Use of 5-methoxy, 6-methoxy and 7-methoxy-α-tetralones in the synthesis of diterpenes, sesquiterpenes and other natural products

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The transformations of 5-methoxy, 6-methoxy and 7-methoxy-α-tetralones are described. Studies on the synthesis of diterpenes veadeiroic acid **12**, triptolide **18**, sesquiterpenes biflorin **25**, mansonone F **26**, cacalol **39** and a potential intermediate for 11-deoxydaunomycinone **59** from 5-methoxy-α-tetralone **1** are discussed. Several intermediates for diterpenoid compounds and a total synthesis of phytoalexin orchinol **53** from 6-methoxy-α-tetralone **2** have been accomplished. 7-Methoxy-α-tetralone **3** has proved to be a suitable starting material for a simple and short synthesis of cadinene dihydrochloride **45**.

Keywords: 5-methoxy, 6-methoxy, 7-methoxy-α-tetralone, diterpenes, sesquiterpenes, phytoalexin orchinol, deoxydaunomycinone

In designing the synthesis of natural and non-natural products the choice of starting material is the key to attaining the objective. The easy availability of the starting material facilitates synthetic work. Our group has a long-term research interest in the synthesis of natural products related to diterpenes and sesquiterpenes which show remarkable structural variations. Many exhibit a range of biological properties, including anticancer drugs, antifeedant products or herbicidal activities of interest as agrochemicals. In the course of our studies on the synthesis of natural products related to terpenes, we have observed the role of the commercially available 5-methoxy, 6-methoxy and 7-methoxy α-tetralone **1**, **2** and **3** as useful starting materials in synthesis of some diterpenes and sesquiterpenes. The present account is largely a survey of work carried out between 1997 and 2007 on the conversions of the above mentioned tetralones to terpenoids compounds at the Department of Chemistry, IVIC, Caracas, Venezuela. Related studies by other workers are mentioned only where they correspond or correlate closely with our studies. This review has been divided into four parts: (i) synthesis of diterpenes, (ii) synthesis of sesquiterpenes, (iii) miscellaneous, and (iv) conclusions.
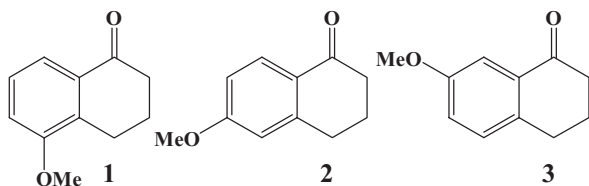
Synthetic studies on diterpenes
Veadeiroic acid
The chemical literature records the importance of 5-methoxy-β-tetralone in the synthesis of diterpenes,[1] but the use of 5-methoxy-α-tetralone **1** as starting material in the synthesis of diterpenes has not yet been reported. In relation of our studies on diterpenes, we tried to develop a synthesis[2] of veadeiroic acid **12**, a diterpene with a rare cleistanthene skeleton. The first total synthesis of veadeiroic acid **12** was reported by Saha and Nasipuri.[3] A retrosynthetic analysis of this acid led us to choose 5-methoxy-α-tetralone **1** as starting material for its synthesis. The synthetic route is depicted in Scheme 1.

5-Methoxy-α-tetralone **1** was converted into the bicyclic ketone **4** and tricyclic α,β-unsaturated ketone **5** following the procedure of Stork *et al.*[4] and Howell and Taylor[5] respectively. The transformation of ketone **5** into the phenol **6** was carried

out by the published procedure.[6] Treatment of the phenol **6** with phenylboronic acid and paraformaldehyde[7] in presence of a catalytic amount of propionic acid yielded a borane complex which with benzene and propylene glycol, led to the formation of diol **7**. Its conversion to aldehyde **8** was accomplished by oxidation[8] with 2,3-dichloro-5,6-dicyanobenzoquinone. Further oxidation of the aldehyde **8** with nickel peroxide in aqueous alkaline solution[9] produced an acid. Esterification with dimethylsulfate and potassium carbonate yielded the ester **9**. Its conversion into the oxazole derivative **10** was effected[3,10] in three steps: (i) hydrolysis with potassium t-butoxide and dimethylsulfoxide,[11] (ii) chlorination with thionyl chloride, and (iii) condensation of the acid chloride with 2-amino-2-methyl-propanol. The product obtained by alkylation of the oxazole derivative **10** with ethyl lithium at –40°C was successively hydrolysed with hydrochloric acid (10%) and methanolic hydroxide (10%) to afford methyl veadeiroate **11** which produced veadeiroic acid **12** by hydrolysis.[11] Its spectral data closely matched that of the reported data.[3]

In summary we have developed a simple, and elegant total synthesis of veadeiroic acid and we believe that by choosing 5-methoxy-α-tetralone as a starting material the synthesis was achieved without any difficulty. The synthesis proceeds through intermediates which can be utilised for the synthesis of other diterpenes by chemical modification of the intermediates at varying levels of functional and structural complexity.

Triptolide
5-Methoxy-α-tetralone **1** was also chosen as the starting material in our synthetic studies[12] on triptolide **18** which is a highly oxygenated diterpene. Kupchan *et al.*[13] first isolated this diterpene from an ethanolic extract of the Chinese medicinal plant *Tripterygium wilfordil Hook F (celastraceae)*. Triptolide is an antitumor diterpene and exhibits in vitro cytotoxic activity against several types of carcinoma.[14–16] It also inhibits DNA synthesis in L-1210 leukaemia cells without directly damaging DNA. Triptolide **18** is a tri-epoxy abietane lactone which has been the subject of synthetic endeavours,[16–18] because of its cytotoxic activity and partly because of its poor availability from natural sources.

In 1982, Graver and Van Tamelen reported[19] the synthesis of the abietane ether **17** and its transformation into triptolide. The published synthesis of **17** involves many steps and only skilled workers can reproduce the results. We tried to develop a concise and practically convenient route to this important compound and after many trials the route[12] depicted in Scheme 2 which utilises 5-methoxy-α-tetralone as a starting material proved satisfactory.

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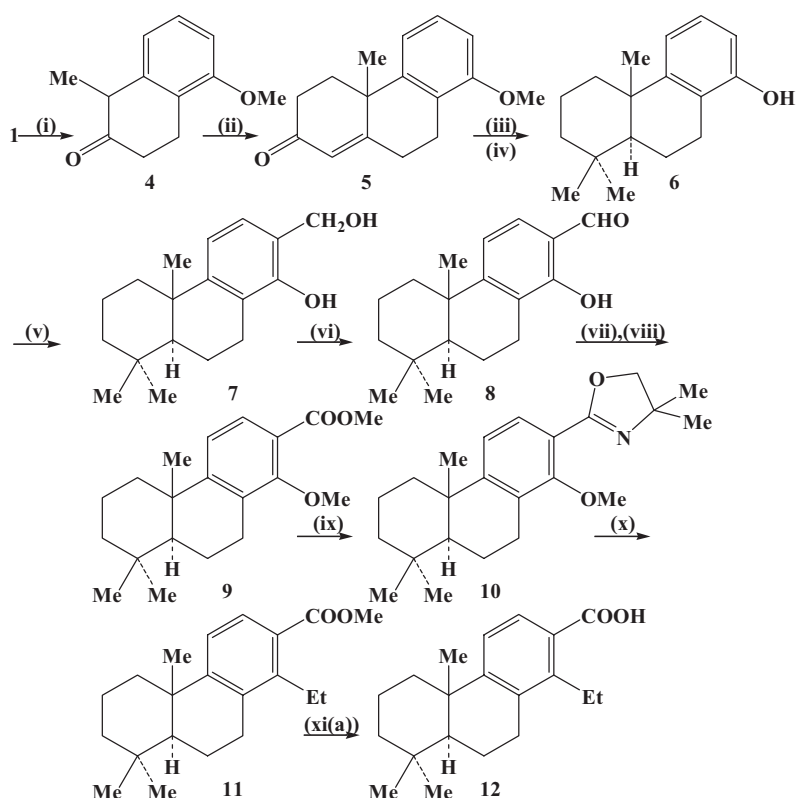
Scheme 1 Reagents: (i) (a) MeI, MeMgI, Et$_2$O, Heat; (b) McPBA, CH$_2$Cl$_2$, (c) HCl, H$_2$O; (ii) H$_2$C=CHCOMe; (iii) (a) MeI, C$_4$H$_9$OK, C$_4$H$_9$OH; (b) NH$_2$NH$_2$, KOH, DEG, (c) H$_2$, Pd-C (10%); (iv) HBr-MeCOOH; (v) (a) PhB(OH)$_2$, (CH$_2$O)n, MeCH$_2$COOH, (b) Benzene, propylene glycol; (vi) DDQ, dioxane; (vii) Ni-peroxide, NaOH, H$_2$O; (viii) K$_2$CO$_3$, Me$_2$SO$_4$; (ix) (a) C$_4$H$_9$OK, DMSO, (b) SOCl$_2$, (c) 2-amino-2-methylpropanol; (x) EtLi, HCl (10%), NaOH in MeOH, CH$_2$N$_2$; (xi) C$_4$H$_9$OK, DMSO.
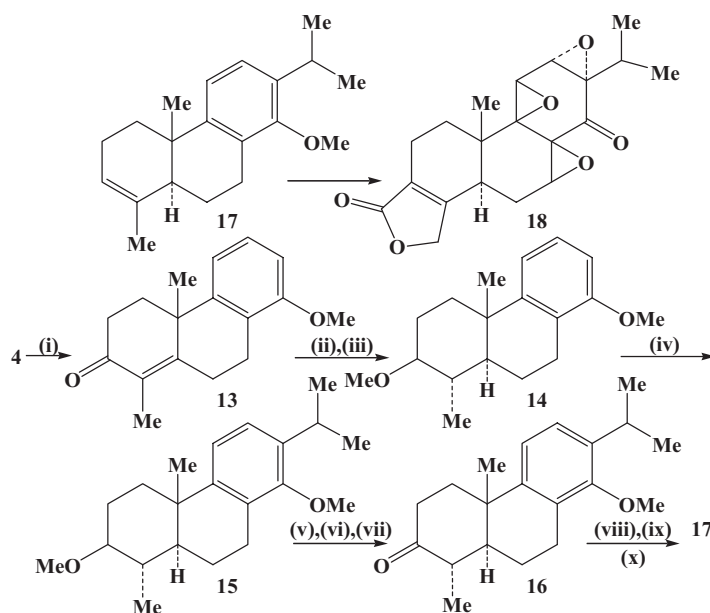
Scheme 2 Reagents: (i) 1-chloro -3-pentanone; (ii) Na, n-propanol; (iii) NaH, THF, MeI; (iv) Me$_2$CHOH, PPA, 80°C; (v) Me$_3$SiCl, NaI, MeCN; (vi) CrO$_3$, H$_2$SO$_4$; (vii) Me$_2$SO$_4$, K$_2$CO$_3$; (viii) NaBH$_4$, MeOH; (ix) TsCl/Py; (x) LiBr, DMF, 80°C.

The condensation of tetralone **4** with 1-chloro-3-pentanone afforded the known[20] tricyclic ketone **13** whose conversion to the compound **14** was effected by reduction[21] with sodium and n-propanol followed by methylation with methyl iodide and sodium hydride. The structural and stereochemical assignment of the compound **14** were made on the basis of previous work.[21,22] The introduction of the isopropyl group at C-7 was accomplished[23] by treatment with isopropanol and

polyphosphoric acid at 80°C to afford compound **15** in 50% yield. Isopropylation with isopropanol and sulfuric acid[23] and isopropanol and boron trifluoride[24] did not afford a satisfactory result. Treatment of compound **15** with trimethylchlorosilane and sodium iodide[24] led to demethoxylation. The resulting alcohol on oxidation with Jones reagent and methylation respectively gave the compound **16**. Its conversion into the compound **17** was achieved in three steps: (i) reduction with

metal hydride, (ii) tosylation, and (iii) elimination of the tosyl group.

Thus the sequence of reactions summarised in Scheme 2 provides an efficient route to compound **17** whose conversion to triptolide **18** has already been published. Subsequent evaluation of some of the intermediates of the Scheme 2 will reveal their possible biological activity.

5-Methoxy-α-tetralone **1** was rarely used in our laboratory for the synthesis of diterpenes. In most of the syntheses of diterpenes, 6-methoxy-α-tetralone **2** was frequently used as the starting material. Scheme 3 discloses our efforts towards the transformations of tetralone **2** into the cyclopropyl ketone[25] **19**, 8-methylene perhydrophenanthrene[26] **20**, ketone[27] **21** and dicarboxylic acid[28] **22**. The cyclopropyl ketone **19** and the 8-methyleneperhydrophenanthrene **20** are the potential intermediates for erythroxydiol X[29] and rosane diterpene dolabradiene[30] respectively. The ketone **21** and the dicarboxylic acid **22** can be utilised for the synthesis of the norditerpene alcohols (±)-4,13-dimethyl-13-vinylpodocarp-8(14)-en-4α and 4β-ols[31] and tetracyclic amine[32,33] **23** respectively. The conversion of the amine **23** into the diterpene alkaloid atisine has already been reported.[33]

As the synthesis of ketone **19**, perhydrophenanthrene **20**, ketone **21** and dicarboxylic acid **22** from 6-methoxy-α-tetralone were reported by us between the years 1972 and 1982, their description has been omitted from this review.

Synthetic studies on sesquiterpenes

Our research group has witnessed the importance of 5-methoxy-α-tetralone **1** for the synthesis of natural products related to sesquiterpenes though its value as starting material has seldom been reported from other laboratories.[34] We describe in this article the conversions of tetralone **1** into the following sesquiterpenes.

Mansonone F and biflorin

Mansonone F and biflorin which possess an unusual oxaphenalene skeleton belong to a series of naturally occurring o-naphthoquinones. Biflorin **24** was isolated from the flowers, leaves and roots of *Capraria biflora L.*[35] and exhibits antibiotic properties. Its structure was determined by Prelog and coworkers.[36,37] Mansonone F **25**, a tricyclic sesquiterpenoid reported as phytoalexin,[38,39] was isolated[40] from the heartwood of a West African tree *Mansonia altissima*

Chev. (Sterculiaceae) and showed highly potent anti-MRSA antioxidant and antifungal activity. Best and Wege have reported[41] the total synthesis of biflorin **24** and mansonone F **25**. In addition, one total synthesis[42] and one formal total synthesis[43] of mansonone F have been published. During the course of a program which had its goal on the total synthesis of sesquiterpenes, we planned to accomplish the transformation of 5-methoxy-α-tetralone **1** into the ketone **31** (Scheme 4) whose smooth conversion into biflorin **24** and mansonone F **25** has already been published.[41]

The Grignard reaction of tetralone **1** with methylmagnesium bromide followed by acid treatment furnished directly the olefin **26** which was transformed quantitatively to phenol **27** by treatment with diisobutylaluminium hydride in toluene. Its conversion into the compound **28** was accomplished in three steps: (i) catalytic hydrogenation with Pd-C (5%), (ii) formylation with triethyl orthoformate and aluminium chloride, and (iii) catalytic hydrogenation with Pd-C (10%) at 500 psi. Formylation was also attempted by Vilsmeir[44] reaction but the desired product was obtained in poor yield. Alkylation of **28** with ethyl bromoacetate in acetone and potassium carbonate produced the compound **29** which underwent dehydrogenation on heating under reflux with palladium-charcoal (10%) in ethylene glycol. The compound obtained in 65% yield, was hydrolysed with sodium hydroxide to the acid **30**. It was subjected to cyclisation with PPE (polyphosphonate ester) to obtain the ketone **31** in 71% yield. Its spectral data were in complete agreement with the proposed structure and identical with literature data.[41] The cyclisation of acid **30** to ketone **31** could not be accomplished with typical reagents like polyphosphoric acid, boron trifluoride etherate, aluminium chloride, *etc*. The reason for the failure is probably due to acid sensitive nature of the OCH$_2$COOH group. In all cases the resulting compound was identified as the known[43] naphthol **32**.

Cacalol

The sesquiterpene cacalol **39**, which has been isolated[45] from the root of *Cacalia decomposita A Gray,* exhibits important biological activities.[46–47] Several syntheses[48-51] of this important natural product have been reported. We have developed a new route for the synthesis of cacalol **39**, which differs considerably from that of the published routes.[48-51] The essentials steps of our synthesis are depicted in Scheme 5.
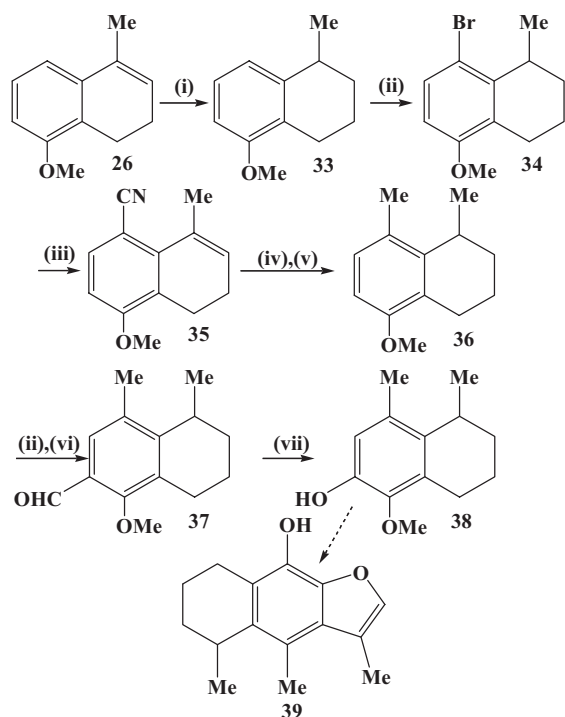
The previously described dihydronaphthalene **26** (Scheme
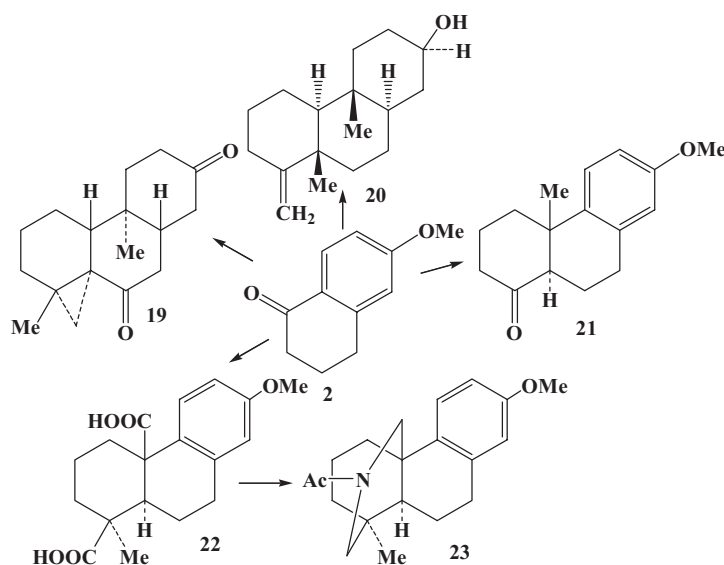
Scheme 3
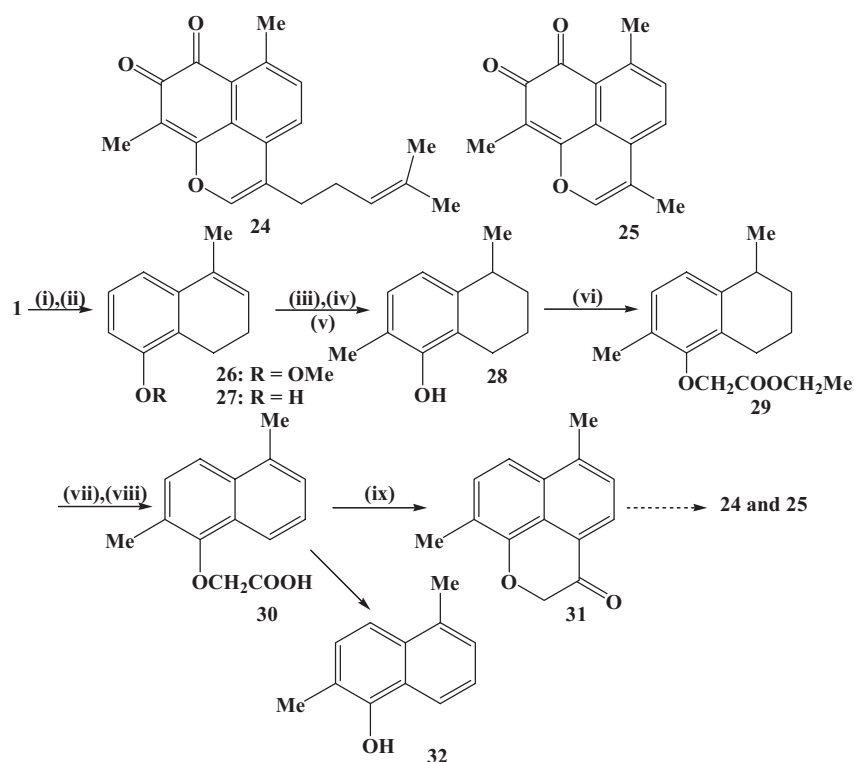
Scheme 4   Reagents: (i) MeMgBr, Et$_2$O, HCl (6N); (ii) DIBALH, toluene; (iii) H$_2$, Pd/C (5%); (iv) HC(OEt)$_3$, AlCl$_3$; (v) H$_2$, Pd/C, ethylacetate; (vi) BrCH$_2$COOEt, K$_2$CO$_3$, Me$_2$CO; (vii) Pd/C (10%), (CH$_2$OH)$_2$; (viii) NaOH, H$_2$O; (ix) PPE.

Scheme 5   Reagents: (i) H$_2$, PtO$_2$, EtOH; (ii) NH$_4$Br, H$_2$O$_2$, AcOH; (iii) CuCN, THF; (iv) DIBALH, Toluene; (v) H$_2$, Pd/C, AcOEt; (vi) DMF, n-BuLi; (vii) H$_2$O$_2$, H$_2$SO$_4$, MeOH.

4) on catalytic hydrogenation, furnished the known[52] tetralin **33**. Bromination[53] with ammonium bromide and hydrogen peroxide in acetic acid produced the bromotetralin **34**, which on heating with cuprous cyanide in tetrahydrofuran[54] gave the cyanotetralin **35**. Its conversion to methyl tetralin **36** was effected by reduction with diisobutylaluminium hydride (DIBALH) and catalytic hydrogenation respectively.

Bromination of **36** followed by formylation with *n*-Butyllithium (n-BuLi) and dimethylformamide (DMF) produced the aldehyde **37** which on oxidative rearrangement,[55] led to the formation of tetralol **38**. Its spectral data were in complete agreement with the proposed structure and quite similar with those reported for the tetralol **38**. As the three steps conversion of **38** to cacalol **39** has already been reported[51] our alternative approach for **38** constitutes a formal total synthesis of cacalol.

Cadinene dihydrochloride

Cadinene dihydrochloride is a bicarbocyclic sesquiterpene **45** whose synthesis has been developed by Dev[56] and Soffer.[57] 6-Methoxy-4-isopropyl-1-tetralone **44**, prepared[58] from 7-methoxy-α-tetralone **3** by a nine step sequence, was the starting material of Dev's synthesis of cadinene dihydrochloride. An alternative synthesis of 6- methoxy-4-isopropyl-1-tetralone was also reported by Bardhan and Mukerjee[59] in six steps. We have developed a very short synthesis of the tetralone **44** from 7-methoxy-α-tetralone **3**. The Scheme 6 describes our approach.

Treatment of the commercially available 7-methoxy-α-tetralone **3** with isopropylmagnesium chloride in the presence of cerium chloride,[60] produced the tertiary alcohol **40** in 91% yield. The same reaction when conducted in the absence of cerium chloride, afforded a mixture (40:60) of alcohols **40** and **41** (as detected by GC and MS). The crude alcohol **40**, which did not exhibit the presence of tetralone **3**, on dehydration with *p*-toluenesulfonic acid produced the olefin **42** in 82% yield. It was converted to tetralin **43** in 95% yield by catalytic hydrogenation with Pd/C(10%). Oxidation of tetralin **43** with chromic acid in acetic acid produced tetralone **44** in 62% yield. The spectral data of **44** agreed with the proposed structure. The product was also characterised by its 2,4-dinitrophenylhydrazone whose melting point was identical with that reported.[59] It can be seen that the synthesis of tetralone **44**, a potential intermediate for cadinene dihydrochloride **45**, has been achieved in only four
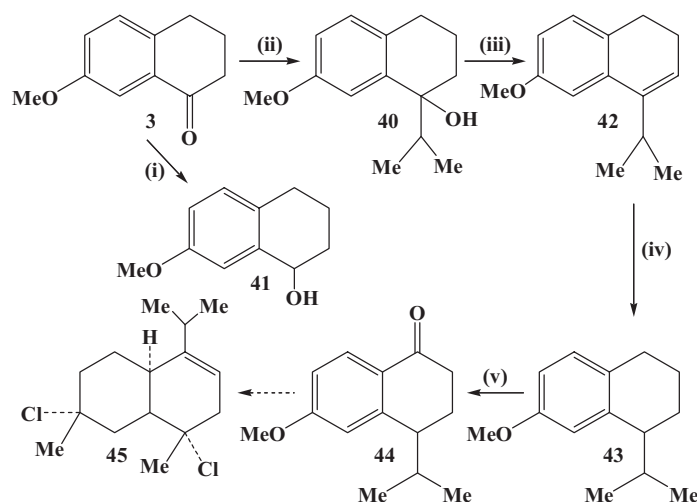
Scheme 6   Reagents: (i) iPrMgCl, THF, 0°C; (ii) i-PrMgCl, CeCl$_3$, THF,0°C; (iii) pTsOH, C$_6$H$_6$; (iv) H$_2$, Pd/C, 10%, 1 atm; (v) 10% aq. CrO$_3$-AcOH.

steps from 7-methoxy-α-tetralone **3**. The synthesis utilises an operationally simple procedure and is suitable for large scale production.

Miscellaneous
In the above discussions the transformations of the tetralones **1**, **2** and **3** into the terpenoid compounds have been described. These tetralones have also been converted into natural products not related to terpenes. The results of our investigation are described below.

Orchinol
The phytoalexin orchinol **53** and related dihydrophenanthrene have been the subject of intense synthetic investigations due

to wide range of biological activities. Several total syntheses of orchinol have been reported.[61] In continuation of our investigations of the transformations of α-tetralones, we wish to describe a total synthesis[62] of orchinol **53**. A retrosynthetic analysis of orchinol demonstrated that 6-methoxy-α-tetralone **2** can be utilised as starting material for its synthesis. The Scheme 7 describes the route chosen.

The transformation of tetralone **2** into the tricyclic ketone **46** was carried out following the same procedure already described in Scheme 1. The dienone **47**, obtained by dehydrogenation of the ketone **46** with 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) underwent dienone-phenol rearrangement on heating with p-TsOH providing the phenol **48** in 50% yield. It was alkylated with bromoacetonitrile[63] to afford the nitrile **49**. This
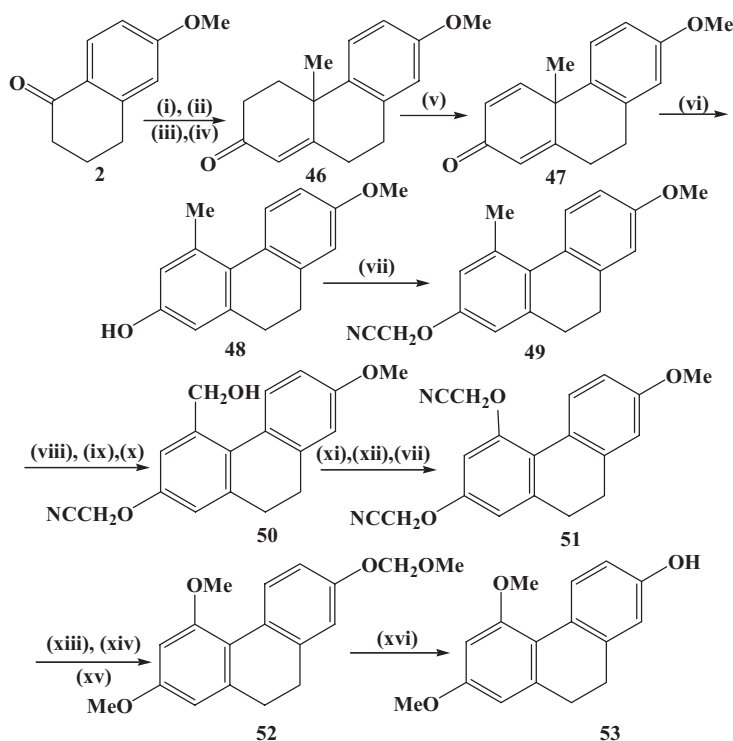
Scheme 7   Reagents: (i) MeMgBr, Et$_2$O; (ii) McPBA, CH$_2$Cl$_2$; (iii) H$_2$SO$_4$; (iv) H$_2$C=CHCOCH$_3$; (v) DDQ; (vi) p-TsOH, C$_7$H$_8$; (vii) BrCH$_2$CN, Me$_2$CO, K$_2$CO$_3$; (viii) KMnO$_4$, Dicyclohexyl-18-crown-6; (ix) Me$_2$SO$_4$, K$_2$CO$_3$; (x) LiAlH$_4$; (xi) BaMnO$_4$, CH$_2$Cl$_2$; (xii) 32% aq H$_2$O$_2$, MeOH, H$_2$SO$_4$, KHSO$_4$; (xiii) BBr$_3$, CH$_2$Cl$_2$; (xiv) DME,PTS, molecular sieves (xv) (a) H$_2$, PtO$_2$, EtOH, (b) Me$_2$SO$_4$, K$_2$CO$_3$; (xvi) MeCOOH.
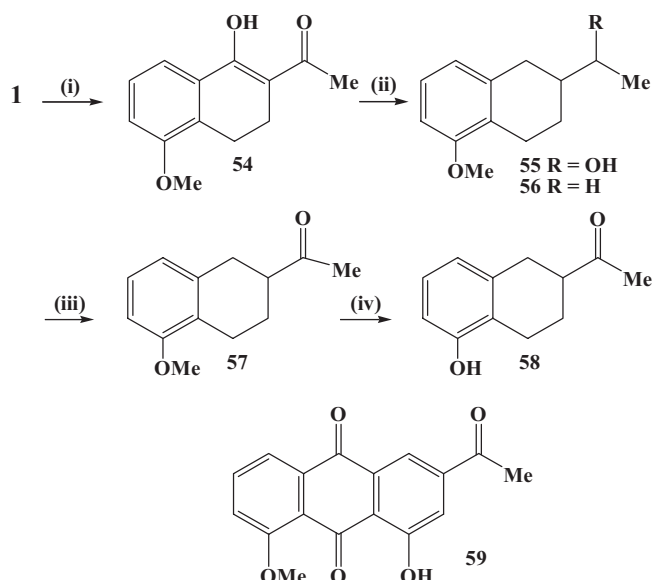
Scheme 8 Reagents: (i) AcOEt, C_6H_6, DMSO, NaOMe; (ii) H_2, , PtO_2, AcOH, EtOH; (iii) CrO_3, Py; (iv) BBr_3, CH_2Cl_2.

was subjected to (i) oxidation with potassium permanganate and dicyclohexyl-18-crown-6 at room temperature,[42] (ii) methylation of the resulting acid with dimethylsulfate and potassium carbonate in acetone and (iii) reduction with lithium aluminium hydride in tetrahydrofuran to furnish the alcohol **50**. This was oxidised with barium permanganate and then treated with 32% aqueous hydrogen peroxide in methanol and concentrated sulfuric acid containing a trace of potassium hydrogen sulfate.[65] The resulting alcohol was alkylated to give **51**. The methoxy group of the dinitrile **51** was replaced by methoxymethyl group via dimethoxylation followed by methoxymethylation. Catalytic hydrogenation of the product and methylation furnished the compound **52**. Treatment with acetic acid led to the formation of phytoalexin orchinol **53**. Its spectral data were identical with that reported.[61]

7,9,11-Trideoxydaunomycinone
Rao and collaborators reported[66,67] the synthesis of 2-acetyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene **58** and its transformation into 7,9,11-trideoxydaunomycinone **59** which can be converted into aglycones of the antitumor antibiotic (±)11-deoxydaunomycinone. The reported synthesis of **58** involves nine steps. It has been possible for us to develop a simple short synthesis[68] of the compound **58** from 5-methoxy-α-tetralone **1**.

Acetylation of the tetralone **1** with ethyl-acetate yielded exclusively the C-acetyl enol **54** in 77% yield, which on catalytic hydrogenation with PtO_2 in ethanol and acetic acid at room temperature and atmospheric pressure produced the enol **55 (**85%) and the compound **56** (12%). The formation of these two compounds can be explained by assuming that hydrogenolysis occurred during hydrogenation of enol **54** leading to the formation of enol **55** which suffered partial hydrogenolysis yielding the compound **56**. Oxidation with the Sarett reagent provided ketone **57**. This was converted to the target compound **58** by demethylation with boron tribromide in dichloromethne. Its spectral data (ir and nmr) closely matched those reported.[67] In conclusion by choosing 5-methoxy-α-tetralone as starting material, it has been possible to develop a simple four step synthesis of compound **58**. We believe that the present method can be utilised for the synthesis in gram quantities of the compound **58** for its transformation into (±)-11-deoxydaunomycenone.

Conclusions

The present review summarises the results of our investigations concerning the synthesis of several diterpenes and sesquiterpenes from 5-methoxy, 6-methoxy and 7-methoxy-α-tetralones. In addition, the utility of these tetralones in the synthesis of valuable intermediates for phytoalexin orchinol and anrarthacycline antibiotic, has been discussed. Our research group has shown the importance of the tetralone **1**, **2**, **3** in developing simple and short steps synthesis of diterpenes and sesquiterpenes. We believe that there is further scope for their applications in the synthesis of terpenoids compounds and many non natural compounds. Just before the submission of the manuscript we observed another formal total synthesis[69] of mansonone F which was not mentioned during our discussion on the synthesis of mansonone F from 5-methoxy-α-tetralone.

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