Tetrahedron Letters,Vol.28,No.3,pp 337-340,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

CHIRAL ZINC HOMOENOLATE OF METHYL ISOBUTYRATE. A NEW BUILDING BLOCK FOR THE SYNTHESIS OF CHIRAL α-METHYLESTERS

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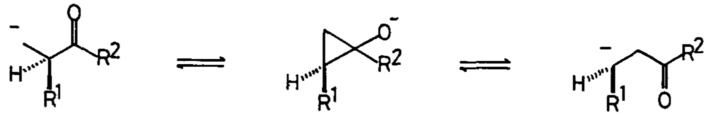
Abstract: Chiral homoenolate of methyl isobutyrate prepared in a few steps from optically active methyl β-hydroxy isobutyrate reacts with carbon electrophiles to give chiral α-methyl esters.

Approaches to asymmetric synthesis employing "chiral building blocks" play important roles in the preparation of chiral molecules.[1] In the passed few years, we have addressed ourselves to this problem by exploring routes to a chiral homoenolate such as **1**, which should find great synthetic utility, if it could at all be prepared in high optical purity, and its chirality maintained during the subsequent C-C bond forming reactions. A potential problem in dealing with such a homoenolate stems from the well-documented equilibrium between the primary (**1**) and the secondary anionic isomers (**3**) via cyclopropanolate **2** (eq 1),[2] since the secondary anionic center is known to have marginal configurational stability,[3] and consequently **1** might racemize via **3**. We now report the first example of an optically active homoenolate by describing that a prototypical species (**1**: R^1 = Me, R^2 = OMe) complexed with Zn(II) remains optically active for an extended period, and reacts with various carbon electrophiles to give chiral α-methyl alkanoates.



(1)

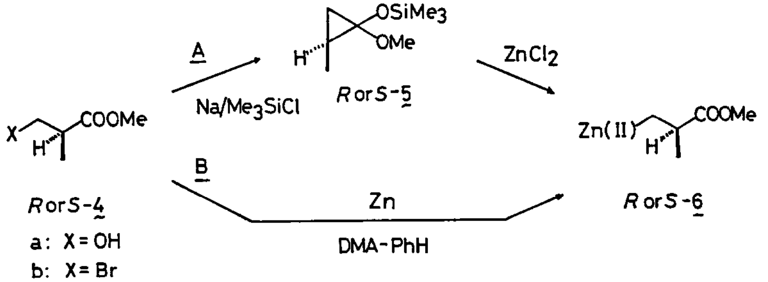
1 2 3

Commercially available R and S β-hydroxy isobutyrate (**4a**, >97% e.e.) was converted smoothly to β-halo isobutyrates (**4b,c**).[4] Transformation of the latter to the desired zinc homoenolate **6** by the following two methods was then examined.

A) Reductive conversion of **4b** into cyclopropane **5** (Na/Me_3SiCl) followed by the reaction with $ZnCl_2$.

B) The reaction of iodide **4c** with activated zinc in dimethylacetamide/benzene mixture.

Method A that we reported previously[5] provides the homoenolate in 60-70% yield as a pure characterizable material suitable for detailed chemical investigation, yet the much simpler Route B recently developed by Yoshida[6] has an apparent practical merit. While our previous attempts to prepare a chiral titanium homoenolate by a route similar to A was hampered by the lack of the regioselectivity of the ring opening of the cyclopropane **5** by $TiCl_4$,[7] the reaction with $ZnCl_2$ proceeded with highly regioselectivity (vide infra).[8]



(2)

(Only one enantiomeric series is indicated.)

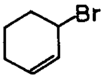
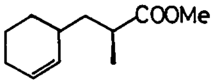
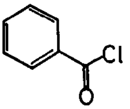
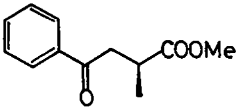
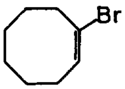
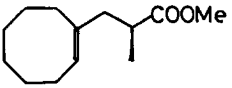
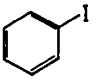
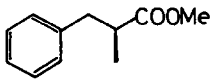
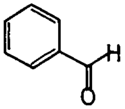
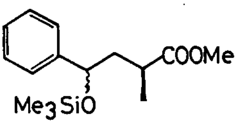
Equation 1 suggests a possibility of racemization already during the initial reductive transformation of the bromide **4b** to **5**, which is likely to proceed via sodium homoenolate.[9] The chirality was however retained during this reaction, as determined by the experiment in which the levorotatory bromide S-**4b** was cyclized to the cyclopropane **5** (1:1 diastereomeric mixture) and then transformed back to the starting bromide S-**4b** (bromine at 0 °C) without loss of optical purity.[10]

The ring opening reaction of the siloxy cyclopropane R-**5** with half an equivalent of freshly fused $ZnCl_2$ in ether at room temperature cleanly gave homoenolate S-**6** in high yield.[11] The optical purity of the chiral isobutyrate moiety in S-**6** was at least 95% e.e. as determined again by conversion (bromine at 0 °C) into the bromide S-**4b**.[10] The chirality was fully retained even after aging the homoenolate for two days in ether either in the presence or absence of Me_3SiCl, which forms together with the homoenolate **6** in the reaction of **5** with $ZnCl_2$.

The chiral isobutyrate homoenolate smoothly reacted with various carbon electrophiles. The reaction types examined involve transition metal catalyzed C-C bond forming reactions of **6**[12-14] and ZnI_2-catalyzed homo-Reformatsky reaction of the cyclopropane **5**,[15] which were performed under conditions previously prescribed for the propionate prototype. All reactions proceeded without detectable racemization,[10] and afforded the expected products in good chemical yields (Table I). The homoenolate generated by Method B also retains the chirality as shown by the palladium catalyzed arylation reaction[16] shown in entry 5.

Although the above results underscore the synthetic utility of the homoenolate **6**, the reasons for the optical stability of **6** still remains speculative. It has been found that a mixture of a zinc homoenolate of propionate and Me_3SiCl in ether exists in equilibrium (K = ca. 20) with the cyclized form, e.g. **5**.[8] According to this observation coupled with the the optical stability of **5**, it seems clear that the right hand side of the equation 1 either does not exist or operates extremely slow for the zinc homoenolate[17].

Table I. Reactions of the Chiral Homoenolate of Isobutyrate (R-6).[a]

entry	substrate	Method[b]	Product	%yield[c]	%e.e.[d]
1		A[e,i]		59	96
2		A[f,j]		55	>91
3		A[f]		85	>90
4		A[f]		79	95
5		B[g]		63	95
6		A[h,j]		72	98

[a] S-Hydroxy isobutyrate (>97%e.e.) was employed as the starting material. [b] All reactions were performed in the same manner as described for the propionate prototype. [c] Isolated yield. [d] The indicated e.e. values determined by ^{1}H NMR refer to the minimal purity (ref 10). Analyses were performed either on the product itself or after suitable derivatization (footnotes i and j). For compounds thus analyzed in entries 1,2,4-6, the α-methyl signals of the S-products appeared at lower field than the R-products. [e] Ref 13. [f] Ref 14. [g] Ref 16. [h] ZnI_2-catalyzed reaction of cyclopropane S-5 (Ref 15). [i] The optical purity was determined for the saturated ester (H_2/Pd). [j] The product was converted to cis and trans α-methyl-γ-phenyl-γ-butyrolactone, diastereomers separated, and analyzed for the optical purity.

Experimental Procedure

Method A: Reaction of R-6 with Cyclohexenyl Bromide: A mixture of S-5 (3.8 mmol, 0.75 ml), freshly fused $ZnCl_2$ (1.8 mmol, 242 mg) in 20 ml of ether was stirred for 5 h at room temperature. Volatile material was removed under reduced pressure, and 10 ml of ether was added to make an ca. 0.30 M solution of R-6. The concentraction can be determined at this point by ^{1}H NMR analysis of this solution (60-70% yield). Cyclohexenyl bromide (0.5 mmol, 81 mg), HMPA (1.0 mmol, 174 micro l), and $CuBr{\cdot}Me_2S$ (5 mg) were added to the solution of the homoenolate (0.5 mmol, 2.8 ml) at 0 °C, and the mixture was stirred for 4 h at room temperature. Aqueous workup gave the product (54 mg, 59%), whose optical purity was determined by ^{1}H NMR after hydrogenation of the double bond.

Method B: To a hot solution of 2 mg of silver acetate in 1.2 ml of acetic acid was added zinc dust (2.8 mmol, 183 mg) in one portion. Acetic acid was removed after 30 sec, the residue was washed 4 times with dry ether, and finally dried under vacuum. The couple was suspended in hot benzene (3 ml, 60 $^{\circ}$C) containing 0.2 ml of DMA, and the iodide R-**4b** (209 micro l, 1.50 mmol) was added. After 3 h at 60 $^{\circ}$, a clear solution of the homoenolate was used for the subsequent reaction on a 1 mmol scale.

References and Notes

1. Cf. J. W. Scott, "Asymmetric Synthesis", Vol 4, Eds. J. D. Morrison and J. W. Scott, Academic Press, Orlando, 1984, Chapter 1.
2. For a highly illustrative example, see R. Goswami and D. E. Corcoran, J. Am. Chem. Soc., **105**, 7182 (1983).
3. Cf. for configurational stability of organometallics, see D. S. Matteson, "Organometallic Reaction Mechanisms", Academic Press, New York, 1974.
4. The bromoesters **R and** S-**4b** were prepared in 71% yield by treatment of the optically active hydroxyester **4a** (>97% e.e.) with Ph$_3$P/NBS: S-**4b** $[\alpha]_D^{25}$ = -22.0 $^{\circ}$ (c = 5, MeOH). Treatment of **4b** with NaI in refluxing acetone gave the iodide **4c** in 83% yield.
5. E. Nakamura, J.-i. Shimada, and I. Kuwajima, Organometallics, **4**, 641 (1985).
6. Y. Tamaru, H. Ochiai, T. Nakamura, K. Tsubaki, and Z. Yoshida, Tetrahedron Lett., **26**, 5559(1985). For zinc silver couple, see J. M. Denis, C. Girard, and J. M. Conia, Synthesis, 549 (1972). For correction, see H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, Organic Reactions, **20**, 1 (1973).
7. E. Nakamura, H. Oshino, and I. Kuwajima, J. Am. Chem. Soc., **108**, 3745 (1986).
8. This result was first obtained for the racemate by E.N. and H. Oshino.
9. The details of this reaction has not previously been discussed. (Cf. K. Rühlmann, Synthesis, 236 (1971). Cyclization of radical anions initiated by electron transfer either to the bromine atom or to the carbonyl group also appears likely.
10. Throughout the present study, the optical purity was determined by analysis of the decoupled α-methyl signals on 200 MHz ^{1}H NMR (CDCl$_3$) by using a chiral shift regent, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato], europium (III). The numerical e.e. data were obtained by graphical curve resolution of the hardly visible small shoulders due to the minor enantiomer using samples of known optical purity as a reference standard.
11. Homoenolate **dl-5** (containing half an equivalent of ether) showed the following spectral properties at 20 $^{\circ}$C: ^{1}H NMR (200 MHz, CDCl$_3$) 0.4 and 0.65 (broad, 1H each), 1.26 (d, J = 7 Hz, 3 H), 2.92 (sextet, J = 7 Hz, 1 H), 3.82 (s, 3 H); ^{13}C NMR (50 MHz, CDCl$_3$) 14.7 (t), 22.0 (q), 39.2 (d), 54.0 (q), 188.3 (s).
12. E. Nakamura and I. Kuwajima, J. Am. Chem. Soc., **106**, 3368 (1984).
13. E. Nakamura, S. Aoki, K. Sekiya, and I. Kuwajima; manuscript in preparation.
14. E. Nakamura and I. Kuwajima, Tetrahedron Lett., **27**, 83 (1986).
15. H. Oshino, E. Nakamura, and I. Kuwajima, J. Org. Chem., **50**, 2802 (1985).
16. Y. Tamaru, H. Ochiai, T. Nakamura, and Z. Yoshida, Tetrahedron Lett., **27**, 955 (1986).
17. Gift of chiral hydroxy isobutyrate from Dr. J. Hasegawa of Kanegafuchi Chemical Industry is greatly acknowledged. E.N. thanks Asahi Glass Foundation for Industrial Technology for financially supporting this research.

(Received in Japan 20 September 1986)