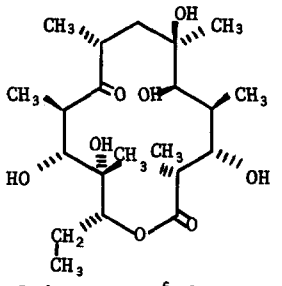
Tetrahedron Letters No. 33, pp 2839 - 2842, 1977. Pergamon Press. Printed in Great Britain.

# A STEREOSELECTIVE METHOD FOR THE GENERATION OF ALDOL-TYPE SYSTEMS

R. E. Ireland* and C. S. Wilcox
Division of Chemistry and Chemical Engineering
California Institute of Technology
Pasadena, California 91125

(Received in USA 3 May 1977; received in UK for publication 23 June 1977)

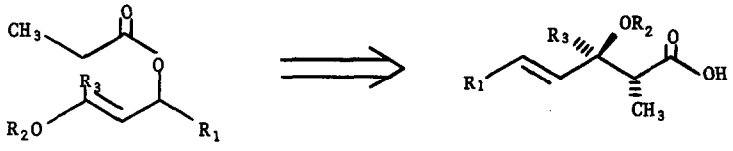
The value of a stereoselective approach to aldol-type products has been recognized for some time.[1-3] The utility of such a technique is readily appreciated upon consideration of possible synthetic routes to the aglycones of macrolide antibiotics, such as Erythronolide A.[4,5]



Erythronolide A

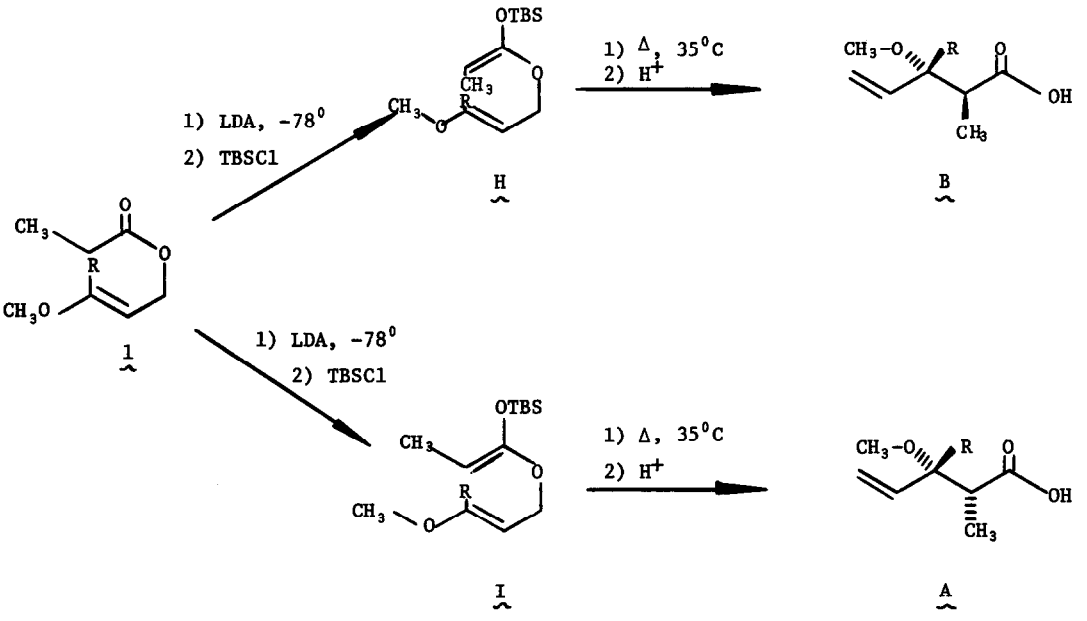
Previous work in this laboratory[6] has established the usefulness of the ester enolate Claisen rearrangement as an efficient and stereoselective technique for carbon-carbon single bond formation. An interest in the total synthesis of macrolide antibiotics has led us to investigate an extension of this rearrangement, generalized in Scheme 1, as one approach to aldol-type products. We report here the initial results of this investigation.

Scheme 1



No difficulties were encountered in the preparation and purification of the primary alcohol esters ($R_1$ = H, Scheme 1). The results of the Claisen rearrangements of the silylketene acetals derived from these esters are summarized in Table 1.[7]

Table 1



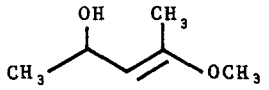

| Ester | -R | Solvent[a] | Yield | A/B[c] | $t_{½}$,min[b] |
|---|---|---|---|---|---|
| 1a | -H | 23% HMPA-THF | 75% | 80/20 | ≤5.0 |
| 1a | -H | 100% THF | 80% | 18/82 | ≤5.0 |
| 1b | $-CH_3$ | 23% HMPA-THF | 80% | 77/23 | 9.4±2 |
| 1b | $-CH_3$ | 100% THF | 76% | 17/83 | 9.4±2 |
| 1c | -Ø | 23% HMPA-THF | 72% | 52/48 | 42±8 |
| 1c | -Ø | 100% THF | 67% | 47/53 | 42±8 |

(TBS = t-Bu$(CH_3)_2$Si)

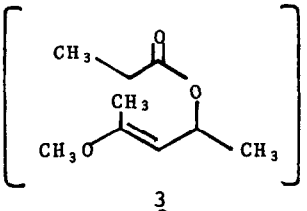
[a]Solvent employed during enolization with LDA. [b]Half-lives for the rearrangements of the silylketene acetals. [c]Ratios of diastereomers obtained as determined by NMR analysis.

Control of product stereochemistry was achieved by stereoselective enolate formation. As previously reported[6], enolization with lithium diisopropylamide (LDA) in THF and trapping of the enolate anion with t-butyl-dimethylchlorosilane (TBSCl) yields the ketene acetal H derived from a Z-type enolate anion. When the solvent is 23% HMPA-THF, the major product is the geometrically isomeric ketene acetal I. Subsequent [3.3] sigmatropic rearrangement of these products yields the diastereomeric products A and B. Assuming the intermediacy

of the thermodynamically preferred chair-like transition state[8], the ratio A/B corresponds to the proportion of I/H obtained via selective enolate formation.

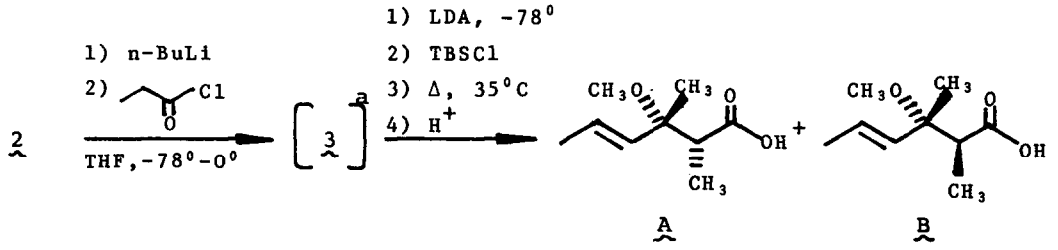


2



3

The extension of this technique to the ester 3 was complicated by the instability of this molecule. Whereas the alcohol 2 was readily prepared and purified, the ester derived from this alcohol substantially decomposed during aqueous work-up. This problem was circumvented by acylation of the alcoholate anion of 2 in THF or 23% HMPA-THF with the required acid chloride, followed by enolization, trapping and rearrangement without isolation of the intermediate ester 3. The overall yields for this direct conversion of alcohol to aldol-type product are comparable to the yields obtained in the stepwise procedure.




A B

| Solvent[b] | Overall Yield | A/B |
|---|---|---|
| 23% HMPA-THF | 59% | 78/22 |
| THF | 60% | 30/70 |

[a]Intermediate ester not isolated. [b]Solvent employed during enolization.

The case of the ester 1c (R = $C_6H_5$, Table 1) is interesting in that a stereoisomeric mixture of rearranged products was formed. Inasmuch as both the starting (E) β-methoxycinnamyl alcohol and its derived propionate are stereoisomerically pure and there would appear to be no reason to expect enolization and silylation of this system to differ from the other reported cases, this result suggests that this phenyl substituted system rearranges through another pathway, such as a boat-like transition state[9] or in a non-concerted fashion. Experiments directed toward an explanation of this observation are currently being pursued.

The foregoing examples are sufficient to establish the feasibility of Scheme 1 as a stereoselective route to aldol-type products. The method is particularly valuable because either product diastereomer is obtainable without regard to relative thermodynamic stability. In this preliminary investigation the methyl enol ethers were chosen as starting materials because of their ease of preparation and uncomplicated spectra simplified product stereochemical analyses. Extensions of this reaction to more complex substrates, and a search for a more easily removed protecting group are currently underway.

References:

1. J.-F. Dubois and M. Dubois, Tetrahedron Letters, 4215 (1967).
2. H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmstead, J. Amer. Chem. Soc., 95, 3310 (1973).
3. C. H. Heathcock, W. A. Kleschick, and C. T. Buse, J. Amer. Chem. Soc., 99, 247 (1977).
4. P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, Jr., O. Weaver, U. C. Quarek, R. R. Chauvette and R. Monahan, J. Amer. Chem. Soc., 79, 6062 (1957).
5. D. R. Harris, S. G. McGeachin and H. H. Mills, Tetrahedron Letters, 679, (1965).
6. R. E. Ireland and R. H. Mueller, J. Amer. Chem. Soc., 94, 5897 (1972); R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Amer. Chem. Soc., 98, 2868 (1976); R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Org. Chem., 41, 986 (1976).
7. Satisfactory combustion analyses were obtained on all new substances.
8. W. v. E. Doering and W. R. Roth, Tetrahedron, 18, 67 (1962).
9. B. Lythgoe and D. A. Metcalfe, Tetrahedron Letters, 2447 (1975).