Efficient Synthesis of Functionalised Ten-membered Lactones *via* Acid-catalysed Intramolecular Reactions of 5-(Tetrahydro-2-furyl)pentanoic Trifluoroacetic Anhydride

David H. Grayson* and Edwin D. Roycroft

University Chemical Laboratory, Trinity College, Dublin 2, Ireland

5-(Tetrahydro-2-furyl)pentanoic trifluoroacetic anhydride reacts in the presence of trifluoroacetic acid to yield 6-trifluoroacetoxy-9-nonanolide together with (*E*)-non-5-en-9-olide; treatment of the same mixed anhydride with titanium(IV) chloride gives 6-chloro-9-nonanolide, and its reaction with trifluoroacetic acid in the presence of sodium iodide leads to 6-iodo-9-nonanolide.

We recently reported[1] a novel route to 5-substituted-2(3*H*)-furanones **1** that involves acid-mediated rearrangements of mixed anhydrides such as **2** for which $n = 2$. Evidence was presented that acylium $\rightleftharpoons$ acyloxonium species **3** are reaction intermediates, and we speculated that macrolides might be formed when anhydrides **2** having larger values of n were rearranged. We now confirm that this expectation can be realised for the anhydride **4** derived from 5-(tetrahydro-2-furyl)pentanoic acid **5**, and show that several different functional groups can be regiospecifically incorporated into the ten-membered lactone ring systems which are products of the various reactions. The chemistry described below provides an exceptionally facile entry into the 9-nonanolide series of compounds.

The pentanoic acid **5** was synthesised by chain extension of the acid **6** *via* $\mathrm{RCH_2OH} \rightarrow \mathrm{RCH_2OTs} \rightarrow \mathrm{RCH_2I} \rightarrow \mathrm{RCH_2CH(CO_2Et)_2} \rightarrow$ **5**. Reaction of **5** with one equivalent of trifluoroacetic anhydride in dry chloroform gave the mixed anhydride **4** which, on heating *in situ* in the presence of the liberated trifluoroacetic acid, was efficiently[†] converted into a 4:1 mixture (85%) of the trifluoroacetoxy lactone **7** and the volatile, sweet-smelling unsaturated lactone **8** which were easily separated by chromatography.[‡]

Gentle hydrolysis of **7** using $\mathrm{NaHCO_3}$–MeOH led to the hydroxy lactone **9** (73%), m.p. 68 °C, which could be oxidised to the known[2] ketolactone **10** (60%). The reverse transformation of **10** into **9** has not been achieved[2] and our methodology therefore provides a practical route to the latter compound.

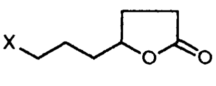
The unsaturated lactone **8**[§] was not mutually interconvertible with **7** under the reaction conditions leading to its formation, and could be hydrolysed to the hydroxy acid **11** (82%) which was easily identified by consideration of its chemical shift data and by ^{1}H NMR decoupling experiments.[¶]

[†] All yields are unoptimised.

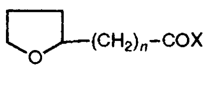
[‡] All new compounds were fully characterised and gave spectroscopic and analytical data in accord with their structures.

[§] *Note added in proof*: Compound **8** has been briefly mentioned in a previous report by M. Ochiai, S. Iwaki, T. Ukita and Y. Nagao, *Chem. Lett.*, 1987, 133.

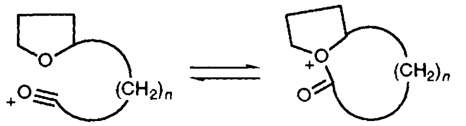
[¶] We thank Dr J. O'Brien for these and other NMR experiments.



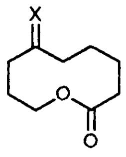
1; X = OCOCF$_3$ or Cl



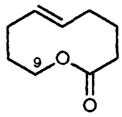
2; n = 2, X = OCOCF$_3$
4; n = 4, X = OCOCF$_3$
5; n = 4, X = OH
6; n = 2, X = OH



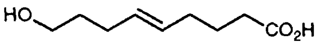
3; n = 2
14; n = 4



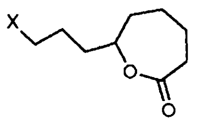
7; X = H, OCOCF$_3$
9; X = H, OH
10; X = O
12; X = H, Cl
13; X = H, I



8



11



15; X = OCOCF$_3$, Cl or I

The lactone **8** shows an AB system in its NMR spectrum for the protons on C-9 which resonate at δ ($CDCl_3$) 4.99 and 3.70, each 1H, J_{gem} 11.5 Hz. This is presumably owing to differential shielding of the intra- and extra-annular hydrogens of this methylene group which is caused by the magnetic anisotropy of the transannular double bond. Thus, at the temperature of the NMR probe (24 °C), the molecule **8** exists as a single conformer and does not undergo 'racemisation' at prochiral C-9 *via* a ring-flipping process. We have carried out a full analysis of the ^{1}H NMR spectrum of **8** and will report this data together with the results of molecular mechanics calculations in due course.

When the mixed anhydride **4** was treated with titanium(IV) chloride in dry chloroform the solid chlorolactone **12**, m.p. 47 °C was obtained (73%). The structure of **12** was confirmed by its alkaline hydrolysis which gave back the pentanoic acid **5** as expected. The chloride **12** could not be converted into the corresponding iodide under Finkelstein conditions. However, if the mixed anhydride **4** was generated in acetone solution in the presence of sodium iodide then the iodolactone **13** was produced (75%).

The formation of lactones **7**, **8**, **12** and **13** from the mixed anhydride **4** can be rationalised by invoking the intermediacy of the acylium $\rightleftharpoons$ acyloxonium ion **14**. Regiospecific β-elimination of a proton from the more flexible seven-membered ring of the bicyclic system **14** leads to **8**, while attack at its bridgehead carbon by the appropriate nucleophile yields **7**, **12** or **13**. The hexanolides **15** are alternative products but were not detected, suggesting that cleavage of the intermediate **14** is subject to electronic control.

The reactions outlined above provide a novel and efficient route to a useful class of macrolides, and should prove to be applicable to the synthesis of natural products based upon these and related carbon frameworks.

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References

1 D. H. Grayson and E. D. Roycroft, *J. Chem. Soc., Chem. Commun.*, 1992, 1296.
2 I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp and G. J. Williams, *J. Org. Chem.*, 1966, **31**, 3032.