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ISOLATION OF THE SESQUITERPENE ALCOHOL (−)-PACIFIGORGIOL FROM *VALERIANA OFFICINALIS*

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Key Word Index—*Valeriana officinalis*; Valerianaceae; sesquiterpenoid alcohol; (−)-pacifigorgiol.

Abstract—A tertiary bicyclic sesquiterpene alcohol has been isolated from *Valeriana officinalis*, and identified as (−)-pacifigorgiol, the optical antipode of the alcohol isolated from *Pacifigorgia adamsii*.

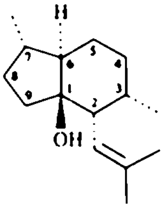
In our work on sesquiterpenoids in the essential oil of *Valeriana officinalis* L. *s. l.* [1, 2] a compound was isolated by means of low pressure column chromatography and preparative TLC which proved to be a tertiary alcohol with a molecular formula $C_{15}H_{26}O$. The percentage of this compound in oils of different *V. officinalis* strains varied from 0.7 to 8.6% [Tittel, G. and Bos, R., unpublished results].

In the 100 MHz ^{1}H NMR spectrum we identified four methyl groups at δ0.75 (*d*, $J = 6.8$ Hz), 0.96 (*d*, $J = 6.2$ Hz), 1.60 (*d*, $J = 1.3$ Hz) and 1.73 (*d*, $J = 1.3$ Hz), a methine proton at 2.53 (*dd*, $J = 10.7$ resp. 4.3 Hz) and a vinylic proton at 5.06 [*m*, $J = 10.7$ Hz (*d*) and 1.3 Hz (*m*)]. The ^{13}C NMR spectrum showed four methyl groups (*q*) at δ18.4, 19.0, 19.5 and 26.3; four CH_2-groups (*t*) at δ24.0, 29.4, 30.2 and 34.7; four CH-groups (*d*) at δ30.3, 34.9, 47.7 and 49.2, carbon(s) of a tertiary alcohol group at δ83.9; and a double bond at δ134.4 (*s*) and 121.0 (*d*). The double bond was part of an isobutenyl group, $\cdot CH{=}CMe_2$, with chemical shifts at δ5.06, 1.73 and 1.60 in ^{1}H NMR, and δ134.4, 121.0, 26.3 and 19.0 in ^{13}C NMR. There are three additional substituents, two methyl groups and a hydroxyl group, so the basic ring system is a bicyclononane system. A coupled ^{13}C NMR spectrum indicated that one of these rings was a cyclopentane ring, with two CH_2-groups and at least one CH-group. The ^{13}C NMR chemical shifts of the bridge carbon atoms correspond with those in a *trans*-bicyclo[4.3.0]nonane system [3], with a hydroxyl group in one of them.

From the chemical shifts on addition of increasing amounts of $Eu(fod)_3$ together with decoupling experiments, the most probable structure for this alcohol was **1**. A similar compound, (+)-pacifigorgiol (**2**) was found by Fenical *et al.* in a Pacific gorgonian coral *Pacifigorgia adamsii* [4], the structure of which was confirmed by ^{1}H NMR (220 MHz) and X-ray analysis of the oxidation product **3**. The published spectral data, IR and NMR, were identical to those of the alcohol from *Valeriana*, except for the optical rotation. (+)-Pacifigorgiol isolated from the coral has an optical rotation $[\alpha]_D + 41°$ (*c* 1.02; $CHCl_3$), and the alcohol isolated from *Valeriana* with $[\alpha]_D - 45.3°$ (*c* 0.724; $CHCl_3$) will be named (−)-pacifigorgiol.

EXPERIMENTAL

NMR spectra were recorded at 99.55 MHz for ^{1}H and at 25 MHz for ^{13}C NMR. $CDCl_3$ was used as a solvent, with TMS as an internal standard. MS were recorded on a Finnigan 9500/3300/6110 GC/MS Computer system for EI-operation; a



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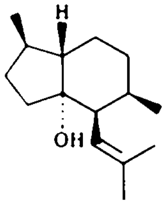

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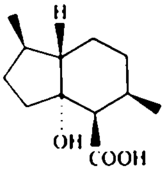

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fused silica capillary column (25 m × 0.32 mm CP sil 5; Chrompack, Middelburg, The Netherlands) was used; temp. program 60–300° at 6°/min; carrier gas helium; 70 eV and a cycle time during acquisition of mass spectra: 1 sec and by direct inlet procedure.

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THE MICROBIOLOGICAL TRANSFORMATION OF CANDIDIOL, *ENT*-15β,18-DIHYDROXY-KAUR-16-ENE, BY *GIBBERELLA FUJIKUROI*

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Key Word Index—*Gibberella fujikuroi*; microbiological transformation; diterpenes; candidiol; *ent*-kaur-16-ene derivatives.

Abstract—Incubation of candidiol, *ent*-15β,18-dihydroxy-kaur-16-ene, with *Gibberella fujikuroi* affords *ent*-11α,15β,18-trihydroxy-kaur-16-ene. Its structure was determined by X-ray analysis.

The fungus *Gibberella fujikuroi* produces a series of metabolites such as the gibberellins and the kaurenolide lactones, which derive biogenetically from the diterpene *ent*-kaur-16-ene [1]. This fungus is able to handle some natural and synthetic diterpenoids. Thus the microbiological transformation of *ent*-kaur-16-ene derivatives hydroxylated at different positions has been carried out [2]. In contrast to these investigations the metabolism of 15α-hydroxylated *ent*-kaurenes has been little studied. *ent*-15β-Hydroxy-kaur-16-en-19-oic acid has been incubated with *G. fujikuroi* and the products obtained tentatively identified as 7β,15α-dihydroxykaurenolide, GA_{14} 7,15-lactone and a hydroxy GA_{14} 7,15-lactone [3]. We now describe the results of incubation with this fungus of candidiol, *ent*-15β,18-dihydroxy-kaur-16-ene (**1**), a diterpene isolated from *Sideritis candicans* [4], and also synthesized from *ent*-18-hydroxy-kaur-15-ene [5].

The fermentation was carried out in the presence of AMO 1618, a compound that inhibits the formation of *ent*-kaur-16-ene without perturbing the post-kaurene metabolism [6, 7], thus facilitating the analysis of the products formed. Candidiol (**1**) was incubated with *G. fujikuroi*, the fermentation harvested after 6 days, and the combined broth and mycelium extracts separated into neutral and acidic fractions.

Chromatography of the neutral fraction afforded a triol, $C_{20}H_{32}O_3$ (**3**). Its ^{1}H NMR spectrum showed resonances for two methyl groups and one hydroxymethylene group, the two protons of an exocyclic double bond and the geminal hydrogens to two secondary hydroxyl groups. This spectrum was very similar to that of candidiol (**1**) [4, 5], the difference being the appearance of a geminal hydrogen to a new alcoholic group. This compound formed a triacetate (**4**). Its ^{1}H NMR spectrum in $CDCl_3$ showed the geminal proton to one of the acetates overlapped with one of the olefinic hydrogens, but in C_6D_6 a doublet centred at δ5.13 was observed. The form of this signal indicated that C-14 was a possible place for this new function, but the ^{13}C NMR spectrum was more in accordance with an alcoholic group at C-11 (Table 1). To solve this ambiguity we submitted the alcohol to an X-ray analysis. In this way the structure of *ent*-11α,15β,18-trihydroxy-kaur-16-ene was assigned to this new metabolite.

The crystal structure of **3** consists of discrete molecules, one of which is shown in Fig. 1. Rings A, B and C have