



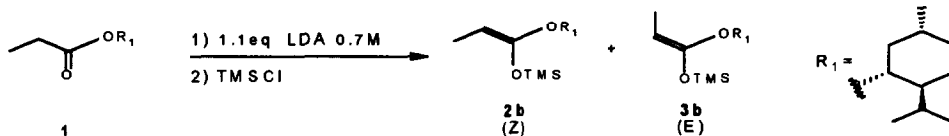
0957-4166(94)00259-2

ON THE ASYMMETRIC INDUCTION INVOLVING LITHIUM ENOLATES OF
1-MENTHYLPROPIONATELENY P. RIBEIRO¹, OCTAVIO A. C. ANTUNES¹, LOTHAR BERGTER¹, PAULO R. R. COSTA^{2*}¹Instituto de Química ²Núcleo de Pesquisas de Produtos Naturais Universidade Federal do Rio de Janeiro, RJ 21941, Brazil

Abstract: The stereoselectivities of the reaction between 1-menthylpropionate 1 with LDA under standard kinetic conditions depend on the solvent. The Z-enolate 2a predominates in LDA/THF (Z/E=7.5/2.5) while the E-enolate 3a is the main product in LDA/THF/hexane (E/Z=8/2). The mixture of these enolates (E/Z=8/2) was allowed to react with allylbromide, benzaldehyde and MoOPH respectively. The higher π -facial diastereoselection was obtained from MoOPH (d.e.=60%).

The trapping of enolates prepared from chiral esters by electrophiles is a powerful tool in asymmetric synthesis^{1a,b}. The efficiency of this protocol depends on two factors: the selectivity of the deprotonation step (E-enolate/Z-enolate) and the π -facial diastereoselection of these enolates towards the electrophiles. Esters of 1-menthol have been extensively used in asymmetric synthesis, although good diastereoselectivities were obtained mainly for pericyclic reactions^{2a,c}, only scattered reports involving enolates of these esters are described in the literature^{3a,c}. In this paper we report the diastereoselectivities of the reactions between lithium enolates prepared from 1-menthylpropionate 1 and allylbromide, benzaldehyde and MoOPH^{4a,c}. Compound 1 was allowed to react with LDA under conventional kinetic conditions^{1a} and the lithium enolates (Z-2a, E-3a) obtained were trapped with TMSCl leading to the corresponding silyl ketene acetals (Z-2b, E-3b) (scheme 1).

SCHEME 1



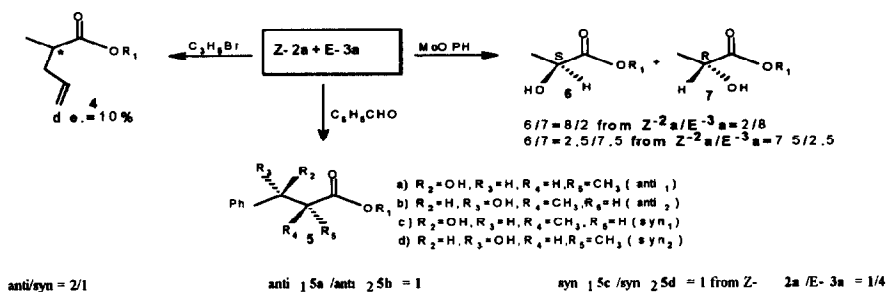
ENTRY	THF/HEXANE	YIELD (%)*	E / Z***
1	100/0	20	35/65
2**	100/0	20	25/75
3	70/30	62	80/20
4	30/70	50	80/20
5	10/90	44	80/20

*- ISOLATED PURE PRODUCT**- 2,0 eq. of LDA were employed in this case, ***-HRGC (HP-1; 50°-250°C, 5°C/min)

In LDA/THF Z-2a was obtained in 30-50% d.e. in (entries 1-2), while E-3a was the main product (d.e.=60% entries 3-5) in LDA/THF/hexane. In these latter conditions both diastereoselectivities and yields were better⁵. The Z and E-silyl ketene acetals 2a and 3a were separated but it was impossible to have the stereochemistry of their double bond assigned by ¹H(300MHz) and ¹³C(75MHz) NMR spectra, even by NOE experiments. The assignment proposed in scheme 1 was based on the result of the aldol reaction of these enolates with benzaldehyde (vide infra). The obtained stereoselectivities of the deprotonation step could be rationalized as follows: the presence of hexane in LDA decreases the polarity of the reaction medium leading to a "tighter" transition state consequently enhancing the steric interaction between the methyl group of the enolate and the isopropyl group attached to the nitrogen atom, favouring therefore the E-enolate. In contrast, in the absence of hexane, the reaction medium becomes more polar and consequently a more "distended" transition state could be expected, decreasing the importance of 1,3-diaxial strain and favouring the Z-enolate. This interpretation is similar to that proposed by Ireland⁶ to explain the effect of the addition of HMPA and DMPU on ester

deprotonation stereoselectivities. When the mixture of lithium enolates ($Z/E=2/8$) was allowed to react with benzaldehyde (scheme 2), a simple diastereoselectivity favouring the anti-products was obtained ($5a+5b/5c+5d=2/1$). This result confirmed the predominance of the E-enolate in entries 3-5 of scheme 2 as previously proposed⁷. Unfortunately no π -facial diastereoselection was observed ($\text{syn}_1/\text{syn}_2=1$, $\text{anti}_1/\text{anti}_2=1$). A poor d.e. was also observed when the same mixture of enolates was trapped with allylbromide to give 4. In contrast, the reaction of Z-2a/E-3a=2/8 with MoOPH led to a mixture of 6/7= 8/2.

SCHEME 2



Since the d.e. of this reaction is the same as observed in the enolization step, it can be proposed that a high π -facial diastereoselection occurred in this case. This high discrimination would probably be due to the steric hindrance of the electrophile. This supposition could be confirmed when a mixture of Z-2a/E-3a=7.5/2.5 was oxidized with MoOPH. As expected the d.e. of the mixture of enolates was maintained in the products, but in this case the main product was 7 (6/7=2.5/7.5). The absolute configurations of 6 and 7 were confirmed by esterification of 1-menthol with natural (S)-(+)-lactic acid and comparison of the resulting ester 7 with the reaction products obtained from reaction with MoOPH by HRGC. From these data one can propose that E-enolate 3a and Z-enolate 2a react with MoOPH by their less hindered π -face, leading to 6 and 7 respectively.

We are now investigating the effect of other bases in the stereoselectivity of the deprotonation of 1. To our knowledge, this is the first report on the solvent effect regarding the deprotonation of esters with LDA.

Acknowledgements: Support from Brazilian National Research Council and José Bonifácio Foundation is gratefully acknowledged

References and Notes:

- D.A. Evans, In *Asymmetric Synthesis*; J.D. Morrison, (Ed), Academic Press: Orlando, 1984, Vol.3, Cap. 1.
 - C.H. Heathcock, In *Asymmetric Synthesis*; J.D. Morrison, (Ed), Academic Press: Orlando, 1984, Vol.3, Cap. 2.
- E.J. Corey, R. Imwinkelried, S. Pikul, Y.B. Xiang, *J. Am. Chem. Soc.*, 1989, **111**, 5493.
 - K. Furuta, K. Iwanaga, H. Yamamoto, *Tetrahedron Lett.*, 1986, **27**, 4507.
 - B.L. Feringa, J.C. de Jong, *J. Org. Chem.*, 1988, **53**, 1125.
- T. Kaneko, D.L. Turner, M. Newcomb, D.E. Bergbreiter, *Tetrahedron Lett.*, 1979, **20**, 103.
 - E.B. Dongala, D.L. Dull, C. Mioskowski, G. Solladie, *Tetrahedron Lett.*, 1973, **1** 4983.
 - J.P. Genet, N. Kopola, S. Juge, J. Ruiz-Montes, O.A.C. Antunes, S. Tanier, *Tetrahedron Lett.*, 1990, **31**, 3133.
- R. Gamboni, P. Mohr, N.W. Sarcevic, C. Tamm, *Tetrahedron Lett.*, 1985, **26**, 203.
 - R. Gamboni, C. Tamm, *Tetrahedron Lett.*, 1986, **27**, 3999.
 - E. Vedejs, D.A. Engler, J.E. Telschow, *J. Org. Chem.*, 1978, **43**, 188.
- M.J. Munchhof, C.H. Heathcock, *Tetrahedron Lett.*, 1992, **33**, 8005.
- R.E. Ireland, P. Wipf, J.D. Armstrong III, *J. Org. Chem.*, 1991, **56**, 650.
- It has been assumed in the literature that E-enolates lead preferentially to anti-aldol adducts and Z-enolates syn-aldol adducts in etheric solvents, see ref. 1b.