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ASYMMETRIC SYNTHESIS OF β-SUBSTITUTED δ-KETOESTERS VIA MICHAEL-ADDITIONS OF SAMP/RAMP-HYDRAZONES TO α,β-UNSATURATED ESTERS. VIRTUALLY COMPLETE 1.6-ASYMMETRIC INDUCTION [1]

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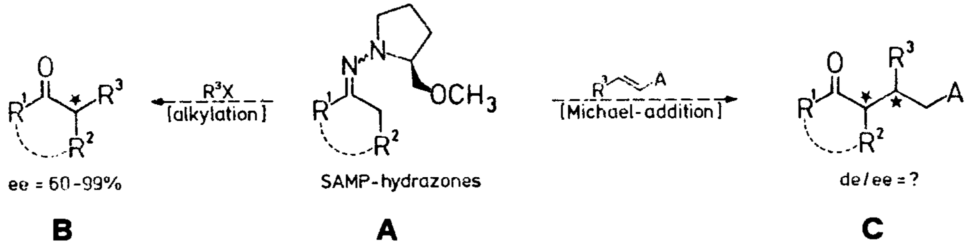
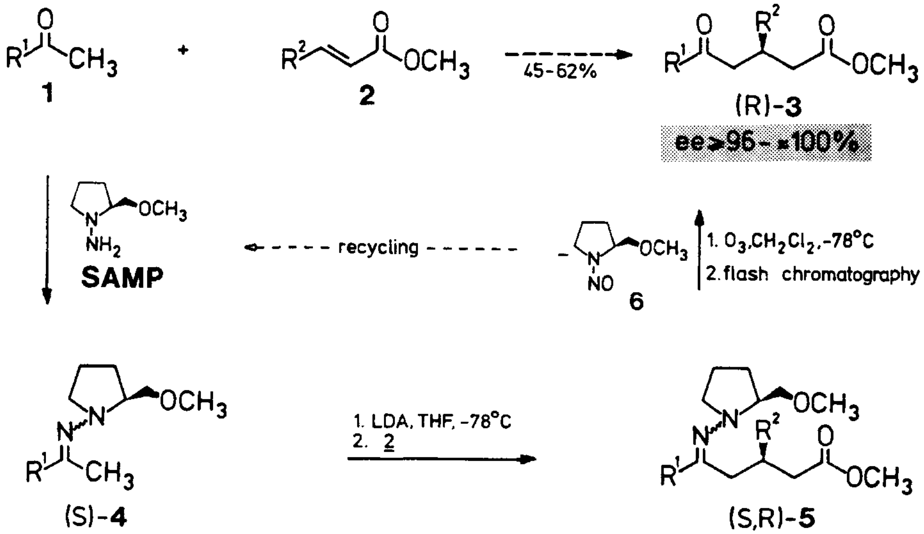
Summary: A simple and efficient 3-step asymmetric synthesis of β-substituted δ-ketoesters 3 in 45-62% overall chemical yield and ≥96-~100% ee is described. The key step is an asymmetric Michael-addition of lithiated methylketone-SAMP- or RAMP-hydrazones to α,β-unsaturated esters 2 with virtually complete 1.6-asymmetric induction.

In recent years we have developed an efficient method for carbon-carbon bond formation α to the carbonyl group of aldehydes and ketones that afforded high levels of asymmetric induction using (S)- or (R)-1-amino-2-methoxymethyl-pyrrolidine (SAMP or RAMP) as chiral auxiliary (A → B) [2,3]. To further extend the synthetic utility of our SAMP/RAMP-hydrazone method, we envisaged asymmetric Michael-additions A → C as an attractive possibility.



Asymmetric conjugate addition reactions have been studied intensively in recent years [4]. The best results achieved to date are those dealing with stoichiometric asymmetric 1.4-additions, in which achiral nucleophiles are added to Michael acceptors bearing the chiral auxiliary, and several procedures routinely allowing asymmetric inductions of greater than 90% enantiomeric excess are now at our disposal [4] (internal asymmetric induction). Although very desirable, asymmetric Michael-additions of achiral nucleophiles to prochiral acceptors in the presence of chiral catalysts, solvents or complexing agents (external asymmetric induction) are still far from being fully developed. This is also true for stoichiometric versions, where the nucleophile bears the chiral information (cf. A → C) and high inductions have been observed only in special cases [4,5].

We now wish to report that lithiated SAMP/RAMP-hydrazones of methylketones undergo conjugate addition to α,β-unsaturated esters in good overall chemical yields and with practically complete 1.6-asymmetric induction! Methylketones 1 are transformed to their corresponding SAMP-hydrazones (S)-4, which are metalated with LDA in THF at -78°C, followed by treatment with the esters 2 to give the 1.4-adducts (S,R)-5 exclusively. Ozonolysis in CH_2Cl_2 at -78°C and separation of the nitrosamine (S)-6 (recycling of the chiral auxiliary [2d]) by flash chromatography (silica gel, ether, n-pentane 1:1) yields the β-substituted δ-ketoesters (R)-3 in 45-62% overall chemical yield and of very high enantiomeric purity (see Table) [6]. The optical antipodes (S)-3 can be prepared in the same manner by simply using RAMP instead of SAMP as chiral auxiliary.



To confirm the exceptionally high degree of asymmetric induction, ^{1}H-NMR shift experiments [Eu(hfc)$_3$, Aldrich] were carried out in all twelve examples. By preparing the racemic esters (rac-3) via the corresponding dimethylhydrazone cuprates [7] and using a 400 MHz NMR instrument, we were able to demonstrate

Table. Optically active δ-ketoesters 3 prepared from methylketones 1 and α,β-unsaturated esters 2 via SAMP/RAMP-hydrazone Michael additions.

3	R^1	R^2	b.p. [°C/torr] [a]	overall yield [%] [b]	α_D^{20} (neat) [°]	ee [%] [c]	(conf.) [d]
a	CH_3	CH_3	99/12	50	-3.35 [e]	≧96	(R)
a	CH_3	CH_3	80/2	61	+3.34	≧96	(S) [f]
b	C_2H_5	CH_3	95/1	45	-2.8	≧96	(R)
c	n-C_3H_7	CH_3	75/0.5	49	-1.84	≧96	(R)
d	i-C_3H_7	CH_3	58/0.7	46	-2.92	≧96	(R)
e	n-C_5H_{11}	CH_3	98/2.5	45	-2.05	≧96	(R)
f	n-C_6H_{13}	CH_3	65-68/0.01	53	-1.85	≧99	(R)
g	C_6H_5	CH_3	85-88/0.01	55	+9.25	≧96	(R)
h	CH_3	C_6H_5	m.p. 48°C	62	+22.35 [g]	≧99	(R)
i	C_2H_5	C_6H_5	80-85/0.01	49	+35.3 [g]	≧96	(R)
j	n-C_3H_7	C_6H_5	105/0.05	50	+32.3 [g]	≧96	(R)
k	n-C_5H_{11}	C_6H_5	110-113/0.01	59	+14.03	≧96	(R)

a) Short path distillations; in the case of (S)-3a and 3b oven temperature of Kugelrohr-distillation. b) Overall yield of the process 1 → 3 (cleavage of the crude product 5); if compounds 5 are distilled prior to cleavage, the overall yields range from 35-55%. c) Determined by 90 and 400 MHz NMR shift experiments with $Eu(hfc)_3$ (Aldrich) and polarimetry (see text). d) Assigned by chemical correlation with the corresponding acids of 3a and 3f of known absolute configuration, the similar rotations of the homologous esters, and assuming a uniform reaction mechanism. e) lit.[10]: $\alpha_D^{16} = -1.02°$ (neat), lit.[11]: $\alpha_D^{16} = -1.1°$ (c= 35.6, Et_2O) (R), this work: $\alpha_D^{22} = -2.7°$ (c= 30.7, Et_2O). f) RAMP was used as chiral auxiliary. g) α_D^{20} (c= 2-3, C_6H_6).

that 1-2% of the other enantiomer would be detectable (methoxy singlet). In this way we can give a lower limit of ≧96-≧98% ee in all cases. The configurations were assigned by saponification of 3a and 3f to the corresponding ketoacids of known absolute configurations [8]. According to the rotations given in the literature [9], the acids are optically pure.

Further investigations involving variation of the hydrazones and the Michael acceptors, as well as on the mechanism of this remarkable reaction are in progress.

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