C H A P T E R - I

EVIDENCE FOR THE KEY INTERMEDIATE IN

TRANS- Δ^1-THC FORMATION:

VIA ORGANOMETALLIC REAGENT

S E C T I O N - I

EVIDENCE FOR THE INTERMEDIATE

ABSTRACT

The elaborative efforts towards the synthesis of hypothetical intermediate (10) are described. Different synthetic proposals, as initially analyzed by a model study (Fig. 3, Eqn. 1), led to utilize an organometallic reagent.

The experimental evidence presented, appears to bear out an intermediacy of (15) in the model sequence and of (10) in the targeted reaction between 2-carene epoxide and olivetol (Fig. 3, Eqn. 2). The latter undergoes facile isomerization under Lewis acidic conditions.

Exquisite behaviour of organometallic reagent is sought to be explained in terms of 'Templet effect'.

I N T R O D U C T I O N

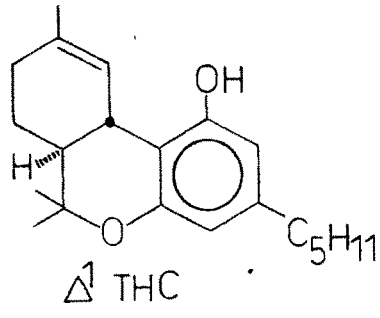
The illicit use of 'Marijuana'[1] was not so popular until 1960's but then assumed the epidemic proportion in the last two decades. By 1970 over 200-300 million people had tried the drug and hence represents the most widely used group of illicit material.

However, since ages, therapeutic use of cannabis preparations were widely practised in Indian, Chinese and Middle Eastern cultures for[2] rheumatism, asthama, insomnia, neuralgia, migraine pain, bronchitis, loss of appetite and; gynaecological and obstetrical problems such as dysmenorrhea. Today it appears that on this folklore foundation an impressive edifice of therapeutic utility is being evolved.

The anecdotes like - "while 'high' on marijuana one can chop onions without the eyes watering", led ophthalmologists - Helper and Frank (1971)[3] to find that it did decrease lacrimation and intraocular pressure (IOP) of the eye. This observation catalysed clinical trials of marijuana and its active constituents Δ^1-THC [(-)-Δ^1-3,4-trans-tetrahydrocannabinol] (1). In 1975 Sallan and co-workers[4] clinically confirmed antinauseant action of Δ^1-THC (1), in patients undergoing cancer chemotherapy. Further it proved effective in the cure of glaucoma. These physiological activities at present, have

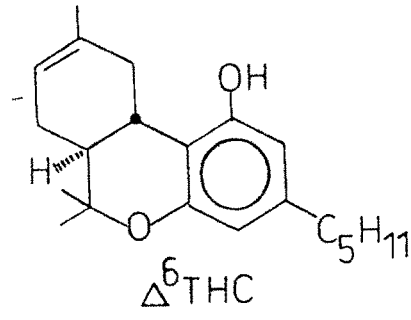
put cannabinoids in the vibrant phase of research.

Isolation and structure elucidation of the active component, trans-Δ^1-THC was as late as in 1964[5] which can be mainly attributed to the complexity of the resinous exudate of the female flowers of Cannabis sativa L.[6] from which trans-Δ^1-THC is obtained.



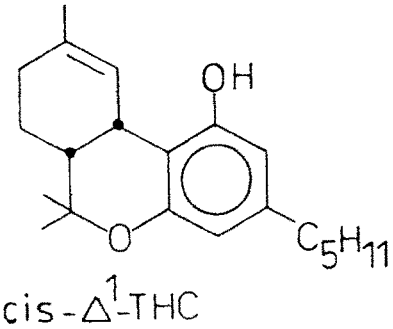
Δ^1 THC

(1)



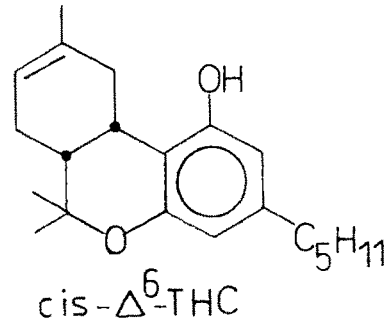
Δ^6THC

(2)



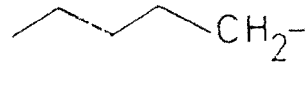
cis-Δ^1-THC

(3)



cis-Δ^6-THC

(4)

$-C_5H_{11}$ = 

The uniqueness of these cannabinoids (typical C_{21} compounds)[7] and their togetherness posed critical problems which has led chemists for new synthetic methodologies towards thermodynamically less stable Δ^1-THC (1) and its biologically useful analogues. Because of alarmingly low yields and trivial mixtures often encountered in the synthesis of Δ^1-THC, synthetists are often seen solving the possible mechanism of its formation.[8] This has, in turn, given way in scrutinizing reaction conditions to make syntheses more competitive.[9,10]

In 1970 Razdan and Handrick[11] reported one-step stereo-specific synthesis of Δ^1-trans-THC (1) and conjectured different mechanism.

Equimolar quantities of (+)-trans-2-carene oxide (5) and olivetol (6) under p-TSA conditions gave a complex mixture which contained Δ^6-THC (2), cetrylidenecannabis (7) and iso-THCs (8), (9) (Fig. 1). Under the same conditions when more of 2-carene epoxide was used major products were Δ^1-trans-THC and Δ^1-cis-THC (3). Similar results were obtained with 1% BF_3Et_2O in methylene chloride.

It was interesting to note that cannabidiol (11) was

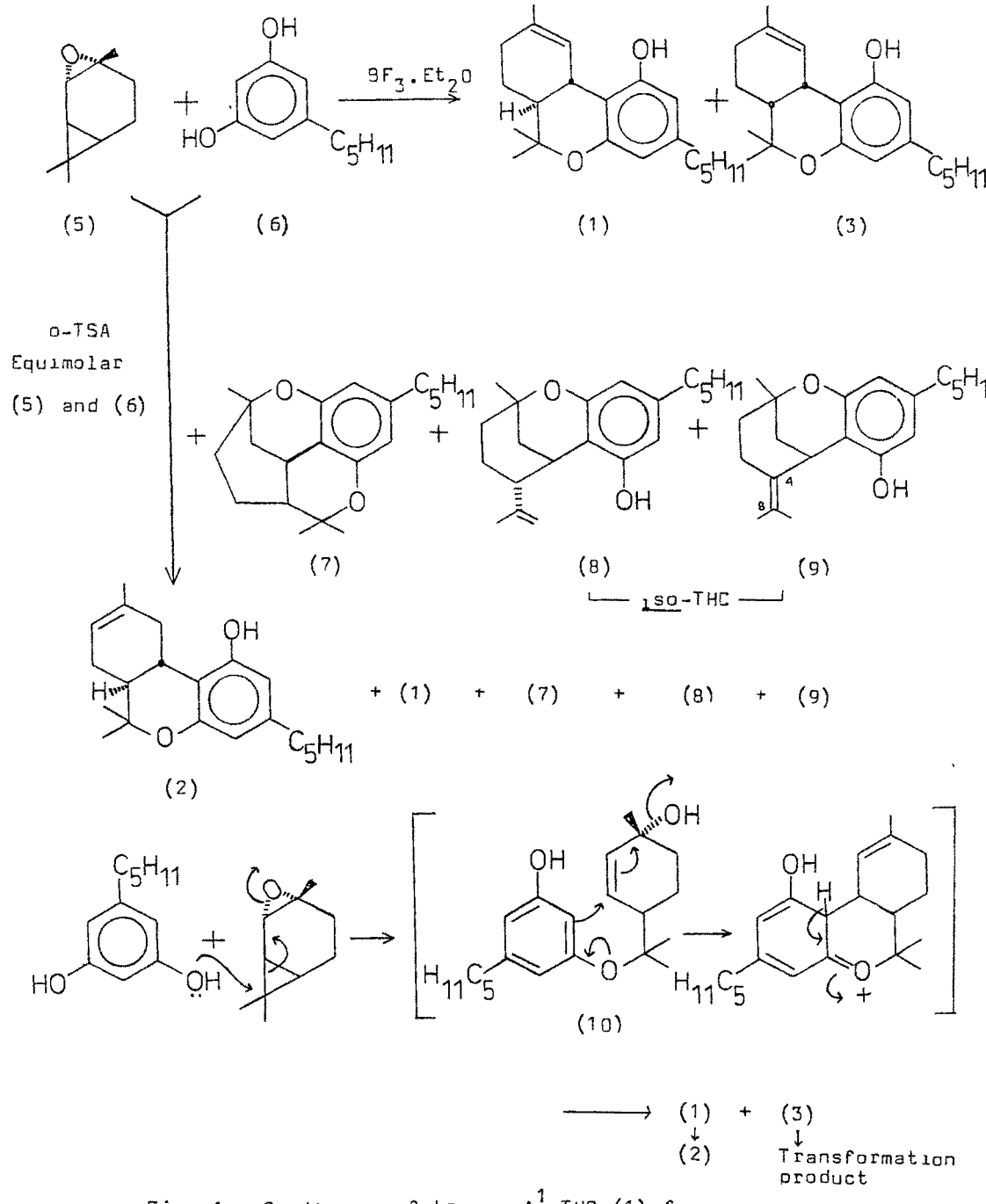
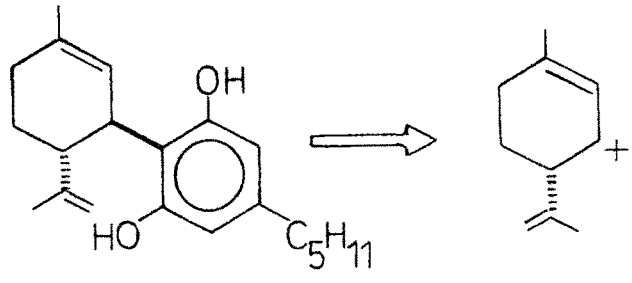


Fig. 1. Synthesis of trans- Δ^1-THC (1) from 2-carene oxide and olivetol

not formed in these reactions.* This suggested initial formation of trans- and cis- Δ^1-THCs which then got converted into their transformation products (Fig. 1).

Based on the above product spread, formation of Δ^1-THCs and their congeners was enucleated via an intermediate phenol ether (10), proposing operation of a distinctly different mechanism. On the other hand, comparable syntheses[12,13] predict the involvement of cannabidiol (11) and hence of 'ion C' (12).



Cannabidiol (11) Ion C (12)

However, it was not possible to comment with any reasonableness about the very existence of (10), which then awaited experimental evidence.

In this regard, our previously reported transformations of 2-carene epoxide by R.S. Prasad and S. Dev[14] prompted us to

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* In a recent publication [J.Chem. Soc. Perkin Trans. I, 1243 (1988)] it has been shown that the reaction between (5) & (6) under p-TSA condition generates cannabidiol (11). This is contrary to the Ref. 11 and invokes the intermediacy of cationic species (12). However, the correction does not have any bearing on our results which clearly show formation of O-alkylated products (15) and (22) (vide infra), under Lewis acidic conditions.

investigate more closely the formation of (10), under controlled conditions. It has been demonstrated that epoxide (5) on exposure to silica gel (chromatographic conditions) furnishes cis-Δ^2-p-menthen-1,8-diol (13). The diol is formed due to the generation of tertiary carbocation, which is quenched by a molecule of water present on the solid matrix. It is reasonable to assume that if one provides suitable nucleophile at this stage of developing C^+ ion instead of H_2O, corresponding substitution product would be obtained. Olivetol would then furnish required intermediate (10) (Fig. 2). It is pertinent here to mention that SN^1 reactions do not require powerful nucleophiles.[15]

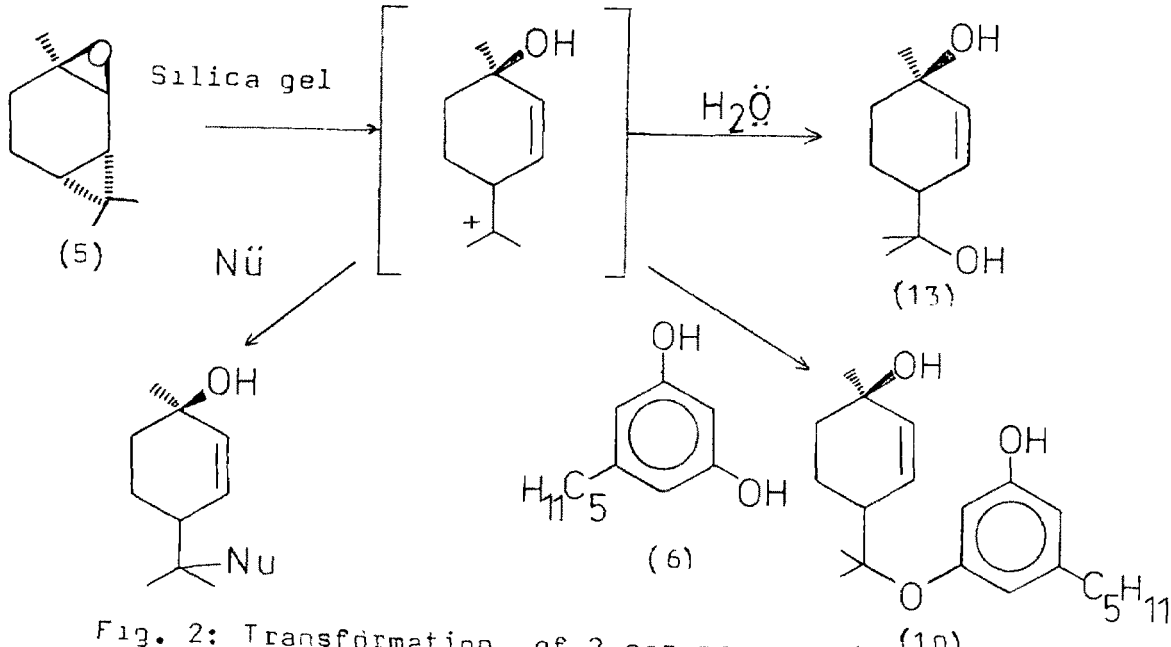


Fig. 2: Transformation of 2-carene epoxide

STRATEGY

Dreiding model of the intermediate (10) clearly points at its well-set functional and spatial juxtaposition to undergo facile intramolecular Friedel-Crafts alkylation, under favourable conditions.[16]

Theoretically, the possible enhancing effect towards such a process can, though partially, be attributed to the 'para-activation' rendered by n-pentyl chain[17] in making (10) more prone to ring closure.

In order to obviate this aiding factor to instability, it was thought to run the theme on a model phenol-resorcinol (14) and trans-2-carene epoxide to obtain intermediate (15) (Fig. 3).

For this purpose, reactants were permitted to interact, in sequence

1) under neutral conditions, i.e.
   a) in aprotic polar solvents
   b) under the conditions of thermolytic opening.

and 2) Lewis acidic environment -
   a) on solid matrix - dehydrated silica gel
   b) with the organometallic reagent.

Optimum conditions thus appraised were then decoded for the targeted reaction.

RESULTS AND DISCUSSION

In the present endeavour, as a first target, strategy was explored on the model reaction between resorcinol and trans-2-carene epoxide to furnish intermediate (15) (Fig. 3, Eqn. 1). Efforts towards this end are described.

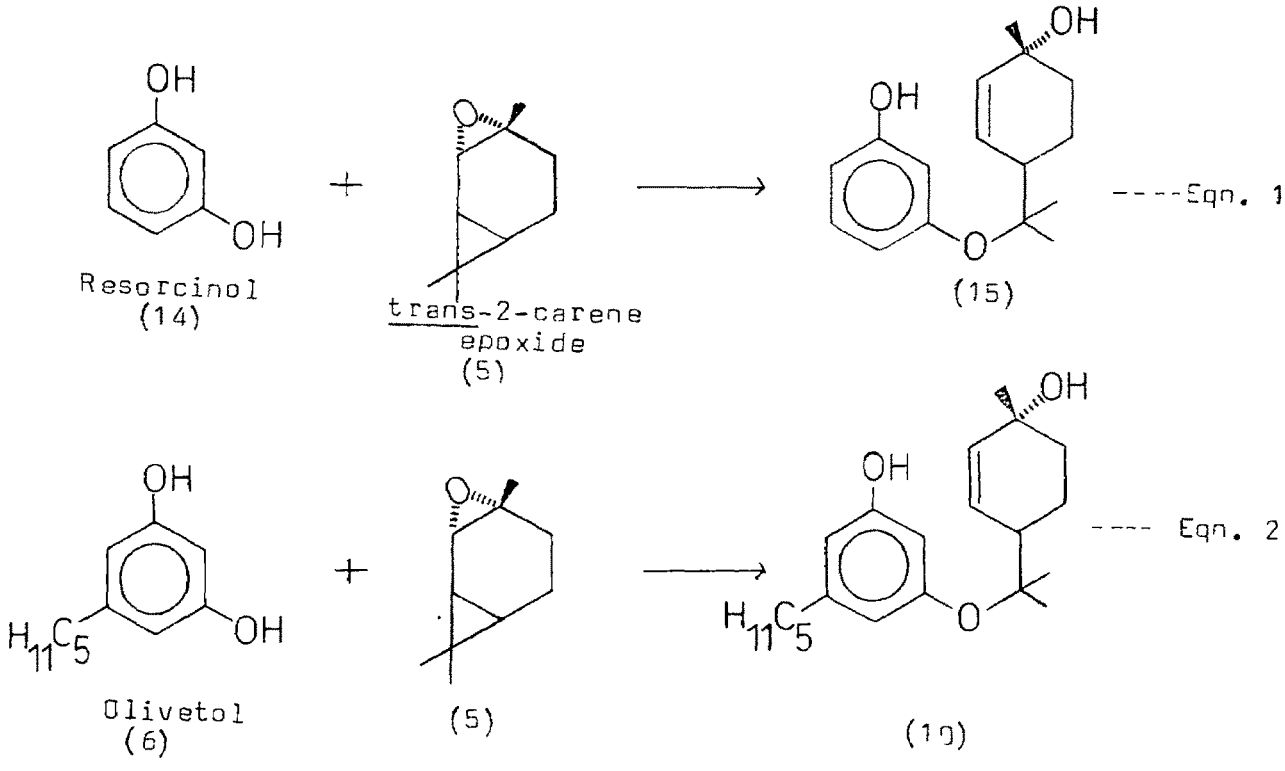


Fig. 3: Model and targeted reactions

2-Carene epoxide required for this purpose was prepared from Δ^2-carene and peracetic acid[14] in cold by scavenging acetic acid formed with powdered potassium carbonate. In certain cases peracetic acid has decided advantage over perbenzoic acid or monoperphthalic acid because both the peracid and corresponding carboxylic acid are volatile and can be readily removed.

The analysis of mechanism in equation 1 (Fig. 3) reveals that the formation of (15) is triggered primarily by oxirane ring opening (Fig. 4). Process gives rise to a thermodynamically,

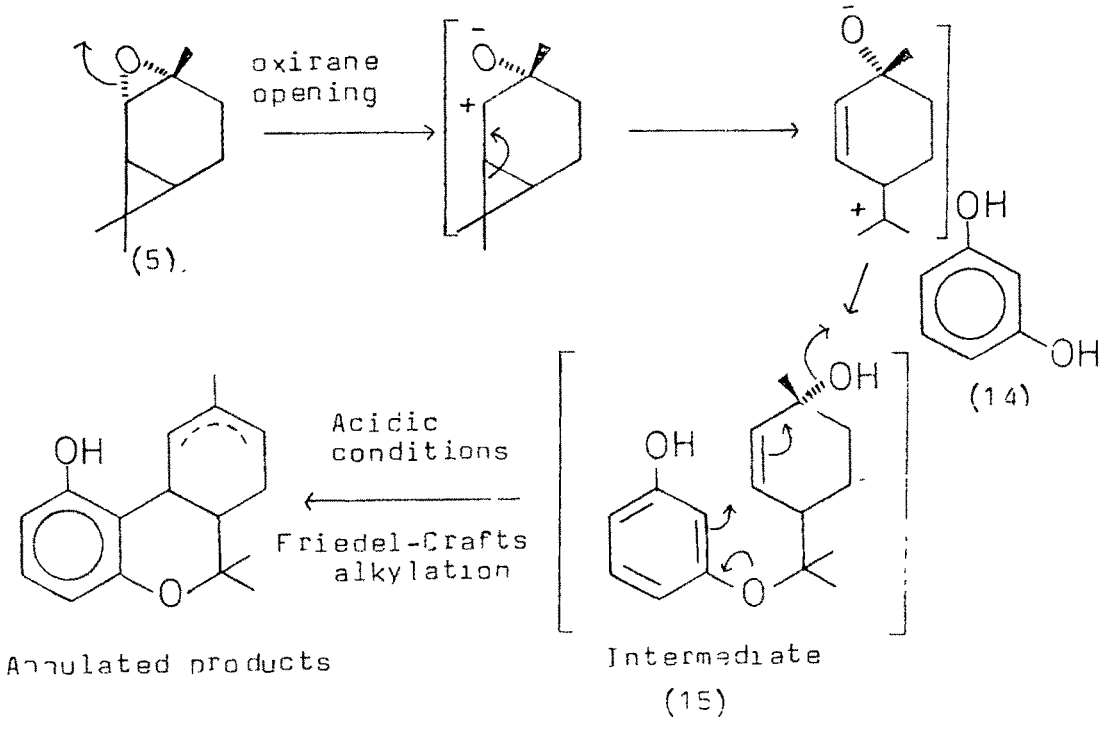


Fig. 4: Mechanism of formation of intermediate (15)

more stable tertiary C^+ due to allylic participation of cyclopropane ring[18] [$(CH_3)_2\overset{+}{C}H$=66 Kcal/mol, $(CH_3)_3-C^+$ = 84 Kcal/mol] [19]. Resorcinol then can attack C^+ ion in the formative stage, to give phenol ether (15).

It is understandable that the successful isolation of (15) - a tertiary allylic alcohol, will depend essentially on reaction conditions, which for obvious reasons must be neutral. Here, the intrinsic acidity of phenolic moiety[20] was thought just sufficient to initiate epoxide opening under neutral conditions.

1. Reactions under neutral conditions

a) Studies in aprotic polar solvents. It is well-known that reactions involving carbonium ions are solvent dependent[21] and can divert the normal reaction pathway. In order to favour 'borderline ionic mechanism' of epoxide opening,[22a,b] tetrahydrofuran and dioxane were chosen, which are the solvents of good nucleophilic solvating power (THF-Lewis basicity = 142 and Dioxane-Lewis basicity = 129).[23] In such a medium cationic species were expected to be solvated and hence relaxed. Another basis for the selection of the above solvents was to outweigh competing C-alkylation concerning ambifunctional phenoxides. Reported data shows over 98% O-alkylation in tetrahydrofuran and 1,4-dioxane.[24]

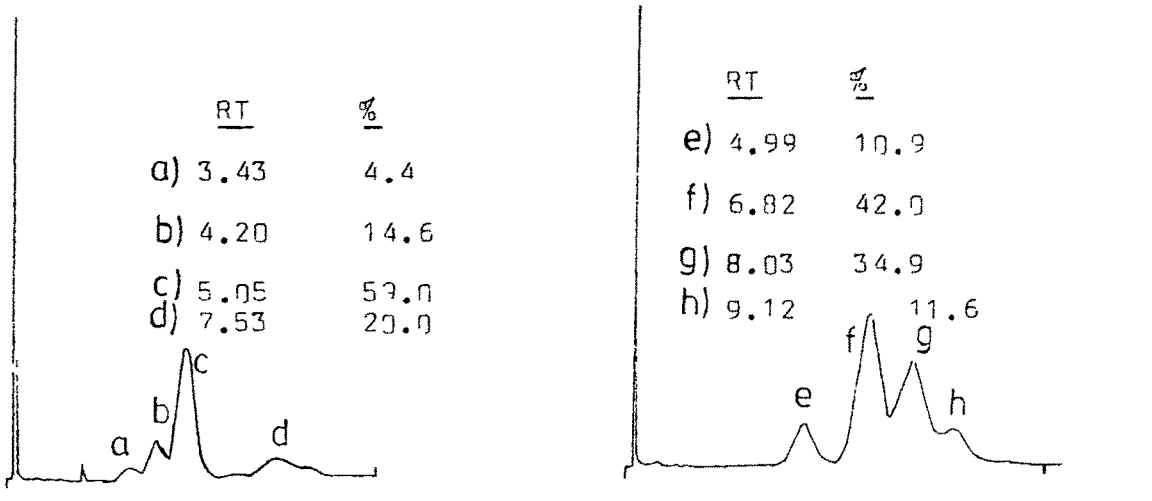
Therefore, 2-carene epoxide and resorcinol were allowed to react at room temperature ($30^{o}C$) in these solvents. However, no reaction was observed. Refluxing in THF ($65^{o}C$) or dioxane ($101^{o}C$) even for prolonged time (24 hr) did not show any reaction. This summoned forth another approach.

b) Attempted thermolytic opening. Three-membered rings have great deal of angle strain [25] since 60^{o} angles represent a large departure from the tetrahedral angle of 109.5^{o}. Therefore,ethylene oxide is quite reactive than other ethers (strain energy = 13 Kcal/mole).[26] Likewise, cyclopropane which is even more strained (heat of combustion/ CH_2 group = 166.3 Kcal/mol)[27] than ethylene oxide, undergoes thermal opening at 450 to $500^{o}C$.

Ease of pyrolysis in the case of conjugated olefinic epoxides over their normal counterparts can be attributed to the π-participation, as observed for benzylic epoxides.[28] Similar anchimeric assistance can be expected from cyclopropane[18] because the bonding orbitals have more 'p character' (33%) and behave in some respects like double bonds.[29] Hence the situation in 2-carene epoxide can be considered complementary, though with limitations, to allylic epoxides and should ease thermolytic opening.

In light of the above discussion, neat epoxide and azeotropically dried resorcinol were allowed to fuse (to provide better proximity) rapidly, in a pyrex tube at 120°C (oil bath). Reaction mixture was stirred magnetically under inert atmosphere. Epoxide disappeared completely in 3 hr and two major products (R_f: 0.56 and 0.46, 20% EtOAc in petroleum ether; spray: anisaldehyde in sulphuric acid) could be seen on chromatoplate.

Products were isolated by flash chromatography over silica gel in fair TLC purity. However, their silyl ethers on GLC probe (10% DV_4, 190°) revealed each to be a mixture of at least 4 components (Fig. 5). This clearly indicated formation of difficult-to-separate mixture.



Silyl ether of frac. (11-19)

Silyl ether of Frac. (23-26)

Fig. 5: GLCs of silyl ethers of frac. (11-19) and Frac. (23-26) (R_f: 0.56 and 0.46 respectively from the fusion reaction between 2-carene epoxide and resorcinol

In order to trace the desired product (15), albeit small, the above mixtures were set for ^{1}H-NMR analysis. Singlet at 1.7δ in both the spectra for olefinic methyl protons, was indicative of the products ensuing from side reactions like, mere epoxide opening or ring closure.

The failure led to try Lewis acidic conditions.

2. Reactions under Lewis acidic conditions

a) Nucleophilic opening on solid matrix-dehydrated silica gel. The inherent polarity and strain of the oxirane ring makes it susceptible to the reactions with a large number of reagents.[30-33] We were especially interested in the reactions of nucleophilic ring opening of more functionalized epoxides like 1,3-diene monoepoxide,[31] which can be viewed functionally equipoised with 2-carene epoxide (Fig. 6). The former has potential to give three different addition products (Fig. 6).

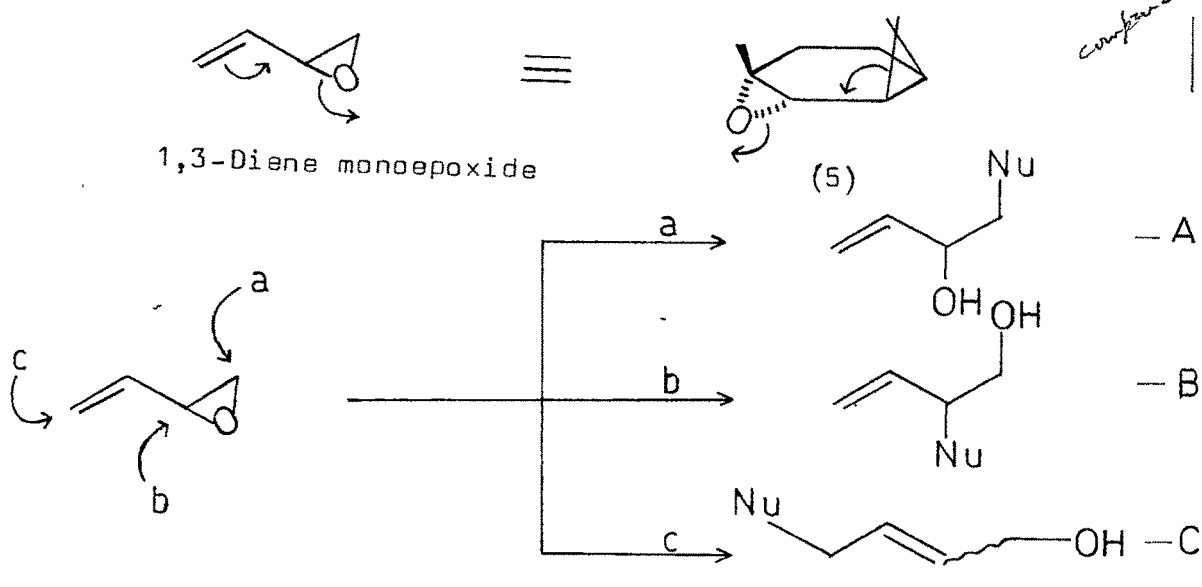


Fig. 6: Different paths of nucleophilic opening of 1,3-diene monoepoxide.

Out of these, path C would provide intermediate from 2-carene epoxide. The factors which favour this course are less clear and, many times 1,2- and 1,4-addition mixtures are obtained[34a,b], though superlative 1,4-adduct control has also been shown[35] in some cases.

A comparative survey of available methods under the reciprocal precinct brought out reactions of nucleophilic epoxide opening under heterogeneous conditions (neutral alumina or silica gel),[14,36] which are further extended to vinyl epoxides.[37] The method has two-fold advantage.

1) Reactions in heterogeneous medium can be carried out under very mild conditions with nonpolarizable oxygen and nitrogen nucleophiles.[38]

2) The Lewis acidity of solid matrix can aid oxirane ring opening.

The disadvantage was, 1,2-disubstitutions were generally observed contrary to homogeneous conditions. However, from the mechanistic point of view, the situation be restricted in the case of 2-carene epoxide for other paths a and b (Fig.6). This is because, the course of oxirane ring opening is solely dictated by the concomitant collapse of the strained cyclopropane ring giving rise to a tertiary C^+ ion, providing better possibility for 1,4-addition.

Therefore, it was reasoned that, by making judicious use of solid matrix doped with the required nucleophile-resorcinol, would furnish the required intermediate.

Super dry silica gel (grade I)[39] was called for as the heterogeneous medium because alumina is known to catalyze decomposition of many organic compounds,[40] causing artifacts among the chemically sensitive compounds.[39] And silica gel essentially behaves as a matrix with electron acceptor sites[41] due to embedded Lewis and Brønsted acidic sites.

In practice, resorcinol doped over dehydrated silica gel (grade I) and 2-carene oxide were stirred in dry petroleum ether (to maintain concentration of resorcinol at the reaction site, i.e. SiO_2-gel surface) under perfectly anhydrous conditions (transfer of materials in the glove box under dry N_2). In 12.5 hr at 30°C epoxide completely disappeared. Reaction was worked up to give brown gum. Product was segregated into phenolic and non-phenolic portions by usual procedure. Phenolic fraction after silylation was examined by GLC. GLC profile showed complex pattern. Resorcinol contents were ~69% while other 3 components were in minor quantities (Fig. 7). This precluded the possibility of intermediate isolation in acceptable yields. Neither there appeared a prominent spot on TLC, for the intermediate (15) at the surmised R_f (just above resorcinol).

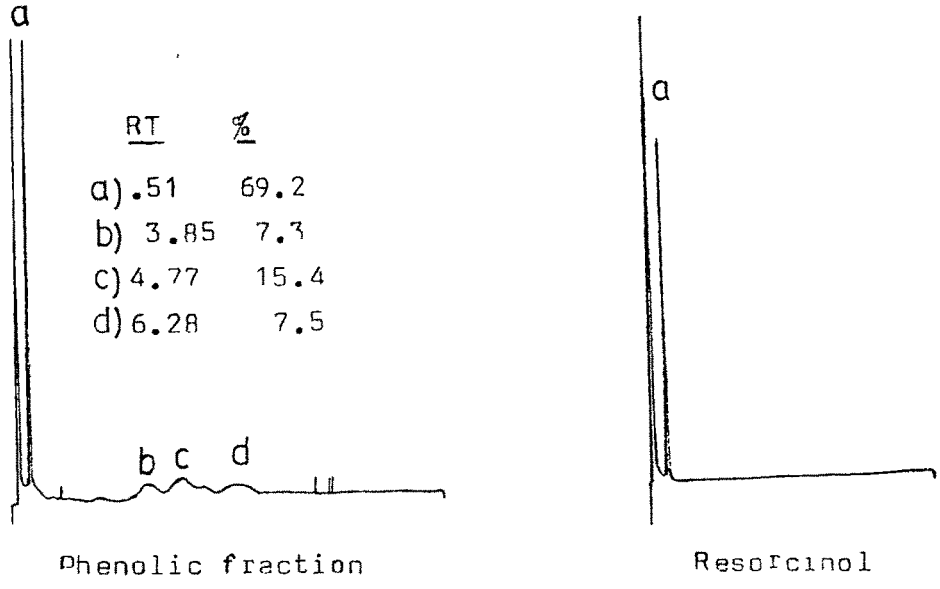


Fig. 7: GLCs of silyl ethers of phenolic fraction from the reaction on solid matrix - silica gel and resorcinol

After this unsuccessful outcome, conceptually different approach was contemplated.

b) Reactions with organometallic reagent. The reactions of 1,3-diene monoepoxides with a variety of organometallic reagents have been carried out for comparative investigations.[42a,b]

Y. Yasuda et al.[35] have highlighted the specificity of 1,4-addition to vinyl oxiranes with organoaluminium reagent-dietnylaluminium benzenethiolate (Fig. 8). The eminent selectivity

producing mainly Z olefinic alcohol was explained implicating cyclic transition state (D), as has been shown for the conjugate addition of diisobutylaluminium hydride to vinyl oxiranes.[43]

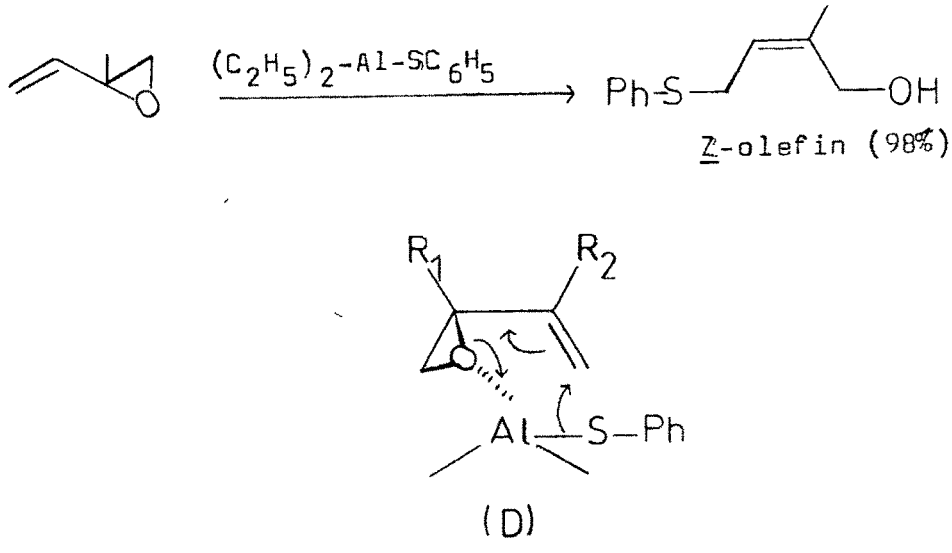


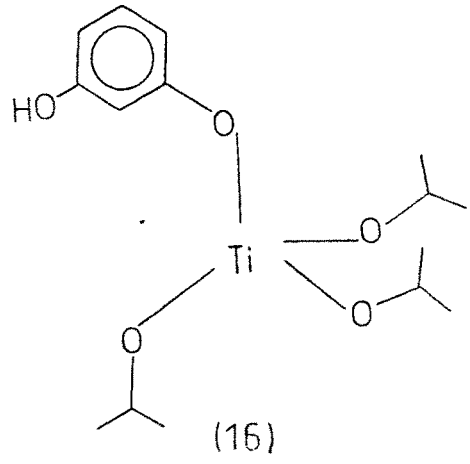
Fig. 8: Amphoteric action and specificity of organoaluminium reagent

It is understandable that these amphoteric reagents[44] can readily react with the ambident substrates like epoxides. Here metal atom serves primarily as a co-ordination site for epoxide oxygen due to its oxiphilicity at one end, with a subsequent nucleophilic attack at the other.

It has been discerned that the concept of ambiphilic systems as in aluminium should be equally applicable to other organometallic reagents of magnesium, boron and titanium.[45,46,47]

Amongst these, choice for organotitanium reagent was considered worthwhile for further exploration. One notable advantage in organotitanium reagents is the ease in preparative method from the readily accessible derivative of tetravalent titanium,[48] like tetraisopropoxy titanium. The actual reagent is many times generated in situ & protected from moisture because of the sensitivity towards stronger ligands like water, which destroy them to oxidehydrates and eventually to titania (TiO_2).

The reagent species like resorcino-triisopropoxy titanium (16) would be endowed with the ambiphilic character in which oxiphilicity is provided by the central titanium atom, through its available d-orbitals (Ti-ground state electronic configuration-$3d^2, 4s^2$).[49]



(16)

The enzymes have similar amphoteric action on the substrate, arising from multifunctional group surface. Therefore,such reactions are hopefully neater, shorter and more efficient because of the specific conformational fit allowed on the reagent surface.

Some important chemical properties of $Ti(O\text{-}i\text{-}Pr)_4$ helped us believe to utilize it for the reagent preparation.

The chemistry of titanium alkoxide $Ti(OR)_4$ shows that bulky group - OR attached to the metal atom has a clear tendency to increase the reactivity of the reagent,[47] which would give chance to employ milder conditions. The X-ray structure analysis of $Ti(OEt)_4$ shows a tetrameric form or trimeric aggregation in dilute solution,[50] however with the branched alkoxides as in $Ti(O\text{-}i\text{-}Pr)_4$, monomeric species can be shown to predominate.[51] Thus the steric hinderance at the metal centre, which hinders aggregate formation, leads to a more reactive reagent,[47] but reduces Lewis acidity. The reduction in acidity would, quite rationally, provide better stability to the intermediate (15), which is a tertiary allylic alcohol.

As well titanium alkoxides are known to undergo exchange reactions with the alcohols and phenols.[47] Reaction is reversible and sets an equilibrium (Eqn. 3) which can be pushed to completion by distilling out R-OH from equilibrium mixture.

$$Ti(OR)_4 + R'\text{-}OH \overset{\Delta}{\rightleftharpoons} Ti(OR')_4 + 4ROH \quad \text{...Eqn. 3}$$

For example chloro-triisopropoxy-titanium reacts with phenol and azeotropical removal of isopropanol in refluxing toluene gives chloro-triphenoxy-titanium[52] (Eqn. 4).

$$Cl\ Ti(OCHMe_2)_3 + 3C_6H_5OH \longrightarrow Cl\ Ti(OC_6H_5)_3 + 3Me_2CHOH \text{ -Eqn. 4.}$$

With this background tetraisopropoxy titanium was used for, <u>in situ</u> generation of reagent. $Ti(O\text{-}i\text{-}Pr)_4$ for this purpose was obtained in laboratory according to the literature procedure[53] from $TiCl_4$ and dry isopropanol using gaseous ammonia as a base.

Thus in practice freshly distilled tetraisopropoxy titanium (1 mol. eq.) was exposed to azeotropically dried resorcinol (2 mol. eq.) in dry benzene under exclusion of water and oxygen. In the resulting deep red suspension[54] was injected 2-carene epoxide (1 mol. eq.) and stirred at room temperature ($30^{\circ}C$) for 6 hr. Substrates showed complete inertness (TLC analysis). Then it was slowly heated to a gentle reflux without azeotropic removal of isopropanol. At the reflux temperature ($78\text{-}81^{\circ}C$), epoxide was seen readily cleaving to products and vanished completely in 1 hr.

A plethora of products was formed, which is a typical of Δ^1-THC syntheses and there appeared a defined spot just above

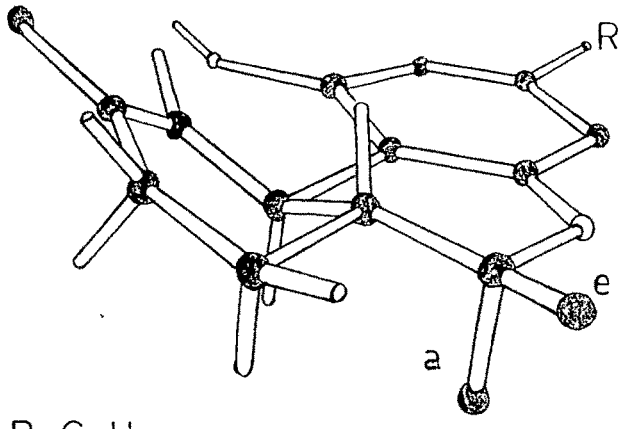
resorcinol at R_f: 0.24 (R_f of resorcinol : 0.18, 20% EtOAc in petroleum ether). Neutral hydrolytic[48] work-up under strictly controlled conditions furnished brick red gummy material. This was segregated into phenolic and non-phenolic portions. Flash chromatography of the phenolic fraction over silica gel (IIB) gave the aimed spot (7.0 mg, yield: 0.41%), after crystalization in 30% ethyl acetate in petroleum ether (m.p. 98-99°C).

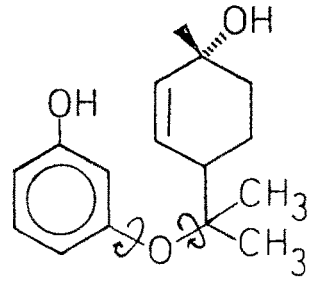
Indeed that it was the required intermediate (15) became clear from the spectral data. A diagnostic singlet in ^{1}H-NMR (Fig. 9) at 1.26δ of 3 proton intensity could be attributed to $C\underline{H}_3$-C-OH.

Presence of hydroxyl function was supplemented by strong OH stretching in IR[55] (Fig. 10) at 3310 cm^{-1} together with the absorption at 1140 cm^{-1} (O-H bending, tertiary alcohol) and 1215 cm^{-1} (O-H bending, phenol). ^{1}H-NMR in addition showed a peculiar pattern of two merged singlets (3H each) at 0.96 and 1.04 δ for O-C $(C\underline{H}_3)_2$. These values for gem-dimethyls can be rationalized as follows:

In the case of Δ^1-THC (1) corresponding gem-dimethyls resonate at 1.08 and 1.38 δ (Fig. 11).[56]

This is due to the fact that in a rigid 6 membered dihydropyran system in (1), one of the methyls is forced to assume an





(15)

Fig. 11: Dreiding model picture of Δ^1-THC (1)[57]

equatorial position and hence due to the deshielding cone[58] shifts downfield. On the contrary in intermediate (15), free rotation along -C-O-C-bond is possible (Fig. 12) which can give both the methyls a reasonable magnetic isotropy to allow close resonance.

Aromatic protons at 7.4-6.9 δ (m, 1H) and 6.7-6.3 δ (m, 3H) displayed m-disubstituted phenyl pattern. A two proton multiplet at 5.8 to 5.32 δ could be assigned for olefinic protons. Tertiary alcoholic proton at 2.66 δ (bs, 1H) could be D_2O exchanged while in case of phenolic-OH (4.43 δ, bs, 1H), it was partial, probably due to strong hydrogen bonding[59]. Further, structure assignment became unambiguous because of other analytical data, compatible with the structure (15).

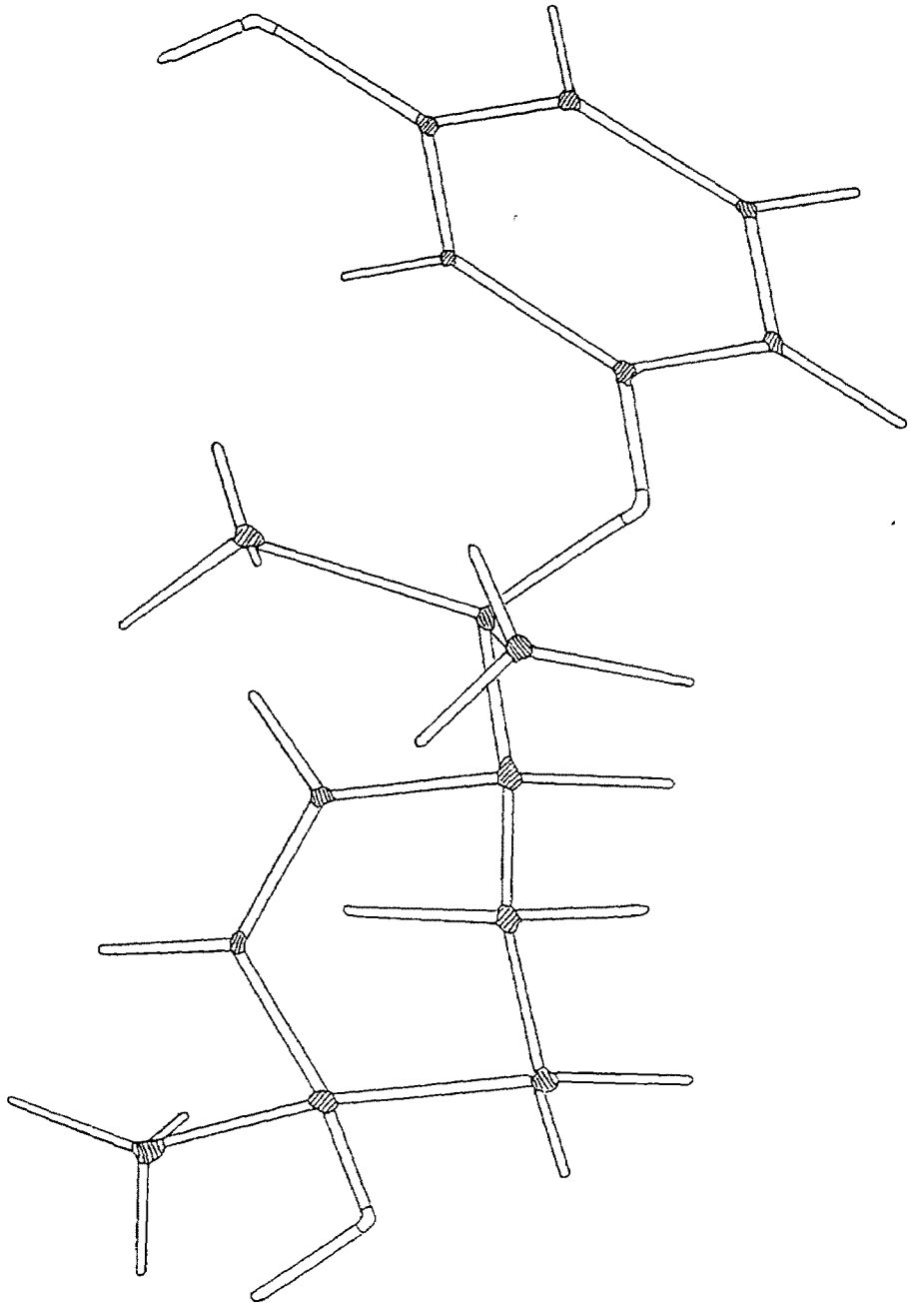


Fig. 12: Dreidimd model picture of intermediate (15)

IR: 1660 cm^{-1} (C=C stretch, disubstituted cis), 685 cm^{-1} (C-H bend, cis olefin); Mass: M^+ 262 (Fig. 13); Rt : silyl ether: 8.24 min. (Fig. 14) (10% OV4, 190°C).

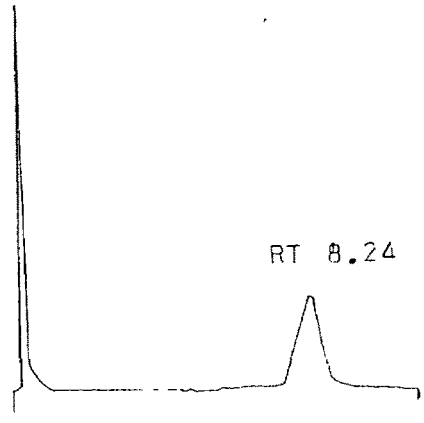


Fig. 14: GLC of silyl ether of (15)

From the above flash chromatography no other compound could be obtained in analytical purity. However, a fairly pure fraction (R_f: 0.44, 20% EtOAc in petroleum ether) on ^{1}H-NMR probe exhibited sharp singlet at 1.67 δ (CH_3-C=C) representing competitive unwanted reactions like annulation.

Further investigations were carried out for the improvement in yield of the intermediate. As a first step, reaction conditions were optimized. A smooth reaction was observed even at 65-70°C (pot temperature) and went to completion in 40 minutes. Then following four sets of experiments were performed with different stoichometries of resorcinol, 2-carene oxide and $Ti(O\text{-}i\text{-}Pr)_4$. Reactions were carefully worked up by neutral hydrolysis (20% aqueous KF). Direct silylation of these crude products under anhydrous conditions furnished silyl ethers. These ethers were readily analyzed on GLC (10%, OV4, 190°C) to give the percentage of intermediate.

Table 1. Experiments with different stoichometries of reactants and GLC percentage of intermediate (15) after silylation.

Expt. No.	Resorcinol mole eq.	Epoxide mole eq.	$Ti(O\text{-}i\text{-}Pr)_4$ mole eq.	GLC % of silyl devt.
1	2	1	1	40
2	2	1	0.25	41
3	1	2	0.25	26
4	1	1	0.25	43

The best yield was obtained when the molar ratio of 1 (resorcinol) : 1 (epoxide) : 0.25 [$Ti(O\text{-}i\text{-}Pr)_4$] was used.*

Having succeeded in the model studies, efforts were directed to explore the possible role of organometallic reagent in the intermediate formation.

Probable mechanism of intermediate formation via organotitanium reagent

A blank experiment: As first step towards this end a blank experiment was conducted in which 2-carene epoxide and resorcinol in a molar ratio 2:1 were allowed to react in refluxing benzene under dry nitrogen. There was no reaction even after 6 hr. This led to the next experiment.

The effect of $Ti(O\text{-}i\text{-}Pr)_4$ on 2-carene epoxide:

Equimolar ratios of epoxide (5) and $Ti(O\text{-}i\text{-}Pr)_4$ were heated in refluxing benzene under identical conditions. TLC monitoring revealed almost no reaction during 6 hr, but a complete decomposition of epoxide could be seen in 16 hr. The experiment, though implies some products arising solely from

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* Surprisingly, GLC peak corresponding to (15) requires 30-40% yield, though only ~1% yield of the crude intermediate was obtained. This indicates that some other compounds in the reaction product have same retention time as that of (15).

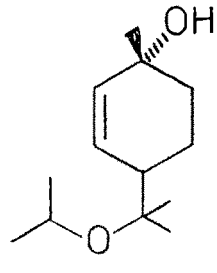
It may also be noted that no internal standard was used for quantitative estimation. Therefore it is likely that non-volatile impurities are retained on the column; thus accentuating the percentage of intermediate.

epoxide opening due to $Ti(O\text{-}i\text{-}Pr)_4$, kinetics being very sluggish become comparatively insignificant.

The above experiments concluded no major impact either due to resorcinol or $Ti(O\text{-}i\text{-}Pr)_4$ alone, on 2-carene epoxide in refluxing benzene. This envisages the requirement of togetherness of epoxide, resorcinol and tetraisopropoxy titanium in the matrix for the induced enhancement in kinetics.

Another alternative could not be absolved in which reaction was thought to proceed just by the activation of oxirane with $Ti(O\text{-}i\text{-}Pr)_4$ followed by the attack of nucleophile-resorcinol. To obviate this possibility the third experiment was performed.

Effect of isopropanol as a nucleophile: 2-Carene oxide, $Ti(O\text{-}i\text{-}Pr)_4$ and dry isopropanol in molar ratio 1:0.25:1 respectively were maintained at the reaction temperature (65-70°C) in benzene for 6 hr. Corresponding product (17) was expected. But no reaction commenced ruling out the above

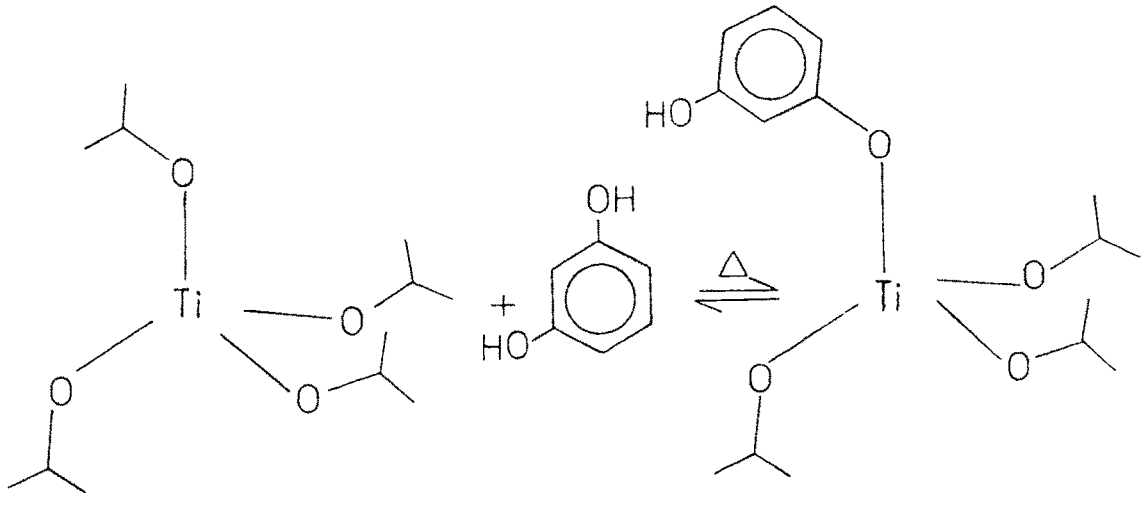


(17)

contention.

On these observations, process arising from the interaction of 2-carene oxide, $Ti(O\text{-}i\text{-}Pr)_4$ and resorcinol can be envisioned.

Tetraisopropoxy titanium can react with resorcinol in refluxing benzene by a number of theoretical ways to furnish parallel organotitanium reagent species such as (16), (18), (19) and (20) (Fig. 15).



(21) (14) (16)

+ i-PrOH ---- Eqn. 5

$(i\text{-}PrO)_2\text{-}Ti\text{-}(O\text{-}C_6H_4\text{-}OH)_2$ $i\text{-}PrO\text{-}Ti\text{-}(O\text{-}C_6H_4\text{-}OH)_3$

(18) (19)

$Ti(O\text{-}C_6H_4\text{-}OH)_4$

(20)

Fig. 15: Formation of organotitanium reagent species.

All these species can have equivalent catalytic effect on the reaction as explained later for (16).

However, under reversible conditions (Fig. 15, Eqn. 5), free isopropanol in the medium can interact instantaneously with resorcino-titanium species to displace resorcinol moiety, which is in compliance with the order of nucleophilicity.[60] Therefore,it is reasonable to assume prepondarance of mono-substituted reagent species (16).* And in keeping with the known processes depending on the facile exchange of titanium alkoxide with alcohols,[61,62] one can expect catalysis from the reagent like (16).

A peculiar catalytic effect observed, was sought to be explained by invoking the possibility of 'Templet effect' (Fig. 16).

The amphoteric reagent (16) formed *in situ* can provide a templet wherein the reacting faces are held in the desired conformation with a binding site at the metal centre *via* $n\pi$-$d\pi$ donation[52,63,64] and a real active site at the -OH function of (16) which leads to a combined "acid-base attack".[65]

The phenomenon is known to affect profoundly the kinetics and specificity because of efficient preassembly of the reactants in highly ordered manner. This can also explain our earlier observation where isopropanol failed to act as a

*At the same time, resorcinol acting as a true bidentate ligand is imponderable under reversible conditions and hence can be discounted.

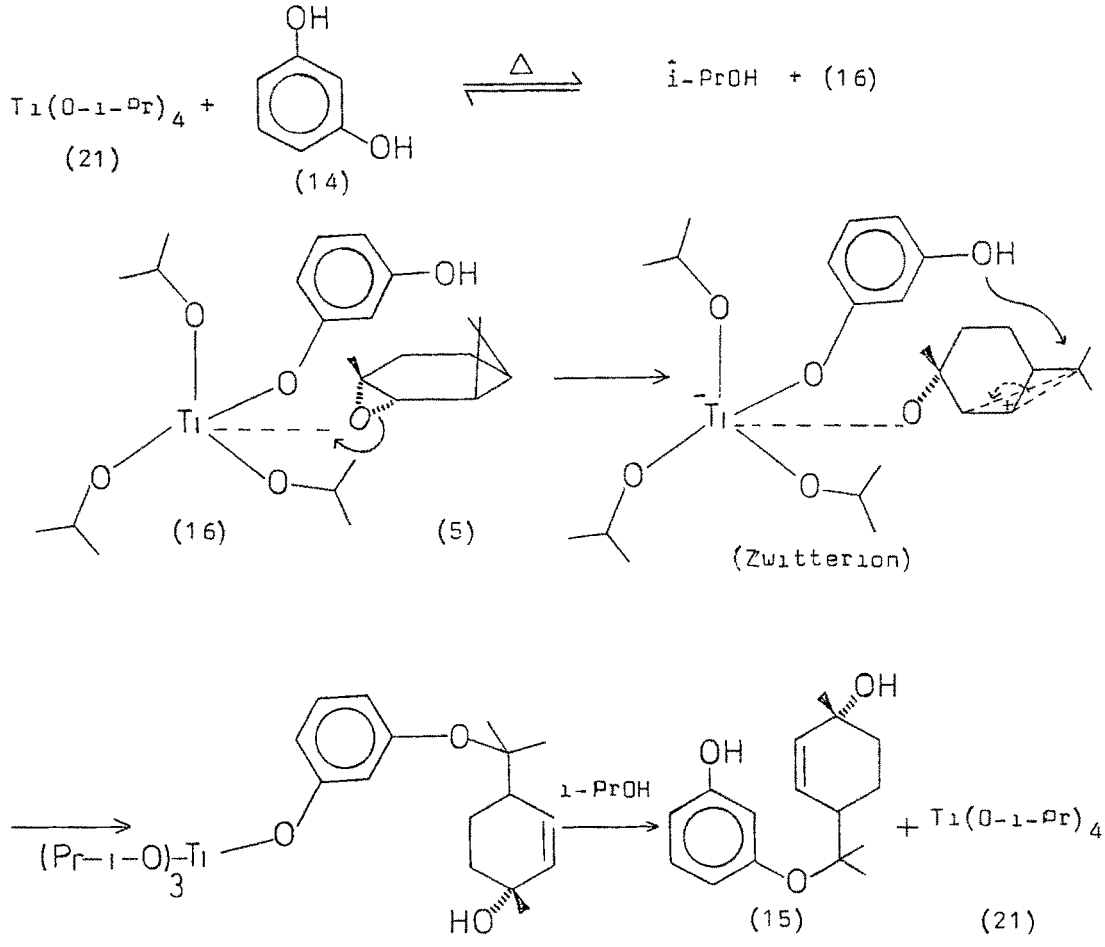


Fig. 16: 'Templet effect' of organotitanium reagent

nucleophile to furnish condensation product.

However, as in other cases it is difficult to say whether these processes are truly 'intramolecular'. Some of them probably are but others may as well involve clusters where a nucleophile co-ordinated at one metal is delivered to a carbocation developing at the adjacent metal centre (Fig. 17).

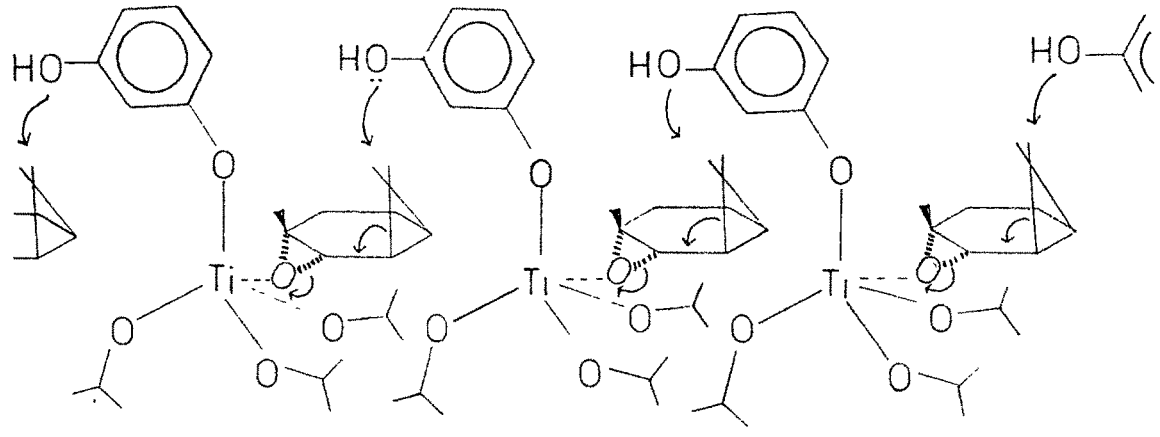


Fig. 17: Intermolecular interaction of the reagent

The latter possibility also might exist here, because the enforced propinquity is more assured in the structures when the reactive ends are dislodged in syn-periplanar manner.[66,67,68] In this case oxirane ring and cyclopropane are anti-periplanar.

In order to resolve the issue of templet still further, a unidentate ligand-phenol, was substituted for resorcinol. It was assumed to show no reaction, because in the corresponding templet OH function would not be available for the nucleophilic attack.

Epoxide, phenol and $Ti(O\text{-}i\text{-}Pr)_4$ in the molar ratio 1:2: 0.25 respectively were heated to 65-70°C under equivalent conditions. The reaction was over in 1.5 hr. Though TLC showed products of higher R_f as compared to phenol condensation products, it is difficult to reconcile this result.

At present, we can only speculate on the origins of enhanced kinetics of resorcino-triisopropoxy-titanium (16), a weak Lewis acid and 2-carene epoxide-a weak Lewis base. Examination of the putative templet suggests one attractive possibility which we have confirmed by Dreiding model.

Thus the first target was accomplished by proving the existence of intermediate (15). The approach was further decoded on the final objective (Fig. 3, Eqn. 2). For this purpose olivetol required was prepared by a new route as depicted in Section II.

Under previously optimized conditions 2-carene oxide, olivetol and freshly distilled tetraisopropoxy titanium in a molar ratio of 1:1:0.25 respectively, were allowed to react at 65-70° in benzene under exclusion of moisture and oxygen.

Epoxide was completely consumed in 1 hr. Typically, multitude of products ensued from the reaction. Reaction was worked up as usual under controlled and neutral hydrolytic conditions with 20% aqueous KF. Resulting red gummy product was segregated into phenolic and neutral portions. Phenolic fraction contained only olivetol. Neutral portion showed yellow spot just above olivetol of R_f 0.34 (20% EtOAc in petroleum ether) on spraying with anisaldehyde / sulphuric acid reagent (R_f of olivetol under identical conditions: 0.25). This required spot could be separated in analytical purity by initial broad separation by uniform-gradient elution,[69] followed by quick flash chromatography on silica gel (yield-3.2%).

That the product was O-alkylated was evident from the singlets in ^{1}H-NMR (Fig. 18) at 0.96 δ and 1.04 δ (3H each) for O-C-($C\underline{H}_3$)$_2$. A prominent singlet at 1.28 δ (3H) represented $C\underline{H}_3$-C-OH. Benzylic protons of pentyl side chain showed triplet at 2.51 δ (2H, J = 8Hz) while its terminal methyl got masked by gem-dimethyl singlets. However, spectrum showed only one proton integration in the olefinic region. This data coupled with the other ^{1}H-NMR signals completely matched with the structure (22). Some peculiar infrared absorptions are given below.

IR (neat) (Fig. 19): 3605, 3340 cm^{-1} (O-H stretch), 3020-2850 cm^{-1} (C-H stretch), 1665 cm^{-1} (C=C stretch, alkene trisubstituted),

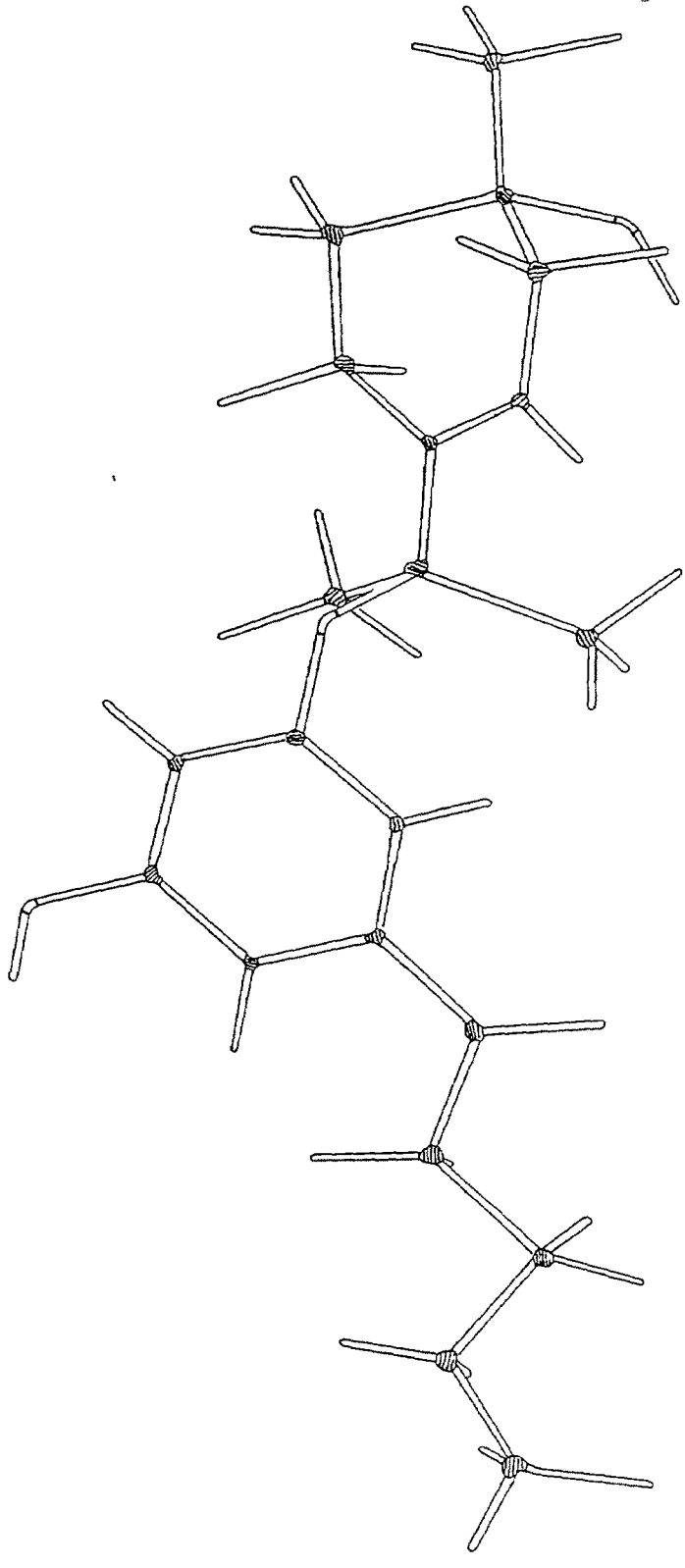


Fig. 21: Dreiding model picture of isomerized intermediate (22)

1600, 1460 cm^{-1} (C=C stretch, aromatic), 1390-1370 cm^{-1} (C-H in phase bend, gem-dimethyl), 1150 cm^{-1} (O-H bending, tertiary alcohol), 855 cm^{-1} (C-H bending, trisubstituted alkene).

Mass: (Fig. 20) M^+ 332 and microanalysis also make structure (22) a mandatory one (Fig. 21).

Observed 1,3-isomerization, in this case is not without the precedence in which greater thermodynamic stability is conferred to the molecule abiding 'Zaitsev's rule', (Fig. 22).

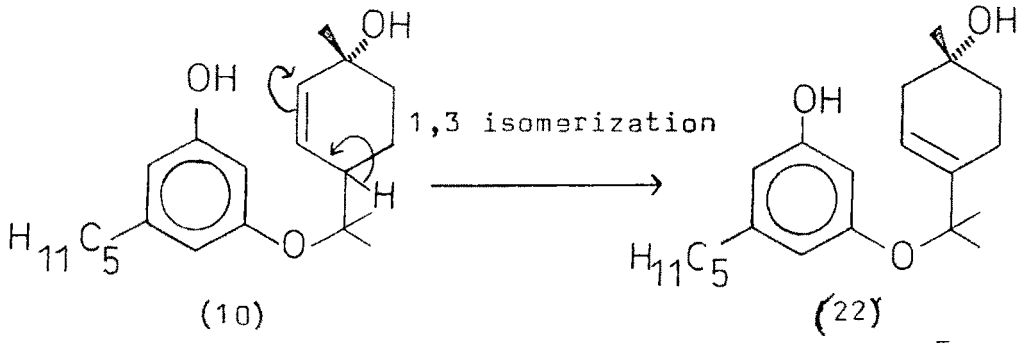


Fig. 22. Isomerization under Lewis acidic conditions

In the above reaction para-activation by n-pentyl chain was supposed to aid Friedel-Crafts alkylation in allylic alcohol[16] (10) to give cyclized products. But no such product could be obtained in isolable yields. Though this observation does not preclude the possibility of formation of such products, albeit in traces, the Lewis acidity of the

medium can be guessed insufficient to bring out such transformations to any significant extent.

The above experimental proofs appear to bear out intermediacy of (15) in the model sequence and of (10) in the reaction of 2-carene epoxide with olivetol. The latter undergoes facile isomerization to give more substituted olefin (22). Products in respective cases show O-alkylation and seem to bypass 'ion C'.

S E C T I O N - II

SYNTHESIS OF OLIVETOL

ABSTRACT

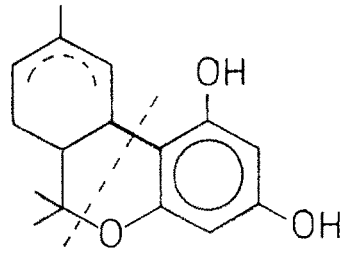
A facile synthesis of olivetol (6) employing 'Wittig olefination' as a key step, is reported.

Reductive 'demethoxylation led to record some mechanistic observations.

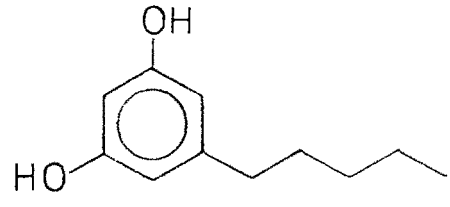
Thus olivetol was obtained in 52% overall yield with a modified approach parallel to that of K. Bailey.[70]

INTRODUCTION

With the upsurge of activity in the field of cannabinoids, their synthons have come to acquire greater attention by synthetists. This is especially true in the case of olivetol (6) which is almost an inevitable synthon in many synthetic designs[71] for natural cannabinoids or their biologically useful analogues.



Δ^1-or Δ^6-THC's



Olivetol
(6)

Reported syntheses

Olivetol (5-pentyl-1,3-benzene diol) was first obtained by Y. Asahina by degradation of lichen acid and olivetonic acid[72] and later number of routes were explored.[73] In general two strategies seem to circumscribe almost all approaches:

i) Starting with suitably functionalized acyclic molecules which are aromatized in terminating stages.[71,74]

ii) Utilizing aromatic precursors such as 3,5-dihydroxy benzoic acid on which n-pentyl chain is built.

The first approach from acyclic starting materials is apparently shorter. However, these specific compounds are generally required to be prepared in lab and hence the limitation.

Syntheses from aromatic precursors use either masked α-resorcylic acid (3,5-dihydroxybenzoic acid)[73,75,76,12b] or symmetrical trimethoxybenzoic acid/aldehyde.[70] Former in fact is expensive and not easily available. Likewise in the case of cheaper trimethoxy derivative, *in situ* 4-demethoxylation as Birch and Slabbe[75] pointed out, results in an inferior quality of olivetol. However, a prerequisite for the synthesis is the ready availability of the starting material and 3,4,5-trimethoxybenzaldehyde (23) was off-the-shelf. Therefore,concerned reported syntheses were studied.

Bailey's[70] approach appeared attractive which involves Grignard reaction on (23) with n-butylmagnesium bromide to give carbinol (24). Carbinol is simultaneously 4-demethoxylated and reduced in the side chain to give dimethoxybenzene by the action of dissolving metal in alcohol (Fig. 23).

Binary mixtures originate from Grignard reaction due to incomplete dehydration and need manipulation at later stages as shown.

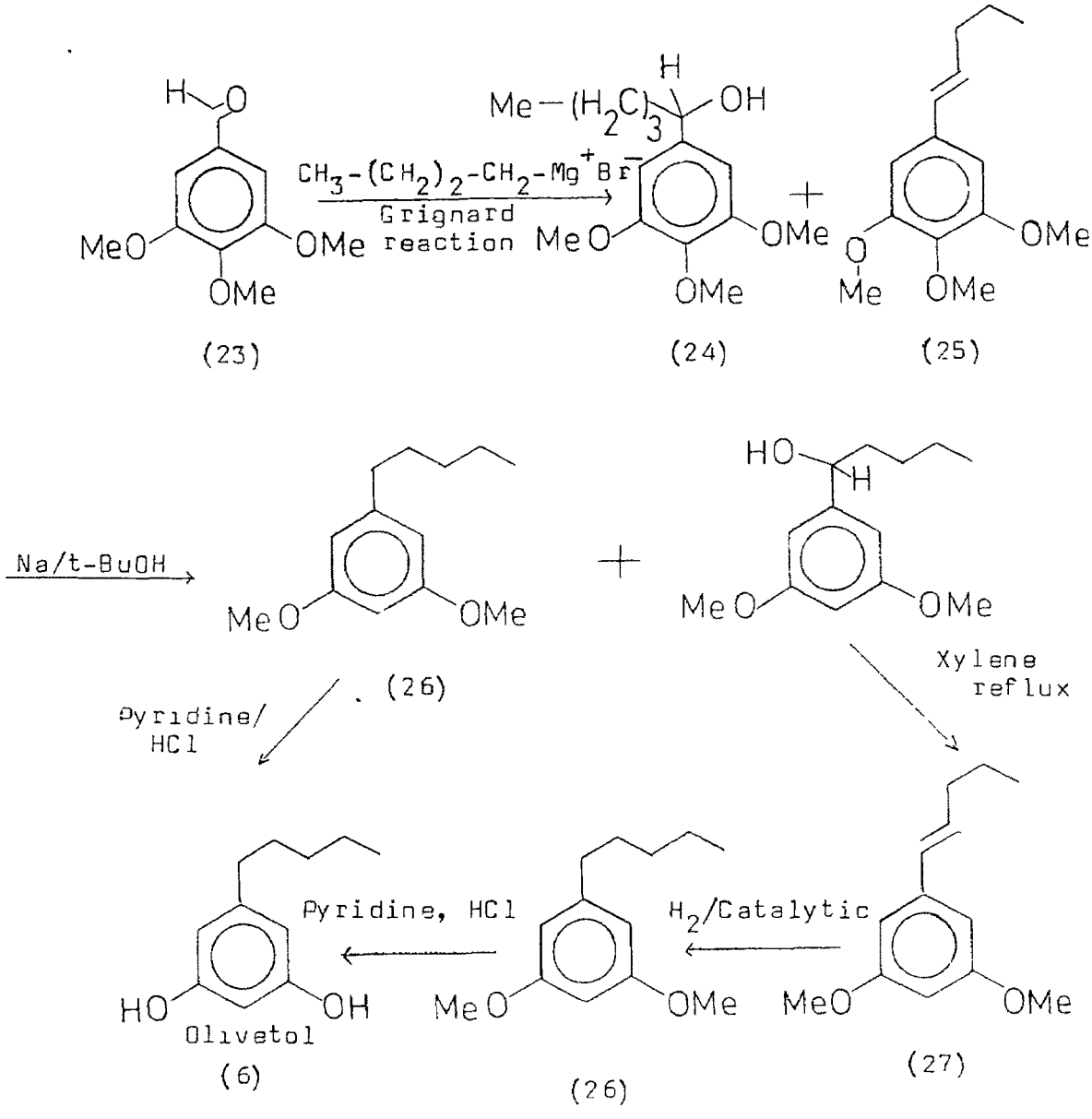


Fig. 23: K. Bailey's synthesis of olivetol (6)

Present synthesis

It was envisioned that constraints in the above sequence would get erased by 'Wittig olefination'. Hence the present synthesis was patterned as delineated below (Fig. 24).

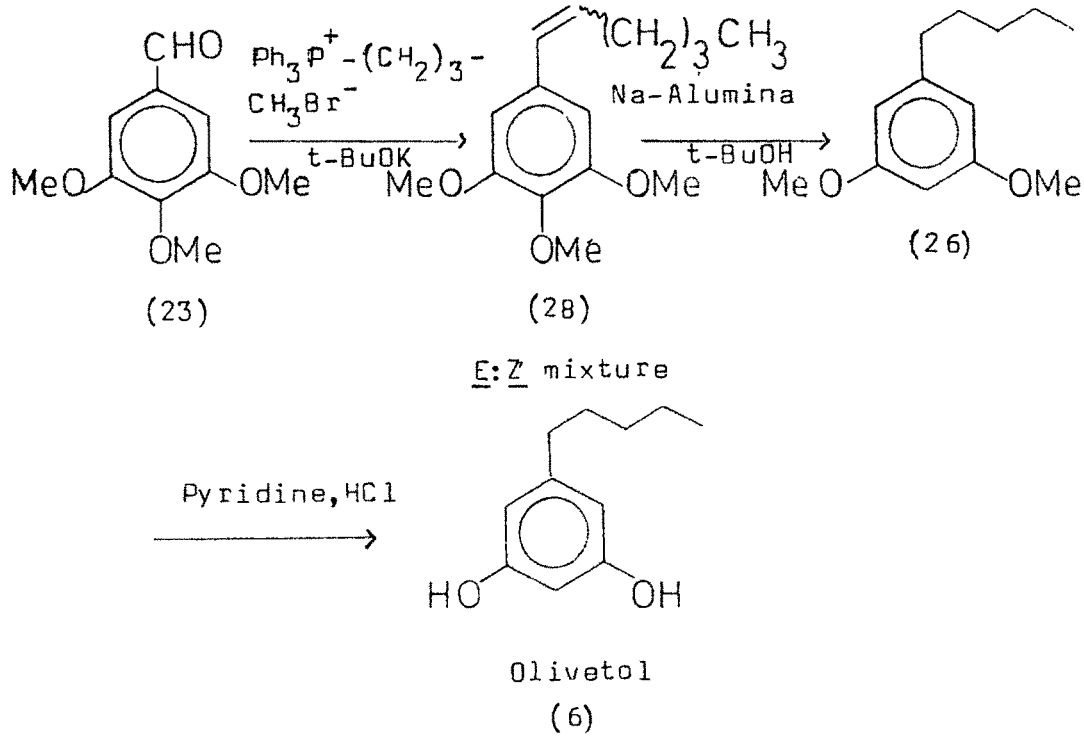


Fig. 24: Present synthesis *via* Wittig reaction

Reactions were carried out as described below.

Wittig olefination: For this purpose butyltriphenylphosphonium bromide was prepared by reported procedure.[77] For the generation of phosphorane *in situ*, potassium tertiary-butoxide could be used conveniently as a base in t-butanol as a co-solvent. In order to enhance the rate of reaction, a mixture of acetonitrile

and t-butanol was found suitable to give required homogeneity.

In the case of unstabilized ylide as ours, it is discerned that protonic polar solvents increase cis/trans ratio.[78] However, for us stereocontrol was unimportant because stereogenic centre was getting destroyed in the next step. Thus aldehyde (23) and corresponding ylide furnished crude Wittig product (28)[79] which after passage through silica gel column gave E/Z mixture in the ratio 73.7% to 26.3%, in 62% yield (GLC purity: + 99%; Rt : Z-isomer-2.32 min and E-isomer-3.16 min, 10% SE 30, 220°C).

Reductive demethoxylation: The next step involved simultaneous 4-demethoxylation and reduction in the side chain to give (26).

The process is essentially similar to the Birch reduction as illustrated for benzene to 1,4-dihydrobenzene[80] (32) (Fig. 25).

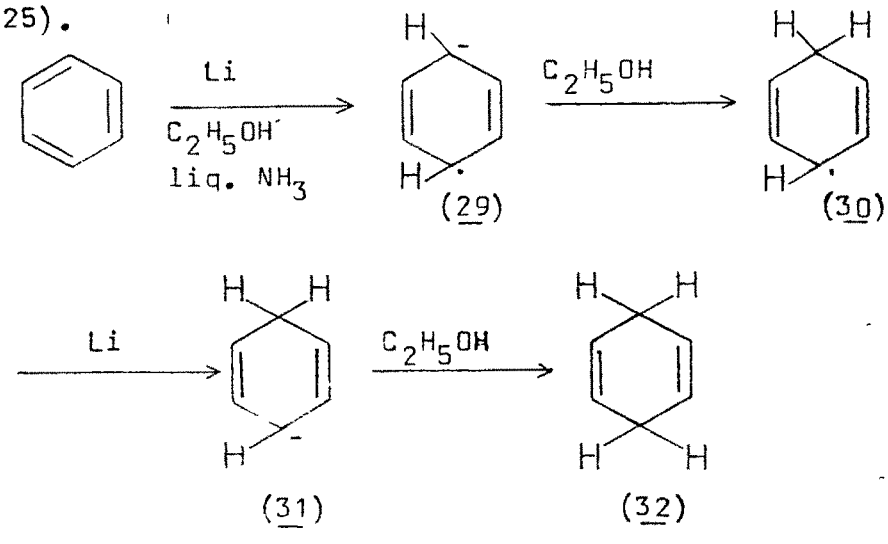


Fig. 25: Metal/alcohol reduction in liq. NH_3

The anion radical (29) is formed reversibly in low concentration and then reacts further with the protonic solvent to form radical (30) and subsequently the anion (31) and the dihydro derivative (32). Thus one important function of alcohol is to provide proton source. This is obligatory in view of the anion formed which is an insufficiently strong base. Stable 1,4-diene exemplifies the operation of 'principle of least motion'[81] proposed by Hyne. Formation of (26) from (28) with sodium metal and alcohol is explicable on parallel lines.

As initially reported by Asahina[82] and later explored by K. Bailey[70] for the same purpose, metal/alcohol procedure clearly indicated want of sodium sand over metal pieces. In spite of this increased availability of metal surface yield and purity of (26) was not satisfactory. In order to achieve expeditious results, molten sodium was uniformly dispersed on neutral alumina[83] (80-200 mesh). This reagent after estimation was used with t-butanol. A definite improvement in the reaction kinetics (reaction time:7 hr) was observed and product was obtained in 93.9% yield (GLC purity: 99.0%, R_t: 1.7 min, 10% SE 30, 220°C). The above reagent has not been used for such reductive demethoxylations.

During this reaction, it was interesting to note the formation and depletion of some products as described below. In an experiment (Expt. 1) in which reaction got interrupted because of power failure, aliquots were taken at regular intervals.

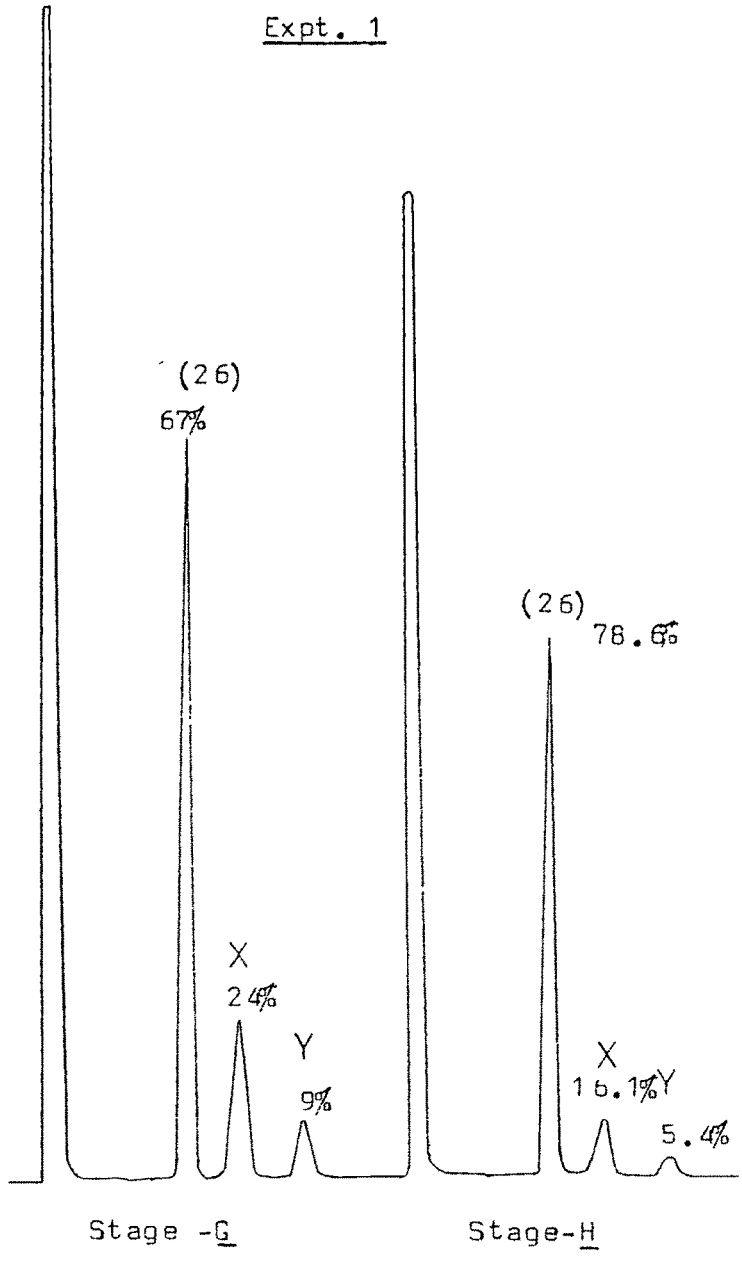


Fig. 26: GLCs of aliquots at stages G and H in 4-demethoxylation reaction

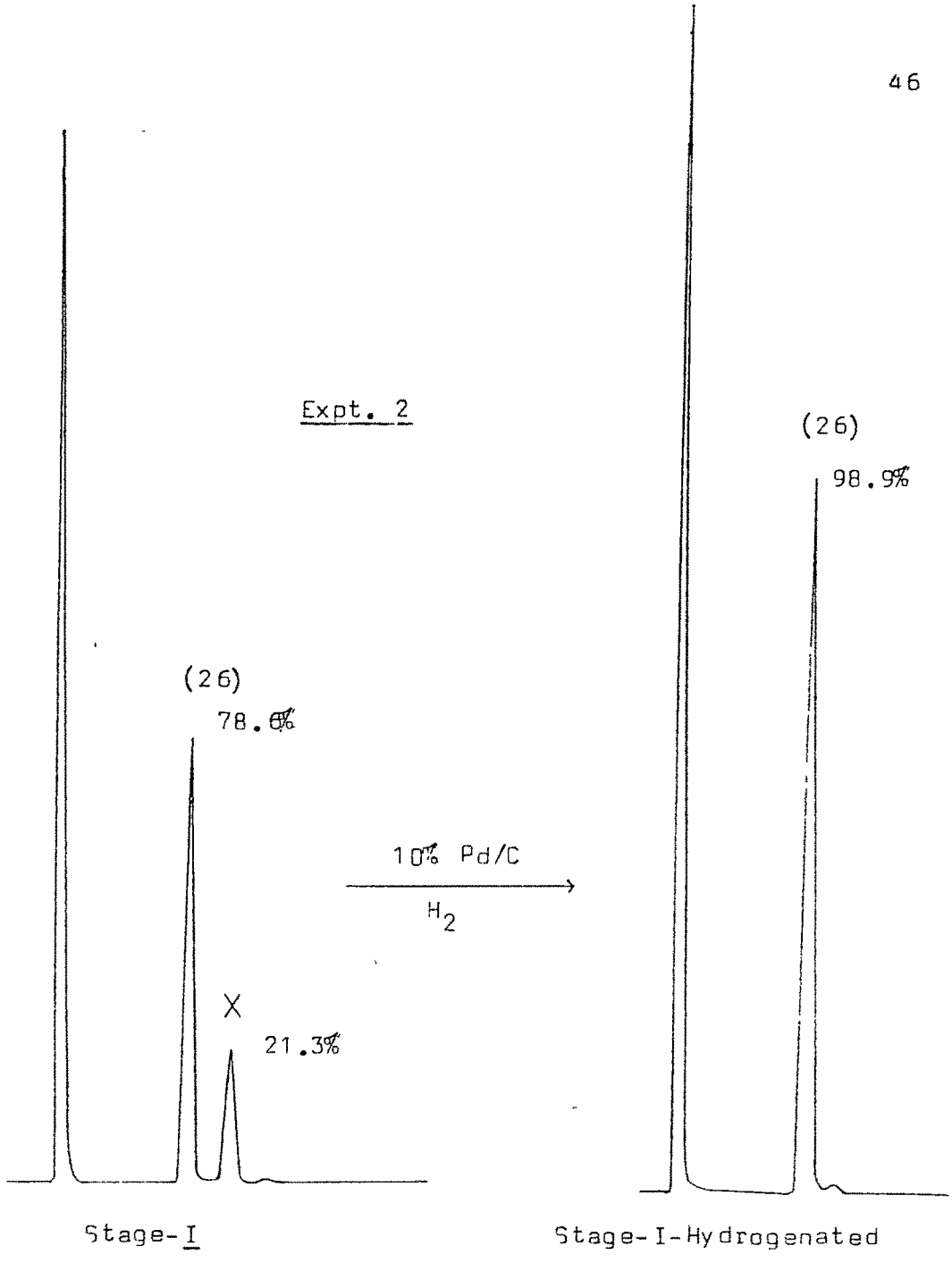


Fig. 27: GLCs of stage I before and after hydrogenation.

After complete disappearance of the starting material, GLC analysis (Fig. 26, stage G & H) showed two peaks other than the required product (26) (peaks X & Y on GLC) at retention times 2.2 min and 2.94 min (10% SE 30, 220°), progressively disappearing and percentage of the required product simultaneously increasing (R_t: 26, 1.7 min, under equivalent column conditions).

In another experiment (Expt. 2), reaction could be stopped after disappearance of Wittig product, at stage I (Fig. 14) and subjected to ^{1}H-NMR probe. Amplified region from 2-2.3 δ (allylic region) showed disturbance and pattern similar to the Wittig Product (28) (isomeric mixture). When the material at stage I was subjected to full catalytic hydrogenation (10% Pd/C, atmospheric pressure) a sudden coalescence of GLC peaks was observed to give (26) in 98.9% purity (Fig. 27: stage I-hydrogenated).

Now it can be surmised that compounds X (R_t: 2.2 min, Z-isomer) and Y (R_t: 2.94 min, E-isomer) are initially formed which are then transformed to (26) *via* radical-anion pathway as shown in Fig. 28.

Process appears to be non-concerted and involves two distinct steps with an obvious preference for 4-demethoxylation. Mechanism incorporating stable aromatic structures X and Y seems reasonable.

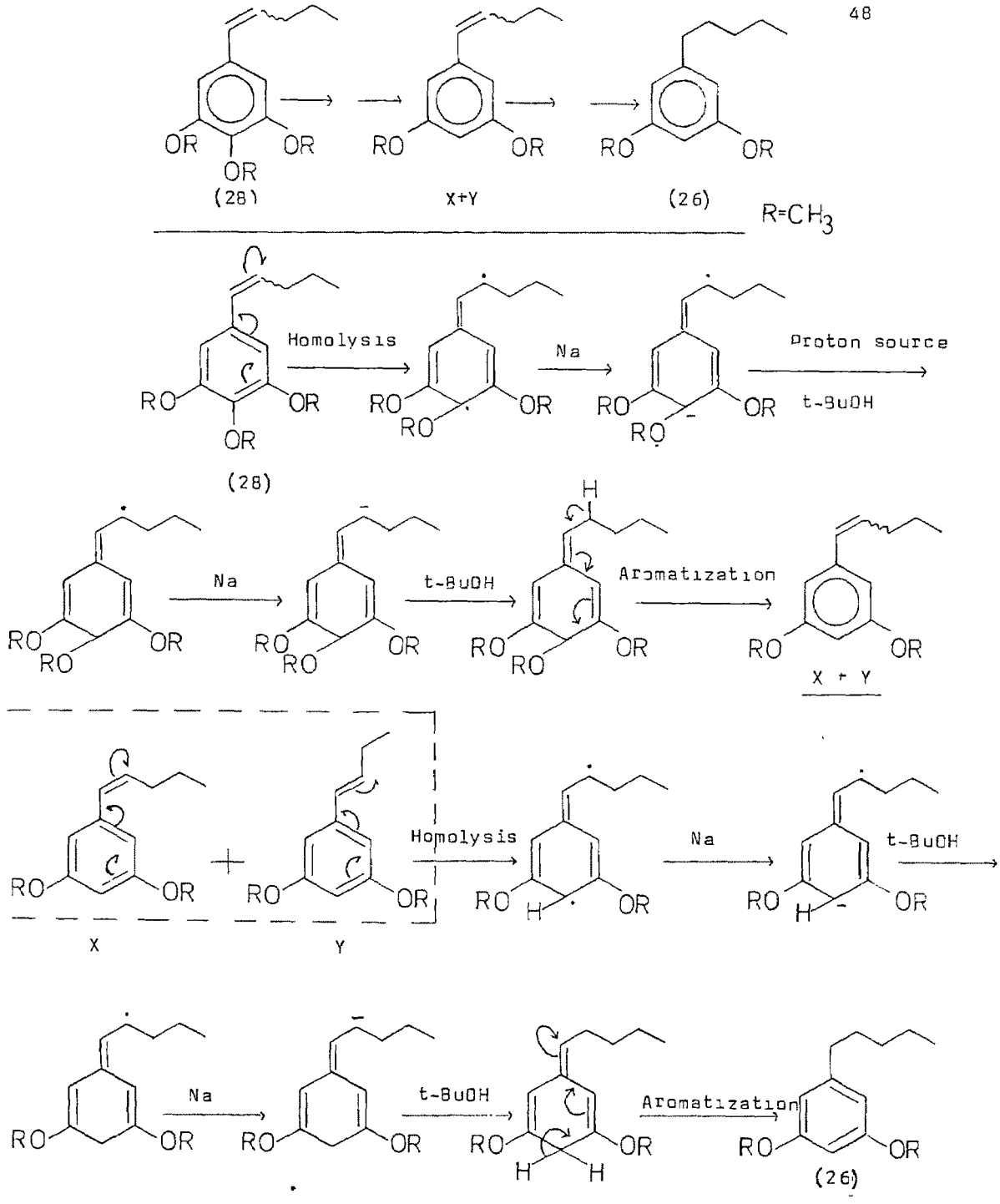


Fig. 28: Mechanism of the conversion of (28) to (26)

It was also noted that E/Z ratio of the Wittig product was 3:1, while in aliquots was 1:3 respectively (GLC, Fig. 26). Probably the kinetics of trans-isomer under these conditions is faster than cis.

Finally hydroxyls were demasked by the reported method in literature[12b] using pyridine/HCl, with the improvement in the yield (90%). For this purpose pyridinium hydrochloride was made completely anhydrous by distilling off some of the salt.

Thus olivetol was obtained in three steps in 52 percent overall yield.

EXPERIMENTAL

General methodology

All m.ps and b.ps are uncorrected. Petroleum ether or light petroleum ether refers to the fraction of b.p. 60-80°C.

The following instruments were used for spectral/analytical data; Perkin-Elmer infrared spectrophotomer, model 267(IR); Perkin-Elmer model 781 (IR); Perkin Elmer spectrophotometer 402 (UV); Perkin-Elmer R-32 (90 MHz) spectrometer (^{1}H-NMR); Varian Mat. mass spectrometer, model CH-7 (mass, 70 eV, direct inlet system; Finnigan-Mat-1020 (mass, 70 eV, direct inlet); V.G. Micro Mass, 70-70H (70 eV-Normal, 18 eV-low, direct inlet); Carbon-Hydrogen-Nitrogen analyser, Hewlett-Packard (Hp) model 185B. Gas chromatography analyses were carried out on Hewlett-Packard, model 5712A; stainless steel columns, 180 cm x 0.3 cm; support; 60-80 mesh chromosorb-W; Stationary Phase 10% SE-30; carrier gas H_2, flow rate: 60 ml/min; Hewlett-Packard, model 5712 A: stainless steel columns, 360 cm x 0.3 cm; support: 60-80 mesh chromosorb-W; stationary phase 10% CW (carbowax), 20M, unless stated contrary; carrier gas H_2, flow rate: 60ml/min; mode TCD; Hewlett-Packard, model 7624A: glass column, 100 cm x 0.15 cm; support: 80-100 mesh chromosorb W; stationary phase 10% $DCQF_1$ carrier gas H_2, flow rate: 60ml/min; mode TCD ; Hewlett-Packard, model 7624A: stainless steel column, 120 cm x 0.3 cm; support 80-100 mesh chromosorb W; Stationary phase 10% OV_4; carrier gas N_2, flow rate: 40 ml/min, mode FID. And 7624A (for

preparative glc): Al columns, 360 cm x 0.9 cm preparative column, support: 45-60 mesh chromosorb W; stationary phase 20% SE 30; carrier gas H_2, flow rate 100 ml/min; TCD 250°; inj = 250°; col. 150°; 30 μl (each inj.) gas chromotograph.

IR spectra were recorded as smears or in nujol or in KBr pellets and values are reported in wavenumbers (cm^{-1}). All ^{1}H-NMR spectra were recorded with 15-20% solution in CCl_4/ $CDCl_3$ or else as stated with TMS as internal standard, signals are recorded in ppm(δ). While citing NMR data, the following abbreviations have been used: s(singlet), d (doublet), t(triplet), q (quartet), m (multiplet) and b (broad). J-values in NMR were mentioned in Hz. While summarising mass spectral data, besides the molecular ion the most aoundant ions (m/e) are reported with their relative intensities. All UV spectra were recorded in 95% ethanol solution.

Silica gel for column chromatography(100-200 mesh, Bhavana Chemicals, Vallabh Vidyanagar, Gujarat) was used as such after gradation (IIA-IIB), unless stated contrary. Super dry silica gel (grade I) was prepared as described by R. Hernandez et.al.[39] TLC was carried out on silica gel G (13% gypsum, 75 microns; Bhavana chemicals, Vallabh Vidyanagar, Gujarat), layers (0.25 mm) and activated at 110-115°C for 2 hrs. Alumina used for chromatography was the commercial basic alumina which was seived (100-200 mesh), washed with 10% nitric acid at 90°, followed by washing with water till neutral. It was activated at 450° and

required grade was prepared and standardized according to Brockmann procedure.[39] Molten sodium dispersed on alumina was taken from the laboratory shelf which was prepared as in ref. 83. Visualization of the spots was done by spraying with anisaldehyde/sulphuric acid, Vanillin/phosporic acid, conc. sulphuric acid, I_2 chamber or suitable reagent as described in Ref. 40.

All solvents were purified and distilled prior to use. Anhydrous, peroxide-free ether was prepared by treating predried ether over fused $CaCl_2$, with sodium-benzophenone ketyl. Alcohols were dried over their respective magnesium alkoxides or by anhyd. K_2CO_3 followed by distillation over sodium and then stored over molecular sieves (4A). Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately prior to use. 1-4 Dioxane was purified and dried according to the detailed reported procedure.[84] All solvent extracts were washed with brine and dried over anhydrous sodium sulphate. Moisture sensitive reactions were carried out in an atmosphere of oxygen free nitrogen. For fractional distillation: Adiabatic Annular Teflon spinning band still, model NFT-51 (80 theoretical plates), supplied by Nester/Faust Manufacturing Corporation, Newark, USA was used.

Preparation of peracetic acid

35% aqueous peracetic acid was prepared by D. Swern's procedure and estimated.[85]

(+)-2α,3α-Epoxycarane (5)

Epoxide (5) was prepared as described by R.S. Prasad *et al.*[14] using NaOAc buffer, from the fractionated (+) Δ^2-carene.

Physical data: b.p. $60^{o}/2$ torr [lit.[14] b.p. $60-75^{o}$(bath)/2 torr]

R_f : 0.58 (10% EtoAc in pet ether).

R_t : 4 min (10% CW, 150^{o}) GLC purity: > 95%.

^{1}H-NMR and IR as described in the literature.[14]

Reaction of (+)-2α,3α-epoxycarane (5) with resorcinol (14) in aprotic polar solvents: THF and dioxane; at room temp and reflux temp.

Freshly distilled epoxycarane (5) (0.5 g, 3.28 mmole) and resorcinol (0.362 g, 3.28 mmol, m.p. 110^{o}C) were stirred magnetically in 8 cc of the respective solvents under exclusion of water & oxygen at room temperature (30^{o}C) for 24 hr. TLC monitoring showed no reaction under these conditions.

Reaction mixture was then vigorously refluxed. Still reactants were inert even after 24 hr.

Fusion reaction of 2-carene epoxide (5) and resorcinol (14)

In a pyrex tube, 2-carene epoxide (0.5 g, 3.28 mmole) and resorcinol (0.724 g, 6.56 mmole) were allowed to fuse while stirred magnetically. At 80^{o} reaction mixture turned homogeneous which was then maintained at 120^{o} bath temp. TLC analysis showed disappearance of epoxide after 3 hr.

Product showed two prominent spots at R_f 0.56 and 0.46 (20% EtOAc in pet ether) and hence it was chromatographed on silica gel as follows, under pressure.

Chromatogram I

Material loaded: 1.05 g; silica gel for loading: 2.0 g

Silica gel for column : 60.0 g ; Grade: II8, (100-200 mesh)

Column length: 44 cm; column diameter: 2.2 cm

Monitor: TLC - 20% EtOAc in petroleum ether; Flow rate: 17 ml/min.

Fraction No.	Solvent system.	Vol. ml /fraction	Wt. in g.	Remarks
1-10	Petroleum ether	100	0.0120	-
11-19	2% EtOAc/pet. ether	100	0.0600	← R_f: 0.56 fairly pure
20-22	2% EtOAc/pet. ether	100	0.0140	
23-26	2% EtOAc/pet. ether	100	0.1400	← R_f:0.46 fairly pure
27-34	2% EtOAc/pet. ether	100	0.0070	
35-49	3% EtOAc/pet. ether	100		
50-58	4% EtOAc/pet. ether	100	0.0030	
59-78	5% EtOAc/pet. ether	100	0.0170	
79-84	6% EtOAc/pet. ether	100	0.0200	
85-110	6% EtOAc/pet. ether	100	0.503	Resorcinol R_f: 0.14
			0.776	

Preparation of silyl ethers of fractions (11-19) and (23-26) was carried out under dry conditions as stated below. All silyl ethers described hereafter were prepared by the same general procedure.

General procedure for silyl ethers.[86]

In a typical experiment 10 mg of the fraction was completely dissolved in 1 ml of dry pyridine and treated successively with 0.3 ml of hexamethyldisilazane (Fluka A.G.) and 0.3 ml of trimethylchlorosilane (Fluka) by injection. Rate of addition of trimethylchlorosilane was controlled so as to keep temperature at $\sim 45^{o}C$. Reaction mixture was stirred for 5 minutes and excess reagents were readily stripped off under vacuum at $50^{o}C$. Residue was taken in 5 ml of dry petroleum ether and salts were filtered to get silyl ether in petroleum ether which after concentration was used for GLC analysis on 10% OV_4, $190^{o}C$.

Each of the above fractions on GLC showed minimum 4 components (Fig. 5).

Nucleophilic opening on solid matrix- superdry silica gel.

Parallel procedure was adopted as in the ref. 36 replacing neutral W-200 alumina with super dry silica gel. Silica gel for this purpose was prepared as described in the General Methodology of this Chapter. Experimental Procedure is described.

Doping of resorcinol on dehydrated silica gel: A single-neck round bottom flask equipped with a magnetic stir bar was dried in an oven at $110^{o}C$ for 1 hr. Flask was stoppered and allowed to cool in dry box. Dehydrated silica gel 24.7g (45 ml dry volume) was transferred to this flask and enough dry solvent ether (80 ml) was added to form a slurry. To the stirred slurry was injected azeotropically dried resorcinol (0.988g, 4% by weight of the

silica used) in appropriate quantity (10 ml) of dry ether. Reaction mixture was stirred for 5 minutes and solvent ether was then carefully distilled off on rotory evaporator for uniform adsorption (all transfers in dry box).

Reaction procedure: After complete removal of solvent ether, dry petroleum ether (75 ml) was injected to form slurry. To this doped slurry at room temp ($30^{o}C$), was shooted 0.5 g of 2-carene epoxide (3.28 mmole, 1 mmole per 7.5 g of silica, $\pm$ 5%) in 10ml petroleum ether; while stirred magnetically under positive pressure of dry N_2. Reaction was continuously monitored on chromatoplates (solvent system: 10% EtOAc in petroleum ether) which showed completion of reaction after 12.5 hr.

Supernatant solution was decanted and silica gel residue stirred with methanol (70 cc) for 2 hr. This was then filtered through celite pad and solid washed well with methanol in portions (3 x 20 ml). The above solvent portions were pooled and complete removal of solvent furnished 1.2 g of brown gum. Product on TLC analysis showed two major spots at R_f: 0.49 and 0.42 (20% EtOAc in pet. ether) together with resorcinol (R_f: 0.14) under identical conditions. This gum was then segregated into phenolic and non-phenolic portions with 20% aq NaOH in usual manner to give 0.8937 g and 0.140 g of the respective fractions.

A part of phenolic fraction (10 mg) was silylated as described earlier for GLC analysis, which indicated 69.2% of resorcinol and other three major components in 7%, 15% and 7% (Fig. 7) with R_tS 3.85, 4.77 and 6.28 minutes respectively. (10% OV_4, $190^{o}C$).

Complexity of the phenolic fraction, thus precluded the possibility of intermediate isolation in acceptable quantity.

Reaction with organotitanium reagent

Preparation of titanium isopropoxide[$Ti(O\text{-}i\text{-}Pr)_4$][53]: Freshly distilled $TiCl_4$ (3.1 g, 0.016 mmole, b.p. 136°C) was added dropwise, to an ice cold mixture (4°C) of dry isopropanol (6.65 g, 0.111 mmole) in 34 ml of dry benzene while being stirred under dry conditions. Dry ammonia gas, generated from liq. NH_3 after passing through conc. KOH solution and fresh CaO tower, was bubbled into it until the exothermic reaction ceased completely. The mixture was then filtered under dry nitrogen using a sintered glass funnel (G-3). NH_4Cl collected was repeatedly washed with dry benzene (3 x 5 ml).

Combined filtrate and washings were evaporated to dryness under reduced pressure. Viscous residue thus obtained was then distilled at 104-106°C/10 torr. to furnish 13.2g of titanium isopropoxide [$Ti\text{-}(O\text{-}i\text{-}Pr)_4$] (yield 69%).

Physical data: b.p. 104-106°/10 torr (Lit.[53] b.p. 80°/2 torr).

Formation of the intermediate (15), in the reaction of $Ti(O\text{-}i\text{-}Pr)_4$, resorcinol and 2-carene epoxide (5)

To a flame-dried three-necked round bottom flask, flushed with dry N_2, was taken recrystallized resorcinol (0.724 g, 6.56 mmole; m.p. 110°C) in 20 ml dry benzene. Benzene was distilled

off in order to make resorcinol azeotropically dry. Traces of benzene were removed under reduced pressure. 20ml of dry benzene was injected into resorcinol and stirred magnetically. To this suspension, freshly distilled $Ti(O\text{-}i\text{-}Pr)_4$ (0.2335 g, 0.82 mmole) in 2 ml dry benzene was syringed in, under dry nitrogen at 15 $\pm$ 1°C. A red colour appeared instantaneously. After stirring for another 10 minutes, 2-carene epoxide (0.5 g, 3.28 mmole) in 5 ml dry benzene was injected dropwise at the same temperature. Reaction mixture was slowly allowed to attain room temperature (30°C). Even after 6 hr substrates were completely inert. Then the reaction mixture was slowly heated in an oil bath to 65-70°C.

Reaction was over in 40 minutes, as monitored by disappearance of the epoxide on TLC (10% EtOAc in pet.ether, Fig. 29).

Reaction was worked up by decomposing titanium complex under neutral hydrolytic conditions as followed by D. Seebach et al.[48] using 20% aqueous KF solution (50 ml) and stirred for 5 minutes. The solution was filtered through celite bed on G-3 sintered disc. Residue was repeatedly washed with benzene (6 x 30 ml) and then with methanol (2 x 20 ml). Aqueous portion was separated and organic phase after solvent removal was taken up in solvent ether and washed with water (2 x 20 ml) till neutral, followed by brine (2 x 20 ml) and dried over anhydrous Na_2SO_4. Solvent removal furnished 0.620 g of red gum. This was then segregated into phenolic (0.530 g) and non-phenolic (0.082 g) fractions.

Phenolic fraction was further taken for flash chromatography on silica gel.

Chromatogram II

Wt. of the fraction loaded: 0.789g; Silica gel used for adsorption: 1.0 g

Wt. of silica gel for column: 50.0g; Grade: IIB, 100-200 mesh

Column length: 31.0 cm ; Column diameter: 2.1 cm

Monitor: TLC- 20% EtOAc in pet.ether; Flow rate: 15 ml/min.

Fig. 29 solvent front	Fr. No.	Solvent system	Vol. ml (each)	Wt. mg	Remarks
	1-13	Petroleum ether	100	3	
	14-18	2% EtOAc in pet.ether	100	12	
	19-25	-do-	100	23	
	26-29	3% -do-	100	20	R_f: 0.44, fair purity
	30-37	-do-	100	4	
	38-50	4% -do-	100	5	
	51-54	5% -do-	100	10	
	55-59	-do-	100	30	
	60-66	-do-	100	100	Intermediate R_f: 0.24 crystals.
*	67-69	6% -do-	100	12	
	70-85	-do-	20	270	
	86-100	15% -do-	20		Resorcinol rich R_f: 0.18 washings.
	Final	20% -do-	500	249	
		Total		738 mg	

Fig. 29: TLC pattern of the reaction between (5) & (14).

Fraction (67-69) obtained as straw-coloured crystals, was recrystallized from 0.4 ml of 30% EtOAc in petroleum ether. Colourless crystals were obtained (7.0 mg m.p. 98-99°C sharp, yield- 0.41%).

Physical data of (15): m.p. 98-99°C

R_f : 0.24 (20% EtOAc in pet ether).

R_t: silyl ether - 8.24 min (10% OV_4, 190°C) (Fig. 14).

GLC purity: 96.6%.

^{1}H-NMR ($CDCl_3$) (Fig. 9): 7.4-6.9 (m, 1H, Ar-H,meta to -OH) 6.7-6.3 (m, 3H, Ar-H), 5.8-5.32(m, 2H, CH=CH,cis), 4.43 (bs, 1H, Ar-OH), 2.66 (bs, 1H, C-OH, D_2O exchangable), 2.5-1.4 (m, 5H, CH_2s and CH), 1.26 (s, 3H, HO-C-CH_3), 1.04 (s, 3H, -O-C-CH_3), 0.96 (s, 3H, -O-C-CH_3).

IR (Neat) (Fig. 10): 3340, 3310, 1660, 1588, 1485, 1460, 1380, 1360, 1315, 1275, 1215, 1170, 1140, 1010, 988, 880, 840, 765, 685 cm^{-1}.

Mass: (Fig. 13): m/e 262(M^+, 15%), 152 (100%), 135 (97%), 110(93%), 109(79%), 153(71%), 93(69%), 95(65%), 137(61%), 161(53%).

Elemental analysis: Found C, 73.36, H, 8.503; $C_{16}H_{22}O_3$ requires C, 73.25, H, 8.45

A blank experiment

In this reaction 2-carene oxide (50 mg, 0.328 mmole) and resorcinol (72 mg, 0.656 mmole) in 4 ml dry benzene were allowed to stir in a 10 ml r.b. flask. Reaction mixture was refluxed for 6 hr under dry N_2 to note no reaction.

Effect of $Ti(O\text{-}i\text{-}Pr)_4$ on 2-carene epoxide: In a flame dried r.b. flask 2-carene epoxide (50 mg, 0.328 mmole) and $Ti(O\text{-}i\text{-}Pr)_4$ (93 mg, 0.328 mmole) in 4 ml dry benzene was refluxed under exclusion of moisture and oxygen. Epoxide completely disappeared in 16 hr (TLC analysis).

Effect of isopropanol as a nucleophile: $Ti(O\text{-}i\text{-}Pr)_4$ (0.117 g, 0.41 mmole), dry isopropanol (0.0987 g, 1.65 mmole) and 2-carene oxide (0.25 g, 1.64 mmole) were taken in r.b. flask and maintained at ($65\text{-}70^{o}$) with all usual precautions, for 3 hr. There was no reaction even after refluxing for 3 hr .

Reaction with phenol: 2-Carene oxide (0.25 g, 1.64 mmole), $Ti(O\text{-}i\text{-}Pr)_4$ (0.117g, 0.41 mmole) and phenol (0.310 g, 3.29 mmole) in 20 ml dry benzene were heated at $70^{o}C$ under inert atmosphere (dry N_2). During 1.5 hr all the epoxide got consumed to give major products of higher R_f (> 0.5, solvent system; 10% EtOAc in petroleum ether).

Formation and isolation of the isomerized intermediate 22, in the reaction of 2-carene epoxide with olivetol

Experiment was performed under the optimized conditions as follows: Olivetol (1.2 g, 6.67 mmole) and freshly distilled $Ti(O\text{-}i\text{-}Pr)_4$ (0.4741 g, 1.67 mmole) were injected in 25 ml dry benzene, in 100 ml flame dried r.b. flask while being stirred , maintaining completely anhydrous conditions at $15 \pm 1^{o}C$. Brick red suspension thus obtained was stirred for another

10 minutes and 2-carene epoxide (1.014 g, 6.67 mmole) was syringed in with 10 ml of dry benzene. Reaction mixture was slowly heated to 70° pot temperature. TLC monitoring after each 10 minutes showed complete consumption of epoxide in 60 minutes (10% EtOAc in pet. ether).

Reaction mixture was cooled to room temp. and then titanium complex was hydrolyzed using neutral 20% aqueous KF solution as described before. 2.1525 g of reddish viscous product thus obtained was segregated into phenolic (0.68 g) and non-phenolic (1.017 g) as usual , by treating with 20% aq. NaOH solution. Phenolic fraction was essentially olivetol (TLC) while neutral portion showed the presumed product just above olivetol on chromatoplate (Fig. 30).

The required product was obtained in two operations.

1) Rapid column chromatography employing uniform gradient elution technique to get broad cuts.
2) Final flash chromatography to furnish sample of analytical purity.

Uniform gradient elution

All the precautions were taken as described in the reference 69.

Exponential elution was carried out with a mobile phase gradient from 100% petroleum ether to 50% ethylacetate in petroleum ether at room temperature (~32°C) with a two vessel mixing system.[69]

Chromatogram-III

Neutral fraction loaded: 0.960 g; wt. of silica used for loading: 3.0 g

Wt of silica gel for column: 60.0g; Grade: IIB, 100-200 mesh

Column height: 34 cm; column diameter: 2.2 cm

Monitor: TLC: 20% EtOAc in petroleum ether.

Uniform gradient variation from petroleum ether to 50% EtOAc in petroleum ether was divided in two phases.

Phase I: To the stock solution of petroleum ether (250 ml) was added 25% EtOAc in petroleum ether (250 ml), with a prescribed rate as in the reference 69 (2:1).

Phase II: To the stock solution of 25% EtOAc in petroleum ether (250 ml) was added 50% EtOAc in petroleum ether (250 ml) with a prescribed rate as above (2:1).

Fractions of 50 ml each were collected.

Frc. No.	Solvent system	Wt. (mg)	Remarks	solvent front
1-6	Phase I- Uniform gradient from pet. ether to 25%	30		
7	EtOAc in pet ether	70		
8	Phase I: Uniform gradient	87		
9	from pet. ether to 25%	80		
10	EtOAc inpet ether	70		
11	Phase II:	107	Required pro-	
12	Uniform gradient from	69	duct(major)	
13	25% EtOAc in pet ether		R_f:0.34	
14	to	60		
15	50% EtOAc in pet ether	35		
16		172		
17		18	Total recovery	
18-19		9	762 mg	
20		8		
		blank		

Fig. 30

Fractions 11 and 12 were pooled and 170 mg of this portion was flash chromatographed on 10.5 g of silica gel (IIB, 1.4 x 2 2 cm), to furnish pure fractions of (22) as under.

Chromatogram IV

Frc. No.	Solvent system	Vol. of each frac (ml)	wt. mg	Remarks
1-2	Pet. ether	50	47.0	
3-4	1% EtOAc in pet. ether	50		
5-8	2% EtOAc in pet.ether	50		
9	3%	50		
10-19	-do-	50	25.8	
20-28	-do-	25	40.7	* Pure R_f 0.34
29-35	-do-	25	30.1	* Pure
36-43	-do-	25	15.2	
44-45	20% -do-	50	-	

Pure fractions 20 to 35 were pooled to give 70 mg of 22.

Physical data: Viscous oil, R_f. 0.34 (20% EtOAc in pet.ether)

^{1}H-NMR ($CDCl_3$) (Fig. 18): 6.6-6.1 (m, 3H, Ar-H), 5.6-5.4 (bs, 1H, -CH=C), 4.45 (bs, 1H, Ar-OH); 2.8 (b, 1H, C-OH), 2.68-1.28 (m, 12H, 4 allylic, $4CH_2$s), 2.51 (t, J= 8Hz, 2H, Ar-CH_2-), 1.28(s,3H,HO-C-CH_3), 1.04 (s, 3H, -O-C-CH_3) 0.96 (s, 3H, -O-C-CH_3) , 1.0-0.72 (submerged, 3H, H_2C-CH_3).

IR ($CHCl_3$) (Fig. 19): 3605, 3340, 2940, 1600, 1460, 1302, 1150, 1038, 1004, 898, 855, 710 cm^{-1}.

Mass: (Fig. 20) m/e 332 (M^+, 1%); 43(100%), 124(71%), 135(49%), 109(38%), 93(35%), 152(32%), 95(32%), 180(30%).

Elemental analysis: C 75.79, H 9.8 $C_{21}H_{32}O_3$ found;
C, 75.86; H, 9.70 requires

SECTION II

Synthesis of olivetol 6.

Preparation of n-butyltriphenylphosphonium bromide

Freshly distilled n-butyl bromide (prepared according to Ref. 87) (1.37 g, 10mmole) was added to a solution of triphenylphosphine (2.1 g, 8 mmole) in dry benzene (25 ml) at room temperature. The mixture was then magnetically stirred and refluxed for 20 hr. Towards the end of reaction, precipitated salt was filtered, washed with hot benzene (2 x 20 ml) and dried under reduced pressure (2.7 g, yield 84%).
Physical data: m.p. 220°C[77]

β-Propyl-3,4,5-trimethoxy styrene(28): To a slurry of potassium t-butoxide (6.6 g, 58.9 mmole) in dry t-butanol was shooted n-butyltriphenylphosphonium bromide (13.5g, 34.1 mmole) in dry acetonitrile (100 ml) and stirred vigorously for 15 minutes to get characteristic orange colour of 'ylide'. The mixture was then cooled to 5°C and introduced 3,4,5-trimethoxybenzaldehyde (23) (5.0 g, 25.5 mmole) in dry acetonitrile (25 ml) during 20 minutes and reaction was stirred overnight. After quenching the reaction with satd. NH_4Cl solution, separated the organic portion by extracting with light petroleum ether (4 x 100 ml). Combined organic layer was washed with water (3 x 50 ml), brine and dried. Removal of solvent gave crude product. This on passage through silica gel (100 g, II8, 3.7 x 20 cm) eluted following fractions:

Frac. 1-15 Petroleum ether (250 ml each)- 2.3 g (pure)

Frac. 16-21 1% EtOAc in pet. ether (100ml each)- 1.2 g (pure)

Frac. 22-25 2% EtOAc in pet. ether (100 ml each) - 0.3 g (pure)

Above viscous oil was distilled under reduced pressure to furnish 3.72 g of Wittig product 28 (yield- 61.8%). Physical data: b.p. 160°bath/0.6 torr (Lit. b.p. 160/0.75 torr)[79].

R_f: 0.16 (10% EtOAc in pet. ether)

R_t : Z-isomer, 2.32 min; E-isomer, 3.16 min (10% SE 30, 220°C), GLC purity, 99.0%.

Spectral data as reported earlier.[79]

Preparation of sodium metal dispersion on neutral alumina as in ref. 82.

5-n-Pentylresorcinol dimethyl ether (26). Wax coated Na/alumina reagent (3.5 g, 0.03 g-atom of Na) was repeatedly washed with dry petroleum ether (3 x 25 ml) and supernatant solvent removed and covered with dry benzene (20 ml) under dry conditions. To it was syringed Wittig product (0.25 g, 1.06 mmole) (28), in 5 ml benzene. Enough more benzene was added so as to make the medium freely mobile (total-80 ml). While stirring vigorously at room temp. dry t-butanol (8 ml, excess) was added dropwise, to control the exothermic reaction. After complete addition, reaction mixture was gently heated to reflux. TLC monitoring showed completion of reaction in 7 hr. Usual work up and pet. ether elution by passage through SiO_2-gel column furnished 4-demethoxylated product (26) (0.207 g, yield 94%).

Physical data: b.p. 110-112°/1 torr (Lit.[88] b.p.114°/2 torr).

R_f: 0.5 (10% EtOAc in petroleum ether).

R_t: 1.7 min. (10% SE 30, 220°). GLC purity: 98.9%.

Spectral features as reported in the literature: ^{1}H-NMR[89], IR[74].

5-Pentyl-1,3-benzenediol-(6): (Olivetol)[12b]: In a 100 ml r.b. flask, fitted with a thermowell and a short-path distillation condenser was taken 31.5 ml of dry pyridine and 35.0 ml of conc. HCl. While magnetically stirred mixture was heated slowly to distil off water, till pot temperature reached to 210°C. A drop of pyridine hydrochloride was allowed to distil and distillation assembly was quickly replaced by a condenser and an addition funnel, when dry N_2 was continuously flushed out. Molten salt was brought to 140°C and dimethyl ether (26) (1.54 g, 7.4 mmole) was added dropwise. Temperature was raised to reflux (200-220°), and maintained for 2 hr. TLC revealed disappearance of the starting ether.

Reaction mixture was worked up as given in the literature and column chromatographed on SiO_2-gel column (40 g, 2.2 x 29 cm) to get following pooled fractions.

Frac. 1	Petroleum ether (250 ml)	
Frac. 2-4	2% EtOAc in pet. ether (100 ml)	0.0920 impurity
Frac. 5	5% EtOAc in pet. ether (1000 ml)	

Frac. 6-7	7% EtOAc in pet. ether	1.20 olivetol
Frac. 8-9.	12% EtOAc in pet. ether	R_f: 0.15
Frac. 10-11	15% EtOAc in pet. ether	(10% EtOAc in pet. ether)

Physical data: m.p. 42°C (Lit.[76] m.p. 41°C)

R_f: 0.15 (10% EtOAc in pet. ether)

R_t: 2.4 min (10% SE 30, 220°C). GLC purity: + 99%.

^{1}H-NMR[12b] ($CDCl_3$) (Fig. 31): 6.26 (d, 2H, J = 2Hz, Ar-H-ortho to n-pentyl chain), 6.19 (d, 1H, J = 2Hz, Ar-H-para to n-pentyl chain), 6.0-5.0 (b, 2H, Ar-OH), 2.42 (t, 2H, J = 7Hz, Ar_2-CH_2-), 1.9-1.0 (m, 6H, -CH_2S), 0.85 (t, 3H, J = 6Hz, -CH_3).

IR (Neat)[90] (Fig. 32): 3340, 2940, 1600, 1475, 1340, 1310, 1210, 1150, 1005, 840, 700 cm^{-1}.

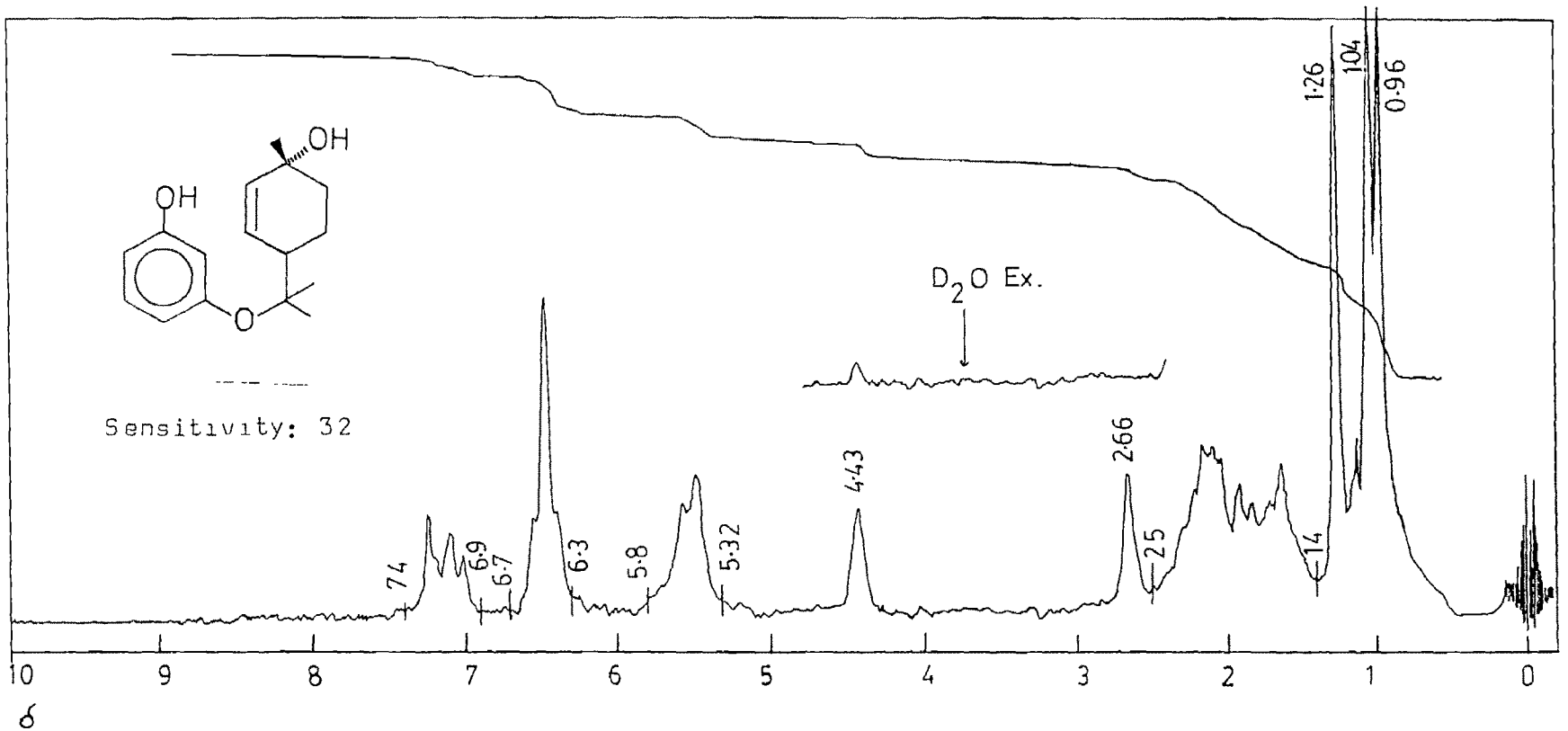


Fig. 9 : ^{1}H-NMR spectrum of intermediate (15)

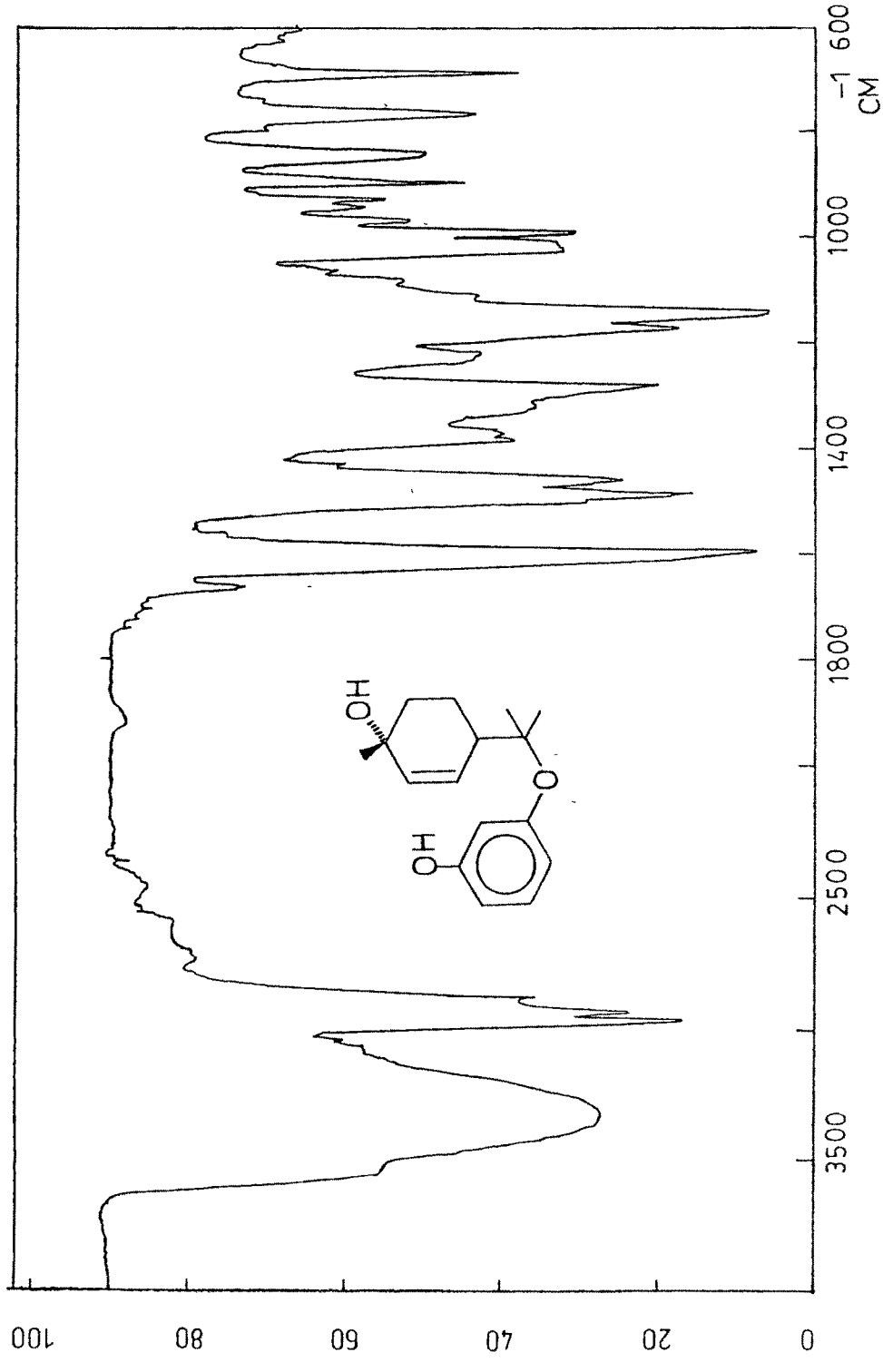


Fig. 10: IR spectrum of intermediate (15)

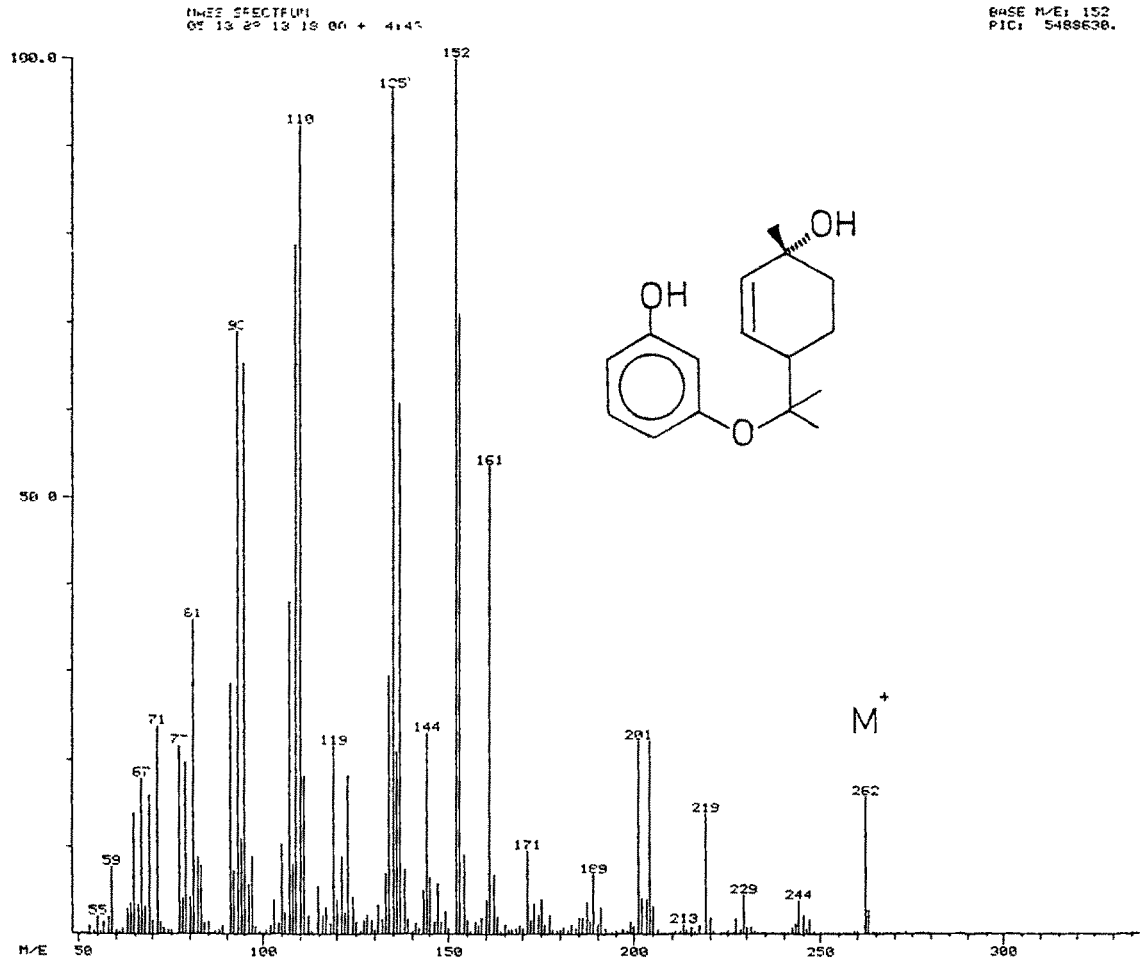


Fig. 13: Mass spectrum of intermediate (15)

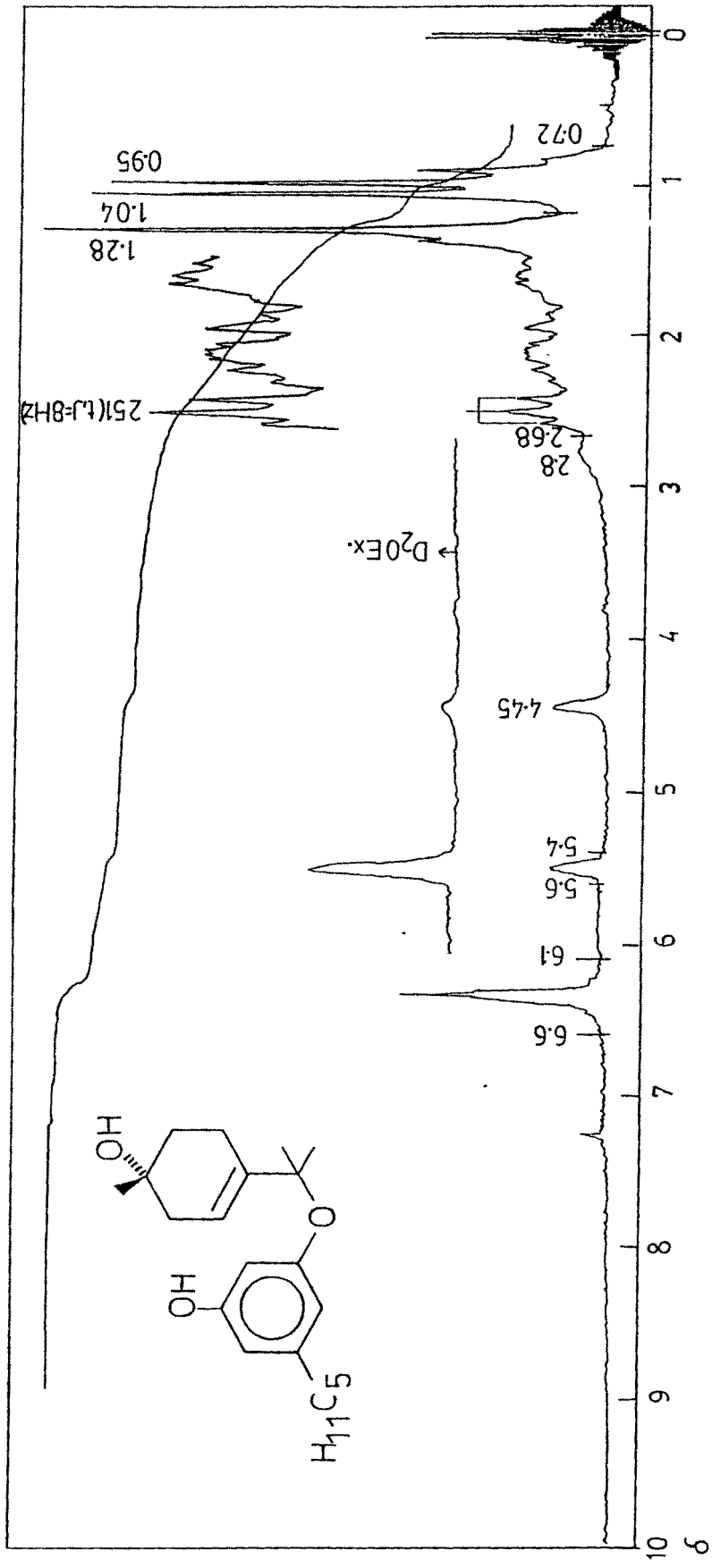


Fig. 18: ^{1}H-NMR spectrum of intermediate (22)

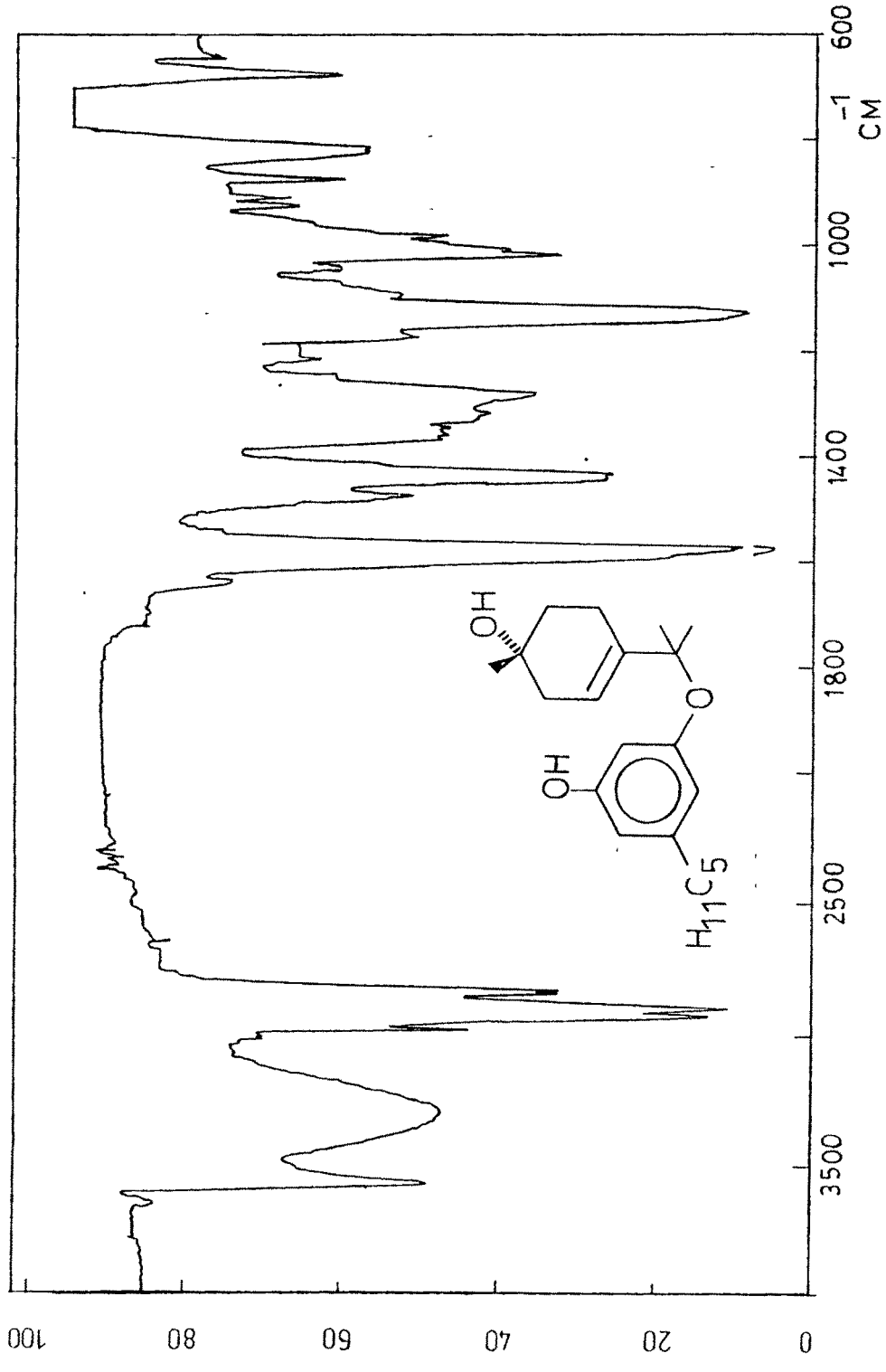


Fig. 19: IR spectrum of intermediate (22)

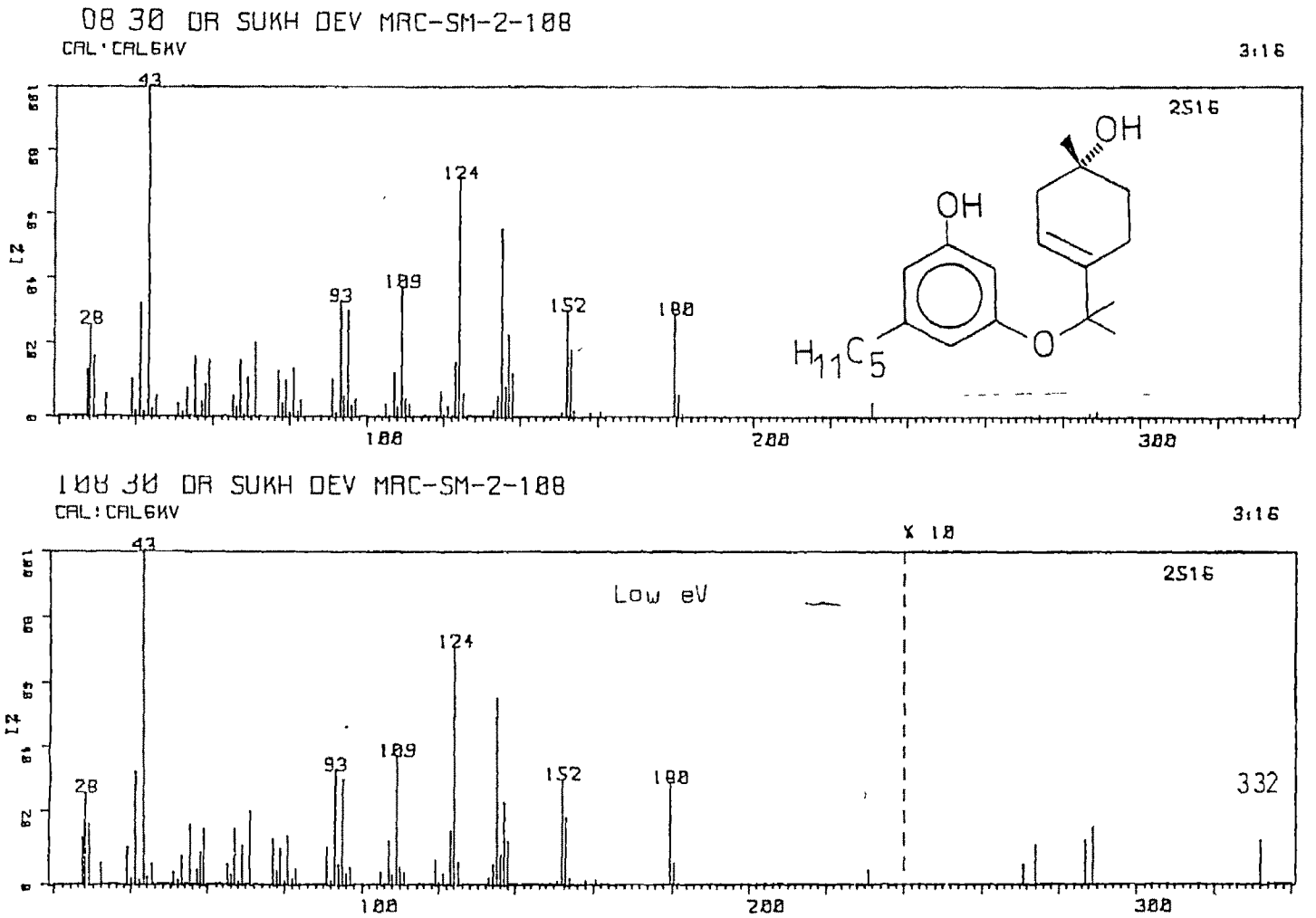


Fig. 20: Mass spectrum of intermediate (22)

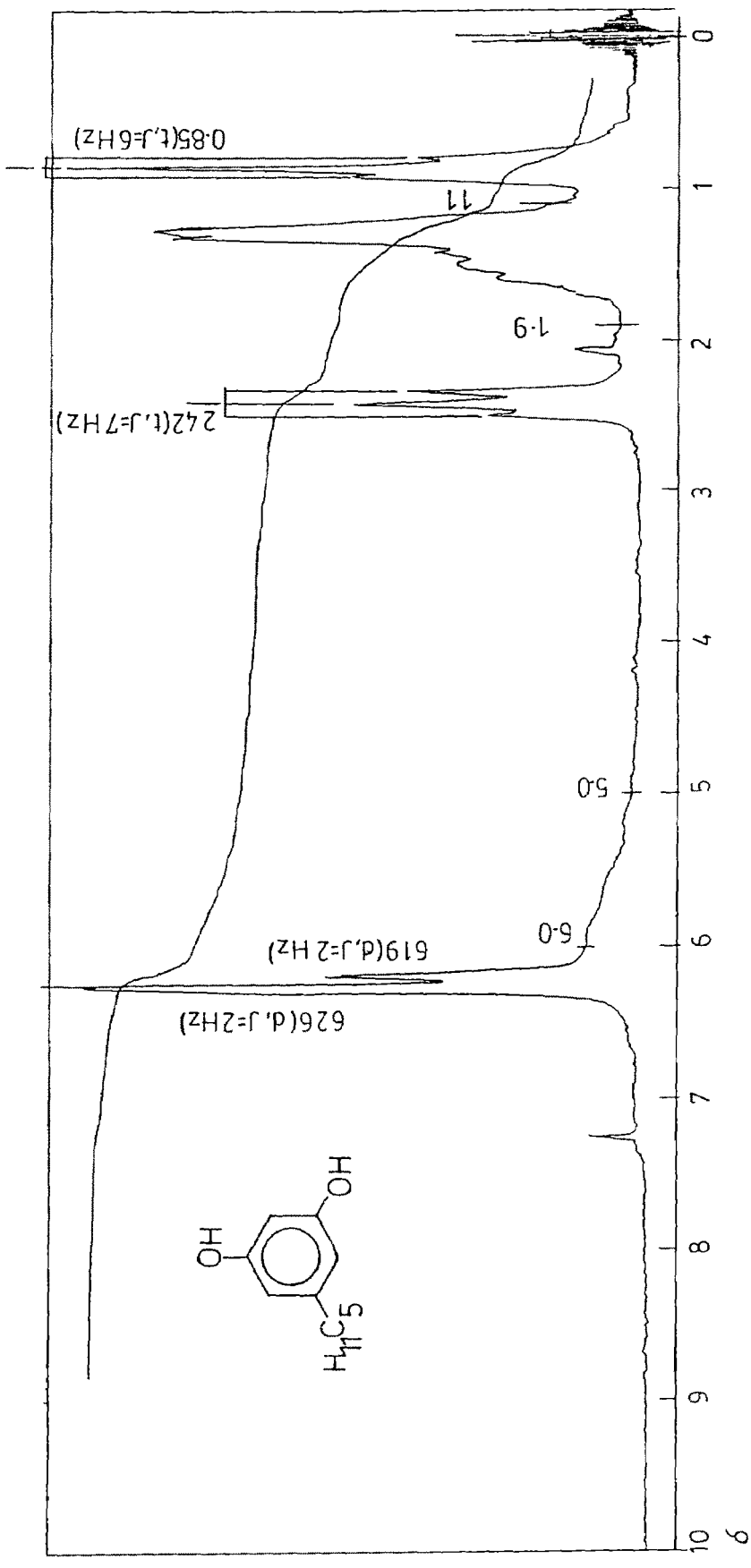


Fig. 31: ^{1}H-NMR spectrum of Olivetol

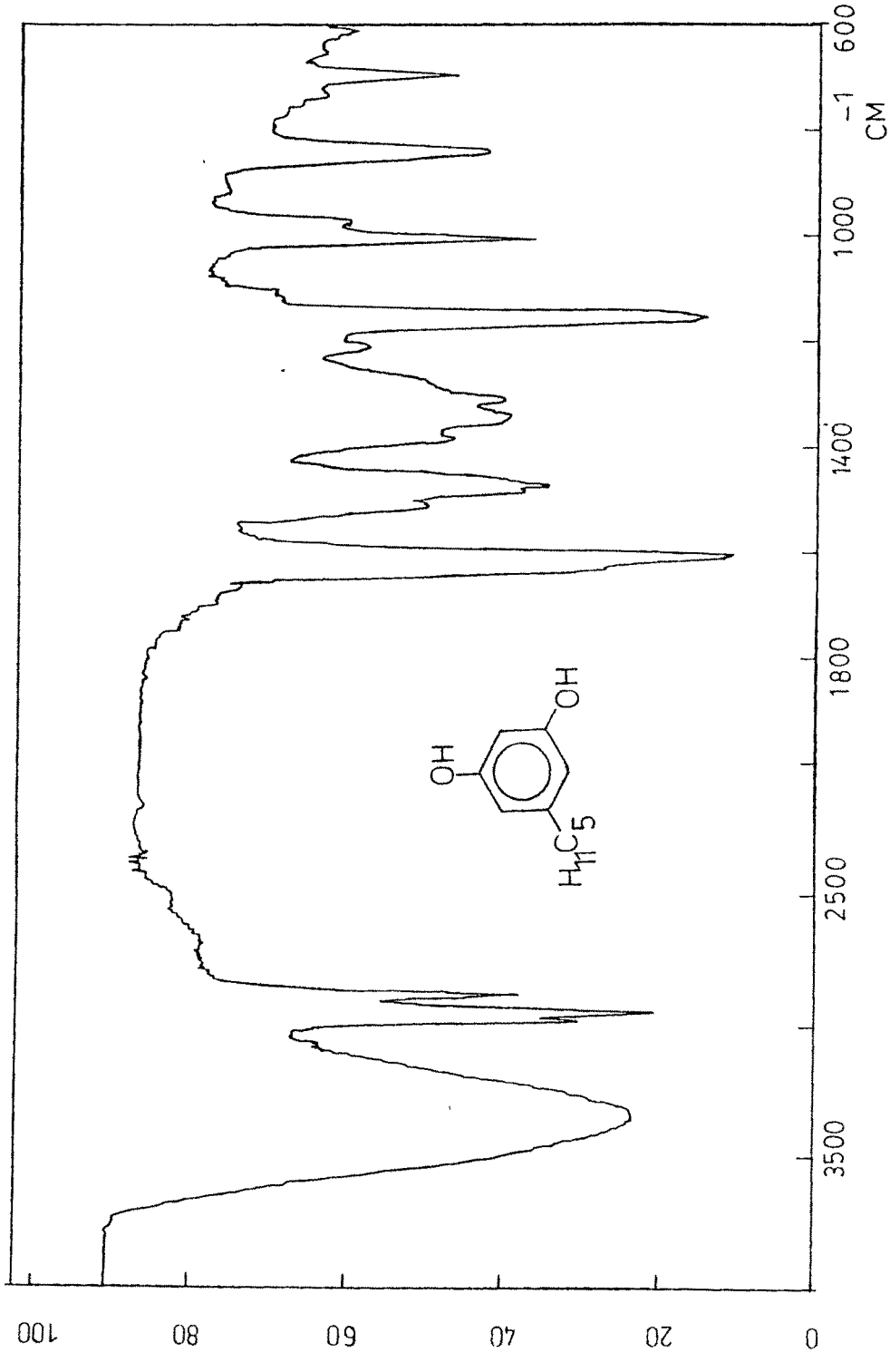


Fig. 32: IR spectrum of Olivetol

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