

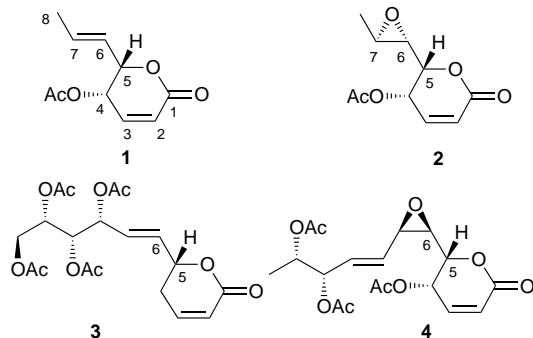
A novel entry to naturally occurring 5-alkenyl α,β -unsaturated δ -lactones from D-glucose: syntheses of (+)-acetylphomalactone and (+)-asperlin

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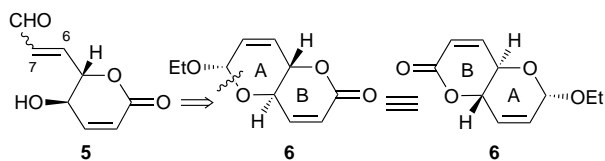
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A bicyclic pyranosidic glycoside **6**, readily obtained from D-glucose, has been used as the key intermediate in enantioselective syntheses of (+)-acetylphomalactone and (+)-asperlin, in which the configuration at C-5 corresponds to that of the hexopyranosides in the L-sugar series.

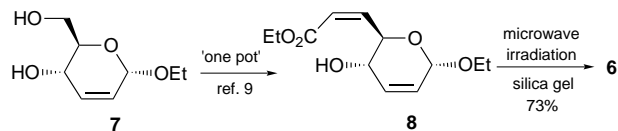
Naturally occurring 5-substituted α,β -unsaturated δ -lactones, e.g. **1–4**, represent an important class of products with a diverse range of biological activity.¹ They have been reported to be plant growth inhibitors, insect antifeedants and antifungal and antitumour agents.¹ They are widely distributed and have been isolated from both plants and fungi. Acetylphomalactone **1**² and asperlin **2**³ are prominent members of this family. (+)-Acetylphomalactone **1** is an antimicrobial metabolite isolated from *Aspergillus caespitosus*,² and (+)-Asperlin **2** was isolated from *Aspergillus nidulans* and possesses antitumour and antibacterial activity.³ Among the more relevant structural characteristics of this family are: (i) the absolute configuration at C-5, and (ii) the presence of a chain at C-5, which normally presents a $\Delta^{6,7}$ unsaturation or an epoxide derived therefrom.¹ The design of a general, enantioselective approach to this family of lactones from currently available carbohydrates (D-series) is not obvious because the absolute configuration at C-5 correlates with that of a hexopyranoside of the L-series. Accordingly, D-sugars have been used in syntheses of unnatural isomers of asperlin **2**^{4,5†} and anamarine **3**⁶ as well as synthetic precursors for *ent*-olguine **4**.⁷ Herein we report the first general approach to this family of lactones, starting from D-glucose, and its application to the syntheses of acetylphomalactone **1** and asperlin **2**.



Our strategy (Scheme 1) is based on the recognition that D-glucose-derived bicyclic glycoside **6** can be viewed as a 5-alkenyl α,β -unsaturated δ -lactone. Chemoselective cleavage of ring A on **6** leads to lactone **5**, which already fulfils the above-mentioned structural requirements.

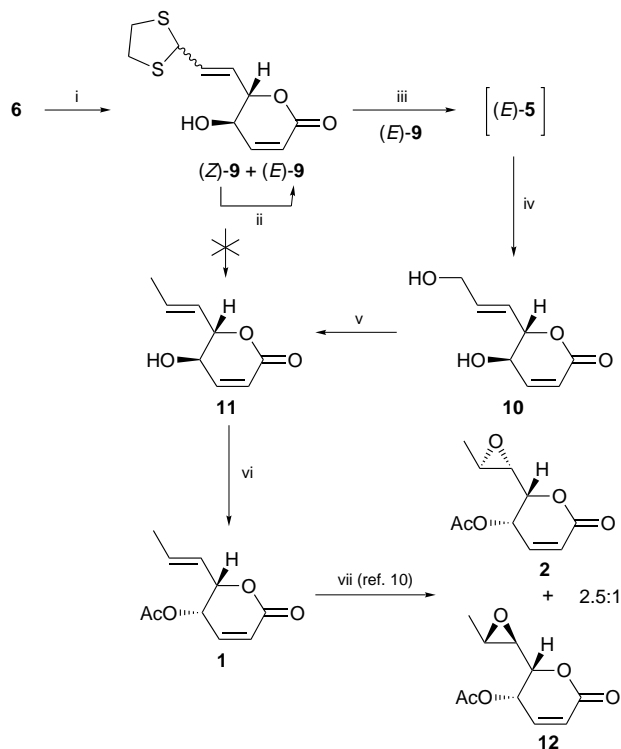


Scheme 1



Scheme 2

Additionally, the feasibility of this approach greatly benefits from the facile preparation of **6** from readily available Ferrier's diol **7**⁸ (Scheme 2). Thus, compound **7** is efficiently transformed, *via* a one pot operation, into hydroxy ester **8**,⁹ and microwave-induced lactonization of the latter on silica gel gives rise to glycoside lactone **6** in fairly good yield (73%).[§] The glycosidic moiety on **6** can be unravelled under acid catalysis in the presence of ethanedithiol to furnish a *ca.* 2:1 mixture of 5-alkenyl lactones (*E*)-**9** and (*Z*)-**9**, which upon further treatment leads to (*E*)-**9** as a single isomer (83% overall) (Scheme 3). At this stage, direct desulfurization of (*E*)-**9** to yield **11** was attempted under a variety of conditions,[¶] although in our hands this transformation still remains elusive. A less direct route to **11** was then designed which involves deprotection of



Scheme 3 Reagents and conditions: i, HSCH₂CH₂SH, BF₃·OEt₂, CH₂Cl₂, –20 °C; ii, BF₃·OEt₂, CH₂Cl₂, 0 °C, 83% from **6**; iii, CaCO₃, MeI, MeCN–H₂O (8:2), 60 °C; iv, BH₃·Me₂S, THF, 0 °C, 66% from (*E*)-**9**; v, *N*-(phenylseleno)phthalimide, PBU₃, CH₂Cl₂, –20 °C, then Bu₃SnH, AIBN, PhMe, 80 °C, 41% from **10**; vi, PPh₃, AcOH, diisopropyl azodicarboxylate, THF, room temp., 61%; vii, MCPBA, CH₂Cl₂, 4 days, room temp.

the dithiane group followed by reduction of the resulting aldehyde function in **5**|| to furnish diol **10** (66% overall). Sequential phenylselenation–tin mediated deselenation of the latter yielded **11** (41% overall). One additional isomer with a $\Delta^{7,8}$ unsaturation, resulting from the reduction of the allylic radical at C-6, was also observed (*ca.* 3.5 : 1 ratio). Mitsunobu inversion of **11** with acetic acid at C-4 led to **1**** (61%), which upon epoxidation gave rise to asperlin **2**,** along with its 6*R*,7*S*-diastereoisomer.¹⁰

In summary, we have developed an efficient synthetic approach to naturally occurring 5-alkyl and 5-alkenyl α,β -unsaturated δ -lactones¹ using D-glucose as the starting material. The approach illustrates the usefulness of bicyclic D-glycoside **6** as a key intermediate for biologically active lactones in which C-5 correlates with that of a hexopyranoside of the L-series. Further studies along this line for the preparation of other lactones are under way.

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Footnotes and References

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‡ Shing and Aloui prepared the 6*R*,7*S* diastereomer of **2** from D-glucose [refs. 4(a) and (b)]. Ramesh and Franck reported the synthesis of (+)-**2** from L-rhamnose (ref. 5).

§ Hydroxyester **8** (300 mg) was adsorbed on silica gel (4.5 g) and placed in a Pyrex vessel with an external bath of about 200 g of silica gel. Irradiation of the mixture in a commercial microwave oven (466 W, 6 min) afforded lactone **6**. A large number of different sets of conditions were investigated for this transformation but were not found to be synthetically useful because of low yields and/or long reaction times.

¶ Treatment of (*E*)-**9** with several kinds of Ni-Raney in different solvents and under different conditions, in our hands, did not result in the formation of **11**.

|| Hydroxy aldehyde **5** is not a very stable compound. It dehydrates slowly at room temperature or upon purification on silica gel.

** Spectral data (300 MHz ¹H NMR) for **1**,^{2b} and **2**,^{10a} are identical with those already reported for the natural compounds.

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