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A practical and enantiospecific conversion of D-galactose to a substituted α,β-unsaturated δ-lactone synthon

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Abstract—A multi-gram synthesis of a substituted α,β-unsaturated δ-lactone synthon, **1**, was developed from commercially available D-galactose. The use of a Horner–Wadsworth–Emmons reaction was able to furnish, with *Z* selectivity, the enone ester that spontaneously lactonised to provide enantiomerically pure **1**.

Substituted α,β-unsaturated δ-lactone skeletons are common in bioactive natural products such as (+)-asperlin,[1] the styryllactones[2] and the bisnorditerpene dilactone[3] family of natural products (Fig. 1). Enantiomerically pure and substituted α,β-unsaturated δ-lactones, such as **I** and **II**, are also used frequently as chiral synthons in carbohydrate or natural product synthesis, typically as Michael acceptors[4] or dipolarophiles in cycloaddition reactions.[5] While the preparative conversion of commercially available D-glucose to the protected α,β-unsaturated δ-lactone synthons such as **2** is relatively efficient[6] a comparably practical method for accessing **1** from D-galactose remains absent.

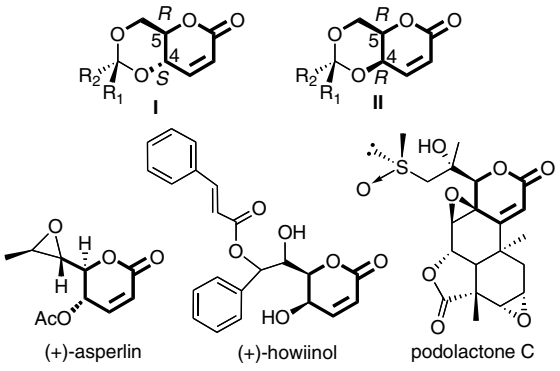
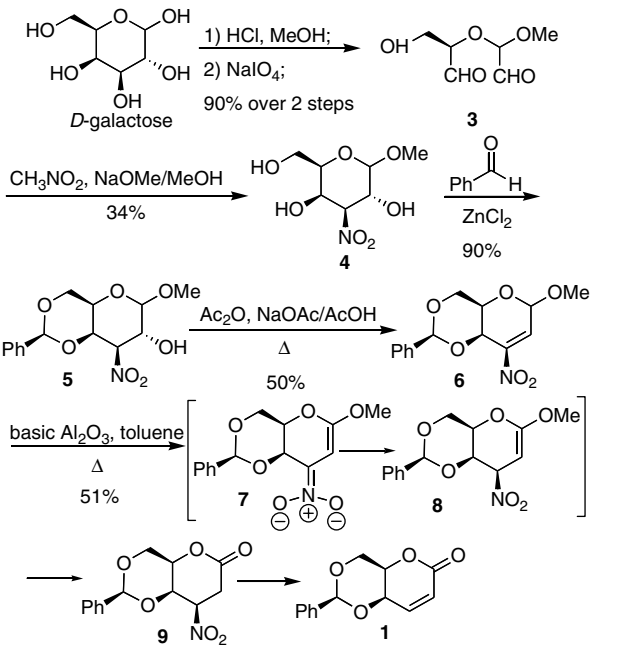


Figure 1. Examples of bioactive natural products containing substituted α,β-unsaturated δ-lactones.

Currently only one synthesis of **1** has been reported (Scheme 1).[7] This sequence requires the conversion of D-galactose to a nitro sugar (**4**) as the key intermediate for the subsequent isomerisation and denitration steps. Other approaches to the analogues of **1**, using different protecting schemes on 4,6-diol, include dehydration of hydroperoxide carbohydrates,[8] stereoselective transformation of sugar-derived vinyl oxiranes[9] and cyclisation



Scheme 1.

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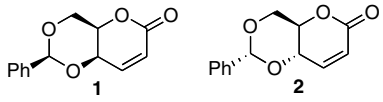
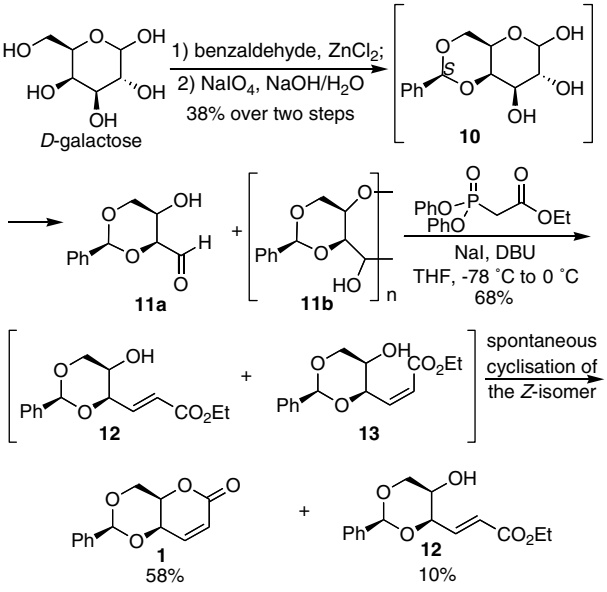
of dihydroxylated vinyl furans.[10] These syntheses, typically six to ten steps from commercially available building blocks with overall yields under 10%, are less suitable to the preparative needs of chiral synthons. Herein is reported a multi-gram conversion of D-galactose to the *D-threo*-α,β-unsaturated δ-lactone **1** in three steps with one column chromatography at the end and an overall yield of 22%.



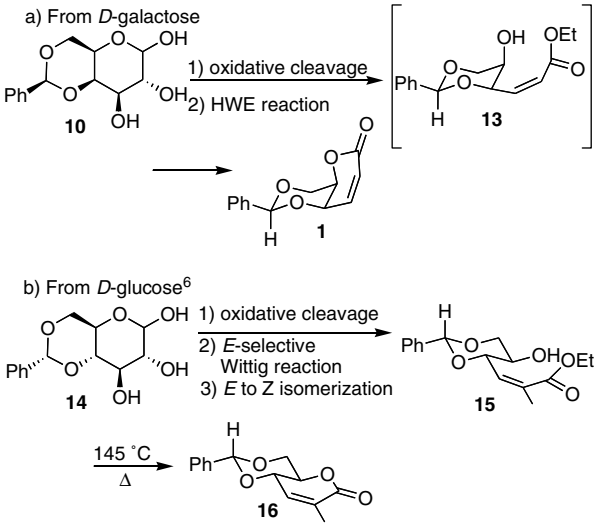
This sequence (Scheme 2) initiates with the diastereoselective benzylidene protection of the 4,6-diols of D-galactose. Although a total of four diastereomers could potentially form due to the benzylidene group and the anomeric centre, only two were produced as an anomeric mixture (**10**) of 6:1 (α:β) ratio with the benzylidene carbon in the *S* configuration. All the common procedures for this reaction involve mechanically stirring or shaking a mixture of D-galactose, benzaldehyde and $ZnCl_2$ for approximately 24 h.[11–16] While 4,6-*O*-benzylidene-D-galactopyranose, **10**, could be isolated by an aqueous work-up followed by lypophilisation, repeated cycles of solvent extraction and recrystallisations,[11–15] Rochlin's protocol,[16] in which the aqueous solution of **10** after work-up could be directly subjected, without further purification, to $NaIO_4$ oxidation, was adopted to provide a comparable, 38% yield of 2,4-*O*-benzylidene-D-threose **11** over two steps from D-galactose. This procedure could be performed on scales of up to 30 kg without reduction in efficiency.[16] Although the oxidation of **10** generally proceeds in nearly quantitative yields at a pH above 7.0–7.5,[11,13] the conversion of D-galactose to **10** is the yield-limiting step due to incomplete reaction of D-galactose[16] as well as the formation of dibenzylated byproducts.[15] However, the unreacted D-galactose and the dibenzylated products could be readily removed during work-up and recycled.[17]

Threose **11** was found to exist as a complex mixture of the monomeric form **11a** and oligomeric form **11b**, as the ^1H NMR spectrum of crude **11** showed only weak resonances attributable to the aldehyde form **11a**. This observation is consistent with that made for the erythroses derived from D-glucose.[18,19] Nevertheless, these compounds react as aldehydes and had previously been subjected to both the Wittig[11–16,20,21] and *E*-selective Horner–Wadsworth–Emmons (HWE)[19] reactions. The *Z*-selective HWE reaction was developed here, on the basis of Ando's work,[22] to convert **11** to two olefinic species, in an *E*:*Z* ratio of 19:81 by ^1H NMR. Interestingly, the olefinic species with the *Z* geometry did not contain an ethyl group, as would be expected from the enone ester **13**. Rather, this *Z*-olefin appeared to be the cyclised lactone **1** resulting from spontaneous cyclisation of **13**. After purification of the reaction mixture by column chromatography, only lactone **1** could be isolated, along with the *E* isomer **12** obtained as a stable crystalline solid.[23] The structure of **1** was ascertained by the comparison of the NMR and specific optical rotation data with those previously reported.[7] Overall, enantiomerically pure **1** was obtained in gram quantities in two to three days requiring one column chromatography at the end for purification.

This tandem olefination–lactonisation approach, while new for the synthesis of **1** from D-galactose, has been reported in the synthesis of **16** from D-glucose.[6] The use of a Wittig reaction is typical in the preparation of **15**, the lactonisation precursor of **16** (Scheme 3). The *E*/*Z* selectivity is not controlled rigorously, and the *E*-isomer for cyclisation can be converted to the *Z*-isomer in moderate yields. The intramolecular lactonisation reaction is performed at elevated temperatures using the *Z*-enone ester precursor in its purified form. However, the *Z*-selective HWE reaction has not been used in preparing



Scheme 2.



Scheme 3.

either **13** or **15** prior to this report. The use of DBU, which is necessary in the HWE reaction to generate the phosphonate ylid in situ, also provided an ancillary advantage of promoting the lactonisation step that would otherwise require much higher temperatures to proceed as reported in the synthesis of **16** using the Wittig reaction. A conformational analysis was performed on the enone ester precursors **13** and **15**.[26] These two esters exhibited comparable distances (difference within 1 Å) between the nucleophilic oxygen centre and the electrophilic carbonyl carbon, without the indication of any conformation bias that would significantly enhance the lactonisation in either case. This supports indirectly the likely kinetic advantage of lactonisation in the presence of an amidine base.

In summary, a three-step, enantiospecific conversion of D-galactose on a preparative scale to a chiral synthon **1** is described for the first time. The enantio-purity of the final product was secured by a spontaneous intramolecular lactonisation of a *Z*-enone ester formed after a Horner–Wadsworth–Emmons reaction.

Acknowledgement

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References and notes

1. Initial isolation and synthesis: (a) Argoudelis, A. D.; Zieserl, J. F. *Tetrahedron Lett.* **1966**, *8*, 1965–1969; (b) Lesage, S.; Perlin, A. S. *Can. J. Chem.* **1978**, *56*, 2889–2896; (c) Murayama, T.; Sugiyama, T.; Yamashita, K. *Agric. Biol. Chem.* **1986**, *50*, 1923–1924.
2. Recent reviews: (a) de Fatima, A.; Modolo, L. V.; Conegero, L. S.; Pilli, R. A.; Ferreira, C. V.; Kohn, L. K.; de Carvalho, J. E. *Curr. Med. Chem.* **2006**, *13*, 3371–3384; (b) Mondon, M.; Gesson, J.-P. *Curr. Org. Synth.* **2006**, *3*, 41–75; (c) Zhao, G.; Wu, B.; Wu, X. Y.; Zhang, Y. Z. *Mini-Rev. Org. Chem.* **2005**, *2*, 333–353; (d) Mereyala, H. B.; Joe, M. *Curr. Med. Chem: Anti-Cancer Agents* **2001**, *1*, 293–300.
3. Initial review: (a) Ito, S.; Kodama, M. *Heterocycles* **1976**, *4*, 595–624; A recent example: (b) Park, H. S.; Yodo, N.; Fukaya, H.; Aoyagi, Y.; Takeya, K. *Tetrahedron* **2004**, *60*, 171–177.
4. Recent examples: (a) Krishna, P. R.; Reddy, P. S.; Narsingam, M.; Sateesh, B.; Sastry, G. N. *Synlett* **2006**, *4*, 595–599; (b) Zhao, G.-L.; Liao, W.-W.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 4929–4932; (c) Sanki, A. K.; Pathak, T. *Tetrahedron* **2003**, *59*, 7203–7214.
5. Recent examples: (a) Stecko, S.; Pasniczek, K.; Jurczak, M.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1085–1093; (b) Pasniczek, K.; Jurczak, M.; Solecka, J.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *J. Carbohydr. Chem.* **2007**, *26*, 195–211; (c) Panfil, I.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Pol. J. Chem.* **2005**, *79*, 239–249; (d) Pasniczek, K.; Socha, D.; Jurczak, M.; Frelek, J.; Suszczynska, A.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *J. Carbohydr. Chem.* **2003**, *22*, 613–629; (e) Dirat, O.; Kouklovsky, C.; Langlois, Y. S.; Lesot, P.; Courtieu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3197–3207.
6. Friedrich, K.; Fraser-Reid, B. *J. Carbohydr. Chem.* **1994**, *13*, 631–640.
7. Baer, H. H.; Rank, W. *Can. J. Chem.* **1969**, *47*, 2811–2818.
8. Mieczkowski, J.; Jurczak, J.; Chmielewski, M.; Zamojski, A. *Carbohydr. Res.* **1977**, *56*, 180–182.
9. Harris, J. M.; O'Doherty, G. A. *Tetrahedron Lett.* **1999**, *41*, 183–187.
10. (a) Domon, D.; Fujiwara, K.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 8285–8288; (b) Bussolo, V. D.; Caselli, M. A.; Pineschi, M.; Crotti, P. *Org. Lett.* **2002**, *4*, 3695–3698.
11. Dulcos, R. I. *Chem. Phys. Lipids* **2001**, *111*, 111–138.
12. Figueroa-Peréz, S.; Schmidt, R. R. *Carbohydr. Res.* **2000**, *328*, 95–102.
13. Zimmermann, P.; Schmidt, R. R. *Liebigs Ann. Chem.* **1988**, 663–667.
14. Kiso, M.; Nakamura, A.; Nakamura, J.; Tomita, Y.; Hasegawa, A. *J. Carbohydr. Chem.* **1986**, *5*, 335–340.
15. Gros, E. G.; Deulofeu, V. *J. Org. Chem.* **1964**, *29*, 3647–3654.
16. Rochlin, E. U. S. Patent 6,469,148, 2000; *Chem. Abstr.* **2000**, *133*, 335434.
17. *2,4-O-benzylidene*-D-*threose* (**11**). Based on the procedure of Rochlin.[16] A mixture of $ZnCl_2$ (3.2 g, 23 mmol) and redistilled benzaldehyde (9.3 mL, 92 mmol) was mechanically stirred for 30 min under a gentle stream of dry nitrogen. To the resulting off-white slurry were added anhydrous D-galactose (4.0 g, 22 mmol) and more redistilled benzaldehyde (8.1 mL, 77 mmol), and this mixture was vigorously stirred for a further 24 h. Unreacted D-galactose was removed by filtration and the residue washed with redistilled benzaldehyde (3 mL). The combined filtrate and washings were diluted with diethyl ether (8 mL) and petroleum ether (11 mL), then extracted with ice-cold water (20 mL then 3×10 mL). A solution of K_2CO_3 (5.1 g, 37 mmol) in water (6.8 mL) was used to adjust the pH of the combined aqueous extracts to 9–10, and the thick white precipitate ($ZnCO_3$) was filtered off and washed thoroughly with water (80 mL). After washing the filtrate with $CHCl_3$ (10 mL) and petroleum ether (10 mL), the resulting solution of crude **10** ($R_f = 0.32$, 25% ethanol in toluene) was buffered with $K_2HPO_4 \cdot 3H_2O$ (1.5 g, 6.5 mmol) and KH_2PO_4 (610 mg, 3.5 mmol) and vigorously stirred during the portionwise addition of $NaIO_4$ (5.3 g in 500 mg portions over 3 h, 25 mmol). The pH was kept in the range 7.0–7.5 by the addition of aqueous KOH (20%) and the formation of **11** was monitored by TLC ($R_f = 0.64$, 25% ethanol in toluene). Once complete, the reaction mixture was lyophilised. The orange residue was suspended in dry THF and filtered. After thoroughly washing the residue with dry THF, the combined extracts were dried over $MgSO_4$, filtered and evaporated at reduced pressure (8 Torr, 35 °C) to afford crude **11** (2.36 g, 8.4 mmol, 38%) as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 0.05H), 9.67 (s, 1H), 9.26 (s, 0.2H), 7.60–7.30 (m, 60H). The remainder of the spectrum was extremely complex with, for instance, at least six broad singlets in the benzylic region (δ 5.7–5.5).
18. Rhee, J. U.; Bliss, B. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2003**, *125*, 1492–1493.
19. Fengler-Veith, M.; Schwardt, O.; Kautz, U.; Krämer, B.; Jäger, V. *Org. Synth.* **2002**, *78*, 123–128.
20. Kiso, M.; Nakamura, A.; Tomita, Y.; Hasegawa, A. *Carbohydr. Res.* **1986**, *158*, 101–111.
21. Schmidt, R. R.; Zimmermann, P. *Tetrahedron Lett.* **1986**, *27*, 481–484.
22. (a) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105–4108; (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939; (c) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406–8408; (d) Ando, K.; Oishi,

T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.

23. *(2S,4aR,8aR)-2-phenyl-4,4a-dihydropyrano[3,2-d][1,3]dioxin-6(8aH)-one* (**1**). Based on the procedure of Ando et al.[22d] To a chilled (ice-bath) solution of ethyl diphenylphosphonoacetate[22c,24] (2.5 g, 7.7 mmol) in dry THF (70 mL) under argon were added sodium iodide (2.2 g, 14.8 mmol) and DBU (1.2 mL, 8.1 mmol). The mixture was stirred for 15 min, then cooled to −78 °C. A solution of crude **11** (1.7 g) in dry THF (20 mL) was subsequently added and stirring continued for 2.5 h, after which time the reaction mixture was transferred to an ice bath and stirred for a further 1.5 h. The reaction mixture was quenched with saturated NH_4Cl (50 mL) and diluted with ethyl acetate (150 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic phases were washed with water (25 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL) then dried over $MgSO_4$. After filtration and evaporation of the solvent at reduced pressure (8 Torr, 35 °C), the resulting yellow residue was purified by dry column vacuum chromatography[25] (0–80% ethyl acetate in hexane) to obtain **1** (1.05 g, 4.5 mmol, 58%) as colourless needles: mp 152–154 °C (lit.[7] mp 156–157 °C); $[\alpha]_D^{23}$ −252 (*c* 1.1, $CHCl_3$) (lit.[7] $[\alpha]_D$ −256 (*c* 1.1, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.47 (m, 2H, Ar), 7.39–7.35 (m, 3H, Ar), 6.93 (dd, $J = 9.7$ Hz, 6.0 Hz, 1H, C*H*=CHC(O)), 6.29 (d, $J = 9.7$ Hz, 1H, CH=C*H*C(O)), 5.62 (s, 1H, C*H*Ph), 4.55 (dd, $J = 13$ Hz, 1.3 Hz, 1H, OCH_2CH), 4.50 (dd, $J = 6.0$ Hz, 2.2 Hz, 1H, C*H*CH=CH), 4.26 (m, 1H, OCH_2CH), 4.22 (dd, $J = 13$ Hz, 2.0 Hz, 1H, OCH_2CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 139.2, 136.5, 129.2, 127.9, 125.9, 124.9, 100.7, 70.2, 68.5, 65.7; MS (EI, *m*/*z*): 231 (M^+-1), 105 ($C_6H_5C(O)^+$, base).
(E)-Ethyl 3-((2S,4R,5R)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)acrylate (**12**). Obtained as colourless needles (211 mg, 0.76 mmol, 10%): mp 101–103 °C; $[\alpha]_D^{24}$ −36.2 (*c* 0.66, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.48 (m, 2H, Ar), 7.42–7.35 (m, 3H, Ar), 6.95 (dd, $J = 16$ Hz, 3.8 Hz, 1H, C*H*=CHC(O)), 6.18 (dd, $J = 16$ Hz, 1.9 Hz, 1H, CH=C*H*C(O)), 5.63 (s, 1H, C*H*Ph), 4.62 (m, 1H, C*H*CH=CH), 4.23 (dd, $J = 12$ Hz, 1.8 Hz, 1H, $CHOCH_2$), 4.19 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 4.09 (dd, $J = 12$ Hz, 1.3 Hz, 1H, $CHOCH_2$), 3.66 (m, 1H, C*H*(OH)), 2.81 (br s, 1H, OH), 1.27 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 143.1, 137.3, 129.1, 128.2, 125.9, 122.7, 101.1, 78.4, 72.2, 65.3, 60.4, 14.1; MS (EI, *m*/*z*): 277 (M^+-1), 107 ($C_6H_5CHOH^+$, base).

24. Olpp, T.; Brückner, R. *Synthesis* **2004**, 2135–2152.
25. Pedersen, D. S.; Rosenbohm, C. *Synthesis* **2001**, 2431–2434.
26. Mohamadi, F.; Richard, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467. Monte Carlo conformational searches, using MM3* force field in 1000 steps as implemented in Macromodel, were performed.