The Absolute Configuration of (+)-Ipomeamarone

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The absolute configuration of the sweet potato phytoalexin (+)-ipomeamarone (**1**) has been unambiguously determined as 1*R*,4*S* by chemical correlations of C-1 and C-4 with authentic, stereochemically defined materials.

The furano-sesquiterpene ipomeamarone (**1**) is produced in large quantities by the sweet potato *Ipomea batatas* in response to fungal infection.[1] Isolated forty years ago as one of the first phytoalexins by Hiura,[2] (**1**) and its *enantiomer* (−)-ngaione (**2**), a sheep and cattle toxin from the Australian desert shrub *Myoporum deserti*,[3] have been the subject of numerous toxicological[4] and biosynthetic studies.[5] Since the determination of the structure and relative stereochemistry by Kubota and Matsuura,[6] two conflicting reports regarding the absolute configuration have appeared.[7,8] Consequently, in recent work involving (**1**), the absolute stereochemistry has been unspecified,[9] or depicted incorrectly.[10]

Oxidative ozonolysis of (**1**) was reported by Kubota *et al.*[7] to afford ipomolactone (**3**), $[\alpha]_D$ + 7.4° (Figure 1). Since the corresponding lactone (**4**), prepared from (*R*)-linalo-ol (**5**), was reported by the same group to possess a positive rotation also ($[\alpha]_D$ + 6.3°), C-4 was (erroneously) assigned an *R* configuration. Hence, in view of the *trans*-relationship of the furyl and methyl substituents on the tetrahydrofuran ring,[6] it was concluded[7] that (**1**) has a 1*S*,4*R* chirality (opposite to that shown). In contrast, Sutherland *et al.*[8] reported that isongaione acetate (**7**), obtained from (**2**) by refluxing with NaOAc in acetic anhydride, afforded partially racemized† dimethyl (*S*)-acetylmalate (**8**), $[\alpha]_D$ −17.3°, lit.[11] −24.5°. As ring opening was assumed to occur with retention at C-1 the 1*S*,4*R* configuration was then assigned to (**2**). The absolute configuration deduced by Kubota *et al.*[7] was rejected by Sutherland *et al.*[12] with the claim that (**2**), on ozonolysis and oxidation under the conditions reported[13] for (**1**), afforded racemic (**4**), $[\alpha]_D$ −0.05° (Figure 1). In our hands, however, degradation of (**1**) (O_3, $CHCl_3$, 0 °C; then excess of K_2CrO_7–H_2SO_4, 48 h) furnished *dextrorotatory* (**3**), $[\alpha]_D$ +5.0° (*c* 18.7, EtOH), in agreement with Kubota *et al.*[7]

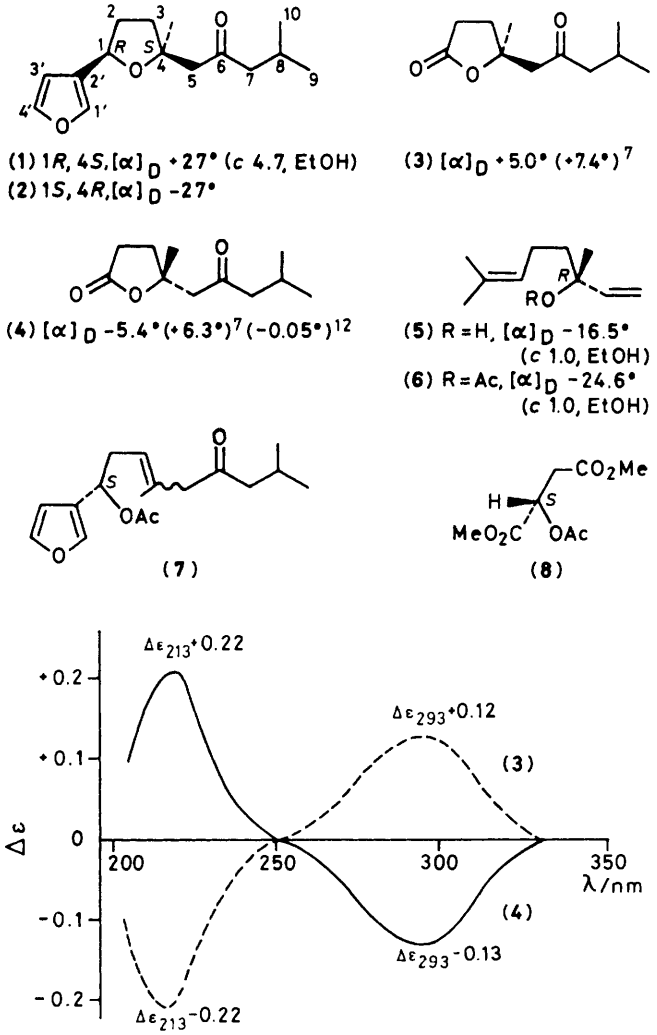
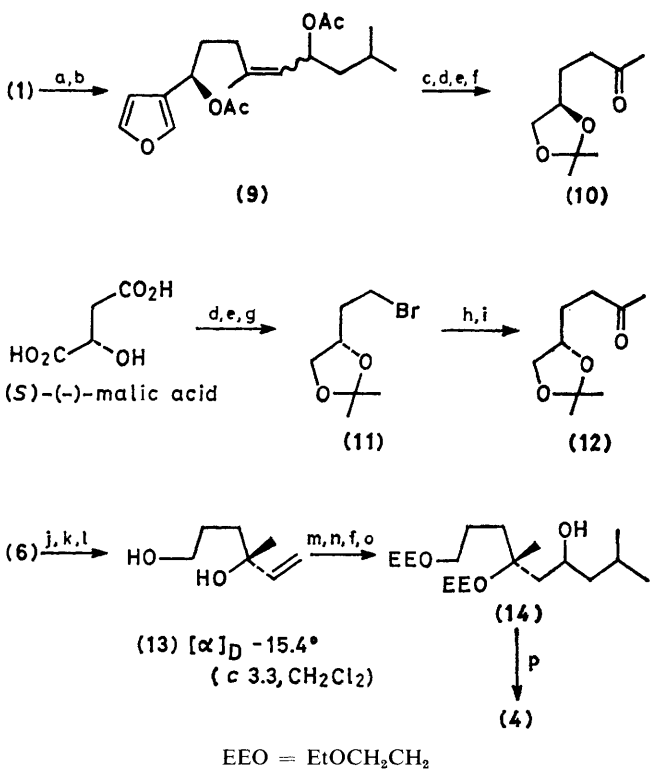


Figure 1. C.d. spectra of (**3**) (– – –) and (**4**) (——) in MeCN.



EEO = $EtOCH_2CH_2$

Scheme 1. *Reagents:* a, $LiNPr^i_2$ (−78 to 0 °C), add to $LiAlH_4$; b, Ac_2O, pyridine; c, O_3, H_2O_2; d, $LiAlH_4$; e, Me_2CO, *p*-Me-$C_6H_4SO_3H$; f, CrO_3·2pyridine; g, *N*-bromosuccinimide, Ph_3P; h, 2-methyl-2-lithio-1,3-dithian; i, *N*-chlorosuccinimide, $NaIO_4$, H_2O; j, *m*-$ClC_6H_4CO_3H$; k, H_6IO_6; l, $NaBH_4$; m, $EtOCH{=}CH_2$, *p*-$MeC_6H_4SO_3H$; n, B_2H_6, H_2O_2; o, Me_2CHCH_2MgBr; p, K_2CrO_7, H_2SO_4.

† Racemization occurs in the ring-opening step.[8] Treatment of (**1**) under these conditions for 44 h has been reported to result in complete racemization.[14]

Although the conflicting data could be accommodated by revision of the *relative* stereochemistry, the proposed *cis*-relationship[6] of 1-H and 4-Me was verified by irradiation of the 4-Me singlet in the ^{1}H n.m.r. spectrum and observing a 3.7% enhancement of the 1-H resonance in the nuclear Overhauser effect (n.O.e.) difference spectrum. Under these circumstances, it became evident that a re-investigation was necessary.

Unequivocal assignment of the C-1 configuration required a stereochemically unambiguous method of opening the tetrahydrofuran moiety. To this end (**1**) was subjected to lithium di-isopropylamide-induced ring opening (−78 to 0 °C) to give an enone alkoxide which was reduced *in situ* to isomeric diols; acetylation furnished the diacetates (**9**) in 55% yield (Scheme 1).‡ Further transformation of the isomeric acetates provided the homogeneous ketone (**10**), $[\alpha]_D$ +3.2° (*c* 0.3, $CDCl_3$), $\Delta\epsilon_{285}$ −0.14 (MeCN). This material was in all respects antipodal to the ketone (**12**), $[\alpha]_D$ −2.8° (*c* 0.3, $CDCl_3$), $\Delta\epsilon_{285}$ +0.13 (MeCN), derived from (*S*)-(−)-malic acid. On this basis, (**1**) must have the 1*R* configuration.

The configuration at C-4, in turn, was established by synthesis of (**4**) from (*R*)-(−)-linalyl acetate (**6**). Epoxidation of (**6**), cleavage with periodic acid, and sodium borohydride reduction gave the diol (**13**). Protection of this material as the bis ethoxyethyl ether, hydroboration, oxidation to the aldehyde level, followed by Grignard reaction produced (**14**) as a mixture of diastereoisomers. Direct treatment of these adducts with an excess of Jones reagent afforded pure (**4**), $[\alpha]_D$ −5.4° (*c* 1.2, EtOH), which is clearly the enantiomer of ipomolactone (**3**) (see Figure 1).

We conclude that (+)-ipomeamarone has, beyond doubt, the 1*R*,4*S* configuration and that its oxidation to (**3**) proceeds with retention of configuration at C-4.

‡ All compounds gave satisfactory n.m.r., i.r., and mass spectral data.

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