Acid-catalysed Transformation of α-Trifluoromethanesulfonates of γ- and δ-Lactones into 2,5-Disubstituted Homochiral Tetrahydrofurans

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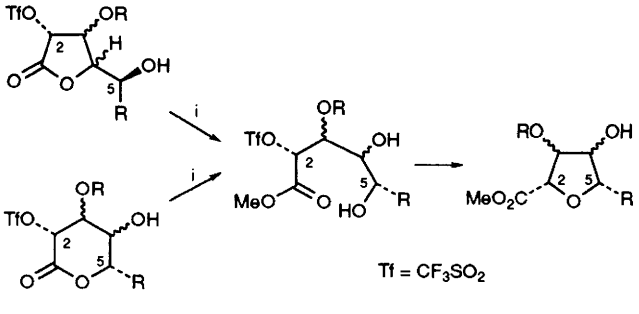
Excellent yields of methyl tetrahydrofuran-α-carboxylates are obtained by treatment of 2-*O*-trifluoromethanesulfonates (triflates) of either 1,4- or 1,5-lactones with acid in methanol; in some cases, very different tetrahydrofurans may result from acid or base treatment of a methanolic solution of the same starting material.

There is much current interest in the synthesis of tetrahydrofurans.[1] Treatment of δ-lactones having a leaving group at the α-position with basic solutions of methanol induces ring opening of the lactone, followed by closure of the open chain intermediate, to provide a general method for the construction of highly substituted homochiral tetrahydrofurans.[2,3] This paper reports a complementary acid-catalysed procedure for the conversion of α-triflates (trifluoromethanesulphonates) of both γ- and δ-lactones with 1% solutions of hydrogen chloride in methanol to tetrahydrofurans. The reactions proceed in excellent yield and with clean inversion of configuration at the carbon bearing the triflate. The lactone triflates probably undergo acid-catalysed ring opening by methanol to intermediate hydroxy triflates which then cyclise (Scheme 1); in some cases, the tetrahydrofuran ring may be formed first, giving an intermediate bicyclic lactone.



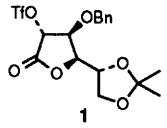
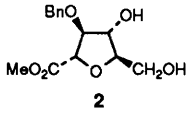
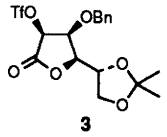
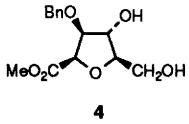
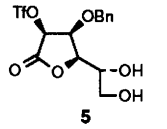
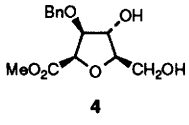
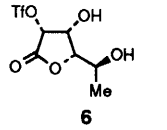
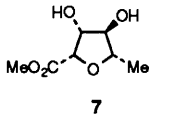
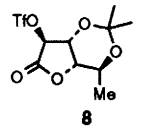
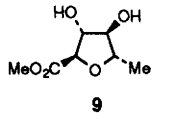
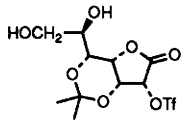
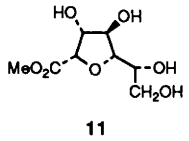
Scheme 1 *Reagent*: i, HCl in MeOH

Attempts to remove the acetonide protecting group from **1** (Table 1) by acid hydrolysis in order to prepare the corresponding diol under a variety of conditions were unsuccessful; however, when **1** was treated with a 1% solution of hydrogen chloride in methanol at room temperature, the fully substituted tetrahydrofuran **2**† was formed in 98% yield. Reaction of the epimeric triflate **3** under similar conditions afforded the tetrahydrofuran **4** in 88% yield. In both cases, the formation of the tetrahydrofurans **2** and **4** occurred in high yield with clean inversion of configuration at C-2. In contrast to the difficulties found in removing the isopropylidene protecting group from **1**, it was possible to remove the acetonide from **3** by acid hydrolysis to give the diol **5** which on treatment with methanolic hydrogen chloride gave **4** in quantitative yield. The acid-catalysed transformation of the γ-lactone triflate **6** to **7** in 96% yield has been utilised in the preparation of a series of muscarine analogues.[4] The isopropylidene triflate **8** afforded the methyl ester **9**, epimeric with **7** in 92% yield. The readily available triflate **10** gave the anhydroheptonic acid derivative **11** in 88% yield. Thus, in all these cases, the γ-lactone triflates form tetrahydrofurans in excellent yield.

α-Triflates of δ-lactones with methanolic hydrogen chloride give a formal ring-contraction reaction (Table 2). Thus, the

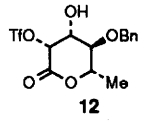
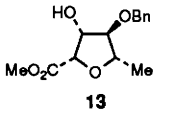
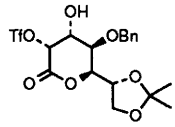
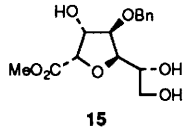
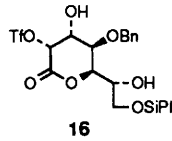
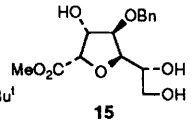
† The stereochemistry of the carboxylate function in the products was established by (*i*) degradation of products to compounds in which the carbon functionality at C-2 of the tetrahydrofuran is identical to that at C-5, and then examining ^1H and ^{13}C NMR spectra for symmetry, or (*ii*) conversion of the products to known compounds or their enantiomers. The structure of **7** was determined by X-ray crystallographic analysis. The structure of the oxetane **17** was established by derivatisation and spectroscopic analysis.

Table 1 Formation of tetrahydrofurans from α-triflates of γ-lactones[a]

Starting material	Product	Yield, data
 1	 2	98%, m.p. 79–85 °C; $[\alpha]_D^{20}$ +56.0 (*c*, 1.0 in $CHCl_3$)
 3	 4	88%, oil, $[\alpha]_D^{25}$ –48.3 (*c*, 1.15 in $CHCl_3$)
 5	 4	100%, oil, $[\alpha]_D^{25}$ –48.3 (*c*, 1.15 in $CHCl_3$)
 6	 7	96%, m.p. 84–85 °C, $[\alpha]_D^{20}$ –9.3 (*c*, 1.0 in MeCN)[b]
 8	 9	92%, m.p. 45–46 °C, $[\alpha]_D^{20}$ –58.4 (*c*, 0.95 in MeOH)
 10	 11	88%, m.p. 127–128 °C, $[\alpha]_D^{20}$ –30.9 (*c*, 0.7 in MeOH)

[a] Bn = $PhCH_2$; Tf = CF_3SO_2. [b] Lit.[2] m.p. 83–84 °C, $[\alpha]_D^{20}$ –12.3 (*c* 1.03 in MeCN).

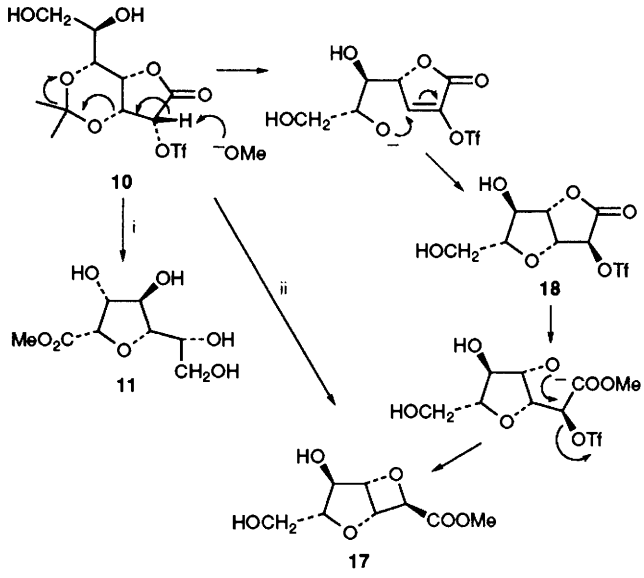
Table 2 Formation of tetrahydrofurans from α-triflates of δ-lactones[a]

Starting material	Product	Yield, data
 12	 13	93%, oil, $[\alpha]_D^{20}$ –50.1 (*c*, 1.1 in $CHCl_3$)
 14	 15	93%, m.p. 93–95 °C, $[\alpha]_D^{20}$ –26.4 (*c*, 1.0 in MeCN)
 16	 15	85%, m.p. 93–95 °C, $[\alpha]_D^{20}$ –26.4 (*c*, 1.0 in MeCN)

[a] Bn = $PhCH_2$; Tf = CF_3SO_2.

benzyl protected lactone **12** gave **13**, used in the synthesis of fluoromuscarine analogues,[5] in 93% yield. Both the acetonide **14** and the silyl ether **16** gave the benzyl protected ester **15**‡ in 93 and 85% yields, respectively. Again, both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans are formed with reliable and clean inversion of configuration at the carbon bearing the triflate.

‡ The structure of **15** was confirmed by hydrogenolysis of the benzyl group to give **11**.



Scheme 2 *Reagents*: i, HCl in MeOH; ii, K_2CO_3 in MeOH

A typical procedure for the formation of the tetrahydrofurans is as follows: a 1% w/w solution of hydrogen chloride in methanol (8 ml) was added to the triflate **1** (2.52 g, 0.57 mmol), and the solution was stirred at room temperature. After 2 h, the reaction was complete; ethyl acetate (40 ml) was added to the reaction mixture which was then washed with water (10 ml) and brine (10 ml) and the organic layer was dried ($MgSO_4$). The solvent was removed to afford a yellow oil which was purified by flash chromatography (ethyl acetate–hexane, 8:2) to give **2**, (1.16 g, 98%).

In complete contrast to the formation of the tetrahydrofuran **11** from treatment of **10** with acidic methanol, reaction of the triflate **10** with potassium carbonate in methanol gave the bicyclic oxetane **17**§ in 80% yield. The course of this reaction may be rationalised (Scheme 2) by initial methoxide-induced elimination of the acetonide group, followed by an intramolecular Michael addition to give the more stable lactone triflate **18**, in which the triflate is *trans* to the C-3 oxygen substituent; **18** undergoes an efficient ring contraction[6] of the γ-lactone to give the fused tetrahydrofuran **17**. The different behaviour of **10** in methanol under these two sets of conditions illustrates the need for care in the handling of triflates, even in acid; very different routes for the efficient formation of oxygen heterocyles may be followed under acidic and basic conditions.

The stereochemistry of the carboxylate function in tetrahydrofuran formed in acidic methanol is determined by the configuration of the trifluoromethanesulfonyl group in the starting lactone; the inversion of configuration at C-2 of the lactone ring during the reaction is the same as that found in the contractions of δ-lactone derivatives induced by basic methanol.[2] This is in contrast to that observed for the base-induced contraction of γ-lactones to form oxetanes in which 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] The method described in this paper is complementary to the base-catalysed procedure reported previously and provides easy and short routes to complex tetrahydrofurans with very simple protecting group strategies.

§ Selected data for **17**: m.p. 122–125 °C (ethyl acetate–hexane), $[\alpha]_D^{20}$ +36.4 (*c* 0.92 in methanol); δ_C (50 MHz, CD_3OD) 171.9 (s, C-1), 93.4, 92.6, 86.1, 81.9, 75.9 (5d, C-2, C-3, C-4, C-5, C-6), 63.3 (t, C-7) and 52.5 (q, OCH_3).

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References

1 For some recent examples, see: I. Marek, J.-M. Lefrancois and J.-F. Normant, *Tetrahedron Lett.*, 1992, **33**, 1747; S. Kobayashi, M. Sato, Y. Eguchi and M. Oyhno, *Tetrahedron Lett.*, 1992, **33**, 1081; D. Craig and A. M. Smith, *Tetrahedron Lett.*, 1992, **33**, 695; H. Dehmlow, J. Mulzer, C. Seilz, A. R. Strecker and A. Kohlmann, *Tetrahedron Lett.*, 1992, **33**, 3607; R. D. Walkup, L. Guan, S. W. Kim and Y. S. Kim, *Tetrahedron Lett.*, 1992, **33**, 3969; W. Ebenezer and G. Pattenden, *Tetrahedron Lett.*, 1992, **33**, 4053; S. J. Mantell, G. W. J. Fleet and D. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3023.

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8 D. R. Witty, G. W. J. Fleet, S. Choi, K. Vogt, F. X. Wilson, Y. Wang, R. Storer, P. L. Myers and C. J. Wallis, *Tetrahedron Lett.*, 1990, **31**, 6927.