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The chemistry of vetivalene-type naturally occurring sesquiterpenoids

P. ANANTHA REDDY* AND G. S. KRISHNA RAO**
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012.

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Abstract

Vetivalene, 1,4-dimethyl-6-isopropylnaphthalene (1) represents a new sesquiterpene skeleton which is presumed to originate from eudesmane by a shift of the angular methyl group. Novel sesquiterpenes related to vetivalene have been isolated from plant sources in recent years. A survey dealing with the chemistry (structure, synthesis and configuration) of members of this interesting new class of sesquiterpenes, comprising occidol, rishitinol and the various emmotins is presented.

Key words : Vetivalene, sesquiterpenoids, occidol, rishitinol, emmotins, structure, synthesis, configuration.

1. Introduction

In recent years, about a dozen sesquiterpenes have been isolated which may be regarded as derivatives of 1,4-dimethyl-6-isopropylnaphthalene (1), called vetivalene.[1] Vetivalene (1) represents a new sesquiterpene skeleton which is presumed to originate from eudesmane (Fig. 1) by a shift of the angular methyl group. The present survey deals with the chemistry (structure, synthesis and configuration) of members of this interesting new class of sesquiterpenes, comprising occidol, rishitinol and the various emmotins.

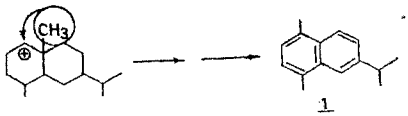

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FIG. 1

* Present address : Department of Chemistry, University College of Swansea, Singleton Park, Swansea SA2 8PP (U.K.).
** Address for correspondence.

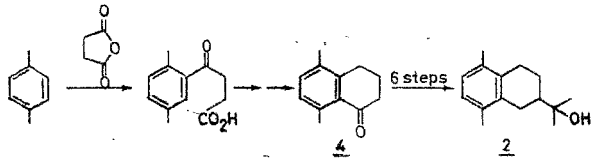
2. Occidol (2)

A major sesquiterpene alcohol ($C_{15}H_{22}O$) (2) named occidol, m.p. 69–70°, $[\alpha]_D^{25}$ + 163·7° ($CHCl_3$) was isolated[2] from the essential oil of *Thuja occidentalis* L. along with occidentalol (3) (Fig. 2). The structure depicted as (2) for occidol was elucidated by Hirose and Nakatsuka[2] and was confirmed by a number of syntheses.

2 3

FIG. 2

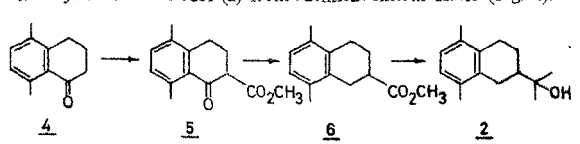
The synthesis of occidol (2) by Hirose and Nakatsuka[3] (Fig. 3) starts from *p*-xylene and proceeds *via* the tetralone (4). The tetralone was converted to (±)-occidol (2) in six steps.



4 2

FIG. 3

A series of three syntheses of occidol have been reported by Ho[4–6] during 1971–73 (Figs. 4–6). Unaware of the earlier synthesis[3], Ho reported[4] in 1971 a more or less identical synthesis of occidol (2) from identical intermediates (Fig. 4).



4 5 6 2

FIG. 4

In this second synthesis of occidol Ho[5] started with 3,6-dimethylphthalic anhydride (7) (Fig. 5). Its reduction to the diol (8) with LAH_4 followed by treatment with phosphorus tribromide, gave the dibromide (9) which was converted to the *o*-quinodimethane (10). Diels–Alder reaction of (10) with methyl acrylate gave the tetralin ester (6). Reaction of the ester (6) with methyllithium gave (±)-occidol (2).

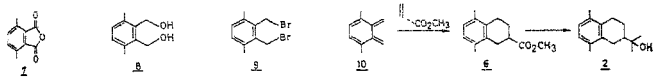


FIG. 5

In his third synthesis[6] of occidol, Ho utilized transition metal catalysis to carboxylate the dihydronaphthalene (13) (obtained by the route indicated in Fig. 6) by photoreaction with nickel carbonyl. Reaction of the resulting tetralin ester (6) with methyl lithium completed the synthesis of (±)-occidol (2).

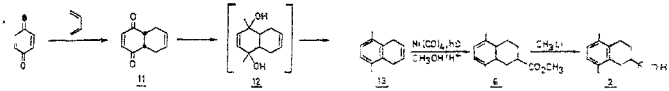


FIG. 6

The synthesis of (±)-occidol by Dauben[7] as depicted in Fig. 7 starts from the carbomethoxy acetylcyclohexene (14), prepared by Friedel-Crafts acylation of methyl cyclohex-3-enecarboxylate. The bicyclic diene ester (15) obtained from the keto ester (14) by treatment with 2-butenylidene triphenylphosphorane was dehydrogenated to the tetralin ester (6) from which (±)-occidol (2) was obtained in the usual way.

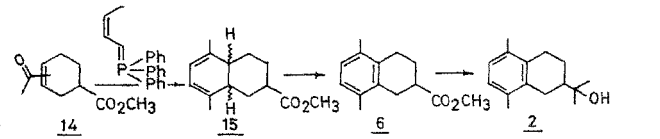


FIG. 7

Wolinsky's[8] synthesis of (±)-occidol starts from 9-chloro-1-*p*-menthene (16) derived from (+)-limonene. Its condensation with vinylacetyl chloride (Fig. 8) gave the chloronaphthalenone (17) as one of the products in 33% yield, resulting from a sequence of hydride and methyl shifts. Addition of methylmagnesium iodide to the ketone (17) was accompanied by dehydration in the work-up, giving the diene (18). Its aromatization, followed by dehydrochlorination gave the isopropenyltetralin (19) which afforded (+)-occidol (2) on oxymercuration-demercuration sequence of reactions.

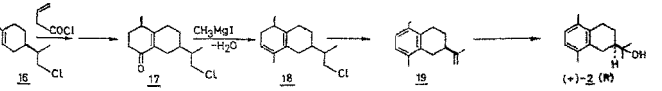


FIG. 8

The synthesis of (±)-occidol developed in our laboratory[9,10] exploits the synthetic potential of Vilsmeier reaction in the key-step. Thus the dihydronaphthaldehyde (21), obtained from 5,8-dimethyl-1-tetralol (20) on Vilsmeier reaction, was converted to the methyl dihydronaphthoate (22) (Fig. 9). Its hydrogenation gave the tetralin ester (6), the well-known precursor for (±)-occidol (2).

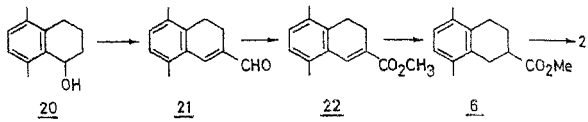


FIG. 9

The absolute configuration (R) of the chiral centre at C_6 of occidol was established by correlation[11,12] with (−)-santonin (23) as outlined in Fig. 10.

Hyposantonous acid (24a) prepared from (−)-santonin (23) was converted to (+)-occidol in six steps *via* the chiral ketone (25) which established identical configurations at C-6 of both (−)-santonin and (+)-occidol.

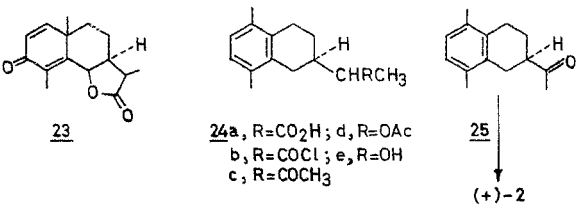


FIG. 10

The conversion of emmotin-A and emmotin-F (*vide supra*) to (+)-occidol by Oliveira *et al*[13] is yet another interesting exercise in configurational correlation involving occidol.

Emmotin-A diacetate (26) and emmotin-F diacetate (27) were reduced by zinc to the keto acetate (26) (Fig. 11). Catalytic hydrogenolysis and saponification of the acetoxy-tetralone (28) gave (+)-occidol.

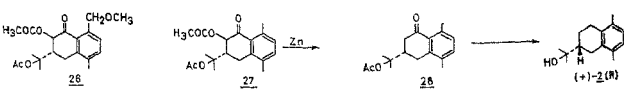
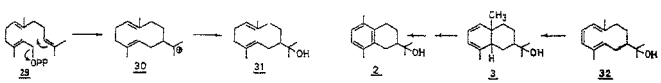


FIG. 11

A possible biogenetic origin of occidol is delineated in Fig. 12. The cyclodecadiene (30) representing the product of initial ring closure of *trans-trans*-farnesylpyrophosphate (29) may be visualised as a precursor for occidol. The charge bearing isopropyl group in (30) accepts a hydroxyl group to give the side chain as in (31), a situation encountered in a number of sesquiterpene alcohols. Dehydrogenation of the dienol (31) could give the 1,3,5-cyclodecatriene system (32). Its further transformation may occur *via* its valence tautomer, occidentalol (3) and finally to occidol (2) involving methyl shift and aromatization or its equivalent on intermediate oxidation states.



29 30 31 2 3 32

FIG. 12

3. Rishitinol (33)

From the infected tuber tissues of white potatoes (*Solanum tuberosum* and *S. demissum*) Katsui *et al*[14,15] isolated a sesquiterpene alcohol, rishitinol (33) along with rishitin (34).

Rishitinol ($C_{15}H_{22}O_2$) (33), m.p. 127–129°, $[\alpha] + 47°$ ($CHCl_3$), M^+ (234) was shown to contain a tetrasubstituted benzene with two vicinal hydrogens. Its failure to undergo oxidation with periodic acid and its co-occurrence with rishitin (34) suggested that rishitinol be represented by one of the structures (33 a), (33 b) and (33 c) (Fig. 13). Since, these structures would represent rishitinol as a hydroxy derivative of occidol (2), the PMR spectra of occidol and its synthetic intermediates were compared with that of rishitinol. The structures (33 b) and (33 c) with hydroxyls *peri* to the methyl groups were excluded and the structure (33 a) was preferred for rishitinol and the assignment was confirmed by synthesis[14,15].

The tetralone carboxylic acid (35), prepared starting from *p*-xylene in several steps, was esterified and reduced to the hydroxy esters (36) which on dehydration gave the dihydronaphthalene ester (37). It was converted to the oxyisopropyl derivative (38), which on hydroboration followed by oxidation afforded a mixture of isomeric 1,3- and 1,4-diols (39 and 40). The required 1,3-diol, *viz.*, (±)-rishitinol (33) was obtained from this mixture after elaborate chromatographic purification. In the PMR spectra of the epimeric alcohols (39) the CHOH proton of one appeared as a multiplet with $W_{H/2}$ of 25 Hz centred at δ 3·5 (*trans*), while in that of the other epimer corresponding to (33) it appeared as a broad singlet with $W_{H/2}$ of 7 Hz at δ 4·76 (*cis*).

Comparative study of the absolute configurations of rishitin[16–18] (34) and occidol[11,12] (2) indicated that the biogenetically related rishitinol (33) also would possess β-oriented oxyisopropyl group. Hence rishitinol was most favourably represented as (33).

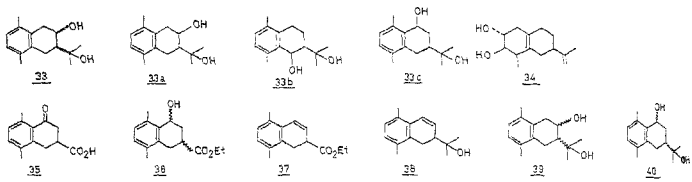


FIG. 13

4. Emmotin A (41)

A hydroaromatic bicyclic sesquiterpene methyl ether ($C_{16}H_{22}O_4$), m.p. 79°, M^+ (278), was isolated from the trunk wood of *Emmotum nitens* (*Icacinaceae*) by Oliveira *et al*[18]. The sesquiterpene called emmotin-A constituted one of a group of four compounds, *viz.*, emmotins-A, B, C and D with closely related structures occurring in the same plant.

The presence of an arylketone moiety in emmotin-A was inferred from its UV and IR spectra, while its PMR spectrum exhibited characteristic signals for (*a*) two aromatic *ortho* hydrogens, (*b*) one aromatic methyl, (*c*) one methoxymethyl group *peri* to a carbonyl function, (*d*) a hydroxyisopropyl group and (*e*) a secondary hydroxyl *α*- to a carbonyl. The *α*-ketol function –COCHOH– was also confirmed from chemical evidence. Based on these chemical and spectral (PMR) evidence of the sesquiterpene and its derivatives (acetylation, dehydration and reduction products), structures (41) and (42) (Fig. 14) were considered for emmotin–A, of which the former was preferred on biogenetic grounds, as well as from CMR spectral support.

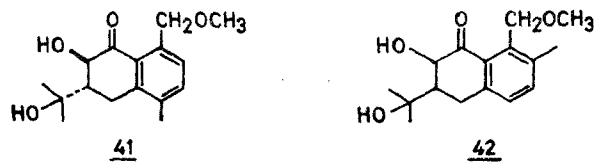
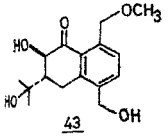


FIG. 14

5. Emmotin–B (43)

The determination of molecular weight (by MS) of emmotin-B[19] showed it to be oxy-emmotin–A ($C_{16}H_{20}O_5$). Its PMR spectrum resembled closely that of emmotin-A (41), differing mainly in the replacement of Ar–CH_3 (δ 2·32) by Ar–CH_2OH (δ 4·67). The presence of an extra OH group in emmotin–B was also revealed by the formation of

triacetate. Further insight into the structure of emmotin–B was provided by CMR. A comparative study of the chemical shifts of the non-aromatic carbons of emmotins–A and –B by application of the theory[20, 21] of chemical shifts, and biogenetic considerations established the structure (43) (Fig. 15) for emmotin–B, excluding the alternate structure (44).



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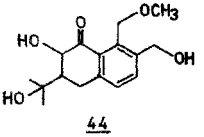

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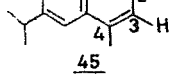
FIG. 15

6. Emmotin–C (45)

The third constituent from *Emmotum nitens* was named emmotin–C[19] ($C_{15}H_{16}O_3$), m.p. 121–124°, M^+ (244) and shown to be structurally related to emmotins–A and –B. The PMR spectrum of emmotin–C exhibited the characteristic signals: 3xAr–H, 2xOH, CHO, Ar–CH_3 and $CH(CH_3)_2$. Together with this information, the probable biogenetic relationship of emmotin–C with emmotin–A (41) suggested structure (45) (Fig. 16) for emmotin–C. Hydrogen bonded nature of an aldehyde carbonyl (O–H···O=C–H) [IR: ν_{max} 3440 (OH) and 1650 cm^{-1} (C=O); PMR: δ 9·66 (CHO) and 12·35 (OH)], *ortho* deshielded hydrogen (δ 7·79, *d*, H_2) coupled strongly (J = 8Hz) to another hydrogen (δ 7·24, *d*, J = 8Hz, H_3) and $W_{H/2}$ of this proton (H_3) signal (δ 7·24) revealing weak long range coupling with the neighbouring Ar–CH_3 (δ 2·77 *bs*) are in agreement with the structure (45) for emmotin–C.



45

FIG. 16

7. Emmotin–D (46)

A minor constituent of *Emmotum nitens*, called emmotin–D[19] (46) (Fig. 17) ($C_{15}H_{14}O_4$), m.p. 209–210°, M^+ (258), exhibited a typical UV spectrum of a naphthol. Its IR

spectrum and that of its diacetate and its aryl methyl ether indicated the presence of a γ-lactone unit (IR: ν_{max} 1745 cm^{-1}).

The PMR spectra of emmotin–D and its derivatives revealed two aromatic *ortho* hydrogens, one isolated aromatic hydrogen, an aromatic methyl group, two hydroxy functions one of which is part of an oxyisopropyl group. These spectral data and biogenetic considerations indicated the structure (46) for emmotin–D.

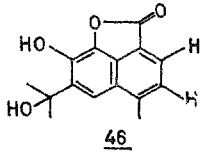


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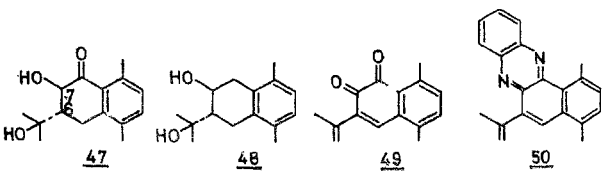
FIG. 17

8. Emmotin–F (47)

A hydroaromatic bicyclic sesquiterpene ($C_{15}H_{20}O_3$) isolated by Oliveira *et al*[13] from the heartwood of *Emmotum nitens* and named emmotin–F, was found to co-occur along with two other closely related compounds (emmotins–G and –H).

The three oxygen atoms of emmotin–F (47) were assigned to one carbonyl and two hydroxy functions (reduction to a triol and formation of a diacetate). The UV and IR spectra as well as the ease of catalytic hydrogenolysis of emmotin–F to a diol (48) showed that the carbonyl function is flanked on either side by an aromatic residue and a hydroxyl function (Fig. 18). The presence of –CHOHCO– grouping was evident from the formation of a red *o*-quinone (49) upon dehydrogenation, the structure of the *o*-quinone being confirmed by derivatization to the quinoxaline (50). The tertiary carbinol of emmotin–F formed part of a hydroxy-isopropyl group. These facts in conjunction with similar PMR spectra of emmotins–F,–A (41) and–B (43) led to the tentative assignment of emmotin–F also as a tetralone (47) (Fig. 18).



47 48 49 50

FIG. 18

The diacetates (27 and 26) of emmotins–F (47) and –A (41) were reduced with zinc and the product (28) (Fig. 11) gave (+)-occidol (2) on hydrogenolysis and saponification. While this correlation established the carbon skeleton of emmotin–F (47), the *trans* diaxial relationship of $\underline{H}_6$ and $\underline{H}_7$ as indicated by the PMR data, fixed the C–6 and C–7 configurations of emmotin–F (47).

The ORD curve of emmotin–F was found to be superimposable on those of emmotins–A (41) and –B (43) in which the substituents at C–6 and C–7 are *trans*, showing that all the three tetralone emmotins–A, –B and –F (41, 43 and 47) possess identical absolute configurations.

9. Emmotin–G (51 a)

Emmotin–G, a sesquiterpene naphthol ($C_{15}H_{18}O_2$) was isolated from *Emmotum nitens*[13], m.p. 112–115°, M^+ (229), IR: ν_{max} 3473 and 3125 cm^{-1} (OH), UV (EtOH): λ_{max} 243 (53,900), shifted in the presence of NaOH to λ_{max} 254 nm (ε 55,200) (naphthol), PMR: two *ortho* (δ 7·08 and 7·18, *dd*, $\underline{J}$ = 8 Hz) and two *para* (δ 7·42 and 7·73, *s*) aromatic protons.

As expected, acetylation of emmotin–G (51 a) caused a strong paramagnetic shift (~0·59 δ) of the $\underline{H}_8$ singlet and oxidation with Fremy's salt gave the naphthoquinone emmotin–H[13] (52) (Fig. 19).

The syntheses of emmotin–G (51a) and its methyl ether[9,23] (51b) have recently been achieved in our laboratory. The key-step in these syntheses is the Vilsmeier formylation of 1,4-dimethyl-6-methoxytetralin (53) (Fig. 19) to the corresponding formyl tetralin (54) which on subsequent dehydrogenation to the naphthaldehyde (55), followed by oxidation and esterification gave the naphthol ester (56b). The hydroxy- (56a) and the methoxy- (56b) naphthoic esters were converted to emmotin–G (51a) and its methyl ether (51b) respectively.

FIG. 19

10. Emmotin–H (52)

An *ortho* naphthoquinone ($C_{15}H_{16}O_2$), m.p. 178–180°, M^+ (246) isolated[13] from *Emmotum nitens* was called emmotin–H (52) [UV: λ_{max} 265 nm (ε 40,800) and IR: ν_{max} 1649 cm^{-1}]. The intense red colour of emmotin–H was slowly discharged by the addition of aqueous sodium dithionate. In the aromatic region of its PMR spectrum it exhibited two *ortho* protons (δ 7·13 and 7·36, *dd*, $\underline{J}$ = 8 Hz) and a *peri* proton

(δ 7·86, *s*). These observations led to the formulation of the structure of the natural product as (52) (Fig. 20).

Reductive acetylation of emmotin–H (52) or dehydration of its quinoxalin derivative (57) gave the isopropenyl compounds (58) and (50) respectively. Since the anhydro-quinoxalin adduct (50) could be prepared from all the three emmotins–F (47), -G (51a) and–H (52), they were presumed to have closely related structural features and the same carbon skeleton as in occidol (2).

The structure (52) of emmotin–H has been confirmed by its synthesis[24] in our laboratory. The tetralone ester (59) (Fig. 20) was oxidized by selenium dioxide to the corresponding *o*-quinone ester (60). Its reductive acetylation afforded the diacetoxy naphthoic ester (61). Grignard reaction on the ester (61) with excess of CH_3MgI gave emmotin–H (52), presumably through aerial oxidation of the intermediate unstable triol (62).

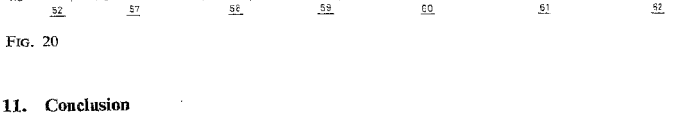


FIG. 20

11. Conclusion

From the above account it is seen that the structures and configurations of occidol, rishitinol and the emmotins are closely related. The co-occurrence of occidol (2) in *Thuja occidentalis*[25] with occidentalol (3), a sesquiterpenic alcohol of the general eudesmane skeleton, and the co-occurrence of all the structurally similar emmotins in another source (*Emmotum nitens*) are striking. A methyl shift in the parent eudesmane (3), accompanied by a diene-benzene rearrangement seems to characterize all these newly discovered vetivalene-type sesquiterpenes.

Acknowledgement

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Added in press

Manicol (2-isopropenyl-5-methyl-7-hydroxy-1,2,3,4-tetrahydro-8-naphthoic acid) recently isolated [J. Polonsky, Z. Varon, H. Jacquemin, D. M. X. Donnelly and M. J. Meegan, *J. Chem. Soc. Perkin* –I, 2065 (1980)] from the root bark of a Guyanan tree (*Dulacia guianensis*) is the latest member to be added to the vetivalene sesquiterpene family. Manicol has been reported to possess moderate antileukemic activity. Its structure and absolute stereochemistry (R-configuration) were assigned on the basis of spectroscopic evidence and partial synthesis.