Stereoselective Synthesis of α-Methylene-β-hydroxy-γ-alkoxy Esters from α-Alkoxy Aldehydes

Luca Banfi, Lino Colombo, Cesare Gennari, and Carlo Scolastico*

Istituto di Chimica Organica dell'Università and Centro C.N.R. per le Sostanze Organiche Naturali, via Venezian 21, 20133 Milano, Italy

The Reformatsky-type condensation between methyl and t-butyl 3-(*N,N*-dimethylamino)propionates (**9**) and (**10**) with α-alkoxy aldehydes, which has been studied on varying the protective group of the aldehyde, proceeds with good diastereoselectivity.

During the course of our studies directed towards the total synthesis of long chain antibiotic compounds like thermozymocidin[1] and conocandin,[2] we needed to develop a method for the stereoselective synthesis of *anti*[3] (*threo*)[4] α-methylene-β-hydroxy-γ-alkoxy esters (**1**).

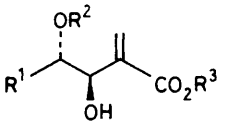
We thought that the synthesis could be realized through a Reformatsky-type condensation between an α-alkoxy aldehyde and methyl or t-butyl 3-(*N,N*-dimethylamino)propionates (**9**) and (**10**) which can be regarded as synthetic equivalents of methyl and t-butyl acrylate.[5] Indeed the reaction of the lithium enolate derived from (**9**) or (**10**) [lithium di-isopropylamide, tetrahydrofuran (THF), −78 °C, 1 h] with α-alkoxy aldehydes (**3**)—(**8**) (THF, −78 °C, 5 min) gave a diastereoisomeric mixture of α-(dimethylaminomethyl)-β-hydroxy-γ-alkoxy esters. This was sequentially treated, without isolation, with methyl iodide (5 equiv., MeOH, 0 °C, 16 h) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (acetone, room temp., 3 h) to give esters (**1**) and (**2**) in an overall yield ranging from 55 to 65% (after chromatography).

The diastereoisomeric ratios are listed in Table 1. The *anti* (*threo*) diastereoisomer is the major product in every case. This result is not unexpected since Heathcock[6] showed that lithium enolates of ketones and esters always give, on reaction with aldehydes, the predominant diastereoisomer predicted by application of Felkin's model for asymmetric induction, by assuming the alkoxy group to be the 'large' group [see equation (1)]. The greatest stereoselectivities are achieved, among the protective groups studied, with the methoxymethyl (MOM) ethers (entries 3, 4, 7, and 8 in Table 1). A sensible increase in the diastereoisomeric ratio is reached by replacing the methyl group in the ester with the more sterically demanding t-butyl group.

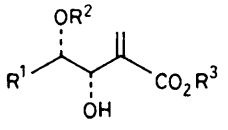
The stereostructures were assigned on the basis of very clear shifts in the ^{13}C and ^{1}H n.m.r. spectra. A full discussion of the spectroscopic results will be published elsewhere.[7]

The relative configuration of (**1**) (R^1 = n-C_6H_{13}; R^2 = $MeOCH_2$; R^3 = Me or Bu^t) has further been confirmed by their transformation [(i) $MeSO_2Cl$, CH_2Cl_2, Et_3N, 0 °C, 15 min; (ii) conc. HCl–THF 1:6, room temp., 5 h; (iii) 40% Bu^n_4NOH, CH_2Cl_2, 0 °C, 5 min, 30 and 50% overall yields] into epoxides (**11**) and (**12**) respectively, which were recognized as '*trans*' by the characteristic 3,4 vicinal coupling constant (2.1 Hz). The 3,4 coupling constant of (**14**), obtained in an analogous manner from (**2**) (R^1 = n-C_6H_{13}; R^2 = $MeOCH_2$; R^3 = Bu^t) was 4.6 Hz. However, all attempts to synthesize the '*cis*' epoxide (**13**) were unsuccessful, probably because of competitive ester hydrolysis in the epoxide ring closure step.

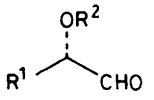
Aldehydes (**3**), (**4**), and (**5**) were prepared in an optically active form from (*S*)-(−)-ethyl lactate by protection ($MeOCH_2Cl$, $PhCH_2OCH_2Cl$, or $MeOCH_2CH_2OCH_2Cl$, CH_2Cl_2, $EtNPr^i_2$, room temp., 80—90%), reduction to the alcohol ($LiAlH_4$, THF, room temp., 100%), and oxidation to the aldehyde (CrO_3 Collins, CH_2Cl_2, 80%). Alternatively a more straightforward method involves the direct reduction of the O-



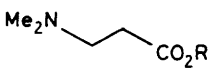
(**1**), *anti*



(**2**), *syn*



(**3**) R^1 = Me; R^2 = $PhCH_2OCH_2$
(**4**) R^1 = Me; R^2 = $MeOCH_2$
(**5**) R^1 = Me; R^2 = $MeOCH_2CH_2OCH_2$
(**6**) R^1 = n-C_6H_{13}; R^2 = $PhCH_2OCH_2$
(**7**) R^1 = n-C_6H_{13}; R^2 = $MeOCH_2$
(**8**) R^1 = n-C_6H_{13}; R^2 = Me

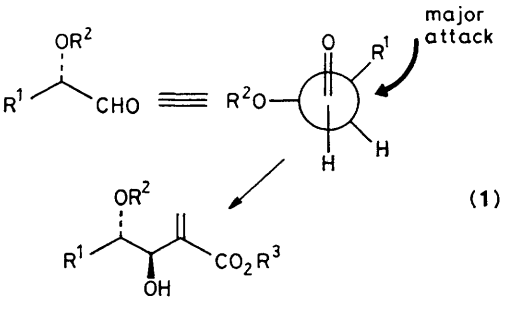


(**9**) R = Me
(**10**) R = Bu^t

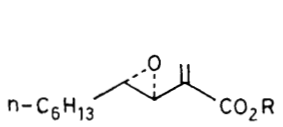
Table 1

Entry	R^1	R^2	R^3	(**1**):(**2**) ratio[a]
1	Me	$PhCH_2OCH_2$	Me	65 : 35
2	Me	$PhCH_2OCH_2$	Bu^t	80 : 20
3	Me	$MeOCH_2$	Me	77 : 23
4	Me	$MeOCH_2$	Bu^t	83 : 17
5	Me	$MeOCH_2CH_2OCH_2$	Me	65 : 35
6	n-C_6H_{13}	$PhCH_2OCH_2$	Bu^t	79 : 21[b]
7	n-C_6H_{13}	$MeOCH_2$	Me	73 : 27
8	n-C_6H_{13}	$MeOCH_2$	Bu^t	80 : 20
9	n-C_6H_{13}	Me	Bu^t	78 : 22

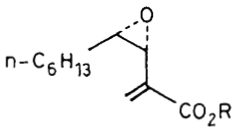
[a] Determined either by g.l.c. (SE-30 10%, 3 m) or by ^{1}H n.m.r. spectroscopy (200 MHz). [b] Determined only by ^{1}H n.m.r. spectroscopy.



(**1**), *anti*



(11) R = Me
(12) R = Bu^t



(13) R = Me
(14) R = Bu^t

protected lactates to the aldehydes with 1 equiv. of di-isobutylaluminium hydride in n-hexane at −100 °C (90%). This reaction showed an unexpectedly high chemoselectivity all along the series of O-protected lactates.

Aldehydes (**6**) and (**7**) were prepared in racemic form by condensation of the lithium anion of di-*p*-tolylthiomethane with heptanal (THF, −78 °C, 98%) followed by protection ($PhCH_2OCH_2Cl$ or $MeOCH_2Cl$, CH_2Cl_2, $EtNPr^i_2$, NaI,[8] 2 days, 80 and 97% respectively) and by hydrolysis of the dithioacetal (HgO, $BF_3{\cdot}Et_2O$, THF–H_2O 85:15, room temp., 1 h, 80%). Also (**8**) was prepared from 1,1-bis-*p*-tolylthio-octan-2-ol by methylation (NaH, MeI, 100%) and hydrolysis (I_2, $NaHCO_3$, 85%).[9]

In summary a method for the selective synthesis of *anti* (*threo*) α-methylene-β-hydroxy-γ-alkoxy esters starting from α-alkoxy aldehydes has been developed. Since optically pure α-alkoxy aldehydes are now easily accessible,[10–12] this method can be applied to the diastereo- and enantio-selective synthesis of α-methylene-β,γ-di-hydroxy esters and α-methylene-β,γ-epoxy esters. The conversion of derivatives of (**1**) into α-methylene-γ-lactones is under investigation as well as the examination of the stereochemical course on varying the base, the counter-ion, and the reaction conditions.

We thank Mr. Roberto Arosio for his enthusiastic collaboration in this work. This research was assisted financially by a grant from the Progetto Finalizzato Chimica Fine e Secondaria del C.N.R.

Received, 6th June 1983; Com. 719

References

1 L. Banfi, M. G. Beretta, L. Colombo, C. Gennari, and C. Scolastico, *J. Chem. Soc., Chem. Commun.*, 1982, 488.
2 J. M. Müller, H. Fuhrer, J. Gruner, and W. Vaser, *Helv. Chim. Acta*, 1976, **59**, 2506.
3 S. Masamune, A. Sk. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, 1980, 557.
4 C. H. Heathcock, C. T. White, J. J. Morrison, and D. VanDerveer, *J. Org. Chem.*, 1981, **46**, 1296.
5 L. C. Yu and P. Helquist, *Synth. Commun.*, 1981, 591.
6 C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, *J. Org. Chem.*, 1980, **45**, 3846.
7 L. Banfi, D. Potenza, and G. Ricca, *Org. Magn. Reson.*, in the press.
8 K. Narasaka, T. Sakakura, T. U. Chimaru, K. Morimoto, and T. Mukaiyama, *Chem. Lett.*, 1982, 455.
9 L. Colombo, C. Gennari, C. Scolastico, G. Guanti, and E. Narisano, *J. Chem. Soc., Perkin Trans.* 1, 1981, 1278.
10 G. Guanti, E. Narisano, L. Banfi, and C. Scolastico, *Tetrahedron Lett.*, 1983, 817.
11 G. Guanti, E. Narisano, F. Pero, L. Banfi, and C. Scolastico, *J. Chem. Soc., Perkin Trans.* 1, in the press.
12 K. Ogura, M. Fujita, T. Inaba, K. Takahashi, and H. Iida, *Tetrahedron Lett.*, 1983, 503.