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Use of 5-methoxy-α-tetralone in synthesis of diterpenes and sesquiterpenes

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Abstract

The transformations of 5-methoxy-α-tetralone are described. Studies on the synthesis of diterpenes veadeiroic acid **9,** triptolide **15** and sesquiterpene cacalol **21** from 5-methoxy-α-tetralone **1** are discussed. Transformation of 5-methoxy-α-tetralone **1** into 8-methoxy-α-tetralone **27** is described. 5-methoxy-α-tetralone was subjected to several organic reactions to obtain diterpenes and sesquiterpene.

Keywords: 5-methoxy-α-tetralone, veadeiroic acid, triptolide, cacalol, 8-methoxy-α-tetralone.

Uso de la 5 metoxi-α-tetralona en la síntesis de diterpenos y sesquiterpenos

Resumen

Se describe la transformación de la 5-metoxi-α-tetralona 1. Se discute la síntesis de diterpenos como el ácido veaderoico **9,** triptolide **15** y del sesquiterpeno cacalol **21** a partir de la 5-metoxi-α-tetralona **1.** También se describe la transformación de la 5-metoxi-α-tetralona **1** en la 8-metoxi-α-tetralona **27**.

Palabras clave: 5-metoxi-α-tetralona, ácido veadeiroico, triptolide, cacalol, 8-metoxi-α-tetralona.

Introduction

The selection of starting material is one of the essential factors for achieving the success in the synthesis of natural and non-natural products objective. The easy availability of the starting material facilitates synthetic work. Since last ten years our research group has shown interest in the synthesis of natural products related to diterpenes and sesquiterpenes which show remarkable structural variations and many exhibits a range of biological properties, including anti-cancer 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 utility of the commercially available 5-methoxy-α-tetralone **1** as start-

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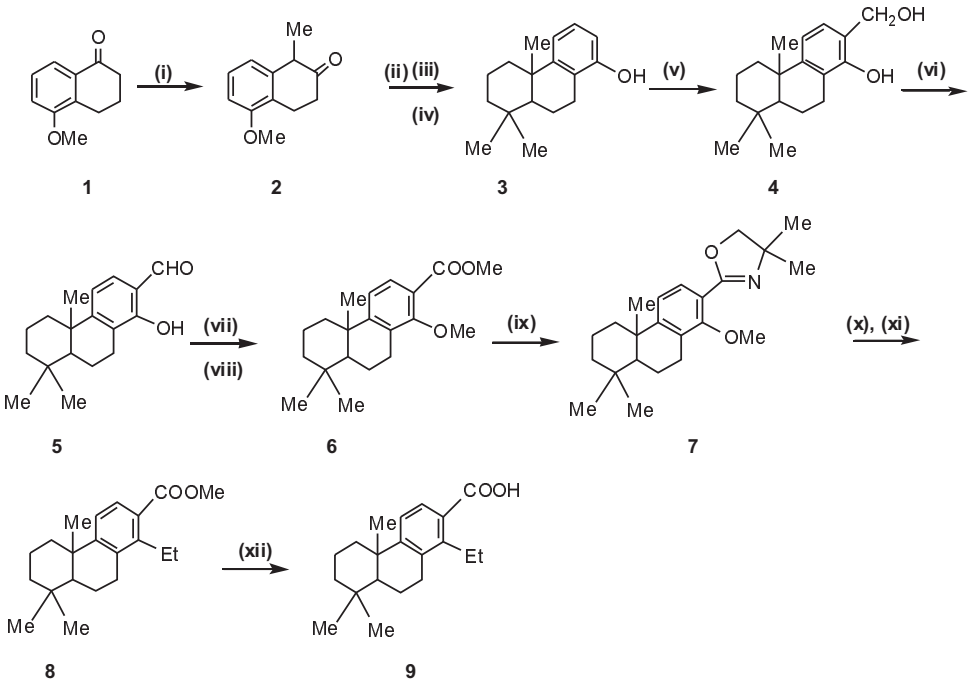
ing materials in synthesis of diterpenes and sesquiterpenes. The present account is largely a survey of work carried on the conversions of the tetralone **1** to the diterpenoid and sesquiterpenoid compounds at the Department of Chemistry, IVIC, Caracas, Venezuela and at the Department of Chemistry, university of Zulia, Maracaibo, Venezuela. Related studies by other workers are mentioned only where they correspond or correlate closely with our studies.

Synthetic studies on diterpenes

Veadeiroic acid

The chemical literature records the importance of 5-methoxy-β-tetralone in the synthesis of diterpenes (1) but very few natural products related to terpenoid compounds have been synthesized from 5-methoxy-α-tetralone. We have tried for the first time to use 5-methoxy-α-tetralone **1** as starting material for the synthesis (2) of veadeiroic acid **9,** a diterpene with a rare cleistanthene skeleton. The first total synthesis of veadeiroic acid **9** was reported by Saha and Nasipuri (3). Our synthetic route is described very briefly in **Scheme 1**.

5-methoxy-α-tetralone **1** was converted into the phenol **3** by the published procedure (4). Subjection of the phenol **3** to hydroxymethylation, oxidation and esterification respectively afforded the compound **6** which was treated with 2-amino-2-methylpropanol to obtain the oxazole derivative **7.** This was alkylated with EtLi and the resulting product was successively hydrolysed with hydrochloric acid (10%) and methanolic hydroxide (10%) to obtain methyl veadeiroate **8** which on hydrolysis yielded veadeiroic acid **9.** Its spectral data closely matched with that of the reported



Reagents: (i) (a) MeI, MeMgI, Et_2O, Heat; (b) MCPBA, CH_2Cl_2, (c) HCl, H_2O; (ii) CH_2=CHCOMe; (iii) (a)MeI, C_4H_9OK, C_4H_9OH; (b) NH_2NH_2, KOH, DEG; (c) H_2, Pd-C(10%); (iv)HBr-MeCOOH; (v) (a) $PhB(OH)_2$, $(CH_2O)n$, $MeCH_2COOH$; (b) benzene, propylene glycol; (vi) DDQ, dioxane; (vii) Ni-peroxide, NaOH, H_2O; (viii) K_2CO_3, Me_2SO_4; (IX) (a) C_4H_9OK, DMSO, (b) $SOCl_2$, (c) 2-amino-2-methylpropanol; (x) EtLi; (xi) HCl (10%), NaOH in MeOH, CH_2N_2; (xii) C_4H_9OK, DMSO.

Scheme 1. Synthesis of veadeiroic acid **9.**

data (3). (Reported[3] data:$_{max}$ (KBr)/cm^{-1} 3250-2950 (br), 1480, 1455, 1410, 1375, 1010-825; *m/z* 286 (M^+,61), 277, 189 (90) and 1.75 (100); δ 0.94 (3H, s, 4Me eq), 0.96 (3H, s, 4-Me ax), 1.21 (3H, t, J=7 Hz, $ArCH_2Me$), 1.23 (3H, s, 10-Me), 1.50-2.40 (9H, m, 1,2,3, +6-H_2 +5-H), 2.80-3.10 (4H, m, 2x$ArCH_2$), 7.22 (1H, d, J=8 Hz, 11-H) and 7.80 (1H, d, J= 8 Hz,12-H), (Obtained[2] data: *m/z* 300 (M^+) and 285 (M^+- Me); $_{max}$/cm^{-1} 3442-2845 (br), δ 0.94 (3H,s), 094.(3H,s), 1.21 (3H, s), 1.24 (1H, t, J=8 Hz, $ArCH_2Me$), 2.86-3.02 (4H, m, 2x$ArCH_2$), 3.56 (3H, s, OMe), 7.23 (1H, d, J= 8Hz*)* and 7.60 (1H, d, J=8 Hz) (aromatic protons).

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 of structural complexity.

Triptolide

5-Methoxy-α-tetralone **1** was also chosen, as the starting material, to achieve the synthesis (5) of a potential intermediate **14** which was already transformed (9) to triptolide **15,** a highly oxygenated diterpene. Kupchan *et al.* (6) 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 (7, 8). It also inhibits DNA synthesis in L-1210 leukaemia cells without directly damaging DNA. Triptolide **15** is a tri-epoxy abietane lactone which has been the subject of synthetic endeavours (5) because of its cytotoxic activity and partly because of its poor availability from natural sources.

In 1982, Graver and Van Tamelen reported (9) the synthesis of the abietane ether **14** and its transformation into triptolide **15**. The published synthesis of **14** involves many steps and therefore we tried to develop a concise and practically convenient route to this important compound and after many trials the route (5) depicted in **Scheme 2** which utilizes 5-methoxy-α-tetralone as a starting material proved satisfactory. Its conversion into the compound **14** was achieved through the intermediates **10-13**.

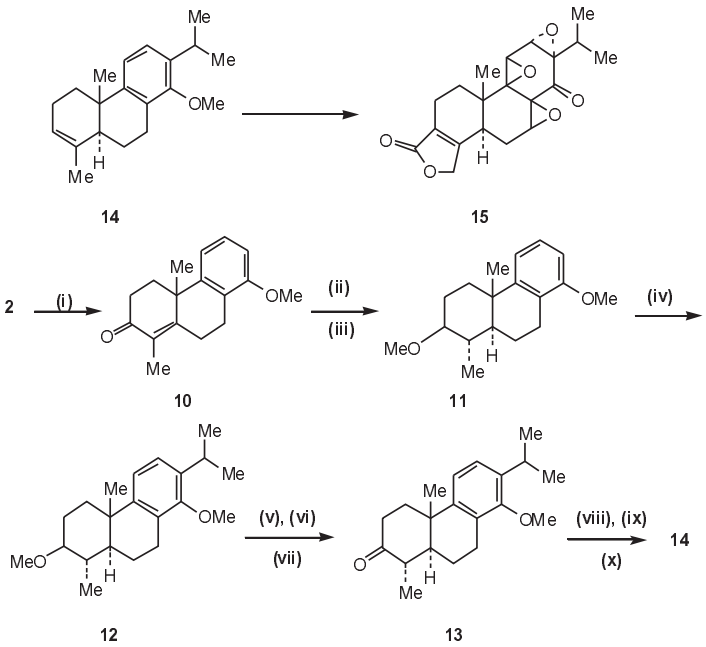
The conversion of the 5-methoxy-α-tetralone to the phenanthrene **11** was accomplished by standard organic reactions. The alkylation of **11** was carried out with isopropanol and polyphosphosphoric acid (PPA).The use of suphuric acid and boron trifluoride etherate did not afford satisfactory yield. The transformation of **12** to the target compound **14** was performed without any difficulty. The sequences of reactions are summarized in **Scheme 2**. 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.

Synthetic studies on sesquiterpenes

Cacalol

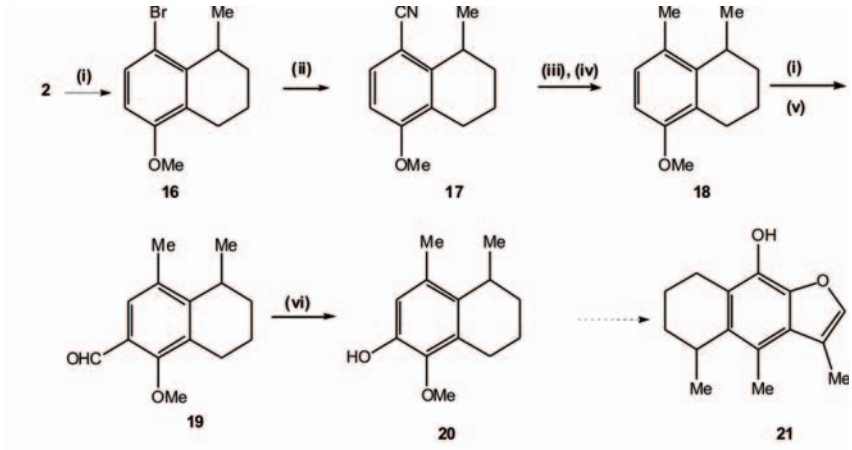
The sesquiterpene cacalol **21,** which has been isolated (10) from the root of *Cacalia decomposita A Gray,* exhibits important biological activities (11, 12). Several syntheses (13) of this important natural product have been reported. We have developed a new route for the synthesis of cacalol (14) which differs considerably from that of the published routes (13).

The essentials steps of our synthesis are depicted in **Scheme 3.** The synthesis of tetraline **19** from the tetralone **1** was carried out without any difficulty employing standard organic reactions. The oxidative rearrangement (13) of tetralin **19** furnished the known tetraol (16) **20**. As the transformation of tetraol **20** into cacalol **21** is well known (13), the synthesis of **20** constitutes an alternative of a formal total synthesis of cacalol **21**.



Reagents: (i) 1-chloro-3-pentanone; (ii) Na, *n*-propanol; (iii) NaH, THF, MeI; (iv) Me_2CHOH, PPA, 80°C; (v) Me_3SiCl, NaI, MeCN; (vi) CrO_3, H_2SO_4; (vii) Me_2SO_4, K_2CO_3; (viii) $NaBH_4$, MeOH; (ix) TsCl/Py; (x) LiBr, DMF, 80°C

Scheme 2. Synthesis of the triptolide **15**

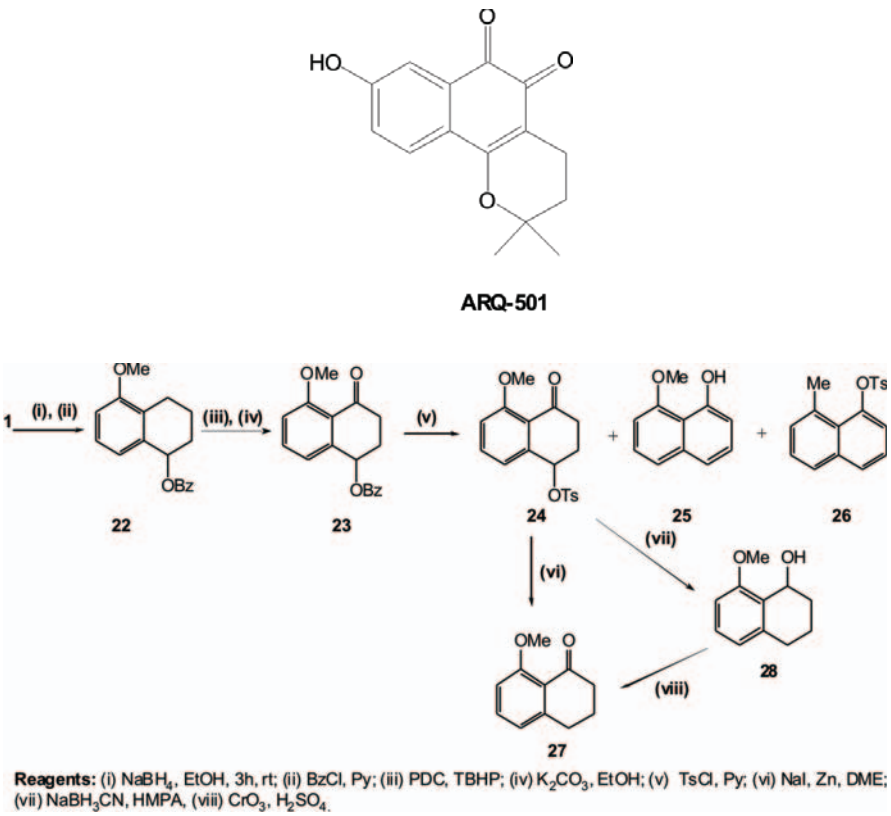


Reagents: (i) (a) MeI, MeMgI, Et_2O, Heat; (b) H_2, PtO_2, EtOH; (c) NH_4Br, H_2O_2, AcOH: (ii) CuCN, THF; (iii) DIBAL, Toluene; (iv) H_2, Pd/C, AcOEt; (v) DMF, *n*-BuLi; (vi) H_2O_2, H_2SO_4, MeOH

Scheme 3. Synthesis of cacalol **21**.

8-methoxy-α-tetralone

Recently we have accomplished the transformation of 5-methoxy-α-tetralone **1** into the 8-methoxy-α-tetralone **22** (16) which is a valuable starting material in the synthesis of ARQ-501. It is a promising anticancer agent currently in multiple Phase II clinical trials (20). ARQ-501 is also effective against human ovarian cancer and prostate cancer xenografs in mice (21). 8-methoxy-α-tetralone **22** has been synthesized by five different routes (19).



Scheme 4. Synthesis of the 8-methoxy-a-tetralona **22**

In course of our studies on the synthesis of natural products related to terpenes we tried to achieve the transformation (16) of 5-methoxy-α-tetralone **1** into 8-methoxy-α-tetralone **27**. The synthetic route is described in **Scheme 4**.

Metal hydride reduction of the tetralone **1** followed by benzoylation of the resulting alcohol produced the derivative **22** which on oxidation with pyridinium dichromate (PDC) and *t*-butylhydroperoxide (TBHP) (70% in water) produced the ketobenzoate **23** in 75% yield. Alkaline hydrolysis of **23** followed by tosylation with *p*-toluene- sulfonylchloride (TsCl) and pyridine (Py) afforded ketotosylate **24** (12%), naphthol **25** (31%) and tosylate **26** (30%). Detosylation (16) of **24** on heating under reflux with sodium iodide (NaI) and zinc (Zn) in dimethoxyethane (DME) afforded tetralone **27** in 22% yields. The ketotosylate **24** on heating with sodium cyanoborohydride ($NaBH_3CN$) and hexamethylphosphoramide (HMPA) (16) underwent detosylation yielding the tetraol **28** (45%) as brown oil which on oxidation with Jones reagent yielded the 8-methoxy-α-tetralona **27** in 87% yield.

In conclusion, a new approach for the synthesis of 8-methoxy-α-tetralone has been developed from 5-methoxy-α-tetralone **1**. Although the yield by the present procedure is not high compared to published methods (19, 20), but it is superior to other methods (21, 22).

Conclusion

The present account describes the use of 5-methoxy-α-tetralone in synthesis of

diterpenes and sesquiterpenes. In addition a new approach for the transformation of 5-methoxy-α-tetralone to 8-methoxy-α-tetralone is described. As the content of the article has been published in different journals, the synthetic details of the present account have been discussed very briefly. .We believes that in near future it will be possible to synthesize many terpenoid and non natural compounds by employing 5-methoxy-α-tetralone as starting material.

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