Phytochemistry, Vol 23, No 6, pp 1325–1326, 1984.
Printed in Great Britain

0031–9422/84 $3.00 + 0.00

THE CONFIGURATION OF THE SESQUITERPENOID 4-HYDROXYMYOPORONE (ATHANAGRANDIONE)

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(*Received* 11 *October* 1983)

Key Word Index—*Ipomoea batatas*; Convolvulaceae; *Fusarium solani*; *Athanasia grandiceps*, sweet potato, sesquiterpenoid; configuration; 4-hydroxymyoporone; athanagrandione; eremoacetal.

Abstract—The conversion of eremoacetal to (−)-1-(furan-3-yl)-4-hydroxy-4,8-dimethylnonane-1,6-dione establishes the configuration of (−)-4-hydroxymyoporone (athanagrandione) as *R*.

Several papers have appeared concerning the furanosesquiterpenoid stress metabolites of the sweet potato, including their biosynthesis [1–4]. Although much of the work has been directed towards 4-ipomeanol [1-(furan-3-yl)-4-hydroxypentan-1-one] and other lung toxins the range of constituents which has been isolated has also given considerable information regarding the oxygenation steps required to convert farnesol to the stress metabolites.

4-Hydroxymyoporone (**1**, stereochemistry not defined) was first reported in 1974 as a constituent isolated from sweet potatoes infected by *Fusarium solani* [5]. It was later found to arise [1] from ipomeamarone† and has been shown to be metabolized to the potent, pulmonary toxins [8]. Unfortunately, the optical rotation of 4-hydroxymyoporone was not reported [5] although it has been stated [3] that oxidation of ipomeamarone with *t*-butyl perbenzoate in the presence of cuprous chloride gave 4-hydroxymyoporone with the same (but not recorded) rotation as a sample isolated from sweet potatoes. Now that the absolute configuration of (−)-ngaione (**2**) [6] (and (+)-ipomeamarone [7]) has been confirmed it is possible to assign the configuration of 4-hydroxymyoporone from infected sweet potatoes as in **1**.

Subsequent to the discovery of 4-hydroxymyoporone, reported in 1974, Bohlmann and Zdero described, in 1978, a substance isolated from *Athanasia grandiceps* Hilliard et Burtt and called it athanagrandione [9]. This sesquiterpene, on the basis of spectral data, was also assigned the structure **1** without stereochemical details. In addition, its optical rotation was reported, $[\alpha]_D - 0.7°$ ($CHCl_3$; *c* 2.8).

In this communication we report the preparation of (*R*)-1-(furan-3-yl)-4-hydroxy-4,8-dimethylnonane-1,6-dione [(−)-4-hydroxymyoporone or athanagrandione] from (+)-eremoacetal (**3**), a substance of established configuration [10]. Hydroboration of eremoacetal with a limited amount of diborane followed by treatment with alkaline hydrogen peroxide is known to give the expected epimeric secondary alcohols [11]. In addition, some of the nonanetriols (**4a** and **5a**), each as a mixture of stereoisomers, were obtained. The use of an excess of diborane and a longer reaction time has now given a high conversion to the nonanetriols. They presumably arise by the known [12] elimination of substituted boranes to generate a double bond followed by hydroboration of the double bond and reduction of the carbonyl group.

The triols (**4a** and **5a**) were easily separated from each other by chromatography of their diacetates (**4b** and **5b**). Reduction of the diacetates (**4b**) to the triols (**4a**) followed by oxidation with Fétizon's reagent [13] gave the diketone, ipomeanine [14], arising from retroaldol cleavage of 4-hydroxymyoporone. This reaction established the structure of the triols (**4a**) because the diketone derived from the triols (**5a**) would not undergo the retroaldol reaction. Oxidation of the triols (**4a**) with pyridinium chlorochromate or dimethylsulphoxide-oxalyl chloride [15] gave a mixture from which 4-hydroxymyoporone could be isolated. This sample had spectral data in agreement with those published [5, 14] and showed an optical rotation of $[\alpha]_D - 1.0°$. Therefore, (−)-4-hydroxymyoporone (anthanagrandione, $[\alpha]_D - 0.7$ [9]) can be assigned the *R* configuration. Although the rotation of 4-hydroxymyoporone from infected sweet potatoes had not been reported its formation from ipomeamarone [3] establishes its configuration as *S* (**1**).

EXPERIMENTAL

^1H NMR spectra were recorded in CCl_4 at 60 MHz with TMS as internal standard.

Treatment of eremoacetal (**3**) *with diborane.* Eremoacetal (**3**) (2.48 g, 10 mmol) in dry THF (30 ml) under N_2 was treated with diborane (14 mmol, 0.9 M in THF) at 0° for 1 hr, followed by standing at room temp for 48 hr. NaOH soln (15 ml, 10%) and H_2O_2 (10 ml, 30%) were added and the mixture stirred for 1 hr The aq. layer was separated and extracted with Et_2O (3 × 20 ml) The combined organic fractions were washed with brine, dried

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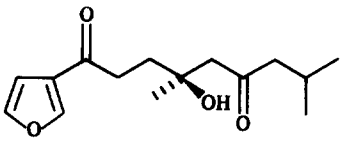
†Although the name ngaione should have priority [6] in the chemical literature ipomeamarone is in common use for its enantiomer [7]. Similarly, 4-hydroxymyoporone should have priority over athanagrandione (its enantiomer). However, both ipomeamarone and athanagrandione are used here because of their acceptance in the literature



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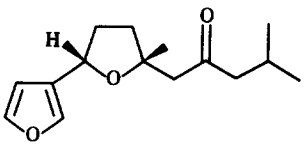

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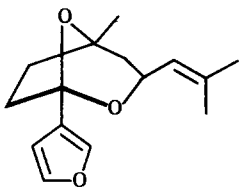

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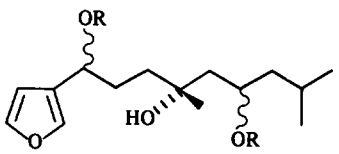
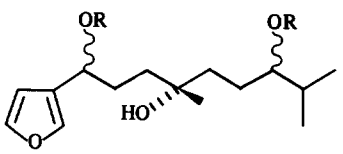
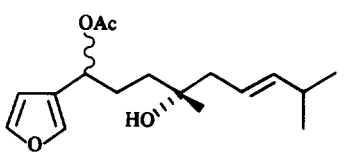


	R
4a	H
4b	Ac



	R
5a	H
5b	Ac



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and the solvents removed under red. pres. to yield a viscous oil (3 g). TLC showed the mixture to consist mainly of two polar components. The mixture was acetylated with Ac_2O and pyridine and the crude acetates were chromatographed on silica gel with mixtures of petrol and Et_2O.

The least polar fractions contained the acetates of the epimeric secondary alcohols (15%) expected from the hydroboration-oxidation sequence [11]. The next product eluted was 1-(furan-3-yl)-4-hydroxy-4,8-dimethylnon-6-enyl acetate (**6**) (9%). (Found: C, 69.4; H, 8.8. $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.9%.) IR ν_{max}^{film} cm^{-1}: 3500, 1740, 1380, 1245, 1030, 880, 800. ^1H NMR: δ 0.9–1.1 (9H, *m*), 2.0 (3H, *s*), 5.4 (2H, *m*), 5 6 (1H, *t*, J = 7 Hz), 6 3 (1H, *m*), 7.3 (2H, *m*).

Further elution gave 6-acetoxy-1-(furan-3-yl)-4-hydroxy-4,8-dimethylnonyl acetate (**4b**), a mixture of stereoisomers, as a viscous oil (1.44 g, 40%). (Found. *m/z* 294.184. $C_{19}H_{30}O_6$ – HOAc requires 294 183.) IR ν_{max}^{film} cm^{-1}: 3500, 1730, 1500, 1240, 1150, 1130, 1020, 940, 870. ^1H NMR: δ 0.93 (6H, *d*, J = 6 Hz), 1.12 (3H, *s*), 2.00 and 2.04 (each 3H, *s*), 2.5 (1H, *br s*, D_2O exch), 5.18 (1H, *m*), 5.75 (1H, *t*, J = 6 Hz), 6.44 (1H, *m*), 7.4 (2H, *m*).

Continued elution gave 7-acetoxy-1-(furan-3-yl)-4-hydroxy-4,8-dimethyl nonyl acetate (**5b**), a mixture of stereoisomers as a viscous oil (0.60 g, 17%). (Found. *m/z* 294 184. $C_{19}H_{30}O_6$ – HOAc requires 294.183.) IR ν_{max}^{film} cm^{-1}: 3500, 1735, 1500, 1240, 1150, 1020, 940, 860. ^1H NMR: δ 0.91 (6H, *d*, J = 7 Hz), 1.12 (3H, *s*), 2.04 (6H, *s*), 2 5 (1H, *br s*, D_2O exch.), 4 67 (1H, *m*), 5 77 (1H, *t*),6 47 (1H, *m*), 7.45 (2H, *m*)

Oxidation of triols (**4a**). (i) Reduction of the diacetate (**4b**) with $LiAlH_4$ gave the triol (**4a**) which was used directly for the oxidation. A mixture of silver carbonate (200 mg) on celite (1 g) and the triols (**4a**, 45 mg) in C_6H_6 (20 ml) was heated under reflux for 3 hr. Filtration through celite and removal of the solvent under red pres. gave 1-(furan-3-yl)pentane-1,4-dione (ipomeanine [14]) (20 mg, 72%) as a yellow oil, bp 90°/0.05 mm (block) (lit. [16] 74–79°/0.001 mm). The product had IR and ^1H NMR spectra identical with those reported [14].

(ii) The triols (**4a**, 250 mg, 0.94 mmol) in CH_2Cl_2 (5 ml) were added to a suspension of pyridinium chlorochromate (1.4 g, 6.7 mmol) and dry NaOAc (0.3 g) in dry CH_2Cl_2 (60 ml) at room temp. TLC showed the presence of four new products and no starting material. After isolation, the crude mixture was separated by prep. TLC (Et_2O–petrol, 3:2). The highest R_f, UV active compound was (*R*)-(−)-1-(furan-3-yl)-4-hydroxy-4,8-dimethylnonane-1,6-dione [(−)-4-hydroxymyoporone or athanagrandione] (40 mg, 17%) isolated as a yellow oil $[\alpha]_{700}^{20}$ +2.7°, $[\alpha]_{600}^{20}$ −0.8°, $[\alpha]_D^{20}$ −1.0°, $[\alpha]_{577}^{20}$ −0.8°, $[\alpha]_{546}^{20}$ −1.7°, $[\alpha]_{436}^{20}$ > +85° ($CHCl_3$; *c* 2.0) [lit. [9] for athanagrandione $[\alpha]_D$ −0 7° ($CHCl_3$; *c* 2.8)]. The IR, ^1H NMR and mass spectra were identical with those recorded [5, 9]. The other products were mainly monoketones and their cyclic acetals, including dihydroeremoacetal [10]. Oxidation of the triols (**4a**) with dimethylsulphoxide–oxalyl chloride [15] gave a similar result.

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