An Example of a Chiral Non-Racemic Carbanion as Versatile Synthon in the Asymmetric Synthesis of Polysubstituted γ-Lactones

Carmen Mª Rodríguez, Miguel A. Ramírez and Victor S. Martín* Centro de Productos Naturales Orgánicos "Antonio González" Instituto Universitario de Bio-Orgánica Carretera la Esperanza, 2 38206 La Laguna, Tenerife, SPAIN

Abstract: The application of a chiral non-racemic carbanion generated from enantiomerically enriched α -sulfonyl- γ -lactones to the asymmetric synthesis of highly substituted and fused γ -lactones is described.

The synthesis of butenolides and saturated γ -lactones as optically active fragments is currently receiving considerable attention considering their utility as useful synthesis for the synthesis of biologically active natural products.¹ Very recently we have described a new approach to the stereocontrolled synthesis of such units in enantiomerically enriched form by an intramolecular Michael addition involving chiral non-racemic thiophenylacetates of γ -hydroxy- α , β -unsaturated esters.² This thermodynamically controlled process provided access to the **all** trans substituted γ -lactones with excellent stereocontrol.²



In order to increase the control in the synthesis of such a valuable synthon we focussed our attention on the α -carbonyl substituent considering the treatment with a suitable electrophile of the carbanion generated via 1, as a possible synthetic alternative to molecules of type 2. Such a carbanion should be conveniently generated from the β -sulfone carbonyl system, some degree of stereoselectivity control being expected by us because of the proximally located stereogenic centres.³



To our surprise, when lactone 3 was treated with sodium hydride and methyl iodide, in DMF at 0 $^{\circ}$ C, the alkylated product 4 was obtained as the sole isolated stereoisomer (Scheme I). The obtained product 4 is

the diastereoisomer of the sulfone of 2,⁴ produced by direct cyclization (the more thermodynamically stable stereoisomer) following the intramolecular Michael methodology.²



The result is consistent with a carbanion 6 generated from 3 with retention of configuration.⁵



In order to investigate the scope and limitations of the method various electrophiles were used (Table I). With all the alkylating reagents tried the carbon-carbon bonds were formed in excellent yields, as a single detectable stereoisomer (¹H NMR 400 MHz) (Entries 1, 2 and 3, Table I), by simply mixing the original lactone, the alkylating agent and NaH, in DMF, at 0 °C. These reaction conditions were not effective when intermolecular Michael addition was tried with methyl acrylate and methyl propiolate. Fortunately smooth reactions were produced when the sulfone 3 was treated with lithium hexamethyldisilylamide, at -78 °C and the unsaturated carbonyl compounds were added, letting the system reach room temperature. In the methyl propiolate case a 5 : 1 mixture of the E : Z products was obtained (Entry 4, Table I). The addition product 7. However, when the reaction was allowed to reach room temperature the cyclic enol 8 was the only observed product (Scheme II). Surprisingly any attempt to attain an addition reaction with a carbonyl compound proved fruitless (Entry 6, Table I). The high nucleophilicity towards alkyl halides was clearly illustrated when the hydroxyl protection of 9 as benzylic ether was attempted, in which case the product 10 resulting from the carbon-carbon bond was the isolated product, when 1 equiv of alkylating agent was used.



Scheme II

		Reaction		
Entry	Substrate	Conditions ^{a)}	Product	Yield
	R^1 H		R^{1} R^{2} $CO_{2}Ph$ $CO_{2}Me$	
1.	$R^1 = n - Pr$	Br, A	$R^{1} = n - Pr;$ $R^{2} = CH_{2} = CHCH_{2}$	97
2.	$\mathbf{R}^1 = n$ -Pr	PhCH ₂ Br, A	$R^{1} = n - Pr;$ $R^{2} = PhCH_{2}$	94
3.	$\mathbf{R}^1 = n$ -Pr	n-BuBr, A	$R^{1} = n - Pr;$ $R^{2} = n - Bu$	83
4.	$\mathbf{R}^1 = n$ -Pr	= CO ₂ Me, B	$R^1 = n$ -Pr; $R^2 = CH = CHCO_2Me$	78
5.	$R^1 = n - Pr$	CH ₂ =CHCO ₂ Me, C	$(E+Z \text{ mixture})$ $O SO_2Ph$ $O HOP HHP$ $O HOP HHP$ $O HOP HHP$ $O HP HHP$ $O HOP HHP$ $O HP HP$ $O HP$	88
6.	$R^{1} = n - Pr$ O $\parallel H$	PhCHO, A PhCHO, B	8 — — — — — — — — —	
7.	O SO ₂ Ph H H OH	PhCH ₂ Br, A	O H H H H H	92
	,		10	

Table I. Substitution of hydrogen by electrophiles with retention of stereochemistry

a) Method A: i) NaH (1.2 equiv), DMF (0.2M), 0 °C, 15 min, ii) Electrophile, 0 °C→ rt; Method B: i) [(CH₃)₃Si]₂N⁻Li⁺ (1.1 equiv), THF : HMPA (1:1) (0.1M), -78 °C, 15 min, ii) Electrophile, -78 °C; Method C: Similar to Method B but letting the reaction mixture reach room temperature

The presence of the sulfone group is essential to achieve such a high degree of stereoselectivity. Thus when the carbanion generation was performed over the sulfide compound 1, a 45 : 55 mixture of 11 and 12 was obtained.



In order to rationalize the obtained results, semiempirical calculations⁶ were carried out on the structure of the carbanion 6 considering the presence of the chelating metal. The minimum energy reached was for the structure 13 (Figure I). When such calculations were performed for the anion generated from the sulfide 1, both structures 14 and 15 showed similar levels of stability (Figure I). Thus the role of the sulfone is interpreted by the chelating action of one of the oxygen atoms of this functional group. The retention of configuration in the alkylated products is conjectured by a steric hindrance with the aromatic ring in the phenyl sulfone group. The obtained proportion in the alkylated products over the sulfide 1 should be the result of the closer levels of energy between the anions 14 and 15.



Figure I

The overall process can be considered as the electrophilic substitution of the α -proton in the β -sulfonylcarbonyl system with retention of configuration at the asymmetric carbon atom. Studies of the use of the described procedure for the synthesis of other valuable synthons are underway and will be reported in due course.

Acknowledgement: This research was supported by grants from the DGICYT (MEC of Spain) PB89-0402, and the Gobierno Autónomo de Canarias 90/31.07.89. Thanks are given to the IBM Corporation for calculation facilities.

References and Notes:

- 1. a) Nagao, Y.; Dai, W.; Ochiai, M.; Shiro, M. J. Org. Chem., 1989, 54, 5211, and references cited therein; b) Corey, E.J.; Cheng, X.M. The Logic of Chemical Synthesis, John Wiley & Sons, Inc., New York, 1989, and references cited therein.
- 2. Rodríguez, C.M.; Martín, V.S. Tetrahedron Lett., 1991, 32, 2165.
- a) Boeckman, R.K.; Heckendorn, D.K.; Chinn, R.L. Tetrahedron Lett., 1987, 28, 3551; b) Evans, D.A. In Asymmetric Synthesis, Morrison, J.D., Ed.; Academic Press, Orlando, 1985, Vol 3, Chapter 1, pp, 37-45, and references cited therein.
- 4. The absolute configuration was determined in all the cases by ROESY experiments over the substitution products (BRUKER AMX400).
- 5. For other examples of generation of α-heterosubstituted carbanions with retention of configuration see: Pearson, W.H.; Lindbeck, A.C. J. Am. Chem. Soc, 1991, 113, 8546, and references cited therein. See: also: Seebach, D.; Boes, M.; Naef, R.; Schweizer, W.B. J. Am. Chem. Soc, 1983, 105, 5390.
- 6. Semi-empirical AM1 and PM3 SCF-MO methods have been employed with MOPAC v. 6.0 program (QCPE nº 455) on IBM Risc 6000. Geometry optimization has been carried out with the keyword PRECISE together with the default BFGS or eigenvector (EF) minimization method, with a final gradient norms ≤0.01Kcal.Å⁻¹. All stationary points on the potential energy surfaces were characterized by calculating and diagonalizing the Hessian matrix and checking the number of negative eigenvalues.
- 7. Satisfactory spectroscopic and analytical data for the new compounds were obtained.