Tetrahedron: Asymmetry Vol. 1, No. 10, pp. 703-706, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Stereoselective Aldol Reaction with Chiral Acetates

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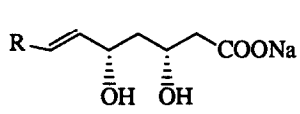
(*Received* 9 *August* 1990)

Abstract: The synthesis of enantiomerically pure **5** is described utilizing chiral acetate **2** and aldehyde **3** employing novel aldol reaction conditions (e.g., the use of excess organic amine compared to n-BuLi for generating the enolate). In addition, some interesting new chiral auxiliaries are also described.

In our efforts to find a practical and an efficient method for the synthesis of enantiomerically pure dihydroxyheptenoates **1**, which are potent HMG CoA reductase inhibitors, we reported earlier[1] a convergent strategy starting from *S*-malic acid. In the present communication we report our results on the stereoselective aldol reactions using enantiomerically pure acetates, obtained from glycols derived from different α-hydroxy acids, for generating the allylic stereogenic carbinol.



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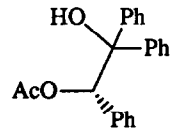

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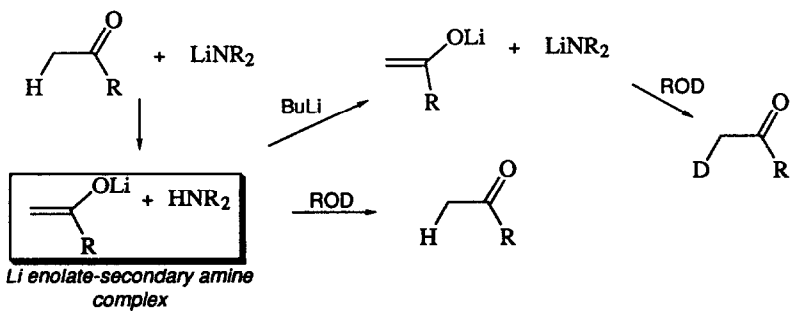
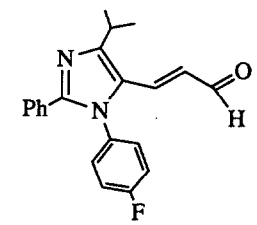
The utilization of *S*-monoacetyltriphenylglycol **2** in the stereoselective aldol reactions was first reported by Braun and Devant[2], and they found that the diastereomeric ratios were better when the magnesium enolate was employed rather than the corresponding lithium enolate. These authors also studied[3] the effect of structural variation of the glycol system on the stereoselectivity of the aldol reactions. Compound **2** was utilized more recently by others[4] employing Braun's conditions[2]. Our work on the mechanism-based optimization of the reaction conditions was mainly prompted by the pioneering work of Seebach[5] on the structure and reactivity of lithium enolates and especially the effect of secondary amines on lithium enolates, as summarized in Scheme 1.



Scheme 1

With the assumption that the nature of the *Li enolate-secondary amine complex* could influence the extent of asymmetric induction, we investigated the aldol reaction[6] (**2** + **3**[7] ⟶ **4** ⟶ **5**) with lithium bases



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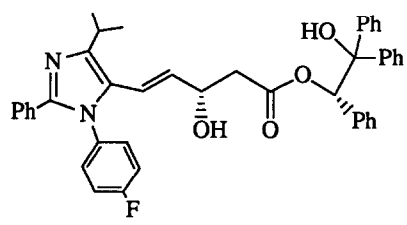

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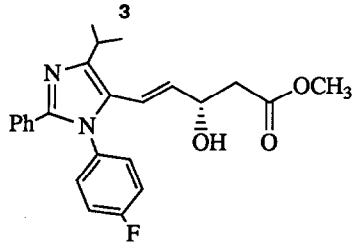

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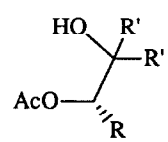

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Table 1: Data on aldol reactions of *S*-acetate **2** with aldehyde **3**.

Entry No.	Amine (eq)	No. of eq. of n-BuLi	Other additives	Temp.(°C)	Compound **5** *ee* (%)
1	Dicyclohexylamine (3)	3	-	−78	84
2	2,2',6,6'-Tetrametyl-piperidine (3)	3	-	−78	90
3	Diisopropylamine (3)	3	-	−78	92
4	Hexamethyldisilazane (HMDS) (3)	3	-	−78	94
5	HMDS (4)	3.6	-	−100	96
6	HMDS (20)	3.6	-	−100	96
7	HMDS (3.6)	3.6	n-BuLi (3.6 eq)	−100	70
8	HMDS (4)	3.6	LiCl	−100	70

derived from different secondary amines; the results are listed in Table 1. As no suitable method[8] could be found for measuring the diastereomeric ratio of **4**, it was converted into the methyl ester **5** by using $MeOH/K_2CO_3$, and the optical purity determinations were made utilizing optically active $[Eu(hfc)_2]$ NMR shift reagent. From these results it is evident that the nature of the base and/or reaction conditions did indeed influence the selectivity: the use of excess amine compared to n-BuLi (entries 5&6) was found to be advantageous while excess n-BuLi (entry 7) was detrimental. Similarly, LiCl (entry 8) appears to disrupt the complex. Compound **5** was easily enriched to >99% *ee* by a single recrystallization with EtOAc/hexane (**5**: mp 166 °C, $[\alpha]_D$ +17 (c = 1, MeOH)).

In addition to the variation of reaction conditions, we also studied the effect of the structural variation of the glycol **6**[9] on the diastereomeric ratio, and the results are listed in Table 2.

Table 2: Data on the aldol reacton of acetate **6** with aldehyde **3**

Entry No.	Acetate 6		Reaction Conditions	Compound **5** *ee* (%)
	R	R'		
1	CH_3	Ph	A	60
2	Isopropyl	Ph	A	58
3	Ph	CH_3	A	42
4	Ph	Ph	A	92
5	Ph	Ph	B	94
6	Ph	Ph	C	94
7	Ph	Ph	D	96
8	Ph	*o*-Toluyl	A	74
9	Ph	*m*-Toluyl	A	60
10	Ph	*p*-Toluyl	A	88
11	Ph	*p*-Vinyl-Ph	B	94
12	Ph	*p*-Fluoro-Ph	B	92
13	Ph	*p*-Methoxy-Ph	B	94
14	Ph	*p*-Methoxy-Ph	D	96

Reaction conditions: **A**: n-BuLi (3 eq), diisopropylamine (3 eq), -78 °C; **B**: n-BuLi (3.6 eq), diisopropylamine (4 eq), -78 °C; **C**: n-BuLi (3 eq), HMDS (3 eq), -78 °C and **D**: n-BuLi (3.6 eq), HMDS (4 eq), -100 °C.

Compound **5** is an intermediate in the synthesis of an enatiomerically pure HMG CoA reductase inhibitor **1** and its other three stereoisomers; the details of these transformations will be published at a later date.

Acknowledgements: We thank Dr. F.G. Kathawala for valuable discussions and Dr. M. Shapiro and his group for NMR measurements.

References and Notes

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6. A general aldol reaction procedure is as follows: To an appropriate amine (3 mmol) in 5 mL of dry THF at -10 °C, n-BuLi (3 mmol) in hexane solution (1.6 M) was added dropwise, stirred for 30 min., followed by the addition of acetate **3**. After stirring for another 30 min., the mixture was cooled to -78 °C, appropriate additive was added if necessary, and a THF/heptane (2:3) solution (5 mL) of aldehyde **3** (1 mmol) was added dropwise followed by the standard work up with ammonium chloride solution, to yield product **4**.

7. J.R. Wareing, *Chem. Abs.*, 1989, **111**, 232813f; US 4,808,607.

8. Our attempts to measure the diastereomeric ratio by HPLC and NMR shift reagent studies on aldol product **4** were unsucessful. Hence optical purity determinations were made on the methanolysis product **5**. However, with other examples (unpublished results) we clearly demonstrated that the diastereomeric ratio at the aldol step and the enatiomeric purity after methanolysis were comparable to one another.

9. Enantiomerically pure acetates that were used in the present study were made in two steps starting from the corresponding methyl ester employing literature methods[3] with Grignard reagents which were freshly made from the corresponding bromides.