Russian Chemical Reviews **62** (2) 169 — 183 (1994)
©1994 Russian Academy of Sciences and Turpion Ltd

UDC 541.63 : 542.91 : 541.64 : 547.366

New methods of synthesis of linear functionalised (*Z*)-isoprenoids and their 2,3-dihydro-derivatives

N Ya Grigor'eva, O A Pinsker

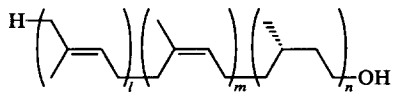
Contents

I. Introduction	169
II. Construction of the (*Z*)-isoprenoid chain with formation of a C–C bond	169
III. Construction of the isoprenoid chain with formation of a new (*Z*)-trisubstituted C=C bond	174
IV. Synthesis of (*Z*)-isoprenoids with formation of new C–C and (*Z*)-trisubstituted C=C bonds	180
V. Regioselective and enantioselective hydrogenation of the Δ^2-bond in α-functionalised isoprenoids	181

Abstract. The chemical and microbiological methods developed for the synthesis of polyprenols and dolichols are examined. These methods involve the construction of regular functionalised (*Z*)-isoprenoids accompanied by the creation of new C–C and/or (*Z*)-trisubstituted C=C bonds. Also considered are the highly regioselective and enantioselective procedures for the conversion of α-functionalised isoprenoids into their 2,3-dihydro-derivatives. The bibliography includes 87 references.

I. Introduction

Polyprenols **1** and dolichols **2** occupy an important place in the series of biologically active isoprenoids.



1, 2

1: l = 3, 4; m > 3; n = 0.
2: l = 3; m = 8÷20; n = 1.

It has now been reliably established that these regular polyisoprenoid alcohols are low-molecular-mass bioregulators of the coenzyme type, ensuring the transport of monosaccharides through cell membranes and their subsequent inclusion in the biosynthesis of carbohydrate-containing biopolymers of the cell wall in prokaryotes and eukaryotes.[1–3] The problem of the total synthesis of the individual polyprenols, dolichols, and their modified analogues, which arose in connection with the study of the mechanism of this process, required for its solution the development of methods for the stereoselective construction of a fairly long (*Z*)-isoprenoid chain — the principal structural element of the molecules of compounds **1** and **2**. In the course of studies carried out on these lines during the last twenty years, general methods have been devised for the construction of (*Z*)-disubstituted methylolefins, a special case of which is the construction of the (*Z*)-isoprene unit, and procedures have been developed for the regioselective and enantioselective transformation of compounds **1** into compounds **2**. These methods have expanded the range of procedures available in synthetic chemistry and can be used for the construction of new natural and biologically active products. The Laboratory of Polyunsaturated Compounds of the Institute of Organic Chemistry of Russian Academy of Sciences, headed by A M Moiseenkov, a Corresponding Member of the Russian Academy of Sciences, has made an appreciable contribution to the development of the above methods. This review has been written in honour of the memory of A M Moiseenkov.

II. Construction of the (*Z*)-isoprenoid chain with formation of a C–C bond

1. Biogenetic-like conversion of isoprenoids into higher (*Z*)-C_5-homologues

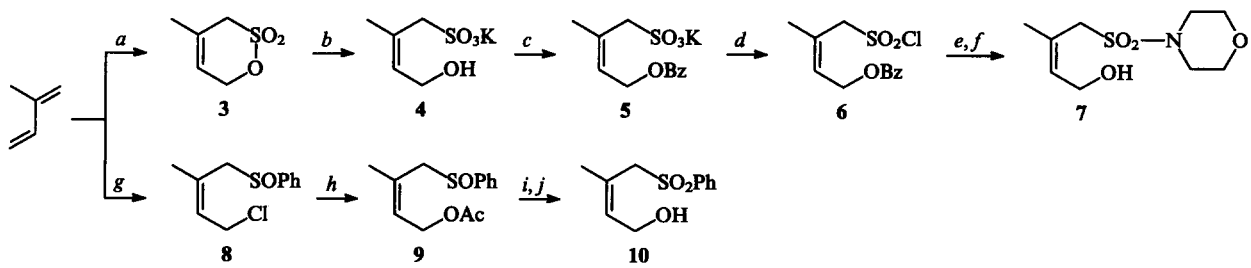
Moiseenkov and coworkers[4–7] showed that the δ-sultone **3**, which can be readily obtained from isoprene, dissociates at the S–O bond during controlled hydrolysis with the exclusive formation of the (*Z*)-sulfonate **4**, which affords the hydroxysulfonamide **7** via the benzoate **5** and sulfonyl chloride **6** stages with complete retention of the configuration (Scheme 1). The hydroxysulfonamide was used as the key block-synthon for the biogenetic-like (*Z*)-C_5 growth of the isoprenoid chain in the construction of the polyprenyl molecule. As shown in Scheme 2, this operation is carried out in three stages. Thus the conversion of (*E,E*)-farnesol **11** into the corresponding bromide **12**, alkylation by the latter of the dilithio-derivative **13** of the hydroxysulfonamide **7**, and finally the reductive desulfurisation of the resulting hydroxysulfonamide **14** to (*Z,E,E*)-geranylgeraniol **15** illustrate the conversion of the sesquiterpenoid skeleton into a diterpenoid skeleton. The repetition of the above transformations starting with compound **15** leads, via the hydroxysulfonamide **16** stage, to the (*Z,Z,E,E*)-sesterterpenol **17**, which is similarly converted, via the hydroxysulfonamide **18**, to a (*Z,Z,Z,E,E*)-triterpenol — the hexaprenol WT_2C_3OH† **19**.

N Ya Grigor'eva, O A Pinsker Laboratory of Polyunsaturated Compounds, Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii prosp. 47, 117913 Moscow. Fax (7-095)135 53 28

Received 1 December 1993
Uspekhi Khimii **63** (2) 177 – 191 (1994); translated by A K Grzybowski

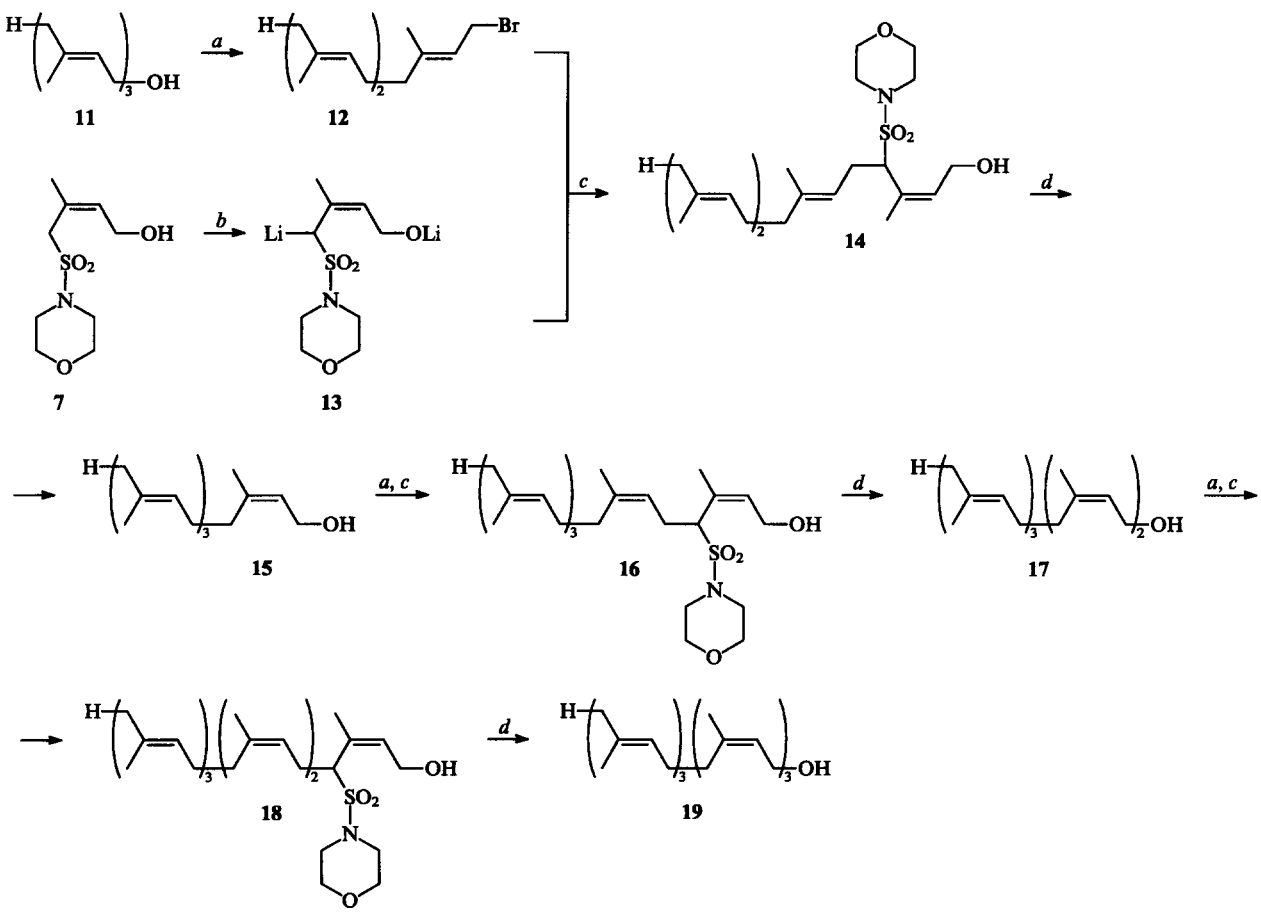
† Here and henceforth the following abbreviations recommended by IUPAC[9] are used to designate the configurations of polyprenols: W is the terminal unit, T and C are the inner (*E*)- and (*Z*)-isoprene units, and S is the 2,3-dihydroisoprene unit.

Scheme 1



Bz = benzoyl;
(*a*) SO_3; (*b*) aq. KOH (pH 7 – 8); (*c*) BzCl/Py; (*d*) $POCl_3$; (*e*) HN⟨O⟩; (*f*) $LiAlH_4$;
(*g*) PhSOCl, 5 kbar; (*h*) AcOK/AcOH; (*i*) *m*-$ClC_6H_4CO_3H/CH_2Cl_2$; (*j*) H_3O^+.

Scheme 2

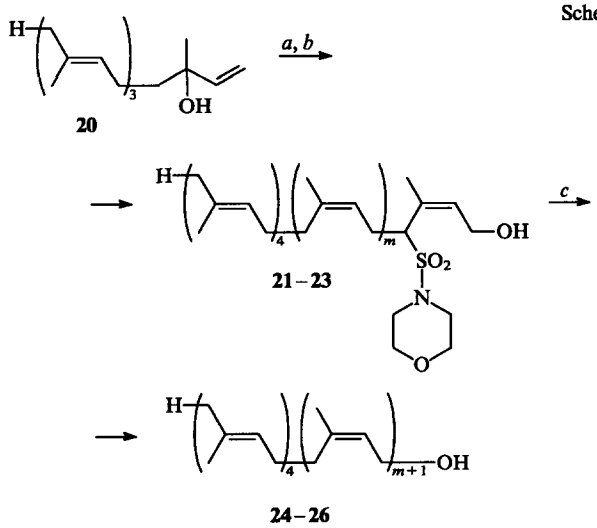


(*a*) PBr_3/Py; (*b*) Bu^nLi; (*c*) **13**/THF, −70 °C; (*d*) $Na/NH_3-C_6H_{14}-Et_2O$, DB18C6
(DB18C6 = dibenzo-18-crown-6).

The reactions presented in Scheme 2 constituted the first reliably documented total synthesis of polyprenols.[8]

The pentaprenol WT_3COH **24**, hexaprenol WT_3C_2OH **25**, and heptaprenol WT_3C_3OH **26** were obtained similarly in succession from geranyllinalool **20** (Scheme 3) via stages involving the sulfonamides **21**–**23** respectively.[10] Compounds **25** and **26** were subsequently isolated from the leaves of the palm *Serenoa repans*.[11]

Scheme 3



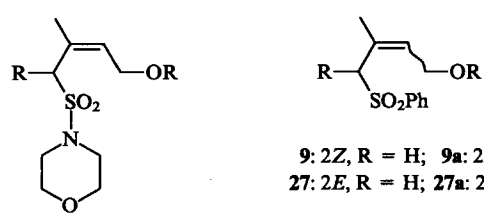
20

21–23

24–26

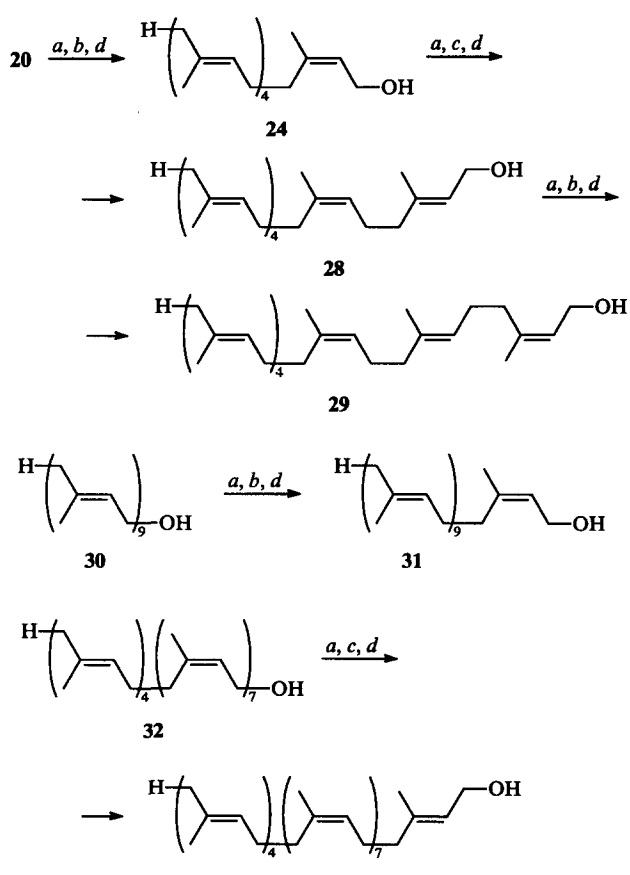
21, 24: $m = 0$; **22, 25**: $m = 1$; **23, 26**: $m = 2$.
(*a*) PBr_3/Py; (*b*) **13**/THF, −50 °C; (*c*) $Na/NH_3-C_6H_{14}-Et_2O$, DB18C6.

Scheme 4



7: R = H.
13: R = Li.

9: 2*Z*, R = H; **9a**: 2*Z*, R = Li.
27: 2*E*, R = H; **27a**: 2*E*, R = Li.



24

28

29

30

31

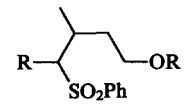
32

33

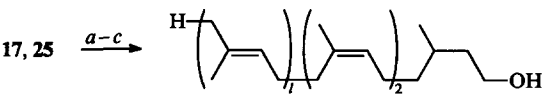
(*a*) PBr_3/Py; (*b*) **13**; (*c*) **27a**; (*d*) $Na/NH_3-C_6H_{14}-Et_2O$, DB18C6.

The approach considered proved to be extremely fruitful in the synthesis of modified polyprenols with a specified nonnatural sequence of the (*Z*)- and (*E*)-isoprene units in the molecule as well as dolichol-like structures. A more readily available block-synthon—the hydroxysulfone **10**—was used successfully together with compound **7** for the formation of (*Z*)-C_5-homologues. Compound **10** was obtained from the acetate **9** via the (*Z*)-chlorosulfoxide **8** (Scheme 1), which is formed smoothly in its turn from isoprene and benzenesulfinyl chloride at a high pressure.[12,13] Accordingly, the (*E*)-hydroxysulfone **27** in the form of its dilithio-derivative **27a** was used as the (*E*)-C_5-block.[14] The heptaprenol WT_3CTCOH **29** was synthesised by the (*Z*)/(*E*)-C_5-homologue formation method from geranylinalool **20** via the pentaprenol **24** and hexaprenol WT_3CTOH **28** stages using the block-synthons **7** and **27**, while the decaprenol WT_8COH **31**[16] and the dodecaprenol WT_3C_7TOH **33**[16] were obtained from the readily available natural products solanesol **30** and moraprenol **32**[15] respectively (Scheme 4).

The use of the saturated block-synthon **34** in the form of its dilithio-derivative **34a** in the concluding stage of the C_5-homologue formation reaction made it possible to obtain the racemates of the dolichol-like hexaprenol WT_2C_2SOH **35**[18] and the heptaprenol WT_3C_2SOH **36**[17] from the pentaprenol **17** and hexaprenol **25** respectively, while the use of the chiral (3*R*)-form of the block-synthon **34** led to the above compounds with the natural (*S*)-configuration of the α-isoprene unit.[19]



34: R = H; **34a**: R = Li.

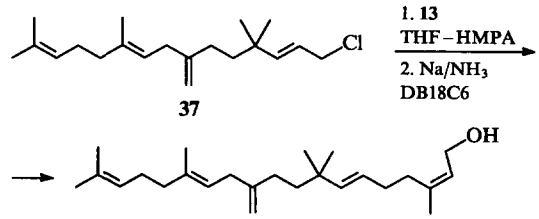


35: $l = 3$; **36**: $l = 4$

(*a*) PBr_3/Py; (*b*) **34a**; (*c*) $Na/NH_3-C_6H_{14}-Et_2O$, DB18C6.

A partial synthesis of a combined preparation of (*S*)-dolichols **2** ($l = 2$, $m = 11-19$, $n = 1$) and their (*R*)-analogues from a mixture of the polyprenols **1** ($l = 2$, $m = 11-19$, $n = 0$), isolated from the leaves of *Ginkgo biloba*, has also been achieved with the aid of the (*R*)- and (*S*)-forms of compound **34**.[20]

The C_5 isoprene chain C_5-homologue formation method, developed for the synthesis of polyprenyl structures, was used successfully subsequently in the synthesis of the (*Z*)-isoprene section of the non-regular sesterterpenol moenocinol **38** from the chloride **37**.[21]



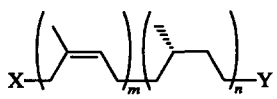
37

38

THF = tetrahydrofuran, HMPA = hexamethylphosphoramide.

2. A block method for the construction of the isoprenoid chain

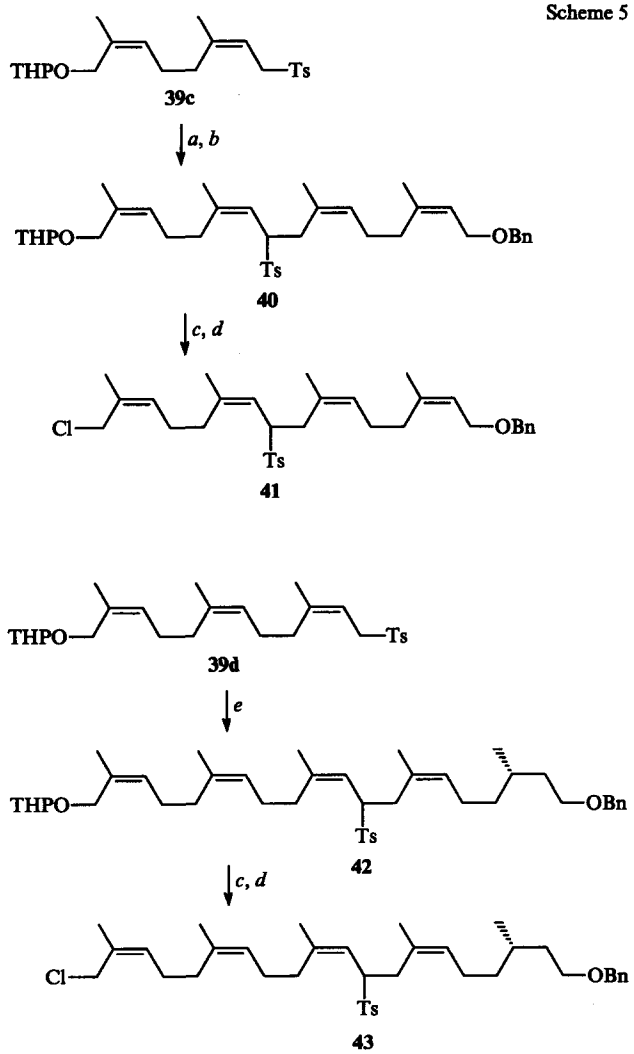
During approximately the same years, Sato et al.[22] proposed that the (*Z*)-isoprenoid chain be constructed by 'cross-linking', via the C–C bonds, block-synthons of type **39** containing two or more (*Z*)-isoprenoid units. Such compounds became available after the observation by the authors of the high (*Z*)-stereoselectivity of the Wittig reaction with participation of hydroxyacetone derivatives.[23] This question is considered in detail in Section III.1. Here one should only note that the key (*Z*)-C_{10} and (*Z*)-C_{15}-bifunctional building blocks of type **39** were obtained precisely from the benzyl ethers of nerol, (*Z,Z*)-farnesol, and (*S*)-citronellol.[22,24,25]



39a–e

39a: $m = 2$, $n = 0$, X = Cl, Y = OBn.
39b: $m = 3$, $n = 0$, X = Cl, Y = OBn.
39c: $m = 2$, $n = 0$, X = OTHP, Y = Ts.
39d: $m = 3$, $n = 0$, X = OTHP, Y = Ts.
39e: $m = 1$, $n = 1$, X = Cl, Y = OBn.
(Bn = benzyl, THP = Tetrahydropyranyl, Ts = toluene-*p*-sulfonyl).

Scheme 5

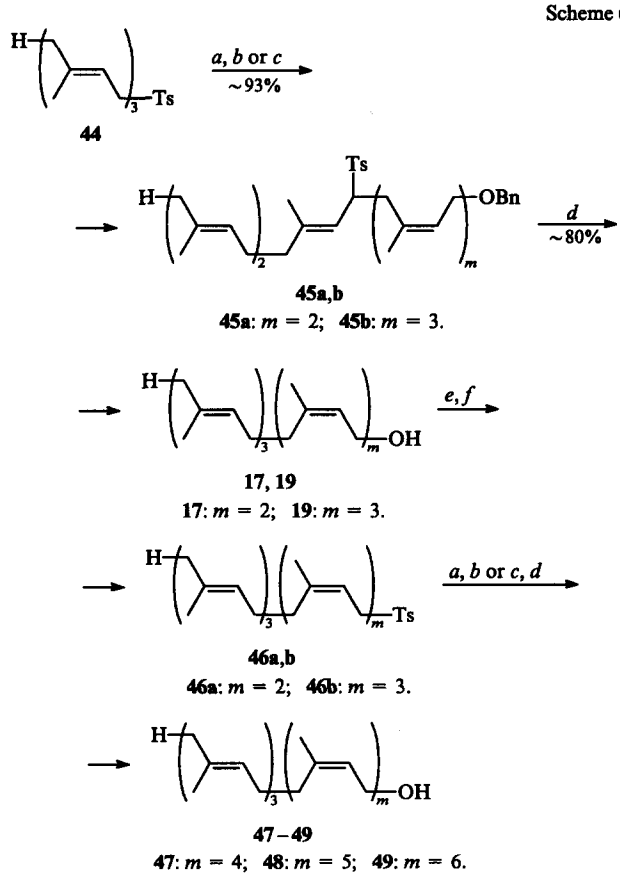


(*a*) Bu^nLi/THF–HMPA, –78 °C; (*b*) **39a**; (*c*) H_3O^+; (*d*) MsCl, LiCl, *sym*-collidine, DMF; (*e*) **39e**, Bu^n_4NBr/50% NaOH, 20 °C (Ms = methanesulfonyl).

In order to construct the (*Z*)-isoprenoid chain with the aid of these blocks, Sato's group[25] used one of the modern versions of the Wurtz reaction, first proposed by Biellmann[26] and then developed in detail by Altman[27] and Masaki[28] for the construction of the regular (*E*)-polyisoprenoid chain. This method includes the alkylation of the carbanions (stabilised by sulfur-containing functional groups) with the aid of allyl halides and the subsequent Birch reductive cleavage of the C–S bond in the reaction products. Thus the alkylation of the tolyl sulfone **39c** with the aid of the chloride **39a** affords the tolyl sulfone **40** containing four (*Z*)-isoprene units. The latter is converted by a standard method into the chloride **41**, used for the subsequent increase in the length of the (*Z*)-isoprenoid chain (Scheme 5). The tolyl sulfone **42** with a (3*S*)-α-isopentane unit, which is smoothly converted into the chloride **43**, was obtained similarly from the block-synthons **39d** and **39e**.

Having at their disposal (*Z*)-C_{10}-, (*Z*)-C_{15}-, and (*Z*)-C_{20}-block-synthons (compounds **39a**, **39b**, and **41** respectively), Sato's group[24,29] achieved the effective syntheses of pentaprenol (WT_2C_2OH, **17**), hexaprenol (WT_2C_3OH, **19**), heptaprenol (WT_2C_4OH, **47**), octaprenol (WT_2C_5OH, **48**), nonaprenol (WT_2C_6OH, **49**) (Scheme 6), and undecaprenol (WT_2C_8OH, **52**) (Scheme 7). (*E,E*)-Farnesyl tolyl sulfone **44** was used to introduce the transoid fragment into the target compound.

Scheme 6

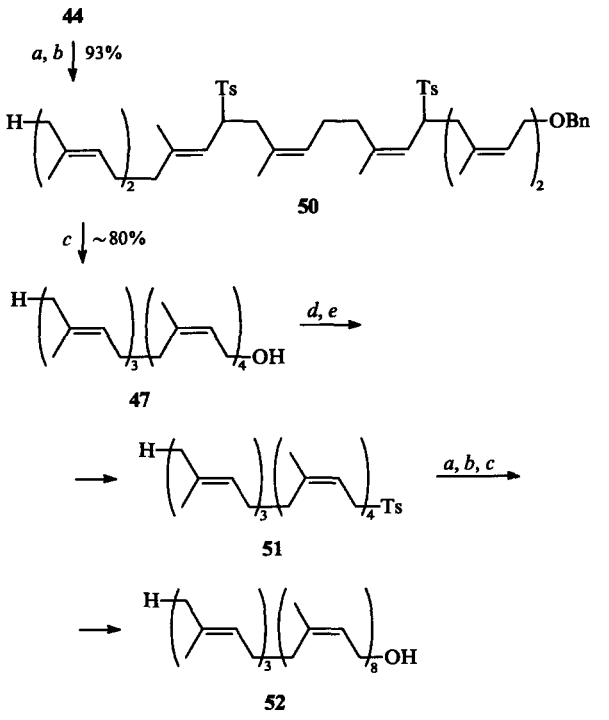


45a: $m = 2$; **45b**: $m = 3$.
17: $m = 2$; **19**: $m = 3$.
46a: $m = 2$; **46b**: $m = 3$.
47: $m = 4$; **48**: $m = 5$; **49**: $m = 6$.

(*a*) Bu^nLi/THF–HMPA, –78 °C; (*b*) **39a**; (*c*) **39b**; (*d*) Li/$EtNH_2$; (*e*) MsCl, LiCl, *sym*-collidine/DMF; (*f*) TsNa/DMF.

As shown in Scheme 6, the alkenylation by the chlorides **39a, b** of the (*E*)-tolyl sulfone **44** deprotonated by treatment with Bu^nLi affords the tolyl sulfones **45a, b**, the reductive desulfurisation of which is accompanied by the removal of the benzyl protecting groups and leads to pentaprenol **17** and hexaprenol **19** respectively. The latter are smoothly converted by a standard method into the tolyl sulfones **46a, b**, the introduction of which into the sequence of reactions described above gives rise to heptaprenol **47**, octaprenol **48**, and nonaprenol **49** respectively.

Scheme 7



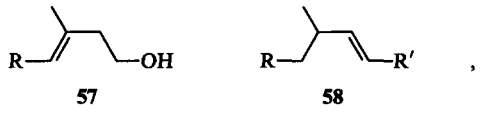
(*a*) Bu^{n}Li/THF–HMPA, –78 °C; (*b*) **41**; (*c*) Li/EtNH$_2$; (*d*) MsCl, LiCl, *sym*-collidine/DMF; (*e*) TsNa/DMF.

The use of the block-synthon **41** proved to be extremely convenient for the synthesis of higher polyprenols. Thus alkylation of the deprotonated tolyl sulfone **44** by the chloride **41** leads to the tolyl sulfone **50** in 93% yield. The latter loses simultaneously the tosyl and benzyl groups on treatment with lithium in EtNH$_2$ and is converted into heptaprenol **47**. The tolyl sulfone **51** obtained from heptaprenol **47** was transformed similarly into undecaprenol **52**.[29]

Undecaprenol **52** served in its turn as the starting material for the total synthesis of (*S*)-dolichol (20-eicosaprenol, WT_2C_{16}. .SOH, **56**), achieved with record speed in the chemistry of prenols by Sato and coworkers[25] via a stage involving the synthesis of pentadecaprenol **54** (Scheme 8) by using the C_{20}-block **41** and the (3*S*)-C_{25}-block **43** to increase the length of the (*Z*)-isoprenoid chain.

It is noteworthy that, as in the synthesis of the C_{25}-block **43**, in this synthesis the authors use successfully the effective and technologically convenient method for the alkylation of the toluene sulfones **39d**, **53**, and **55** under phase transfer catalytic conditions.

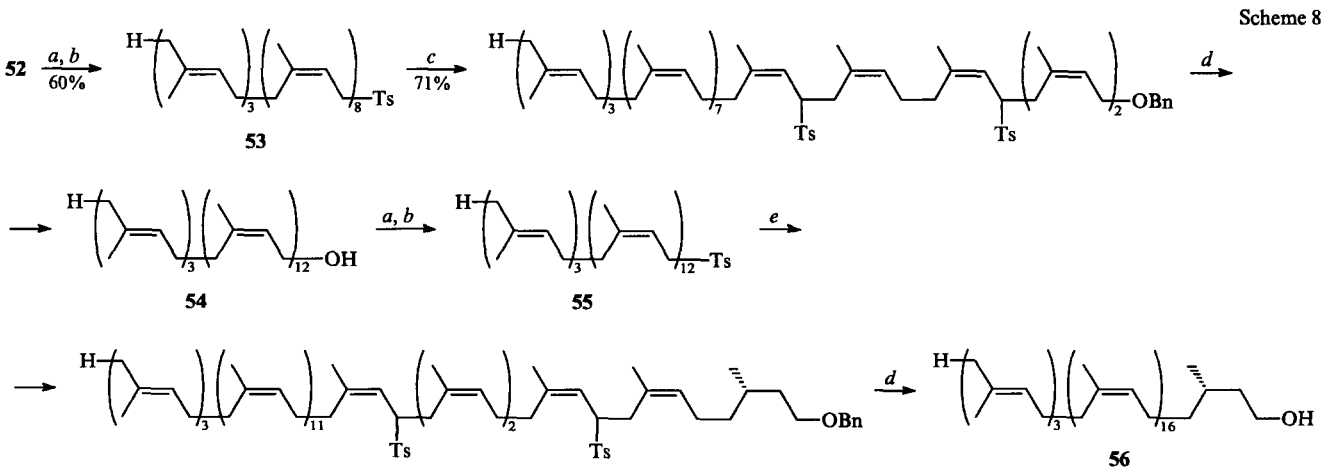
The version of the Wurtz reaction examined in Section II can be used successfully for the construction of the (*Z*)-isoprenoid chain. However, despite all its advantages, the method suffers from a significant disadvantage, which was noted by the authors of the studies quoted above. In the reductive cleavage of the C–S bond in sulfones of type **21**–**23** and in tolyl sulfones of type **45a, b**, the formation of the target products is accompanied by the formation of their regioisomers, which can be explained by the migration of the C=C bond in the carbanionic intermediate: in the case of the C_5-homologue formation reaction, these are the homoallyl alcohols **57**, while in Sato's block syntheses they are products of type **58**:



where R and R′ are the corresponding polyprenyl groups.

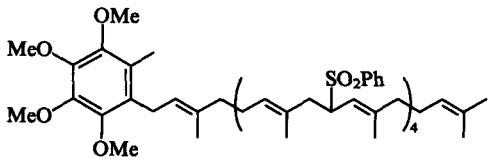
Systematic study of the desulfurisation conditions in relation to the tolyl sulfones **21**–**23**, undertaken to overcome this disadvantage, showed[10,18,30] that, when the reaction is carried out with the aid of sodium in the 4:4:1 ammonia–hexane–ether emulsion in the presence of 10 mol.% of DB18C6 at –50 °C, it is possible to reduce to 5%–10% the admixture of the isomer **57** and also to suppress completely the hydrogenolysis of the allylic C–O bond. The residual homoallyl alcohol **57** either decomposes in the conversion of the corresponding isoprenols (for example, compounds **15** and **17**) into the corresponding bromides[10,31] or can be removed (as well as an admixture of type **58**) with the aid of precision chromatography on silica gel impregnated with $AgNO_3$.[22,24,29]

Scheme 8



(*a*) MsCl, LiCl, *sym*-collidine/DMF; (*b*) TsNa/DMF; (*c*) **41**, Bu$^n_4$NBr/50% NaOH, 20 °C; (*d*) Li/EtNH$_2$; (*e*) **43**, Bu$^n_4$NBr/50% NaOH, 20 °C.

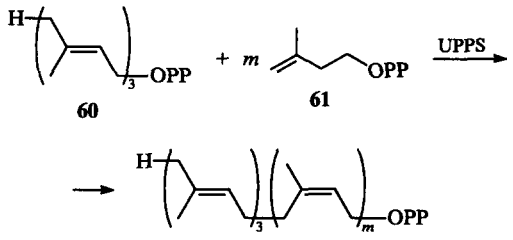
In this connection, one should note an interesting procedure for the selective reduction of allyl sulfones,[32] which was used by the authors of one of the specific syntheses of ubiquinone (10),[33] who showed that all four $PhSO_2$ groups can be removed from the sulfone **59** (without shift of the C=C bond) by means of $LiBHEt_3$ in the presence of catalytic amounts of 1,3-bis-(diphenylphosphino)propanopalladium dichloride.



59

3. Construction of the chain with the aid of enzyme catalysis

Studies in recent years on the biosynthesis of polyprenols have led to the isolation and characterisation of the enzyme responsible for the construction of the (*Z*)-isoprenoid section of the molecule of compound **1**, which has been called undecaprenyl pyrophosphate synthetase (UPPS).[34] Preparations of this enzyme, obtained from various bacterial sources,[34–37] exhibited *in vitro* a high and virtually identical activity in the successive (*Z*)-C_5-homologue formation reactions of the phosphates of isoprenols[38] using isopentenyl pyrophosphate **61** as the source of the (*Z*)-C_5-unit. Thus pyrophosphates of decaprenol (WT_2C_7OH, **62**) and undecaprenol (WT_2C_8OH, **63**) have been synthesised from (*E,E*)-farnesyl pyrophosphate **60**, which is the primary substrate of UPPS *in vivo*.



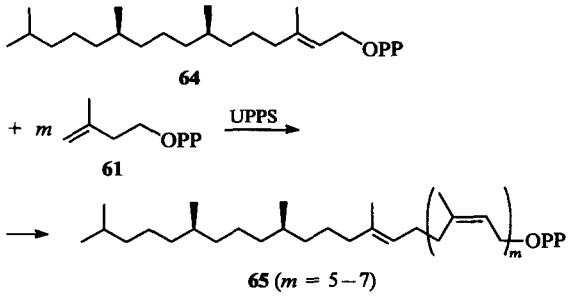
60 **61**

62, 63

62: m = 7; **63**: m = 8.

OPP = pyrophosphate.

The enzyme UPPS does not exhibit a high substrate specificity in relation to the primary substrate and can 'work' with allyl alcohols having different structures.[34–36] For example, the $C_{45}-C_{55}$ glycinoprenols **65**, detected recently in the leaves of the soya bean *Glycine max Merrill*,[40] have been obtained from phytyl pyrophosphate **64** with the aid of the UPPS preparation isolated from *Escherichia coli*.[39]



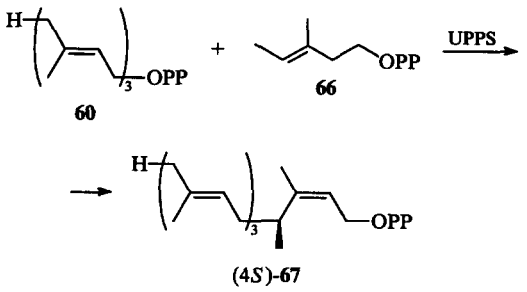
64

61

65 (m = 5–7)

The requirements of UPPS as regards the structure of the homoallyl substrate are more definite. The enzyme exhibits an adequate activity in relation to only one non-natural homoallyl substrate—the pyrophosphate **66**. The presence of the methyl group at the C(4) atom in compound **66** completely alters the nature of the reaction: regardless of the chain length of the allyl substrate, the enzyme catalyses only its conversion into the C_6-homologue, forming 4-methylpolyprenol with the (*S*)-configuration of the C_4 centre, which is illustrated by the conversion of farnesyl pyrophosphate **60** into the phosphate (4*S*)-**67** (Scheme 9).[41]

Scheme 9



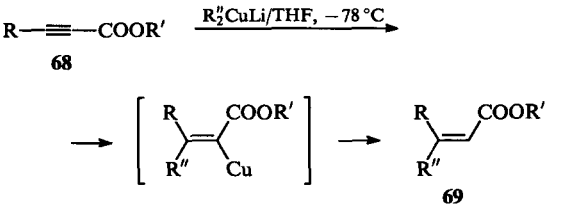
60 **66**

(4*S*)-**67**

It may be hoped that the high stereo- and enantio-selectivity of this reaction will find further practical application, as has been shown in relation to farnesyl pyrophosphate synthetase, with the aid of which, the syntheses of faranal and 4-methyl-substituted juvenile hormones have been achieved.[42–44] Thus studies on the biosynthesis of polyprenols provided chemists engaged in organic synthesis with a new valuable reagent for the construction of the (*Z*)-isoprenoid chain.

III. Construction of the isoprenoid chain with formation of a new (*Z*)-trisubstituted C=C bond

The elucidation of the biological functions of (*E*)-isoprenoids, in the first place the acyclic steroid precursor squalene, and insect juvenile hormones aroused at the end of the 1960s and the beginning of the 1970s an explosion of interest by chemists concerned with organic synthesis in the development of stereoselective methods for the construction of the (*E*)-trisubstituted C=C bond.[45,46] On the other hand, the methods for the synthesis of (*Z*)-trisubstituted olefins in general and (*Z*)-isoprenoids in particular did not develop adequately before the start of systematic studies on the synthesis of polyprenols. Nevertheless, towards the beginning of the 1970s several methods were described in the literature for the stereoselective construction of (*Z*)-trisubstituted olefin systems. Thus Corey and Katzenellenbogen[47] showed that the addition of dialkyl cuprates to α,β-acetylenic acids and their esters in THF at low temperatures proceeds exclusively as a *cis*-process[47] and they suggested that it be used, in particular, for the conversion of esters of β-alkyl- and β-alkenyl-propiolic acids **68** into esters of type **69**.



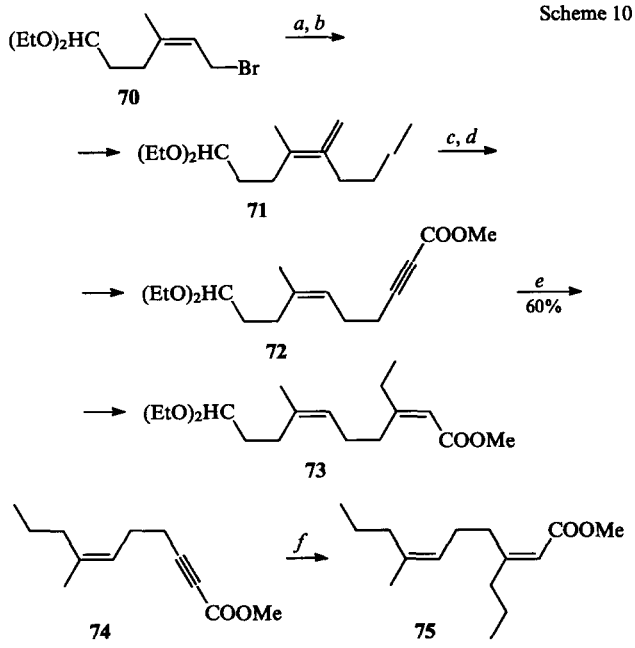
68

69

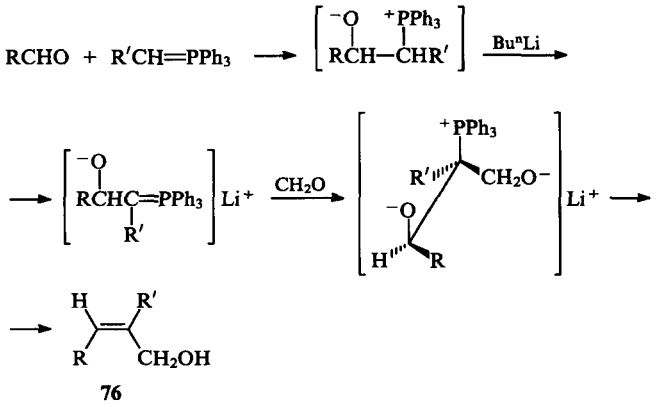
R = Me, Et, Bu^n, Ph; R′ = Me, Et, Bu^s; R″ = Me, Et.

The application of the method is illustrated in Scheme 10. The allyl bromide **70** is synthesised and converted via the enyne **71** and ester **72** stages into the ester **73**—the key block-synthon in the synthesis of the natural ionophore monensin,[48] while the ester **74** is converted into the pheromone of the lesser apple-worm *Laspeyresia pomonella L.* **75**.[49]

Scheme 10

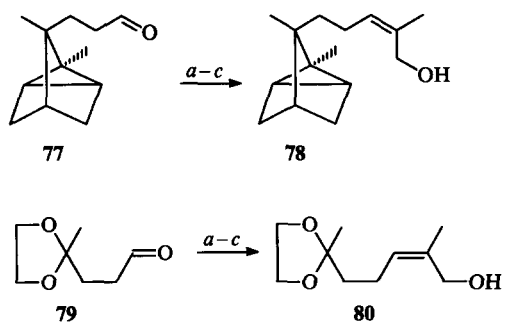


(*a*) $LiCH_2C{\equiv}CSiMe_3$; (*b*) $AgNO_3$, NaCN; (*c*) Bu^nLi; (*d*) $ClCO_2Me$; (*e*) Et_2CuLi/THF, −70 °C; (*f*) Pr^n_2CuLi/THF, −70 °C.



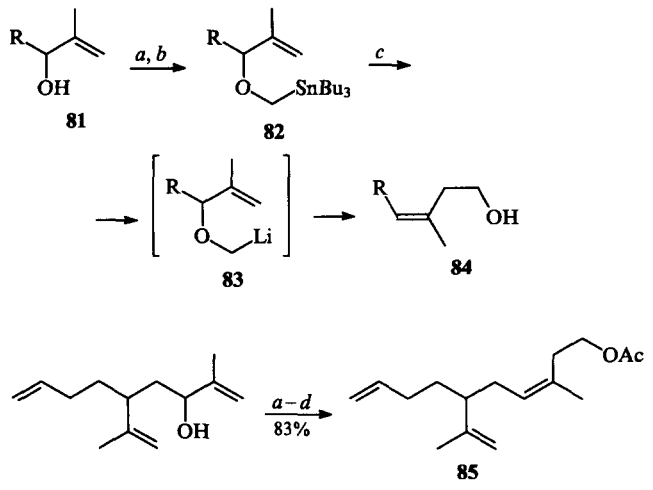
A highly stereoselective method for the construction of allyl alcohols **76** with the aid of two consecutive Wittig reactions achieved in one reactor (using formaldehyde as the carbonyl component in the second reaction) was developed simultaneously in Corey's laboratory.[50]

For R′ = Me, this sequence of reactions makes it possible to construct the terminal (*Z*)-isoprene unit, as shown for the conversion of the aldehyde **77** into α-santalol **78**[50] and of the aldehyde **79** into the ketal alcohol **80**. The latter is a key block-synthon for the synthesis of (±)-trisporal B and (±)-trisporic acid.[51]



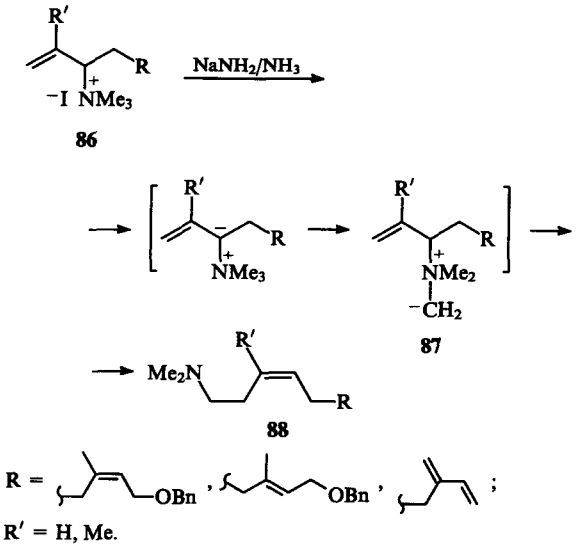
(*a*) $MeCH{=}PPh_3$; (*b*) Bu^nLi; (*c*) CH_2O.

An effective method of synthesis of (*Z*)-homoallyl alcohols **84** is also noteworthy. It was developed by Still and Mitra[54] on the basis of the stereochemically unusual [2,3]-sigmatropic rearrangement (cf. Masaki et al.[52] and Inoue et al.[53]) of the methylallyloxymethyllithio-derivatives of compound **83**, which they observed. The rearrangement takes place *in situ* on treatment of the tributylstannylmethyl ethers of the methylallyl alcohols **82** with Bu^nLi.[54] The method has been used successfully in the synthesis of the component **85** of the pheromone of the red San Jose scale.[54]



(*a*) KH; (*b*) Bu_3SnCH_2I; (*c*) Bu^nLi; (*d*) Ac_2O–Py.

Yet another example of the [2,3]-sigmatropic rearrangement, leading to the highly stereoselective synthesis of di- and tri-substituted (*Z*)-olefins, appeared later in the literature. It was discovered by Sato's group[55] in relation to the ylides **87**, which are converted into the amines **88** on treatment with $NaNH_2$ in NH_3 at the instant of formation from the quaternary ammonium salts **86**.[55] The amines **88** can be readily transformed by standard methods into the corresponding (*Z*)-homoallylic aldehydes or alcohols.

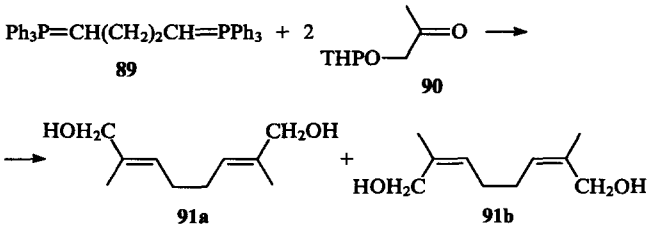


All the methods considered above yield satisfactory results in the synthesis of the terminal (*Z*)-isoprene unit (for example, in the alcohol **76** for R′ = Me or in compound **84**), but they are fundamentally unsuitable for the synthesis of the disubstituted (*Z*)-methylalkene fragment in the middle of the chain. The attempt to construct a fairly long (*Z*)-isoprenoid chain from them by the multistage growth of the (*Z*)-C_5-units was also relatively ineffective because the construction of each succeeding unit requires a multistage preparatory step involving the preparation of the necessary starting materials. These disadvantages were overcome in the method of synthesis of (*Z*)-trisubstituted olefins examined below, which were developed for the synthesis of polyprenols.

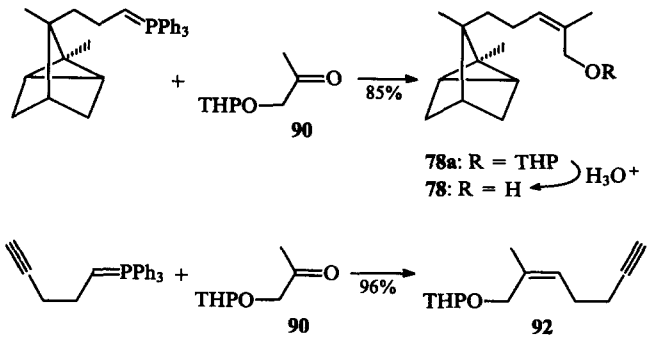
1. Conversion of derivatives of hydroxyacetone into olefins by the Wittig reaction

As already mentioned in Section II. 2, Sato and coworkers [22, 24, 25] suggested that fairly large (*Z*)-(C_{20}–C_{25})-isoprenoid blocks, obtained by alkylating (*Z*)-tolyl sulfones **39c, d** by the chlorides **39a, b, e** be used for the synthesis of polyprenols and dolichols. On the other hand, the authors used the Wittig reaction between unstabilised phosphonium ylides and derivatives of hydroxyacetone, for example its THP-derivative **90**, in order to synthesise the ω-functionalised (*Z*)-block-synthons of type **39**, which are otherwise difficult to obtain.

The considerable predominance of the (*Z*)-isomer in products of this reaction was first noted by Bhalerao and Rapoport [56] in the conversion of the ketone **90** into an olefin by treatment with the bisylide **89**, which led to a mixture of the diols **91a** and **91b** in proportions of 1 : 4.

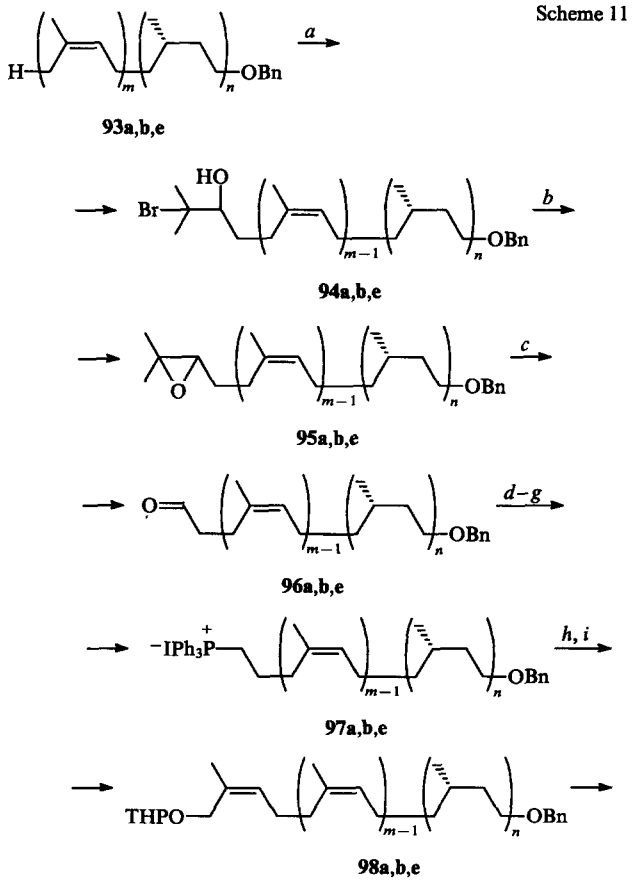


Systematic study of the influence of the reaction conditions on reaction stereochemistry, carried out simultaneously by Sato's [57] and Still's [58] groups, made it possible to increase the (*Z*)-stereoselectivity of the process to 95%–99% with virtually quantitative yields of the product. Still's group synthesised α-santalol **78** with precisely such stereochemical purity, [58] while Sato's group obtained the enyne **92** — a key block-synthon in the total synthesis of (*Z*,*Z*)-farnesylacetone — with the same stereochemical purity. [57]

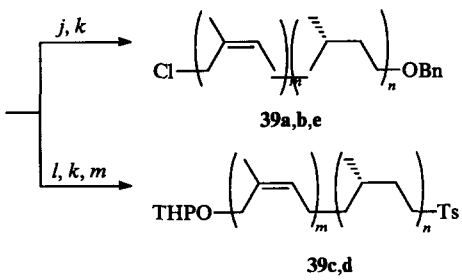


On the basis of the above results, Sato's group [22, 24, 25] achieved the stereoselective synthesis of the block-synthons **39**, having obtained by a standard procedure the phosphonium salts **97a, b, e** required for this purpose from the aldehydes **96a, b, e**, which were prepared in their turn by transforming, by means of the van Tammelen method, the benzyl ethers of nerol (**93a**), (*Z*,*Z*)-farnesol (**93b**), and (3*S*)-citronellol (**93e**) via stages involving the formation of the bromohydrins **94a, b, e** and the epoxides **95a, b, e** (Scheme 11). The condensation of the ylides generated from the phosphonium salts **97** with the THP-derivatives of hydroxyacetone **90** affords the (*Z*)-isoprenoids **98** containing hydroxy-groups in different positions — the α- and ω-positions. As a result of this, the blocks **98a, b, e** can be selectively converted by standard methods both into the chlorides **39a, b, e**, modelling the 'tail' (OH-containing) fragment of polyprenols of types **1** and **2**, and into the tolyl sulfones **39c, d** containing the central (*Z*)-fragment of these compounds.

Scheme 11



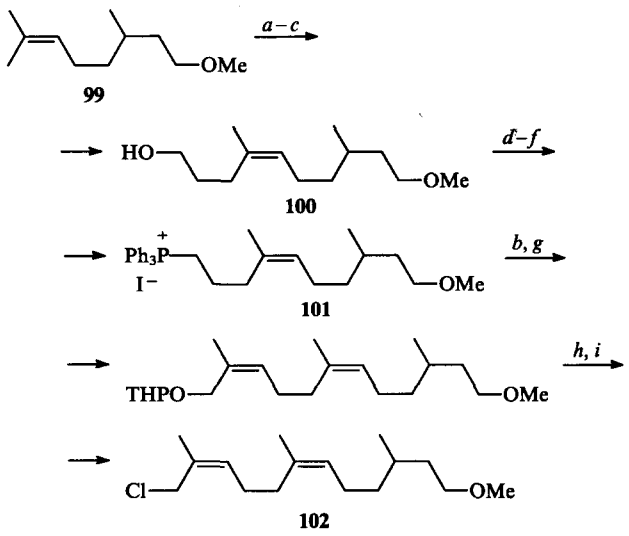
Scheme 11 (continued)



a,**c**: $m = 2, n = 0$; **b**,**d**: $m = 3, n = 0$; **e**: $m = n = 1$.
(*a*) NBS; (*b*) K_2CO_3/NaOH; (*c*) H_5IO_6; (*d*) $NaBH_4$; (*e*) TsCl; (*f*) NaI; (*g*) PPh_3; (*h*) Bu^nLi; (*i*) **90**; (*j*) H_3O^+; (*k*) MsCl, LiCl; (*l*) Na/NH_3; (*m*) TsNa.

The same authors[59] recently patented yet another method for the (*Z*)-functionalisation of isoprenol ethers. It consists in the successive treatment of the methyl ether of the corresponding isoprenol, for example citronellol **99**, with strong bases and epoxyethane. This affords the (*Z*)-bishomoallyl alcohol **100**, which can be readily converted into the phosphonium salt **101** and the latter is subsequently transformed, as shown above for the phosphonium salt **97**, into the chloride **102** (Scheme 12).

Scheme 12

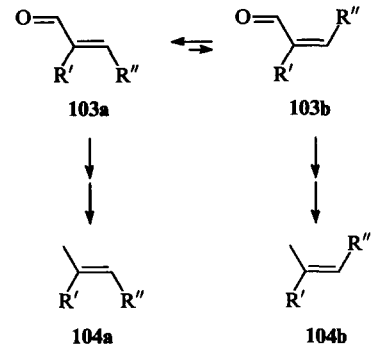


(*a*) Bu^tOK; (*b*) Bu^nLi; (*c*) $H_2C(O)CH_2$; (*d*) TsCl; (*e*) NaI; (*f*) Ph_3P; (*g*) **90**; (*h*) H_3O^+; (*i*) MsCl, LiCl.

It was demonstrated in Section II, 2 how polyprenols **1** and **2**, containing up to 16 (*Z*)-isoprene units, were synthesised with the aid of the sulfones **39c**, **d** and the chlorides **39a**, **b**, **e**, **41**, and **43**.

2. A general method for the construction of the (*Z*)-trisubstituted C=C bond by specific aldol condensation

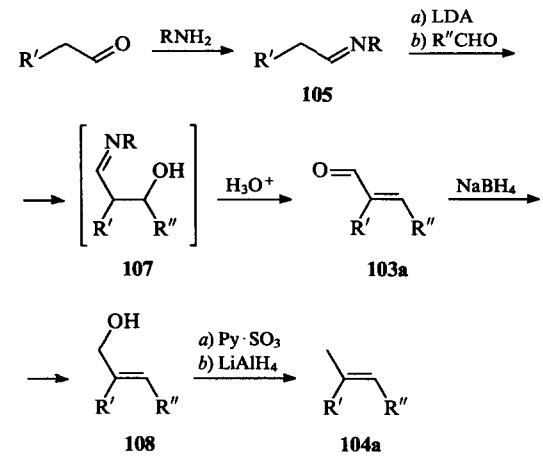
Another approach to the construction of (*Z*)-trisubstituted olefins has been developed in the Laboratory of the Chemistry of Polyunsaturated Compounds of the Institute of Organic Chemistry of Russian Academy of Sciences. It is based on the fact, observed by Grigor'eva et al.,[60] that α,β-disubstituted (*E*)-acroleins **103a** are thermodynamically preferable to their (*Z*)-isomers **103b**, which ensures the presence of more than 95% of the (*E*)-isomer **103a** in the equilibrium mixture (^1H NMR data).[61] This rule is general in the case of acroleins **103** without a branched chain at the allylic carbon atom.[60]



Since the acroleins **103** can be converted by Corey's method[62] into the methylalkenes **104** with complete retention of the configuration, the observed ability of the CHO group to fix the configuration of compound **103a** opened a highly stereoselective path to the construction of the disubstituted (*Z*)-methylalkenes **104a** (involving the synthesis of compound **103a**) and their subsequent stereospecific reductive transformation.

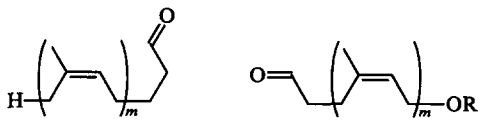
In order to obtain the key (*E*)-acroleins **103a**, the authors applied a version of the cross-condensation of aldehydes, one of which is in the form of the aldimine **105** (Scheme 13). In the literature, this reaction is known as the specific Wittig condensation.[63] The interaction of aldimines **105** deprotonated by means of lithium diisopropylamide (LDA) with the aldehyde **106** leads, after mild acid hydrolysis of the intermediate β-hydroxyimines **107**, to the (*E*)-acroleins **103a**, the stereochemical purity of which in all the cases investigated exceeds 95%.[64] The subsequent reductive transformation of compound **103a** via the stage of the allyl alcohols **108** and the corresponding sulfoesters by the method of Corey and Ahiwa[62] affords the (*Z*)-methylalkenes **104a**.

Scheme 13



R = *tert*-C_4H_9, *cyclo*-C_6H_{11}; R′ = C_2H_5, n-C_4H_9, n-C_6H_{13}, n-C_7H_{15}; R″ = n-C_5H_{11}, n-C_6H_{13}, n-C_7H_{15}, $(CH_2)_nOTHP$ (n = 5, 8), $(CH_2)_nOAc$ (n = 8).

α-Trishomoisoprenals of type **109** and ω-bisnorisoprenals of type **110** are necessary for the construction of the (*Z*)-isoprenoid chain with the aid of this method.

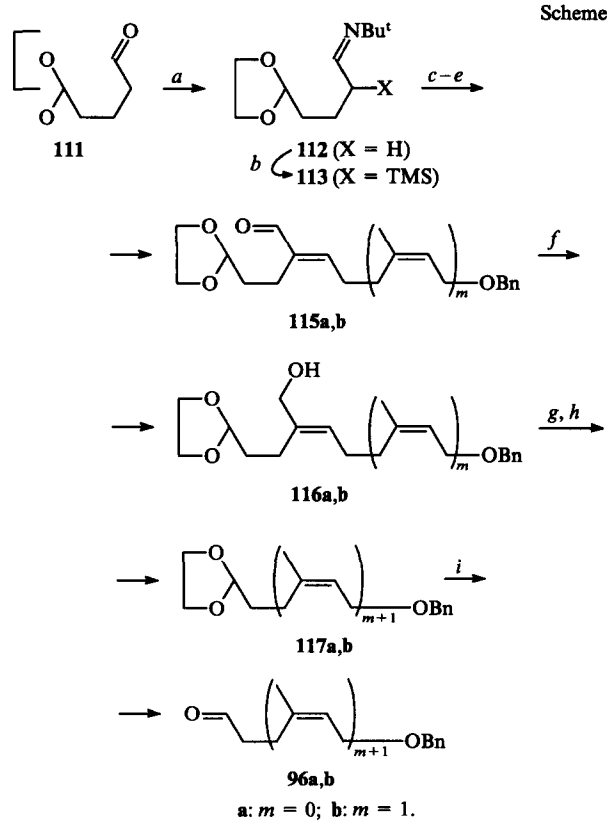


109 **110**

Compounds **109** and **110** can be obtained by the transformation of natural (*Z*)-isoprenoids, as shown above for the aldehydes **96a, b, e** (Scheme 11) or aldehydes which can be readily obtained by oxidising the alcohols **100** (Scheme 12). The method of synthesis of disubstituted (*Z*)-methylalkenes considered leads to the possibility of synthesising aldehydes of types **109** and **110** from non-isoprenoid compounds. The monoacetal of glutaraldehyde **111** and the corresponding *tert*-butylimine **112** are convenient starting materials for this purpose. Block synthons of both types indicated have been synthesised from them.[65]

Thus the synthesis of the aldehyde **96b** from the α-TMS-derivative of *tert*-butylimine **113** is illustrated in Scheme 14.[66] The process includes the condensation of the TMS-derivative of compound **113**, deprotonated by means of LDA, with benzyloxyacetaldehyde **114**, which leads to the (*E*)-acrolein **115a** in a preparative yield and with a stereoselectivity in excess of 95%. On reductive transformation via stages involving the formation of the allyl alcohol **116a** and the corresponding sulfoester, the acrolein **115a** is converted into the acetal **117a** in an overall yield of 25%. When the aldehyde **96a**, formed on hydrolysis of the acetal **117a** via the (*E*)-acrolein **115b** ($E \geqslant 95\%$), the alcohol **116b**, and the acetal **117b** stages, was introduced into the sequence of reactions described, the target aldehyde **96b** was obtained. By repeating the above chain of reactions, it is possible, in principle, to continue the growth of the (*Z*)-isoprenoid chain still further from its α-unit to its ω-unit.

Scheme 14



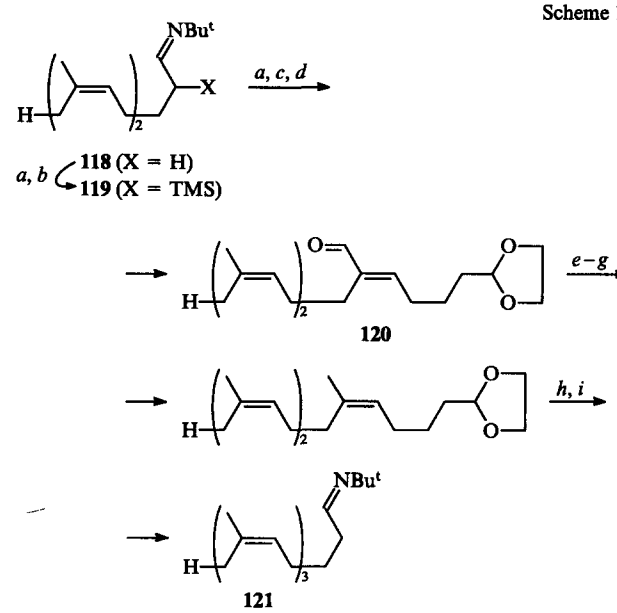
111 **112** (X = H), **113** (X = TMS) **115a,b** **116a,b** **117a,b** **96a,b**

a: $m = 0$; **b**: $m = 1$.

(*a*) Bu^tNH_2; (*b*) LDA, Me_3SiCl; (*c*) LDA; (*d*) O=⟨ OBn (**114**); (*e*) H_3O^+ (pH 4); (*f*) $NaBH_4$; (*g*) $Py \cdot SO_3$; (*f*) $LiAlH_4$; (*i*) H_3O^+.

The conversion of the aldehydes **96a, b** into olefins by the Wittig method[67] affords the stereochemically pure nerol and (*Z,Z*)-farnesol. The latter were used to synthesise with the aid of the monoacetal **111** the imines of trishomoprenals of type **109**, which is illustrated (Scheme 15) by the conversion of the α-TMS-derivative of the aldimine **119**, prepared in six stages from nerol,[68] into the aldimine **121** via the key (*E*)-acrolein **120** stage in an overall yield of ~10%.

Scheme 15

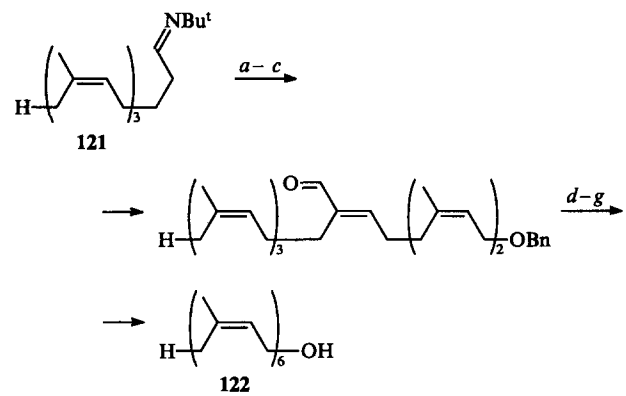


118 (X = H), **119** (X = TMS) **120** **121**

(*a*) LDA; (*b*) Me_3SiCl; (*c*) **111**; (*d*) H_3O^+ (pH 4); (*e*) $NaBH_4$; (*f*) $Py \cdot SO_3$; (*g*) $LiAlH_4$; (*h*) H_3O^+; (*i*) Bu^tNH_2.

The aldimine **121** and the aldehyde **96b** obtained in this way were used to construct the (*Z*)-isoprenoid chain in the synthesis of the fully cisoid hexaprenol WC_5OH **122** with a nonnatural configuration of the ω-section of the chain (Scheme 16).[66]

Scheme 16

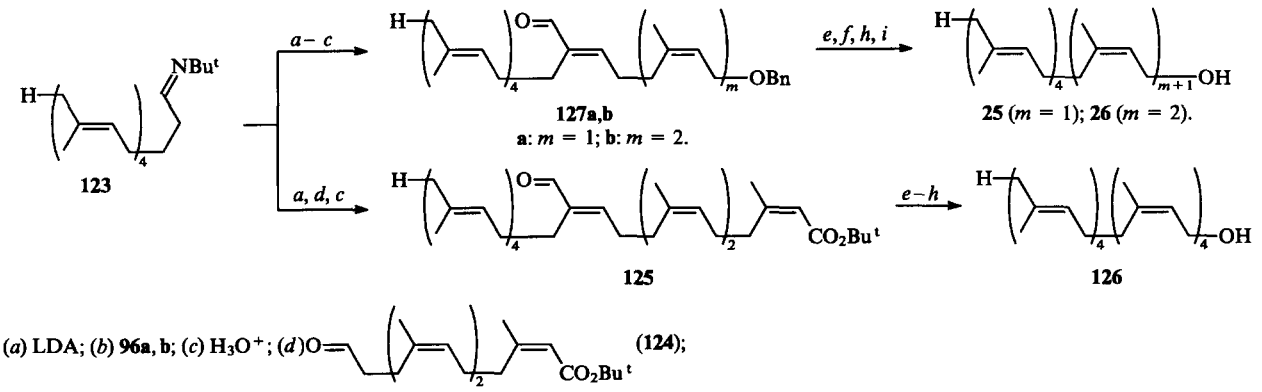


121 **122**

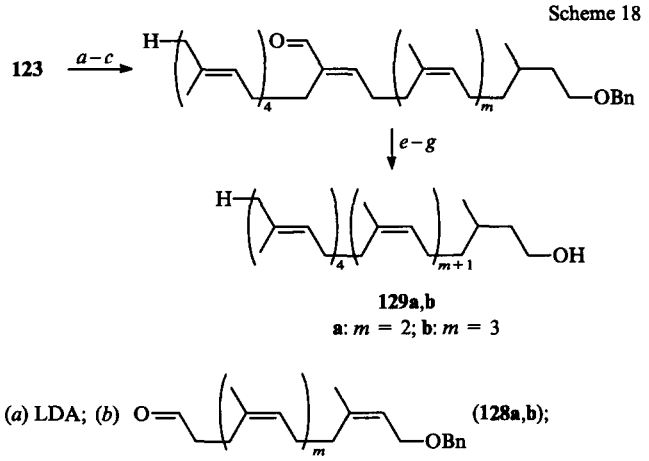
(*a*) LDA; (*b*) **96b**; (*c*) H_3O^+; (*d*) $NaBH_4$; (*e*) $Py \cdot SO_3$; (*f*) $LiAlH_4$; (*g*) Li/NH_3.

The approach considered proved to be extremely effective also in the construction of natural polyprenols, as shown in relation to hexaprenol (WT_3C_2OH, **25**),[69] heptaprenol (WT_3C_3.OH, **26**),[10] and octaprenol (WT_3C_4OH, **126**)[70] isolated from the juice of the palm *Serenoa repens* (Scheme 17).[11] They were synthesised with participation of the aldimine **123**, containing a ω-transoid fragment of the above polyprenols and prepared from geranyllinalool,[71] and the aldehydes **96a, b** and **124** respectively[70] via key stages involving the formation of the (*E*)-acroleins **127a, b** and **125**.

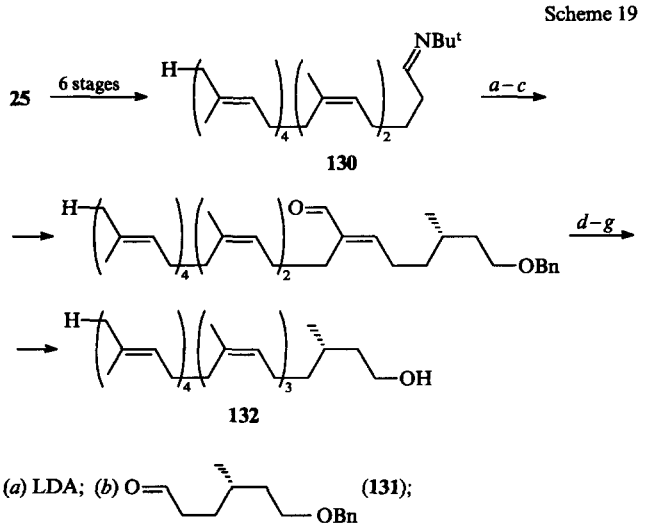
Scheme 17



Scheme 18



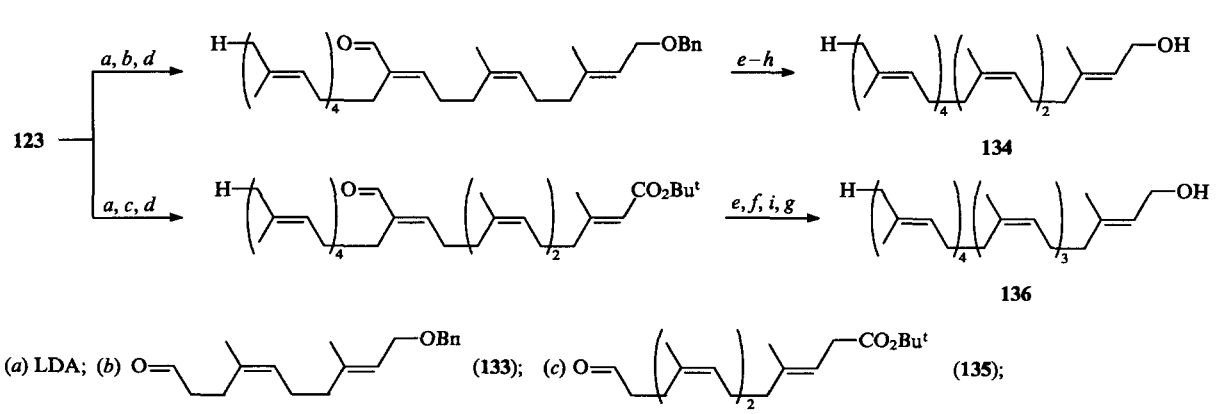
Scheme 19



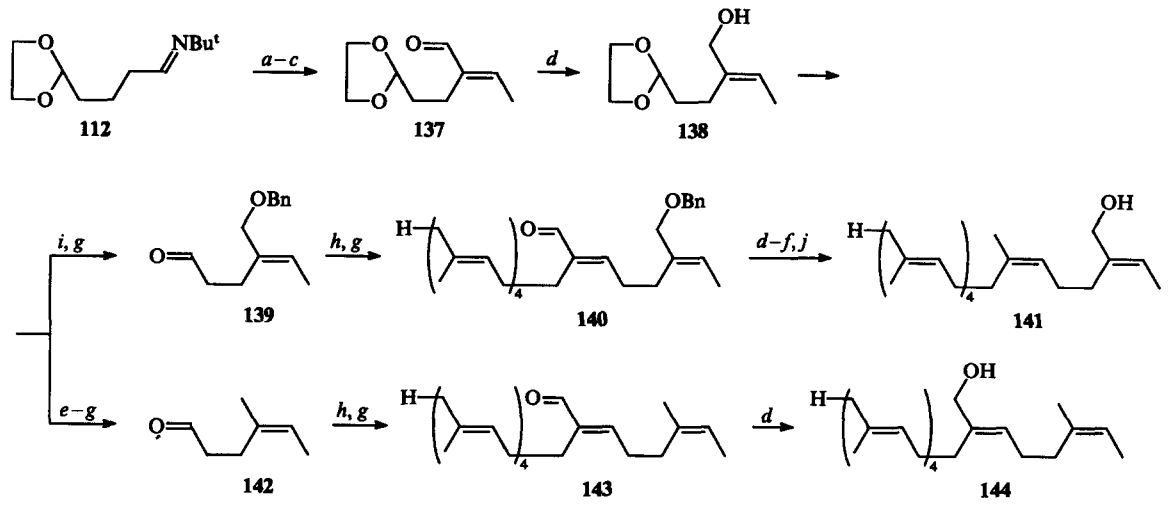
By means of the same methodology,[72] the racemic octaprenol (WT_3C_3SOH, **129a**) and nonaprenol (WT_3C_4SOH, **129b**), related to dolichols, were obtained from the aldimine **123** and the aldehydes **128a, b** (Scheme 18), while the dolichol-like octaprenol WT_3C_3SOH **132**,[69] with the natural (*S*)-configuration of the α-unit, was synthesised from the aldimine **130** prepared from the hexaprenol **25** described above and the chiral aldehyde **131** (Scheme 19).

The method has also found a successful application in the synthesis of modified polyprenols necessary for biochemical research. Thus the polyprenols **134**[71] and **136**,[70] with the non-natural (*E*)-configuration of the α-unit, have been obtained with its aid using the aldimine **123** block and the aldehyde **133** and **135** blocks (Scheme 20).

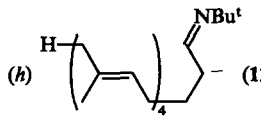
Scheme 20



Scheme 21



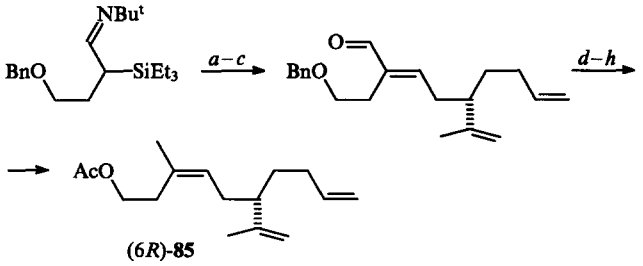
(*a*) LDA; (*b*) CH_3CHO; (*c*) H_3O^+ (pH 4); (*d*) $NaBH_4$; (*e*) Py·SO_3; (*f*) $LiAlH_4$; (*g*) H_3O^+;



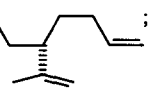
(*h*) (**123a**); (*i*) BnCl/NaH; (*j*) Li/NH_3.

The modified hexaprenols **141** and **144**,[73] with a nonnatural disposition of the OH group, were synthesised similarly from the same aldimine **123** and the aldehydes **139** and **142**. We may note that the block-synthons **139** and **142** were also obtained with the aid of the method, considered here, for the construction of (*Z*)-isoprenoids from the common precursors **137** and **138** (Scheme 21).

French chemists showed recently[74] that the method under discussion is optimal for the synthesis of the (6*R*)-**85** component of the pheromone of red San Jose scale and that its stereoselectivity is superior to that of other procedures[54,75] proposed for the synthesis of this compound.



(6*R*)-**85**

(*a*) LDA; (*b*) ; (*c*) H_3O^+; (*d*) $LiAlH_4/Et_2O$;

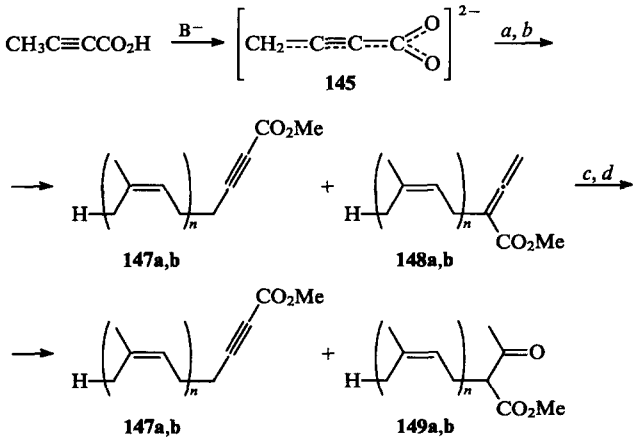
(*e*) Py SO_3; (*f*) $LiAlH_4$/THF; (*g*) Li/NH_3; (*h*) Ac_2O–Py.

Thus the method for the construction of (*Z*)-trisubstituted olefins, based on the thermodynamic preference for α,β-disubstituted (*E*)-acroleins, leads to extensive possibilities for the synthesis of biologically active (*Z*)-isoprenoids.

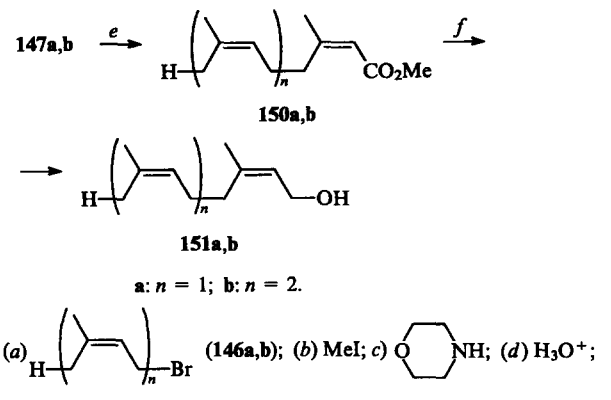
IV. Synthesis of (*Z*)-isoprenoids with formation of new C–C and (*Z*)-trisubstituted C=C bonds

In 1975, Baran and coworkers[76,77] investigated the possibility of the specific γ-alkylation of α,β-unsaturated acids in order to use the above reaction in the synthesis of polyprenols. They showed that the alkylation of the dianion of 2-butynoic acid **145** by prenyl bromide **146a** or neryl bromide **146b** leads to mixtures of products of γ- and α-alkylation stabilised in the form of the methyl esters **147a, b** and **148a, b**, which can be readily separated chromatographically after the conversion of the allene esters **148a, b** into the ketoesters **149a, b** (Scheme 22). The regioisomers ratio **147** : **148** is to a large extent determined by the nature of the base used to generate the dianion **145** and amounts to 2 : 1 in the case of lithium tetramethylpiperidide[76] and 3 : 1 in the case of LDA.[77] The use of the Bu^nLi–TMEDA (TMEDA = tetramethylethylenediamine) system made it possible to obtain the target ester **147** virtually free of compound **148**.[78]

Scheme 22



Scheme 22 (continued)

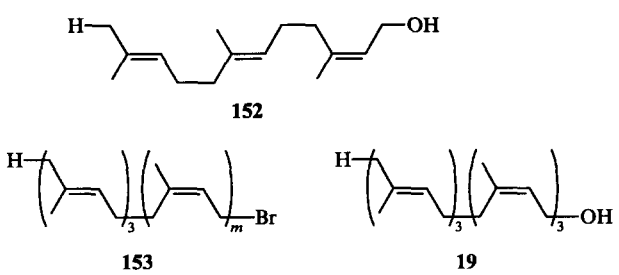


a: n = 1; **b**: n = 2.

(*a*) (**146a,b**); (*b*) MeI; (*c*) NH; (*d*) H_3O^+; (*e*) $Me_2CuLi-CuMe$; (*f*) AlH_3.

The stereoselective addition of dimethyl cuprate to the acetylenic fragment **147** by Corey's method[47] completes the formation of the new (*Z*)-isoprene unit and affords the esters **150** with an isomeric purity of about 98%, which can be smoothly reduced to the target (*Z*)-isoprenols **151**.

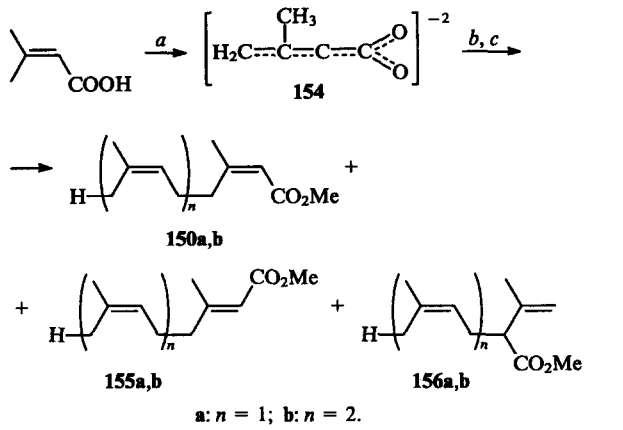
The involvement of geranyl bromide in the reaction chain presented in Scheme 22 led to (*Z,E*)-farnesol **152**[77] and the successive employment in these reactions of the isoprenoid bromides **153** (m = 0–2) enabled Baran et al.[79] to achieve the total synthesis of the hexaprenol WT_2C_3OH **19**, which they published without experimental details.



The version, investigated by the same authors,[77] of the synthesis of (*Z*)-isoprenols **151a,b** by alkylating the dianion of 3-methylcrotonic acid **154**, which is *a priori* more attractive than the γ-alkylation of 2-butynoic acid examined above since it makes it possible to construct in one stage the required isoprenoid skeleton (Scheme 23), proved to be less successful. Experimental tests showed that the interaction of the dianion of the acid **154** with prenyl bromide **146a** or neryl bromide **146b** affords, after methylation of the carboxy-group, a mixture of the products of γ-(*Z*)-alkylation (compound **150**), γ-(*E*)-alkylation (compound **155**), and α-alkylation (compound **156**) in proportions of 1:4:11. The γ:α product ratio can be increased[77] to ~4:1 and even to ~13:1 by using the cuprate complex.[154] This procedure has little effect on the stereochemistry of the reaction. The isomer ratio **150**:**155** in this reaction does not exceed ~5:3 and the isolation of the target product **150** requires repeated chromatography.

The data described in Section IV make it possible to conclude that, although the method involving the regioselective γ-alkylation of 2-butynoic acid developed for the synthesis of polyprenols is less effective than the alternative methods for the construction of the (*Z*)-isoprenoid systems examined in Sections II and III, nevertheless it can be used successfully for the synthesis of acetylenic esters of type **147**, which are convenient block-synthons in organic synthesis.

Scheme 23



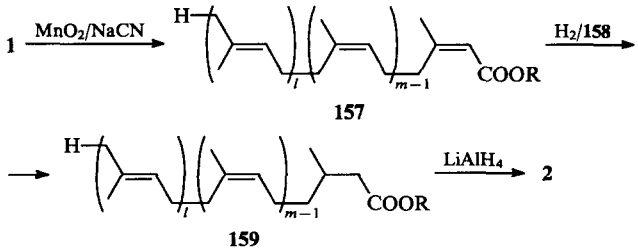
a: n = 1; **b**: n = 2.

(*a*) LDA; (*b*) **146a,b**; (*c*) MeI.

V. Regioselective and enantioselective hydrogenation of the Δ^2-bond in α-functionalised isoprenoids

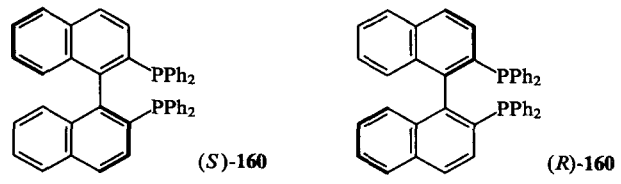
The methods for the construction of the (*Z*)-isoprenoid chain examined above made it possible to achieve the total syntheses of polyprenols **1**, dolichols **2**, and their modified analogues. At the same time, the possibility of the regioselective and enantioselective hydrogenation of the Δ^2-bond of polyprenols **1** is of significant interest for the partial synthesis of dolichols (which are a characteristic type of polyprenols in mammals) from much more readily available polyprenols of plant origin. The first attempt on these lines was by Polish biochemists[80] but did not yield the required results. Hydrogenation of the undecaprenol WT_2C_8OH **52** in alcohol over a platinum catalyst in the presence of $NaBH_4$, which they investigated, led to a mixture of the undecaprenols WT_2C_7SOH, WT_2C_6SCOH, $WT_2C_5SC_2OH$, and $WT_2C_4SC_3OH$.

The regioselective reduction of the α,β-unsaturated esters **157**, described in a patent,[81] proved more successful. The esters were obtained by standard methods from polyprenols **1** of plant origin with the aid of lithium in NH_3 or hydrogen in the presence of a metal complex catalyst—μ,μ'-dichlorobis-(cycloocta-1,5-diene)-rhodium/neopentyldiphenylphosphine **158**. The racemic esters **159** formed in this reaction are reduced smoothly by $LiAlH_4$ to the target dolichols **2**.

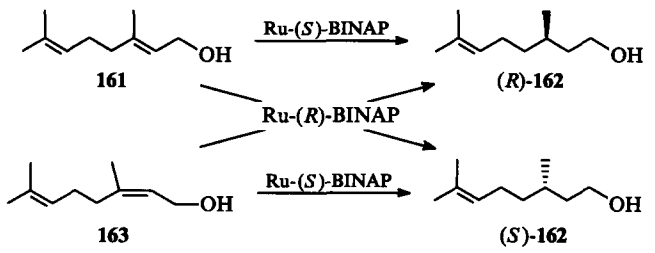


R = H, Alk; l = 2, m = 15.

The introduction of metal complex catalysts with optically active ligands into practical organic synthesis made possible the single-stage conversion of polyprenols **1** into (*S*)- or (*R*)-dolichols. Ruthenium complexes of the (*S*)- or (*R*)-form of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) **160** proved to be optimal for this process.[82]



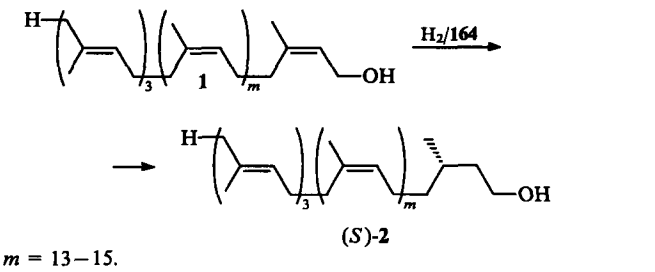
It was shown in relation to the simplest isoprenols—geraniol **161** and nerol **163**—that there is a rigorous correlation between the olefinic geometry of the substrate, the configuration of the chiral ligand in the catalyst, and the configuration of the chiral centre in the reaction product. Thus hydrogenation of the alcohol **161** in the presence of a ruthenium dicarboxylate complex with (*S*)-BINAP ligands affords (*R*)-citronellol **162**, whilst in the presence of the analogous complex with (*R*)-BINAP ligands the product is (*S*)-citronellol **162**. On the other hand, hydrogenation of compound **163** in the presence of the complexes with (*S*)-BINAP and (*R*)-BINAP ligands leads to (*S*)-**162** and (*R*)-**162** respectively.[83]



The method involving hydrogenation using the above catalysts has all the qualities necessary to achieve total asymmetric synthesis: high yields and enantiomeric purity in excess of 96%, a high regioselectivity of the reaction, the absence of the migration of the C=C bond and of the *E*/*Z* isomerisation, a high substrate/catalyst molar ratio, and, ease of recovery and regeneration of the catalyst without loss of its activity and selectivity.

The asymmetric hydrogenation of the mixture of polyprenols **1** isolated from *Ginkgo biloba*, catalysed by Ru-(*S*)-BINAP bistrifluoroacetate **164** and carried out taking into account the above features, led to a mixture of the corresponding dolichols **2** in a high yield and with an enantiomeric purity in excess of 95%. The mixture contained less than 2% of the products involving the reduction of other C=C bonds (Scheme 24).[84]

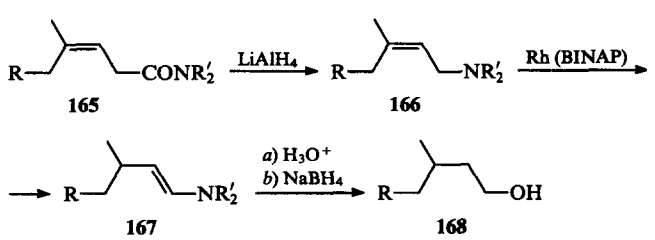
Scheme 24



m = 13–15.

The synthesis of dolichols **2** with the aid of metal complex catalysis can also be achieved starting with derivatives of polyprenylcarboxylic acids isolated, together with polyprenols **1**, from plant raw material. Thus it has been found[85] that BINAP-containing rhodium catalysts exhibit a high activity in the isomerisation of tertiary allylamines **166**, formed smoothly on hydride reduction of the amides **165** (Scheme 25).

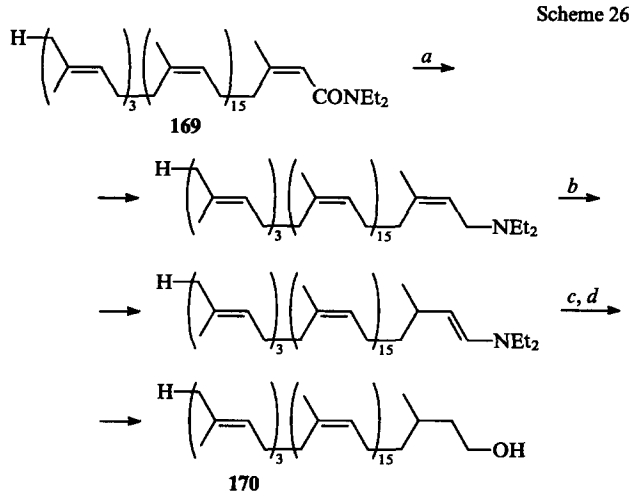
Scheme 25



R = Alk, ; R' = Alk, cycloalk, Ar.

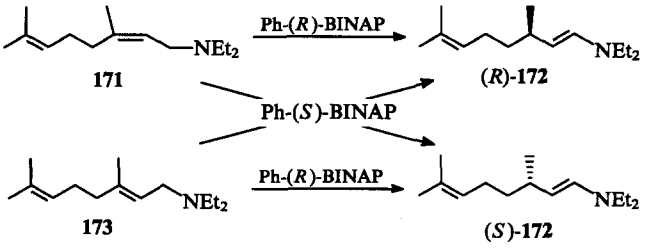
The enamines **167** thus obtained can be readily converted by standard methods into the correpsonding 4-C-substituted isopentanols **168**. The method has been applied successfully in the synthesis of the racemic dolichol $WT_2C_{15}SOH$ **170** from the amide **169** (Scheme 26).[86]

Scheme 26



(*a*) $LiAlH_4$; (*b*) $Rh[BINAP(COD)]ClO_4$; (*c*) H_3O^+; (*d*) $NaBH_4$
COD = cycloocta-1,5-diene.

The successful use of the Rh-(*R*)- and Rh-(*S*)-BINAP catalysts for the conversion of *N*,*N*-diethylnerylamine **171** and *N*,*N*-diethylgeranylamine **173** respectively into the enamines (*R*)- and (*S*)-**172**, which are intermediates in the synthesis of (*R*)- and (*S*)-citronellol, permits the hope that it will be possible also to achieve the synthesis of chiral dolichols with the aid of these catalysts.



By virtue of its high effectiveness and enantioselectivity, the method for the asymmetric hydrogenation of polyprenols **1** examined above appears to be the best of the known procedures for the conversion of (*Z*)-isoprenols into their (*S*)- or (*R*)-2,3-dihydro-derivatives.[18,87]

* * *

The data described show that the synthetic studies on polyprenols and dolichols provided organic chemistry with a series of effective and highly stereoselective methods for the construction of disubstituted (*Z*)-methylalkene systems, as well as regioselective and enantioselective procedures for the conversion of α-functionalised isoprenoids into their 2,3-dihydro-derivatives, which have already found interesting applications in the synthesis of other biologically active compounds.

References

1. F W Hemming, in *Biochemistry* Vol. 4 (MTP Int. Rev. Sci. Ser. 1) (Ed. T W Goodwin) (London: Butterworths, 1974) p. 39
2. F W Hemming *Biosynthesis of Isoprenoid Compounds* Vol. 2 (New York: Wiley, 1983) p. 303
3. J W Rip, C A Rupar, K Ravi, K K Carrol *Prog. Lipid Res.* **24** 269 (1985)
4. A M Moiseenkov, E V Polunin, I M Zaks, A V Semenovskii *Dokl. Akad. Nauk SSSR* **236** 124 (1977)
5. A V Semenovskii, E V Polunin, I M Zaks, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1327 (1979)
6. E V Polunin, A M Moiseenkov, A V Semenovskii *Izv. Akad. Nauk SSSR, Ser. Khim.* 1354 (1981)
7. A M Moiseenkov, E V Polunin, A V Semenovsky *Tetrahedron Lett.* **20** 4759 (1979)
8. A M Moiseenkov, E V Polunin, A V Semenovsky *Tetrahedron Lett.* **22** 3309 (1981)
9. V N Shibaev *Usp. Biol. Khim.* **17** 187 (1976)
10. A V Semenovskii, N Ya Grigor'eva, I M Avrutov, V V Veselovskii, M A Novikova, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 152 (1984)
11. G Jommi, L Verotta, P Gariboldi, P Gabetta *Gazz. Chim. Ital.* **118** 823 (1988)
12. V V Veselovskii, Z G Makarova, A I Lutsenko, V A Smit, A M Moiseenkov, V M Zhulin *Izv. Akad. Nauk SSSR, Ser. Khim.* 811 (1987)
13. A M Moiseenkov, V V Veselovsky, Z G Makarova, V M Zhulin, W A Smit *Tetrahedron Lett.* **25** 5929 (1984)
14. W E Truce, C T Goralski, L W Christensen, R H Bavry *J. Org. Chem.* **35** 4217 (1970)
15. G I Vergunova, I S Glukhoded, L L Danilov, G I Eliseeva, N K Kochetkov, M F Troitskii, A I Usov, A S Shashkov, V N Shibaev *Bioorg. Khim.* **3** 1484 (1977)
16. M A Novikova, A V Lozanova, V V Veselovskii, V A Dragan, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 356 (1987)
17. H Julia, D Uguen, A Callipolitis *Bull. Soc. Chim. Fr.* 519 (1976)
18. V A Koptenkova, V V Veselovskii, M A Novikova, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 817 (1987)
19. V V Veselovskii, V A Koptenkova, M A Novikova, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2052 (1989)
20. Eur. P. 87 638; *Chem. Abstr.* **100** 68 570z (1983)
21. D Bottger, P Welzel *Tetrahedron Lett.* **24** 5201 (1983)
22. K Sato, O Miyamoto, S Inoue, F Furusawa, Y Matsuhashi *Chem. Lett.* 725 (1983)
23. K Sato, A Onishi, K Watanabe, in *The 35th National Meeting of the Chem. Soc. of Japan, Saporo, 1976 (Abstracts of Reports)* p. 3128
24. K Sato, O Miyamoto, S Inoue, F Furusawa, Y Matsuhashi *Chem. Lett.* 1105 (1984)
25. S Inoue, T Kaneko, Y Takahashi, O Miyamoto, K Sato *J. Chem. Soc., Chem. Commun.* 1036 (1987)
26. J E Biellmann, J B Ducep *Tetrahedron* **27** 5861 (1971)
27. L J Altman, L Ash, S Marson *Synthesis* 129 (1974)
28. Y Masaki, K Hashimoto, T Kaji *Tetrahedron Lett.* **19** 5123 (1978)
29. K Sato, O Miyamoto, S Inoue, Y Matsuhashi, S Koyama, T Koneko *J. Chem. Soc., Chem. Commun.* 1761 (1986)
30. A M Moiseenkov, M A Novikova, E V Polunin, S I Torgova *Izv. Akad. Nauk SSSR, Ser. Khim.* 1558 (1983)
31. N Ya Grigor'eva, I M Avrutov, A V Semenovskii, V N Odinokov, V R Akhunova, G A Tolstikov *Izv. AN SSSR, Ser. Khim.* 382 (1979)
32. M Mohri, H Kinoshita, K Inomata, H Kotake *Chem. Lett.* 451 (1985)
33. D Eren, E Keinan *J. Am. Chem. Soc.* **110** 4356 (1988)
34. I Takahashi, K Ogura *J. Biochem. (Tokyo)* **92** 1527 (1982)
35. S Fujisaki, T Nishino, H Kattsuki *J. Biochem. (Tokyo)* **99** 1327 (1986)
36. C M Allen, M V Keenan, J Sack *Arch. Biochem. Biophys.* **175** 236 (1976)
37. T Baba, C M Allen *Arch. Biochem. Biophys.* **200** 474 (1980)
38. L L Danilov, V N Shibaev, N K Kochetkov *Synthesis* 404 (1985)
39. S Ohnuma, T Koyama, K Ogyra *Tetrahedron Lett.* **32** 241 (1991)
40. T Suga, S Ohta, A Nakai, K Munesada *J. Org. Chem.* **54** 3390 (1989)
41. S Ohnuma, M Ito, T Koyama, K Ogyra *Tetrahedron* **45** 6145 (1989)
42. T Nishino, K Ogyra, S Seto *J. Am. Chem. Soc.* **94** 6849 (1972)
43. M Kobayashi, T Koyama, K Ogyra, S Seto, F J Pitter, I E M Bruggeman-Rotgaus *J. Am. Chem. Soc.* **102** 6602 (1980)
44. T Koyama, K Ogyra *J. Am. Chem. Soc.* **109** 2853 (1987)
45. J Reucroft, P G Sammer *Quart. Rev. Chem. Soc.* **25** 135 (1971)
46. D J Foulkner *Synthesis* 175 (1971)
47. E J Corey, J A Katzenellenbogen *J. Am. Chem. Soc.* **91** 1851 (1969)
48. D M Walba, P D Edwards *Tetrahedron Lett.* **21** 3531 (1980)
49. S B Bowlus, J A Katzenellenbogen *J. Org. Chem.* **38** 2733 (1973)
50. E J Corey, H Yamamoto *J. Am. Chem. Soc.* **92** 229 (1970)
51. H P Prisbylla, K Takanabe, J D White *J. Am. Chem. Soc.* **101** 762 (1979)
52. Y Masaki, K Hashimoto, K Kaji *Tetrahedron Lett.* **21** 5123 (1980)
53. S Inoue, N Iwase, O Miyamoto, K Sato *Chem. Lett.* 2035 (1986)
54. W C Still, A Mitra *J. Am. Chem. Soc.* **100** 1927 (1978)
55. K Honda, S Inoue, K Sato *J. Am. Chem. Soc.* **112** 1999 (1990)
56. U T Bhalerao, H Rapoport *J. Am. Chem. Soc.* **93** 5311 (1971)
57. K Sato, O Miyamoto, S Inoue, T Kobayashi, F Furusawa *Chem. Lett.* 1711 (1981)
58. C Sreekumar, K P Darst, W C Still *J. Org. Chem.* **45** 4260 (1980)
59. Jpn. P. 62-59 237; *Chem. Abstr.* **107** 217 882b (1987)
60. N Ya Grigor'eva, E P Prokof'ev, A V Semenovskii *Dokl. Akad. Nauk SSSR* **245** 366 (1979)
61. E P Prokof'ev, N Ya Grigor'eva, A V Semenovskii *Izv. Akad. Nauk SSSR, Ser. Khim.* 834 (1980)
62. E J Corey, K Ahiwa *J. Org. Chem.* **34** 3667 (1969)
63. G Wittig, H D Flommeld *Chem. Ber.* **97** 3548 (1964)
64. N Ya Grigor'eva, I M Avrutov, O A Pinsker, O N Yudina, A I Lutsenko, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1824 (1985)
65. N Ya Grigorieva, O N Yudina, A M Moiseenkov *Synthesis* 591 (1989)
66. N Ya Grigor'eva, O N Yudina, E D Daeva, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 89 (1990)
67. G Wittig, U Schollkopf *Chem. Ber.* **87** 1318 (1954)
68. N Ya Grigor'eva, O N Yudina, O A Pinsker, E D Daeva, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 97 (1990)
69. N Ya Grigor'eva, O A Pinsker, E D Daeva, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2325 (1991)
70. N Ya Grigor'eva, O A Pinsker, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2333 (1991)
71. N Y Grigorieva, I M Avrutov, A V Semenovsky *Tetrahedron Lett.* **24** 5531 (1983)
72. N Ya Grigor'eva, O A Pinsker, V N Odinokov, G A Tolstikov, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1546 (1987)
73. N Ya Grigor'eva, O N Yudina, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2036 (1986)
74. R Baudouy, P Prince *Tetrahedron* **45** 2067 (1989)
75. D Caine, E Crews *Tetrahedron Lett.* **25** 5359 (1984)
76. B S Pitzele, J S Baran, D H Steinman *J. Org. Chem.* **40** 269 (1975)
77. B S Pitzele, J S Baran, D H Steinman *Tetrahedron* **32** 1347 (1976)
78. S S Shen, C Ainsworth *Tetrahedron Lett.* **20** 82 (1979)
79. J S Baran, B S Pitzele, D D Langford, D H Steinman, L Hansen, T Kosobud, J Mueller, in *The 174th National Meeting, Chicago, 1979 (Abstracts of Reports)* p. 1076
80. T Mankowski, W Jankowski, T Chojnacki, P Franke. *Biochemistry* **15** 2125 (1976)
81. Jpn. P. 60-41 628; *Chem. Abstr.* **103** 160 733q (1985)
82. R Noyori, H Takaya *Acc. Chem. Res.* **23** 345 (1990)
83. H Takaya, T Ohta, N Sayo, H Kumoboyashi, S Akutagawa, S Inoue, I Kasahara, R Noyori *J. Am. Chem. Soc.* **109** 1596 (1987)
84. B Imperiali, J W Zimmerman *Tetrahedron Lett.* **29** 5342 (1988)
85. K Tani, T Yamagata, S Akutagawa *J. Am. Chem. Soc.* **106** 5208 (1984)
86. Jpn. P. 69-42 343; *Chem. Abstr.* **103** 142 217v (1985)
87. S Suzuki, F Mori, T Takigawa, K Ibata, J Ninagawa, T Nishida, M Mizuno, J Tanaka *Tetrahedron Lett.* **24** 5103 (1983))