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ENANTIOFACE DIFFERENTIATING MICHAEL REACTION OF ETHYL ACETOACETATE WITH ALKYLIDENEMALONATES *VIA* CHIRAL ENAMINE

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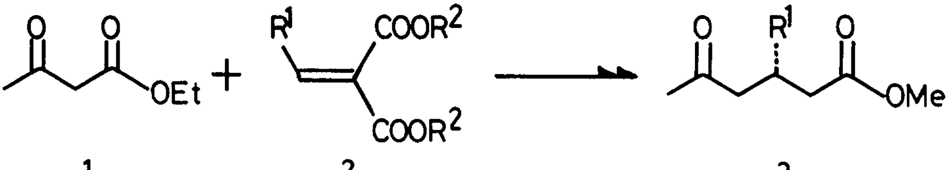
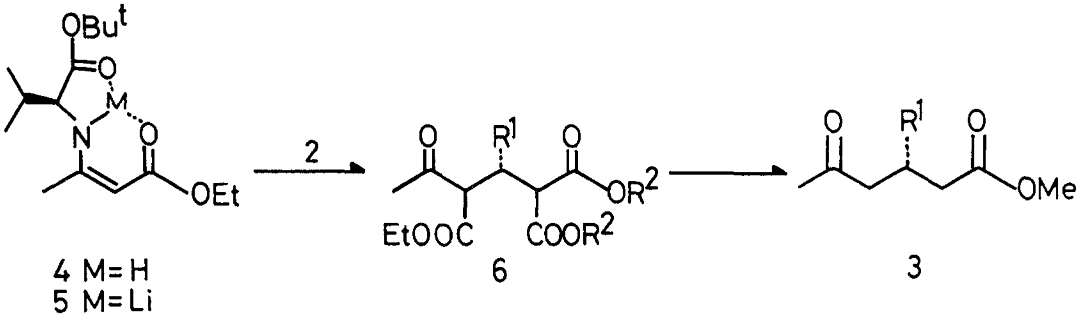
Summary: Utilizing the L-valine-based chiral lithioenamine (**5**) of ethyl acetoacetate (**1**), enantioface differentiating Michael reaction with alkylidenemalonates (**2**) gave, after decarboxylation, β-substituted δ-keto esters (**3**) in a fair to good enantiomeric excess. Kinetic diastereoenrichment of the initial Michael adducts (**7**) was also studied. Combination of both processes provides the procedure for the synthesis of **3** in 55-93% ee.

In spite of recent and impressive progresses in highly diastereoselective asymmetric Michael reactions, enantioface differentiating carbon-carbon bond forming Michael reactions still present a significant challenge of substantial international interest.[1] As part of a program involved in asymmetric carbon-carbon bond forming reactions of L-valine-based chiral enamines of β-keto esters, which has thus far led to the highly efficient diastereoface differentiating alkylation of α-alkyl β-keto esters with alkyl halides[2b,c] and Michael reaction with di-*tert*-butyl methylenemalonate,[2d] we have tested a methodology with a view to reach the enantioface differentiating Michael reactions of ethyl acetoacetate (**1**) with alkylidenemalonates (**2**). It seems to be probable that, in the Michael reaction of **1** with **2**, good enantioface selection of **2** will be obtainable if **2** reacts with the chiral lithioenamine (**5**) of **1** on the restricted diastereoface of **5**. We now report some of the results of our approaches to the enantioface differentiating Michael reaction of **5** with **2** producing, after decarboxylation, β-substituted δ-keto esters (**3**) based on the aforementioned expectation.



1 2 3

The chiral enamine (**4**) ($[\alpha]_D^{23}$+162° (benzene)) was prepared in 83% yield by the condensation of ethyl acetoacetate (**1**) and L-valine *tert*-butyl ester using standard procedure.[2,3] At first, reactions of **4** with dimethyl,[4] diethyl,[4] and di-*tert*-butyl[5] benzylidenemalonates (**2**: R^1=Ph, R^2=Me, Et, *t*-Bu) were studied using several solvent systems. The chiral enamine (**4**) was lithiated with LDA in the solvent at -78 °C (1 h) and **2** was added. The whole was stirred at -78 °C for several hours and then treated with 10% aq. HCl at room temperature for 12 h. Standard work-up gave the crude adduct (**6**) which was then decarboxylated with 20% aq. HCl in AcOH under reflux and methylated with diazomethane in ether. Purification by silica gel column chromatography (ether-hexane) afforded δ-keto ester (**3**: R^1=Ph) in a reasonably good overall yield. The enantiomeric excess was determined by ^{1}H NMR in the presence of Eu(hfc)$_3$ in CCl_4 and optical rotation.[6] The absolute configuration was determined by correlating **3** (R^1=Ph) (i. $HSCH_2CH_2SH$, BF_3-Et_2O/CH_2Cl_2; ii. Raney-Ni/EtOH) *to methyl* (S)*-3-phenylhexanoate.*[7] As summarized in the Table I, dimethyl benzylidenemalonate (**2**: R^1=Ph, R^2=Me) is the Michael acceptor of choice (Run 1-4) and toluene-HMPA or THF is the solvent of choice. It is *noteworthy that bulky* tert*-butyl ester* (**2**: R^2=t-Bu) is a poor Michael acceptor in the term of enantioface selectivity, probably because of poor coordinating ability to the lithium cation in **5** (Run 7,8). The enantiomeric excess up to 93% was realized (Run 2).



Then we studied the reaction of **4** with some dimethyl alkylidenemalonates (**2**: R^1=Me, Et, i-Pr, c-Hex, R^2=Me) bearing methyl,[8] ethyl,[9] isopropyl,[10] and cyclohexyl[11] substituents. The results are summarized in the Table II. On the contrary to the reaction with benzylidenemalonate, higher enantiomeric excesses were obtained when the reaction was conducted in THF, not in toluene-HMPA solvent system, excepting Run 1. In the latter solvent system (Run 1-4) any meaningful relationships between enantiomeric excess and bulkiness of the substituents in **2** are not apparent. For example, dimethyl ethylidenemalonate (**2**: R^1=Me) afforded 56% ee over the other bulkier malonates (Run 1). However, in THF (Run 5-8) the enantiomeric excesses were in good relation to the bulkiness of the substituents. These results probably suggest that in THF alkylidenemalonate preferentially reacted on the bottom face of **5** as has been shown in the diastereoselective Michael reaction recently reported by us.[2d]

Then we turned our attention to the kinetic diastereoenrichment of the initial Michael adducts (**7**: R^1=Et, i-Pr, c-Hex) obtained by the reaction using toluene-HMPA as a solvent (Run 1-4). The mixture of crude adducts **7** was treated with satd. aq. NH_4Cl in THF at room temperature for 15 h.[12] The process of kinetic diastereoenrichment was monitored by HPLC (Waters Radial Pak B, hexane-AcOEt/10:1, 2 ml/min, 280 nm). It was shown that the initial ratios of diastereomers 1.6:1 (**7**: R=c-Hex), 1.5:1 (**7**: R=i-Pr), and 2:1 (**7**: R=Et) were improved to 15:1, 15:1, and 3.4:1, respectively, by the selective retro-Michael reaction of the minor isomer. After hydrolysis followed by decarboxylation and methylation as above, enantiomerically enriched **3** was successfully obtained in 55-88% ee as shown in the Table II (Run 9-11).

Thus, combination of asymmetric Michael reaction and kinetic diastereoenrichment provided the procedure for the synthesis of β-substituted δ-keto esters (**3**) with the absolute configuration indicated in 55-93% ee and in 27-88% overall yield. The possible origins of enantioface differentiation are probably related, at least in THF solvent, to the formulated structure **8** where carbonyl oxygen of **2** coordinates to lithium cation of **5** from the bottom face.[2d]

Table I Asymmetric Synthesis of Methyl (S)-5-Oxo-3-phenylhexanoate (**3**: R^1=Ph)^a

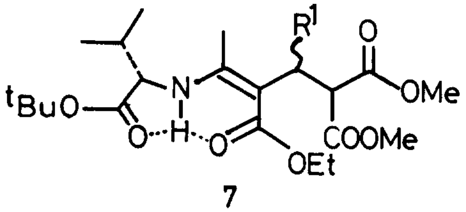
Run	R^2	Solvent^b	$[\alpha]_D^{20°}$ (PhH)	ee(%)^c	Yield(%)^d
1	Me	Toluene	-18.0	82	79
2	Me	Toluene-HMPA	-20.7	93	88
3	Me	THF	-20.4	91	83
4	Me	THF-HMPA	-19.7	91	43
5	Et	Toluene	e	68	85
6	Et	THF	-22.3	90	83
7	t-Bu	Toluene-HMPA	-11.7	55	78
8	t-Bu	THF	-18.4	80	68

a) Reaction was run at -78 °C for 1-7 h. b) Two equivalent of HMPA was used. c) Enantiomeric excess was determined by ^{1}H NMR in the presence of Eu(hfc)$_3$ in CCl$_4$ and optical rotation. See reference 6. d) Overall yield from **4**. e) Not determined.

Table II Asymmetric Synthesis of Methyl (S)-5-Oxo-3-substituted-hexanoate (**3**)^a

Run	R^1	Solvent^a	$[\alpha]_D^{20°}$	ee(%)	Yield(%)^b	Run^c	$[\alpha]_D^{20°}$	ee(%)	Yield(%)^b
1	Me	Toluene-HMPA	$+1.87^d$	56	66				
2	Et	Toluene-HMPA	$+1.39^e$	33	67	9	$+2.31^e$	55	39
3	i-Pr	Toluene-HMPA	$+1.28^f$	17	81	10	$+6.41^f$	86	30
4	c-Hex	Toluene-HMPA	$+1.33^g$	22	53	11	$+5.42^g$	88	27
5	Me	THF	$+0.95^d$	28	73				
6	Et	THF	$+1.54^e$	37	61				
7	i-Pr	THF	$+2.98^f$	41	74				
8	c-Hex	THF	$+2.90^g$	50	76				

a) Reaction was run at -78 °C. Two equivalent of HMPA was used. b) Overall yield from **4**. c) Kinetic diastereoenrichment procedure. See the text. d) Optical rotation was taken as a neat. See the reference 1e. e) Optical rotation was taken as a neat. Absolute configuration and ee were determined by correlating to (S)-3-ethylhexanoic acid (i. $HSCH_2CH_2SH$, BF_3-Et_2O/CH_2Cl_2; ii. Raney Ni/EtOH; iii. KOH/EtOH). A. I. Meyers, R. K. Smith, and C. E. Whitten, J. Org. Chem., **44**, 2250 (1979). f) Optical rotation was taken as a benzene solution. Absolute configuration and ee were determined by converting to (S)-3-isopropylbutan-4-olide (i. CF_3CO_3H/CH_2Cl_2; ii. MeOH-K_2CO_3). M. Kendall and R. J. Wells, Aust. J. Chem., **27**, 2293 (1974). g) Optical rotation was taken as a benzene solution. Absolute configuration and ee were determined by correlating (S)-**3** (R^1=Ph) to (S)-**3** (R^1=c-Hex) (5% Rh/alumina, H_2/AcOH-H_2O (9:1)).



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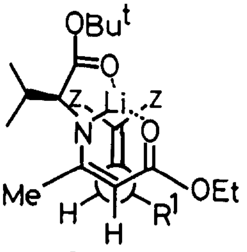

8 Z=COOMe

Further mechanistic studies and application of this procedure to the synthesis of biologically active compounds are the subjects of our current interests.13)

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