The Ring Contraction of δ-Lactones with Leaving Group α-Substituents: a Strategy for the Synthesis of 2,5-Disubstituted Highly Functionalised Homochiral Tetrahydrofurans

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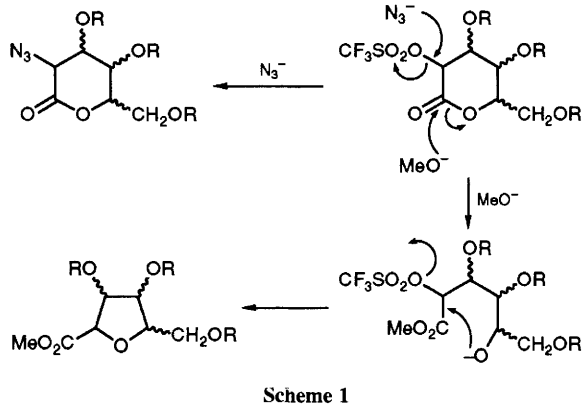
Treatment of derivatives of δ-lactones having a leaving group at C-2 with methanol in the presence of base gives methyl tetrahydrofuran-α-carboxylates in good to excellent yield with a high degree of stereocontrol of the carbon substituents at C-2 and C-5.

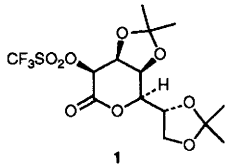
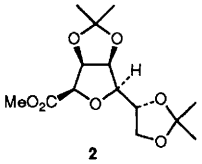
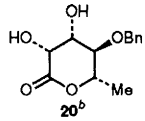
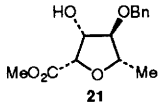
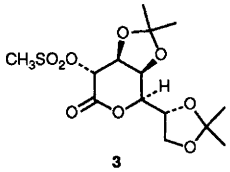
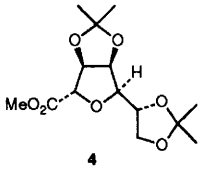
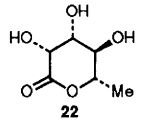
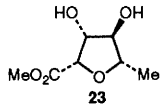
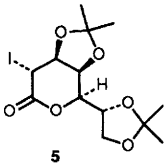
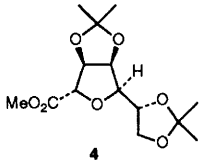
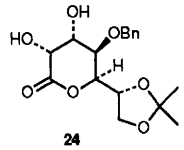
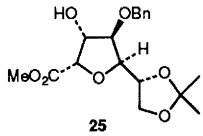
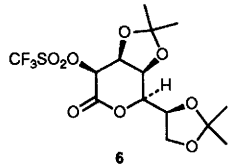
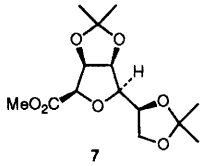
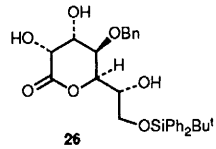
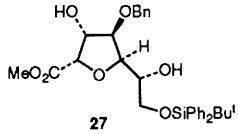
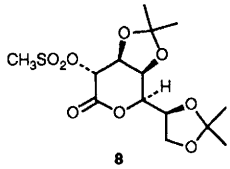
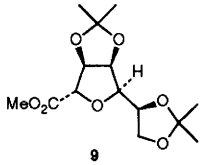
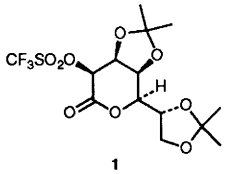
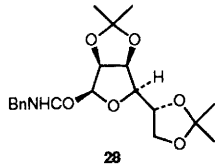
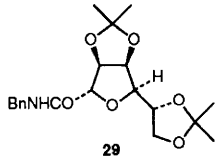
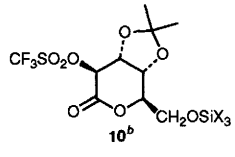
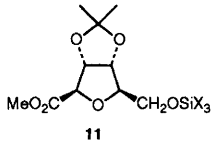
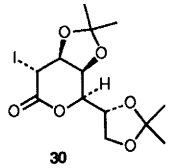
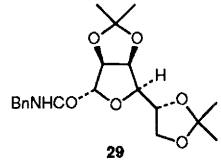
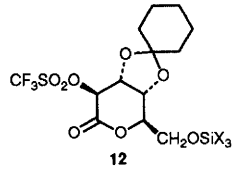
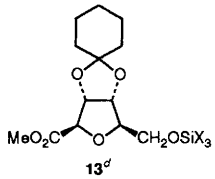
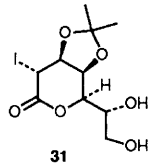
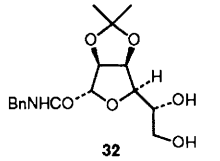
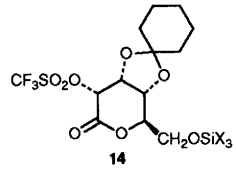
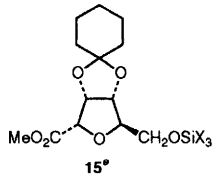
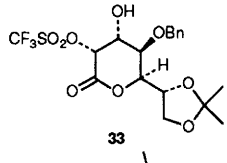
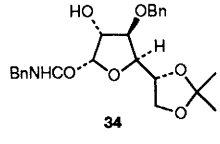
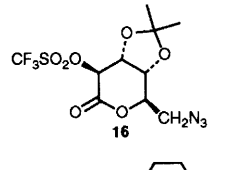
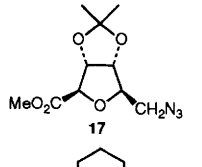
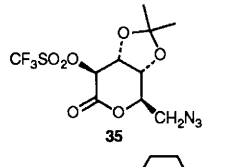
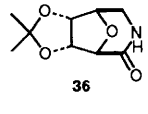
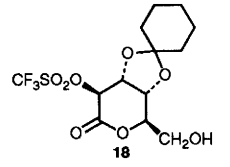
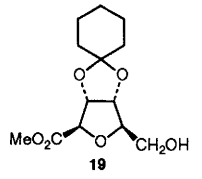
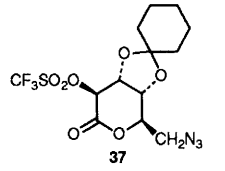
Carbohydrate lactones with an α-triflate (trifluoromethanesulfonate) leaving group have proved to be versatile intermediates for the syntheses of highly substituted carbocycles,[1] and of nitrogen[2] and oxygen[3] heterocycles. In particular, the treatment of a methanolic solution of γ-lactones containing an α-triflate substituent with potassium carbonate results in the formation of a ring contracted oxetane in good to excellent yields, allowing access to antiviral oxetane nucleosides.[4] A wide range of α-hydroxy-δ-lactones are readily available from the Kiliani ascension of suitably protected aldoses;[5] this paper describes some 20 examples of the use of such materials in the synthesis of complex tetrahydrofurans.

Whereas reaction of δ-lactone α-triflates with sodium azide induces nucleophilic displacement of the leaving group by azide, methoxide causes ring contraction by nucleophilic addition to the carbonyl group and ring opening; subsequent ring closure by attack of the original ring oxygen onto C-2 of the sugar affords a methyl tetrahydrofuran-α-carboxylate with overall inversion of configuration at C-2 (Scheme 1). Thus, treatment of the triflate **1** in methanol with solid potassium carbonate gave **2** in 81% yield; however, neither the mesylate nor the iodide corresponding to **1** gave any significant amount of **2** under the same conditions. In complete contrast to these observations, both the mesylate **3** and iodide **5**, with the leaving groups epimeric at C-2 to that in **1**, gave the ring-contracted tetrahydrofuran **4** in good yield; the corresponding triflate, however, was very sensitive to base and decomposed without any significant formation of tetra-



Scheme 1

Table 1 Ring contraction of δ-lactones to give tetrahydrofuran derivatives

Starting material	Product[a]	Yield, data, conditions[c]	Starting material	Product[a]	Yield, data, conditions[c]
 **1**	 **2**	81, 104–106, +17.9 (1.0), A	 **20**[b]	 **21**	72[f], oil, –50.1 (1.1), B
 **3**	 **4**	80, 79–80, –11.4 (1.0), A	 **22**	 **23**	62[f], 83–84, –12.4[g] (1.0), B
 **5**	 **4**	80, 79–80, –11.4 (1.0), A	 **24**	 **25**	78[f], 94–96, –31.7 (1.0), B
 **6**	 **7**	79, 139–142, +37.2 (0.61), A	 **26**	 **27**	57[f], oil, –18.7 (1.0), B
 **8**	 **9**	80, 40–42, –17.9 (0.75), A	 **1**	 **28** +  **29**	29, 114–116, +27.5 (3.45), C 62, oil, –16.8 (1.02), C
 **10**[b]	 **11**	60, 33–34, –32.8 (1.0), A	 **30**	 **29**	89, oil, –16.8 (1.02), C
 **12**	 **13**[d]	68, oil, –36.7 (1.2), A	 **31**	 **32**	88, oil, –7.6 (0.5), C
 **14**	 **15**[e]	69, 80–81, –31.3 (0.8), A	 **33**	 **34**	63, 117–118, –67.4 (0.7), C
 **16**	 **17**	70, oil, +24.9 (0.3), A	 **35**	 **36**	91, 175–177, +13.9[h] (0.66), D
 **18**	 **19**	94, oil, –53.8 (0.47), A	 **37**	**38**	86, 199–201, +20.0[i] (0.36), D

[a] All new compounds (other than some of the more unstable triflates) have satisfactory microanalytical and spectral data; the stereochemistry of the carboxylate function in the products has been established by degradation of products to compounds in which the carbon functionality at C-2 of the tetrahydrofuran is identical to that at C-5, and then examining ^1H and ^{13}C NMR spectra for symmetry. The structure of **23** was established by X-ray crystallographic analysis. [b] X_3 = Me_2Bu^t; Bn = $PhCH_2$. [c] Presented as: yield (%), m.p. (*T*/°C), $[\alpha]_D$ (*c* in $CHCl_3$ unless otherwise noted), conditions. Method A. Addition of an excess of solid potassium carbonate to a methanol solution of the triflate at 0 °C. Method B. The alcohol was converted to the triflate by treatment with triflic anhydride in the presence of pyridine, and the reaction worked up in the presence of methanol. Method C: Reaction with benzylamine in tetrahydrofuran. Method D: Hydrogenation of azidotriflate in ethyl acetate in the presence of palladium black. [d] Together with 4% of **15**. [e] Together with 16% of **13**. [f] In these cases, the triflates were relatively unstable and the yield is given based on the alcohol including the formation of the triflate. [g] In MeCN. [h] In EtOH. [i] In $Me_2C{=}O$.

hydrofuran product. Similar behaviour was found for the triflate **6** and mesylate **8** (epimeric at C-6 with **1** and **3**, respectively) which gave **7** and **9**. Although some investigation of the leaving groups was necessary, all the above reactions proceeded in about 80% yield; there was no detectable epimerisation of the carboxylate function in any of the above reactions.

The ring contraction of a series of compounds, in which the carbon substituent at C-5 of the δ-lactone was *trans* to the protected diol, was investigated as a source of potential precursors to C-nucleosides and polyoxins. Thus the acetonide **10** and the cyclohexylidene derivatives **12** and **14** gave the tetrahydrofurans **11**, **13** and **15** in 60–70% yields; in these cases, some formation of epimeric tetrahydrofuran-carboxylates was observed. A similar yield was also found in the contraction of the azide **16** to **17**. The hydroxytriflate **18** gave the tetrahydrofuran **19** in 94% yield, showing that there is effectively no competition for the formation of a tetrahydropyran over a tetrahydrofuran in this system.

This ring contraction may also proceed in good yield even when the adjacent oxygen function to the leaving group is not protected, although the intermediate triflates are frequently relatively unstable. However, in these circumstances, pyridine in methanol was found to provide a better set of conditions for the contraction, because (the presumably more basic) potassium carbonate gave rise to epoxide formation. Thus the alcohols **20**, **22**, **24** and **26** were converted to the corresponding triflates and work-up in the presence of pyridine in methanol gave the tetrahydrofurans **21**, **23**, **25** and **27** in 72, 62, 78 and 57% overall yields.

Nucleophiles other than methoxide can also induce ring contraction. Thus the triflate **1**, on treatment with benzylamine in tetrahydrofuran, affords a relatively small amount (29%) of amide **28** in which the ring contraction has occurred with the inversion of configuration at C-2; the major product is the secondary amide **29** in which the ring contraction has occurred with *overall retention of configuration* at C-2 of the carbohydrate. The same amide **29** is also formed by treatment of the iodide **30** under the same conditions. This result can be attributed to relatively easy epimerisation of the open-chain intermediates before the ring closure and is consistent with the benzylamine-induced ring contractions of γ-lactone derivatives to oxetanes.[6] Reaction of the iododiol **31** with benzylamine in tetrahydrofuran gives the tetrahydrofuran **32** in 88% yield, again demonstrating that in these systems tetrahydrofuran formation completely predominates over any competition to produce tetrahydropyrans. A further example of the benzylamine-induced ring contraction is the conversion of **33** into **34**. Intramolecular amines can also efficiently cause the same transformation: thus the azides **35** and **37** form the δ-lactams **36** and **38** in excellent yield on hydrogenation in the presence of palladium catalysts.

Although the ring contractions of δ-lactone derivatives induced by basic methanol occur in high yields and are thus parallel to the ring contractions of γ-lactones to oxetanes, there are also marked differences between the two sets of reactions. In particular, the stereochemistry of the carboxylate group in the tetrahydrofuran arises almost exclusively by overall inversion of configuration at C-2 by nucleophilic attack of the ring oxygen; the stereochemistry of the carboxylate is determined by the configuration at the α-position of the lactone. In contrast, in the formation of oxetanes from γ-lactones, the stereochemistry of the carboxylate is determined principally by the oxygen substituent at C-3 rather than by that of the leaving group at C-2[7] (although this is not the case with carbon substituents at C-3).[8] Also, oxetane formation usually requires a triflate leaving group α to the carbonyl function, whereas formation of the tetrahydrofuran ring may happen with a wider range of leaving groups. It is clear, however these differences in the stereochemical courses of the reactions may arise, that the ring contraction of δ-lactone derivatives provides a very powerful strategy for the easy synthesis of complex tetrahydrofurans with carbon substituents at C-2 and C-5.

This work was supported by the SERC (S. J. M., A. J. F.), CASE (B. M. S.) and Oxford Centre for Molecular Studies (C. J. F. B., J. C. S.) awards/fellowships, and by the AIDS Committee of the MRC (S. S. C.); we are grateful to Louise Johnson and Kimberly Woods for discussions and for evaluation of some of these compounds as potential phosphorylase inhibitors.

Received, 15th July 1992; Com. 2/03780G

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