Pergamon

Tetrahedron Letters, Vol. 35, No. 40, pp. 7467-7468, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01563-5

Aspects of Control and Selectivity in Anion Mediated Cascade Reaction Sequences: Applications in Homochiral Synthesis.

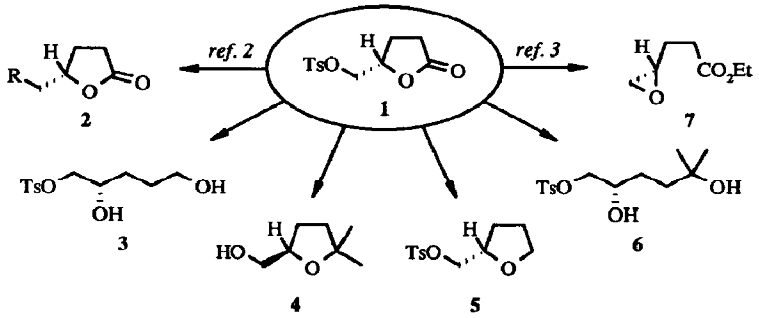
David C. Harrowven*, Shelagh T. Dennison and Jonathan S. Hayward.

Department of Chemistry, University of Wales, Bangor, Gwynedd, LL57 2UW.

Abstract : The transformation of the homochiral lactone 1 into the diols 3 & 6, the tetrahydrofurans 4 & 5 and a number of analogues thereof is described.

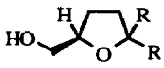
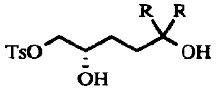
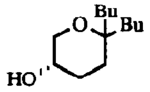
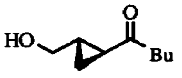
The ready availability of the chiral lactone **1** from L-glutamic acid[1] has rendered this molecule considerable status as a building block in enantioselective syntheses. To date, attention has primarily been focused on the elaboration of this molecule by nucleophilic displacement of the tosylate group.[2] Reports concerned with the manipulation of the carbonyl moiety have been scant by comparison, undoubtedly reflecting the myriad transformations that could ensue in such circumstances.[3]

Our interest in the development of new '*tandem*' and '*cascade*' reaction sequences[4] prompted us to examine the reactions of **1** with polar organometallic reagents. The aim was two fold: to highlight circumstances under which this material might be transformed into synthetically useful homochiral products and to delineate further those factors that influence successive bond manipulations in anionically driven cascade reaction sequences.[5] In this *letter* we detail some of our preliminary studies that have revealed new entries towards the products **3** to **6** and analogues thereof.



We first examined the reaction of **1** and methyllithium. To our delight we found that by adding two equivalents of methyllithium to a cooled (-90°C) solution of the lactone **1**, maintaining the reaction at that temperature for a further hour then allowing the whole to attain ambient temperature over a period of 5h, the tetrahydrofuran **4**[6] could be attained in near quantitative yield. Furthermore, by conducting the reaction in an identical manner but quenching with aqueous ammonium chloride prior to warm up, the diol **6** was furnished in 92% yield.[7]

The reactions of lactone **1** with *n*-BuLi, PhLi and allylmagnesium chloride were also examined. In each case these exhibited a similar reaction profile, providing compounds **8** to **13** in good yield using the above protocols. The influence of temperature upon the outcome of these reaction sequences was dramatic. For example, when **1** was exposed to butyllithium at -50°C a complex mixture, that included the tetrahydrofuran **8** (38%), tetrahydropyran **14** (23%) and cyclopropane **15** (15%), resulted.

4 (95%)	R = Me	**6** (92%)	**14**	**15**
8 (85%)	R = Bu	**9** (78%)		
10 (82%)	R = Ph	**11** (72%)		
12 (54%)	R = allyl	**13** (60%)		

We have also found that the diol **3** can be prepared from **1** in a yield of 95% by treatment of a THF solution of this material with DiBAlH at -78°C. The tetrahydrofuran **5**[8] (83%) too may be accessed from **1** by exposing a methanol solution to excess lithium metal at ambient temperature.

Acknowledgement: The authors wish to thank the European Social Fund for the provision of an M.Sc. studentship to Miss Dennison and for some additional support to Mr. Hayward. Our gratitude is also extended to Dr. O. Howarth for his invaluable assistance through the SERC high field NMR service.

References and Notes:

1. **a.** Mori, K. *Tetrahedron*, **1975**, *31*, 3011; **b.** Gringore, O.H. and Rouessac, F.P. *Org. Synth.*, **1984**, *63*, 121; **c.** Eguchi, C. and Kakuta, A. *Bull. Chem. Soc. Jpn.*, **1974**, *47*, 1704 and **d.** Austin, A.T. and Howard, J. *J. Chem. Soc.*, **1961**, 3593.
2. For some pertinant examples see **a.** Mattes, H., Hamada, K. and Benezra, C. *J. Med. Chem.*, **1987**, *30*, 1948; **b.** Normant, J.F., Villieras, J. and Scott, F. *Tetrahedron Lett.*, **1977**, 3263; **c.** Ravid, U. and Silverstein, R.M. *Tetrahedron Lett.*, **1977**, 423; **d.** Mukaiyama, T., Taguchi, T. and Nishi, M. *Bull. Soc. Chem. Jpn.*, **1971**, *44*, 2797 and **e.** Pirillo, D., Leggeri, P., Veronelli, G., Malamidi, A. and Traverso, G. *Boll. Chim. Farm.*, **1986**, *125*, 355.
3. See for example **a.** Tanaka, M., Tomioka, K. and Koga, K. *Heterocycles*, **1985**, *23*, 2347; **b.** Ho, P.-T. and Davies, N. *Synthesis*, **1983**, 462; **c.** Kitahara, T. and Mori, K. *Tetrahedron*, **1984**, *40*, 2935 and **d.** Shin, D.-S., Yadagiri, P., Falck, J.R., Masferrer, J.L. and Schwartzman, M.L. *Tetrahedron Lett.*, **1989**, *30*, 3923.
4. See for example **a.** Harrowven, D.C., Dennison, S.T. and Howes, P. *Tetrahedron Lett.*, **1994**, *35*, 4243; **b.** Harrowven, D.C. *Tetrahedron*, **1993**, *49*, 9039; **c.** Harrowven, D.C. *Tetrahedron Lett.*, **1993**, *34*, 5653; **d.** Harrowven, D.C. *Tetrahedron Lett.*, **1992**, *33*, 2879 and **e.** Harrowven, D.C. and Dennison, S.T. *Tetrahedron Lett.*, **1993**, *34*, 3323.
5. **a.** Hulce, M. and Chapdelaine, M.J. 'Nucleophilic Addition - Electrophilic Coupling with a Carbanion Intermediate'. In *Comprehensive Organic Synthesis*, Trost, B.M. Ed., Pergamon, Oxford, Vol. 4, 1991, pp. 237; **b.** Thebtaranonth, C. and Thebtaranonth, Y. *Tetrahedron*, **1990**, *46*, 1385; **c.** Biehl, E.R. and Khanapure, S.P. *Acc. Chem. Res.*, **1989**, *22*, 275 and **d.** Posner, G. *Chem. Rev.*, **1986**, *86*, 831 and **e.** Ho, T.-L. *Tandem Organic Reactions*, Wiley, N.Y., 1992.
6. **a.** Kitagawa, I., Nishino, T., Kobayashi, M., Matsuno, T., Akutsu, H. and Kyogoku, Y. *Chem. Pharm. Bull.*, **1981**, *29*, 1942 and **b.** Yoshimura, J., Ohgo, Y., Ajisaka, K. and Konda, Y. *Bull. Chem. Soc. Jpn.*, **1972**, *45*, 916.
7. All temperatures were measured internally and yields refer to the quantity of isolated material. All compounds exhibited satisfactory spectral characteristics.
8. **a.** Balfe, M.P., Irwin, M. and Kenyon, J. *J. Chem. Soc.*, **1941**, 312; **b.** Strirling, C.M. and Palmer, R.J. *J. Am. Chem. Soc.*, **1980**, *102*, 7888; **c.** Guindon, Y., Therien, M., Girard, Y. and Yoakim, C. *J. Org. Chem.*, **1987**, *52*, 1680 and **d.** Descours, D., Festal, D., Leger, J.M. and Carpy, A. *Helv. Chim. Acta*, **1991**, *74*, 1757.

(*Received in UK* 15 *July* 1994; *revised* 5 *August* 1994; *accepted* 12 *August* 1994)