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ASYMMETRIC MICHAEL ADDITIONS VIA SAMP-/RAMP-HYDRAZONES ANTI-DIASTEREO- AND ENANTIOSELECTIVE SYNTHESIS OF 3,4-DISUBSTITUTED 5-OXO-ALKANOATES[1]

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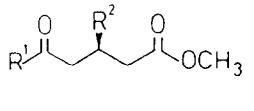
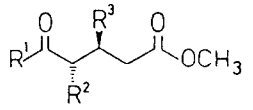
SUMMARY: An efficient and highly anti-diastereo-(de=90-≈100%) and enantioselective (ee=92-≈100%) synthesis of 3,4-disubstituted 5-oxo-alkanoates 3 in good overall chemical yields is described. The procedure involves the asymmetric Michael addition of aldehydes or ketones to enoates via their lithiated SAMP-/RAMP-hydrazones. Both enantiomers are accessible at will.

Michael additions are among the most important processes for C-C bond formation and stereoselective variants have been studied extensively in recent years[2]. Using our SAMP-/RAMP--hydrazone method[3] we previously reported an efficient 3-step enantioselective synthesis of β-substituted δ-ketoesters (A) with virtually complete asymmetric induction [4]. In this communication we describe a useful extension of this method leading to 3,4-disubstituted aldehyde- (R^1=H) or ketoesters of type B in excellent anti-diastereo- and enantioselectivities.

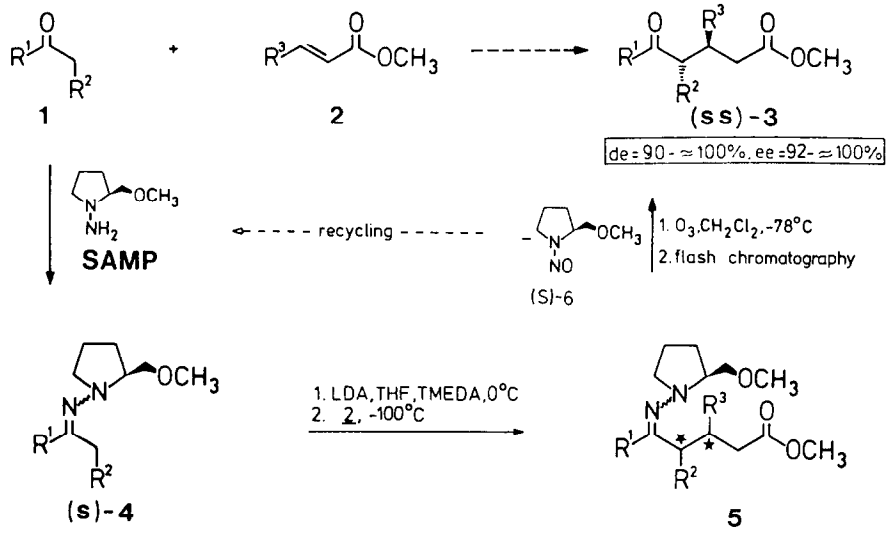


A ee = 96 - ≈ 100%



B de = 90 - ≈ 100%
ee = 92 - ≈ 100%

As shown in the scheme, aldehydes or ketones 1 are transformed to their corresponding SAMP-hydrazones (S)-4 , which are metalated with LDA in THF in the presence of 2 equiv. TMEDA[5] at 0°C for 4 h, followed by treatment with the enoates 2 at -100°C. After purification of the Michael adducts 5 by distillation or column chromatography (silica gel, ether, n-pentane, 1:1) the hydrazoneesters are cleaved by ozonolysis in CH_2Cl_2 at -78°C.



Separation of the nitrosamine (S)-6 by flash chromatography (recycling of the chiral auxiliary by LAH-reduction) affords the 5-oxo-esters 3 in good overall chemical yields and with excellent diastereo- and enantioselectivities.

The de and ee values are easily determined by ^{1}H NMR-LIS techniques on the sharp ester methoxy singlet and by ^{13}C NMR spectroscopy (see table). Because the diastereomeric excesses were the same for compounds 5 and 3 within the limits of detection, the cleavage procedure is free of epimerization. In each case the racemic products and thus all possible stereoisomers of 3 were prepared via the corresponding DMH-cuprates[6]. For instance, as is shown for 3e (Fig. 1) virtually complete asymmetric inductions could be detected this way.

The relative(anti) and absolute configuration of the 5-oxo-alkanoates 3 was deduced from the x-ray structure analysis of 5g, which showed the (ESSS)-configuration (Fig. 2). The (E)-geometry of the hydrazone again reflects the Z_{CN}-configuration of the intermediate azaenolate. Alternatively, the enantiomeric products with (RR)-configuration are obtained by simply changing the auxiliary from SAMP to RAMP.

It should be mentioned that virtually complete asymmetric inductions are also observed, if methyl acrylates are used as the Michael acceptors (R^3=H). Thus, 4-monosubstituted 5-oxo--alkanoates can be synthesized by this method as well.

In summary, aldehydes and acyclic ketones can be added to enoates in a conjugate fashion leading to anti-3.4-disubstituted 5-oxo-alkanoates of very high diastereo- and enantiomeric excess[8,9]. Further investigations, e.g. on the syn/anti-control and esterenolate trapping experiments resulting in three new stereocenters in a row, will be reported in due course.

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Table. Optically active, 3,4-anti-disubstituted 5-oxo-alkanoates 3 prepared from ketones or aldehydes 1 and enoates 2 via SAMP-/RAMP-hydrazone Michael additions.

3	R^1	R^2	R^3	b.p. [°C/torr][a]	overall yield[%]	α_D^{20} (neat) [°]	de[%][b]	ee[%][b]	confg.[c]
a	H	CH_3	CH_3	90-95/1.3	58	+26.3	>96	> 96	SS
b	H	CH_3	C_2H_5	95-100/1.5	59	+55.75	>96	> 96	SS
b	H	CH_3	C_2H_5	95-100/1.5	52	-57.7	> 96	> 96	RR[d]
c	H	C_2H_5	C_6H_5	e	38	-16.9	> 96	> 96	SS
d	H	$C_6H_5CH_2$	C_6H_5	e	38	+25.0	> 96	> 96	SS
e	C_2H_5	CH_3	CH_3	40-45/0.04	45	+20.05	90	92	SS[f]
e	C_2H_5	CH_3	CH_3	40-45/0.04	40	-22.4	> 96	> 96	RR[d]
f	C_6H_5	CH_3	CH_3	105-110/0.04	45	+48.0	> 96	> 96	SS
g	C_6H_5	CH_3	C_6H_5	m.p.80[°C]	43	+63.3 (C=2.0,benzene)	~ 100	~ 100	SS[g]
h	n-C_4H_9	n-C_3H_5	C_6H_5	e	40	+27.15	92	> 96	SS

a) Oven temperature of Kugelrohr distillation; 3e: short path distillation. b) Determined by ^{1}H NMR-LIS (90 MHz , $CDCl_3$,ester methoxy singlet) on 5a-d[Eu(fod)$_3$], 3e-h[Eu(hfc)$_3$] or 3a-d (^{13}C NMR, $CDCl_3$, 22.63 MHz). c) Based on the X-ray analysis of 3g and assuming a uniform mechanism for all 1.4-additions. d) RAMP was used as chiral auxiliary. e) Purified by column chromatography (silica gel, ether, n-pentane, 1:1). f) 2 equiv. of HMPA instead of TMEDA were used. g) No change of optical rotation after several recrystallizations.

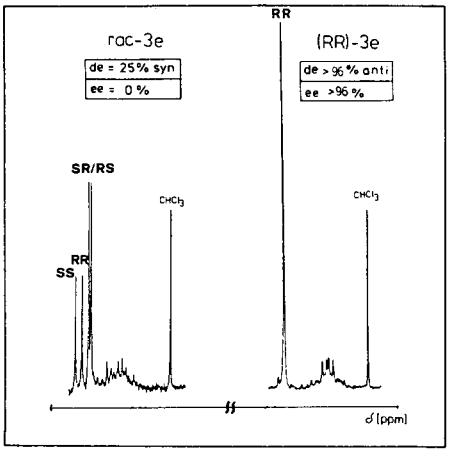

Fig. 1. Determination of % ee and de by ^{1}H NMR-LIS technique [ester methoxy singlet, Eu(hfc)$_3$].

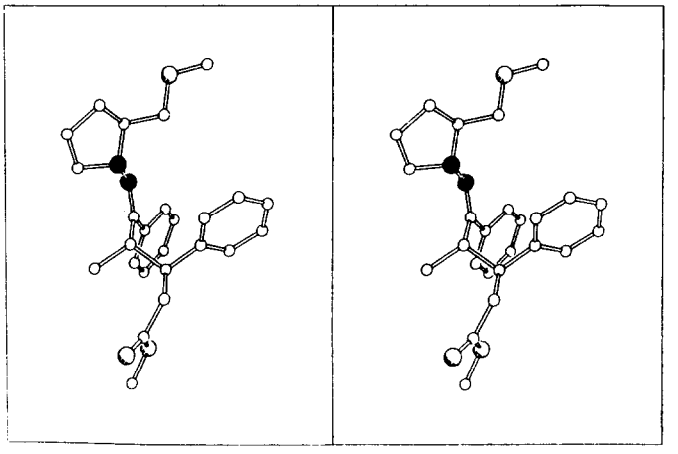

Fig. 2. Stereoview of crystalline (ESSS)-5g, m.p. 88°C (n-pentane); H atoms have been omitted[7].

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7) Crystal data of 3g: orthorhombic, space group $P2_12_12_1$, a= 769.2 (3) pm, b= 784.5 (3) pm, c= 3826.6 (19) pm, U= 2309.3 x 10^6 pm^3, D_c= 1.18 g cm^{-3}, Z=4. The structure was solved by direct methods (SHELXTL) from 3601 unique reflections and refined to R= 6.1 % (R_W= 4.8 %). Additional details of the crystallographic analysis are available on request from the Fachinformationszentrum Energie Physik Mathematik, D- 7514 Eggenstein-Leopoldshafen 2. Any request should be accompanied by the code number CSD 51883 and the full literature citation for this communication.

8) The spectroscopic data (NMR, IR, MS) and elementary analyses of all new compounds are in agreement with the structures given.

9) For a first application in pheromone syntheses see: D. Enders, B.E.M. Rendenbach, Tetrahedron 42 (1986), in press.

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