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Stereocontrolled solution and solid phase enolate alkylations and hydroxylations — generation of three and four contiguous stereogenic carbon atoms in acyclic systems

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Abstract

Potassium enolates of γ-alkoxy-α-methyl pentanoates can be alkylated with allylic and benzylic halides in solution and on solid phase with high 2,3-*syn* selectivity. Polypropionate units can be constructed on solid phase by a series of stereocontrolled conjugate additions and enolate hydroxylations relying on 1,2-induction.

Keywords: solid phase chemistry; enolate alkylation; polypropionate synthesis; 1,2-asymmetric induction.

The generation of acyclic carbon chains with differentiated end-groups and harboring vicinally situated carbon substituents of a desired absolute configuration is not a trivial task.[1] In this regard, the alkylation of ester enolates with reactive electrophiles such as allylic halides and aldehydes is a well documented process.[2] The most popular methods to achieve practical levels of stereocontrol in such alkylations normally rely on the use of chiral auxiliaries.[3] An alternative strategy in such reactions is to exploit internal asymmetric induction (1,2-, or 1,3- for example),[4,5] from a resident group on a stereogenic carbon.

Herein, we report the alkylation of enantiopure γ-alkoxy-β-methyl enolates in solution and on solid phase with a variety of allylic halides to afford α,β-*syn*-substituted products as single isomers in high yield (Scheme 1). Treatment of the potassium enolate generated from the readily accessible ester **1**,[4,6] with allyl bromide led to the α-allylated ester **2** in 86% yield. The same reaction was equally successful with other allylic electrophiles as shown in Scheme 1. Confirmation of the proposed stereochemistry was secured by formation of lactone **3** and NMR analysis. As in other enolate reactions in this series (hydroxylation,[4,7] azidation[8]), the stereochemical outcome can be rationalized based on a Felkin-type transition state **6** shown in Scheme 1.

The same type of highly stereoselective enolate alkylations could also be realized on solid support as shown in Scheme 2. Thus, the 2-pyridylthiocarbonate ester **7** prepared from the Wang resin[9,10] was

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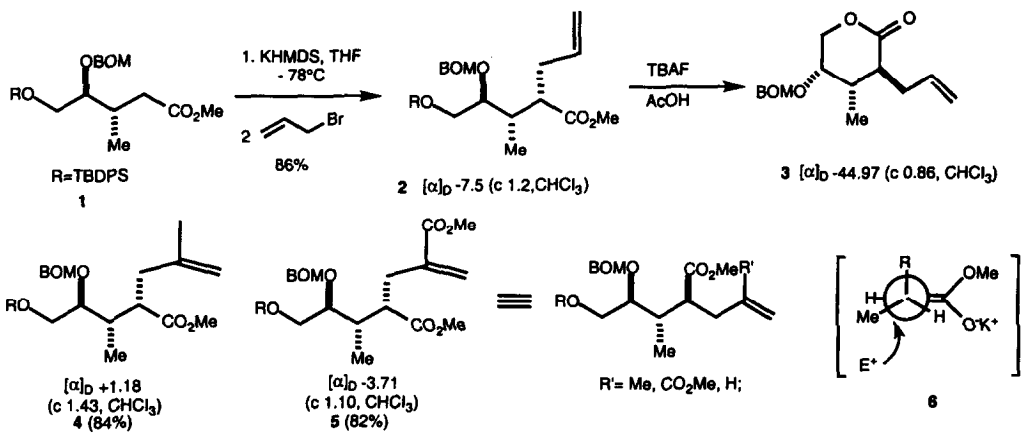
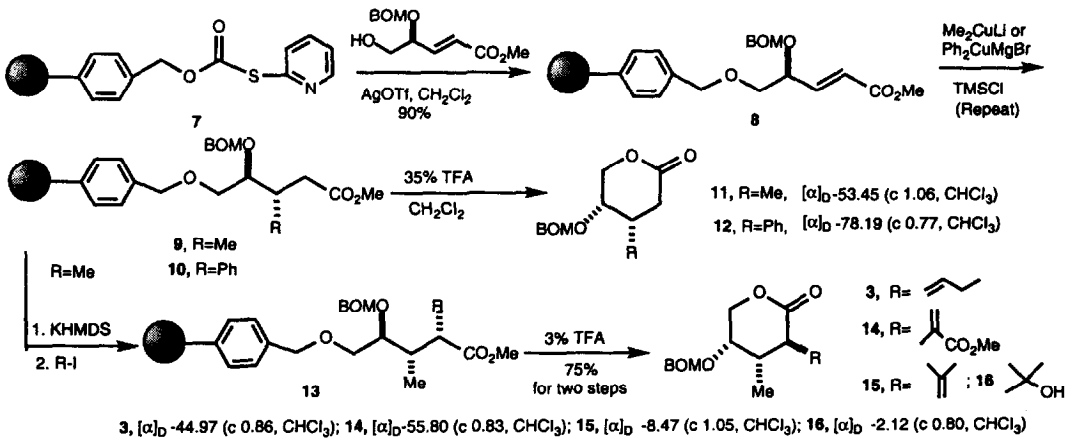


Scheme 1.

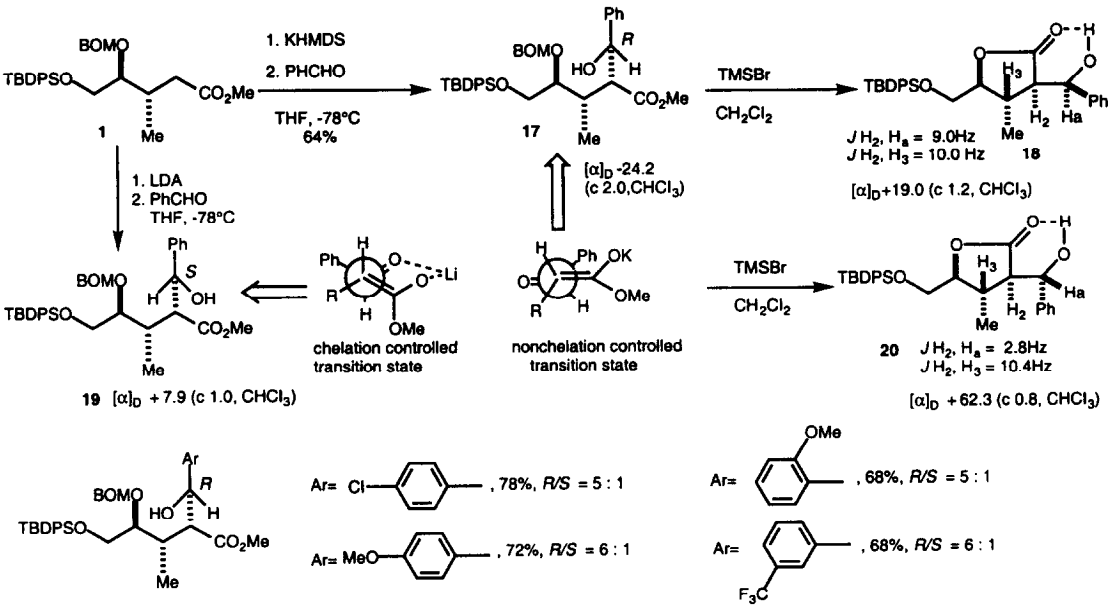
alkoxylated to afford maximum loading (0.7 mole/mole). Treatment with the appropriate cuprate reagent led to the corresponding adducts **9** and **10** which were individually cleaved from the resin to afford the corresponding enantiopure lactones **11** and **12** (Scheme 2). Treatment of the immobilized ester **9** with KHMDS in THF, as done in solution, followed by addition of the allylic halides or benzyl bromide, led to the corresponding α-substituted products which were isolated as the corresponding δ-lactones **3**, **14** and **15** in excellent yields and as enantiopure compounds after cleavage.



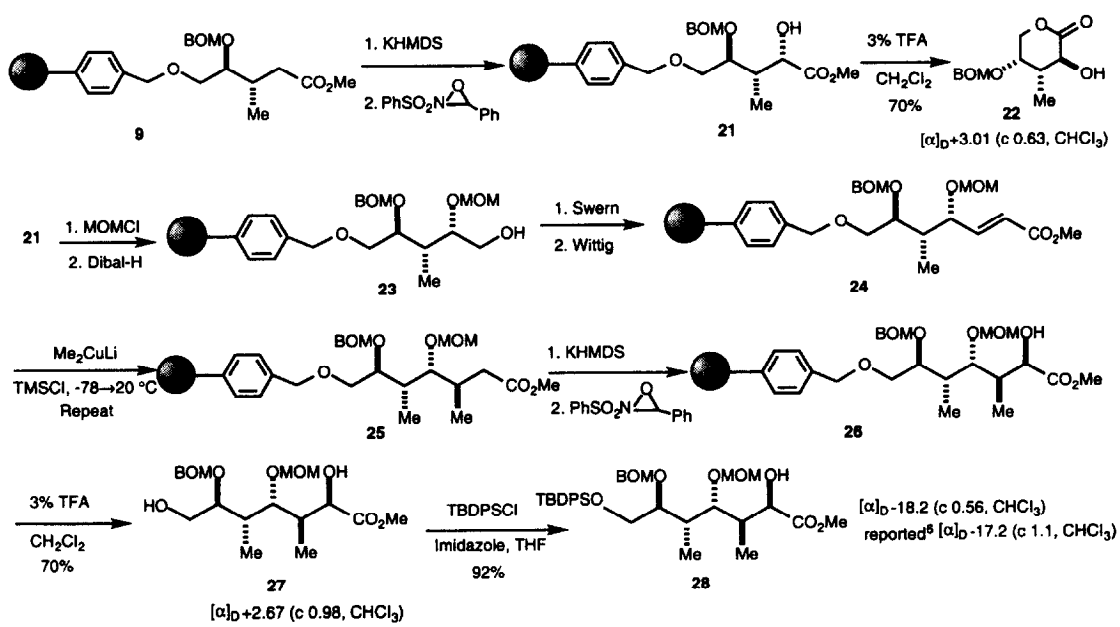
Scheme 2.

We also explored the aldol-type condensation of the enolate derived from **1** in an effort to generate four contiguous stereogenic centers on acyclic motifs. As shown in Scheme 3, the reaction is surprisingly selective to produce a major benzylic alcohol isomer with a diverse set of aromatic aldehydes. Furthermore, the selectivity at this off-template center could be reversed by changing the base used. Thus, with KHMDS the *R*-alcohol **17** was the major product while with LDA, the *S*-alcohol **19** predominated. A rationalization of these results is given in Scheme 3, based on the existence of non-chelated (for K enolates) and chelated (for Li enolates) transition states.[11] Convincing evidence for the stereochemical assignment at the benzylic alcohol in both *R*- and *S*-isomers was secured from NMR coupling constants of the lactones **18** and **20**.

The prospects of cuprate addition and enolate hydroxylation in an iterative and stereocontrolled manner, previously successfully realized in solution,[6] was next studied on solid support (Scheme 4).



Scheme 3.



Scheme 4.

Treatment of the K enolate generated from **9** with the Davis oxaziridine reagent[12] afforded the α-hydroxy ester **21** which, upon cleavage gave an enantiopure lactone **22**. Protection of **21** and end-group manipulation led to **23** and **24** which was reacted with lithium dimethyl cuprate to afford the *syn,anti* propionate triad within the seven-carbon immobilized ester motif **25**. Finally, a second Davis hydroxylation afforded the α-hydroxy ester **26**, which upon cleavage gave the enantiopure ester **27**. Conversion to the TBDPS ether afforded **28** which was identical to a known reference compound.[6]

We have shown that vicinal stereochemistry in acyclic γ-alkoxy-β-methyl pentanoates can be reliably

controlled in enolate alkylations and aldol reactions to afford 2,3-*syn*- or 2,3-*anti*-substituted products depending on how the original ester group is placed (Scheme 1). The high degree of 1,2-induction in the α-alkylation and α-hydroxylation reactions can also be extended to solid phase. Polypropionate synthesis can be achieved on solid phase with excellent 1,2-induction through two cuprate additions and two enolate hydroxylation cycles.[13]

Acknowledgements

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