191. Synthesis of Urinary Metabolites of Retinoic Acid

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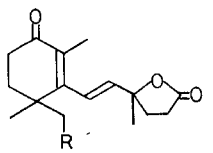
Summary

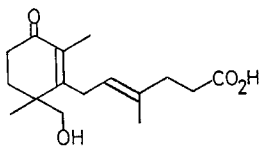
Urinary metabolites 5-methyl-5-[2-(2,6,6-trimethyl-3-oxo-1-cyclohexen-1-yl)-vinyl]-2-tetrahydrofuranone (**1**) and 5-[2-(6-hydroxymethyl-2,6-dimethyl-3-oxo-1-cyclohexen-1-yl)vinyl]-5-methyl-2-tetrahydrofuranone (**2**) of retinoic acid have been synthesized from 4-[2,2,6-trimethyl-3-(tetrahydro-2*H*-pyran-2-yl)oxy-1-cyclohexen-1-yl]-3-buten-2-one (**4**) and methyl 2-(3,3-ethylenedioxy-1-butenyl)-1,3-dimethyl-4-oxo-2-cyclohexene-1-carboxylate (**5**).

Retinoic acid posseses vitamin-A-like activity [1] and has been applied in acne therapy. Three urinary metabolites 5-methyl-5-[2-(2,6,6-trimethyl-3-oxo-1-cyclohexen-1-yl)vinyl]-2-tetrahydrofuranone (**1**), 5-[2-(6-hydroxymethyl-2,6-dimethyl-3-oxo-1-cyclohexen-1-yl)vinyl]-5-methyl-2-tetrahydrofuranone (**2**) and 6-(6-hydroxymethyl-2,6-dimethyl-3-oxo-1-cyclohexen-1-yl)-4-methyl-4-hexenoic acid (**3**) have been isolated in microgram amounts after the intraperioneal administration of retinoic acid to rats [2]. Although metabolites of retinoic acid posseses biological activity [3], nothing is known about the biological activity of these three urinary metabolites.



1 R=H

2 R=OH



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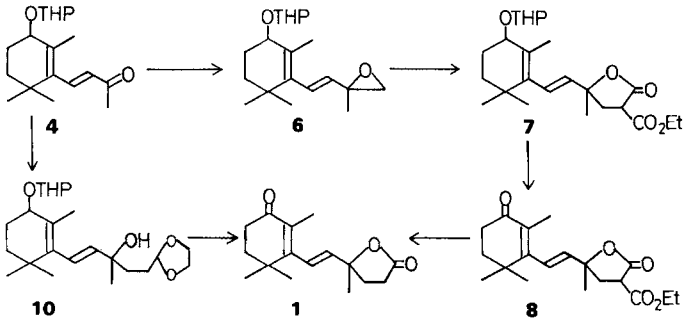
As an extension of our synthetic study of biologically active metabolites of carotenoides [4] [5], we are interested in the synthesis of the metabolites of retinoic acid. We now describe the first synthesis of metabolites **1** and **2**.

For the synthesis of **1** starting material 4-[2,2,6-trimethyl-3-(tetrahydro-2*H*-pyran-2-yl)oxy-1-cyclohexen-1-yl]-3-buten-2-one (**4**) was transformed into 1-[2,6,6-trimethyl-3-(tetrahydro-2*H*-pyran-2-yl)oxy-1-cyclohexen-1-yl]-3,4-epoxy-3-methyl-1-butene (**6**) in high yield by raising the temperature to 110–120° after treatment with dimethylsulfonium methylide at −15°. Treatment of **6** with diethyl malonate (NaOEt, EtOH) gave ethyl 5-methyl-5-{2-[2,6,6-trimethyl-3-(tetrahydro-2*H*-pyran-2-yl)oxy-1-cyclohexen-1-yl]vinyl}-2-oxotetrahydrofuran-3-carboxylate (**7**) (72% from **4**). Deprotection (TsOH, aq. THF) of **7** followed by oxidation (CrO_3/pyridine complex) yielded ethyl 5-methyl-5-[2-(2,6,6-trimethyl-3-oxo-1-cyclohexen-1-yl)-vinyl]-2-oxotetrahydrofuran-3-carboxylate (**8**) (75% from **7**) which was hydrolyzed (KOH, aq. EtOH), and decarboxylated to afford **1** (51% from **8**). Metabolite **1** was also prepared from **4** [6] by reaction with 3,3-ethylendioxypropylmagnesium bromide (**9**) affording 3-methyl-1-[2,6,6-trimethyl-3-(tetrahydro-2*H*-pyran-2-yl)-oxy-1-cyclohexen-1-yl]-6,6-ethylenedioxy-1-hexen-3-ol (**10**) (77%), which was deprotected (TsOH, aq. THF) and oxidized (CrO_3/pyridine complex) to give **1** (45% from **10**).

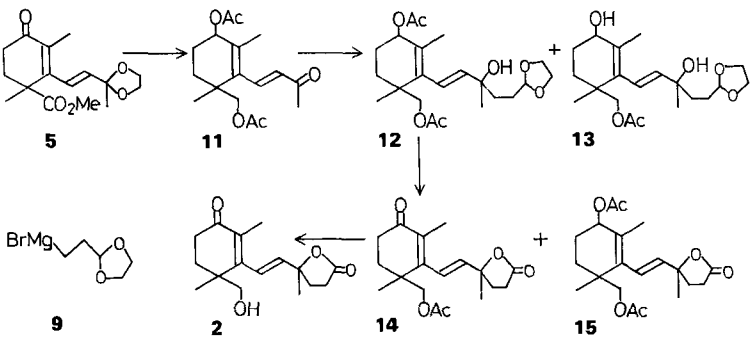
Next, synthesis of **2** was achieved by the *Grignard* reaction. Methyl 2-(3,3-ethylenedioxy-1-butenyl)-1,3-dimethyl-4-oxo-2-cyclohexene-1-carboxylate (**5**) was selected as starting material, which was the intermediate in our early synthesis of trisporic acids [5]. Conversion of **5** into 4-(acetoxymethyl)-2,4-dimethyl-3-(3-oxo-1-butenyl)-2-cyclohexen-1-yl acetate (**11**) was carried out as usual (*i.* LAH, ether; *ii.* Ac_2O, pyridine; *iii.* 50% AcOH; 87.5% from **5**). *Grignard reaction* of **11** with **9** (THF, 5°, 20 h) afforded 4-(acetoxymethyl)-3-(6,6-ethylenedioxy-3-hydroxy-3-methyl-1-hexenyl)-2,4-dimethyl-2-cyclohexen-1-yl acetate (**12**) and [2-(6,6-ethylenedioxy-3-hydroxy-3-methyl-1-hexenyl)-4-hydroxy-1,3-dimethyl-2-cyclohexen-1-yl]-methyl acetate (**13**) (69.1%) in a ratio of 4:1. Treatment of **12** with TsOH in aq. THF yielded the corresponding hemiacetal, which, without purification, was oxidized by *Collins* reagent to give {2-[2-(2-methyl-5-oxo-2-tetrahydrofuryl)vinyl]-1,3-dimethyl-4-oxo-2-cyclohexene-1-yl}methyl acetate (**14**) (47%) together with 4-(acetoxymethyl)-3-[2-(2-methyl-5-oxo-2-tetrahydrofuryl)vinyl]-2,4-dimethyl-2-cyclohexene-1-yl acetate (**15**) (21.5%). Finally hydrolysis of **14** (K_2CO_3, aq. MeOH) followed by lactonization (TsOH, THF, r.t., 20 h) gave **2** (65% from **14**).

Scheme 1



The ^{1}H-NMR and IR spectra and MS fragmentation of the synthetic metabolites **1** and **2** are consistent with those of the biological metabolites **1** and **2**.

Scheme 2



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