMP, 25°C (97%)

Scheme 18

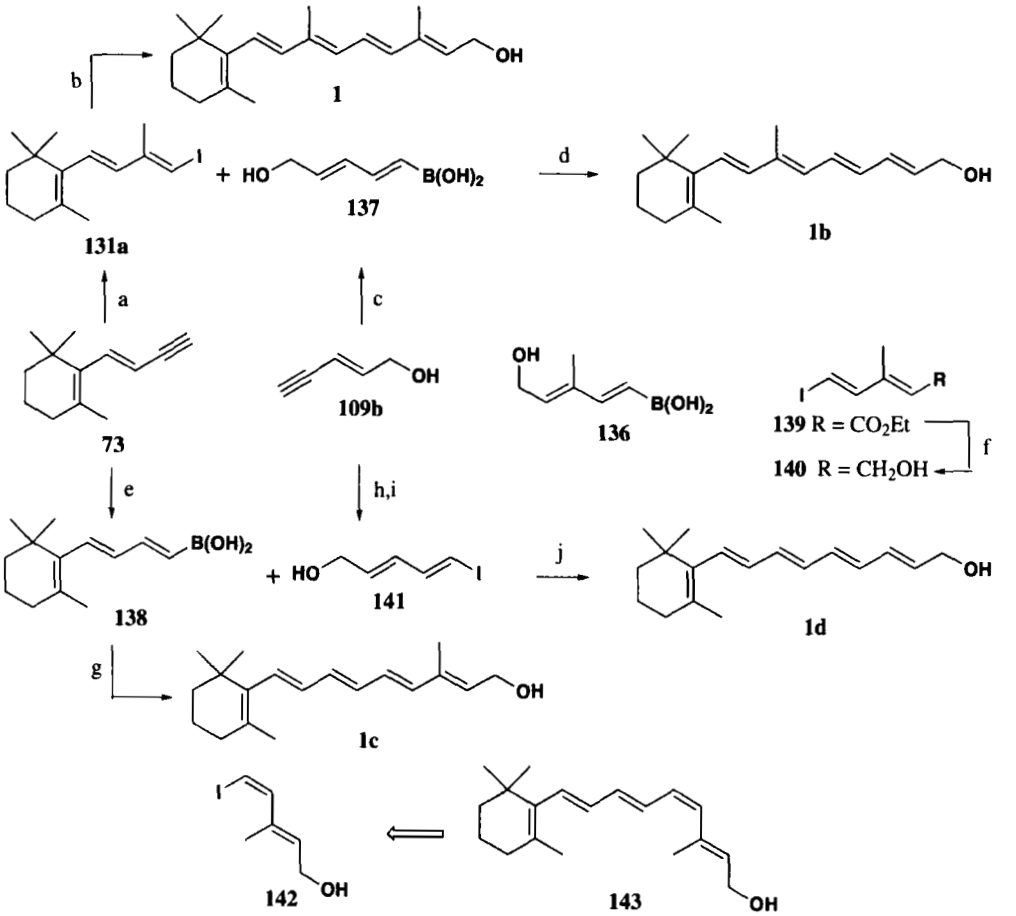
This comprehensive survey provided appropriately matched components for the construction of every single bond joining Csp^2-Csp^2 atoms of the retinoid side chain. The findings should provide guidelines for synthetic applications of the Stille reaction to other substituted polyenes, since comparison of the reactivity of different coupling partners with different degrees of steric hindrance was made where appropriate.

4. Suzuki Reaction

The organoboron compounds, together with the tin compounds, are the most frequently used organometallics in metal-catalyzed cross-coupling reactions. Although both share the tolerance of a broad range of functional groups and the choice of preparation by a variety of methods, non transferable groups on the organoboron compounds are more easily incorporated into the organometalic, and the non-toxic inorganic by-products are readily removed by simple work-up procedures.[45] In addition, aqueous conditions are normally used, due to the strict requirement of the Suzuki reaction by at least two equivalents of an inorganic base.[45a] An additional advantage of organoboranes relative to organostannanes is their greater tolerance to steric hindrance on both coupling partners. This can be advantageous on the synthesis of sterically hindered substances.

The Pd-catalysed cross-coupling reaction of organoboron derivatives and organic electrophiles (Suzuki reaction) has been successfully exploited on the synthesis of several natural and synthetic retinoids.[46] An example of this useful methodology is the stereoselective preparation of retinol (**1**) and its 9- and/or 13-demethyl analogues (**1b-d**) (see *Scheme 19*).[46a] The method allows to choose among differently functionalized coupling partners to construct the pentaene side chain of retinoids in what can be considered as the conjugation-extended variant of Suzuki's classical diene synthesis. The boronic acid could be attached to either a diene (**136** and **137**) or a triene skeleton (**138**), whereas the vinyl iodide fragment should display a complementary match,

i.e. trienyl iodide **131a** or dienyl iodides **140** and **141**. Alkynes are again the ideal precursors of both alkenyl partners, using the highly *syn* selective Negishi's carboalumination-iodination[30] or the hydroboration (iodination) reaction protocols.[47] For the latter, the effect of catalytic quantities

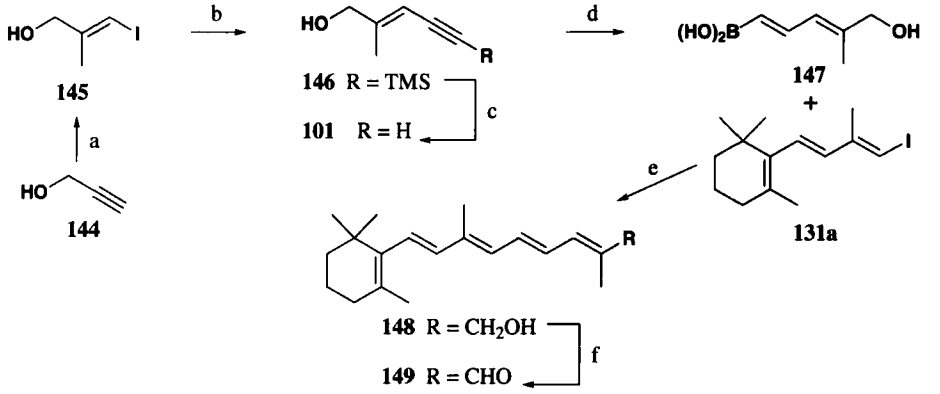


a) *i.* Cl_2ZrCp_2, $AlMe_3$, CH_2Cl_2, 0 to 25°C; *ii.* ICN, THF, 0°C (72%); b) **136**, $Pd(PPh_3)_4$, 10% aq. TlOH, THF, 25°C (83%); c) *i.* Catecholborane, 0 to 25°C; *ii.* H_2O, 25°C (64%); d) $Pd(PPh_3)_4$, 10% aq. TlOH, THF, 25°C (60%); e) *i.* Catecholborane, BH_3•*N,N*-diethylaniline, PhH, 25°C; *ii.* H_2O, 25°C (74%); f) DIBAL-H, THF, 0°C (88%); g) **140**, $Pd(PPh_3)_4$, 10% aq. TlOH, THF, 25°C (50%); h) *i.* Catecholborane, 0 to 25°C; *ii.* H_2O, 25°C (64%); i) I_2, NaOH, Et_2O, 0°C (62%); j) $Pd(PPh_3)_4$, 10% aq. TlOH, THF, 25°C (40%)

Scheme 19

of BH_3•*N,N*-diethylaniline proved beneficial, allowing the hydroboration reaction to proceed at room temperature. The conditions developed by Kishi were chosen for the Suzuki cross-coupling reaction of these fragments.[48] Thus, stirring a degassed THF solution of the boronic acid and the alkenyl iodide in the presence of 10% aqueous TlOH and $Pd(PPh_3)_4$ for 30 minutes at room temperature, retinol (**1**) and its analogues **1b-d** were obtained with excellent stereocontrol and in moderate to good yields (*Scheme 19*). Polyenes with sensitive *cis* double bonds such as 11-*cis*-9-demethylretinol (**143**) can be prepared likewise with retention of the starting dienyliodide **142** *cis* geometry. [28]

Positional exchange of the methyl and H substituents along the side-chain can expand the range of retinal analogues prepared using this methodology. In connection with a study of the steric tolerance displayed by the binding site of the protein bacteriorhodopsin, the light-energy conversion system of Halobacteria,[5] we prepared the side-chain methyl-shifted retinals with *E* geometry.[46c] The synthesis of one of these analogues, 13-demethyl-14-methylretinal (**149**), is represented in *Scheme 20*. As shown previously for the synthesis of retinol, the C_{10}-C_{11} bond of

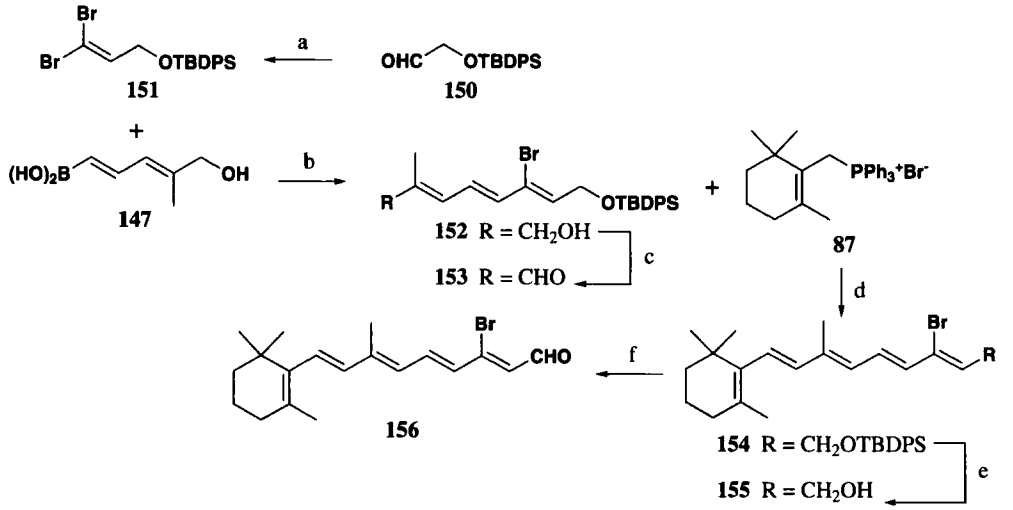


a) *i.* Cl_2ZrCp_2, $AlMe_3$, CH_2Cl_2, 0°C; *ii.* ICN, THF, 0°C (60%); b) TMS-acetylene, pyrrolidine, CuI, $Pd(PPh_3)_4$, 25°C (91%); c) *n*-Bu_4NF, THF, 25°C (93%); d) *i.* Catecholborane; *ii.* H_2O, 25°C (52%); e) $Pd(PPh_3)_4$, 10% aq. TlOH, THF, 25°C (61%); f) MnO_2, CH_2Cl_2, 25°C (95%)

Scheme 20

analogue **148** was constructed in 61% yield by Pd-catalysed cross-coupling reaction of alkenyl iodide **131a** and alkenyl boronic acid **147**. The synthesis of the latter started from propargyl alcohol **144**. Zirconium-catalysed methylalumination/iodination, followed by Sonogashira-type coupling (see Section IV.6) with trimethylsilylacetylene, afforded **146**. Deprotection of **146** led to enynol **101** that was finally transformed into boronic acid **147** by treatment with catecholborane followed by hydrolysis.

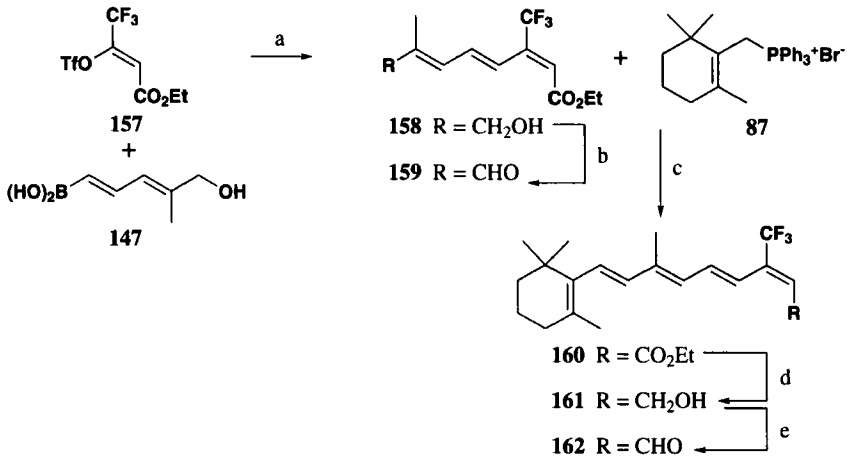
The Suzuki reaction has also been used in the preparation of retinal analogues with unnatural substituents.[49] The synthesis of (13*Z*)-13-bromo-13-demethylretinal (**156**) illustrates the use of alkenyl *gem*-dibromides in the Suzuki reaction.[50] Dibromide **151**, obtained from aldehyde **150** in 75% yield by the Corey-Fuchs procedure, reacted with boronic acid **147** under very mild conditions to afford the bromo-substituted trienol **152** in 88% yield (*Scheme 21*). The considerable rate differences between the *Z* and *E* bromides in favour of the latter[50] allowed the coupling reaction to proceed with remarkably high stereoselectivity. Oxidation of trienol **152** with MnO_2 yielded the corresponding trienal **153** which was treated with the ylide derived form the phosphonium salt **87** to afford the Wittig condensation product **154** in 87% yield, displaying the entire retinoid polyene side-chain. Deprotection of the alcohol followed by oxidation of **155** with MnO_2 provided the target compound (13*Z*)-13-bromo-13-demethylretinal (**156**).



a) PPh_3, CBr_4, CH_2Cl_2, 0 to 25°C (75%); b) $Pd(PPh_3)_4$, 10% aq. TlOH, THF, 25°C (88%); c) MnO_2, CH_2Cl_2, 25°C (98%); d) *n*-BuLi, THF, -30 to 0°C (87%); e) *n*-Bu_4NF, THF, 25°C (80%); f) MnO_2, CH_2Cl_2, 25°C (98%)

Scheme 21

As discussed for the Stille reaction, alkenyl triflates are versatile electrophile partners in Pd-catalyzed cross-coupling reactions, since they can be regioselectively obtained in geometrically homogeneous form starting from cyclic and (oftentimes) acyclic ketones. As an application of this the preparation of (13*E*)-20,20,20-trifluororetinal (**162**) is shown in *Scheme 22*.[49a] The



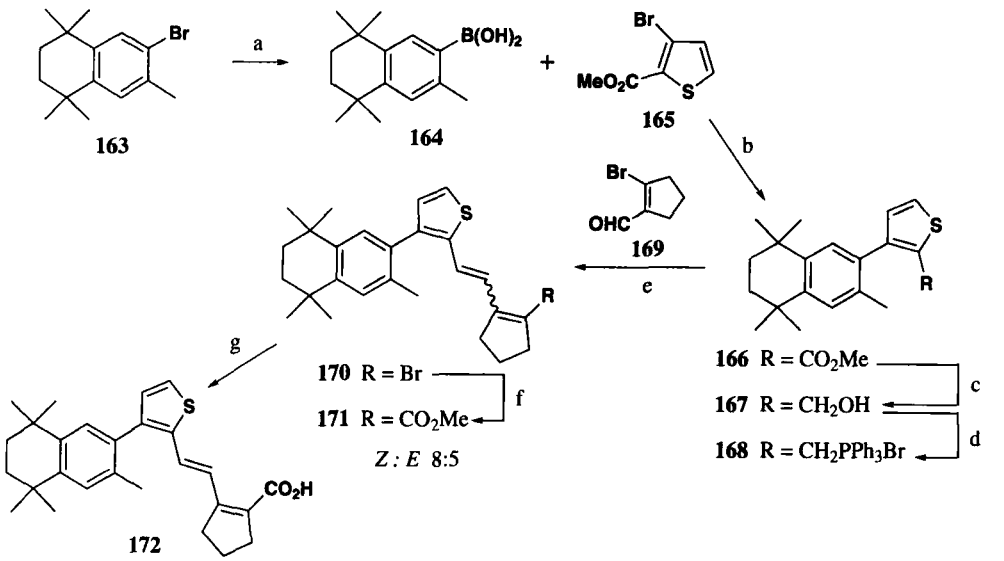
a) $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, 80°C (83%); b) MnO_2, CH_2Cl_2, 25°C (98%); c) *n*-BuLi, THF, -30 to 0°C (75%); d) DIBAL-H, THF, -78 to 0°C (94%); e) MnO_2, CH_2Cl_2, 25°C (98%)

Scheme 22

sequence involves the coupling of (*Z*)-alkenyl triflate **157** (stereoselectively prepared from the corresponding β-ketoester) and boronic acid **147**. Application of the modified conditions

described by Suzuki for coupling triflates to boronic acids [$Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, 80°C] afforded trienol **158** in 80% yield, with retention of configuration in both coupling partners. The relatively high temperatures that are required for Suzuki coupling involving the less reactive triflates could become a limitation for the stereoselective synthesis of the thermally unstable *cis* isomers. Oxidation of **158** with MnO_2, followed by Wittig condensation of **159** with the ylide derived from phosphonium salt **87** afforded ethyl (13*E*)-20,20,20-trifluororetinoate (**160**) in good yield (75%). Reduction with DIBAL-H, followed by oxidation of alcohol **161** with MnO_2 in CH_2Cl_2 gave (13*E*)-20,20,20-trifluororetinal (**162**) in excellent yield.

The Suzuki cross-coupling reaction has also been widely applied to the synthesis of arotinoids due to the commercial availability or easy preparation of aryl boronic acids and electrophiles.[51] To illustrate the use of aryl bromides as electrophiles in cross-coupling reactions was selected the preparation of 9,13-di*cis* locked retinoic acid **172**.[51a] Reaction of aryl bromide **163** with *t*-butyllithium and triisopropylborate, followed by hydrolysis afforded aryl boronic acid **164** in 75% yield. The Pd–catalyzed Suzuki cross-coupling of boronic acid **163** and aryl bromide **165** in DME in the presence of $NaHCO_3$ gave the ester **166** in 98% yield (*Scheme 23*). The unusually



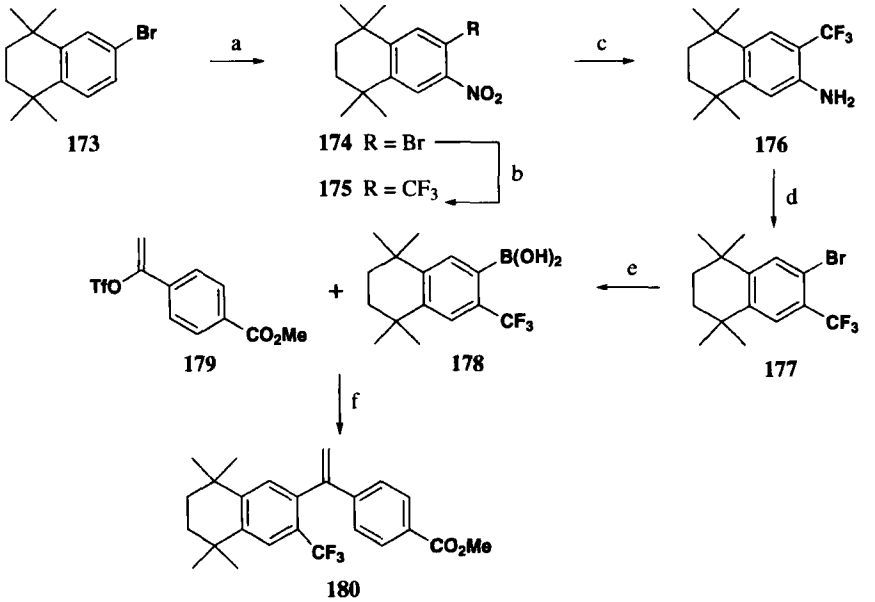
a) *i.* *t*-BuLi, -78°C; *ii.* $B(Oi\text{-}Pr)_3$, 25°C; *iii.* HCl (75%); b) $Pd(PPh_3)_4$, $NaHCO_3$, DME, 25°C (98%); c) $LiAlH_4$ (quant.); d) $Ph_3P{\bullet}HBr$, MeOH (quant.); e) *t*-BuOK, CH_2Cl_2 (95%); f) CO, $Pd(PPh_3)_4$, MeOH, Et_3N, DMF, 85°C (78%); g) *i.* KOH, MeOH, H_2O, 100°C; *ii.* HCl; *iii.* Recrystallization from ethyl alcohol (45%)

Scheme 23

mild conditions for aryl-aryl coupling could be a consequence of the increased reactivity of **165** due to the effect of the ester substituent and the ring heteroatom. Subsequent reduction and treatment of alcohol **166** with triphenylphosphine hydrobromide provided phosphonium salt **168**. Wittig olefination of **168** with bromoaldehyde **169** afforded an inseparable 8:5 mixture of *Z*/*E* isomers of bromide **170**. A second Pd-catalysed reaction, the carbonylation of bromides **170** with

nucleophilic abstraction of the σ-acyl-Pd complex by MeOH completed the preparation of the modified side chain. Arotinoid **172** was obtained in geometrically pure form by saponification of the mixture of esters **171** followed by recrystallization.

Alkenyl triflates have also become suitable coupling partners in the Suzuki reaction for the synthesis of arotinoids. Quing and Fan reported the preparation of **180** by cross coupling of arylboronic acid **178** and alkenyltriflate **179**.[51b] The trifluoromethyl compound **180** is an analogue of Targretin® (LGD1069 **15**, *Fig. 2*), a selective agonist of RXR. *o*-Trifluoromethylarylboronic acid **178** was prepared from bromide **173** using straightforward functional group transformations (*Scheme 24*). Nitration of **173** at 60°C gave exclusively regioisomer **174** in 75% yield. Bromide **174** was then treated with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA to afford the



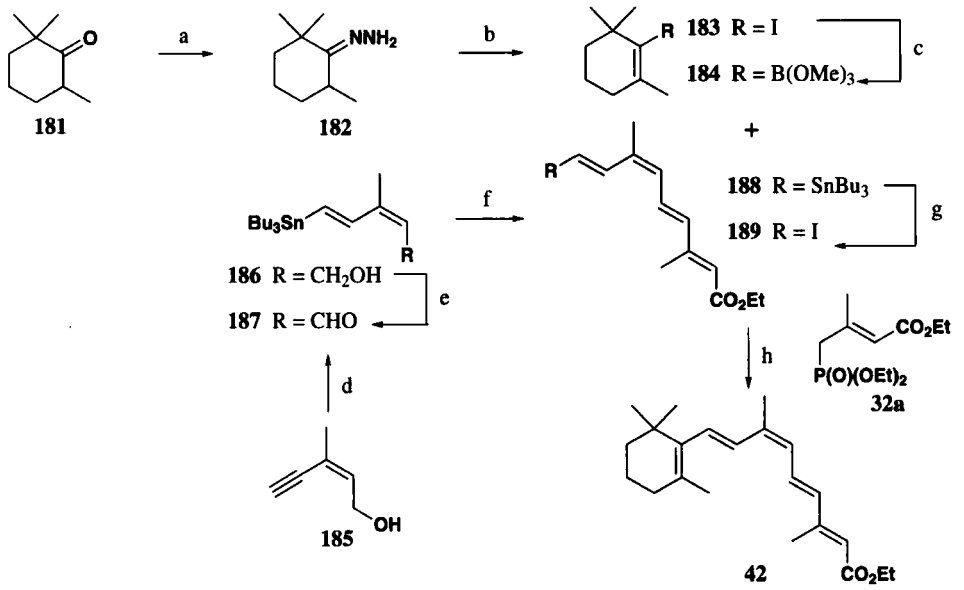
a) HNO_3, H_2SO_4, 60°C (75%); b) $FSO_2CF_2CO_2Me$, CuI, DMF, HMPA, 70°C (85%); c) Fe/HCl, CH_3OH, 80°C (95%); d) $NaNO_2$, H_2SO_4, KBr, CuBr, 60°C (80%); e) *i.* *t*-BuLi, THF, -78°C; *ii.* $B(Oi\text{-}Pr)_3$, -78°C; *iii.* aq. NH_4Cl, 0°C (65%); f) $Pd(PPh_3)_4$, potassium triphosphate trihydrate, dioxane, reflux (95%)

Scheme 24

trifluoromethyl derivative **175** in 85% yield. The nitro compound **175** was reduced to the corresponding arylamine **176**, which was then converted into the bromide **177** through the corresponding diazonium salt. Finally, treatment of the bromide **177** with *t*-butyllithium followed by triisopropylborate at –78°C afforded the desired arylboronic acid **178** in 65% yield. Vinyl triflate **179** was easily prepared from methyl-4-acetyl benzoate. Pd-catalyzed cross-coupling reaction of fragments **178** and **179** using 3 equivalents of potassium triphosphate trihydrate in refluxing dioxane afforded compound **180** in 95% yield.

The efficiency of the previously described C_6-C_7 bond-forming strategy by Stille reaction for the synthesis of retinoids (see *Scheme 14*) was somehow limited by the high tempera-

tures required for coupling hindered cycloalkenyltriflates and tetraenylstannanes. These temperatures (40 to 80°C) are not compatible with *cis* geometries on the tetraenylstannane component. The Suzuki reaction, being less sensitive to steric hindrance, solves this limitation. A new synthesis of 9-*cis*-retinoic acid (**5**) using cycloalkenylboronate **184** and tetraenyliodide with 9Z geometry **189** was developed (*Scheme 25*). Interestingly, both components are conveniently generated *in situ*, thus overcoming the tedious purification of boronic acids and the instability of highly conjugated iodides. The Suzuki coupling of **184** and **189** proceeds at room temperature providing ethyl 9-*cis*-retinoate (**42**) in 84% yield.[52]



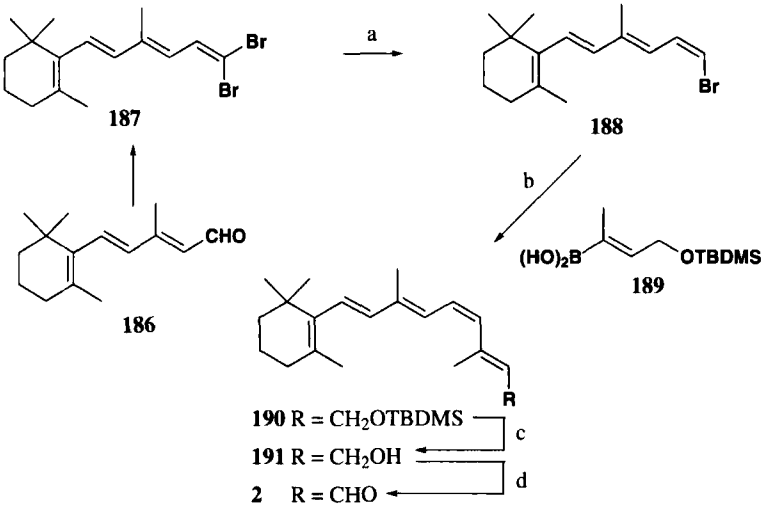
a) $H_2NNH_2 \cdot H_2O$, Et_3N, EtOH (80-90%); b) I_2, DBN, Et_2O (70-75%); c) *i.* *t*-BuLi, THF -78°C; *ii.* $B(OMe)_3$, -78 to 0°C; d) *n*-BuLi, *n*-Bu_3SnH, CuCN, THF, -78 to -40°C (70%); e) MnO_2, K_2CO_3, CH_2Cl_2, 0 to 25°C (86%); f) **32a**, *n*-BuLi, DMPU, THF, -115 to -40°C (93%); g) I_2, CH_2Cl_2, 25°C; h) $Pd(PPh_3)_4$, 10% aq TlOH, THF, 25°C (84%)

Scheme 25

Although this method constitutes a synthetic alternative to the Stille reaction, both Pd-catalyzed processes exploit the availability of cyclohexanones and tetraenylstannanes as starting materials. In this latter example, cyclohexanone **181** can be converted to cycloalkenyliodide **183** by oxidation of hydrazone **182** with iodine. Tin-iodine exchange provides the highly conjugated iodide **189** from stannane **188**. Stannylcupration reaction of enynol **185** to form dienylstannane **186** defines the stereochemistry of tetraenylstannane **188**. The synthetic strategy depicted in *Scheme 25* can also been applied to the preparation of ring-demethylated analogues,[52b] as well as other mono-*cis*[52c] and poli-*cis* isomers of native retinoids.

Much of the success on the metal-catalyzed cross-coupling reactions rests on the availability of configurationally homogeneous fragments. In this regard, 1,1-dibromo-1-alkenes are versatile intermediates. As mentioned (*Scheme 21*) the bromine atoms exhibit differential reac-

tivity with organometallic nucleophiles.[50] As an extension of this rate difference, it is possible to transform 1,1-dibromo-1-alkenes into stereodefined (*Z*)-1-bromo-1-alkenes using Pd-catalyzed hydrogenolysis.[53] The reactions of alkenyl gem-dibromides with Bu_3SnH in the presence of $(PPh_3)_4Pd$ in benzene is complete after short reaction times (0.2-2h) at room temperature. Interestingly, a rate enhancement was observed for the more conjugated systems. Hydrogenolysis of dibromide **187** (obtained from the precursor aldehyde **186** using the Corey-Fuchs protocol) afforded stereoselectively *Z*-bromide **188** in 86% yield (*Scheme 26*). Suzuki cross-coupling of



a) $Pd(PPh_3)_4$, Bu_3SnH, C_6H_6, 25°C (86%); b) **188**, $Pd(PPh_3)_4$, KOH, Ag_2CO_3, THF, 25°C (77%); c) *n*-Bu_4NF, THF, 25°C; d) $BaMnO_4$, CH_2Cl_2, 25°C (85%)

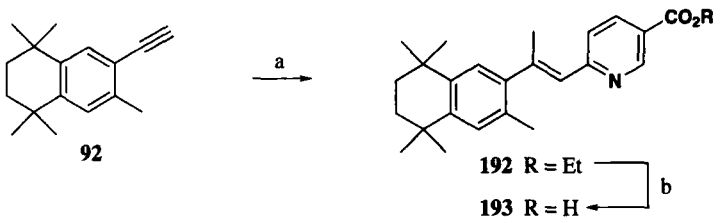
Scheme 26

188 with alkenylboronic acid **189** exploited the rate-enhancement effect of silver salts,[53c] affording **190**. Upon removal of silylether protecting group and oxidation a short, stereocontrolled route to the chromophore of the visual pigments, 11-*cis*-retinal **2** was completed.

5. Other metal-catalyzed cross-coupling reactions

Besides organozincs, organostannanes and organoboranes, other alkenylmetal derivatives (of Al, Mg, Cu and Zr) were employed in Negishi's comparative work on the performance of different metals for the preparation of vitamin A.[27a] The use of these organometals has not been developed in the same extent as the formers due to limitations in preparation and functional group compatibility.

However, good yields can be obtained when substrates do not present an unstable polyene structure. This is the case of the heterocyclic analogues **193**,[54] that can be synthesised in a single step from arylalkyne **92** by carrying out a Zr-catalyzed methylalumination followed by the Pd-catalyzed cross coupling of the obtained alkenylaluminum with ethyl 6-iodonicotinate (*Scheme 27*).



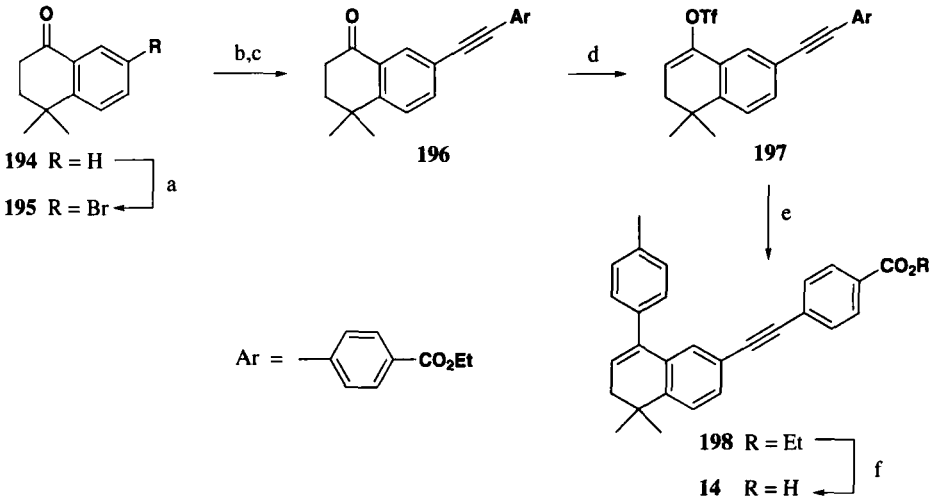
a) *i.* $AlMe_3$, Cp_2ZrCl_2; *ii.* ethyl 6-iodonicotinate, $Pd(PPh_3)_4$ (52%); b) *i.* KOH, EtOH, H_2O; *ii.* 10% aq. HCl

Scheme 27

6. Sonogashira Reaction

The presence of a triple bond on the retinoid side-chain imparts local linearity to the polyene. The substitution of alkene by alkyne functional groups in a retinoid or arotinoid, with the purpose of inducing directionality in the interaction with its receptor, has been a recurrent tactic in retinoid research. Undoubtedly, the most versatile method to synthesize internal alkynes is the Sonogashira cross-coupling reaction.[55] The process involves the Pd-catalyzed cross coupling in amine solvents of organic electrophiles and terminal alkynes in the presence of CuI. The mildness of the reaction conditions together with the recent development of acetylene chemistry make this process synthetically appealing.

An example of the application of this reaction in the retinoid field is the synthesis of AGN193109 (**14**), a very high affinity antagonist of RA-induced function at all three RAR isotypes.[9g,56] The synthesis of AGN193109 (**14**) starts with the bromination of tetralone **194** in the presence of $AlCl_3$ at 70°C (80% yield) to provide the arylbromide **195** as shown in *Scheme 28*.



a) $AlCl_3$, Br_2, CH_2Cl_2, 70°C (80%); b) *i.* TMS-acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, 60°C; *ii.* K_2CO_3, MeOH (76%); c) 4-I-$C_6H_4CO_2Et$, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, 25°C (64%); d) *i.* $NaN(SiMe_3)_2$, THF, -78°C; *ii. N*-(5-chloro-2-pyridyl)triflimide, 0 to 25°C (77%); e) *i.* 4-BrC_6H_4Me, *t*-BuLi, $ZnCl_2$, THF, -78 to 25°C; *ii.* $Pd(PPh_3)_4$, 5°C (72%); f) LiOH, THF, H_2O (97%)

Scheme 28

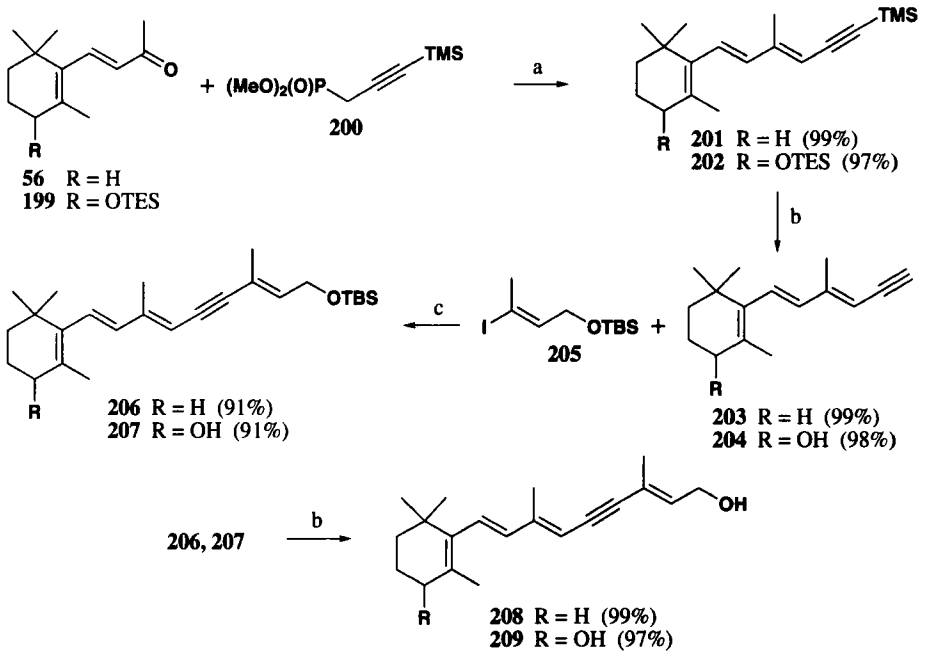
Then, palladium-catalysed cross-coupling reaction of **195** with an excess of TMS-acetylene at 60°C affords the substituted alkyne. Removal of the TMS group with K_2CO_3 in MeOH gives the corresponding terminal acetylene in 76% overall yield that then undergoes a second palladium-catalyzed cross coupling with ethyl 4-iodobenzoate to give keto ester **196** in 64% yield. In preparation for the last metal-catalyzed cross-coupling in the sequence, **196** is converted into triflate **197** in 77% yield by treatment with NaHMDS and *N*-(5-chloro-2-pyridyl)triflimide (Comin's reagent). Triflate **197** is finally coupled with the organozinc prepared from 4-bromotoluene at 5°C to provide ester **198** in 72% yield. Lastly, **198** is saponified to the corresponding acid **14** in 97% yield using LiOH in THF.

Several analogues of AGN193109 (**14**) differing in the substituents of the phenyl group incorporated in the last Negishi-type coupling reaction, have also been prepared starting from triflate **197**.[9] In addition, the same sequence depicted in *Scheme 28* can provide other analogues with a range of alkyl substituents on the heteroatom by replacing the tetralone ring by a 3,4-dihydro-2(1*H*)-quinolinone.[56] Given the limited number of RAR antagonists discovered to date, these series could become an invaluable tool to determine potential applications of RAR antagonists in disease models, as well as to further our understanding of retinoid hormonal pathways.

The Sonogashira cross-coupling reaction has also been applied to the preparation of retinoid analogues that include a triple bond in the polyenic side-chain. Nakanishi *et al.* have recently reported the preparation of the 11-yne retinols **208** and **209**, en route to 11-*cis*-retinol (**191**) and its 4-hydroxy-analog (**210**) respectively.[57] The synthesis starts with the HWE condensation of β-ionone (**56**) and TES-protected 4-hydroxy-β-ionone (**199**) (readily prepared from β-ionone) with dimethyl (3-trimethylsilyl-2-propynyl)phosphonate (**200**) to afford alkynes **201** and **202** in excellent yields (99% and 97% respectively) but moderate stereoselectivity (e.g., for **202** C_9-C_{10} 5:1 *E/Z*) (see *Scheme 29*). Deprotection of both silyl groups with *n*-Bu_4NF releases the terminal alkynes **203** and **204** in almost quantitative yields (99% and 98%), that are then coupled with vinyliodide **205** in the presence of $Pd(PPh_3)_4$, CuI and *i*-$PrNH_2$ to afford 11-yne precursors **206** and **207** in 91% yield with retention of configuration. Finally, removal of the silyl protective groups affords the corresponding 11-yne retinal analogues **208** and **209** in 99% and 97% yield.

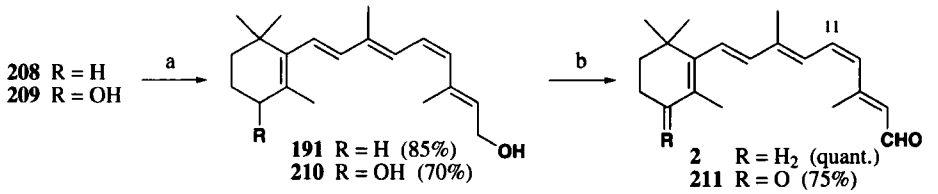
Zinc-mediated semi-hydrogenation of **208** and **209** with Cu/Ag activated Zn dust in methanol/water at room temperature gave retinols **191** and **210** in good yields (85% and 70% respectively) and mainly as 11-*cis* isomers (>95% for **210** and $\Delta^{11\text{-}12}$ *Z:E* 13:1 for **191**) (*Scheme 30*). Oxidation of **191** with tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide gave 11-*cis*-retinal (**2**) in quantitative yield, whereas double allylic oxidation of 11-*cis*-4-hydroxyretinol (**210**) with manganese dioxide provided 11-*cis*-4-oxo-retinal (**211**) in 75% yield.

Another example of the use of the Sonogashira cross-coupling reaction in retinoid synthesis is the stereocontrolled synthesis of ethyl (13*E*)-trifluoromethyl retinoate **214**.[58] This



a) *n*-BuLi, THF; b) *n*-Bu_4NF, THF; c) $Pd(PPh_3)_4$, CuI, *i*-$PrNH_2$

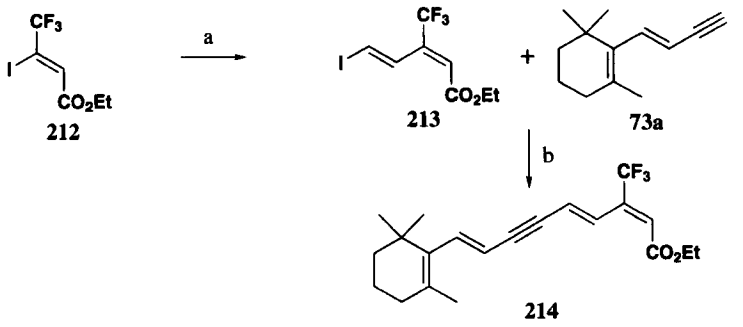
Scheme 29



a) Zn(Cu/Ag), MeOH, H_2O; b) for **191**: TPAP, NMO; for **210**: MnO_2

Scheme 30

synthesis starts with the Stille coupling of (*E*)-1,2-bis-(tributylstannyl)ethylene and (*Z*)-vinyliodide **212**, which results from the regio- and stereoselective hydroiodination of ethyl (*Z*)-4,4,4-trifluorobutynoate with HI, in the presence of 3 mol% dichlorobisacetonitrile palladium to provide the corresponding dienylstannane with retention of the configuration of both double bonds, that then underwent iododestannylation to afford dienyliodide **213** in 80% yield (*Scheme 31*). After exploring reaction conditions for the Sonogashira coupling of dienyliodide **213** with different alkynes, the authors implemented their improved procedure to the coupling of the enyne **73a** and dienyliodide **213**. By treatment of a mixture of **73a** and **213** with tetrakis(triphenylphosphine)palladium, cuprous iodide and *n*-butylamine in toluene at room temperature the expected trifluororetinoid **214** was obtained in 64% yield with retention of the configuration of the double bonds.



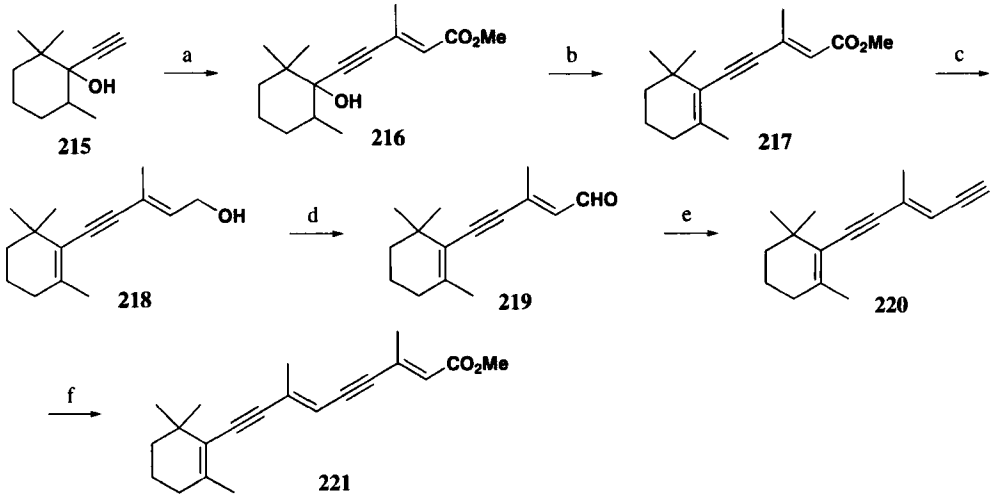
a) *i.* (*E*)-$Bu_3SnCHCHSnBu_3$, $(MeCN)_2PdCl_2$, DMF; *ii.* I_2, Et_2O, 0°C (80%); b) $Pd(PPh_3)_4$, CuI, PhH, *n*-$BuNH_2$ (64%)

Scheme 31

7. Palladium-catalyzed Cross-Coupling of Alkynes with Activated Internal Alkynes

It is well known that alkynes coordinate to transition metals with great efficiency and that their insertion into C-H bonds is one of the most favoured reactions from Pd-alkyne complexes. A palladium-catalysed cross coupling reaction with activated internal alkynes can be promoted from these intermediate complexes. The resulting product is an enyne that can be considered as the addition product of both alkynes, built in an atom-economical fashion. This mild method for C-C bond formation has been applied to the preparation of conformationally rigid analogues of retinoic acid in which the two-disubstituted double bonds have been replaced with alkynes.[59]

To illustrate this methodology we chose the route depicted in *Scheme 32*. The coupling



a) Methyl 2-butynoate, $Pd(OAc)_2$, TDMPP, THF, 25°C (88%); b) $POCl_3$, py, reflux (64%); c) DIBAL-H, $PhCH_3$, -78°C (63%); d) Dess-Martin periodinane, CH_2Cl_2, 0°C (quant.) or NMO, TPAP, 3Å M CH_2Cl_2, 25°C (87%); e) *i.* PPh_3, CBr_4, CH_2Cl_2; *ii.* *n*-BuLi, -78 to 25°C (58%) or $TMSCHN_2$, LDA, THF, -78 to 25°C (72%); f), $Pd(OAc)_2$, TDMPP, THF, 25°C (53%)

Scheme 32

of alkyne **215** as an epimeric mixture at C_1 and methyl 2-butynoate took place in the presence of 3 mol% of palladium acetate and 3 mol% of the sterically-encumbered tris(2,6-dimethoxyphenyl)phosphine (TDMPP) in THF at room temperature. These reaction conditions afforded ynenoate **216** in 88% yield. Dehydration of **216** gave **217** in 64% yield, which was then reduced with DIBAL-H to alcohol **218** in 63% yield. Alcohol **218** was quantitatively oxidized to aldehyde **219** using the Dess-Martin periodinane or alternatively in 87% yield using the catalytic perruthenate protocol described by Ley.

In preparation for a second C-H insertion-addition sequence, the one-step procedure using lithiated trimethylsilyldiazomethane was found superior (72% yield) to the standard Corey-Fuchs method (58%) to convert aldehyde **219** to terminal alkyne **220**. Finally, a second palladium-catalyzed addition to alkyne **220** using identical conditions to the one previously described provided diyne **221** in 53% yield.

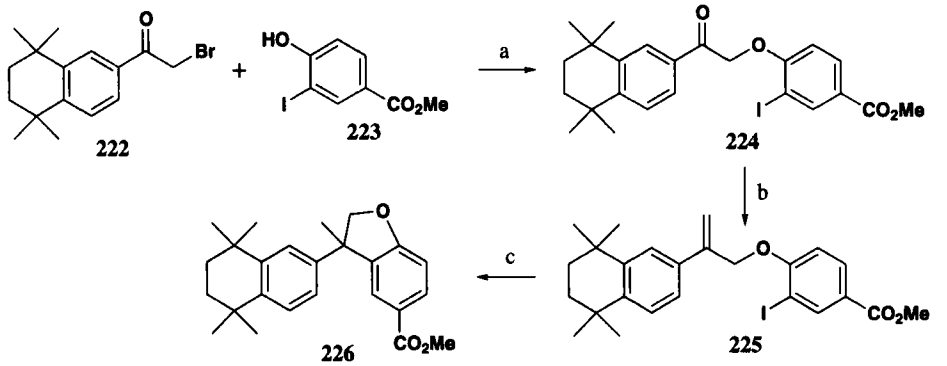
V. OTHER TRANSITION-METAL CATALYZED PROCESSESS

1. Heck Reaction

The palladium catalysed coupling of aryl or vinyl halides and triflates with alkenes or Heck reaction,[60] is another powerful tool for the creation of new Csp^2-Csp^2 bonds. It is mechanistically unrelated to the cross-coupling reactions using organometallic reagents, since a C-Pd bond inserts into the double bond, being a base required for the additional elimination step. However, the mechanistic scheme is not yet fully understood, and the existence of two general variants, the "cationic" and "neutral", further complicates the analysis. The process has undergone important developments, particularly with the discovery of highly active palladium catalysts and useful additives, as well as asymmetric versions.[60] Although the multiple reactive sites of one of the coupling components limit the construction of polyenes using Heck reactions, shorter fragments (β-ionone and analogues) have been prepared joining cycloalkenyl triflates and activated alkenes. Palladium-catalyzed arylation and vinylation have been successfully applied to the preparation of arotinoids, due to the easy accessibility of halogen substituted aryl compounds and their high reactivity in Heck coupling reactions.

The first reported application of the intramolecular Heck reaction to the synthesis of retinoids was the construction of the dihydrobenzofuran skeleton of some conformationally restricted retinoids represented by **226** (*Scheme 33*).[61] The precursor, styrene derivative **225**, was obtained by Wittig reaction of ketone **224**, itself resulting from nucleophilic displacement of bromoacetophenone **222** with o-iodofunctionalized phenol **223**. Efficient Heck coupling was achieved using $Pd(OAc)_2$, Bu_3N and formic acid as hydride source. A tandem intramolecular insertion/hydride capture was postulated to explain the Heck reaction sequence since the intermediate formed, lacking a H vicinal to the palladium is unable to proceed along the cycle with a less-efficient hydride source such as that obtained from complexes originating from Pd insertion into the C-H bond vicinal to nitrogen of the amine and subsequent tautomerizations. The enan-

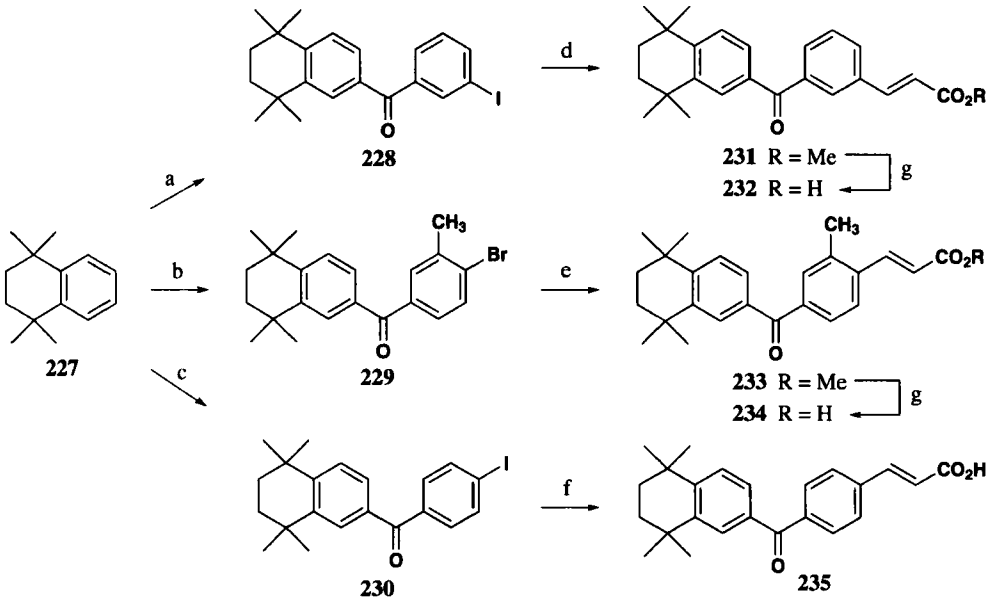
tioselective construction of the quaternary center in dihydrobenzofurans was examined next. Using 0.2 equiv of (*R*)-BINAP, compound **225** provided product **226** in 81% *ee*, but in moderate yield (42%).[61]



a) K_2CO_3, ethylmethylketone (70-80%); b) CH_3PPh_3Br, CH_3ONa/CH_3OH, THF (73%); c) $Pd(OAc)_2$, HCO_2H, Bu_3N, CuCN (70%)

Scheme 33

A series of truncated naphthoic retinoic acids, compounds that are selective for the receptors RAR (isotypes β and γ), have been prepared using a Heck arylation of methyl acrylate.[62] The required intermediates **228**, **229** and **230** were obtained in good yields (60-90%) by Friedel-Crafts acylation of 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (**227**) with different iodo- and bromo-substituted benzoyl chlorides (*Scheme 34*). Iodide **228** underwent Heck

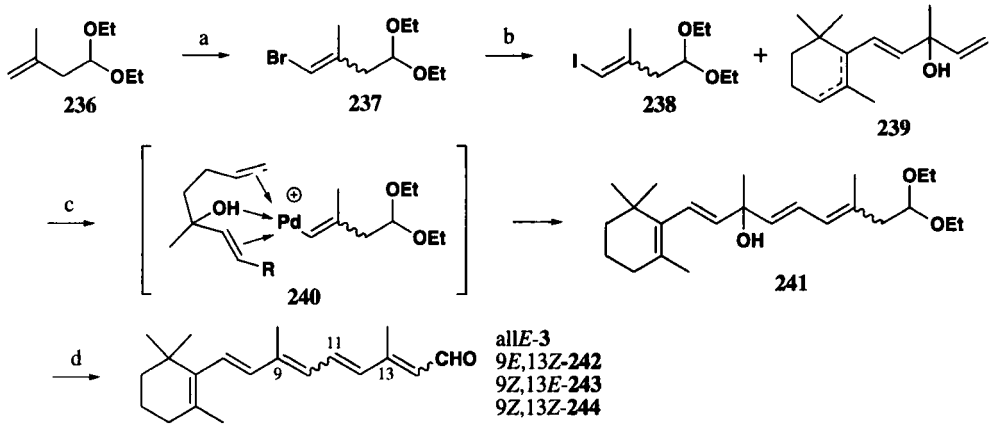


a) $AlCl_3$, 3-iodobenzoyl chloride (90%); b) $AlCl_3$, 4-bromo-3-methylbenzoyl chloride; c) $AlCl_3$, 4-iodobenzoyl chloride (60%); d) Methyl acrylate, $Pd(OAc)_2$, $P(2\text{-tol})_3$, Bu_3N (74%); e) Methyl acrylate, $Pd(OAc)_2$, *n*-Bu_4NCl, K_2CO_3 (84%); f) Acrylic acid, $Pd(OAc)_2$, $P(2\text{-tol})_3$, Bu_3N (19%); g) NaOH

Scheme 34

coupling reaction with methyl acrylate in the presence of palladium acetate, tri(2-toluyl)phosphine and tributylamine to afford methyl ester **231** in 74% yield. The coupling of arylbromide **229** required the use of potassium carbonate as base and a phase transfer catalyst, *n*-Bu_4NCl (Jeffery's conditions), providing arotinoid **231** in 84% yield. Both methyl esters **231** and **233** were conveniently hydrolyzed in basic media to the corresponding carboxylic acids **232** and **234**, respectively. In an attempt to shorten the sequence, acrylic acid was used as the coupling counterpart of aryl iodide **230**, but the yield of the corresponding acid **235** was only a disappointing 19%.

The β-elimination step on the Heck reaction limits its applicability in the synthesis of conjugated polyenes. However, dienes are formed in Heck vinylation reactions of tertiary allylic alcohols. If vinyliodides of C_5-acetals are used as components of the Heck coupling, the subsequent acid hydrolysis/dehydration of the resulting ω-hydroxy acetal allows the preparation of conjugated polyenals such as retinal.[63] The vinyliodide **238**, obtained as a 40:60 *E*:*Z* mixture, was treated with the C_{15} allylic alcohol **239** in the presence of a catalytic amount of palladium acetate and stoichiometric amounts of silver or thallium salts, affording the condensation products in good to excellent yields (82% with Ag_2CO_3 at 65°C for 3 hours) as mixtures of isomers reflecting the composition of the starting iodide (*Scheme 35*). Dilute hydrobromic acid in aqueous acetone at 50°C gave acetal hydrolysis/dehydration leading to mixtures of diastereoisomers where the all-*trans* isomer predominates (46:28:16:10).[63]

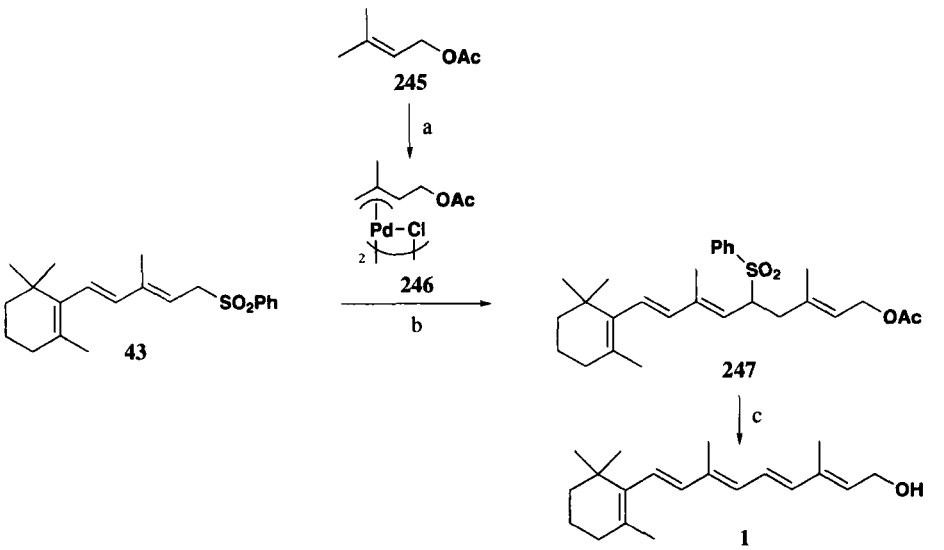


a) *i*. Br_2, Na_2CO_3, CCl_4, -20°C. *ii*. *t*-BuOH, Et_2O, 0°C (43%, *E*:*Z* 40:60); b) KI, $NiBr_2$, Zn, DMF, ultrasound, 60-90°C (59%, *E*:*Z* 40:60); c) $Pd(OAc)_2$, Ag_2CO_3, DMF, 65°C (82%); d) HBr, H_2O, acetone, 50°C (75%, **3**:**242**:**243**:**244** 46:28:16:10)

Scheme 35

2. Allylic Alkylation of π-allyl Pd Complexes

An early report on this topic exploited the electrophilicity of the π-allyl palladium complex **246** in the Julia-type coupling shown in *Scheme 36*.[64a] The π-allyl-Pd complex **246** was prepared from acetate **245** as stoichiometric reagent, and the π-bond-coordinated Pd on the

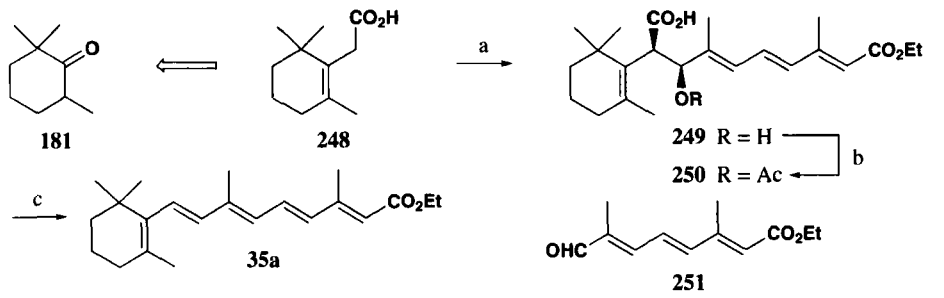


a) $PdCl_2$, $CuCl_2$, NaOAc, NaCl (71%); b) NaH, PPh_3 (52%); c) NaOEt, EtOH (81%)

Scheme 36

resulting product was captured with the anion of sulphone **43** in the presence of PPh_3 to afford the alkylated sulphone **247**, an advanced intermediate in the synthesis of retinol (**1**). A mixture of one- and two double bond isomers of retinol was obtained in the elimination step, with the all-*trans* predominating (67%). The process was later implemented with the catalytic version.[64b]

Trost *et al.* reported a decarboxylative elimination mediated by Pd(0) upon formation of the allyl-Pd(II) complex which creates stereoselectively the C_7-C_{10} bond of ethyl retinoate (see *Scheme 37*).[65] The acetate precursor, alcohol **249**, is the aldol product of the C_{11}-acid + C_9-aldehyde condensation (**248** + **251**). The Pd(0)-induced elimination of *syn* acetoxy acids thus constitutes a conceptually different method for processing the aldol products (see Section VII).



a) Base, THF, 0°C then **251**, THF, -20°C; b) CH_3COCl, pyridine, CH_2Cl_2, 0°C then $NaHCO_3$, THF, H_2O, 25°C; c) $Pd(PPh_3)_4$, Et_3N, DMSO, 80°C (60%)

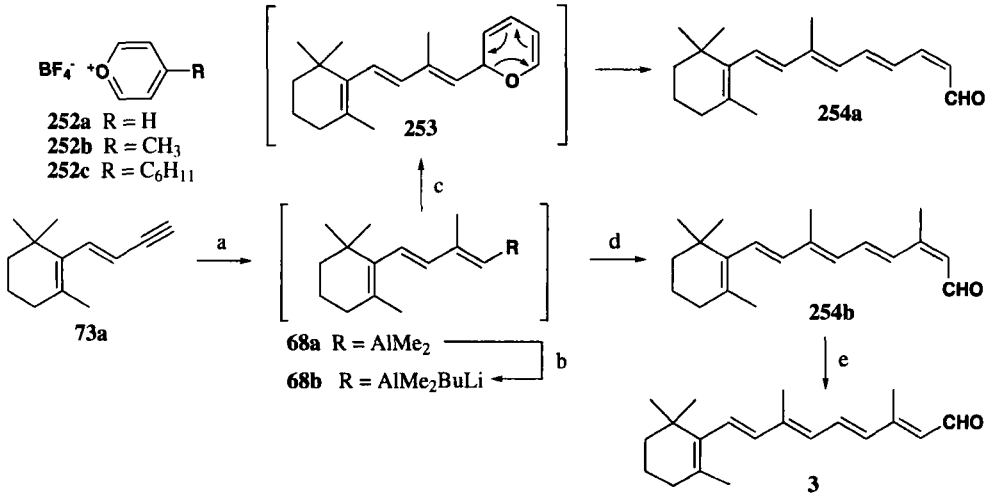
Scheme 37

VI. PERICYCLIC REACTIONS

Among the variety of pericyclic reactions,[66] only sigmatropic rearrangements of acyclic precursors, chelotropic reactions or electrocyclic ring opening of cyclic precursors can yield the entire polyene side-chain exhibited by native retinoids, or one of their fragments.

1. Electrocyclic Ring Opening

Taylor *et al.* proposed in 1994 the use of a 4-alkylpyrylium salt as an equivalent of a six-carbon homologation building block leading to alkyl substituted dienals with 2*Z*,4*E* geometry. The procedure would hold potential in the synthesis of retinoids if combined with a method to incorporate the rest of the structure as substituent of the heterocycle.[67] It was expected that upon reaction with an appropriate organometallic reagent, the 2*H*-pyran intermediate should experience a unidirectional electrocyclic ring opening reaction to afford the fully conjugated retinoid with a terminal 2*Z*,4*E* geometry.[67] To test the viability of the process they converted alkyne **73a** into vinylalane **68a** using Negishi's procedure. Addition of excess **68a** to pyrylium tetrafluoroborate **252a** at –78°C gave 13-demethyl-13-*cis* retinal (**254a**) in 31% yield. The use of the corresponding ate complex **68b**, obtained by treatment of alane **68a** with *n*-BuLi at -78°C, increased the overall yield to 43%. Application of identical methodology using methyl substituted pyrylium tetrafluoroborate **252b** allowed the preparation of 13*Z*-retinal (**254b**) in 48% yield, which could be easily isomerized to retinal (**3**) in the presence of iodine (*Scheme 38*).

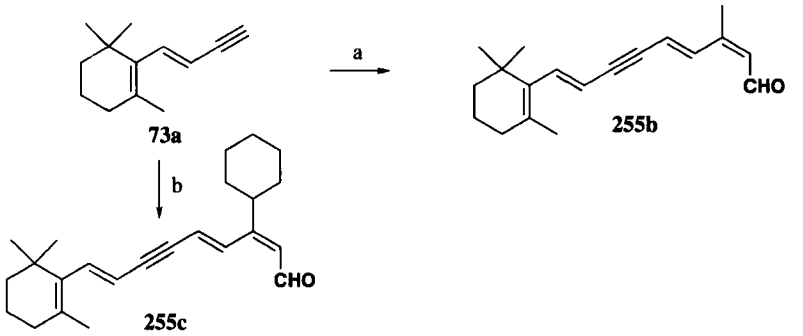


a) *i.* $AlMe_3$, Cl_2ZrCp_2, CH_2Cl_2, 0 to 25°C; *ii.* THF; b) *n*-BuLi, THF, -78 to 0°C; c) **252a**, THF, -78°C (31% to 43%, see text); d) **252b**, THF, -78°C (48%); e) I_2, Et_2O, PhH, 25°C (91%)

Scheme 38

The versatility of this route to 13-substituted retinals has been extended by variation of the organometallic component. The reaction of **73a** (previously treated with *n*-BuLi at -78°C) with **252b** afforded **255b** in 57% yield. In addition, placing substituents at the C_4 position of the

pyrylium component allow for a greater diversity.[67] Under identical conditions, the reaction of **73a** with 4-cyclohexylpyrylium tetrafluoroborate **252c** gave retinal analogue **255c** in 52% yield (*Scheme 39*).



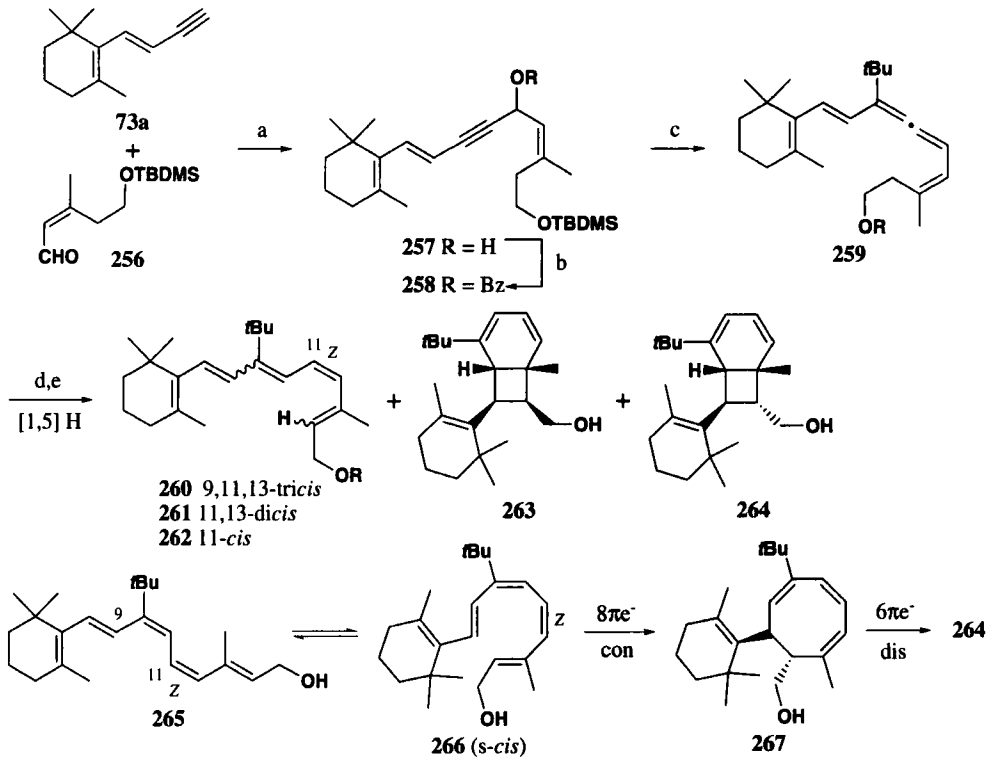
a) *i.* *n*-BuLi, THF, -78°C. *ii.* **252b**, THF, -78°C (57%); b) *i.* *n*-BuLi, THF, -78°C. *ii.* **252c**, THF, -78°C (52%)

Scheme 39

2. Sigmatropic Rearrangements

The feasibility of [1,j]-H sigmatropic rearrangements to interconvert conjugated systems is limited by the high temperatures needed to overcome the high activation energies of these pericyclic reactions. Fortunately, in the case of allenes, the rearrangements generally takes place below 100°C due to the lower steric hindrance to hydrogen migration. In addition, the "decumulation" of the allene leads to an essentially irreversible process. Okamura took advantage of these particular features of sigmatropic rearrangements of vinylallenes in order to develop some stereoselective approaches to the triene and pentaene fragments of vitamin D and 11-*cis*-retinol (**191**), respectively. The subject has been authoritatively reviewed,[68] and only some recent work will be included here.

As an extension of the "allene" approach to 11-*cis* isomers of vitamin A, a series of derivatives with bulky *tert*-butyl groups were prepared.[69] Those substituents could be attached to the reactive polyene chain during the formation of the allene functionality, using the regioselective (S_N2') displacement of a propargylic benzoate by a cyano-Gilman cuprate. The condensation of the alkynyl anion derived from **73a** and enal **256** provided the propargylic alcohol **257**, immediate precursor of the benzoate **258** (*Scheme 40*). Heating a solution of dienyl-vinylallene **259** in hexanes at 69°C for 22 hours afforded a mixture of products derived from the thermal rearrangement manifold, which were separated after deprotection of their hydroxyl groups. HPLC purification yielded, in order of elution, bicyclo[4.2.0]octa-2,4-dienes **262** and **263** (individual assignment is tentative, 11 and 20% yield), 9-*tert*-butyl-11,13-di*cis*-retinol (**261,** 19%), 9-*tert*-butyl-9,11,13-tri*cis*-retinol (**260,** 7%) and 9-*tert*-butyl-11-*cis*-retinol (**262,** 10%, 67% overall yield). The bicyclic compounds **263** and **264** are thought to arise from the 9,11,13-tri*cis* isomer (as a control experiment, upon subjecting **260** to the same reaction conditions, **263** was isolated in 70% yield, being the remaining recovered starting material) and from the non-isolated

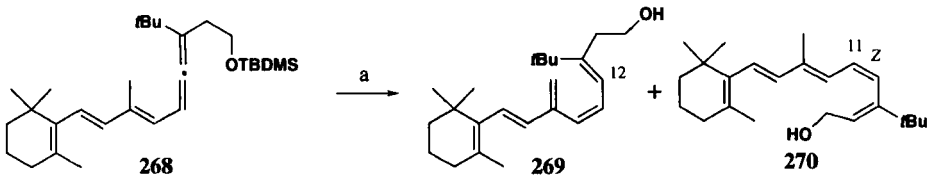


a) n-BuLi, THF, -78°C; then **256** (85%); b) PhCOCl, DMAP, Et_3N (95%); c) tBu_2CuLi•LiCN, ether, -78°C (94%); d) hexane, 69°C, 22h; e) *i.* *n*-Bu_4NF, THF, 2h; *ii.* HPLC separation (67% combined)

Scheme 40

9-*tert*-butyl-9,11-di*cis*-retinol (**265**). Two consecutive electrocyclic ring closure reactions, the first a $8\pi e^-$ conrotatory cyclization from the s-*cis* conformer of **265** to give cyclooctatriene **267**, and the second a $6\pi e^-$ disrotatory cyclization of the latter could mechanistically explain the genesis of bicyclo[4,2,0]octa-2,4-diene **264**. Steric effects might justify the relative configuration tentatively assigned to structures **263** and **264** derived from a torquoselective electrocyclic ring closure.

A similar synthetic scheme was then applied to the synthesis of positional isomers with the bulky *tert*-butyl replacing the methyl at C_{13}. 11,12-Allene **268** was heated in isooctane (98°C) for 64 hours and the mixture, after being treated with TBAF, was subjected to HPLC separation (*Scheme 41*). In this case, only two polyenes were obtained, the 13-*tert*-butyl-11,13-di*cis*-retinol (**270**, 32%)[69b] and the 12-*trans*-19,14-*retro*retinol (**269**, 16%). The latter arises from a [1,5]-H sigmatropic shift, a process that, albeit *Z*-selective for the central bond, is generally unselective for the terminal double bonds, yielding a mixture of isomers. The 12-*cis*-double bond isomer of **269** subsequently enters a second sigmatropic rearrangement pathway leading to the 13-*tert*-butyl-11,13-di*cis*-retinol (**270**). It is likely that the stereoselectivity of the second rearrangement (13-*cis* geometry) is induced by the bulk of the *tert*-butyl substituent.



268 269 270

a) Isooctane, 98°C, 64 h; *ii.* TBAF; *iii.* HPLC separation (**269**, 16%; **270**, 32%)

Scheme 41

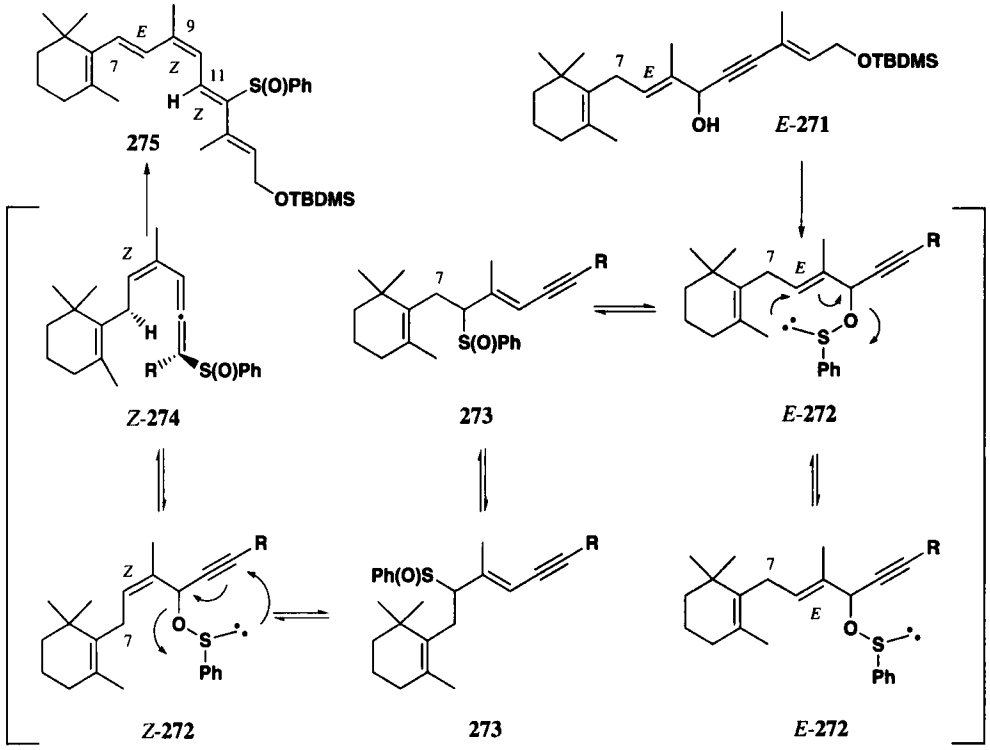
The consecutive [1,5]-H – [1,7]-H sigmatropic hydrogen shift described above, as well as the [1,5]-H shift - $8\pi e^-$ disrotatory cyclization - $6\pi e^-$ disrotatory cyclization giving rise to **264** and **263** (*Scheme 40*), are examples of pericyclic-pericyclic sequential transformations, since the functionality of the second process is built-up by a previous rearrangement. These combined reactions, also named *tandem*, *domino*, or *cascade* reactions,[70] are powerful and atom-economical bond-forming sequences.

The involvement of pericyclic reactions in domino processes has the limitation of alternative pathways leading to stereoisomers of the final polyene. However, in some cases, the entire sequence has proven to be highly peri- and stereoselective.

A domino reaction that is pericyclic in nature has been proposed to be triggered upon treatment of alkenynol **271** with arylsulfenyl chlorides, leading to 9-*cis*-retinoids **275** stereoselectively.[71] The process comprises an ordered sequence of sigmatropic rearrangements: a reversible [2,3]-allyl sulfenate to allyl sulfoxide shift which interconverts the isomers *E*-**272** and *Z*-**272**, followed by a [2,3]-rearrangement of the propargyl sulfenate with *Z* geometry to allenyl sulfoxide *Z*-**274**, and lastly a stereodifferentiating [1,5]-sigmatropic hydrogen migration leading to polyene **275** (*Scheme 42*).[71b] The migration of the C_7 to C_{11} hydrogen was demonstrated by labeling experiments. The double diastereoselection of the [1,5]-sigmatropic hydrogen shift to afford a single isomer of the final polyene **275** is thought to arise from a combination of the electronic effect of the sulfoxide at one terminus[72] and the steric effect imparted by the bulky trimethylcyclohexenyl substituent at the other terminus.

The overall process thus constitutes a stereoselective synthesis of an *E,Z,Z*-triene fragment from alkenynol *E*-**271** and, in particular, a retinoid with the 7*E*,9*Z*,11*Z*,13*E* configuration on the conjugated polyenic side chain. The complete control of the side-chain geometry of 9-*cis*-retinoids has been synthetically exploited, and 7,11-doubly labelled and ring-modified 9-*cis*-retinoids have been prepared according to the general scheme indicated above for the parent compound 9-*cis*-retinol.[71b] The synthesis of the (9*Z*)-4,6-*retro*retinoic acid (**283**) was undertaken as an application. Darzen's glycidic acid condensation of racemic α-ionone (**276**) led to unsaturated aldehyde **277** in 58% yield (*Scheme 43*). Alkenynol **279** was obtained in 56% yield by addition of the lithium anion derived from **278** to aldehyde **277**. The key sequence of pericyclic

reactions afforded, as anticipated from the results described above, the protected 9-*cis*-12-arylsulfinyl-4,6-*retro*retinol (**280**). The role of the sulfoxide is to provide stereochemical control of the [1,5]-H rearrangement by directing the migrating H *anti* to its location.[72] It was then reduced

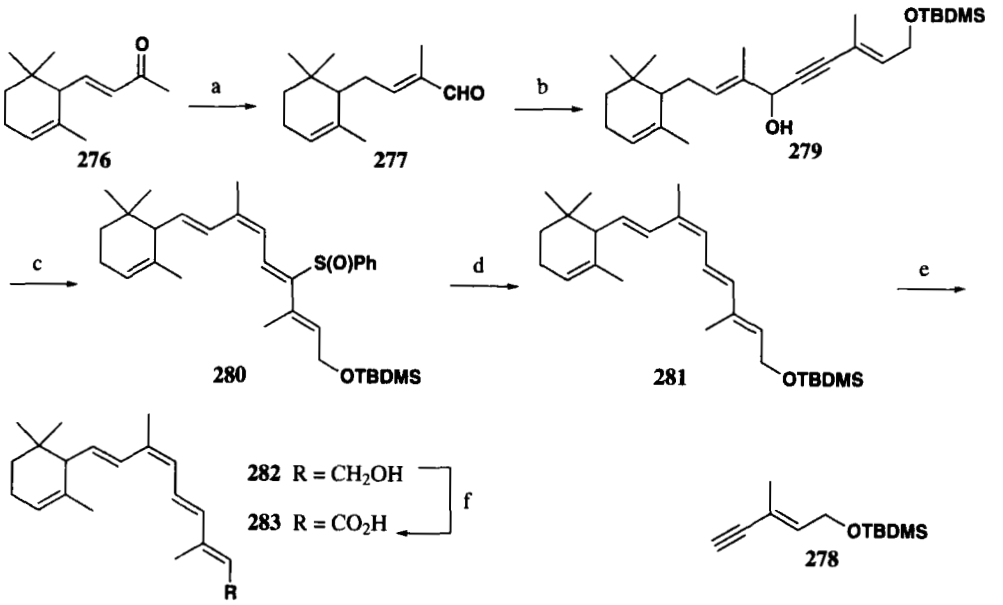


a) PhSCl, Et_3N, THF, -78°C (61%)

Scheme 42

stereoselectively with *t*-BuLi in the presence of MeOH yielding polyene **281** in 40% yield.[73] This step was followed by deprotection of **281** (TBAF) and oxidation of alcohol **282** with Ag_2O/MnO_2 to afford the final carboxylic acid **283** in a combined yield of 53%.

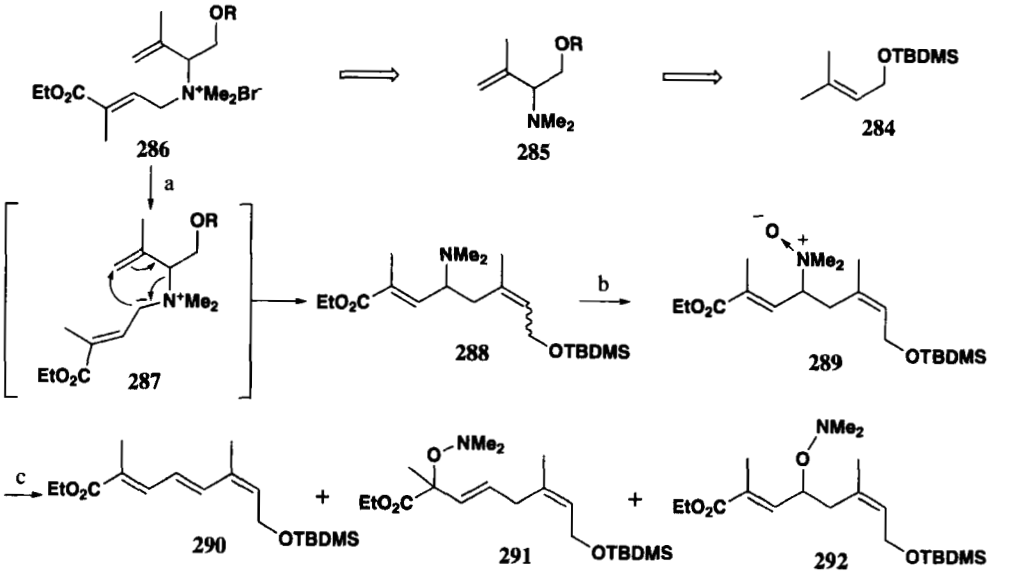
An additional sigmatropic rearrangement has been used for the generation of the terminal double bond of 13*Z*-retinol (**296**).[74] The key step of this synthesis is the [2,3]-aza Wittig rearrangement of zwitterion **287** obtained upon treatment of the quaternary salt **286** with potassium ethoxide in ethanol (*Scheme 44*). This reaction afforded (*Z*:*E*, 95:5) the (*Z*)-olefin **288** with high stereoselectivity in 71% yield. The functionalized triene system **290** was obtained in 69% yield by Cope elimination of the *N*-oxide intermediate **289**, obtained by treatment of **288** with peracetic acid in the presence of sodium carbonate at -60°C. The [2,3] sigmatropic rearrangement product **291** and the [1,2] rearrangement product **292** were also present in the reaction mixture in 11% and 7% yield, respectively.



a) $ClCH_2CO_2Me$, MeOH, MeONa, 0 to 25°C (58%); b) *n*-BuLi, **278**, -78 to 25°C (56%); c) PhSCl, Et_3N, THF, -78 to 25°C (40%); d) *t*-BuLi, MeLi, MeOH, THF, -78°C (73%); e) *n*-Bu_4NF, THF, 25°C; f) Ag_2O, MnO_2, MeOH, 1 M NaOH, 60°C (53%, two steps)

Scheme 43

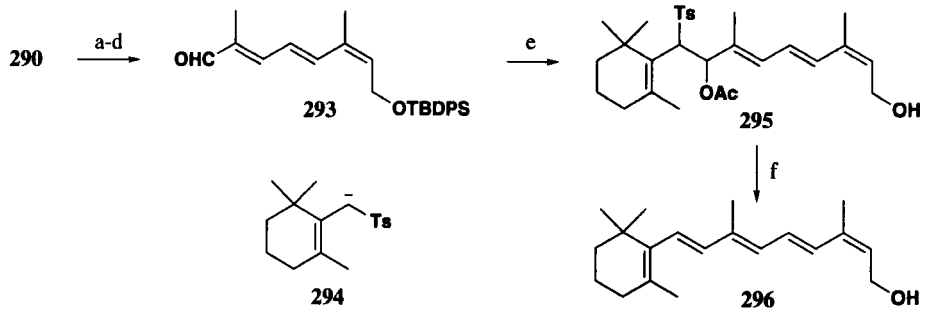
The lability of the *tert*-butyldimethylsilyl protective group to the presence of $AlCl_3$ demanded a protective group exchange to the more robust *tert*-butyldiphenylsilyl group. Reduction of the ester moiety was carried out by treatment with AlH_3 generated *in situ* by mixing $AlCl_3$



a) KOEt, EtOH, -78°C (71%, *Z*:*E* 95:5); b) AcOOH, Na_2CO_3, CH_2Cl_2, -60°C; c) -60 to 0°C (**290**, 69%; **291**, 11%; **292**, 7%)

Scheme 44

and $LiAlH_4$, affording the corresponding alcohol in 96% yield. This was subsequently oxidized with manganese dioxide to give quantitatively trienal **293** (*Scheme 45*). A Julia olefination was then envisaged to yield the desired retinoid skeleton. To this end, trienal **293** was treated with the



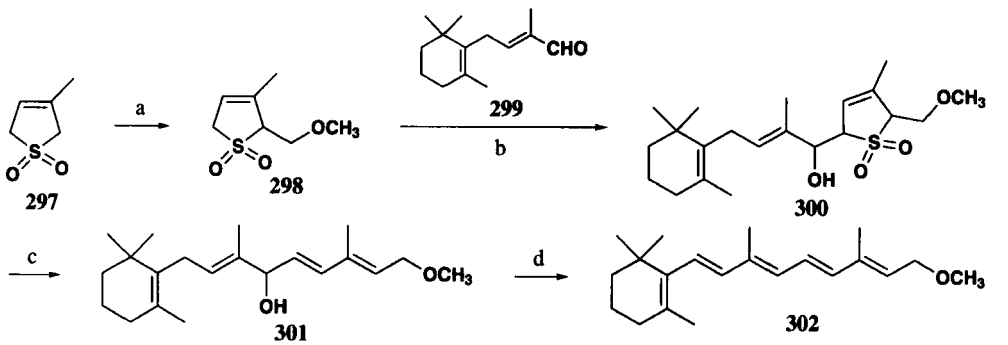
a) *n*-Bu_4NF (quant.); b) TBDPSCl (98%); c) $AlCl_3$, $LiAlH_4$ (96%); d) MnO_2 (quant.); e) *i.* **294**; *ii.* Ac_2O; *iii.* *n*-Bu_4NF (80%); f) Na/Hg, KH_2PO_4, MeOH, EtOH, 25°C (63%)

Scheme 45

carbanion of β-cyclogeranyl *p*-tolyl sulfone (**294**) and the alkoxide was captured with acetic anhydride. Deprotection with fluoride afforded β-acetoxysulfone **295** quantitatively, which upon treatment with sodium amalgam, finally afforded the desired 13*Z*-retinol (**296**) in 63% yield through reductive cleavage.

3. Cheletropic Reactions

The cheletropic extrusion of sulfur dioxide from five membered ring sulfones, known to occur with retention of configuration, offers the possibility to unmask a stereodefined diene when required. The sulphone group moreover adds versatility to the sequence due to the acidity of the hydrogens at its α-position. Upon treatment with a strong base, the stabilized sulphone anion can be alkylated or added to a carbonyl compound. Therefore, starting from 2-methyl-sulfolene **297**, regioselective alkylation at –90°C with bromomethyl methyl ether takes place at the most hindered position. The derived sulphone **298** becomes the C6 component of a new route to the retinol skeleton by its reaction with the C_{10} aldehyde **299** (*Scheme 46*). The sulfur dioxide



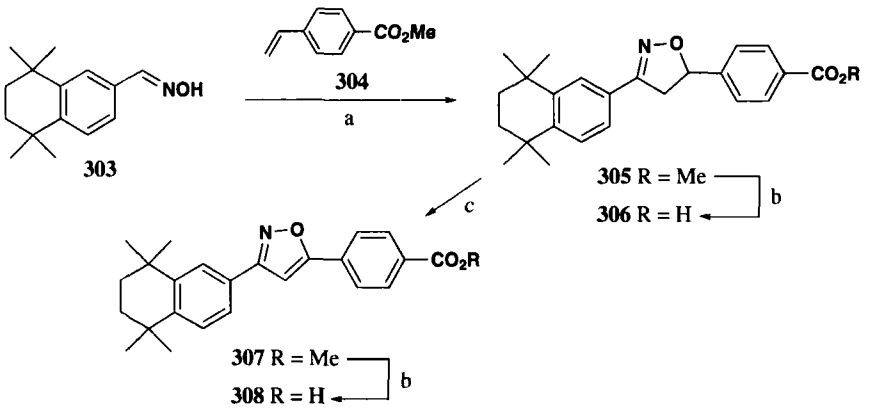
a) CH_3OCH_2Br, LiHMDS, THF, -90°C (88%); b) LiHMDS, THF, -90°C (73%); c) Pyridine, reflux (67%); d) $POCl_3$, Pyridine, toluene (54%)

Scheme 46

extrusion on allyl alcohol **300** (no relative configuration reported) leads to tetraene **301**. Dehydration of the latter by treatment with $POCl_3$ and pyridine in $CHCl_3$ took place with rearrangement affording retinol methylether **302** in 54% yield as a single isomer.[75]

4. Cycloadditions

Since the incorporation of a heteroatom in an arotinoid structure reduces the toxicity 1000-fold, efforts have been carried out to replace the retinoid alkenyl side chain by heterocycles. The (3+2) dipolar cycloaddition offers a highly convergent solution to the preparation of five-membered ring heteroarotinoids, profiting from the high regio and stereocontrol of these concerted reactions. Nitrile oxide resulting from treatment of oxime **303** with NCS, was added to styrene derivative **304** to provide regioselectively isoxazoline **305**. Oxidation of the isoxazoline ring of **305** was accomplished by treatment with NBS and dehydrobromination of the 3-bromo derivative with Et_3N in CH_2Cl_2 to provide isoxazol **307** in 85% overall yield (*Scheme 47*). Saponification with LiOH in MeOH then afforded analog **308**, a promising retinoid that exhibited high apoptotic activity in multidrug-resistant leukemic cell lines.[76]



a) Pyridine, NCS, Et_3N, $CHCl_3$ (63%); b) LiOH, H_2O (**306**, 84%; **308**, 80%); c) CCl_4, NBS then Et_3N, CH_2Cl_2 (80%)

Scheme 47

VII. ALDOL REACTIONS/CONDENSATIONS

The aldol reaction and its variants are considered as one of the most powerful synthetic methods for C-C bond formation.[77] The recent developments on the control of the aldol product relative and absolute configuration, using stereodefined "preformed" metal enolates has increased its synthetic potential. "Latent" enolate equivalents, such as silyl enol ethers (Mukaiyama reaction) and "latent" carbonyl compounds, such as acetals, offer additional versatility with respect to the choice of starting materials and reaction conditions.

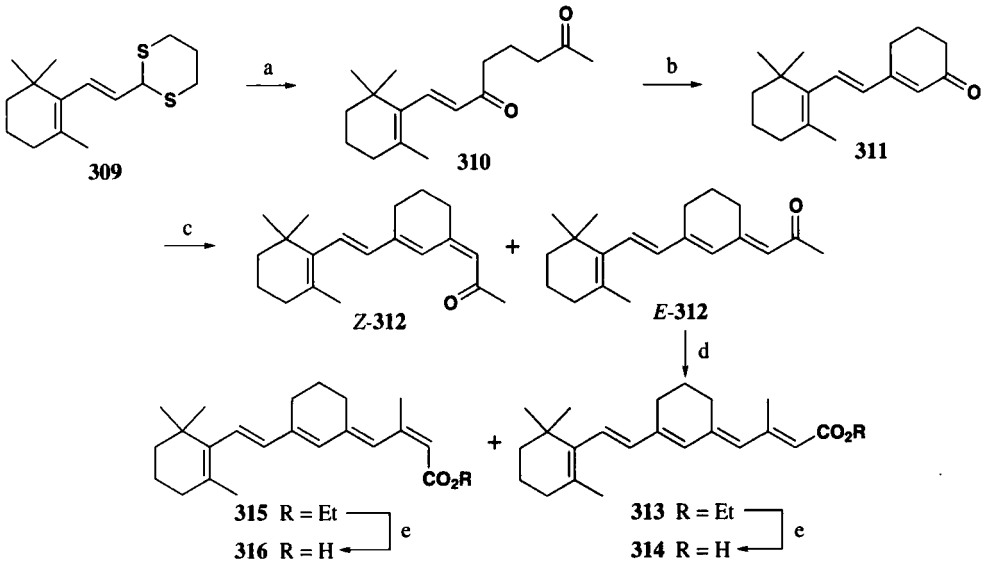
For the purpose of this review, the aldol condensation of appropriate fragments should yield either the entire retinoid skeleton or one of its precursors. The mixed aldehyde-ketone aldol condensation has been applied in numerous occasions to the synthesis of retinoids. In particular,

the $C_{15} + C_5$ approach to retinoids using aldol reactions is well documented, in part aimed at the development of synthetic equivalents of the C_5 isoprenylation units, and their application to the synthesis of other terpenes. This particular approach with C_5 units is a vinylogous version of the aldol reaction.[78] In its application to retinoid synthesis, the vinylogous aldol strategy faces regio- and stereoselectivity limitations. Although conditions have been developed for the regioselective γ-addition, competing addition modes have been observed. In addition, little control can be exerted on the stereoselectivity of the dehydration reaction, which generally leads to mixtures of isomers that reflect the thermodynamic stability of the different retinoid isomers. Therefore, separation of the geometric isomers or enrichment of the mixture in the most stable component usually follows the aldol condensation.

We will divide this chapter in four subheadings: simple enol condensations as steps of the synthetic sequence, vinylogous aldol reactions using prenal metal dienolates, Mukaiyama reactions with enoxysilanes, and Refortmatsky reactions. The latter are included in this chapter under the assumption that ester zinc enolates are a class of metal enolates in reactions with carbonyl compounds.

1. Simple Aldol Condensations

A series of aldol condensations were used in the preparation of retinoic acid analogues configurationally locked by the presence of a ring spanning the C_9 and C_{11} carbons.[79] Alkylation of the lithium derivative of dithiane **309** with 5-chloropentan-2-one ethylene ketal and deprotection of both carbonyls led to 1,5-diketone **310** (*Scheme 48*). A first intramolecular aldol condensation

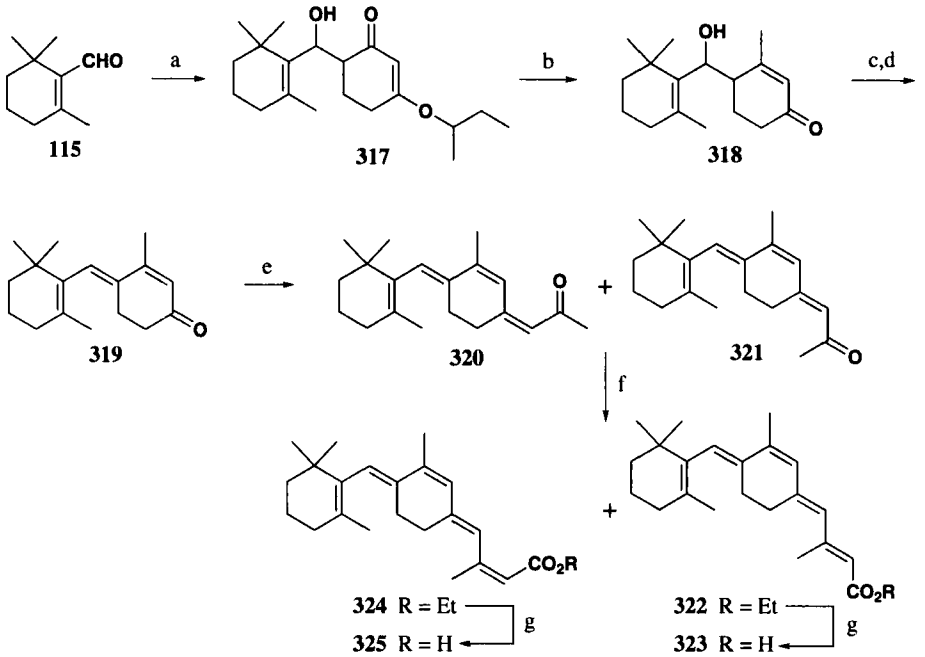


a) *i.* *n*-BuLi, 5-chloropentan-2-one ethylene ketal, THF, -78°C; *ii.* HgO, $HgCl_2$, MeOH, 25°C; *iii.* *p*-TsOH, acetone, 25°C (57%); b) MeONa, THF, 25°C (quant.); c) *i.* LDA, Me_2NNCMe_2, THF, 25°C; *ii.* AcOH, THF, H_2O, NaOAc, 25°C (72%); *iii.* separation of the 1:1 mixture; d) *i.* LDA, $Me_3SiCH_2CO_2Et$, THF, -78°C (92%); *ii.* separation by HPLC (in the dark) of the 1:1 mixture; e) NaOH, EtOH, 50°C (**314**, 81%; **316**, 92%)

Scheme 48

afforded β-dienylcyclohexenone **311**, a partner of the second aldol reaction using a metalated acetone *N,N*-dimethylhydrazone. The condensation led to **312**, which is obtained as a mixture of geometric isomers at the semicyclic double bond. The retinoid skeleton was completed by treatment of the resulting condensation product *E*-**312** with a silicon-stabilised anion. The Peterson olefination likewise afforded a 1:1 *E/Z* mixture of retinoic acid isomers at the terminal trisubstituted double bond.

The preparation of the configurationally restricted 9*Z* retinoids (those with a ring between positions C_8 and C_{11} of the side chain) illustrates the use of an aldol product as precursor of an unsaturated carbonyl compound.[79] β-Cyclocitral (**115**) was treated with the lithium enolate obtained upon treatment of 3-(1-methylpropoxy)cyclohex-2-enone with LDA at -78°C to afford β-hydroxyketone **317** (*Scheme 49*). Addition of MeLi provides the corresponding diol. Hydrolysis of the enol ether induced dehydration, thus revealing unsaturated ketone **318**. Through this



a) 3-(1-Methylpropoxy)cyclohex-2-enone, LDA, THF, -78°C (61%); b) *i.* MeLi, THF, -78 to 0°C; *ii.* 15% H_2SO_4, 25°C (60%); c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25°C (83%); d) DBU, PhMe, 90°C (83%); e) *i.* LDA, Me_2NNCMe_2, THF, 25°C; *ii.* AcOH, THF, H_2O, NaOAc, 25°C (41%); *iii.* Separation by HPLC of the 1:1 mixture; f) *i.* LDA, $Me_3SiCH_2CO_2Et$, THF, -78°C (quant.); *ii.* Separation by HPLC of the 1:1 mixture; g) NaOH, EtOH, 50°C (**323**, quant.; **325**, 92%)

Scheme 49

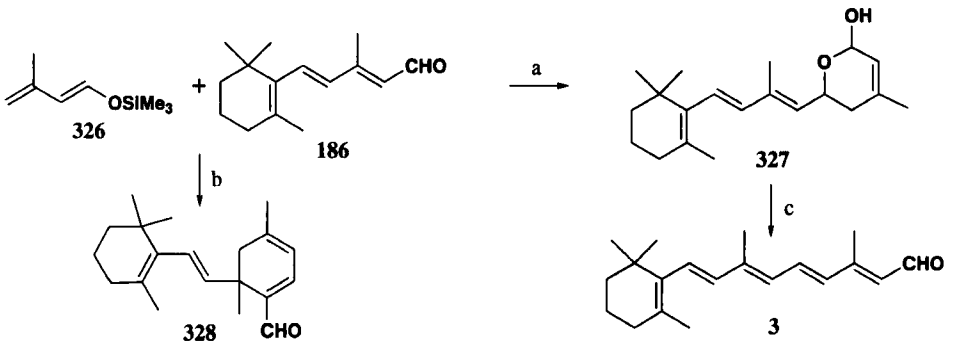
route, the starting cyclohexenone is formally acting as a synthetic equivalent of a dienolate (vinylogous enolate) that reacts regioselectively at the γ-position. The low pKa of that position in the acetate derived from **318** was used to induce an β-elimination leading to trienylketone **319**. Completion of the retinoid skeleton followed the general scheme already explained for analogues **314** and **316**.

2. Metal Dienolates

The easy availability of C_5 building blocks, such as 2-methylcrotonic acid and its esters made them popular starting materials for retinoid synthesis by direct condensation of the corresponding dienolates with C_{15}-aldehydes. Matsui first discovered that the choice of the base and counterion employed in the preparation of the dienolate derived from ethyl 2-methylcrotonic acid determined the configuration of the terminal double bond.[80] The lithium dianion obtained from 2-methylcrotonic acid was also successfully used for the direct preparation of retinoic acid (**4**).[81]

Limitations on the use of extended enolates in synthesis are the self-condensation of the enolate with the starting carbonyl compound, the control of the regioselectivity of enolate attack (α vs γ vs ω) and the stereoselectivity of the subsequent dehydration. In addition, if the reactive partner is an unsaturated carbonyl compound, regioselectivity issues (1,2 vs 1,4) complicates matters.

A γ-regioselective 1,2-prenylation of unsaturated carbonyl compounds as direct route to retinoids was developed in the laboratories of Duhamel.[82] This optimized procedure uses the potassium enolate of prenal, generated by treatment of the preformed silyl enol ether with KO*t*Bu, as C_5 unit, which adds to the C_{15}-aldehyde **186** in a γ-1,2-fashion under kinetic control (-78°C, 3 h, see *Scheme 50*). The intramolecular attack of the potassium alkoxide to the released



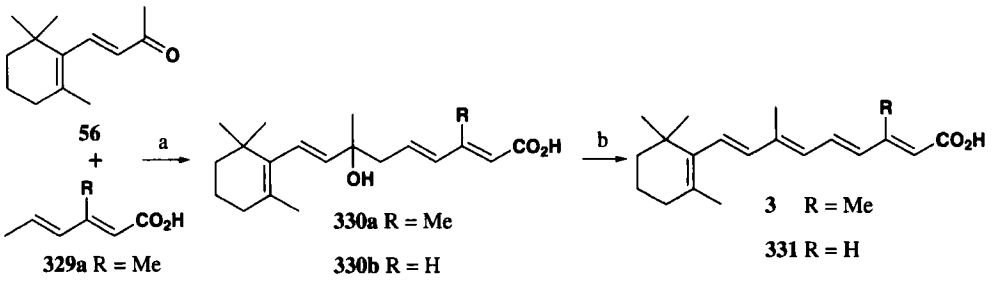
a) *i.* KO*t*Bu, 1 h, -78°C; *ii.* **326**, 3 h, -78°C; *iii.* H_2O (68%); b) *i.* KO*t*Bu, 1 h, -78°C; *ii.* **326**, 3 h, -10°C; *iii.* H_2O (59%); c) DMF, toluene, pyridine, HCl (90%)

Scheme 50

aldehyde yields the dihydropyran **327**. The γ-1,4-addition mode is favoured under thermodynamic control (-10°C, 3 hours), redirecting the sequence to afford a cyclohexadienal **328** after intramolecular aldol condensation. The use of substoichiometric quantities of KO*t*Bu (1-10 mol%) offers additional advantages. It is conceived that the intermediate alkoxide is O-silylated under these conditions, thus preventing retro-aldolization and inhibiting the formation of the undesired γ-1,4 product. The dihydropyran **327** is a direct precursor of the final polyenal **3**, a transformation requiring acidic treatment (pyridinium hydrochloride in DMF and toluene or 10% HCl in 1,2-dichloroethane). The yield of retinal (**3**) from the hydroxy dihydropyrans is 90%, although four isomers were obtained in a 54:28:16:2 ratio. An alternative treatment of the dihy-

dropyran with an oxidant, followed by elimination with base leads to the ring-opened product, the retinoic acid with 13*Z* geometry.

The use of the even more extended vinylogous enolates represents an alternative construction approach for direct access to the retinoid skeleton starting from carbonyl compounds (*Scheme 51*). Lithium trienediolates derived from hexa-2,4-dienoic acids (**329**) or



a) *i.* $LiNEt_2$, THF, -70 to 0°C; *ii.* **56**, THF, -70°C; *iii.* H_2O (**330a**, 35%; **330b**, 30%); b) *i.* *p*-TsOH, CH_2Cl_2, 50°C; *ii.* I_2, Et_2O, PhH, 25°C (**3**, 95%; **331**, 94%)

Scheme 51

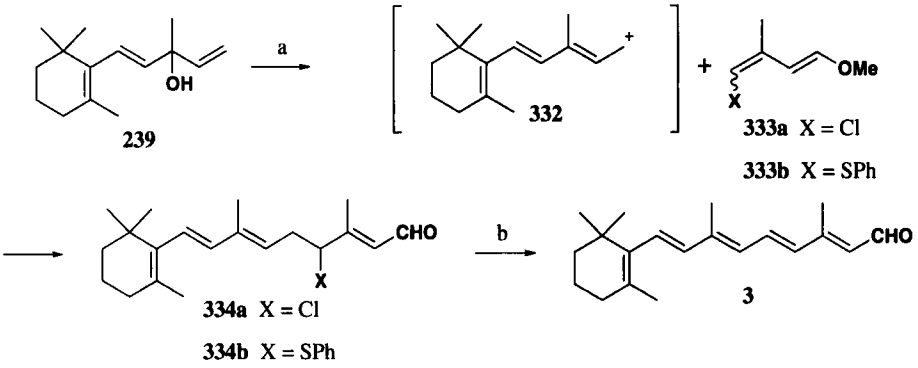
dihydropyranones (C_7 units) have been condensed with β-ionone (C_{13}) to afford the 1,2-ω addition product **330** in low yield (35%) under equilibration conditions. This hydroxy acid was subsequently dehydrated by acid treatment and the mixture of double bond isomers was enriched in the desired *trans* isomer by isomerization with iodine. For other ketones (such as diarylketones) the regioselectivity of the aldol reaction is altered, and 1,4-β and γ-adducts are obtained as major products.[83]

3. Mukaiyama-Type Aldol Reactions

Silyl enol ethers are also partners of the classical Mukaiyama reaction, a Lewis-acid promoted aldol coupling between those latent enolates and carbonyl compounds or the corresponding acetals. For the latter electrophilic component, a new 3-alkoxyacetal is formed, which is converted to a free unsaturated aldehyde.[84] The resulting chain is lengthened depending on the number of carbons supplied by the enol ether. For retinoids, the best-developed enol ether derivatives are C_5-prenyl units. Mukaiyama found in 1975 that 1-trimethylsiloxybuta-1,3-dienes react in the presence of $ZnCl_2$ or $TiCl_4$ with C_{15} acetal units in a regioselective γ-1,4-addition mode to afford the corresponding δ-alkoxy-α,β-unsaturated aldehydes in high yields. These intermediates were easily transformed into retinal and other polyunsaturated aldehydes.[85]

Duhamel has also reported a variant of the enol ether condensation in which the components are an allylic alcohol and a C_2-substituted enol ether. Since the oxidation state of the electrophilic reagent is decreased from carbonyl to alcohol, and the oxidation state of the nucleophilic component can be increased if the substituent is a heteroatom (Br, SPh), this process has been termed Oxidation State Modification (OSM). No change on the overall balance of the reaction mixture is involved.[86]

Vinyl-β-ionol (**239**) was condensed with dienol ethers **333a** and **333b**, *via* the carbocation **332**, in nitroethane at –30°C in the presence of catalytic amounts of boron trifluoride etherate or zinc dichloride and one equivalent of iso-propanol affording aldehydes **334a** and **334b**, both precursors of retinal (**3**). Aldehyde **334a** was dehydrohalogenated in 86% yield using DBU at 50°C whereas aldehyde **334b** was oxidized with MCPBA affording retinal (**3**) in 92% yield after spontaneous elimination of the sulfoxide moiety. In both cases retinal was obtained as a mixture of isomers that could be enriched in the most stable all-*trans* isomer according to well-established procedures (*Scheme 52*).



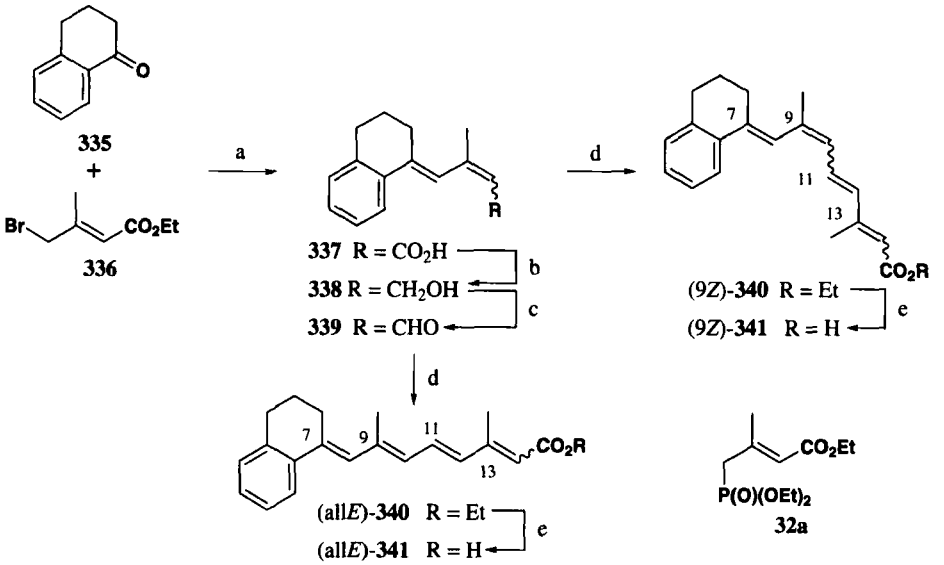
a) BF_3•Et_2O or $ZnCl_2$, *i*-PrOH, $EtNO_2$, -30°C (**334a**, 50%; **334b**, 53%); b) From **334a**: DBU, CH_2Cl_2, 50°C (86%). From **334b**: *i*. MCPBA, CH_2Cl_2; *ii*. CCl_4 (92%)

Scheme 52

4. Reformatsky Reaction

The reaction of a α-haloester with an aldehyde or ketone in the presence of zinc metal, the classical Reformatsky condensation, can be considered as a variant of the general aldol reaction.[87] Compared to the classical base-promoted aldol procedures, the Reformatsky reaction uses a metal-halogen redox reaction rather than an acid-base reaction to form the ester enolate. The metal of the enolate is zinc, and the usual product is a β-hydroxyester that can be dehydrated in subsequent steps to give an unsaturated ester. One of the significant advantages of the Reformatsky reaction is its success with highly hindered and easily enolizable ketones. Although nowadays largely superseded by other condensation reactions, the vinylogous version is useful for the preparation of *Z*-trisubstituted α,β-unsaturated esters, since the regioselectivity can be controlled under thermodynamic conditions, and the intermediate δ-lactones are transformed by elimination into the corresponding esters with 13*Z* geometry.

Recent applications of the Reformatsky reaction have allowed the preparation of retinoic acid derivatives modified in the hydrophobic ring. Tetralone **335** was reacted with the vinylogous zinc enolate derived from ethyl bromocrotonate (**336**) to afford a 1:1 mixture of unsaturated acids **337**.[88] The mixture was converted in a two-step process to aldehydes **339**. These were individually transformed into the retinoates **340** upon HWE olefination reaction, and the obtained mixtures were separated by HPLC (*Scheme 53*).



a) Zn, dioxane [86%, (9*Z*)-**337**:(all*E*)-**337** 1:1]; b) $LiAlH_4$ (67%); c) MnO_2, molecular sieves (59%); d) **32a**, NaH, THF [from (9*Z*)-**339**: 78%, (9*Z*)-**340**:(9*Z*-13*Z*)-**340** 2:1; from (9*E*)-**339**: 92%, (all*E*)-**340**:(13*Z*)-**340** 4:1; isomers separated by HPLC]; e) KOH [(9*Z*)-**341** 98%, (all*E*)-**341** 93%)

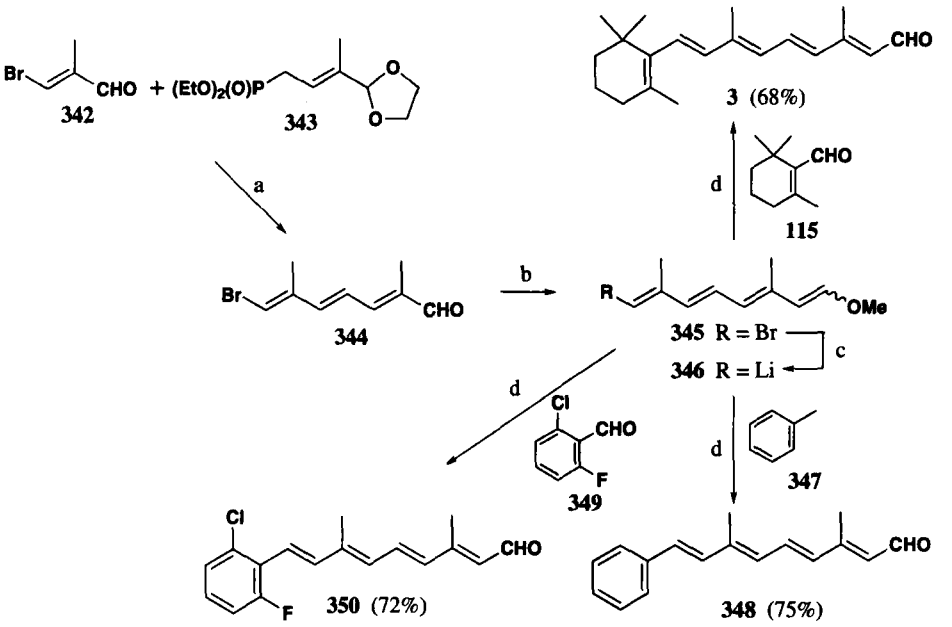
Scheme 53

VIII. ALKENYL- AND ALKYNYLLITHIUM REAGENTS

1. Alkenyllithium Reagents

The organometal compounds obtained by exchange of halide-substituted silyl enol ethers or acetals can be considered synthetic equivalents of the extended metal enolates used in the preceding chapter. They have been used for retinoid synthesis, in particular the prenal C_5-derivatives. Upon addition to aldehydes, the resulting allylic alcohols undergo dehydration under the same conditions employed for the hydrolysis of the silyl enol ether or acetal, unmasking the carbonyl compound.

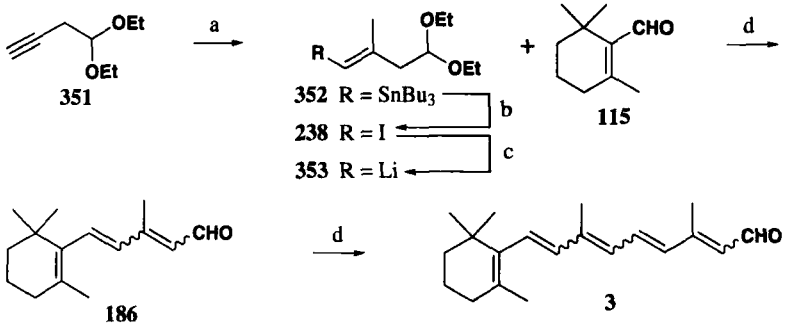
The synthesis of retinal (**3**) using a $C_{10} + C_{10}$ approach showed in *Scheme 54* is representative of this general methodology.[89] The vinyl organometallic reagent **346** is prepared by bromine-lithium exchange of **345**. This extended bromosilyl enol ether was synthesized by Wittig condensation of a bromotrienal **344** with methoxy methylenetriphenyl phosphorane. The lithium enol ether reacts at low temperature with the C_{10} aldehyde **115** to afford the intermediate hydroxy polyene enol ether which, without isolation, was smoothly hydrolyzed to a mixture of retinal isomers in 68% combined yield. The C_{10}-vinyllithium reagent thus becomes a synthetic equivalent of ω-lithio dehydrocitral, another extended vinylogous aldol anion, and can provide aryl retinal analogues **348** and **350** upon reacting with (substituted) benzaldehyde.



a) *i.* *t*-BuOK, THF, -70°C; *ii.* 3N HCl, 0°C (75%); b) *i.* $CH_3OCH_2PPh_3Cl$, *t*-BuOK, THF, -70°C; *ii.* 5% Na_2CO_3 (85%); c) *t*-BuLi, Et_2O, -78°C; d) *i.* Aldehyde, -78 to 0°C; *ii.* 1N HCl, 0°C

Scheme 54

In addition, dehydration to retinal can be promoted after reaction of an aldehyde with a γ-vinyllithium reagent of a β,γ-unsaturated acetal.[90] The vinylic-branched C_5-unit is functionalized as stannane by the stannylcupration-alkylation of the homopropargylic acetal **351** (*Scheme 55*).



a) *i.* *n*-$Bu_3SnMgMe$, CuCN, THF, -20°C; *ii.* MeI (54%); b) I_2, Et_2O, -20°C; c) *n*-BuLi or *t*-BuLi, Et_2O, -60°C; d) *i.* **353**; *ii.* HBr, H_2O (47% from **115**)

Scheme 55

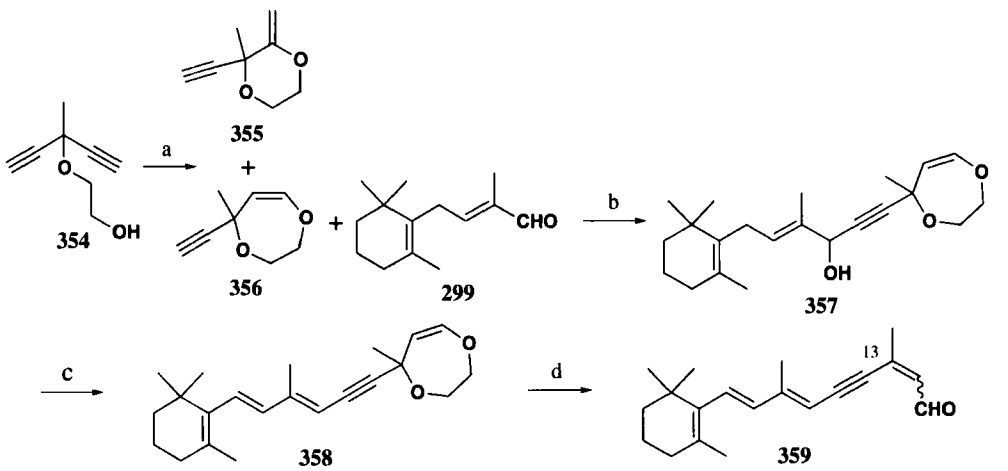
Nozaki's procedure was selected for this transformation due to the high reactivity of vinylmagnesium derivatives in alkylation reaction. Transformation of **351** to the vinyliodide **238** and treatment of the latter with alkyl lithium provides the halogen-metal exchange product **353**. The

vinyllithium adds first to C_{10}-aldehyde **115** and a second time to C_{15}-aldehyde **186** affording a mixture of retinal isomers (68% *E*) in 47% overall yield after treatment of the condensation product with HBr.

2. Alkynyllithium Reagents

In contrast to the Csp^2-M reagents, the use of Csp-M counterparts in addition to carbonyl compounds requires further manipulation of the propargyl alcohols in order to unravel the system that becomes the unsaturated conjugated polyene upon dehydration. This idea was implemented in one of the industrial synthesis of vitamin A ($C_{14} + C_6$ route) developed at Roche through Lindlar hydrogenation and dehydration.[91]

The long-standing problem of aldol condensation between an aliphatic ketone and an acetaldehyde equivalent can be solved by the combination of a nucleophilic addition of acetylene to the ketone and subsequent isomerization of the resulting 3-hydroxy-1-alkyne to the corresponding 2-alkenal. The latter step can be induced by a silylated vanadium catalyst, but it is restricted to acid-insensitive substrates.[92] A milder method that extends the scope of this procedure was reported in 1998 in an approach to 11,12-dehydroretinal (**359**).[93] Condensation of the C_{14} unit **299** with the anion of alkyne **356** (a surrogate of an alkenal which will be revealed upon hydrolysis of the 2*H*-1,4-dioxepin) afforded propargylic alcohol **357** (*Scheme 56*). The conjugated trienyne system was exposed upon heating alcohol **357** with Burgess reagent at 80°C. Mild



a) *t*-BuOK, *t*-BuOH, 85°C (72%, **355**:**356** 16:84); b) *n*-BuLi, THF, -75 to 25°C (91%); c) Burgess reagent, PhMe, 80°C (65%); d) 6M HCl, THF, 25°C [62%, (13*Z*)-**359**:(13*E*)-**359** 4:1]

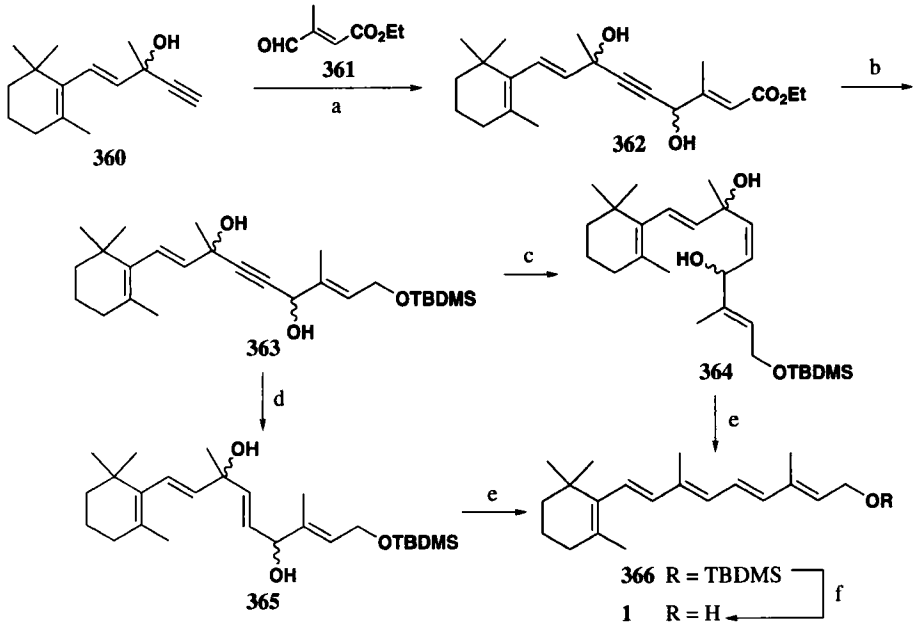
Scheme 56

acidic treatment of dioxepin **358** unmasked the α,β-unsaturated part encompassing C_{13}-C_{15} atoms of the retinal analogue chain **359**, which is obtained as a 4:1 at the terminal C_{13}-C_{14} bond. Thus, the 3,5-dihydro-5-ethynyl-5-methyl-2*H*-1,4-dioxepin funtions as an equivalent of an isoprenoid C_6 unit.

IX. OTHER METHODS

1. Titanium(0)-induced Reductive Elimination

In 1988 Solladié *et al.* reported the application of the low-valent titanium-induced reductive elimination[94] to the formation of the *E,E*-1,3-diene central unit of retinol (**1**).[95] The synthesis starts with the addition of the Grignard derived from ethynyl β-ionol (**360**) to ethyl χ-oxysenecionate (*E*-**361**) to afford the diol **362** in 90% yield as a mixture of diastereoisomers (*Scheme 57*). After reduction of the ester function and protection of the primary alcohol it was



a) *i.* EtMgBr; *ii.* **361** (90%); b) *i.* DIBAL-H. *ii.* TBDMSCl (90%); c) Lindlar catalyst (85%); d) $LiAlH_4$ (80%); e) $TiCl_3$, $LiAlH_4$, THF, 25°C (85%); f) *n*-Bu_4NF (80%)

Scheme 57

possible to convert the triple bond into a *cis* double bond (**364**) using Lindlard catalyst or into a *trans* double bond (**365**) employing lithium aluminium hydride, both reactions being high yielding. The key step of this synthesis, the reductive elimination, was conducted in diols **364** and **365** using low-valent titanium prepared by reacting a mixture of lithium aluminium hydride and titanium trichloride in a 1:2 ratio at room temperature. Both isomers **364** and **365** gave TBDMS-protected retinol (**366**) in 85% yield that after deprotection afforded retinol (**1**) in 80% yield.

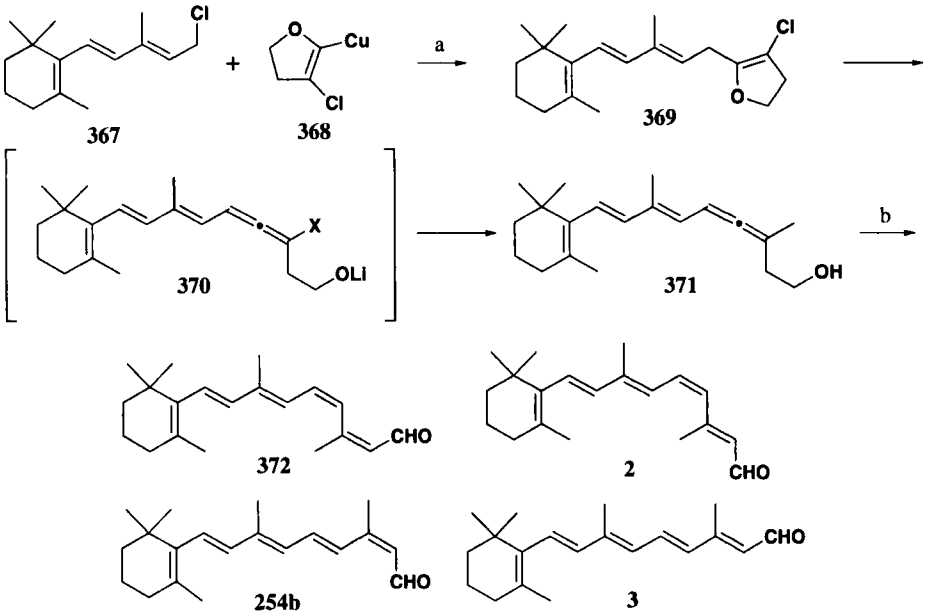
This choice of the TBDMS protecting group seems to be critical for the stereoselectivity of the reductive elimination. When substituted by an acetate group the reductive elimination with Ti(0) afforded a mixture of *cis* and *trans* isomers.

The same authors also employed this versatile methodology for the preparation of different retinoids. Thus, employing oxysenecionate *Z*-**361** in the Grignard addition instead of its

E isomer it was possible to easily obtain 13-*cis* retinoic acid. The greater sensitivity of aldehydes to electron transfer determined the use of the corresponding dithioacetals for the direct preparation of retinal **2**.[95b,c]

2. Isomerization of β-Allenic Retinals

The isomerization of β,γ-allenic aldehydes can afford the conjugated system, and that approach to retinoids was already reported in 1982.[96] In this route a one-pot reaction using 2-β-ionylideneethyl chloride (**367**) as starting material led to the useful intermediate isoretinol **371** that could be easily converted into four different isomers of retinal (*Scheme 58*). 2-β-Ionylideneethyl chloride (**367**) reacts with the key intermediate 3-chloro-4,5-dihydro-2-furylcopper (**368**),



a) MeLi (55%); b) DMSO, *N,N*-dicyclohexylcarbodiimide (**372**:**2**:**254b**:**3** 1:1:4:5)

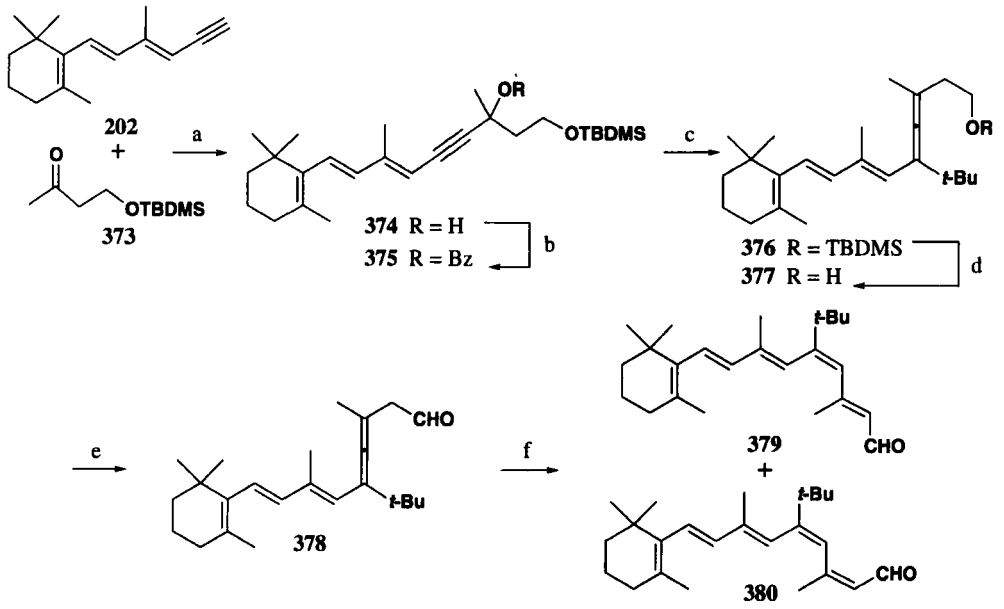
Scheme 58

accessible by treatment of the corresponding lithium compound with copper iodide, to afford the 5-substituted 4-chloro-2,3-dihydrofuran **369** that can then react with methyllithium to undergo ring opening and substitution of the chlorine to give the mentioned isoretinol **371** (14,12-*retro*retinol) in 55% yield.

Oxidation of **371** with dimethyl sulfoxide in the presence of *N,N*-dicyclohexylcarbodiimide afforded a 1:1:4:5 mixture of the four 11,13-stereoisomeric retinals (*Z,Z*)-**372**, (*Z,E*)-**2**, (*E,Z*)-**254b** and (*E,E*)-**3**, which can be separated by liquid chromatography.

A similar route to retinals modified at the C_{11} or C_{13} positions by bulky *tert*-butyl groups (see *Scheme 40* for the synthetic sequence) allows to apply stereochemical control since the relative configuration of the resulting *tert*-butyl bearing double bonds of the side-chain is

cis.[69b] Moreover, the isolation of the allenic retinal **378** was made possible by the use of the Dess-Martin reagent, and conditions were developed (1.0 M NaOEt, EtOH, 0°C, 2 h; activated Al_2O_3, benzene, 25°C, 48 hours) for high yielding rearrangements of **378** to these extremely twisted retinal analogues **379** and **380** (*Scheme 59*).[97]



a) *n*-BuLi, THF, -78 to 25°C (72%); b) *i.* *n*-BuLi, THF, -78°C; *ii.* PhCOCl, 25°C (82%); c) *t*-Bu_2CuLi•LiCN, Et_2O, 0°C (70%); d) *n*-Bu_4NF, THF (80%); e) Dess-Martin periodinane, CH_2Cl_2 (77%); f) 1.0 M NaOEt, EtOH, 0°C, 2 h (**379**, 28%; **380**, 28%); activated Al_2O_3, benzene, 25°C, 48 h (**379**, 50%; **380**, 30%)

Scheme 59

X. SUMMARY

The succesful treatment of acute promielocytic leukemia (APL) with *trans*-retinoic acid, which leads to a cure of more than 80% of the patients diagnosed with this cancer, constitutes the first example of a genetic-based disease that can be reverted by intervention at the molecular biology level. The role of retinoids as ligands of nuclear receptors makes them attractive drugs for therapeutic applications. Natural and synthetic retinoids, rexinoids (RXR-selective ligands) and the so-called atypical retinoids are currently being intensively investigated to assess their cancer therapeutic and cancer chemopreventive activities. Their synthesis still constitutes an enormous challenge, in particular when a particular stereoisomer of the intact polyene side-chain is desired. The only general method that leads to a predictable stereochemical outcome, and almost the exclusive procedure for accessing the least stable *cis*-stereoisomers is based on metal-catalyzed cross-coupling processes. Issues that need to be addressed in future work will be the development of milder reaction conditions, thus overcoming the existing limitations for certain combinations of coupling partners, and the construction of retinoids using atom-economical

protocols, involving the summation of reactants to create the desired products with minimal waste in order for industry to adopt these otherwise powerful methodologies.

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