The First Direct Preparation of Chiral Functionalised Ketones and their Synthetic Uses

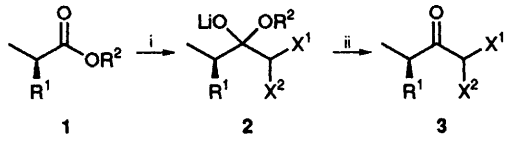
José Barluenga,* Beatriz Baragaña, Alejandro Alonso and José M. Concellón

Instituto Universitario de Química Organometálica 'Enrique Moles', Julián Clavería s/n, Universidad de Oviedo, 33071-Oviedo, Spain

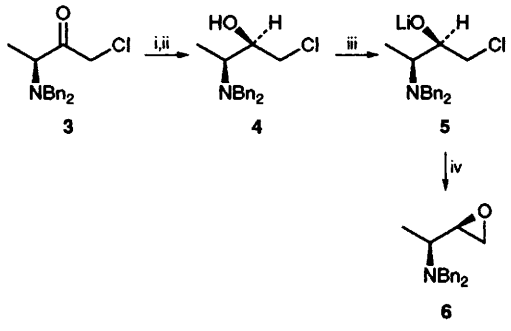
Almost enantiomerically pure halogenated α-hydroxy and α-amino ketones can be prepared from *O*-protected lactates and tribenzylated alanine, respectively; whilst amino ketones **3g** have also been transformed into the amino epoxide **7** with high diastereoselectivity.

Chiral α-hydroxy[1] and α-amino ketones[2] are interesting building blocks in organic synthesis. However, no direct procedure has been reported to prepare chiral α-hydroxy or α-amino ketones starting from protected α-hydroxy or α-amino acids.†

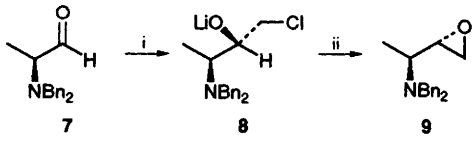
In previous papers[3] we have described a methodology for the direct preparation of α-haloketones by reaction of carboxylic acid esters with *in situ* generated mono- or di-halomethyllithium. Here we report an easy, direct and general method to obtain, without racemisation, halogenated α-hydroxy or α-amino ketones from starting materials such as the *O*-protected natural ethyl lactates **1a–f** or the tribenzylated alanine **1g**. We also describe the transformation of **1g** to other chiral products, with high diastereoselectivity and with full retention of the stereochemistry at the α-carbon of the starting ketone.



Scheme 1 *Reagents and conditions*: i, CH_2ClI, LiBr and then MeLi (X^1 = H) or $CH_2X^1X^2$ and LDA (X^1 = Br, Cl), −78 °C, 30 min; ii, NH_4Cl/H_2O, −78 °C



Scheme 2 *Reagents and conditions*: i, $NaBH_4$/MeOH, −20 °C, 4 h; ii, H_2O, −20 °C; iii, MeLi, −78 °C; iv, 25 °C, 2 h



Scheme 3 *Reagents and conditions*: i, CH_2ClI, LiBr and then MeLi, −78 °C, 30 min; ii, 25 °C, 2 h

Treatment of *O*-protected ethyl lactates **1a–f** or tribenzylated alanine **1g** with mono- or di-halomethyllithium generated *in situ* at −78 °C gave, after hydrolysis, the corresponding mono- or di-halogenated alkoxy **3a–f** or aminoketone **3g**, respectively. (Scheme 1 and Table 1).

Compounds **1a–f** were prepared by treatment of ethyl lactate with benzyl bromide–Ag_2O (93% yield),[4] *tert*-butyldimethylchlorosilane (97% yield)[5] and 2-methoxyethoxymethyl chloride (78% yield)[6] respectively. The *N,N*-dibenzylamino benzyl ester **1g** was synthesised by reaction of alanine with benzyl bromide in the presence of KOH (70% yield).[7] Chloromethyllithium, dibromo- and dichloro-methyllithium were generated *in situ*.[3]

Although mono- or di-halomethyllithium was used in excess, the addition of two molecules of the organolithium compound to the starting ester was not observed since the intermediate **2** was found to be stable under the reaction conditions.‡

In order to check whether any racemisation occurs, the enantiomeric excess of several ketones **3** was determined by chiral HPLC (Chiracel OD-H) analysis. The enantiomeric excess (e.e.) values turned out to be 98.4–96.5% showing that essentially no racemisation occurs in the synthesis of ketones **3**.§

A typical reaction was performed as follows. To a −78 °C stirred solution of the corresponding protected α-hydroxy or α-amino ester (10 mmol) and dihalomethane (20 mmol) or chloroiodomethane (20 mmol) in THF (15 ml) was added dropwise, under N_2, lithium diisopropylamide (20 mmol) in THF (10 ml) or methyllithium (20 mmol; 13.3 ml of 1.5 mol dm^{-3} solution in diethyl ether) over a period of 5 min. After stirring at −78 °C for 30 min, the mixture was treated with a saturated aqueous solution of NH_4Cl (10 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was subjected to column flash chromatography over silica gel with mixtures of hexane–ethyl acetate to provide pure ketones **3**. For the reduction of **3g**, the starting ketone was used without purification.

We also tested the synthetic applications of the amino

Table 1 Compounds **3** prepared from **1**

Product	R^1	R^2	X^1	X^2	Yield (%)[b]	[α] (*c*)[c]
3a	OCH_2Ph	Et	H	Cl	94[d]	−23.7(9)
3b	OCH_2Ph	Et	Br	Br	71[e]	−41.6(9.1)
3c	OCH_2Ph	Et	Cl	Cl	77[f]	−54.5(8.2)
3d	$OSiBu^tMe_2$	Et	H	Cl	89	−5.1(7)
3e	$OSiBu^tMe_2$	Et	Br	Br	64	−2.4(5)
3f	$OCH_2OCH_2CH_2OMe$	Et	H	Cl	62	−13.8(10)
3g	$N(CH_2Ph)_2$	CH_2Ph	H	Cl	86[g]	−116.5(4.2)

[a] All products were fully characterized by spectroscopic methods (IR, ^1H and ^{13}C NMR, and mass spectrometry). [b] Isolated yield based on the starting α-alkoxy or α-amino ester **1**. [c] g l^{-1} of ketones **3** in $CHCl_3$. [d] E.e. = 97.7%. [e] E.e. = 98.4%. [f] E.e. = 96.6%. [g] E.e. = 98.2%.

ketone **3g**. Subsequent reduction of **3g** with $NaBH_4$ in methanol gave the alcohol **4** in 83% yield, which upon treatment with methyllithium afforded the amino oxirane **6** (Scheme 2) in 74% yield, with a diastereoisomeric excess of 76% (^{1}H NMR 200 MHz spectroscopy). This diastereoisomer was easily purified by flash chromatography over SiO_2 (hexane–ethyl acetate 15:1) and this amino epoxide **6** was isolated as pure diastereoisomer with an enantiomeric excess >98% (chiral HPLC analysis).

Amino epoxides of this type are useful intermediates in the synthesis of certain dipeptide isosteres and other pharmacologically important ethanolamino compounds.[8] This fact prompted us to synthesise the other diastereoisomeric amino epoxide **9**. The reaction of the aminoaldehyde[7] **7** with chloromethyllithium generated *in situ* from chloroiodomethane and methyllithium, gave the corresponding lithium alcoholate **8**. When the reaction mixture was allowed to warm to room temperature (Scheme 3), the amino epoxide **9** was isolated (72% yield) with a diastereoisomeric excess (d.e.) of 91% (^{1}H NMR 200 MHz spectroscopy). This amino epoxide **9** was easily purified under the same conditions as **6**.

The configurational assignment of **6** and **9** was made by comparison with the *anti* amino epoxide **9** obtained from amino aldehyde **7** and methylsulfonium ylide, previously described.[9] The synthesis of **9** described here with chloromethyllithium proceeded with better diastereoselectivity than with methylsulfonium ylide (d.e. 74%).

The addition of chloromethyllithium to **7** takes place under non-chelation control, which is in agreement with the previously reported results for the addition of organolithium compounds to dibenzylated amino aldehdyes.[10]

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Footnotes

† Recently, the first systematic synthesis of chiral α-amino ketones from α-amino acids in a multi-step sequence was reported, with a yield ranging from 50 to 60%, based on the amount of recovered starting materials (M. T. Reetz, M. W. Dreves, K. Lennick, A. Schmitz and X. Holrgün, *Tetrahedron Asymmetry*, 1990, **1**, 375).

‡ The stability of intermediate **2** is due to the presence of the electronegative halogen and oxygen substituents that hindered the elimination of the ethoxide group. Recently a similar intermediate has been isolated as the monosilylketal derivative (J. Barluenga, B. Pedregal, and J. M. Concellón, *Tetrahedron Lett.*, 1993, **31**, 4563).

§ Partial racemization (about 5%) appears to have occurred during the chromatographic purification of **3g** with either SiO_2 or Al_2O_3 as the solid phase.

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