An Efficient Route to α,β-Epoxy Ketones of High Enantiomerical Purity

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Acylepoxides were obtained in high enantiomeric purity (ee = 92–99%) by addition of organolithium or Grignard reagents to enantiomerically pure methyl or ethyl 2,3-epoxypropanoates at low temperature (−85°C).

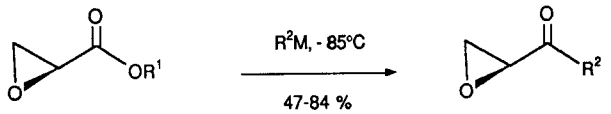
Optically active epoxy ketones are of great importance because they are the precursors of chiral synthons of definite relative stereochemistry useful for the synthesis of various biologically active substrates such as epoxyalcohols or epoxyamines.[1] They may be prepared by oxidation of secondary epoxyalcohols obtained by kinetic resolution according to Sharpless' method.[2] Alternatively, the addition of organometallics to optically active epoxynitriles prepared by asymmetric epoxidation was reported.[3]

We wish to report here a more direct route to epoxy ketones by addition of organolithium and organomagnesium reagents to glycidic esters. Ethyl or methyl 2,3-epoxypropanoates **1** are easily prepared by nitrous deamination of D- or L-serine followed by basic cyclization and esterification of the resulting α-bromo-β-hydroxy acid.[4] They may be opened by various organometallic compounds such as dialkyl-, diaryl- and divinyllithium cuprates, dialkylmagnesium cuprates, trialkylalanes and aluminium acetylides. The epoxide ring is attacked regiospecifically in the β-position and produces exclusively α-hydroxy esters without racemization.[5]

However, when the epoxypropanoates **1** were reacted at low temperature with an organolithium reagent, we observed the addition on the ester function without any opening of the epoxide ring. Moreover, by operating at −85°C, it was possible to isolate the epoxy ketones **2** almost exclusively and to avoid the formation of tertiary alcohols resulting from a further addition of the organometallic compound on the ketone. Good yields were obtained not only with alkyllithium reagents but also with acetylides (Table). Such a result was presumably due to a stabilization of the anionic intermediate by chelation with the epoxide oxygen, as previously observed during the reaction of organolithium compounds with *O*-protected α-hydroxy esters.[6]

The reaction is also possible with Grignard reagents, although these reagents are not as reactive as the corresponding alkyllithium reagents. The best results are obtained in this case when the reaction is conducted in the presence of an excess of chlorotrimethylsilane.[7]

The course of the reaction is then significantly accelerated by this additive and the procedure allows the reaction to be completed in twelve hours at −85°C. By contrast, the reaction of the 2,3-epoxypropionic acid[8] with butyllithium in the presence of cerium chloride as recently described[9] gave the corresponding ketone in 7% yield only.



1 (S or R) ee > 99%

2 (S or R) ee = 92-99%

1	R^1	2	R^2	2	R^2
a	CH_3	a	CH_3	e	C_6H_5-CH_2
b	C_2H_5	b	i-C_3H_7	f	C_6H_{11}-CH_2
		c	n-C_4H_9	g	$(CH_3)_3Si$-C≡C
		d	i-C_4H_9		

Scheme

The enantiomeric excesses of the epoxy ketones were measured by chiral VPC on a 50 m Cydex B column (SGE) and were found to be better than 92% (Table).

Products were purified by distillation or by medium pressure liquid chromatography on a Jobin-Yvon Modulprep (Kieselgel 60 H Merck) or by flash chromatography (Kieselgel 60 Merck: 230–400 Mesh; solvent cyclohexane/EtOAc) and analyzed by VPC (BP5, 25 m capillary column) or by TLC (silica gel 60F 254). Optical rotations were measured on a Perkin-Elmer 141 polarimeter. NMR spectra were recorded on a Bruker AC at 250 MHz for ^1H and 100.56 MHz for ^{13}C NMR. $CDCl_3$ was used as solvent with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 599. Mass spectra were recorded on a Nermag R 10-10 (fitted with a VPC-mass coupling; column: CP Sil 5,40 m).

(2R)-Methyl 2,3-Epoxypropanoate (1a):

L-Serine (21.0 g, 0.2 mol) and potassium bromide (80 g, 0.7 mol) were dissolved in water (165 mL). 47% hydrobromic acid (50 mL, 0.43 mol) was added at r.t. and the mixture was stirred and cooled under N_2 to −12°C. Sodium nitrite (15.2 g, 0.22 mol) was slowly added in small portions (0.5 g). After each addition the mixture became brown and decoloration was waited for before further addition; total addition time was 8 h. The solution was allowed to warm to 0°C and was stirred overnight. Excess nitrous oxide was then removed by bubbling N_2 through the solution for 1 h and the pale green solution was extracted with Et_2O (6 × 300 mL). After drying ($MgSO_4$) the solvent was removed in vacuum (0.1 Torr). The residual oil (32 g) was dissolved in abs. EtOH (250 mL) and cooled to −40°C under N_2. A solution of KOH (21.3 g, 0.38 mol) in abs. EtOH (115 mL) was slowly added. The mixture was then allowed to warm to −20°C and stirred for 2 h at this temperature, and then for a further 14 h at 0°C. Half the solvent was removed in vacuum without warming and anhydr. Et_2O (800 mL) was added to precipitate the salts which, after filtration, were dried under vacuum to give a KBr–potassium glycidate mixture (42 g). Potassium glycidate was extracted by refluxing this mixture with stirring for 45 min in 97.5% EtOH (abs. EtOH/water, 470 mL:11 mL). After filtration of the hot suspension, the glycidate crystallized from

Product 2	Yield (%)	bp (°C/Torr)	$[\alpha]_D^{20}$ (c, MeOH)	ee (%)	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS m/z (%)
(*S*)-**2a**	55	71/62 Lit: 71/77[11]	−108.9 (4.69)[a]	>99	2.06 (3H, s, CH_3−CO), 2.89 (dd, 1H, *J* = 5.6, 2.5, CH−O), 3.00 (dd, 1H, *J* = 5.6, 4.7, CH−O), 3.40 (dd, 1H, *J* = 2.5, 4.6, O−CH−CO)	23.60 (CH_3), 45.76 (CH_2−O), 53.60 (CH−O), 205.63 (C=O)	104 (M + 18, 100), 85 (8)
(*S*)-**2b**[b]	74	66/18	−102.6 (4.88)	98	1.11 (d, 3H, *J* = 6.8, CH_3), 1.15 (d, 3H, *J* = 6.9, CH_3), 2.73 (m, 1H, $CH(CH_3)_2$, 2.83 (dd, 1H, *J* = 6.1, 2.5, CH−O), 3.00 (dd, 1H, *J* = 6.1, 4.5, CH−O), 3.53 (dd, 1H, *J* = 2.5, 4.7, O−CH−CO)	17.28 (CH_3), 18.17 (CH_3), 35.73 (CH−CO), 46.32 (CH_2−O), 51.93 (CH−O), 206.30 (C=O)	132 (M + 18, 100), 99 (22), 88 (9)
(*S*)-**2c**	73	70/12	−71.0 (2.88)	99	0.90 (t, 3H, *J* = 7.2, CH_3), 1.31 and 1.57 (2m, 2×2H, CH_2), 2.29 (dt, 1H, *J* = 17.2, 7.2, CH_2−CO), 2.44 (dt, 1H, *J* = 16.8, 7.0, CH_2−CO), 2.87 (dd, 1H, *J* = 5.8, 2.5, CH−O), 3.00 (dd, 1H, *J* = 5.8, 4.7, CH−O), 3.44 (dd, 1H, *J* = 2.5, 4.6, O−CH−CO)	13.61 (CH_3), 22.08 (CH_2), 24.99 (CH_2), 36.14 (CH_2−CO), 45.92 (CH_2−O), 53.19 (CH−O), 207.68 (C=O)	146 (M + 18, 100), 85 (68)
(*S*)-**2c**[c]	62	92/20	−70.0 (2.52)	98			
(*R*)-**2d**	84	65/10 Lit: 67/12[12]	+75.8 (4.59)	99	0.91 (d, 3H *J* = 7.25, CH_3), 0.94 (d, 3H, *J* = 6.8, CH_3), 2.1–2.3 (m, 1H, $CH(CH_3)_2$), 2.17 (dd, 1H, *J* = 18.0, 6.8, CO−CH_2), 2.33 (dd, 1H, *J* = 18.0, 8.6, CO−CH_2), 2.85 (dd, 1H, *J* = 5.8, 2.5, CH−O), 2.99 (dd, 1H, *J* = 5.8, 4.7, CH−O), 3.42 (dd, 1H, *J* = 2.5, 4.7, O−CH−CO)	22.21 (CH_3), 22.33 (CH_3), 23.82 (CH), 45.14 (CH_2−CO), 45.62 (CH_2−O), 53.23 (CH−O), 207.16 (C=O)	146 (M + 18, 100), 129 (4), 102 (4), 85 (40)
(*S*)-**2e**[b,d]	47	–	−51.4 (5.58)	95	2.81 (dd, 1H, *J* = 5.8, 2.5, CH−O), 2.93 (dd, 1H, *J* = 5.8, 4.7, CH−O), 3.43 (d, 1H, *J* = 4.7, 2.5, O−CH−CO), 3.56 and 3.67 (2d, 2H, *J* = 15.5, CH_2−C_6H_5), 7.0–7.4 (m, 5H, C_6H_5)	43.73 (CH_2−CO), 46.25 (CH_2−O), 53.20 (CH−O), 126.69, 127.17, 129.59, 132.67 (ArC), 204.66 (C=O)	180 (M + 18, 42), 164 (100), 147 (36), 118 (8)
(*S*)-**2f**[b]	73	–	−56.0 (5.63)	92	0.7–1.0 (m, 10H, CH_2), 1.8 (m, 1H, CH), 2.08 (dd, 1H, *J* = 7.0, 16.3, CO−CH_2), 2.24 (dd, 1H, *J* = 6.6, 16.2, CO−CH_2), 2.77 (dd, 1H, *J* = 5.9, 2.5, CH−O), 2.91 (dd, 1H, *J* = 5.8, 4.7, CH−O), 3.35 (dd, 1H, *J* = 2.5, 4.6, O−CH−CO)	25.92 (CH_2), 25.94 (CH_2), 26.04 (CH_2), 33.03 (CH_2), 33.11 (CH_2), 33.25 (CH), 43.91 (CH_2−CO), 45.71 (CH_2−O), 55.42 (CH−O), 207.31 (C=O)	186 (M + 18, 100), 170 (27), 153 (21), 125 (33)
(*R*)-**2f**	75	–	+62.5 (5.57)	96			
(*S*)-**2g**	79	–	+41.5 (1.60)[a]	>99	0.26 (s, 9H, $(CH_3)_3C$), 3.03 (dd, 1H, *J* = 4.2, 5.3, CH−O), 3.09 (dd, 1H, *J* = 2.4, 5.3, CH−O), 3.54 (dd, 1H, *J* = 4.2, 2.4, O−CH−CO)	46.73 (CH_2−O), 53.62 (CH−O), 98.39 (C≡C−CO), 101.92 (C≡C−CO), 183.2 (C=O)	186 (M + 18, 100), 170 (15), 153 (5), 90 (3)

[a] CH_2Cl_2.
[b] For new compounds satisfactory microanalyses obtained: C ± 0.47, H ± 0.21.
[c] From BuMgCl in THF.
[d] From BnMgBr in THF.

the solution to give the salt (10.5 g). The remaining solid was boiled again for 30 min in the mother solution, and the same procedure allowed isolation of an additional crop of glycidate (9.5 g). The recrystallized glycidate contained a small amount of KBr (15%).

To a suspension of the dry KBr–potassium glycidate mixture (12.6 g of a 85:15 mixture, 85 mmol) and benzyltriethylammonium chloride (22.78 g, 100 mmol) in anhydr. CH_2Cl_2 (100 mL) was slowly added dimethyl sulfate (12.0 g, 95 mmol). The suspension was stirred for 20 h at r.t. The solvent was evaporated at reduced pressure and the resulting solid extracted with Et_2O (4 × 60 mL). The solution was dried ($MgSO_4$) and distilled. Yield: 5.8 g (67%); bp 52°C/15 Torr (Lit: 65–66°/28 Torr),[10] $[\alpha]_D^{20}$ +9.8° (*c* = 3.4, MeOH), ee > 99%.

IR (neat): $\nu = 1730$ (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): $\delta = 2.95$ (dd, 2H, $J = 3.5$, 1.1 Hz, CH_2–O), 3.46 (dd, 1H, $J = 1.9$, 1.1 Hz, CH–$COOCH_3$), 3.80 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$): $\delta = 46.21$, 47.14, 52.41, 169.68.

Epoxy Ketones 2a–f; General Procedure:

The organolithium reagent in hexane (3.7 mL of a 1.5 M solution, 5.5 mmol) was slowly added to a solution of methyl 2,3-epoxypropanoate (0.51 g, 5 mmol) in pentane–Et_2O 1:1 (20 mL) at −85 °C. The homogeneous mixture was stirred at this temperature for 6 h and hydrolyzed by adding 1 M HCl (10 mL) at low temperature (−85 °C). After extraction with Et_2O (4 × 20 mL), the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give an oil which was purified by chromatography on a silica gel column (cyclohexane or hexane–EtOAc, 9:1) or by distillation.

With Grignard reagents and methyllithium, the reaction was conducted in THF and freshly distilled chlorotrimethylsilane (1.63 g, 15 mmol) was added to the epoxide before addition of the organometallic compound. After addition, the mixture was stirred for 12 h (2 h for methyllithium) at −85 °C before hydrolysis.

(2*S*)-1,2-Epoxy-5-trimethylsilylpent-4-yn-3-one (2g):

Butyllithium (1.5 M, 2.5 mL, 3.75 mmol) was slowly added under Ar to a solution of trimethylsilylacetylene (0.368 g, 3.75 mmol) in anhydr. Et_2O (4 mL) cooled to 0 °C. After stirring for 45 min, this mixture was slowly cannulated onto a solution of (*S*)-methyl 2,3-epoxypropanoate (0.306 g, 3 mmol) in 1:1 Et_2O–pentane (20 mL) cooled to −85 °C. The solution was stirred for 1 h at this temperature and hydrolyzed with aq sat. NH_4Cl (6 mL). After extraction with Et_2O (4 × 20 mL), the organic layer was dried ($MgSO_4$) and the solvent was removed by distillation. The product was not stable enough to be chromatographed on silica gel (cyclohexane–EtOAc, 9:1).

(1) Wood, J.L.; Jones, D.R.; Hirschmann, R.; Smith III, A.B. *Tetrahedron Lett.* **1990**, *31*, 6329.
Pégorier, L.; Petit, Y.; Larchevêque, M. *J. Chem. Soc., Chem. Commun.* **1994**, 633.
(2) Molander, G.A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596.
(3) Urabe, H.; Aoyama, Y.; Sato, F. *J. Org. Chem.* **1992**, *57*, 5056.
(4) Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993.
(5) Larchevêque, M.; Petit, Y. *Bull. Soc. Chim. Fr.* **1989**, 130; *Janssen Chimica Acta* **1990**, *8*, 10.
(6) Larchevêque, M.; Petit, Y. *Synthesis* **1986**, 60.
(7) Cooke Jr, M.P. *J. Org. Chem.* **1986**, *51*, 951.
(8) Payne, G.B.; Van Ess, P.R. *J. Org. Chem.* **1961**, *26*, 2984.
(9) Ahn, Y.; Cohen, T. *Tetrahedron Lett.* **1994**, *35*, 203.
(10) Séquin, U. *Tetrahedron Lett.* **1979**, 1833.
(11) Yang, N.C.; Finnigan, N.A. *J. Am. Chem. Soc.* **1958**, *80*, 5845.
(12) Nazarov, I.N.; Akhrem, A.A. *Zh. Obshch. Khim.* **1952**, *22*, 442; *Chem. Abstr.* **1953**, *47*, 5368a.