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TOTAL SYNTHESIS OF ALLIXIN; AN ANTI-TUMOR PROMOTER FROM GARLIC

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Abstract: *The first synthesis of allixin, an anti-tumor promoter from garlic Allium sativum* L., *is described. The highly oxidized γ-pyrone moiety was synthesized via a 2-methylene tetrahydropyran derivative.*
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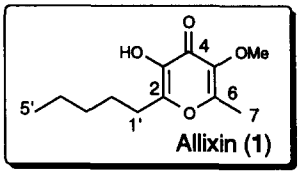
Carcinogenesis is thought to occur through multi-sequence processes. Complete prevention of the first initiation stage by environmental carcinogens is difficult, thus effective suppressants for subsequent promotion stage are in great demand.

Allixin(**1**) was isolated from garlic *Allium sativum* L., as a stress compound[1], and its anti-tumor promoter activity *in vivo*[2a, 3] and radical scavenging effect[4] were reported later. It was recently discovered that allixin also inhibited the aflatoxin B_1-induced mutagenesis *in vitro*.[2b]



Allixin (**1**)

The mechanism of its preventive effect on tumor promotion is an interesting problem, but it has not been clear. Lack of functionality in the side chain makes derivitizations of **1** difficult, which presents a major problem for understanding structure-activity relationships.

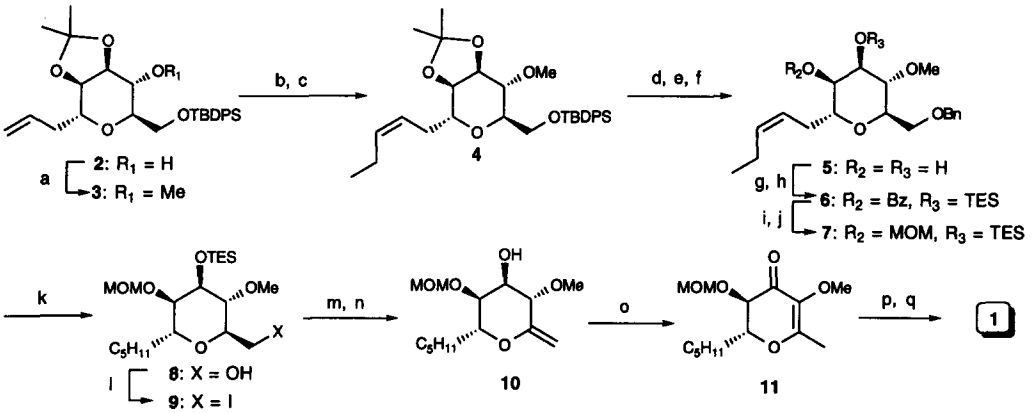
Although several methods for the construction of 3,5-dihydroxy-(4*H*)-pyran-4-ones have been published[5], to the best of our knowledge no report has appeared for 2, 6-dialkyl substituted compounds. A further challenge is presented by the instability of the oxygenated γ-pyrone ring to basic, nucleophilic, and oxidative conditions, thereby necessitating careful choice of strategy and reagents.

We report here the first total synthesis of this biologically important natural product, in which the oxidation of an appropriately functionalized 2-methylene tetrahydropyran **10** (Scheme) is a key step.

Our synthesis of **1** started from known tetrahydropyran **2**, readily available in large quantity from D-mannose(Scheme).[6] Following introduction of desired O-methyl group, the terminal alkene was cleaved by OsO_4-$NaIO_4$ oxidation. Subsequent C3-homologation by a Wittig reaction yielded **4**, which has the complete carbon skeleton of **1**. Through a series of conventional protective group manipulations, compound **4** was transformed to **7**. Catalytic hydrogenation of **7** effected removal of benzyl and reduction of side chain olefin, and was followed by Mitsunobu reaction to provide iodide **9**. Dehydrohalogenation with DBU, followed by deprotection of TES under neutral conditions, furnished the key intermediate, enol ether**10**.

Among the variety of conditions examined, only SO_3-pyridine complex at room temperature yielded

desired dihydropyrone **11** in 90% yield.[7] The removal of MOM protecting group with TMSBr at -30°C gave corresponding alcohol in excellent yield. Although Shaw *et al.* reported successful oxidation of closely related 2, 3-dihydro-3, 5-dihydroxy-6-methyl-(4*H*)-pyran-4-one with CrO_3-pyridine system,[8] the same conditions did not work for our substrate.[9] Finally, an SO_3-pyridine oxidation was proved to afford allixin (**1**), which was in good agreement with reported data in all aspects.[10]



Reagents and conditions: (a) MeI, NaH, THF, rt (93%); (b) OsO_4 cat., $NaIO_4$, THF/H_2O (92%); (c) Ph_3PPrI, NaHMDS, THF, -78 °C to rt (89%); (d) TBAF, THF, 0 °C (quant.); (e) BnBr, NaH, Bu_4NI cat., rt (94%); (f) 2M aq.HCl, 50°C (quant.); (g) BzCl, pyridine, CH_2Cl_2, 0 °C (66%); (h) TESCl, imidazole, DMF, rt (86%); (i) DIBAL-H, CH_2Cl_2, -78 °C (71%); (j) MOMCl, *i*-Pr_2NEt, Bu_4NI cat., reflux (quant.); (k) $Pd(OH)_2$, K_2CO_3 cat., H_2, EtOH, rt (95%); (l) MeI, DEAD, PPh_3, THF, rt (82%); (m) DBU, toluene, MS4A, 90°C, 3 days (66%); (n) TBAF, THF, 0 °C (quant.); (o) SO_3-pyr., Et_3N, DMSO, rt (94%); (p) TMSBr, CH_2Cl_2, -30 °C (91%); (q) SO_3-pyr., Et_3N, DMSO, rt (60%)

Scheme

In summary, we have described the first synthesis of the potent anti-tumor promoter allixin, in which the key step is an oxidation of 2-methylene tetrahydropyran derivative to dihydropyrone. The synthesis will allow access to a variety of side chain analogs, which would give mechanistic insight to the tumor promotion mechanism.

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7. Swern oxidation gave a product, mono-chlorinated at allylic methyl group of **11**.
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9. Other conditions including Dess-Martin oxidation, Jones oxidation, PCC, TPAP were also failed. Swern oxidation (-78 °C-0 °C) gave allixin in10 % yield.
10. ^1H NMR(400MHz, $CDCl_3$) δ: 0.90 (3H, t, *J*= 7.0 Hz), 1.33 (4H, complex), 1.66 (2H, tt, *J*= 7.2, 7.2 Hz), 2.33 (3H, s), 2.66 (2H, t, *J*= 7.7 Hz), 3.88 (3H, s); ^{13}C NMR(100 MHz, $CDCl_3$) δ: 13.9, 15.0, 22.3, 26.3, 28.3, 31.3, 60.1, 141.9, 141.9, 150.1, 157.9, 169.5; IR(KBr, cm^{-1}) 3450, 1660; UV_{max} 279 nm; HRMS calcd for $C_{12}H_{18}O_4$ 226.1204, found 226.1204; mp 78 °C

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