



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. © 1999 Elsevier Science Ltd. All rights reserved.

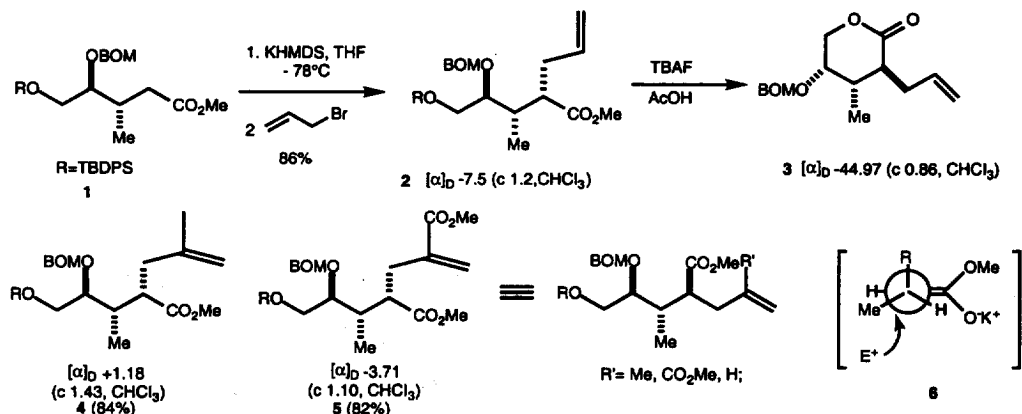
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The generation of acyclic carbon chains with differentiated end-groups and harboring vicinally situated carbon substituents of a desired absolute configuration is not a trivial task.¹ In this regard, the alkylation of ester enolates with reactive electrophiles 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} azidation⁸), the stereochemical outcome can be rationalized based on a Felkin-type transition state **6** shown in Scheme 1.

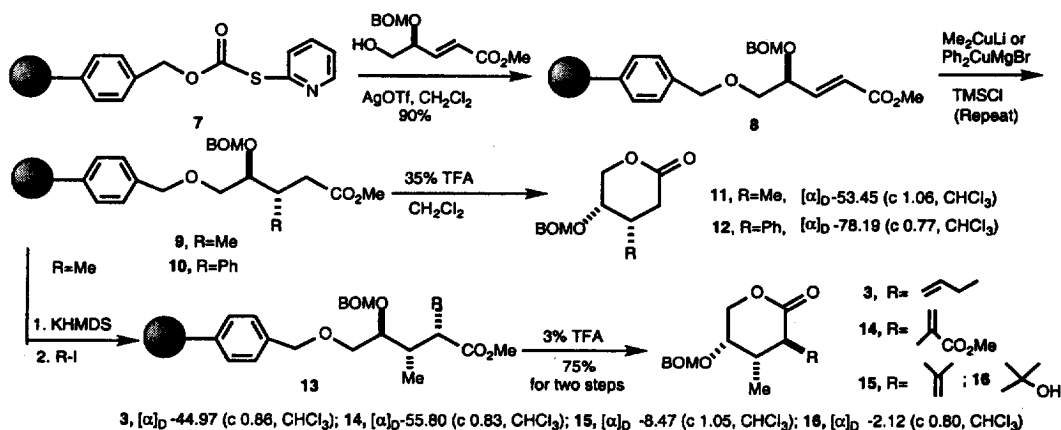
The same type of highly stereoselective enolate alkylations could also be realized on solid support as shown in Scheme 2. Thus, the 2-pyridylthiocarbonate ester **7** prepared from the Wang resin^{9,10} was

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Scheme 1.

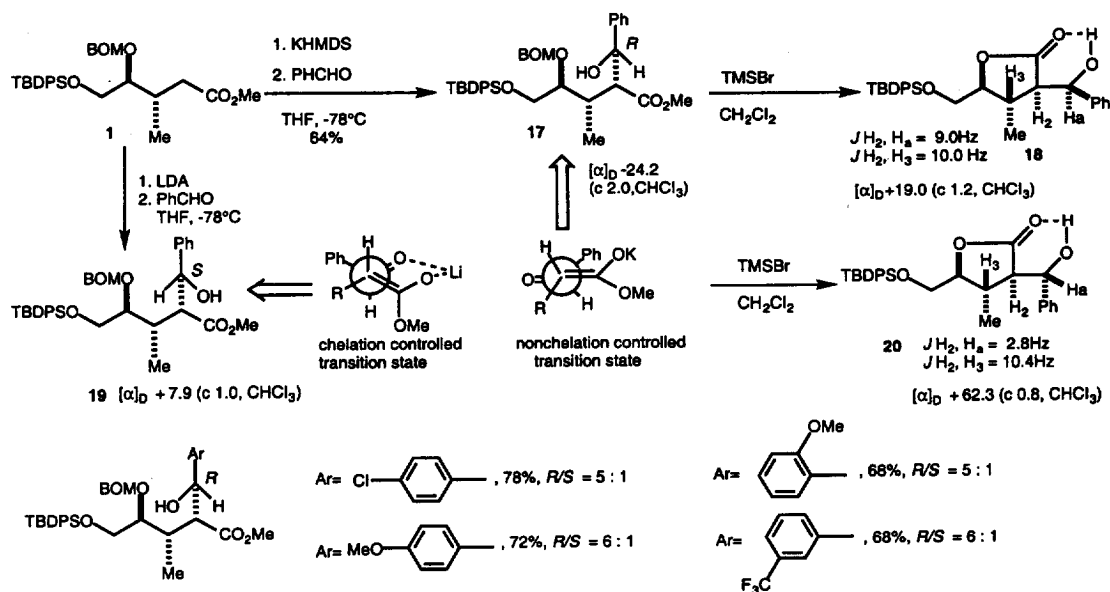
alkoxylated to afford maximum loading (0.7 mole/mole). Treatment with the appropriate cuprate reagent led to the corresponding adducts **9** and **10** which were individually cleaved from the resin to afford the corresponding enantiopure lactones **11** and **12** (Scheme 2). Treatment of the immobilized 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.



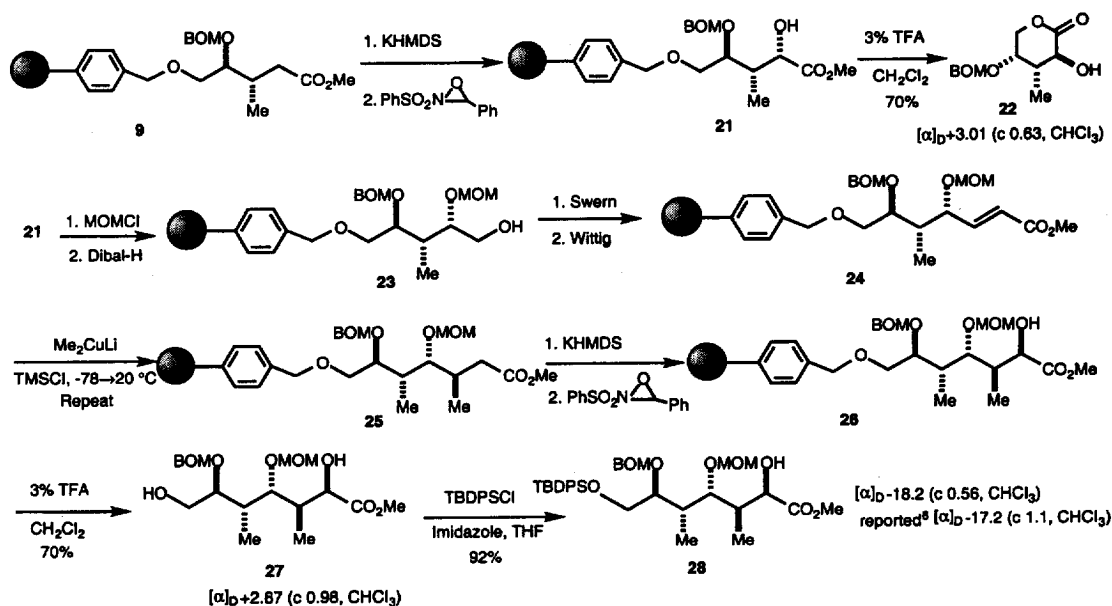
Scheme 2.

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 reagent¹² 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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References

1. For three diverse approaches, see for example, Kokke, W. C. M. C.; Varkevisser, F. A. *J. Org. Chem.* **1974**, *39*, 1535; Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668; Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025.
2. For a text book perspective, see House, H. O. In *Modern Synthetic Reactions*; 2nd ed.; Benjamin: New York, 1972; p. 492; Stowell, J. C. In *Carbanions in Organic Synthesis*; Wiley: New York, 1979; p. 144.
3. For excellent summaries, see Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Pergamon: New York, 1996; p. 75; Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC: New York, 1995; p. 97; for a selection of early seminal individual contributions, see Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, 1984; Vol. 3, p. 1; Lutomsky, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, 1984; Vol. 3, p. 213; Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969, 4057.
4. Hanessian, S.; Gai, Y.; Wang, W. *Tetrahedron Lett.* **1996**, *37*, 7473.
5. Hanessian, S.; Schaum, R. *Tetrahedron Lett.* **1997**, *38*, 163; see also Narasaka, K.; Yukata, U. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 571.
6. Hanessian, S.; Gai, Y.; Wang, W.; Olivier, E. *J. Am. Chem. Soc.* **1997**, *119*, 10034.
7. Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4627.
8. Hanessian, S.; Wang, W.; Gai, Y. *Tetrahedron Lett.* **1996**, *37*, 7477.
9. For recent reviews concerning reaction on solid supports, see Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385; Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293; *Combinatorial and Solid Phase Organic Chemistry; Advanced Chemtech Handbook*; Bennett, W. D.; Christensen, J. W.; Hamaker, L. K.; Peterson, M. L.; Rhodes, M. R.; Saneii, H. H., Eds.; Advanced ChemTech Inc., Louisville, Kentucky, 1998.
10. Hanessian, S.; Huynh, H. K. *Tetrahedron Lett.* **1999**, *40*, 671; For related papers, see Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 733, 737; Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5835.
11. For a review on enolate formation, see Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis. Selectivity, Strategy, and Efficiency in Modern Organic Chemistry*; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, p. 99.
12. Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1991**, *92*, 919; Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1987**, *66*, 203.
13. New compounds were characterized by standard analytical techniques. ¹H and ¹³C NMR spectra are available upon request.