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SYNTHESIS OF TERPENOPHENOLS VIA DIRECT ALKYLATION OF PHENOLS BY TERPENES

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Literature data on the alkylation of phenolic compounds by mono-, sesqui-, and diterpenes in the presence of various catalysts are reviewed.

Key words: review, alkylation, phenolic compounds, terpenes, terpenophenols.

Terpenes and phenolic compounds are two common classes of plant biosynthesis products. They are interesting due to their structural variety. Representatives of both classes act as interspecies communicants on a chemical level. The biological functions of many of them are well known. A large quantity of literature is dedicated to each class. However, very many compounds that are products of mixed biogenesis of both classes, so-called terpenophenols, have been found in nature. Many terpenophenols possess a wide spectrum of activity for warm-blooded organisms (Table 1). At present it cannot be confidently stated whether the biological activity of terpenophenols results from synergism of the properties of their precursors, for example, the antioxidant activity of the terpenoid moiety and P-vitamin (capillary strengthening) properties of polyphenols. From a biological viewpoint, terpenophenols combine both hydrophilic ("phenolic" part) and lipophilic properties ("isoprene" part). This regulates their localization in membranes and in many instances greatly simplifies their recognition by receptors. In general, terpenophenols can be considered to be an important and widely distributed class of natural compounds [1-3]. Table 1 gives a short list of important biological properties of known terpenophenols.

The properties of terpenophenols listed in Table 1 and other potential properties have created interest in their synthesis and the study of their biological properties. The problems that have been resolved are as follows:

1. Proof of structure and stereochemistry of certain polycyclic compounds isolated from natural sources;
2. Investigation of synthetic potential of terpenes, search for new paths and side products involving them, study of the stereo- and regioselectivity in the reaction of terpenes and phenolic compounds. The temporal priority in cyclization of the isoprenoid moiety, alkylation of the phenol, and heterocyclization involving the hydroxyl group of phenol has been partially established as a function of the nature and mutual placement of functional groups in the terpenoid synthon and the type and activity of the catalyst.
3. Modeling of mixed biogenesis occurring *in vivo*, development of approaches to the synthesis of difficultly accessed biologically active terpenophenols, preparation of "unnatural" analogs of terpenophenols possessing similar or new biochemical action compared with the natural compounds.

The methodology of such synthesis is based, on one hand, on typical alkylation of phenols by terpenoid synthons generated from various terpenes with variation of the type and activity of the catalysts. On the other hand, the wide structural variety of terpenes and phenols and the broad possibilities of preparing the necessary terpenoid synthons from functionally varied compounds are responsible for the extensive but scattered literature that has been compiled on the reaction of phenols with isoprenes. The goal of the present review is to generalized and somewhat preliminarily systematize these data.

An analysis of the literature shows that certain investigations of terpenophenols can be considered complete. However, the current trend is to revert to past work and employ new technology and instrumental techniques (heterogeneous catalysis, improved methods of separating reaction mixtures, etc.). As yet unknown variations of these reactions involving not only monoterpenes but also isoprenes of higher molecular weight can be described.

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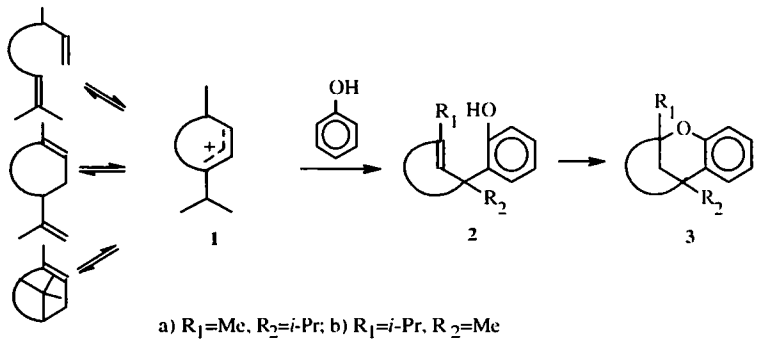
TABLE 1. Biological Properties of Terpenophenols

Compound type	Biological activity	Reference
Prenyl- and geranylhydroquinones	Radioprotectors, anticancer prophylactic preparations	[4, 5]
Cannabinoids	Psychotropic compounds	[6-11]
Zonaroles	Pathogenic fungus growth inhibitors	[12]
Modified spiro-benzofuran sesquiterpenes	Complement inhibitors, anti-allergic and antitumor agents	[13]
Tocopherols (vitamin E)	Exogenic antioxidants, hepatoprotectors, antisteryl factors, etc.	[14, 15]
Naphthotocopherols, phytylhydroquinones (provitamin K)	Antihemorrhagic and thrombosis factors (coagulants)	[15]
Stypotriol compounds	Icthyotoxins	[16]
Polyprenylhydroquinones (vitamin Q)	Electron transfer in respiratory tract, endogenous antioxidants	[17, 18]
Solanochromenes	Vasodilators	[19]

First we will briefly discuss the most well known alkylation of phenols by monoterpenes as a function of the nature of the functional group in the substrate and the structural types of the products. It is noteworthy that terpenes with various types of cyclic systems clearly exhibit similar chemistry in the aforementioned reactions. It will be shown later that the same products are often formed from monoterpenes both from acyclic and cyclic precursors. The quantity of hydroxyl groups and the nature of the substitution in the phenol influence greatly the occurrence of further heterocyclization and the formation of new cyclic systems. The quantity and placement of double bonds in the starting terpenoid synthon and the reaction conditions, the medium and type (activity) of catalyst, also affect the structure of the products.

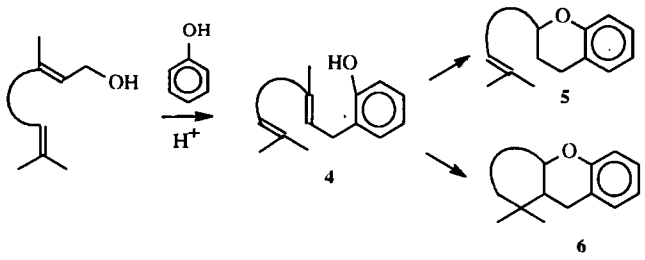
Polyenes in the Presence of Acidic Catalysts [20-22]. The reaction usually proceeds through monocyclic intermediates (**1**), regardless of the number of rings in the starting terpene, i.e., the isoprenoid moiety in acyclic terpenes cyclizes (or opens in bicyclic ones) before alkylation occurs. The final products are usually tricyclic simple ethers (**3a** and **-b**) in various ratios with their precursors (**2a** and **-b**).



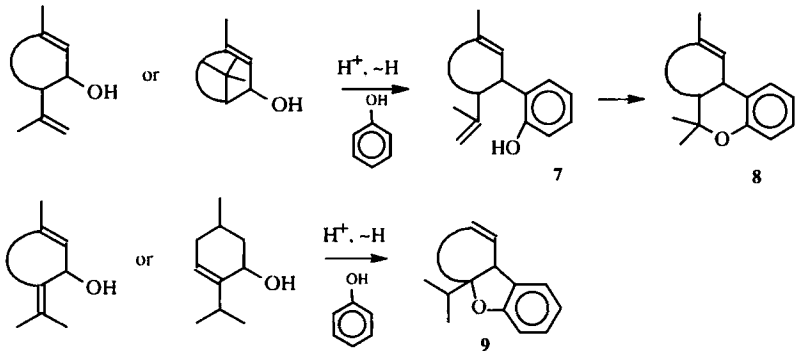
a) R_1=Me, R_2=*i*-Pr; b) R_1=*i*-Pr, R_2=Me

Terpenes with the bicyclo-[2.2.1]-heptane framework, in contrast with those containing bicyclo-[3.1.1]-heptane, do not yield heterocyclic products owing to the presence of only one double bond and the inability to open the bicyclic framework. For example, camphene and olefins related to it exhibit such behavior. A special section is dedicated to this in the present review.

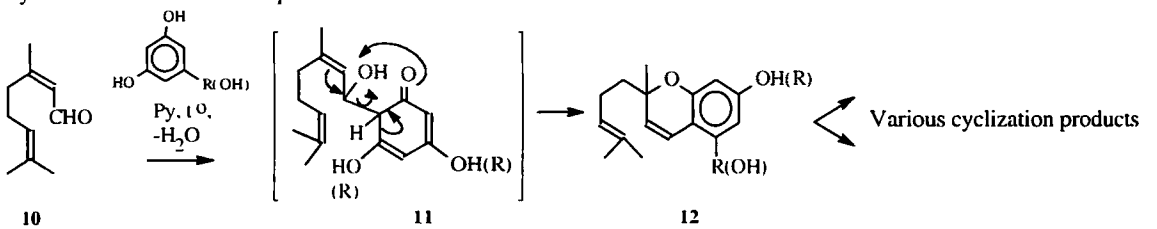
Allyl Alcohols in the Presence of Acids [20, 23-26]. The isoprenoid framework of an acyclic alcohol can cyclize both before (tertiary alcohols) and after (primary alcohols) alkylation. Apparently this is due to the different rates of elimination of the hydroxyl group for tertiary and primary alcohols. For tertiary alcohols, the reaction takes the same path as for the dehydration products, olefins. For primary alcohols, a different version of the reaction occurs:



The catalyst activity influences greatly the ratio of acyclic (**4**) and cyclic (**5**) and (**6**) products. For monocyclic allyl alcohols, products with a different type of cyclic system (**8**) and (**9**) form depending on the location of the double bond in the substrate.



α,β-Unsaturated Aldehydes [27-29]. Of terpenes containing an aldehyde group, only citral (**10**) is used as starting material. A peculiarity of the behavior of **10** in the reaction with phenols is the fact that the substrate cyclizes after alkylation. Furthermore, the composition and structure of the products formed by acidic and nucleophilic catalysis of the reaction of unsaturated aldehydes with phenols are completely different. This is due to the different cyclization mechanisms of the primary alkylation adducts. Alcohols (**7**) and simple ethers (**8**) are formed in the presence of acids, like in the preceding examples, depending on the conditions. The reaction of citral with polyphenols that is catalyzed by pyridine produces chromene (**12**), which cyclizes further to various products.



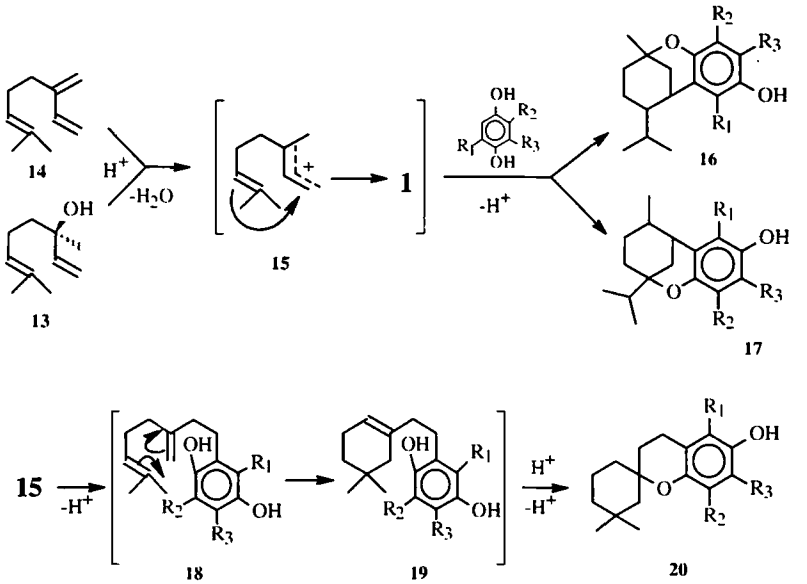
All types of reactions will be illustrated below, using actual compounds as examples where possible.

CONDENSATION OF MONOTERPENES WITH PHENOLS

The reaction of acyclic monoterpenes with various phenols is widely studied. The substrate cyclizes (before alkylation) most often under acid-catalysis involving polyenes and tertiary alcohols, as already noted. The reactive intermediate is a cyclic ion of type (**1**). The rates of these processes are inversely related for primary alcohols.

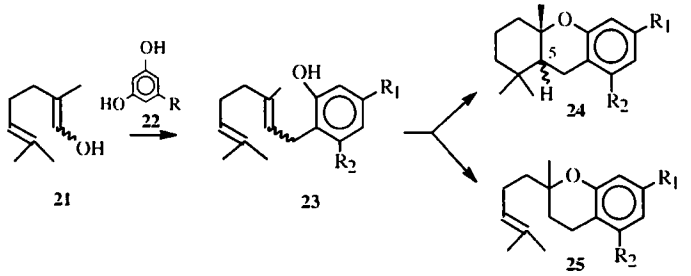
Thus, linalool (**13**) or myrcene (**14**) react with various trisubstituted hydroquinones in catalysis by Lewis acids (LA) or CH_3CO_2H to give only tricyclic products: isomeric ethers **16** and **17** and a spiro-compound (**20**) [20]. It was proposed that olefin **14** is protonated or alcohol **13** is dehydrated to give the ion **15**, which manages to cyclize into a cyclic intermediate before reacting with hydroquinone, like ion **1**. The final heterocyclization of the intermediate adducts is facile owing to the spatial

proximity of the phenol hydroxyl group and the olefinic fragment of the terpene.



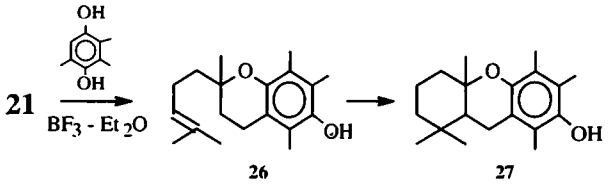
However, the hypothetical ion **15** reacts only partially with an aromatic system in this instance, apparently even before it cyclizes into the ion, similar to **1**, because a small quantity of an unusual product, the spiro-compound **20**, was isolated from the reaction mixture. The formation of such a product can be explained by the sequence "alkylation of phenol - cyclization of the isoprene - heterocyclization" that passes through intermediates **18** and **19** as shown in the scheme.

Products with a varying degree of cyclization can be obtained by varying the reaction conditions. This was demonstrated using the primary alcohols geraniol (**21**) and its *cis*-isomer nerol. Alkylation of orcine (**22**, R = Me) by geraniol in the presence of HCO_2H (50%) gives mainly tricyclic ethers (**24a** and **-b**, Alk = Me) [23]. If oxalic acid (1%) is used, the product is geranylorcines (**23a** and **-b**, Alk = Me). In this instance, cyclic products (**24a** and **-b**, Alk = Me) exist in the mixture as minor components. Analogous results were obtained by Mechoulam [24]. Addition of geraniol or nerol to olivetol (**22**, R = amyl) in the presence of toluenesulfonic acid produced only *trans*- (**23a**, Alk = amyl) or *cis*-cannabigerol, respectively. Attempts to cyclize each of these prenylphenols under more forcing conditions produced in both instances mixtures of two epimers at C-5 (**24a**, Alk = amyl) and a chromane compound (**25a**, Alk = amyl). It was noted that *cis*- or *trans*-substituents in the precursors greatly influenced the ratio of epimers (**24a**, Alk = amyl).



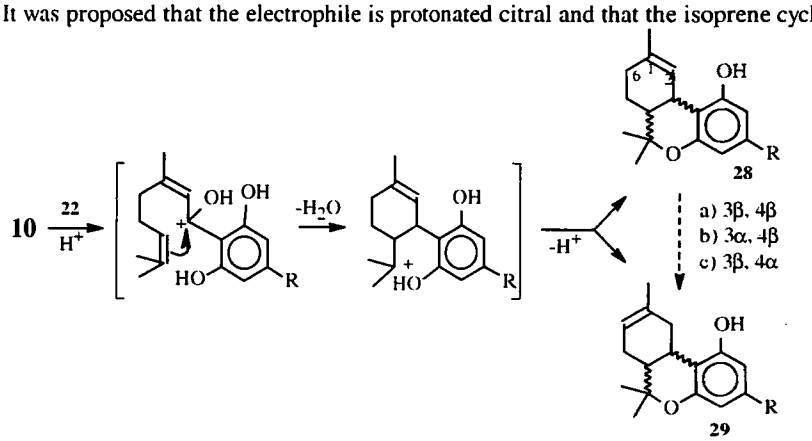
a) R_1=Alk, R_2=OH; b) R_1=OH, R_2=Alk

Moderately active catalysts (BF_3 and certain other LA) create conditions under which bicyclic chromanes can be selectively formed. In particular, Japanese researchers demonstrated that geraniol condenses in the presence of BF_3 with trimethylhydroquinone to form chromane **26**, a homolog of α-tocopherol, in practically quantitative yield whereas further cyclization of this chromane into the corresponding tricyclic ether (**27**) occurs if acetic acid is used as the catalyst [30].

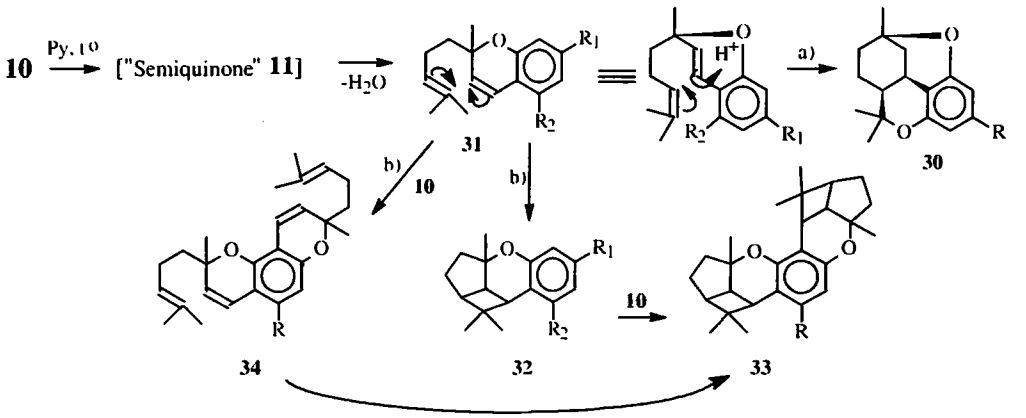


The ability of a substrate to react with phenols is substantially expanded if an aldehyde is present in the acyclic monoterpene. Citral (**10**), which is one of the substrates used most often in these reactions, is used here as an example. The reactions of this aldehyde with phenols are definitely interesting because isomeric tetrahydrocannabinols (THCs), which are interesting for their psychochemistry, are rather easily and relatively selectively obtained from this terpene [8-11].

Nearly identical results were obtained in this area in a relatively short time by various research groups. Thus, the product mixture from condensation of citral with olivetol in the presence of various acids contains *cis*-Δ^1- (**28a**, R = amyl) and *trans*-$\Delta^{1(6)}$-THC (**29b**, R = amyl) [31]. Another research group under the direction of Crombie used a dilute alcoholic solution of HCl as the medium and obtained a mixture of *cis*- (**28a**) and *trans*-Δ^1-isomers (**28b**) and the $\Delta^{1(6)}$-isomers (**29a** and **-b**) corresponding to them [29]. It was demonstrated that the last two are thermodynamically more stable and partially formed from the Δ^1-isomers [32]. It was proposed that the electrophile is protonated citral and that the isoprene cyclizes after alkylation.



These same tendencies were observed for the reaction of citral with phloroglucine (**22**, R = OH). Hydroxyl analogs of only Δ^1-THC (**28a** and **b**, R = OH) were observed in the mixture in a 40:60 ratio. The $\Delta^{1(6)}$-isomers were not observed [27]. Addition products of nucleophiles to the double bonds of still uncyclized intermediates were found in trace quantities if the reaction was carried out in aqueous ethanol. Hydroxyl or ethoxide added to the isopropylidene group; phenoxide, to the endocyclic double bond. The addition of solvent here probably occurs immediately after alkylation of the phenol. As a result, the phenoxide attacks the olefinic atom 1. These facts are consistent with long-lived intermediates, which are shown in the scheme in brackets.

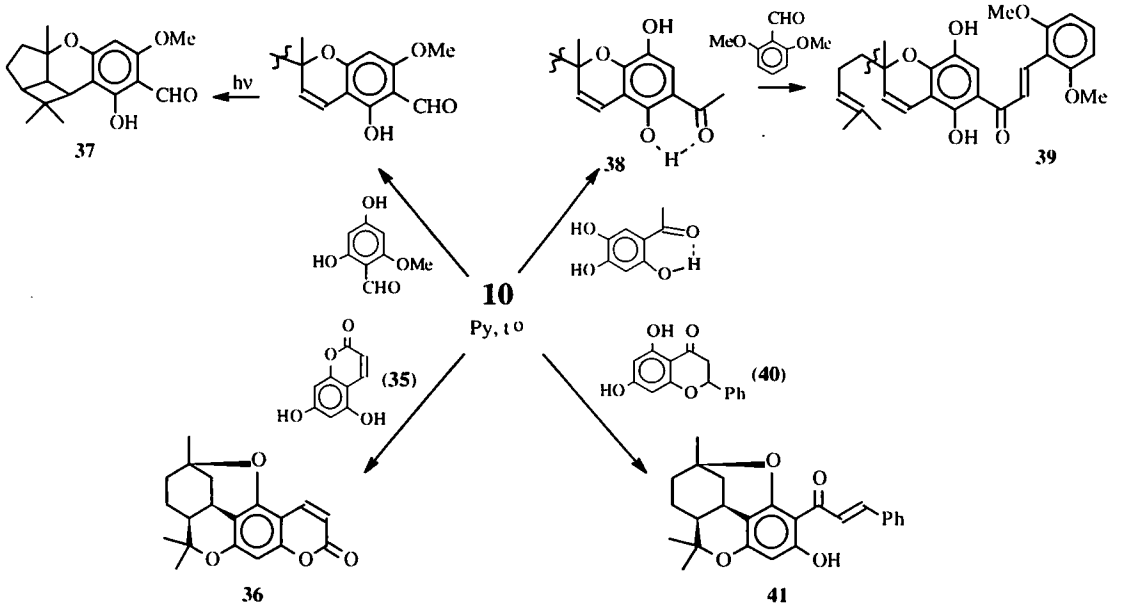


a) R_1 =amide, R_2 =OH; b) R_2 =OH, R_1 =amide

The reaction of **10** with the two phenols mentioned above may also occur through a mechanism different from the one given that drives the reaction along a different path to give a more varied product mixture. Condensation of olivetol and citral in the presence of equivalent amounts of pyridine [29] produces a mixture of citrillidene-cannabis (**30**, R = amyl) (main product), regioisomeric cannabichromenes (**31a** and **-b**), and cannabicyclols (**32a** and **-b**) in addition to two products of olivetol alkylation by an excess of citral (**33** and **34**, R = amyl). In this instance, two aspects are interesting: 1) the formation of **30**, in which both phenol hydroxyls are cyclized into pyrans and 2) nonphotochemical [2+2]-cycloaddition to give products with the cyclol framework (**32** and **33**).

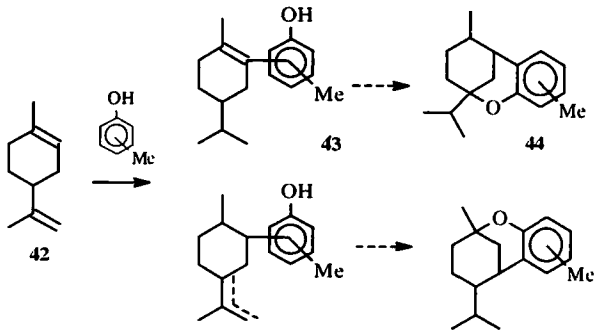
It is noteworthy that these same researchers proposed an intermediate that explains the formation of each of these unusual adducts (**30** and **32**), a semiquinone similar to **11**. The reaction of citral with phloroglucine under these conditions gives a single product, a tetracyclic diether (**30**, R = OH) called "citrillidenephloroglucine," in 40% yield [27].

The observed reactions provided a basis for several interesting synthetic innovations by the Crombie group. It was found that desoxybruceol (**36**) is formed in a single step if 5,7-dihydroxycoumarin (**35**) is used as the phenolic synthon in the reaction [28]. The reaction of citral and 2,4-dihydroxy-6-methoxybenzaldehyde and a photochemically induced [2+2]-cycloaddition to increase the yield of the corresponding cyclol lead to the precursor eriobrucine (**37**) [33]. Then the group reported and confirmed that chelation of the phenolic hydroxyls, which usually participate in the cyclization, can stop the reaction at the chromene stage. In particular, condensation of citral and 2,4,5-trihydroxyacetophenone (pyridine, 110° C) gives the dihydroxy adduct **38**, aldol condensation of which with 2,6-dimethoxybenzaldehyde gives a product with the chalcone structure, flemingin B (**39**), the active principal of the exotic East African medicine "wars," which is prepared from *Flemingia rhodocarpa* species. The dioxolan "rubranine" (**41**) identical to the natural product is synthesized analogously from pinocembrine (**40**). This enabled the structure of **41** to be determined [34].

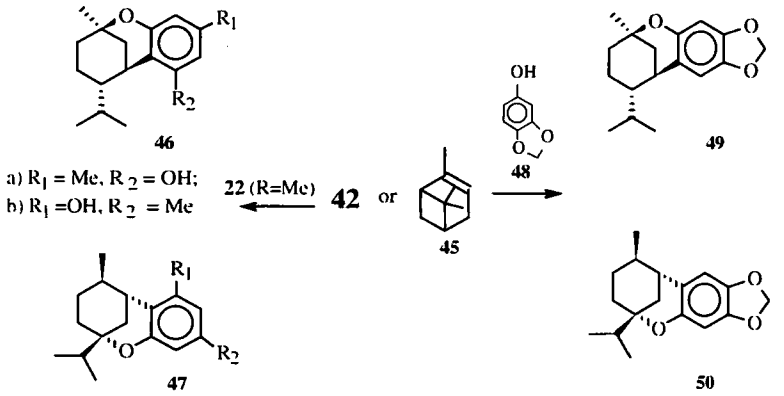


Cyclic monoterpenes exhibit fewer types of reactions with phenols. Menthane, pinane, and carane monoterpenes, as already noted, often give the same product set owing to opening of the cyclobutane and cyclopropane moieties under acid-catalysis conditions.

Hydrocarbons. Alkylation of various phenols by limonene (**42**) is rather well studied. The reaction of **42** with isomeric cresols in the presence of KU-2 cation-exchange resin produces various ratios of terpenylphenols (**43**) and cyclic oxides (**44**), which decrease from *o*-cresol to *p*-cresol [21]. Obviously such a trend is due to the tendency to form alkylation products in the position *ortho* to the hydroxy group. The amount of *o*-alkylated products increases with decreasing steric hindrance and increasing number of alternative *o*-positions. On the other hand, the quantity of cyclized compounds (**44**) that is formed from these isomers increases.



Others have reported that limonene treated with orcine (**22**, R = Me) in the presence of HCO_2H (50%) gives only tricyclic regioisomeric ethers (**46a** and **-b**) and (**47a** and **-b**). Replacing orcine by sesamol (**48**) produces only the two corresponding 2-alkylated products and further cyclization to **49** and **50**. These same product sets in the same ratios are formed under these conditions from β-pinene (**45**) because both pinene and limonene in this medium are assumed to react with phenols as the protonated terpinenes and terpinolenes [22].

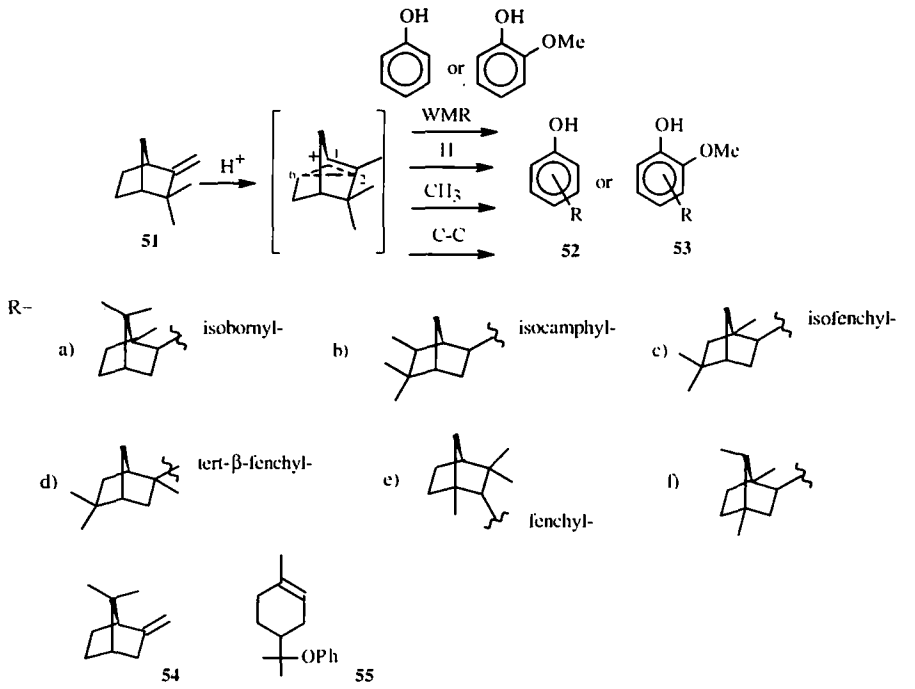


Kheifits et al. have made the greatest contribution to the study of alkylation of monofunctional phenols by bicyclic camphane olefins. Most of their results are summarized in the doctoral dissertation of Kheifits [35]. In addition to establishing the rules for alkylation of monofunctional phenols by terpenes, this compilation is interesting as an investigation of the framework rearrangements to which camphane terpenes and related compounds are especially prone. For example, camphene (**51**) does not form heterocyclization products in the reaction with phenols because it contains only one double bond. The alkylation agent in the instance of **51** is a mixture of ions formed through a series of rearrangements and subsequent hydride shifts. The principal products from the reaction of camphene and phenol are isobornyl- (**52a**) and isocamphylphenol (**52b**).

It is noteworthy that products of a 6,2-hydride shift (**52b**) predominate in the presence of BF_3 or acetic acid. Decreasing the amount of catalyst increases the amount of phenol isobornyl ethers. The product mixture from the reaction of camphene and guaiacol contains not only **53a** and **-b** but also isofenchylphenols (**53c**), products of more extensive rearrangements. In contrast with camphene, fenchene forms only products of a 6,2-shift, *p*- and *o*-isofenchyl (**53c**) and *p*-fenchylphenol. β-Pinene (**45**), which is intermediate between camphane and fenchane, undergoes a Wagner—Meerwein rearrangement (WMR) and a 6,2-hydride shift catalyzed by LAs and Al alkoxides. This enabled the formation of several products, **52c-f** and also a terpenylphenyl ether (**55**), through opening of the cyclobutane moiety.

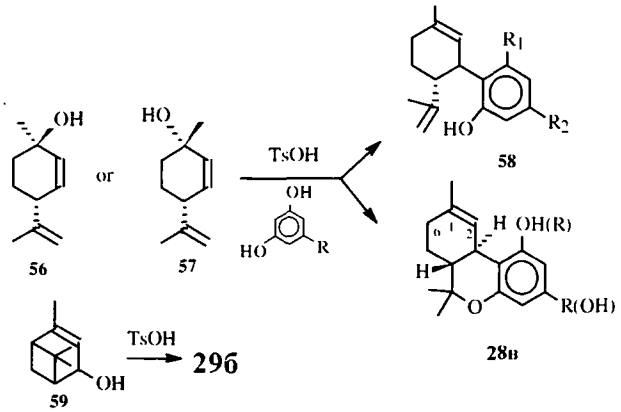
Foreign researchers obtained analogous results for the reaction of camphene with alkylphenols in the presence of other catalysts, KU-2 cation-exchange resin or BF_3-etherate [21, 36].

It was recently demonstrated that crystalline aluminosilicates can be used as catalysts of such reactions in order to make the conditions milder and increase the selectivity. Thus, alkylation of phenol, anisole, and their methyl-substituted derivatives by camphene on wide-pore β-zeolite at room temperature gave terpenylphenol (**52**), terpenylanisoles, and terpenylphenyl ethers. It was demonstrated that the reaction involves C- or O-alkylation depending on the order of addition of the reagents, the phenol structure, and the solvents. For C-alkylation, the principal product has an unusual terpenoid structure with methyl substituents in the 1,4,7-positions [(*e*), see below] [37].



The various camphyl- and other phenol products synthesized in these reactions have important practical application because they are intermediates in the synthesis of fragrances [38].

Allylalcohols (menthane type) undergo a wide variety of reactions with phenols. Petrzilka et al. performed a series of investigations on the synthesis of optically active cannabinoids and homologs in which the composition of the side chain in the resorcinol portion was varied. The starting compound was (+)-*cis*-menth-1,8-dienol (**56**) and its epimer (**57**), which dehydrate under these conditions. Therefore, they give identical products [25]. Like previous studies [23, 24], it was noted that using weak acids produces less cyclized adducts, in this instance 2- and 4-substituted olivetols (**58a** and **-b**, Alk = amyl) (cannabidiols, CBD) and their resorcinol homologs (Alk = H).



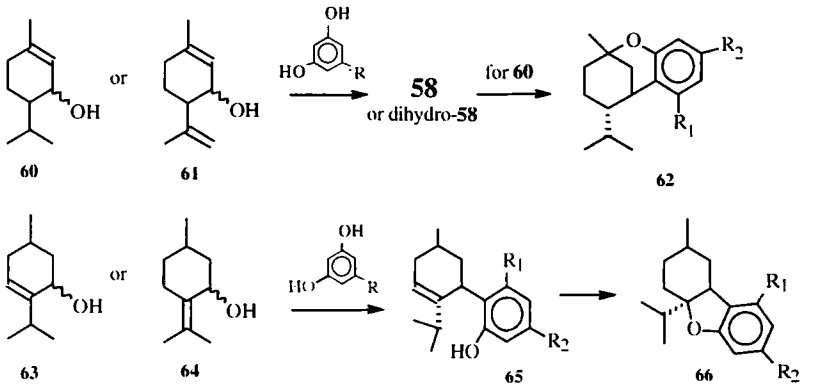
a) R_1 =Alk, R_2 =OH; b) R_1 =OH, R_2 =Alk

Introducing more branching in the R substituents increases the steric hindrance and increases the relative yield of the 2-substituted resorcinols. Alcohol **56** or its epimer **57** treated with olivetol in the presence of TsOH or strong acids transforms into THC (**28a**) and its regioisomer. Bicyclic (-)-verbenol (**59**) behaves similarly [39]. Then, alcohol **56** or its derivatives and

resorcinol phenols were used to prepare Δ^1- (**28**) and $\Delta^{1(6)}$-THC (**29a**) and various thioderivatives [40-42].

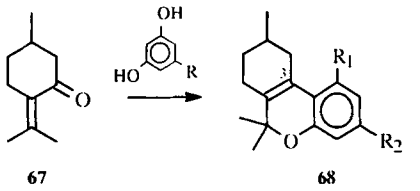
Cannabinoid homologs are formed relatively easily by reaction of various cyclic allylic alcohols and resorcinols in the presence of BF_3-etherate [43]. The preparation of new cannabinoid derivatives and analogs by modifying the side chain or introducing new groups into the cyclic system was at one time a very popular area of investigation [3].

The position of the double bond in the allylic alcohol strongly influences the structure of the adducts. Piperitol **60** or isopiperitenol **61**, which contain a Δ^1-bond (like limonene), react with orcine or olivetol in aqueous citric acid (5%) to give cannabidiol homologs. Then, attack of the phenol hydroxide (at the endocyclic bond and not at the isopropenyl fragment) converts them to cyclic ethers (**62a** and **-b**). However, menth-4-en-3-ol (**63**) or pulegol (**64**) are alkylated and cyclized at the olefinic atom 4 in the adducts (**65a** and **-b**) to give compounds with a tetrahydrofuran ring, i.e., the isomeric ethers (**66a** and **-b**) [26].



a) R_1 =Alk, R_2 =OH; b) R_1 =OH, R_2 =Alk

Other Compounds. If the starting compound does not have an endocyclic double bond, like for pulegone (**67**), that does not react as the protonated form, then adducts with an unusual placement of the double bond, e.g., Δ^3-THC (**68a** and **-b**) are formed because dehydration of the intermediate alcohol produces a more thermodynamically stable C=C bond [44].

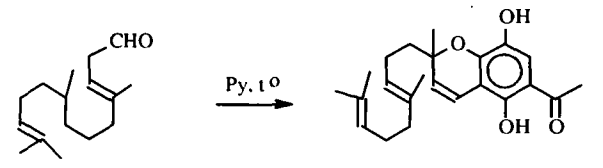


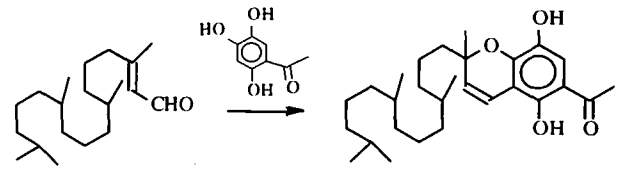
a) R_1 =Alk, R_2 =OH; b) R_1 =OH, R_2 =Alk

CYCLOCONDENSATION OF SESQUI- AND DITERPENES WITH PHENOLS

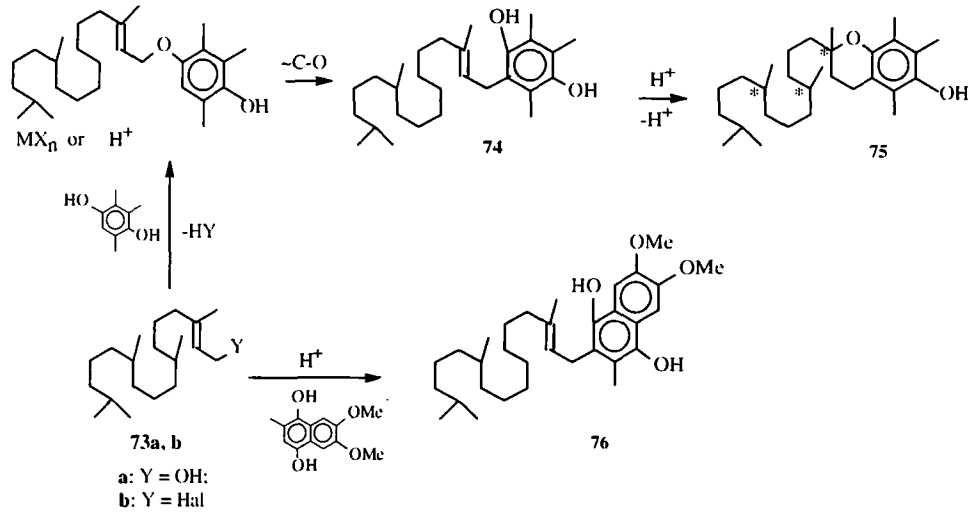
Few reactions of higher molecular weight terpenes with phenols are known because systematic investigations in this area have not been performed. Sesqui- and diterpenoid substrates have been reacted with phenols for only one well defined purpose, to synthesize particular products that have valuable types of biological activity or other properties.

Acyclic Compounds. The single exception to the above is the work of Crombie et al. where the preparation of chromenes from acyclic sesqui- and diterpenes of unsaturated aldehydes farnesal (**69**) and phytal (**70**) was examined in addition to an investigation of the reactions of monoterpenes with phenols [34]. 2,4,5-Trihydroxyacetophenone was used as the reagent. The adducts **71** and **72** were synthesized in slightly lower yields compared with those of citral.

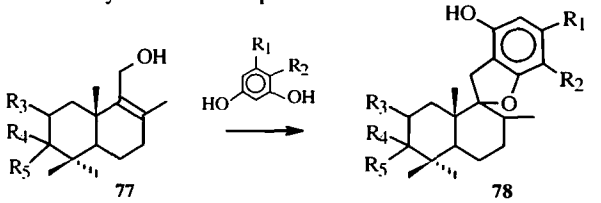




The syntheses of tocopherols (vitamin E, **75**) and phytylnaphthohydroquinones (provitamins K, **76**) via condensation of phytol (**73a**) or phytylhalogenides (**73b**) with trimethylhydroquinone or other substituted hydroquinones are some of the well known and developed reactions of acyclic diterpenes with phenols [15, 45]. The catalysts in both steps of vitamin E (**75**) preparation are LAs and proton acids. However, cyclization of the intermediate adducts (**74**) into the chroman derivatives (**75**) requires more forcing thermal conditions (80-200 C). Various heterogeneous catalysts have been used to effect this sequence of reactions [46]. The synthesis of provitamins K (**76**) is carried out under mild conditions in the presence of slightly active catalysts (e.g., 1% oxalic acid) in order to avoid heterocyclization.

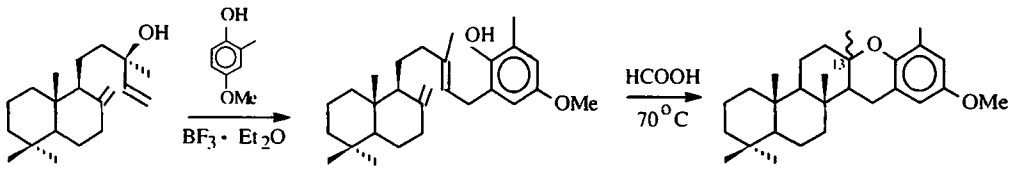


Bicyclic Sesqui- and Diterpenes. Japanese researchers have reported the synthesis of anti-allergic and antitumor derivatives (**78**) from modified sesquiterpenes of allyl alcohols (**77**) via alkylation with resorcinol phenols and further cyclization [13]. The pharmacologic properties of the synthesized compounds have been studied.



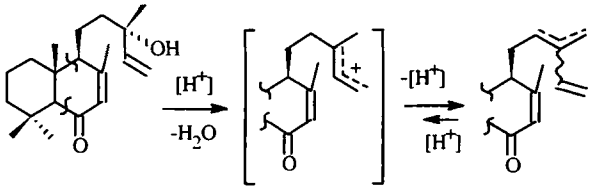
Cyclic analogs of tocopherols are found in marine organisms [47]. Their biological role has not been clearly elucidated. However, similar metabolites exhibit ichthyotoxicity [16] discouraging potential recipients of this product and thereby participating in interspecies (allelochemical) relationships. Many similar compounds may play a role as allomones (intensifying the product) and chymorones (useful for the recipients) in addition to depressants or even autotoxins [48]. Little has been published on their synthesis. We found only a communication by Gonzalez Gonzalez et al. on the preparation of the methyl ether of taondiol (**80**) starting from the diterpene of the tertiary alcohol manool (**79**) and methylguaiacol [49]. The work was

performed in order to prove the structure of taondiol itself, one of the components in the extract of *Taonia atomaria*. The desired product (**80**), as was shown later [50], was an equimolar mixture of C-13 epimers.



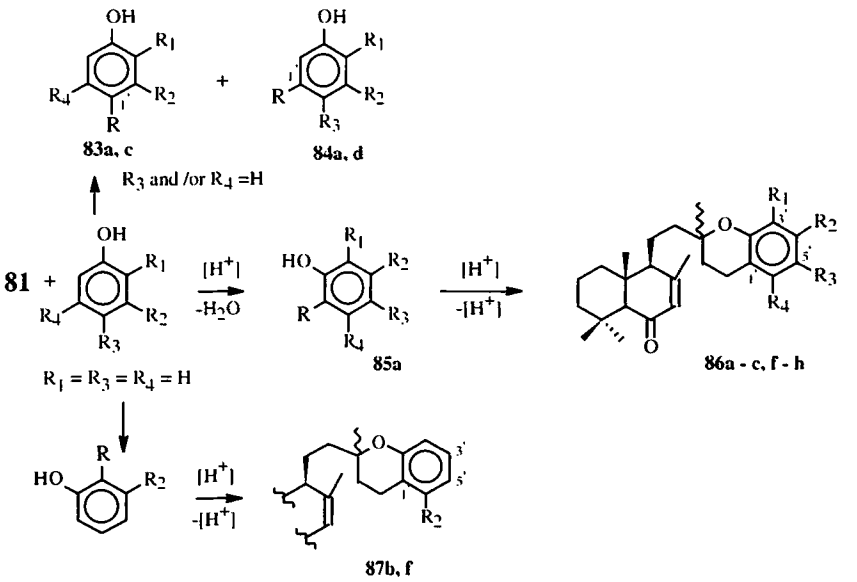
79 80

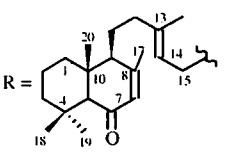
We demonstrated relatively recently the alkylation of phenols by a labdane-type allylic alcohol, (13S)-6-oxolabd-7,14-dien-13-ol (**81**), in the presence of heterogeneous aluminosilicate catalysts. The use of these catalysts enabled a one-step preparation without isolation of the intermediates of the desired chromane derivatives (owing to the Lewis and Bronsted acidity of aluminosilicates). The reaction center in this instance is probably the ion formed by dehydration of the alcohol (analogous to linalool [20]).



81 82

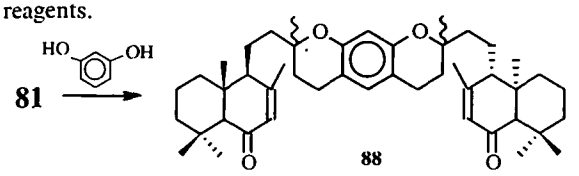
The yields of chromane products (**86** and **87**) starting from alcohol **81** were highest in the presence of ascanite-bentonite clay with boiling in dichloroethane [51]. The catalyst imposes a substantial limitation on the yield of certain products. The yield of alkylation products **83-87** for hindered phenols is rather low (3-10%). The reason for this is apparently the fact that alkylation at the unsubstituted aromatic C atom, which has two nonhydrogen substituents in the *o*-position, is severly hindered even with a favorable electronic influence of the phenol substituents. However, the influence of this same factor for less hindered phenols produces not only a sharp increase in the yield of alkylation products (60-90%) but also the selective formation of chromanes (**86**) compared with other isomers (**87**) (resorcinol, *m*-cresol).





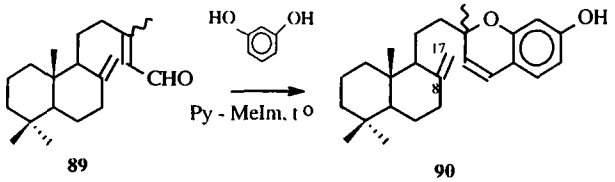
a) R_1 = Me, $R_2 = R_3 = R_4$ = H
b) $R_1 = R_3 = R_4$ = H, R_2 = Me
c) $R_1 = R_2 = R_4$ = Me, R_3 = H
d) R_1 = OMe, R_3 = allyl, R_2=R_4=H
e) R_1=CHO, R_2=R_3=R_4=H
f) $R_1 = R_3 = R_4$ = H, R_2 = OH
g) $R_1 = R_2 = R_4$ = H, R_3 = OH
h) $R_1 = R_3$ = H, $R_2 = R_4$ = OH

A double alkylation product, the cyclization of **88**, also occurs in the reaction of resorcinol. The yield depends on the ratio and order of addition of the reagents.



Employing unsaturated ketones (**82**), products of dehydrating alcohol **81** on clay, in this reaction produces the same product set as for **81**. Apparently the acidity of the clay is sufficient to protonate the double bonds of these compounds. This expands the list of possible substrates for this reaction.

Alcohols with an exocyclic 8(17)-bond do not react with phenols in the presence of organic acids or aluminosilicates because they undergo under these conditions a rapid intramolecular cyclization. However, aldehydes with such a bond (**89**), a mixture of *cis*- and *trans*-isomers (1:1), were successfully reacted with resorcinol in the presence of pyridine with added methylimidazole. The principal product of the condensation is the chromene derivative **90**, which is a mixture of C-13 epimers.



The following tendencies in this area can be noted. It is obvious from the literature that low-molecular-weight representatives of several terpenes can be used as synthons to synthesize terpenophenols. This is probably due to the fact that most natural terpenophenols are derivatives of monoterpenes. This prompted researchers to reproduce the natural processes and to prepare numerous analogs of low-molecular-weight terpenophenols. Despite the fact that this area is at present rather mature, research on the reaction of monoterpenes with phenols continues with the intent to develop a qualitatively new twist.

With respect to sesqui- and diterpenes, their use in synthesis (and in other areas involving chemical transformations) is comparatively rare. Interest is concentrated mainly on phytochemical research. Nevertheless, sesqui- and diterpenes are common among forest products. A broad development of the chemistry of these compounds is needed, including their reactions with phenols. The stimulus for this could be the fact that increasing the number of isoprenoid units facilitates a nonadditive increase in the antioxidative activity of the adducts. An example is the aforementioned tocopherols, in which shortening the side chain to two isoprenoid units decreases the E-vitamin activity by ten times. Besides explaining the synthetic potential of high-molecular-weight terpenes, such research may have great applied significance, the ability to prepare "unnatural" analogs of terpenophenols with similar or new biochemical activity compared with the native or synthetic ones (based on monoterpenes).

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