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# An Expeditious Approach to Polysubstituted Chiral Butanolides

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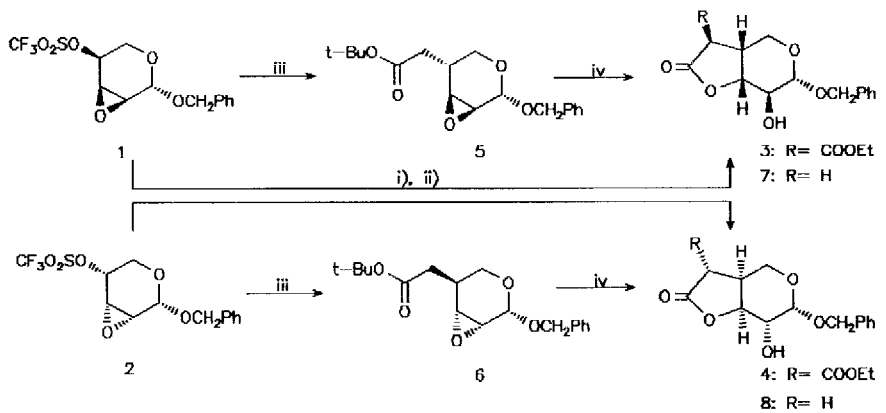
***Abstract:*** *Reaction of sugar derived epoxy triflate 1 and 2 with ester enolates followed by acid catalyzed ring closure affords poly-substituted chiral butanolides in excellent yield.*

Di- and trisubstituted γ-butyrolactones are ubiquitous structural subunits of a variety of natural products,[1] many of which exhibit interesting pharmacological activities.[1,2] Stereospecifically substituted butanolides have also been used for stereo-controlled construction of complex functionalized acyclic or macrocyclic molecules.[3] Several methods for the synthesis of this class of compounds have been developed,[3-5] but relatively few affford optically pure material. One of the attractive approaches towards chiral butyrolactones would involve annulating a butanolide ring onto a carbohydrate template. Subsequent elaboration of the carbohydrate moiety would afford functionalized side chains suitable for further modifications. Such an approach has indeed been realized,[5] where the butyrolactone ring was built onto a protected sugar derivative in a multistep sequence. The off-template chiral centre was later introduced in a separate step. We describe here an extremely efficient construction of a butanolide ring onto a pyranoside template with a simultaneous stereocontrol on the off-template chiral centre.

The regiochemistry of our annulation reaction banks upon the tremendous difference in the reactivity of a suitably disposed oxirane ring, and a trifluoromethanesulfonyl (triflyl) group towards nucleophilic attack.Thus reaction of benzyl 4-O-trifluoromethanesulfonyl-2,3-anhydro-ß-L-ribopyranoside (**1**)[6] or benzyl 4-O-trifluoromethanesulfonyl-2,3-anhydro-α-D-ribopyranoside (**2**)[6] with sodio diethyl malonate in a mixture of THF and ethanol followed by acidic aqueous work up affords the trisubstituted γ-butyrolactones (**3**)[7,12] or (**4**)[8,12] in 76% and 72% respectively in a single laboratory operation (scheme 1).

A complete control on the off template chiral centre was obtained due to thermodynamic reason. Similarly, the lithium enolate of tert-butyl acetate reacts with the triflates **1** and **2** in THF-HMPA (9:1) at -120 °C to afford the ester **5** and **6** in 85% and 90% yields, respectively.[9] Treatment of **5** and **6** with TFA-$CH_2Cl_2$ (2:5) at room temperature for 20 min quantitatively converts them to the γ-butyrolactones **7**[10,12] and **8**.[11,12]




Scheme 1 : i) $NaCH(CO_2Et)_2$/ THF/ EtOH/ r.t./ 30 min. ii) Acid workup iii) $LiCH_2CO_2Bu^t$/ THF/HMPA/ -120 °C/ 30 min. iv) TFA/ $CH_2Cl_2$/ r.t./ 20 min.

Further elaboration of the newly prepared chiral butyrolactones are being carried out.

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7. All $^1$H NMR spectra were recorded on 400 MHz in $CDCl_3$, $\delta$ in ppm. $^1$H NMR of **3**: 7.38-7.24 (5H, Phenyl), 4.87 (d, J=11.6 Hz, OCHPh), 4.58 (d, J=11.6 Hz, OCH'Ph), 4.52 (dd, J=7.9 Hz, H-3), 4.28 (d, J=7.5 Hz, H-1), 4.25 (q, J=14.1, 7.0 Hz, $C\underline{H}_2CH_3$), 3.95 (dd, J=13.1, 1.7, H-5), 3.69 (dd, J=13.1, 3.7 Hz, H-5'), 3.62 (d, J=12.0 Hz, H-6), 3.49 (dd, J=7.5 Hz, H-2), 3.12 (m, H-4), 2.79 (bs, OH), 1.3 (t, J=7.1Hz, $CH_2C\underline{H}_3$)· FD-MS: m/z 337 $[M+H]^+$. $[\alpha]_D$ -161.6° (c= 1, $CHCl_3$).
8. $^1$NMR of **4**: 7.39-7.31 (5H, Phenyl), 4.87 (d, J=3.7Hz, H-1),4.72 (d, J=11.6 Hz, OCHPh), 4.68 (dd, J=7.9 Hz, H-3), 4.51 (d, J=11.6 Hz, OCH'Ph), 4.24 (q, J=14.1, 7.0 Hz, $C\underline{H}_2CH_3$), 3.99 (dd, J=12.7, 3.9 Hz, H-5), 3.58 (d, J=12.7 Hz, H-5'), 3.53 (d, J=12.0 Hz, H-6), 3.49 (dd, J=8.0, 3.7 Hz, H-2), 3.12 (m, H-4), 2.85 (bs, OH) 1.29 (t, J=7.1 Hz, $CH_2C\underline{H}_3$). FD-MS: m/z 337 $[M+H]^+$. $[\alpha]_D$ +10.2° (c= 0.57, $CHCl_3$).
9. This is the improved procedure for preparing **5** and **6**; see: Fatima, A.; Zaman, F.; Shekhani, M. S.; Malik, A.; Voelter, W. *Liebigs Ann. Chem.* **1990**, 389.
10. $^1$H NMR of **7** : 7.26-7.36 (5H, Phenyl), 4.85 (d, J=11.7 Hz, OCHPh), 4.57 (d, J=11.7 Hz, OCH'Ph), 4.46 (dd, J=7.4 Hz, H-3) 4.37 (d, J=6.9 Hz, H-1), 4.37 (dd, J=7.4 Hz, H-2), 3.88 (dd, J=12.7, 4.0 Hz, H-5), 3.67 (dd, J=12.7, 4.5 Hz, H-5'), 3.63 (dd,J=7.3 Hz, H-2), 2.79 (2H, m, H-4+ OH), 2.49(d, J=9.5 Hz, H-6,6'). FD-MS: m/z 265 $[M+H]^+$. $[\alpha]_D$ +21.3° (c= 1, $CHCl_3$).
11. $^1$H NMR of **8** : 7.24 -7.40 (5H, Phenyl), 4.87 (d, J=3.4 Hz, H-1), 4.78 (d, J=11.7 Hz, OCHPh), 4.62 (dd, J=7.0 Hz, H-3), 4.55 (d, J= 11.7 Hz, OCH'Ph), 4.01 (dd, J= 12.3, 4.4 Hz, H-5), 3.75 (dd, J=7.0, 3.4 Hz, H-2),, 3.63 (dd, J=12.3, 3.0 Hz, H-5'), 2.80 (m, H-4), 2.78 (bs, OH), 2.58 (dd, J=17.5, 8.3 Hz, H-6), 2.49 (dd, J= 17.5, 9.8 Hz, H-6'). FD-MS: m/z 265 $[M+H]^+$. $[\alpha]_D$ +60.2° (c= 1, $CHCl_3$).
12. The $^{13}$C NMR data are consistent with the assigned structure.


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