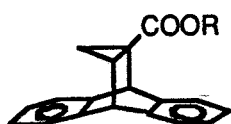
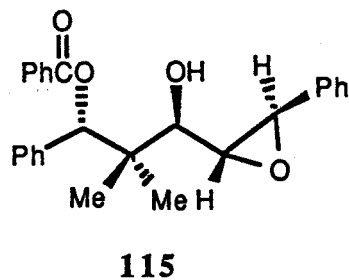
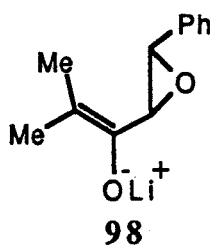
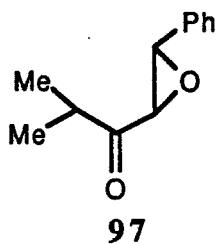


Thesis Title	Meerwein-Ponndorf-Verley Reaction of α -Ketoepoxides. A Stereocontrolled One-Step Synthesis of Epoxy-1,3-Diol Monoesters and The Study of Thermal Rearrangement of Cyclopropene-Anthracene Adducts
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Degree	Doctor of Philosophy (Organic Chemistry)
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Date of Graduation	28 April B.E. 2535 (1992)

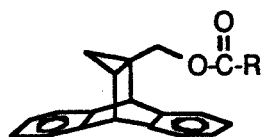
Abstract


The first part of this thesis deals with the Meerwein-Ponndorf-Verley reaction of **98** derived from α -ketoepoxide **97** with two molecules of aldehyde to stereospecifically yield **115**. Its mechanistic pathway has been proved by various experiments, including the use of deuterium labelling substrate.

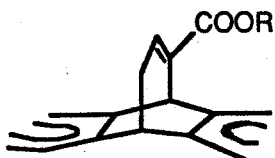
The second part of this thesis describes flash vacuum pyrolysis of cyclopropene-anthracene adducts. Products **201-204** were isolated from starting materials **195-198** while the hydrocarbon **251** was isolated from pyrolysates of **243-246**. The reaction mechanism is, again, enlightened by the use of deuterium labelling substrates.



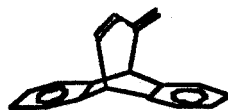
- 195, R = Me
 196, R = Ph
 197, R = CH₂Ph
 198, OR = NEt₂



- 243, R = Me
 244, R = Ph
 245, R = -OMe
 246, R = -CH=CH-Ph



- 201, R = Me
 202, R = Ph
 203, R = CH₂Ph
 204, OR = NEt₂



251

Meerwein-Ponndorf-Verley Reaction of α -Ketoepoxides. A Stereocontrolled One-step Synthesis of Epoxy-1,3-diol Monoesters

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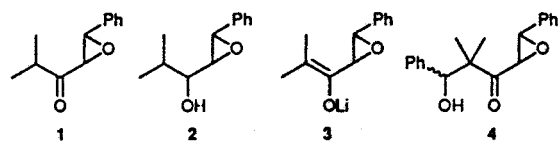
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Lithium enolate **3**, derived from ketoepoxide **1**, adds to two molecules of an aldehyde with concomitant hydride transfer to produce **5** stereospecifically.

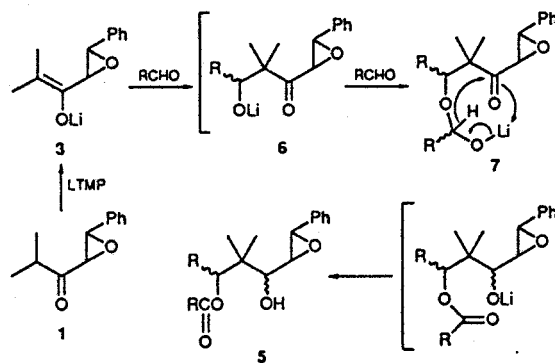
It has been known for some time¹ that certain enolizable α -halo and α -methoxy ketones, upon treatment with lithium diisopropylamide (LDA), undergo reduction in a Meerwein-Ponndorf-Verley fashion² in addition to the expected enolate formation. This type of reaction has lately gained interest amongst chemists and is finding useful applications in organic synthesis. A recent example which prompted us to record our findings is that by Evans³ where a samarium-catalysed reaction between a β -hydroxy ketone and an aldehyde leads, via a cyclic transition state, to a 1,3-diol. Here we report that the carbonyl group α - to an epoxide function (e.g. **1**) is exceptionally prone to the Meerwein-Ponndorf-Verley hydride transfer reaction.

Thus treatment of racemic **1** with one equivalent of LDA at various temperatures invariably produces, after protonation, alcohol **2** as a single stereoisomer in 18–23% isolated yields,[†] together with recovered starting material **1** (50–62%) apparently from protonation of enolate **3**. However, by simple modification, i.e. substituting lithium tetramethylpiperidide (LTMP, a lithium amide base with no α -hydrogen) for LDA, we find that **3** can be specifically generated and employed as a

nucleophile. Accordingly, reaction of **1** with LTMP in tetrahydrofuran (THF) at -78°C followed by quenching with an alkyl halide affords the corresponding alkylated product in good yield (74–86%). Trapping enolate **3** with one equivalent of benzaldehyde at -78°C in THF in the absence of a chelating agent, followed by immediate work-up, yields **4** (58%) as a mixture of two stereoisomers together with recovered **1** (30%). At higher temperatures and longer reaction times (i.e. room temperature, overnight) however, **4** is detected (TLC) only as a minor component in the crude reaction product which is composed mainly of a single isomer of **5a** (26%) and recovered **1** (59%).

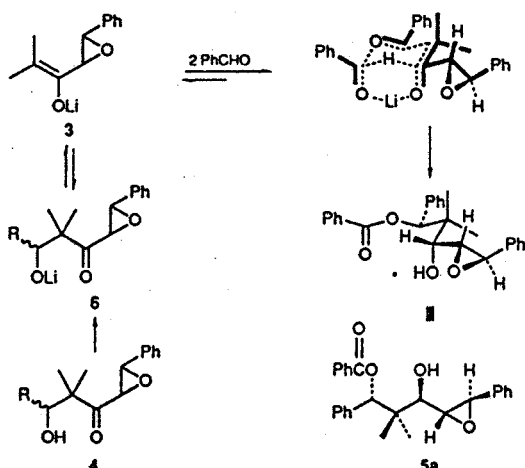


[†] This is an example of a stereospecific Meerwein-Ponndorf-Verley reduction of acyclic ketone by LDA [cf. Ref. 1]. The relative stereochemistry of **2** has not been determined.



a; R = Ph
b; R = 4-OMe-C₆H₄
c; R = 4-Me-C₆H₄
d; R = 4-Cl-C₆H₄
e; R = 4-Br-C₆H₄
f; R = Me

Scheme 1



Scheme 2

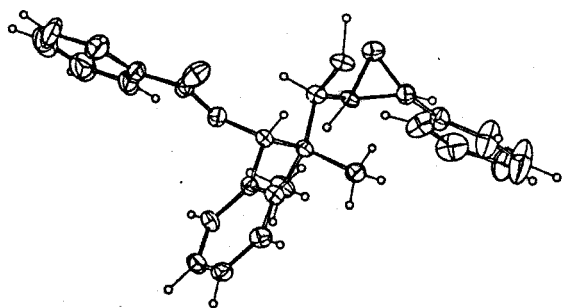


Fig. 1 ORTEP drawing of compound 5a

We have been able to promote the formation of 5a by increasing the ratio of aldehyde. Thus, treatment of enolate 3 with excess of benzaldehyde (3 equiv.) followed by stirring overnight at room temperature results in a single isomer of compound 5a (63%), again accompanied by starting material 1 (27%). This behaviour appears to be quite general and reproducible, for example, single isomers of 5b-f are obtained when the corresponding aldehydes are employed.‡

Mechanistically the above reaction might at first be envisaged as involving consecutive additions of enolate 3 to two molecules of aldehyde followed by a Meerwein-Ponndorf-Verley hydride transfer as illustrated in Scheme 1. However, Scheme 1 suffers a serious drawback in failing to justify the specific stereochemistry of final product 5, it having already

been noted that addition of the first molecule of benzaldehyde to 3 is non-stereospecific, giving 4 as a mixture of stereoisomers. The mechanistic picture of the reaction did not improve until a surprising observation was made in that treatment of 4 (isomeric mixture) with equimolar amounts of base (Bu^nLi , LDA or LTMP) and benzaldehyde also yields a single isomer of 5a (47%), identical in all respects with that obtained earlier.§ The fact that the same stereoisomer of 5a is obtained whether from 3 or an isomeric mixture of 4 seems, to us, to suggest that the addition of 3 (generated either from 1 or from a retroaldol reaction of 4) to the two molecules of aldehyde, as well as the hydride transfer, all occur in a concerted fashion involving a cyclic transition state 9 in which all large substituents occupy equatorial positions.¶ In fact, cyclic transition states have been proposed earlier by Molander⁴ and Evans³ for the samarium-catalysed Reformatsky and Meerwein-Ponndorf-Verley reactions. Here, it is interesting to note the exclusive approach of the first molecule of benzaldehyde on the apparently less hindered side of starting epoxy-enolate 3. Transition state model 9 nicely accommodates our experimental results in that stereospecific production of 5 is possible either from 1 or an isomeric mixture of 4. It is also probable that an equilibrium exists between 3 and 9 under the conditions employed, judging from the fact that we were unable to drive the reaction to completion (Scheme 2).‡

The stereochemical integrity of 5a is fully confirmed by X-ray analysis (Fig. 1).|| Also, the use of deuteriated benzaldehyde in the reaction with 3 gives, as anticipated, the corresponding deuteriated 5a.**

This reaction provides an expedient and stereocontrolled entry to epoxy 1,3-diol monoesters such as 5 by simultaneous creation of both diol chiral centres in one single operation.

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References

- 1 C. Kowalski, X. Creary, A. J. Rollin and M. C. Burke, *J. Org. Chem.*, 1978, 43, 2601.
- 2 A. L. Wilds, *Org. Reactions*, 1944, 2, 178.
- 3 D. A. Evans and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1990, 112, 6447.
- 4 G. A. Molander and J. B. Etter, *J. Am. Chem. Soc.*, 1987, 109, 6556.

¶ It is arguable that the step-wise mechanism in Scheme 1 is still viable since the isolation of isomeric aldol products 4 was carried out under kinetically controlled conditions (-78°C), whereas at higher temperatures a retroaldol-aldol process might first allow interconversion to a single, thermodynamically more stable isomer of 4 which would then proceed to the single final product 5.

|| Crystal data for 5a: $\text{C}_{20}\text{H}_{20}\text{O}_4$, monoclinic, space group $P2_1/c$ with $a = 17.312(8)$, $b = 6.090(2)$, $c = 21.675(8)$ Å, $\beta = 96.53(3)^\circ$, $V = 2270(2)$ Å³ and $D_c = 1.177$ g cm⁻³ for $Z = 4$. The structure was solved by direct methods using the XTAL 88 program system which revealed the positions of all of the non-hydrogen atoms; $R = 0.062$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See notice to Authors, Issue No. 1.

** Deuteriated benzaldehyde (≈ 0.5 atom d) was prepared by H \rightarrow D exchange of the corresponding aminonitrile precursor (cf. S. F. Dyke, E. P. Tiley, A. W. C. White and D. P. Gale, *Tetrahedron*, 1975, 31, 1219). Determination of deuterium incorporation was made by NMR analysis.

‡ 5b, 56% (36); 5c, 60% (26); 5d, 74% (18); 5e, 71% (19); 5f, 46% (40) purified yields as calculated from 1 (number in parentheses indicates percentage of recovered starting material 1). All compounds described are fully characterized. Elemental analyses were performed by the Scientific and Technological Research Equipment Centre, Chulalongkorn University, Bangkok and by the Elemental Analysis Unit, Department of Chemistry, Faculty of Science, Silpakorn University, Nakorn Pathom.

§ Accompanied by 1 and recovered 4 in yields of 15 and 10% respectively.