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Asymmetric [2,3]-Wittig Rearrangement Involving a Chiral Ester Enolate Terminus. A Chiral Synthesis of erythro-α-Hydroxy-β-alkyl Carboxylic Acid Derivatives#

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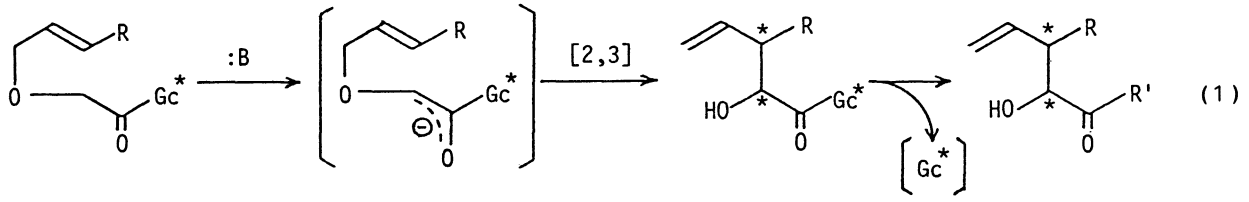
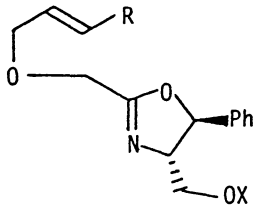
The title rearrangement of the (E-2-alkenyloxy)acetic esters derived from (-)-8-phenylmenthol has been shown to afford the corresponding 3-alkyl-2-hydroxy-4-pentenoic ester with an extremely high level of diastereoface selection (95-97% de) along with a high erythro selectivity (90-93%).

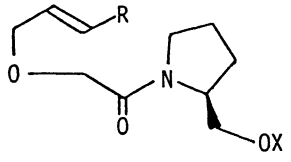
In our continuing study on the asymmetric [2,3]-Wittig rearrangement involving a chiral enolate terminus (Eq. 1), we have recently reported the enolate rearrangement of the chiral oxazolines (1)[1] and the chiral amides (2).[2] However, their synthetic utility is limited by the insufficient levels of diastereoface and/or diastereo selection. In a continuation of these studies, we now wish to report that the enolate [2,3]-Wittig rearrangement of the (-)-8-phenylmenthol-derived[3] esters (3) exhibits a remarkably high level of diastereoface selection along with a high erythro selectivity.



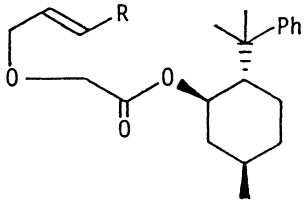
(1)



1 : X=H, CH_3



2 : X=H, $CH_2OCH_2CH_2OCH_3$



3

We studied the enolate rearrangement of the five chiral esters (3a-e) which were prepared in 81-99% yields from the corresponding (2-alkenyloxy)acetic acid or its chloride and (-)-8-phenylmenthol.[4,5] The chiral ester (3) was treated

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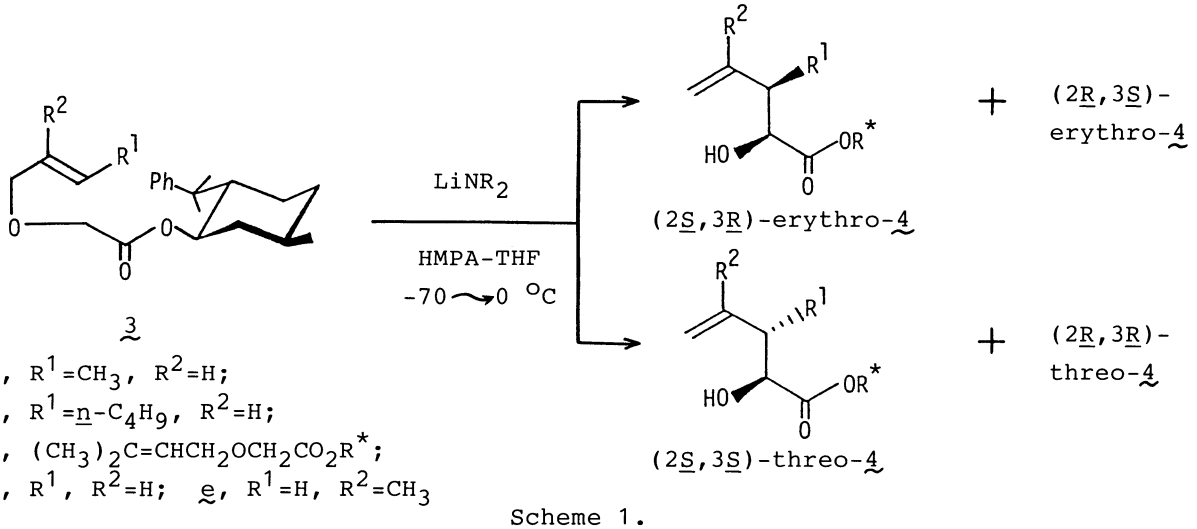
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

with a lithium amide base in hexamethylphosphoramide (HMPA)-THF (1:4 by vol.)[6] at -70 °C. The reaction mixture was stirred at that temperature for ca. 10 h and then slowly warmed to 0 °C. Hydrolytic workup afforded the rearranged product (4) in 75-88% isolated yield after column chromatography (Scheme 1). Table 1 shows the stereochemical outcomes.



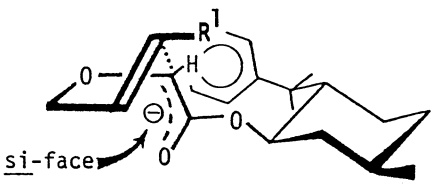
3

a, R^1=CH_3, R^2=H;
b, R^1=n-C_4H_9, R^2=H;
c, $(CH_3)_2C{=}CHCH_2OCH_2CO_2R^*$;
d, R^1, R^2=H; e, R^1=H, R^2=CH_3

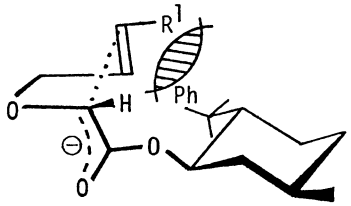
Scheme 1.

Several significant trends are evident from the data in Table 1. (1) In the rearrangement of 3a-c, a remarkably high (2S)-preference (>95% de) is observed, along with a relatively high erythro selectivity (>90%). (2) In contrast, however, the (2S)-preference is considerably lowered with 3d and 3e having no γ-alkyl-substituent on the allylic moiety. These trends indicate that the alkyl-substitution pattern on the allylic moiety plays a vital role in dictating the level of asymmetric induction. (3) The nature of the amide bases employed has little influence on the stereoselectivity concerned.

The observed (2S)-preference is readily interpreted as the result that the enolization leads to the (E)-enolate (solvent-separated or free)[6] which undergoes [2,3]-shift preferentially from the sterically less congested front-side (si-face) of the enolate as depicted in T_1, since the back-side (re-face) rearrangement should suffer a large steric repulsion[7] between the phenyl group and the allylic moiety, particularly the γ-alkyl substituent (R^1) as shown in T_2. The high erythro selectivity observed for 3a and 3b is explicable by essentially the same argument used to rationalize the high erythro selectivity previously observed for the rearrangement of 1 and 2.[1a,2] Thus, both the (2S)-preference and the erythro selection can be visualized by the transition state (T_1) in which the ester terminus occupies the pseudo-axial position of the envelope conformation[8] and the phenyl group situates at the back-side (re-face).

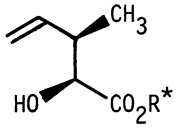
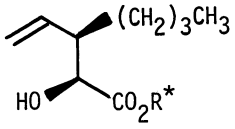
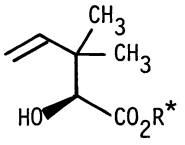
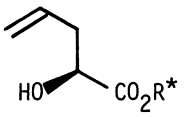
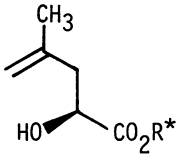


T_1 ⟶ (2S,3R)-erythro-4



T_2 ⟶ (2R,3S)-erythro-4

Table 1. The Chiral α-Hydroxy Esters (4) via Rearrangement of 3

Substrate	Base[a]	Product	Erythro : Threo[b]	% de[b]	Config.[c]
3a	LDA		90 : 10	97[d]	2S
3a	LHDS		93 : 7	96[d]	2S
3a	LTMP		92 : 8	97[d]	2S
3b	LDA		92 : 8[e]	95[d]	2S[f]
3c	LDA			96	2S[f]
3d	LDA			11	2S
3e	LDA			4	2S[f]

a) LDA = lithium diisopropylamide, LHDS = lithium hexamethyldisilazide, LTMP = lithium 2,2,6,6-tetramethylpiperidide. b) Determined by capillary GLC (XE-60, 30 m) and ^{1}H NMR analyses. c) Unless otherwise noted, the configuration was assigned after conversion to the corresponding methyl ester as described in Ref. 1a. d) Refers to the major erythro isomer. e) For the assignment of the erythro configuration of 4b, see: Ref. 9. f) The configuraion was assigned by similarity in GLC analysis.

From a synthetic point of view, the present asymmetric rearrangement is of particular value, since it permits ready access to erythro-α-hydroxy-β-alkyl carboxylic acid derivatives with a high optical purity, an important class of intermediates for natural product synthesis. For instance, (-)-verrucarinolactone can be easily synthesized from (2S,3R)-4a as previously reported[3f] and unnatural (-)-blastmycinone could be prepared from (2S,3R)-4b according to the reported procedure.[10]

In summary, the results of this work demonstrate that the asymmetric enolate [2,3]-Wittig rearrangement of the chiral ester 3 provides a new and highly efficient method for diastereo- and enantio-selective synthesis of α-hydroxy-β-alkyl carboxylic acid derivatives. Further efforts are in progress to apply the present methodology to natural product synthesis.

References

1) a) K. Mikami, K. Fujimoto, T. Kasuga, and T. Nakai, Tetrahedron Lett., 25, 6011 (1984); b) K. Mikami, T. Kasuga, K. Fujimoto, and T. Nakai, ibid., in press.

2) K. Mikami, O. Takahashi, T. Kasuga, and T. Nakai, Chem. Lett., 1985, 1729.

3) For different types of asymmetric reactions using 8-phenylmenthol derivatives, see: a) E. J. Corey and H. E. Ensley, J. Am. Chem. Soc., 97, 6908 (1975); b) E. J. Corey and R. T. Peterson, Tetrahedron Lett., 26, 5025 (1985); c) W. Oppolzer, C. Robbiani, and K. Battig, Tetrahedron, 40, 1391 (1984); d) J. K. Whitesell, Acc. Chem. Res., 18, 280 (1985); e) J. K. Whitesell, J. N. Younathan, J. R. Hurst, and M. A. Fox, J. Org. Chem., 50, 5499 (1985); f) Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, and K. Maruyama, Tetrahedron, 40, 2239 (1984); g) G. Quinkert and H. Stark, Angew. Chem., Int. Ed. Eng., 22, 637 (1983); h) S. W. Remiszewski, J. Yang, and S. M. Weinreb, Tetrahedron Lett., 27, 1853 (1986).

4) The chiral phenylmenthol was prepared in more than 99.5% of diastereomeric purity (GLC assay) from commercially available (R)-(+)-pulegone according to the reported procedure[3a] followed by careful column chromatography.

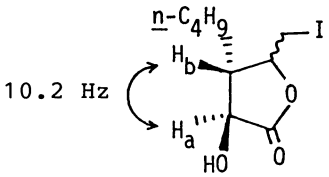
5) The chiral esters (3a, 3b, and 3d) were prepared using the corresponding (allyloxy)acetyl chloride. On the other hand, 3c and 3e were obtained directly from the corresponding (allyloxy)acetic acid using dicyclohexylcarbodiimide: cf. K. Holmberg and B. Hansen, Acta Chem. Scand., B., 33, 410 (1979). It should be noted that the ^{1}H NMR signal due to the α-methylene ($OC\underline{H}_2CO_2R^*$) of 3 appears at a remarkably higher field as an AB-pattern than that of the corresponding methyl ester [e.g., δ 3.10 and 3.38 (J=16.5 Hz) for 3a vs. δ 3.90 (s) for its methyl ester (in CCl_4)].

6) For the importance of the specific solvent system, see: O. Takahashi, T. Saka, K. Mikami, and T. Nakai, Chem. Lett., 1986, 1599.

7) The effective blocking by the phenyl group is suggested by the remarkably high-field resonance of α-methylene protons as mentioned in Ref. 5. For a pertinent discussion of the specific orientation of the phenyl group in 8-phenylmenthol derivatives, see: Ref. 3e.

8) For a general discussion of the transition-state model for [2,3]-Wittig process, see: K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, J. Org. Chem., 48, 279 (1983); T. Nakai and K. Mikami, Chem. Rev., in press.

9) The erythro configuration of 4b was assigned through iodolactonization reaction [cf. B. B. Snider and J. W. van Straten, J. Org. Chem., 44, 3567 (1979)]. Thus, 4b was treated with I_2 and KI after hydrolysis (1N aq. NaOH) to give the trans-lactone 5 ($J_{a,b}$=10.2 Hz).



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10) T. Fujisawa, H. Kohama, K. Tajima, and T. Sato, Tetrahedron Lett., 25, 5155 (1984).

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