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SYNTHESIS OF HOMOCHIRAL TRISUBSTITUTED γ-BUTYROLACTONES

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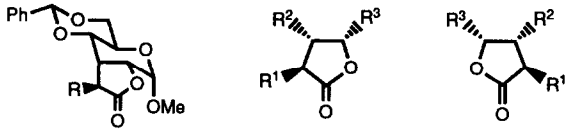
Summary; Efficient syntheses of homochiral, trisubstituted γ-butyrolactones via the highly stereoselective alkylation of a carbohydrate-derived γ-lactone are described.

In our efforts to prepare optically pure γ-butyrolactones we elected to use carbohydrates as chiral templates in which the conformation of the carbohydrate was used to control the stereochemistry at the α-position of the lactone. In particular we were interested in synthesising optically pure trisubstituted γ-butyrolactones, since this functionality is present in a wide range of natural products, many of which have interesting biological activity.[1] As part of these studies we recently reported the highly stereoselective methylation of lactone (**1**) which provided a short and general route to homochiral trisubstituted γ-butyrolactones of the general formula (**3**).[2]



(**1**) R=H
(**2**) R=Me

(**3**)

(**4**)

Figure 1

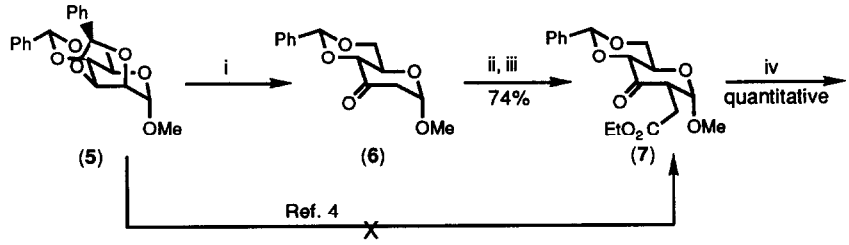
In order to demonstrate the generality of this method, we also wished to synthesize enantiomers of (**3**), *i.e.* the trisubstituted lactones (**4**), which we intended to use in other studies towards the total synthesis of naturally-occurring terpenoid lactones. Based on our success with (**1**) we reasoned that the fused lactone (**9**) would alkylate preferentially on the *exo*- face to give (**10**). Following this, suitable synthetic modification by well-known methods[3] would allow conversion of (**10**) to γ-butyrolactones of the type (**4**), in which R^2 and R^3 may also be chiral.

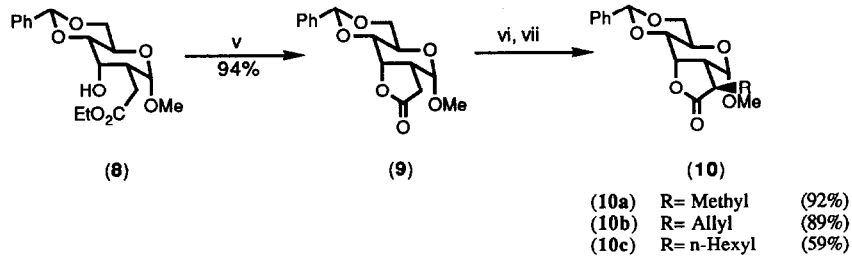
Our proposed synthetic route began with the known keto-ester (**7**).[4] We expected that the reduction of the ketone group would favour formation of the axial hydroxy-ester (**8**) and that cyclisation of (**8**) would furnish the target lactone (**9**). Not only did this strategy offer a short, and therefore potentially high-yielding route to (**9**), it also made use of cheap and readily-available D-mannose. We now report the successful realisation of this goal.

The published synthesis of keto-ester (**7**),[4] a one-pot procedure involving Klemer-Rodemeyer fragmentation[5] of (**5**) (^{n}BuLi, THF, -30 °C) followed by *in situ* alkylation of the resulting enolate ($BrCH_2CO_2Et$, HMPA-THF, -30 °C), proved to be unreliable and yields obtained were poor. Additionally chromatographic separation of (**7**)

from ketone (**6**) (arising from incomplete alkylation) was problematical and an alternative preparation had to be sought.

Ketone (**6**) was prepared according to Horton and Weckerle[6] in 98% yield, but then required recrystallisation from 95% ethanol prior to the alkylation step. Alkylation of the lithium enolate of (**6**) with ethyl bromoacetate ($LiNTMS_2$, THF, -45 °C; then $BrCH_2CO_2Et$, HMPA-THF, -45 °C) was very slow, taking typically 6 hours to completion; competitive *O*-alkylation was also observed under these conditions. Under optimum conditions, a maximum of 2:1 *C*-:*O*- alkylation was achieved. Changing the electrophile to ethyl iodoacetate produced a significant decrease in reaction time but dialkylation became an additional problem. The addition of more co-solvent (HMPA or DMPU) only served to increase the extent of dialkylation observed.





(**10a**)	R= Methyl	(92%)
(**10b**)	R= Allyl	(89%)
(**10c**)	R= n-Hexyl	(59%)

Reagents: i. $^{n}BuLi$, THF, -45 °C, then $sat^{d.}$ NH_4Cl (aq); ii. $KNTMS_2$, PhMe, -45 °C; iii. ICH_2CO_2Et, PhMe, 0 °C; iv. $NaBH_4$, MeOH, r.t.; v. NaH, wet THF, r.t.; vi. $LiNTMS_2$, THF, -78 °C; vii. R-X, -78 °C to r.t.

Scheme 1

Knowing that the reactivity of simple alkali metal enolates at carbon increases with increasing 'softness' of the cation,[7] we envisaged that the potassium enolate could be employed to overcome the problem of *O*-alkylation. The potassium enolate of (**6**) was therefore prepared and, in agreement with our reasoning, did not alkylate at oxygen on reaction with ethyl iodoacetate. However, the reaction was still very slow and gave poor yields, and warming the reaction to 0 °C only caused the enolate to decompose. We reasoned that by altering the reaction medium to a non-coordinating solvent such as toluene, the enolate would be stabilized at higher temperatures. Accordingly, the potassium enolate of (**6**) was found to be stable in toluene at 0 °C and at this temperature, alkylation with ethyl iodoacetate was complete inside one hour. This alternative synthesis of (**7**) from ketone (**6**) (see **Preparation**) was reproducible in 74% yield following purification by column chromatography and proved to be an excellent alternative to the published procedure.

Reduction of (**7**) ($NaBH_4$, MeOH, r.t.; quantitative) gave a single product (d.r. >95:5) as a white crystalline solid (m.p. 109-110 °C, $[\alpha]_D$ +60.6°, *c* 0.1 in $CHCl_3$). The structure of (**8**) was apparent from its ^1H n.m.r. spectrum,[8] in which $J_{2,3}$ and $J_{3,4}$ (both 3 Hz) indicated an axial-equatorial-axial arrangement of H-2, -3 and -4. This was confirmed by reaction with $Cl_3CCONCO$ and n.m.r. analysis of the subsequently-formed 3-*O*-carbamate.[9] Cyclisation of hydroxyester (**8**) was readily accomplished (NaH, wet THF) to give (**9**) in 94% yield as a white crystalline solid (m.p. 199-200 °C, $[\alpha]_D$ +265° *c* 0.1 in $CHCl_3$). Interestingly, as no reaction was observed in anhydrous THF, we thought it highly likely that the reaction proceeds *via* the hydroxy acid. This was confirmed by the addition of a drop of water to the anhydrous reaction mixture whereupon rapid conversion to (**9**) was observed. The structure of (**9**) was assigned from its ^1H n.m.r. spectrum.[10] Compared with the spectrum of (**8**), H-2 showed further coupling to the protons α to the lactone, H-7 (*exo*) and H-7' (*endo*): interaction with H-7' was small (1 Hz), whereas $J_{2,7}$ was 7 Hz. Furthermore, the size of $J_{1,2}$ (5 Hz) pointed to a marked distortion of the pyranoside ring, which was interpreted as resulting from the newly-formed 5-6-fused ring system.

As we anticipated, alkylation of (**9**) occurred on the *exo*-face of the molecule. Treatment of (**9**) with $LiNTMS_2$ at -78 °C followed by quenching with methyl iodide (1 eq. MeI, -78°C → r.t.) gave (**10a**) as colourless rhombi in 92% yield (m.p. 177-179 °C, $[a]_D$ +212° *c* 0.99 in $CHCl_3$). The ^1H n.m.r. spectrum of the crude product material showed only one component and thus a diastereomeric ratio of products (d.r.) of >95:5 could be assigned. The structure of (**10a**) was initially deduced from spectral data, but unambiguous proof of the stereochemistry of alkylation was provided by an X-ray structure (**Figure 2**).

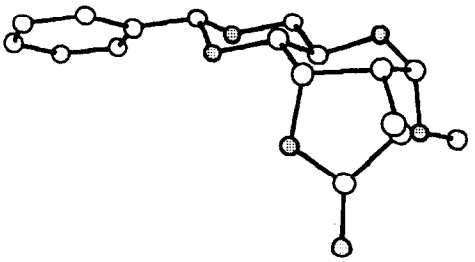


Figure 2 X-Ray Structure of (10a)

Reaction with allyl bromide under the same conditions furnished the allyl derivative (**10b**) with the same stereospecificity in 89% yield (m.p. 131-133 °C, $[\alpha]_D$ +178° *c* 0.5 in $CHCl_3$). As a control experiment, the *n*-hexyl derivative (**10c**) was prepared from the lithium enolate of (**9**) ($^nC_6H_{13}I$, -78°C→r.t.) in 59% yield (d.r. >95:5) as colourless needles (m.p. 96-97 °C, $[\alpha]_D$ +72.0°, *c* 1.0 in $CHCl_3$). Not surprisingly, the electrophile was less reactive towards the enolate and alkylation was only observed at room temperature. However, under these conditions some decomposition of the lactone enolate was also apparent, which would account for the comparatively low yield.

In conclusion, the fused lactone (**9**) can be prepared in excellent yield (44% over five steps[11]) from readily available starting materials involving a novel preparation of the synthetically useful ketoester (**7**). Alkylation of (**9**) proceeds with a very high degree of stereoselectivity (d.r. >95:5) and the method provides a general route to the family of optically pure γ-butyrolactones (**4**).

Preparation of (7): A solution of (**6**) (6g, 22.7mmol) in anhydrous PhMe (60ml) at -45 °C was treated with $KNTMS_2$ (1M in PhMe; 25ml, 25mmol) and stirred for 30 minutes. Ethyl iodoacetate (2.7ml, 22.7mmol) was then added in one portion and the reaction stirred at -45 °C for 10 minutes, then at 0 °C for 60 minutes. The mixture was quenched with 2% aqueous NH_4Cl solution (100ml) and the aqueous phase extracted with CH_2Cl_2 (3 x 100ml). The combined organic phases were dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (silica; PhMe-EtOAc, 15:1) gave (**7**) as a white crystalline solid (5.2g, 74%).

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8. **Hydroxy-ester** (**8**): δ_H ($CDCl_3$, 250 MHz) 1.27 (3 H, t, *J* 7 Hz, CH_3CH_2O), 2.44 (1 H, ddd, *J* 6, 3.5 and 3 Hz, 2-H), 2.64 (2 H, dd, *J* 7.5 and 6 Hz, 7-H and 7-H'), 2.75 (1 H, d, *J* 7.5 Hz, OH), 3.41 (3 H, s, CH_3O), 3.63 (1 H, dd, *J* 10 and 3 Hz, 4-H), 3.79 (1 H, t, *J* 10.5 Hz, 6-Hax.), 4.09 (1 H, t, *J* 3 Hz, 3 H), 4.12 (1 H, td, *J* 10, 10 and 5 Hz, 5-H), 4.16 (2 H, q, *J* 7 Hz, CH_3CH_2O), 4.36 (1 H, dd, *J* 10.5 & 5 Hz, 6-Heq.), 4.75 (1 H, d, *J* 3.5 Hz, 1-H), 5.62 (1 H, s, PhC*H*), 7.33-7.39, 7.47-7.52 (5 H, m, Ph).
9. P.E. Butler and W.H. Müller, *Anal. Chem.* 1966, **38**, 1407.
10. **Lactone** (**9**): δ_H ($CDCl_3$, 250 MHz) 2.46 (1 H, dd, *J* 16.5 and 7 Hz, 7-H), 2.60 (1 H, dd, *J* 16.5 and 1 Hz, 7-H'), 2.85 (1 H, dddd, *J* 7, 5.5, 4.5 and 1 Hz, 2-H), 3.36 (3 H, s, CH_3O), 3.76 (1 H, t, *J* 10.5 Hz, 6-Hax.), 3.79 (1 H, dd, *J* 10 and 3.5 Hz, 4-H), 4.18 (1 H, ddd, *J* 10.5, 10 and 5 Hz, 5-H), 4.35 (1 H, dd, *J* 10.5 and 5 Hz, 6-Heq.), 4.69 (1 H, dd, *J* 4 and 3.5 Hz, 3-H), 4.73 (1 H, d, *J* 5.5 Hz, 1-H), 5.60 (1 H, s, PhC*H*), 7.33-7.40 and 7.48-7.54 (5 H, m, Ph).
11. All compounds were fully characterised and gave satisfactory elemental analyses and mass spectra.

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