Tetrahedron: Asymmetry Vol. 2, No. 11, pp. 1107-1110, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

DIASTEREO- AND ENANTIOSELECTIVE ALLYLIC $S_{N'}$ SUBSTITUTION BY PHENYLACETIC ESTERS ENOLATES.

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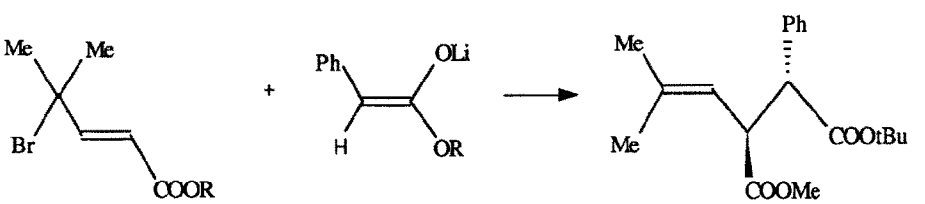
(*Received* 7 *October* 1991)

Abstract : *The Anti-Michaël $S_{N'}$ substitution of γ-bromo-α,β-unsaturated esters* ***1a-c*** *by Li t.butyl phenylacetate enolate is highly diastereoselective. Asymmetric synthesis can be performed (ee ⩾ 95%) using the enantiomerically pure (1'R,2'S) 2-phenyl cyclohexyl ester* ***1c***.

Although there are some examples of highly stereoselective $S_{N'}$ allylic substitution of chiral γ-substituted α,β-unsaturated esters by organo copper reagents there are, up to our knowledge, no reported asymmetric induction due to chiral auxiliaries on similar systems. However, STORK and SCHOOFS [2] and QUINKERT and coworkers [3] have reported asymmetric induction in $S_{cN'}$ reactions of properly substituted malonic esters bearing either a chiral leaving group or chiral alkoxy ones.

In our previous studies of the reaction of carbon nucleophiles with tertiary γ-bromo-α,β-unsaturated ester **1a** [4], we observed that, at low temperature, the reaction of Li methyl phenylacetate enolate **2** in THF-HMPA was regioselective but poorly stereoselective ; however when using the t.butyl ester analogue **3**, the reaction was regio- and stereoselective, the **anti** isomer **4** being predominantly formed at low temperature [4b].

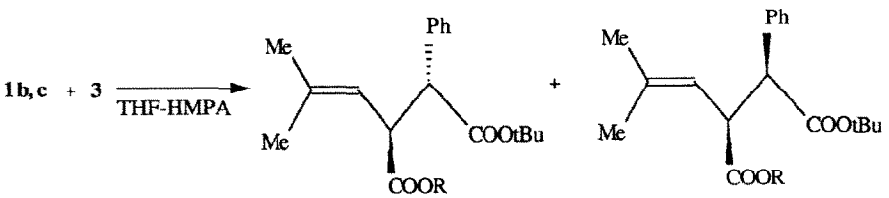


1a R = Me
1b R = t.Bu
1c R = trans 2-phenyl cyclohexyl

2 R = Me
3 R = t.Bu

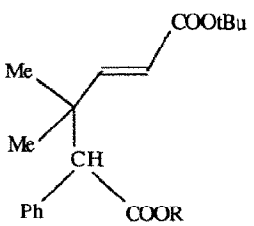
4 anti

It seemed worthy to examine to what extent, such a stereoselective reaction could take place when changing the bromoester moiety from Me (**1a**) to t.Bu (**1b**). In order to perform an asymmetric synthesis, the use a chiral bromoester **1c** was also considered. The reaction of t.Bu 4-bromo-4-methylpent-2 enoate **1b** with lithiated t.Bu phenylacetate enolate **3** in THF-HMPA was regio- and stereoselective, **anti 5** being predominantly obtained (de = 92%) provided that it was run under kinetic control, i.e. below -40°C as, at higher temperature, some epimerization took place, the amount of **syn 5** increasing 5. Next to these $S_{N'}$ products **5**, a small amount (8%) of S_N compound **6** could also be characterized. A similar result was obtained when reacting **1b** with the methyl ester analogue **2**, although the diastereoselectivity was lower (de = 80%).



5 or 7 anti **5 or 7 syn**

5 R = tBu
7 R = (1'R,2'S) 2-phenyl cyclohexyl
7* R = trans 2-phenyl cyclohexyl



6 R = tBu
8 R = trans-2-phenyl cyclohexyl

The reaction of **3** with racemic or enantiomerically pure (1'R,2'S) **1c** was regio- (75%) and stereoselective (de ⩾ 95%) : **anti 7*** and **7** were obtained by fractionate crystallization (isolated yield 60-65%). No **syn** isomer could be detected in the crude reaction mixtures by ^{13}C or by ^{1}H NMR in the presence of Eu(fod)$_3$. The X-ray structural determination [7] of a single crystal of **7*** showed the relative configuration of the four chiral carbon atoms as (2R*,3S*,1'R*,2'S*) according to Fig. 1, confirming thus the previous **anti** assignment.

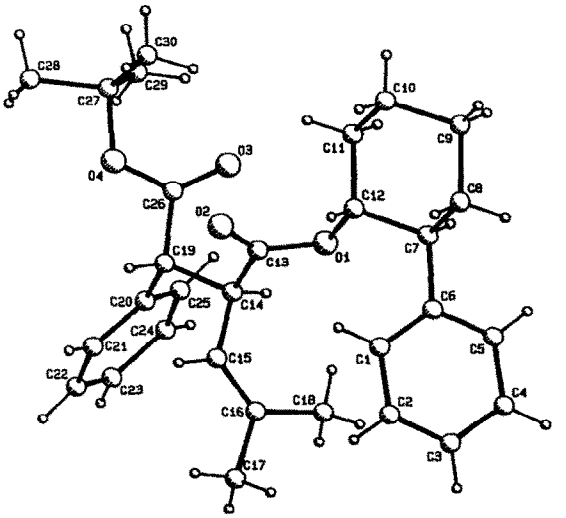
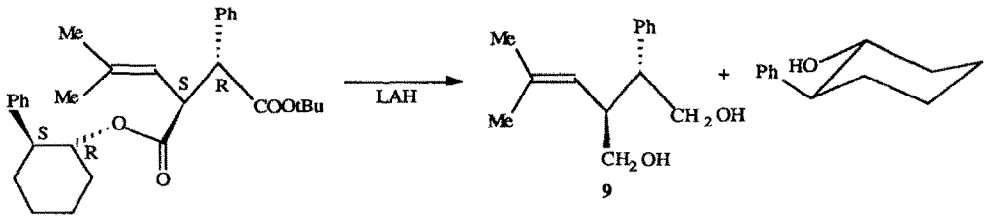


Fig. 1

When the reaction was run from enantiomerically pure (1'R,2'S) **1c**, a single enantiomer was obtained (ee $\geqslant$ 95%) as indicated by ^1H NMR spectroscopy in the presence of Eu-D-3-heptafluorobutylcamphorate [6]. Although the chiral auxiliary could not be recovered by LiOH or LiOOH hydrolysis [8], LAH reduction of (2R,3S,1'R,2'S) **7** led to (2R,3S) diol **9** [6] and (1R,2S)-2-phenylcyclohexanol which were separated by column chromatography.



The high asymmetric induction observed in this $S_{N'}$ Anti-Michaël process can be interpreted by attack of the Re face of bromoester **1c**, lying under **s-cis syn** conformation, which has been shown to be the favored conformation of α,β-unsaturated esters [9]. Indeed, molecular modeling (Alchemy 2 on IBM PC) shows that under such a favored conformation, the phenyl ring in (1'R, 2'S) **1c** was lying over the Si face of the double bond (Fig. 2).

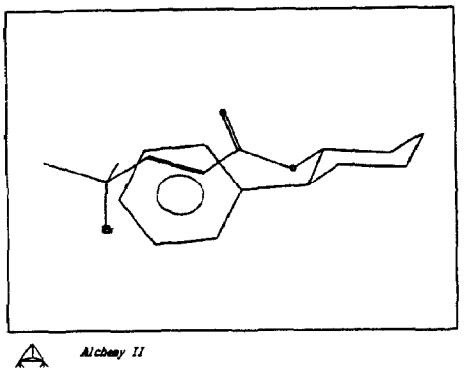


Fig. 2

However, the attack of the quaternary bromine substituted carbon seemed less hindered : indeed, **8** was obtained in 8% yield by column chromatography as a 1:1 mixture of stereoisomers.

In conclusion, it has been shown that the Anti-Michaël attack of γ-bromo-α,β-unsaturated esters **1a-c** by phenylacetate enolates can be highly stereoselective when using t.butyl esters ; asymmetric induction with (1'R,2'S)-2-phenylcyclohexyl ester takes place with ⩾ 95%ee.

References and Notes

1) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864 and quoted references.

2) Stork, G.; Schoofs, A.R. *J. Am. Chem. Soc.* **1979**, *101*, 5081.

3) Quinkert, G.; Stark, H. *Angew. Chem. Int. Ed.* **1983**, *22*, 637.

4) a) Roux-Schmitt, M.-C.; Petit, A.; Sevin, A.; Seyden-Penne, J.; Nguyen Trong, A.; *Tetrahedron* **1990**, *46*, 1263 ; b) Roux-Schmitt, M.-C.; Sevin, A.; Seyden-Penne, J. *Bull. Soc. Chim. France* **1990**, 857.

5) All new compounds gave IR, ^1H and ^{13}C NMR spectra and microanalysis in agreement with the proposed structures. The **anti/syn** assignments rely on ^1H NMR grounds as previously proposed (4b).

6) ^1H NMR in the presence of chiral Eu shift reagent : tBu signals : **anti 7*** : 1.5 and 1.6 ppm ; (2R,3S,1'R,2'S) **7** : 1.5 ppm.
anti 7* : m.p. (hexane) 153.5°C
(2R,3S,1'R,2'S) **7** : m.p. (hexane) 149.8°C $[\alpha]_D$ ($CHCl_3$, c = 0.75) : -188.5
(2R,3S) **9** : m.p. = 91.2°C $[\alpha]_D$ ($CHCl_3$, c = 0.85) : +42.3 .

7) The structural parameters will be given in the full paper submitted to *J. Chem. Res.*

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