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ENHANCEMENT OF ERYTHRO-SELECTIVITY IN THE [2,3]-WITTIG REARRANGEMENT VIA MEYERS' AZAENOLATES. A FACILE ENTRY TO ERYTHRO-α-HYDROXY-β-METHYL CARBOXYLIC ACID DERIVATIVES

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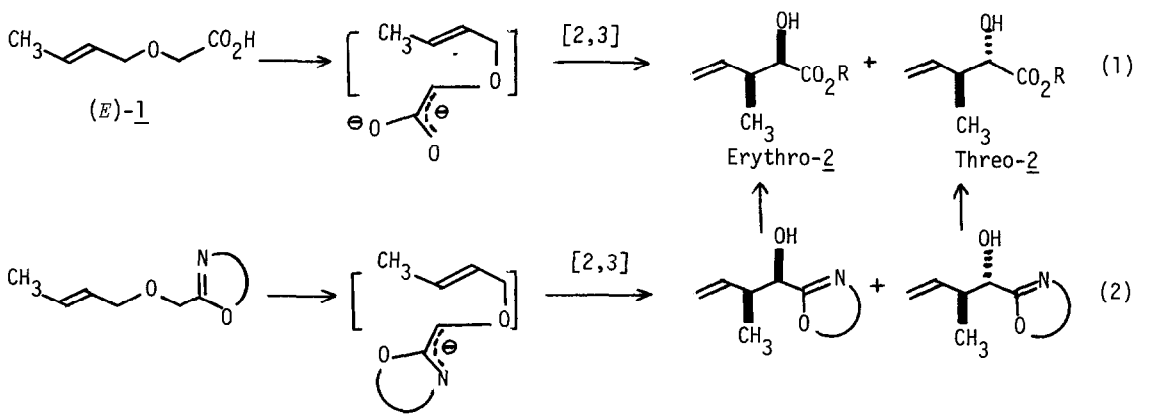
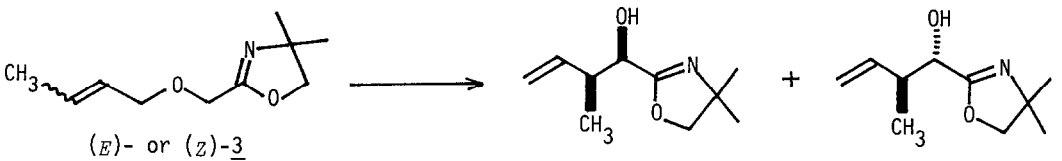
SUMMARY: A highly erythro-selective [2,3]-Wittig variant involving the azaenolate derived from 5,6-dihydro-1,3-oxazine system as the migrating terminus is described which eventually permits ready access to erythro-2-hydroxy-3-methyl-4-pentenoic acid derivatives.

As part of our research program designed to develop the [2,3]-Wittig rearrangement into a new, basic methodology for acyclic stereocontrol,[1,2] we have recently reported that the dianion rearrangement of (*E*)- and (*Z*)-crotyloxyacetic acid (1) exhibits only a moderate level (65-75%) of erythro- and threo-selectivity, respectively (eq 1).[3,4] In view of the great importance of α-hydroxy-β-methyl carboxylic acid derivatives as intermediates for natural product synthesis, the enhancement of diastereoselection in this type of [2,3]-Wittig variant is highly desirable. To this end, we have now examined the diastereoselection in the [2,3]-Wittig variants employing Meyers' heterocycles,[5] 2-oxazoline and 5,6-dihydro-1,3-oxazine systems which have been well established to serve as various latent functionalities including carboxyl (eq 2). Herein we wish to report an impressive enhancement of erythro-selectivity by using the dihydro-1,3-oxazine system rather than the 2-oxazoline system.



First, we studied the rearrangement of (*E*)- and (*Z*)-2-(crotyloxy)methyl-2-oxazolines (3)[6,7] easily obtainable[8] from the corresponding acid (1) and 2-amino-2-methyl-1-propanol (eq 3). Thus, treatment of 3 with butyllithium or lithium diisopropylamide (LDA) in THF at -85°C followed by stirring at that temperature for *ca.* 1 h afforded the [2,3]-rearranged product (4) as a diastereomeric mixture.[7,9] After its conversion to the α-hydroxy methyl ester (2, R=CH_3) via the reported procedure,[10] the erythro/threo ratio was determined by GLC analysis (PEG 20M, 120°C) as described in the literature.[11] The results are given in Table I. Unfortunately, the oxazoline systems exhibit only a moderate degree of either erythro or threo selection, while (*E*)-3 shows a significantly higher degree (84%) of erythro-selectivity than (*E*)-1 (65%).



(*E*)- or (*Z*)-3 Erythro-4 Threo-4 (3)

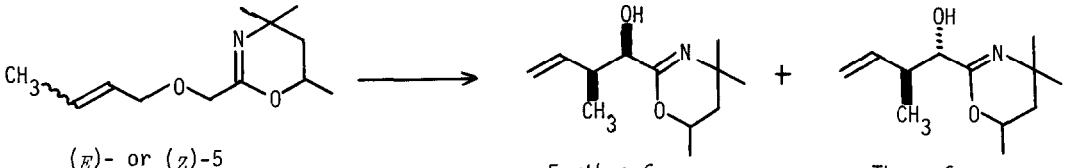
Table I

Substrate (stereopurity)	Base	Yield	Erythro : Threo*
(*E*)-3 (93%)	*n*-BuLi	98%	66 : 34
(*E*)-3 (93%)	LDA	80%	84 : 16
(*Z*)-3 (94%)	LDA	80%	28 : 78

*Refers to the diastereomeric ratio of 2 (R=CH_3)

Next, we examined the use of dihydro-1,3-oxazine system in place of the 2-oxazoline system. Thus, (*E*)- and (*Z*)-2-(crotyloxy)methyl-5,6-dihydro-1,3-oxazines (5)[7,12] were prepared via reaction of the potassium salt of crotyl alcohol with 2-chloromethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine[13] and each was rearranged under the same conditions as described above (eq 4). The erythro/threo ratio for the resulting diastereomeric mixture (6)[7,14] was determined after its conversion to 2 (R=CH_3) as described above. The results are shown in Table II.

As seen from the data in Table II, these dihydro-1,3-oxazine systems have led to some useful and surprising stereochemical results. The most striking is the remarkably high erythro-selectivity (98%) obtained with (*E*)-5; surprisingly enough, the observed degree slightly exceeds the geometrical purity of the substrate employed. Also notable is the finding that, unlike (*Z*)-1 and -3, (*Z*)-5 exhibits erythro-selection, albeit not so high,



(4)

(*E*)- or (*Z*)-5 Erythro-6 Threo-6

Table II

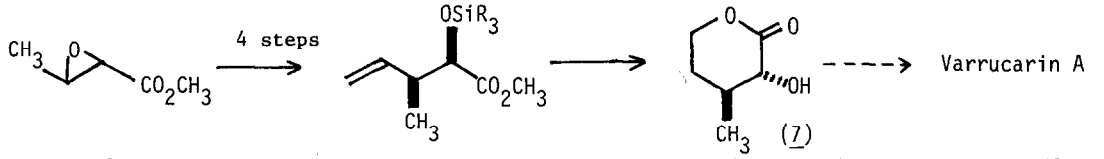
Substrate (stereopurity)	Base	Yield	Erythro : Threo*
(*E*)-5 (95%)	*n*-BuLi	92%	98 : 2
(*E*)-5 (95%)	LDA	86%	96 : 4
(*Z*)-5 (98%)	LDA	82%	65 : 35

* Refers to the diastereomeric ratio of 2 ($R=CH_3$)

which is apparently responsible for the exceedingly high erythro-selectivity of (*E*)-5.

Both the observed enhancement of erythro-selectivity and the unusual sense of diastereoselection have no straightforward explanations at the present time and still await detailed studies. However, these results are of mechanistic interest, indicating that the azaenolate derived from the dihydro-1,3-oxazine system is quite different in nature from that derived from the 2-oxazoline system and thus plays a very specific role in dictating product stereochemistry.

Regardless of the origin of the observed high erythro-selectivity, the present [2,3]-Wittig variant of (*E*)-5 provides an extremely facile entry to erythro-2-hydroxy-3-methyl-4-pentenoic acid derivatives (2), a class of compounds which can serve as key intermediates for macrolide total synthesis. In fact, for example, Roush and co-workers have quite recently reported an interesting elaboration of the silyl-protected erythro-2 ($R=CH_3$) prepared via an entirely different route to verrucarinolactone (7), an acyclic portion of verrucarin A.[15]



Finally, it should be noted that the high stereoselectivity, coupled with the fertile, well-defined chemistry of the Meyers' heterocycles,[5] enormously expands the synthetic potential of this particular [2,3]-Wittig variant. We are now actively investigating the feasibility of asymmetric synthesis via the [2,3]-Wittig rearrangement involving *chiral* 2-oxazolines[5] as the chiral auxiliary. The results will be disclosed in due course.

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References

1. For an excellent review on acyclic stereocontrol, see: P. A. Bartlett, *Tetrahedron*, 36, 2 (1980).

2. For our previous paper on this subject, see: T. Nakai, K. Mikami, S. Taya, and Y. Fujita, *J. Am. Chem. Soc.*, 103, 6492 (1981).

3. T. Nakai, K. Mikami, S. Taya, Y. Kimura, and T. Mimura, *Tetrahedron Lett.*, 22, 69 (1981).

4. It should be noted here that this sense of diastereoselection is opposite to those reported for the [2,3]-Wittig processes of allyl crotyl ethers and crotyl propargyl ethers (ref 2).

5. For reviews on synthetic utilities of these heterocycles, see: A. I. Meyers, "Heterocycles in Organic Synthesis," John Wiley, New York, 1974; A. I. Meyers and E. D. Mihelich, *Angew. Chem. Int. Ed. Engl.*, 15, 270 (1976); A. I. Meyers, *Acc. Chem. Res.*, 11, 375 (1978); A. I. Meyers, *Pure Appl. Chem.*, 51, 1255 (1979).

6. (*E*)-3 (*E*/*Z*=93 : 7): 50%; bp 60-65°C/0.8 mmHg; (*Z*)-3 (*E*/*Z*=6 : 94): 62%; bp 65-68°C/0.5 mmHg.

7. The spectroscopic properties (IR and NMR) of these compounds are fully consistent with the assigned structures.

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9. The GLC retention times (PEG 20M, 190°C) for erythro- and threo-4 were 8.4 and 8.8 min, respectively. The two diastereomers are also distinguishable by the NMR signals due to the carbinol hydrogen (>CH-OH); δ_{CDCl_3} 4.22 (d, J=6.5 Hz) for erythro-4 and 4.02 (d, J=4.5 Hz) for threo-4.

10. A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, *J. Org. Chem.*, 39, 2778 (1974).

11. B. B. Snider and J. W. van Straten, *J. Org. Chem.*, 44, 3567 (1979); also see ref 3.

12. (*E*)-5 (*E*/*Z*=95 : 5): 82%; bp 99-103°C/2.5 mmHg; (*Z*)-5 (*E*/*Z*=2 : 98): 91%; bp 79-85°C/3 mmHg.

13. G. R. Malone and A. I. Meyers, *J. Org. Chem.*, 39, 618 (1974).

14. The two diastereomers are distinguishable by the NMR signals due to the carbinol hydrogen (>CH-OH); δ_{CDCl_3} 3.96 (d, J=3.6 Hz) for erythro-6 and 3.87 (d, J=3.6 Hz) for threo-6.

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