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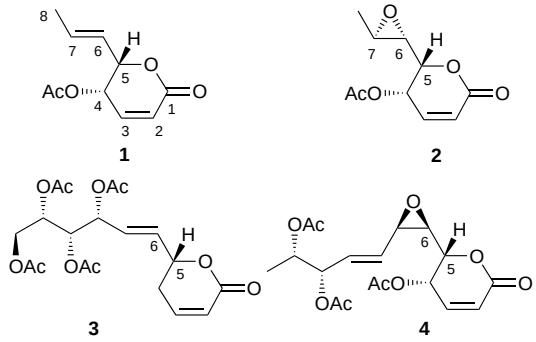
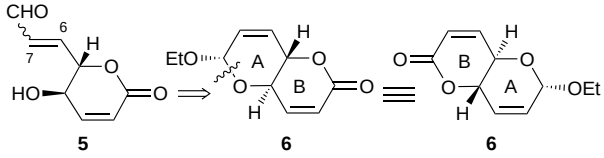
A bicyclic pyranosidic glycoside 6, readily obtained from D-glucose, has been used as the key intermediate in enantioselective syntheses of (+)-acetylphomalactone and (+)-asperlin, in which the configuration at C-5 corresponds to that of the hexopyranosides in the L-sugar series.

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 caespitous*,[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**.



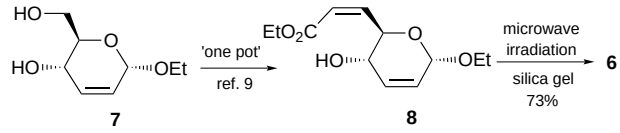
1 **2** **3** **4**

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.



5 **6** **6**

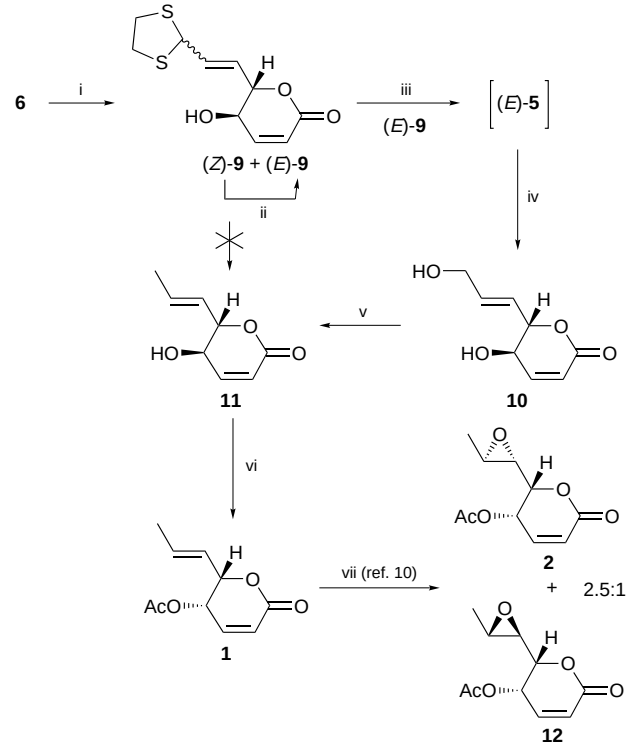
Scheme 1



7 **8**

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-alquenil 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, $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C; ii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 83% from **6**; iii, $CaCO_3$, MeI, MeCN–H_2O (8 : 2), 60 °C; iv, $BH_3{\cdot}Me_2S$, THF, 0 °C, 66% from (*E*)-**9**; v, *N*-(phenylseleno)phthalimide, PBu_3, CH_2Cl_2, −20 °C, then Bu_3SnH, AIBN, PhMe, 80 °C, 41% from **10**; vi, PPh_3, AcOH, diisopropyl azodicarboxylate, THF, room temp., 61%; vii, MCPBA, CH_2Cl_2, 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 raise 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-lactones[1] 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 ^{1}H NMR) for **1**,[2b] and **2**,[10a] are identical with those already reported for the natural compounds.

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