Some Aspects of the Stereospecific Synthesis of Terpenoids by means of Isoprene Units

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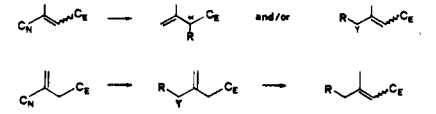
In recent years the isolation of some aliphatic terpenoids with outstanding biological activity, such as abscisic acid,[1] juvenile hormone,[2] trisporic acids,[3] and the growing interest in the field of vitamin A[4] and carotenoids and their derivatives[5] stimulated the search for practical stereospecific syntheses of these head-to-tail polyprenyl compounds.[6]

The syntheses of these compounds require methods which permit the stereospecific building up of an isoprene unit with the appropriate stereochemistry. Depending upon the degree of unsaturation of the molecule to be synthesized, the prenyl unit may be linked by a double bond in the *E* configuration (A and B of Figure 1) or by a single bond (C and D of Figure 1). Partial structures A and B, for instance, are present in vitamin A and abscisic acid, respectively; C is typical for many mono-, sesqui-, and diterpenes like geraniol, farnesol, etc.; whereas D, although less common, is present in some terpenes, e.g., nerol.

It appears that one of simplest approaches to the synthesis of such repetitive structures is the sequential introduction of one prenyl unit containing the appropriate olefinic stereochemistry by joining it with the growing chain by a single or double bond, as required. The biosynthetic condensation of isopentenyl pyrophosphate with an allylic pyrophosphate is, in fact, just such a transformation.

Conceptually, the synthetic scheme may be envisaged as involving an attack of a prenyl allylic nucleophile upon a prenyl electrophile. In order to obtain a synthon capable of leading to a repetitive sequence, it is necessary that the prenyl unit to be introduced bears, in an actual or masked state, both the nucleophilic (C_N) and the electrophilic (C_E) carbon atoms at the ends of the molecule.[7] In the following, two types of synthons meeting the above indicated requirements will be considered. The difference between them depends on the position of the allylic double bond.

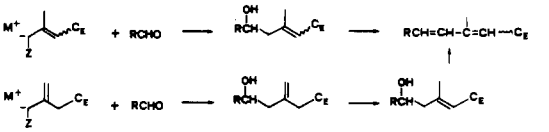
Some major difficulties have to be overcome in the practical application of this scheme in order to meet the required high standards of regio- and stereospecificity. The ambidentate nature of the allylic nucleophilic center involved in the synthesis may lead, in the case of synthons of type E (Figure 2), to an attack on both the α and γ position, and it is clear that the α attack leads to branched, non-head-to-tail structures. On the other hand, synthons of type F (Figure 2) lead only to γ substitution, as a consequence of their inherent symmetry. In order to get the correct natural structure, an isomerization of the first formed methylenic double bond is necessary in this last case. Moreover, the use of an allylic electrophile of type E may cause S_N2' in addition to S_N2 attack. Furthermore, the stereochemistry of the double bonds in the reaction products may differ from that of the reagents owing to some peculiar feature of the reaction mechanism or to isomer equilibration occurring during the reaction.



Recently developed prenyl synthons having the general structure E and F indicated in Figure 2 and their application in regio- and stereospecific head-to-tail syntheses of terpenoids will be considered in this account.

Synthesis of Terpenoidic 1,3-Dienes

The introduction of a double bond between two prenyl units in compounds of the type with partial structure A or B (Figure 1) requires an addition-elimination or a substitution–elimination sequence. In the



first case the nucleophilic center is a stabilized carbanion while the electrophilic center is invariably an aldehyde.

The elimination step may occur through an acid- or base-catalyzed reaction on the adduct as in aldol-like condensations (Z = H) or it may be directly induced by

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(1) For a review, see R. L. Wain, *Chem. Soc. Rev.*, **6**, 261 (1977).
(2) For reviews, see C. E. Berkoff, *Q. Rev., Chem. Soc.*, **23**, 372 (1969); B. M. Trost, *Acc. Chem. Res.*, **3**, 120 (1970).
(3) L. Caglioti, G. Cainelli, B. Camerino, R. Mondelli, A. Prieto, A. Quilico, T. Salvatori, and A. Selva, *Tetrahedron Suppl.*, **7**, 175 (1966); for a review, see J. D. Bu'Lock, B. E. Jones, and N. Winskill, *Pure Appl. Chem.*, **47**, 191 (1976).
(4) For a review, see W. H. Sebrell and R. S. Harris in "The Vitamins", Vol. I, 2nd ed., Academic Press, New York, 1967, p 570.
(5) For a review, see: "Carotinoids", O. Isler, Ed., Birkhaeser Verlag, Basel, 1971.
(6) For a review, see O. Isler and P. Schudel, *Adv. Org. Chem.*, **4**, 115, (1973).
(7) All the synthons described below may in principle be used for an iterative terpenoid synthesis, although in the most cases they have been utilized for the introduction of only one prenyl unit.

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Table I
Dependence of Regioselectivity of the Alkylation of Benzaldehyde on the Counterions of 2a[a]

M M.	Li -Sn-*n*-Bu_3	Al-*i*-Bu_3 Li	Li Li	Na Li	K Li	K K
relative yield, %						
α attack (6)	100	67	54	46, 35[b]	22, 21[b]	0[b]
γ attack (4 + 5)		33	46	54, 65[b]	78, 79[b]	100[b]

[a] The reaction has been performed in THF at -78 °C. [b] Dianion preparation with addition of 10% HMPA.

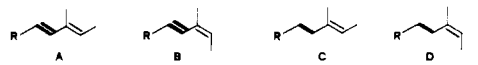


Figure 1.

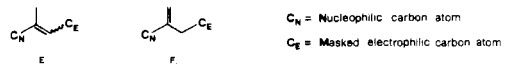
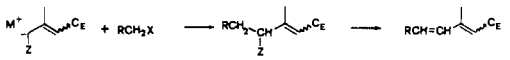


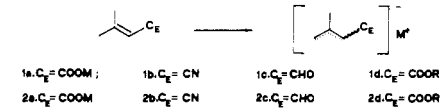
Figure 2.

the very nature of the adduct created by the attacking nucleophilic center as in the case of phosphorus stabilized carbanions (Z = $(Ph)_3P^+X^-$ or $P(O)(OEt)_2$).

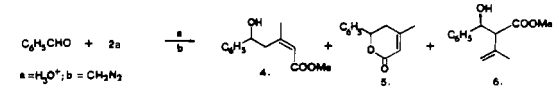
On the other hand, if the stabilizing group Z has leaving group properties (Z = SO_2R), the electrophilic center may be an halide and the γ,δ double bond is in this case generated by a substitution–elimination sequence:



Synthesis by an Addition–Elimination Sequence. A simple way to introduce a nucleophilic center in a proper prenyl derivative is the abstraction of a proton by means of a suitable base.



A valuable reagent of this kind is obtained by metalation of a salt of the isomeric 3-methyl-2-butenoic and 3-methyl-3-butenoic acids, e.g., with lithium diisopropylamide in THF.[8] This synthon (**2a**) may be directly prepared starting from easily available materials and, owing to the presence of the less electrophilic carboxylate anion as the electron-withdrawing group, it is quite stable and can be handled at room temperature without any self-condensation. The tridentate nature of the reagent influences the regioselectivity of the electrophilic attack which may be directed to the α or γ position. The α/γ ratio has been correlated, using benzaldehyde as electrophile, with the nature of the counterions and the solvent.

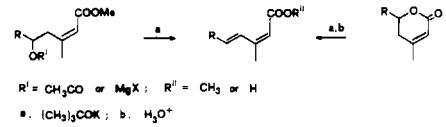


The results obtained indicate that at −78 °C, under kinetic control, the γ-electrophilic attack increases with the ionic character of the organometallic bonds involved and with the polarity of the solvent[8] (Table I). At reflux temperature the electrophilic α attack becomes reversible with the consequent exclusive formation of the thermodynamically more stable γ-hydroxy acids.[9,10]

Concerning the stereospecificity of the addition, one interesting property of this synthon lies in its ability to introduce the prenyl unit exclusively in the 2*Z* configuration.[11] The same regio- and stereospecificity in the addition to aldehydes has been observed for the synthon (**2b**, M = Li) obtained by metalation of 3-methyl-2-butenenitrile (**1b**) with lithium diisopropylamide in THF.[12]

The organozinc synthon (**2d**, M = ZnBr) derived from alkyl 4-bromo-3-methylbutenoate by treatment with zinc in dimethoxymethane at 0 °C reacts with carbonyl compounds to give both the α and γ adducts, the α reverting to the γ derivatives on heating. Concerning the stereochemistry of the newly introduced double bond, these Reformatsky reagents are less stereospecific; a mixture of 2*E* and 2*Z* isomeric γ adducts is generally obtained. In favorable cases, e.g., using relatively crowded ketones as electrophiles and high reaction temperature, the lactones arising from the cyclization of the 2*Z* γ adduct may be exclusively obtained as the thermodynamically more stable product.[13]

The elimination reaction, which constitutes the second step of the synthesis, is easily performed by basic treatment. The lactones or the acetoxy esters arising from the reaction of the prenyl synthons with the aldehydes easily and stereospecifically react with strong bases like potassium *tert*-butoxide in THF to give α,β*Z*, γ,δ*E* unsaturated derivatives.[8,14]



The same elimination reaction may be achieved utilizing a rather uncommon leaving group.[15] In fact, the magnesium alcoholate obtained on adding a solution of methylmagnesium iodide to a solution of the hydroxy ester in THF eliminates readily and quantitatively on treatment with potassium *tert*-butoxide at room temperature.[8]

(8) G. Cainelli, G. Cardillo, M. Contento, G. Trapani, and A. Umani Ronchi, *J. Chem. Soc., Perkin Trans. 1*, 400 (1973).

(9) C. A. Henryck, W. E. Willy, D. R. McKean, E. Baggiolini, and J. B. Siddal, *J. Org. Chem.*, **40**, 8 (1975).

(10) I. Casinos and R. Mestres, *J. Chem. Soc., Perkin Trans. 1*, 165 (1978).

(11) This result is generally explained by assuming that the allylic system in the transition state has a certain amount of carbanionic character and therefore a preferred cis geometry. Cf. ref 8 and references therein. For some theoretical work on this topic, cf., for instance, P. v. R. Schleyer, J. D. Dill, J. A. Pople, and W. J. Hehre, *Tetrahedron*, **33**, 2497 (1977); A. Bongini, G. Cainelli, G. Cardillo, P. Palmieri, and A. Umani Ronchi, *J. Organomet. Chem.*, **92**, C1 (1975).

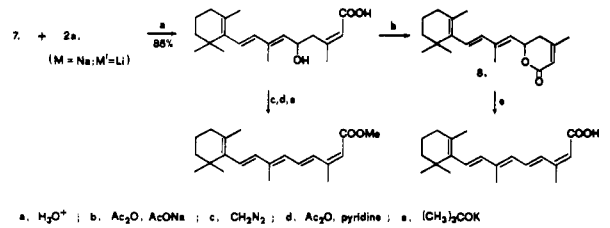
(12) G. Cainelli, G. Cardillo, M. Contento, and G. Trapani, unpublished work.

(13) R. Couffignal and M. Gaudemar, *J. Organomet. Chem.*, **60**, 209 (1973); R. Couffignal and M. Gaudemar, *ibid.*, **96**, 149 (1975).

(14) K. Eiter, E. Truscheit, and H. Oediger, *Angew. Chem.*, **72**, 948 (1960).

(15) F. Bertini, P. Grasselli, G. Zubiani, and G. Cainelli, *Tetrahedron*, **26**, 1281 (1970).

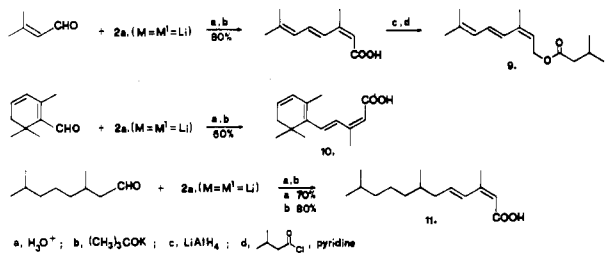
The isoprene synthon (**2a**, M = Na, M′ = Li) obtained by metalation of the sodium salt of 3-methyl-2-butenoic acid (**1a**) by means of lithium diisopropylamide in THF/heptane reacts with β-ionilideneacetaldehyde (**7**) to give, in high yield, exclusively the γ-hydroxy acid with a 2*Z* configuration of the double bond. Treatment with potassium *tert*-butoxide of the



a. H_3O^+ ; b. Ac_2O, AcONa ; c. CH_2N_2 ; d. Ac_2O, pyridine ; e. $(CH_3)_3COK$

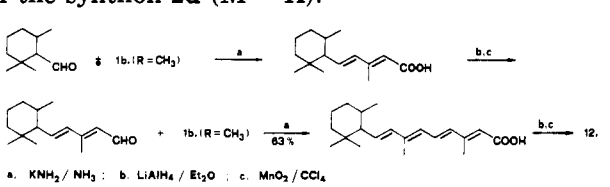
corresponding lactone or acetoxy ester leads exclusively to the 2*Z* vitamin A acid or ester, respectively.[16]

In the same way, using **2a** (M = M′ = Li) as synthon, dehydronerol isovalerate (**9**), a component of *Anthemis montana* L.,[17] dehydroionilideneacetic acid (**10**),[18] a key intermediate in the synthesis of the abscisic acid, and ethyl 3,7,11-trimethyl-2,4-dodecadienoate (**11**),[9] an insect growth regulator, have been synthesized. The acid



a. H_3O^+ ; b. $(CH_3)_3COK$; c. $LiAlH_4$; d. , pyridine

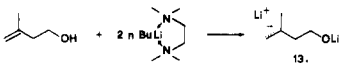
form of 2*Z* vitamin A has also prepared through the lactone **8** by means of the Reformatsky reagent (**2d**, M = ZnBr) following the same reaction scheme.[14] Analogously (2*Z*)-β-ionilideneacetic acid has been obtained[14] starting from β-cyclocitral. The synthon **2c** (M = K) was used as intermediate in the base-promoted condensation between 3-methyl-2-butenal and **7**. This reaction was claimed to give an impure specimen of vitamin A in low yield.[19] Analogously, the condensation of ethyl 3-methyl-2-butenoate with **7** in liquid ammonia[20] or ether[21] with sodium or potassium amide leads, after hydrolysis with potassium hydroxide, to isomeric vitamin A acids in low yield. The synthesis of *all-trans*-5,6-dihydroretinal (**12**), a synthetic visual chromophore, constitutes a recent example of iterative use of the synthon **2d** (M = K).[22]



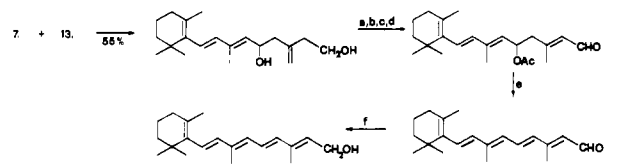
a. KNH_2 / NH_3 ; b. $LiAlH_4$ / Et_2O ; c. MnO_2 / CCl_4

(16) G. Cainelli, G. Cardillo, M. Contento, P. Grasselli, and A. Umani Ronchi, *Gazz. Chim. Ital.*, **103**, 117 (1973).
(17) G. Cardillo, M. Orena, and S. Sandri, *Tetrahedron*, **32**, 107 (1976).
(18) G. Cainelli, G. Cardillo, and M. Orena, *J. Chem. Soc., Perkin Trans. 1*, 1597 (1979).
(19) R. Kuhn and C. J. O. R. Morris, *Chem. Ber.*, **70**, 853 (1937).
(20) M. Matsuri, S. Okano, K. Yamashita, M. Miyano, S. Kitamura, A. Kobayashi, T. Sato, and R. Mikami, *J. Vitaminol. (Osaka)*, **4**, 178 (1958); M. Matsui, K. Yamashita, R. Miyano, S. Kitamura, S. Okano, A. Kobayashi, T. Sato and R. Mikami, *ibid.*, **4**, 190 (1958).
(21) U. Schwieter, C. V. Planta, R. Ruegg, and O. Isler, *Helv. Chim. Acta*, **45**, 528 (1962).

An attractive prenyl reagent of the type F in Figure 2 useful for the synthesis of (2*E*,4*E*)-terpenes may be prepared by metalation of 3-methyl-3-buten-1-ol[23] by means of suitable bases, e.g., the TMEDA/*n*-butyllithium complex.[24] The reagent **13** adds to aldehydes

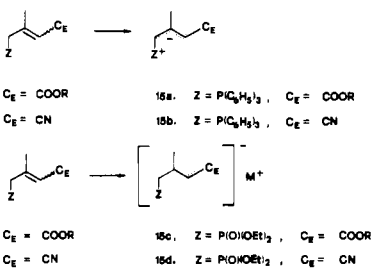


to give the corresponding diols in good yields. The 2*E*,4*E* double bond sequence is then generated through a stereospecific base-induced isomerization and elimination on the corresponding carbonyl compounds. A stereospecific all-trans vitamin A synthesis utilizing this reagent has been accomplished.[25]

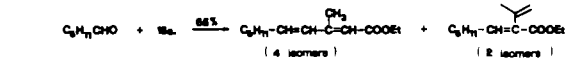


a. AcCl/Pyr; b. $n\text{-}Bu_4N^+\ ^-OCH_3$ /CH_3OH ; c. CrO_3 /Pyr; d. $t\text{-}C_4H_9OK$ / THF, 0°, <10′ ; e. $t\text{-}C_4H_9OK$/ / THF, 0°, >10′ ; f. $NaBH_4$

Both the Wittig reaction and its Horner variant have been used for directly linking a prenyl building block with a double bond. A variety of synthon units of general formula



has been described. In the Wittig type synthons, Z is a triphenylphosphonium. In the Wittig-Horner type, Z is dialkylphosphonate group. Owing to the relatively high acidity of the hydrogen atoms, sodium acetylide, alkali metal alkoxides, and even aqueous alkali suffice to obtain the carbanions required for olefination. The phosphorylated derivatives are easily obtained from the corresponding 4-bromoprenyl derivatives by reaction with triphenylphosphine or triethylphosphite, respectively. The bromo derivatives are, however, relatively difficult to obtain in high yield and stereochemical purity, their synthesis often requiring purification and fractional distillation of lachrymatory allylic bromides. While aldehydes normally condense with allylic phosphonium ylides at the phosphorus-bearing carbon atom,[26] the Wittig reaction of **15a**, obtained from ethyl 4-bromo-3-methylbut-2(*E*)-enoate, with hexanal furnished all four geometric isomers of ethyl 3-methyl-2,4-decadienoate the normal γ-condensation product,

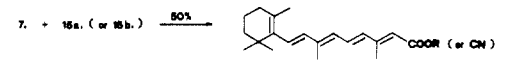


(22) P. E. Blatz, P. Balasubramaniyan, and V. Balasubramaniyan, *J. Am. Chem. Soc.*, **90**, 3282 (1968).
(23) G. Cardillo, M. Contento, and S. Sandri, *Tetrahedron Lett.*, 2215 (1974).
(24) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); R. J. Crawford, *J. Org. Chem.*, **37**, 3548 (1972).
(25) G. Cardillo, M. Contento, S. Sandri, and M. Panunzio, *J. Chem. Soc., Perkin Trans. 2*, 1729 (1979).
(26) For a review, see A. Maercker, *Org. React.*, **14**, 270 (1965); A. W. Johnson, "Ylid Chemistry", Academic Press, New York, 1966.

and both geometric isomers of ethyl 2-isopropenyl-2-octenoate, the "branched" α-condensation product. The α/γ product ratio varied from 9:1 to 1:9, depending on the base and group 2B metal halide present.[27]

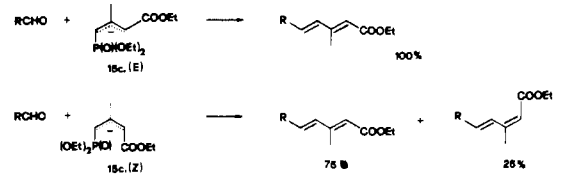
The prenyl unit (**15a**, R = Et) exists as two cis–trans conformers in a ratio 70:30 at 24 °C, as showed by NMR analysis.[28]

These Wittig type synthons have been extensively used in the vitamin A and carotenoid field: all-trans vitamin A esters and nitriles, for instance, have been obtained in satisfactory yield from β-ionilideneacetaldehyde (**7**) and **15a** or **15b** by using sodium ethoxide or some other base to promote condensation.[29,30] The easy isomeri-



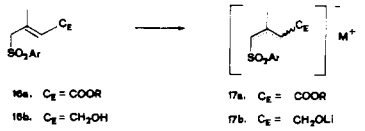
zation of these highly unsaturated compounds and the fact that only the desired products have been isolated and identified do not permit one to draw exact conclusions about the regio- and stereospecificity of these syntheses.

The stabilized phosphonate carbanion with prenyl structures **15c** and **15d** condense with carbonyl compounds position specifically on the phosphorus-bearing carbon atom. Concerning the configuration of the introduced prenyl unit, condensation of **15c** in the *E* configuration with benzaldehyde as well with (*E*) and (*Z*)-citral proceeds with retention of stereochemistry, leading exclusively to the corresponding 2(*E*),4(*E*)-dienoate. The same allylic phosphonate synthon (**15c**) in the *Z* configuration was instead observed to condense regiospecifically but not stereospecifically with propanal, benzaldehyde, and (2*E*)-geranial; in each case the ratio of the 2*Z*,4*E* isomer to the 2*E*,4*E* isomer was 1:3.[31]

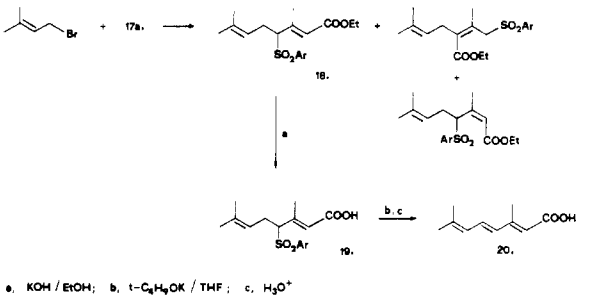


Synthons **15c** and **15d**, generally as *E*/*Z* mixture, have been widely applied in the synthesis of terpenoidic compounds, especially of the Vitamin A family.[29]

Synthesis by a Substitution–Elimination Sequence. In the last decade some versatile isoprene synthons of general formula

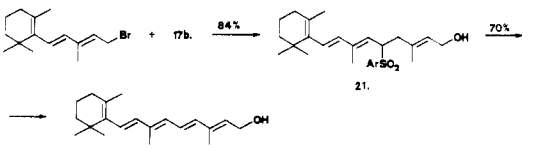


have been reported which contain the sulfone group as temporary auxiliary element. The sulfonyl function acts as a strong electron-withdrawing group, capable of stabilizing a carbanion. Furthermore, it possesses a leaving group ability which allows it to be removed by base-induced elimination. A synthon of this type (**17a**, M = K) arises by the deprotonation of ethyl or methyl 4-arenesulfonyl-3-methyl-2-butenoate by means of potassium *tert*-butoxide in tetrahydrofuran at room temperature. The starting sulfonyl ester is obtained as a mixture of *E*/*Z* isomers from alkyl 4-bromo-3-methyl-2-butenoate by treatment with sodium arylsulfinate. Both olefinic isomers, which may be separed in a pure state by chromatography, give rise to the same equilibrium mixture of metalation products on basic treatment. The alkylation of **17a** (M = K), however, seems to lack regio- and stereospecificity. In fact, treatment of the synthon with allylic halides, e.g., 1-bromo-3-methylbut-2-ene, gave a mixture of isomeric sulfonyl esters arising from γ and α attack. Following this procedure the trienic acid **20** was obtained in 35% yield through the acid **19**, which easily undergoes basic



elimination. The corresponding ester (**18**) does not eliminate under the same conditions, owing to the higher stability of the C-4 carbanion in comparison to the C-5 one.[32]

In the same way, small amounts of vitamin A acid could be isolated from **17a** (M = K) and 1-bromo-3-methyl-5-(2,6,6-trimethylcyclohexen-1-yl)penta-2,4-diene.[32] Higher yields of vitamin A have been obtained on utilizing the metalation product of the 1-(arylsulfonyl)-2-methyl-4-hydroxy-2(*E*)-butene with 2 equiv of lithium diisopropylamide or butyllithium (**17b**). This reagent undergoes a regioselective alkylation cleanly at the carbon α to the sulfonyl group, the configuration of the newly introduced double bond depending upon the reaction temperature. Thus formation of the dianion **17b** and its alkylation at −70 °C followed by overnight warming gave mainly the 2*Z* C_{20} sulfone. If metalation and alkylation are carried out between −50 and −70 °C, the (2*E*)-sulfone **21** is obtained. Appar-



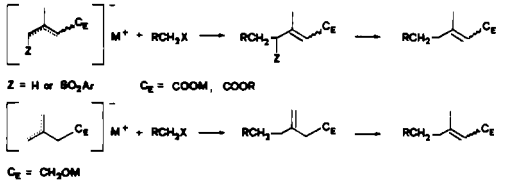
ently the synthon arising from the metalation of **16b** with the *E* configuration has considerable stability toward *E*/*Z* isomerization below −50 °C.[33]

Synthesis of Terpenoidic 1,5-Polyolefins

Some of the above-discussed allylic organometallic prenyl synthons may be used also for the synthesis of

(27) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **39**, 821 (1974).
(28) R. K. Howe, *J. Am. Chem. Soc.*, **93**, 3457 (1971).
(29) H. Pommer, *Angew. Chem.*, **72**, 811 (1960); P. J. Van den Tempel and H. O. Huisman, *Tetrahedron*, **22**, 293 (1966).
(30) H. Pommer, *Angew. Chem.*, **16**, 423 (1977).
(31) G. Pattenden and B. C. L. Weedon, *J. Chem. Soc. C*, 1997 (1968).
(32) M. Julia and D. Arnould, *Bull. Soc. Chim. Fr.*, 743 (1973).
(33) G. L. Olson, H. C. Cheung, K. D. Morgan, C. Neukom, and G. Saucy, *J. Org. Chem.*, **41**, 3287 (1976).

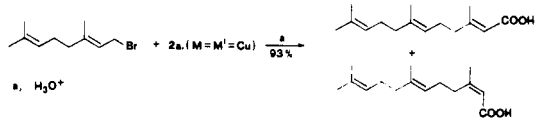
terpenoidic molecules containing partial structure C or D (Figure 1). In such structures the two prenyl units are linked head to tail through a single bond. This goal may be achieved by γ-alkylation of synthons of type **2**, **13**, or **17**, followed, if necessary, by reductive cleavage of the electron-withdrawing group Z or by isomerization of the methylenic double bond.



Synthesis by Substitution. Since alkylation of these ambidentate anions is irreversible, the branched products arising from the α attack cannot undergo transformation to the γ products, as in the case of the condensation with aldehydes. In order to obtain a suitable terpene synthesis, it is therefore necessary to control the regioselectivity of the attack. The α/γ ratio in the substituted products depends on the nature of the groups Z and C_E and, to a lesser extent, on the counterions and the reaction conditions.

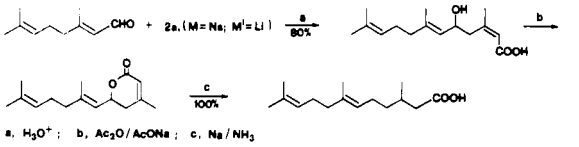
The dianions of 3-methyl-2-butenoic and 3-methyl-3-butenoic acids (**2a**) react with alkylating reagents such as methyl iodide to give C-2 and C-4 alkylation products, the C-4 vs. C-2 attack increasing with the ionic character of the organometallic bonds involved in the dianions.[34] The trend is the same as in the already discussed addition of these dianions to benzaldehyde.[8] However, even with potassium as counterion and THF/HMPA as solvent, the C-4/C-2 ratio is only 35/65. Interestingly enough the γ-alkylation derivatives have been obtained almost exclusively in the *Z* configuration.

The copper salt obtained by transmetalation of **2a** (M = Na, M′ = Li) with copper iodide in THF at −78 °C shows a greater tendency to undergo selective γ alkylation. In fact, an α/γ ratio of 10:90 is observed in

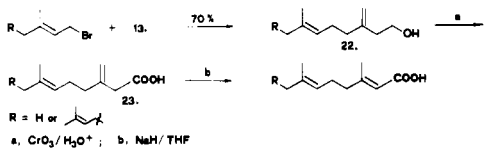


the reaction with allylic electrophiles. Allylic electrophiles that are unsubstituted or monosubstituted at the γ carbon undergo, in variable amounts, S_N2' attack, giving products in which the allylic portion has been transposed; electrophiles with isoprene structure, on the other hand, being disubstituted at the γ position, react exclusively by direct S_N2 displacement, leading to natural head-to-tail terpenes. Unfortunately the alkylation is not stereospecific concerning the geometry about the 2,3-double bond in the alkylated product. Both *E* and *Z* isomers are obtained in a ratio of about 60/40.[35]

Methyl 2,3-dihydrofarnesoate has been obtained by condensation of geranial with **2a** (M = Na, M′ = Li) followed by reduction with sodium in liquid ammonia of the corresponding lactone.[36] In contrast, a stereo-



specific synthesis of the geranyl and farnesyl skeleton has been obtained by the alkylation of the synthon **13** with a suitable allylic halide. The acid **23** can be

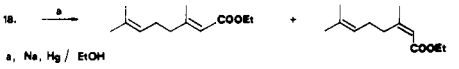


quantitatively and stereospecifically isomerized to the corresponding 2*E*-α,β-unsaturated derivative by treatment with NaH in THF.[23]

In another modification, the methylenic alcohol **22** was easily oxidized to the corresponding aldehyde which could be quantitatively isomerized to the corresponding 2*E*-α,β-unsaturated aldehyde with a trace of potassium *tert*-butoxide in THF.[23]

Synthesis by Substitution Followed by Reductive Removal of the Activating Group Z. The alkylation of allylic sulfones and the subsequent reductive removal of the sulfonyl group are a synthetic method which has been extensively studied in the last years. Sodium amalgam in ethanol,[37] aluminum amalgam in THF/water,[38] lithium in ethylamine,[39] zinc in acetic acid,[40] potassium graphite,[41] sodium amalgam in the presence of Na_2HPO_4,[42] and tri-*n*-butyltin hydride[43] are the reagents commonly employed to achieve the reductive cleavage of the carbon–sulfur bond, the choice depending on the presence of other functionalities. Unfortunately the cleavage of allylic sulfones lacks stereospecificity, extensive isomerization of the allylic double bond being almost invariably observed.

The alkylation of the sulfonyl synthon **17a** to yield **18** has been discussed above.[32] The same reaction may

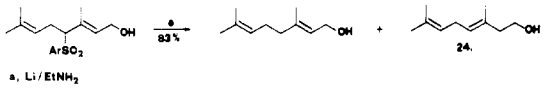


be also performed under phase-transfer conditions.[44] Reductive removal of the sulfonyl group with sodium amalgam has been used for a new synthesis of geranic and farnesoic acid derivatives.[32]

Terpenic alcohols have also been obtained from the synthon **17b**. The reduction step seems to be critical in this case. While treatment with sodium amalgam in methanol leads almost exclusively to the hydrocarbon ocimene (*Z* + *E* isomers), reduction with lithium in ethylamine of the lithium alkoxide gives rise in good

(34) G. Cainelli, G. Cardillo, M. Contento, and A. Umani Ronchi, *Gazz. Chim. Ital.*, **104**, 625 (1974).
(35) J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **98**, 4925 (1976).
(36) G. Cainelli, G. Cardillo, and M. Contento, unpublished results.
(37) M. Julia and J. M. Paris, *Tetrahedron Lett.*, 4833 (1973).
(38) E. J. Corey and M. Chaykowsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).
(39) W. E. Truce, D. P. Tate, and D. N. Burdge, *J. Am. Chem. Soc.*, **82**, 2872 (1960).
(40) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 61 (1967).
(41) D. Savoia, C. Trombini, and A. Umani Ronchi, *J. Chem. Soc., Perkin Trans. 1*, 123 (1977).
(42) B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, *Tetrahedron Lett.*, 3477 (1976).
(43) Y. Ueno, S. Aoki, and M. Okawara, *J. Am. Chem. Soc.*, **101**, 5415 (1979).
(44) G. Cardillo, M. Contento, M. Panunzio, and A. Umani Ronchi, *Chem. Ind. (London)*, 873 (1977).

yield to a 80:20 mixture of geraniol and the corresponding allylic isomer **24**.[45]



Concluding Remarks

The results discussed in this Account give a picture of head-to-tail terpenoid synthesis starting from anionic synthons containing the entire prenyl unit. Synthons of this kind, easily obtained from commercially available materials, utilize simple reaction schemes and give high yields. Although many of them are ambidentate in nature, the experimental conditions regioselectively leading to the correct γ attack are now known. Moreover, most synthons described are attractive in terms of their stereoselectivity. Although a great deal of work has been done in the last two decades on this topic, further efforts will be surely and richly rewarding.

(45) M. Julia, D. Uguen, and A. Callipolitis, *Bull. Soc. Chim. Fr.*, 519 (1976).